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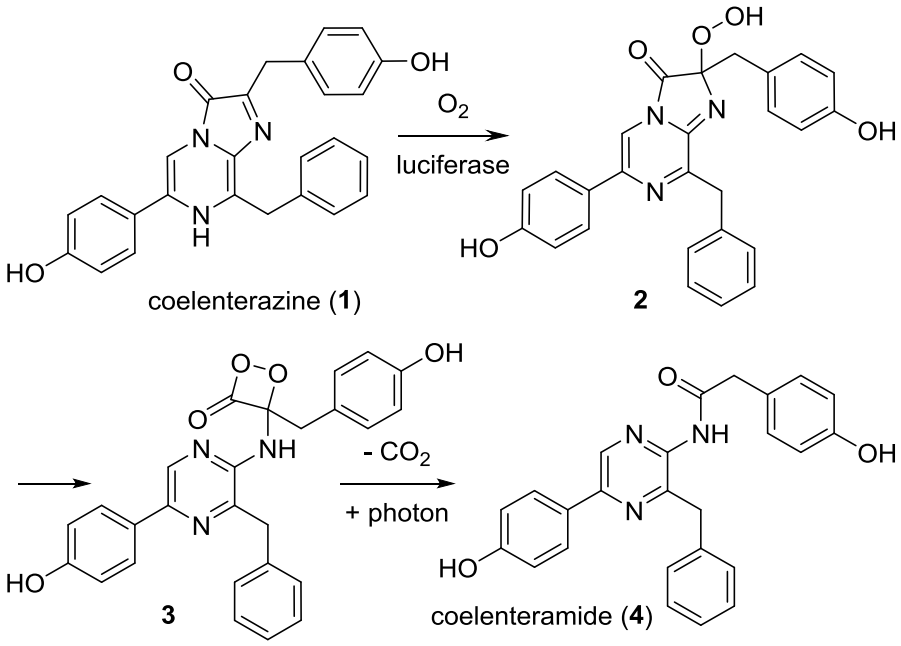
Abstract

We describe here an extensive structure-bioluminescence relationship study of a chemical library of analogues of coelenterazine, using nanoKAZ/NanoLuc, a mutated luciferase originated from the catalytic subunit of the deep-sea shrimp *Oplophorus gracilirostris*. Out of the 135 *O*-acetylated precursors, prepared using our recently reported synthesis and following their hydrolysis to give solutions of the corresponding luciferins, notable bioluminescence improvements were achieved in comparison with furimazine, currently amongst the best substrates of nanoKAZ/NanoLuc. For instance, the rather more lipophilic analogue 8-(2,3-difluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one provided a 1.5-fold improvement of the total light output over a two hours period, a close to 3-fold increase of the initial signal intensity and a signal-to-background ratio 5 times greater than furimazine. The kinetic parameters for the enzymatic reaction were obtained for a selection of luciferin analogues and provided unexpected insights in the luciferase activity. Most prominently, along with a general substrate-dependent and irreversible inactivation of this enzyme, in the case of the optimized luciferin mentioned above, the consumption of 2664 molecules was found to be required to produce, by bioluminescence, a single Relative Light Unit (RLU; a luminometer-dependent fraction of a photon).

Introduction

As very well related in Prof. Osamu Shimomura's book,[1] bioluminescence is based on the catalyzed oxidation of a substrate (a luciferin) by enzymes such as luciferases or photoproteins. A remarkably diverse set of marine genera,[2] such as *Renilla, Metridia*, *Gaussia, Periphylla* or *Oplophorus* as well as *Aequorea* and *Obelia*, are using coelenterazine (**1**) as their substrate to produce a blue light, the most visible color undersea, with the help of very different enzymes encoded in their respective genome.[3] The generally accepted mechanism of this photon emission was established using the photoprotein of *Aequorea* which can, arguably, be considered as a calcium-dependent luciferase.[4] As depicted in the scheme 1, this mechanism starts with an oxidative process leading to the hydroperoxide **2**, which undergoes a cyclisation to give the endoperoxide/dioxetanone **3**. This is followed by its decarboxylation leading to the occurrence of coelenteramide **4** in an exited state which can relax via the emission of a photon or via non radiative processes.[5] Of note is that, because of its inherent reactivity, coelenterazine can, without the recourse to a luciferin and under a variety of conditions, undergo a similar reaction leading to the production of a photon although in a far less efficient manner.[1]



Scheme 1. Mechanism for coelenterazine (**1**) bioluminescence.

Because of the ever-growing usefulness of bioluminescence-based reporting systems in life sciences,[6] research have focused on improving the characteristics of the light signal (intensity, duration, and/or wavelength). In the case of the marine bioluminescent systems using coelenterazine (**1**), it is from the *Oplophorus gracilirostris* luciferase that the best optimization was achieved. The investigations on this luciferase first pointed out that few coelenterazine analogues were acceptable substrates[7] and, probably more important, that its rather small 19kDa catalytic subunit was enough to produce a signal.[8] From these results, an extensive mutation campaign of the catalytic subunit, combined with an array of substrates analogues, provided greatly improved bioluminescent reporting systems.[9] These achievements included a better luciferase expression, a longer protein half-life as well as a far more intense and long-lasting signal. This was especially true when combining the mutant luciferase known as nanoKAZ/NanoLuc with furimazine (**5**) as its optimized substrate.[9d] However, some other luciferin analogues, such as compounds **6**-**9** and **10**-**12** (figure 1), were also reported to provide improved signals.[7, 9a, b, 10] In an attempt to see if even more improvements were possible, we used our recently reported original synthesis of such luciferins[11] and undertook a thorough structure-bioluminescence relationship study using the nanoKAZ/NanoLuc luciferase.

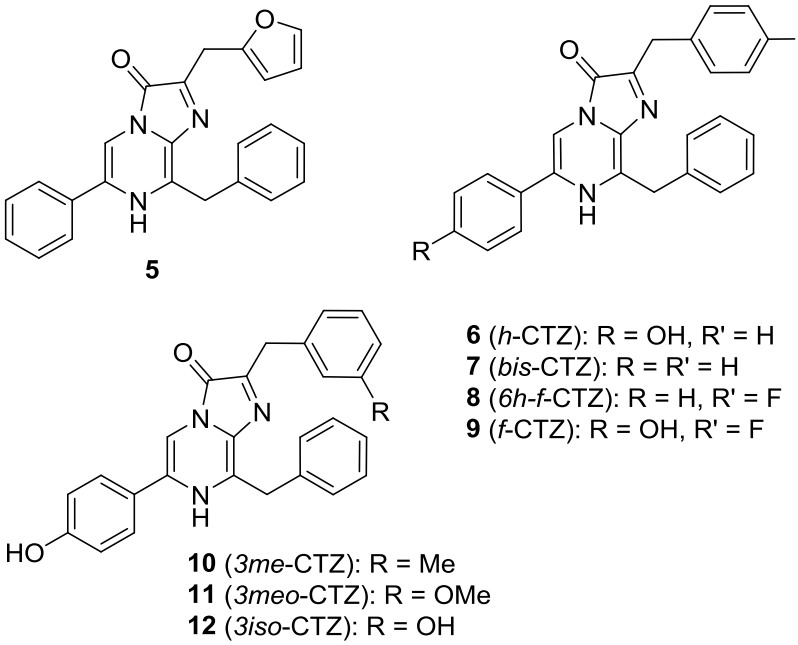
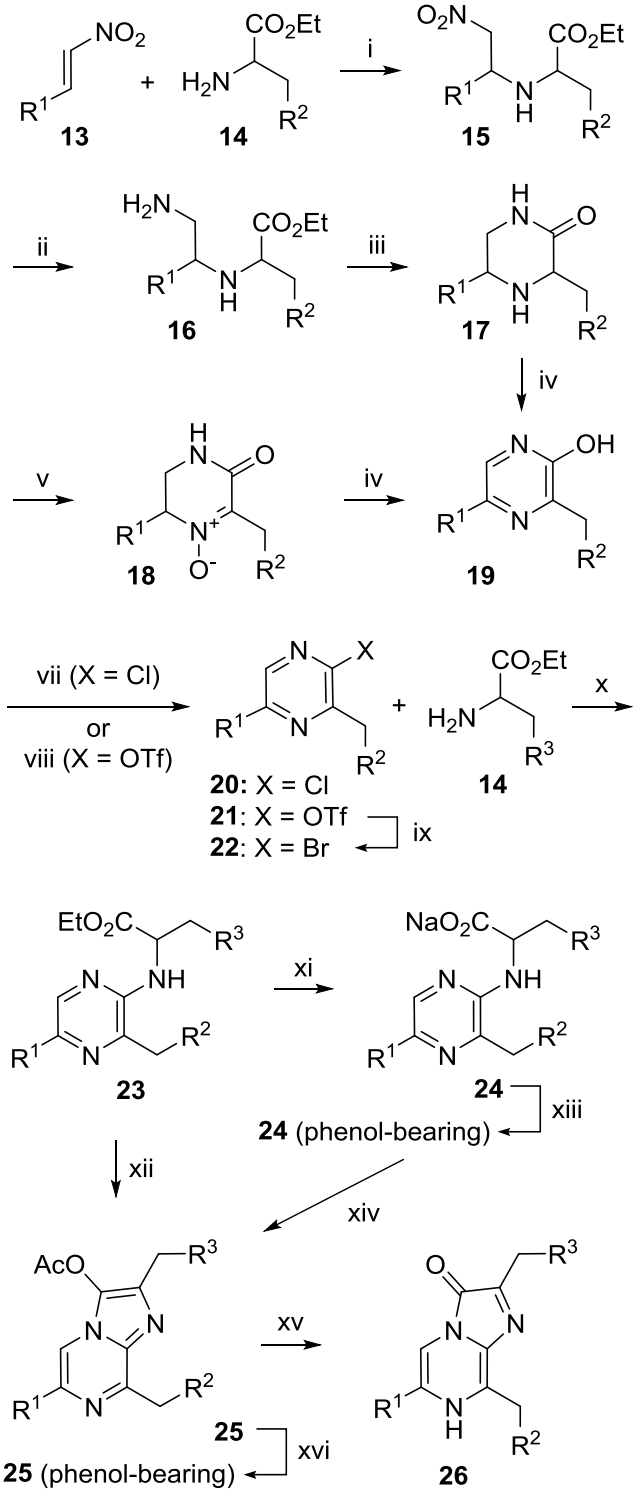


Figure 1. Structures of selected artificial imidazo[1,2-*a*]pyrazin-3(7*H*)-ones luciferins.

Results and discussion

As depicted in the general synthetic scheme 2, our original synthetic approach is providing stable *O*-acetylated luciferins **25** which, for the vast majority, could be stored at room temperature for up to two years (no changes were seen in ^{1}H NMR spectra). The hydrolysis of their acetyl function (step xv, hydrochloric acid in ethanol and DMSO) then provides fresh acidic solutions of the considered luciferins **26**. As opposed to the commercially available solution of furimazine (**5**) which is shipped in dry ice and has to be stored at -20 °C, these *O*-acetylated luciferins **25** are thus providing some improvement in the synthesis and handling of this class of reagents. The decision to provide users with the proluciferins **25** (which we have named hikarazines®) was also based on disastrous purification trials of compounds **26** using chromatography. Accordingly, LC/MS analysis was the only method used to check the purity of the luciferin solutions resulting from this acidic hydrolysis. When undertaken, the LC/MS monitoring clearly proved that the hydrolysis of compounds **25** into the luciferins **26** was clean and complete in two hours at 50 °C or in 12 hours at 18 °C. Moreover, thanks to the hydrochloric acid present,[1] these solutions appears to be rather stable in closed vial for at least an additional 12 hours at 18°C and a relatively modest decay was noted after 14 days (see supplementary info). When stored for up to three months at -20 °C, such solutions still provided a robust bioluminescence signal. The occurrence of traces amount of, plausibly, a dehydroluciferin was noted in most cases (see supplementary info) but such compounds were absent from the ^{1}H NMR spectra of the starting material. Finally, extensive decomposition (mentioned in the tables below) was observed in few instances but this behavior was also seen for the corresponding *O*-acetylated precursors **25** (transformation of the isolated solid/wax into a black oil). In this regard, since we could not check the completeness and purity of every solutions made, we assumed that the hydrolysis of clean *O*-acetylated precursors **25**, always led to clean solutions of the corresponding luciferins **26**. This was of course double-checked to further establish the most important results described in the following (see supplementary info). Concerning the chemistry, to reach even more original luciferin analogues, we also extended the scope of some of the steps in this synthetic pathway. For instance, the hydroxypyrazines **19** were prepared either directly from the piperazin-2-ones **17**, by an aromatization using sulfur and heat (step iv), or via an original reaction based on the sodium hydroxide-based dehydration (step vi) of the corresponding nitrone **18**. When running reaction on relatively large scale (20 g) we usually found that undertaking this aromatization step via the nitrone **18** gave more reproducible results since any excess of sulfur, past two equivalents, tended to over-oxidize compound **19** and thus lower the reaction yield. The vast majority of the halogenated pyrazines were obtained using hot phenylphosphonic dichloride (**20**, X = Cl, step vii), but in a few more delicate cases (e.g. R_2 = tetrahydrofuran-2-yl) we resorted to a much milder procedure. This started (step viii) with the synthesis of the triflate intermediates (**21**, X = OSO_2CF_3) and the corresponding bromo

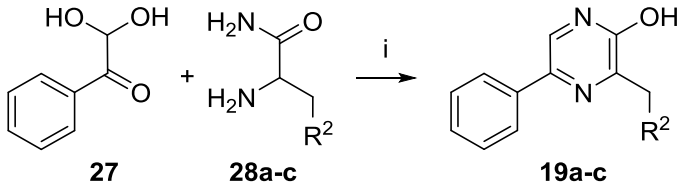
derivatives (**22**, X = Br) were then prepared via an aromatic Finkelstein reaction (step ix) using sodium bromide.[12] The N-arylation (step x) of halogenopyrazines **20** or **22** most often proceeded well in acetonitrile at 60 °C although, in some problematic cases, the recourse to toluene at 90 °C greatly improved the yields. From the *N*-arylated compounds **23**, a one pot procedure (step xii) proceeding via the sodium salt of acid **24** and leading directly to the *O*-acetylated luciferins **25** was used. When relevant, the removal of the benzyls protecting the hydroxyl groups to give analogues featuring phenolic functions was then achieved (step xvi).[11b] However, in at least five cases (**25**, R^2 or R^3 = $BnOC_6H_4$), over-hydrogenation of the heterocyclic system and/or lack of an effective debenzylation became such an issue that we resorted to the preparation of the (deprotected) phenol-bearing acids **24** (steps xi and xiii). From these, a controlled cyclisation, using two equivalent of acetic anhydride (step xiv), led to the phenol-bearing *O*-acetylated luciferins **25** without too much over-acetylation.



Scheme 2. i: neat, 20 °C, 10 min-12 h. ii: Zn, 37 % $H_3O^+Cl^-$, dioxane, 0-20 °C, 2 h. iii: neat, 140 °C, 3 h. iv: S_8, 1,3-$Cl_2C_6H_4$ or decaline, reflux, 10 h. v: AcOOH, AcOEt, 20 °C, 12 h. vi: NaOH, EtOH, 65 °C, 1 h. vii: $PhPOCl_2$, 100 °C, 12 h. viii: Tf_2O, NEt_3, CH_2Cl_2, 20 °C, 40 min. ix: NaBr, TfOH, DMF, 120 °C, 12 h. x: Cs_2CO_3, $Pd(OAc)_2$, BINAP, MeCN, 60 °C or toluene, 90 °C, 12 h. xi: a) NaOH, THF, 20 °C, 12 h, b) NH_4Cl, H_2O. xii: a) NaOH, THF, 20 °C, 12 h, b) Ac_2O, 20 °C, 2 h. xiii: Pd/C, $NH_4^+HCO_2^-$, EtOH, reflux, 90 min. xiv: Ac_2O, AcOEt, reflux, 30 min. xv: 37 % $H_3O^+Cl^-$, DMSO, EtOH, 50 °C, 2 h. xvi: H_2, Pd/C, AcOEt, AcOH, EtOH, 20 °C, 12 h.

We also explored the alternative preparation of some hydroxypyrazines **19** based on the regioselective condensation of 1,2-dicarbonyls and α-amino amides.[13] As depicted in scheme 3, the hydroxypyrazine intermediates **19a-c** were obtained in rather modest yields from phenylglyoxal (**27**) and α-amino amides **28a-c**

with this attractively simple method. However, we have so far failed to generalize the use of this preparation since, as commented before,[14] a lack of condensation regioselectivity plagued many of our trials, especially when starting from phenylalanine amide (**28**; $R^2 = C_6H_5$). As hinted in the three examples depicted here, the reaction selectivity and yields are regularly better when starting from aliphatic α-amino amides than from aromatic ones.



27 **28a-c** **19a-c**

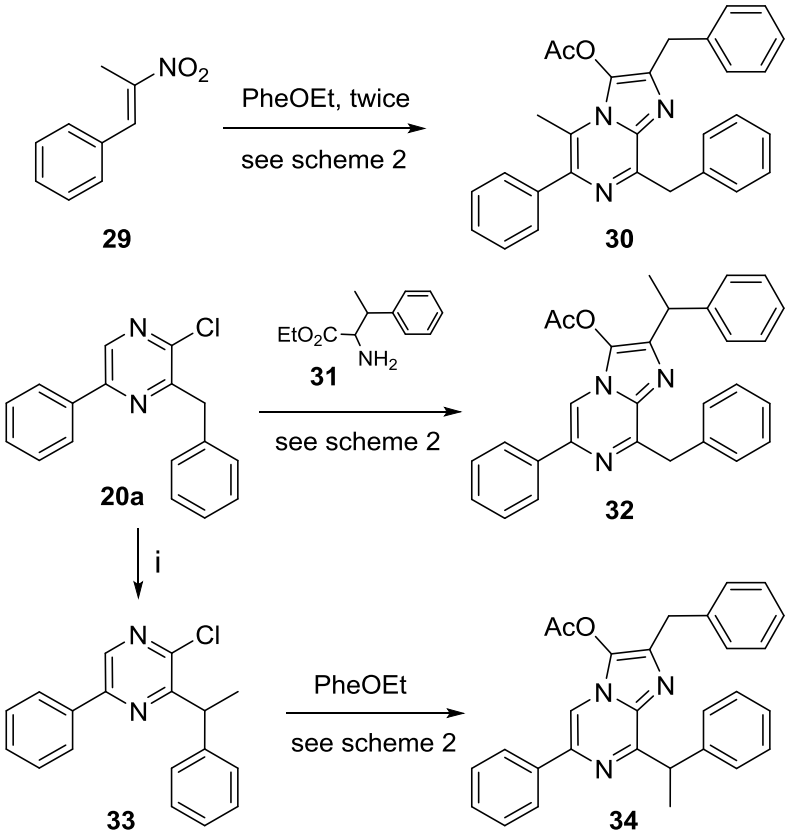
a: R^2 = H: 53%

b: R^2 = tetrahydrofuran-2-yl: 43 %

c: R^2 = pyridin-3-yl: 11 %

Scheme 3. i: a) NaOH, MeOH, -78 °C b) $H_3O^+Cl^-$

With these approaches, out of selected combinations of 12 different nitrostyrenes **13**[15] and two distinct α-amino esters **14** chosen amongst 60 previously reported,[16] we prepared 135 *O*-acetylated imidazo[1,2-*a*]pyrazin-3(7*H*)-ones proluciferins **25**, which led after deprotection to the luciferins **26** listed in tables 1-7. An extensive description of the synthesis of these *O*-acetylated precursors along with a characterization of most of the synthetic intermediates is provided in the supplementary information section. Moreover, as depicted in scheme 4, the chemistry used to prepare the methyl-bearing proluciferins **30**, **32** and **34** leading to the corresponding luciferins **35-37**, also used the synthetic pathways shown in scheme 2. Compound **30** was thus obtained in 6 steps from the β-methyl nitrostyrene **29** and phenylalanine ethyl ester (PheOEt) in an 8% overall yield. The second proluciferin **32** was easily obtained in two steps from chloropyrazine **20a** and the β-methyl phenylalanine derivative **31**.[16c] One note is that our attempt to prepare a β,β-dimethyl homologue of compound **32** failed when trying to N-arylate (step x in scheme 2) the corresponding β,β-dimethyl phenylalanine ester. Finally, a two steps preparation of compound **34** was achieved using the methyl-bearing chloropyrazine **33**. This chloropyrazine was actually obtained by the more straightforward methylation of the chloropyrazine **20a** which avoided a far longer synthetic alternative starting with compound **31**. Again, a more detailed description of this chemistry is provided in the supplementary information section.



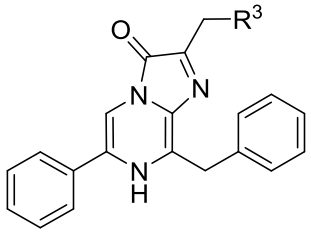
Scheme 4. i: a) LDA, THF, -78 °C, b) MeI. -78 °C to 20 °C, 0.5 h.

As listed in tables 1-7, the bioluminescence profiles of the resulting solutions of luciferins **26** were assessed with the nanoKAZ/NanoLuc luciferase using a Berthold Centro XS^3 luminometer. These values were obtained in relative light unit (RLU) which only corresponds to a fraction of the photons emitted, this fraction actually depends on the luminometer used as well as its age. In any case, these values are completely appropriate for comparison if the same setting and the same machine are used throughout the experiments. Our assays thus led to bioluminescence profiles over two hours for each compound and we analyzed the results using four values which we normalized to the bioluminescence of furimazine (**5**) rather than the very weak one obtained with coelenterazine (**1**). The first value (I_{max}) corresponds to the maximum intensity. In few cases, this value (as well as the $t_{1/2}$) can be strongly dependent on the laps of time existing between the addition of the luciferase and the beginning of the bioluminescence monitoring. Indeed, as we previously reported,[11b] initial intensities about three times more intense than furimazine but lasting only a few seconds after the addition of the luciferase in the medium were sometimes observed. In the main experimental setting, a (fixed) delay was unavoidable. For this reason, the I_{max} reported in table 1-7 may not do justice to the ephemeral brightness of few of the "flashy" luciferins tested. The second value ($t_{1/2}$) corresponds to a comparison of the time when the signal has reached half of its measured initial intensity (over the two hours monitoring period). It is also dependent on the experimental setting but provides an idea of the signal decay compared to furimazine (**5**). The third value (S_{120}) is the sum of the signal observed over two hours relative to furimazine (**5**). Finally, measurement of the spontaneous emission of photons in the phosphate buffer in the absence of enzyme (autoluminescence) was systematically performed for all analogues. This provided a signal-to-background value (S/B), characteristic of the relative stability of these luciferins in this buffer, once again in comparison with furimazine (**5**).

Table 1 is illustrating some of the avenues we explored in the design of analogues featuring various aryls on position R^3. Since variations on this position have been extensively investigated in the past, we only sought a confirmation of some of the results reported when using nanoKAZ.[9d, 10a, i, 17] As previously reported,[10a] bis-coelenterazine (**7**) is endowed with signal characteristics in par with furimazine (**5**) although the $t_{1/2}$ and S_{120} values both indicate a faster decay over two hours. The *para*-fluoro luciferin *6h-f*-coelenterazine (**8**) also displayed the reported[10a, i] strong initial intensity but, as illustrated by its $t_{1/2}$ value, it was short-lived in comparison with

furimazine (**5**). Interestingly, bioluminescence of the *ortho*- or *meta*-fluoro luciferins **26a** and **26b** displayed in both cases a loss of this strong initial intensity. An attempt to improve this with the 2,4-fluoroluciferin **26c** only led, as reported,[10i] to a signal pretty much equal to the 4-fluoroluciferin **8**. Moreover, replacing the 4-fluoro group by a 4-chloro (analog **26d**) or a 4-bromo (analog **26e**) led to luciferins of lesser interest. We also checked the three possible methyl-bearing luciferins, but only the *meta*-substituted analogue **26g** displayed an improved bioluminescence. Indeed, the corresponding *ortho* isomer **26f** was of no interest and the bioluminescence characteristics of the *para* isomer **26h** were decreased by a factor of four compared to the *meta*-methyl isomer **26g**. A similar investigation with the three possible trifluoromethyl-bearing luciferins (**26i-k**) or methoxy-bearing luciferins (**26l-n**) pointed out a similar "*meta* effect" for analogues **26j** and **26m** in comparison with their respective isomers. The relatively important initial intensity of the *para*-methoxy analogue **26n** has actually been noted before,[10i] and the same group claimed[17] the slightly more intense signal for the *meta*-methoxy analogue **26m** which we also observed. The two analogues featuring respectively a 3- and a 4-hydroxyphenyl group on R^3, **26o** and **26p**, turned out to be of little interest in agreement with what has been reported in the past.[10a, 17] Finally, since the (original) *meta*-methyl luciferin **26g** displayed the strongest initial intensity, we prepared and assayed the five alkyl-bearing analogues listed in at the end of table 1. However, this met little success aside from the observation that the $t_{1/2}$ of the *meta*-substituted alkyl derivatives **26q** and **26r** were rather better than their *para*-substituted homologues **26s** and **26u**.

Table 1. Variations on R^3

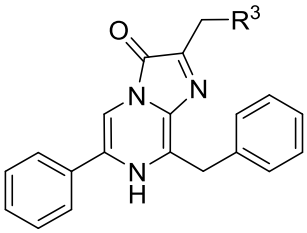


	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
5	furan-2-yl	1	1	1	1
7	C_6H_5	1.3	0.4	0.8	1.4
26a	2-FC_6H_4	0.4	1.0	0.4	0.6
26b	3-FC_6H_4	0.7	0.7	0.6	0.9
8	4-FC_6H_4	1.2	0.4	0.6	1.5
26c	2,4-$F_2C_6H_3$	1.0	0.3	0.5	1.5
26d	4-ClC_6H_4	0.4	0.4	0.2	0.5
26e	4-BrC_6H_4	0.3	0.2	0.1	0.5
26f	2-MeC_6H_4	<0.1	1.4	<0.1	<0.1
26g	3-MeC_6H_4	1.3	0.6	1.0	1.6
26h	4-MeC_6H_4	0.3	0.3	0.1	0.3
26i	2-$CF_3C_6H_4$	0.1	0.9	0.1	0.2
26j	3-$CF_3C_6H_4$	0.4	1.1	0.4	0.6
26k	4-$CF_3C_6H_4$	0.2	0.4	0.1	0.2
26l	2-$MeOC_6H_4$	0.4	0.5	0.2	0.4
26m	3-$MeOC_6H_4$	1.2	0.7	0.9	1.3
26n	4-$MeOC_6H_4$	0.7	0.3	0.3	0.9
26o[a]	3-HOC_6H_4	0.2	0.1	<0.1	-
26p[a]	4-HOC_6H_4	0.1	0.1	<0.1	-
26q	3-*n*-PrC_6H_4	0.5	1.0	0.5	0.6
26r	3-*c*-PrC_6H_4	0.6	0.9	0.5	0.6
26s	4-*n*-PrC_6H_4	0.2	0.2	0.1	0.2
26t	4-*i*-PrC_6H_4	0.3	0.4	0.1	0.3
26u	4-*c*-PrC_6H_4	0.3	0.3	0.1	0.4

[a]: This luciferins were assessed using the same experimental setting but in the course of another batch of evaluation.

Another direction, listed in table 2, was explored with the introduction of whole array of (hetero)cycles on R^3. Since many analogues featuring this type of modifications have been previously reported[9d, 10i] or patented,[17] we also made and assessed some of these compounds along with original derivatives. In view of the bioluminescence of furimazine (**5**), the tetrahydrofuranyl and the dioxolane derivatives **26v** and **26w** were made. Their very disappointing bioluminescence characteristics hinted for the necessity of an aromatic moiety on position R^3. This requirement was further confirmed with the very weak bioluminescence of the cyclohexyl or cyclopentyl-bearing analogues **26x** and **26y**. Moreover, the benzyl homolog **26z** turned out to be of little interest. The 2-pyridyl derivative **26aa** was disappointing as the corresponding proluciferin turned out to be very unstable, thus prohibiting a proper assay of this luciferin. In view of all the work already published[10i] on many 3-pyridyl derivatives, we did not study further variations on this heterocycle. Interestingly, the isomeric furan-3-yl derivative **26ab** was found to provide about half the signal of furimazine (**5**) and the previously described (without bioluminescence data)[9d] thiophen-2-yl analogue **26ac** led to a quite intense signal which decreased twice as fast as furimazine (**5**). Finally, we assessed the replacement of the furan by an oxazole or an isoxazole ring systems but none of the four analogues **26ad-26ag** were of notable interest.

Table 2. Further alterations of R^3



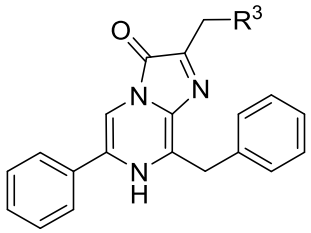
	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
5	furan-2-yl	1	1	1	1
26v	tetrahydrofuran-2-yl	<0.1	1.8	0.1	<0.1
26w	1,3-dioxolan-2-yl	<0.1	1.7	<0.1	<0.1
26x	cyclohexyl	<0.1	1.8	<0.1	<0.1
26y	cyclopentyl	<0.1	1.8	<0.1	<0.1
26z	benzyl	0.1	0.6	0.1	0.1
26aa[a]	2-pyridyl	-	-	-	-
26ab	furan-3-yl	0.5	0.9	0.5	0.1
26ac	thiophene-2-yl	1.2	0.5	0.9	1.8
26ad	3-Meisoxazol-5-yl	0.2	0.2	0.1	<0.1
26ae	3-Etisoxazol-5-yl	0.3	0.2	0.1	<0.1
26af[b]	5-Meoxazol-2-yl	0.2	1.8	0.2	-
26ag	4,5-Me_2oxazol-2-yl	0.2	0.9	0.2	0.2

[a]: The corresponding *O*-acetyl derivative **25** decomposed over few days. [b]: This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation.

As depicted in table 3, a fairly large number of alkylfurans derivatives were also evaluated. The initial impetus for this part of our work was the half-life improvement seen in table 1 for the *meta*-tolyl derivative **26g**, in comparison with bis-coelenterazine (**7**), which only differs by one methyl group. This approach turned out to be handsomely rewarding, although not as initially expected. Indeed, the 5-methylfuran-2-yl **26ah** turned out to be endowed with a very strong initial intensity and half of the $t_{1/2}$ of furimazine (**5**). A patent published in the course of this study has actually depicted this luciferin analogue but, surprisingly, no mention of its bioluminescence properties was provided.[17] Following these results, 5-alkylfuran-2-yl analogues **26ai-al** were made and this pointed out that the methyl of **26ah** or the ethyl group of **26ai** led to the most intense signals. Moreover, past the *n*-propyl side chain of compound **26ak**, the more hindered cyclopropyl side chain of **26aj** caused a slight drop in intensity, and the *n*-pentyl-bearing analog **26al** displayed a very weak bioluminescence. Of even more interest for these improved luciferins were the signal-to-background ratios which were about three times better than the reference furimazine (**5**). We also noted that despite a more modest intensity gain, the *n*-propyl derivative **26ak** had a signal which

lasted substantially longer than furimazine (**5**). A similar phenomenon was observed for the previously claimed[17] 5-trifluoromethyl bearing analogue **26am** although this took place with a fivefold loss of initial intensity. Further work led to the 4,5-dimethylfuran-2-yl derivative **26an**, which retains some of these improved bioluminescence properties but, as seen for the 4,5,6,7-tetrahydrobenzofuran-2-yl analogue **26ao** or the polyalkyl derivatives **26ap-ar**, further crowding of these positions was counterproductive. In view of these results, we also tried this approach with the alkylthiophene-bearing derivatives **26at-av**. However, in comparison with the unsubstituted thiophene-bearing luciferin **26ac**, no such drastic improvement was observed. A more hindered 5-*iso*-butyl-bearing thiophene derivative was previously claimed although it appears to display only a third of furimazine initial intensity.[17] Of note in this study was the much improved signal stability of the 3-methylthiophene derivative **26au**.

Table 3. few analogues related to furimazine (**5**)

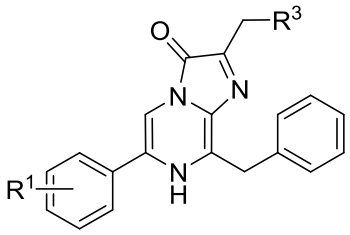


	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
5	furan-2-yl	1	1	1	1
26ah	5-Mefuran-2-yl	2.0	0.5	1.3	3.2
26ai	5-Etfuran-2-yl	1.9	0.6	1.3	3.8
26aj	5-*c*-Prfuran-2-yl	1.3	0.6	0.9	2.9
26ak	5-*n*-Prfuran-2-yl	1.4	1.0	1.5	3.4
26al	5-*n*-Pentfuran-2-yl	0.1	0.8	0.1	0.2
26am	5-CF_3furan-2-yl	0.2	1.8	0.3	0.2
26an	4,5-Me_2furan-2-yl	1.4	0.5	0.9	2.9
26ao	tetrahydrobenzofuran-2-yl	0.6	0.5	0.4	1.2
26ap	4-Me-5-Etfuran-2-yl	0.9	0.8	0.7	1.8
26aq	4-Et-5-Mefuran-2-yl	0.9	0.4	0.4	2.2
26ar	4-Me-5-*i*-Prfuran-2-yl	0.4	1.0	0.4	0.8
26as	thiophene-2-yl	1.2	0.5	0.9	1.8
26at	5-Etthiophen-2-yl	1.1	0.4	0.6	2.0
26au	3-Methiophen-2-yl	0.2	1.8	0.2	0.2
26av	4,5-Me_2thiophen-2-yl	0.5	1.1	0.6	1.0

The beginning of table 4 is depicting our efforts to introduce an array of substituents on the aryl R^1, while retaining either a 5-methylfuran-2-yl or a furan-2-yl on R^3. These pointed out bioluminescence I_{max} improvement for the luciferins **26aw**, **26ax** and **26ay** featuring an *ortho*- or *meta*-fluorophenyl as R^1. However, shifting the fluorine atom on the *para* position, as seen for compound **26az**, drastically lowered this I_{max}. Moreover, if a *meta*-tolyl as R^1 provided luciferin **26ba** with a less intense but remarkably stable signal, a similar signal collapse was observed if the methyl group was moved to the *para* position as seen for compound **26bb**. No such contrast was seen for the *ortho*-, *meta*- or *para*-methoxy-bearing derivatives **26bc**-**be**, which all led to an even weaker bioluminescence than the one observed for coelenterazine (**1**) itself. Concerning hydroxy-bearing derivatives, we have already reported[11b] the bright and short-lived bioluminescence of the furan-bearing coelenterazine analogue **26bf** and a very similar observation was made for the 5-methylfuran-2-yl derivative **26bg** in contrast with the rather less intense phenyl-bearing *h*-coelenterazine (**6**). A recent patent is actually confirming this observation for compound **26bf** along with the mention that an irreversible inhibition of the luciferase is taking place.[18] Concerning the irreversible aspect mentioned in this document, a two stage oxidation process can be suggested which would lead to reactive quinoid-bearing products. This "flash" behavior was also reported for an array of hydroxy-bearing analogues such as compounds **10-12** depicted in figure 1.[10a] When moving this hydroxyl group to position 3 of aryl R^1, we have already noted[11b] the far more stable signal provided by the furan-bearing analogue **26bh**, but the introduction of a methyl on R^3 as seen for the 5-methylfuran-2-yl derivative **26bi** only slightly increased the initial

bioluminescence intensity and lasted far less than furimazine (**5**). Moreover, in all appearance because of its hydroxyl function on aryl R^3, compound **26bj** – the bis-hydroxylated isomeric analogue of coelenterazine (**1**) – lost all its signal intensity. Finally, for the last four compounds **26bk-bn** listed in this table, we retained a 2-fluorophenyl as R^1 and varied the nature of the R^3 aryl group. For each case, an initial intensity improvement was seen, especially for the alkylfuran derivatives **26bm** and **26bn**, but this took place along with a faster signal decay. At this stage, we stopped pursuing similar alteration because, as mentioned in the footnote of this table, all too often the corresponding 2-fluoro-bearing proluciferins **25** turned out to be much less stable.

Table 4. More elaborated analogues of furimazine



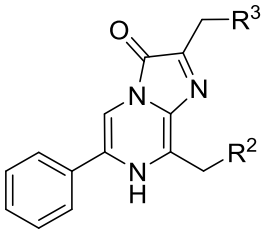
	R^1	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
5	H	furan-2-yl	1	1	1	1
26ah	H	5-Mefuran-2-yl	2.0	0.5	1.3	3.2
26aw[a]	2-F	5-Mefuran-2-yl	2.2	0.4	1.9	-
26ax	2-F	furan-2-yl	1.4	0.8	1.2	1.2
26ay	3-F	5-Mefuran-2-yl	1.7	0.5	1.1	3.6
26az	4-F	5-Mefuran-2-yl	0.1	1.8	0.1	0.1
26ba	3-Me	5-Mefuran-2-yl	0.4	1.2	0.4	0.7
26bb	4-Me	5-Mefuran-2-yl	<0.1	1.4	<0.1	<0.1
26bc[a]	2-MeO	furan-2-yl	<0.1	1.8	<0.1	<0.1
26bd	3-MeO	5-Mefuran-2-yl	<0.1	2.2	<0.1	-
26be	4-MeO	5-Mefuran-2-yl	<0.1	1.8	<0.1	<0.1
1	4-HO	4-HOC_6H_5	0.1	0.6	0.1	<0.1
26bf	4-HO	furan-2-yl	3.1	0.1	0.1	0.1
26bg[b]	4-HO	5-Mefuran-2-yl	2.6	<0.1	0.1	-
6	4-HO	C_6H_5	0.5	<0.1	<0.1	0.1
26bh	3-HO	furan-2-yl	0.9	0.8	0.8	1.2
26bi	3-HO	5-Mefuran-2-yl	1.2	0.5	0.7	2.1
26bj	3-HO	4-HOC_6H_5	<0.1	1.9	0.1	<0.1
26bk	2-F	C_6H_5	1.3	0.4	0.8	2.6
26bl	2-F	4-FC_6H_4	1.3	0.2	0.5	2.2
26bm[a]	2-F	5-Etfuran-2-yl	2.6	0.4	2.3	-
26bn[a]	2-F	4,5-Me_2furanyl	2.1	0.3	2.0	-

[a]: The corresponding *O*-acetylated derivatives **25** were not stable over time, initial bioluminescence results only. [b]: This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation.

In table 5, we then set out to investigate the influence of substituents on R^2, initially while retaining a phenyl on R^3. First of all, removing the phenyl ring on R^2 as seen for **26bo** led to a compound which was not a substrate of nanoKAZ luciferase. The introduction of the tetrahydrofuran-2-yl group seen in compound **26bp** was not so good either and the 3-pyridyl of **26bq** led only to a modest increase of initial intensity and overall signal. Moreover, nothing of interest was observed with the three hydroxyl-bearing isomers **26br-bt**. On the other hand, when investigating the effect of a fluorine atom on the same R^2 ring, the *ortho*- and *meta*-fluoro isomers **26bu** and **26bv** turned out to be substrates as good as bis-coelenterazine (**1**) whereas the *para*-fluoro analogue **26bw** led to a very diminished bioluminescence. The same loss was observed for the *para*-fluoro derivative **26bx** in which the phenyl on R^3 was replaced by a furan-2-yl moiety. Replacing the fluorine atom by a chlorine in position 2 of the R^2 aryl led to compounds **26by**, **26bz** and **26ca** which displayed very similar and pretty good bioluminescence profiles

although of a lesser interest than analogue **26bu**, featuring a 2-flurophenyl on R^2 and a phenyl on R^3, or furimazine (**5**). Shifting this chlorine atom to the *meta* position led to compound **26cb**, which lost a lot of signal intensity in comparison with the *meta*-fluoro homologue **26bv**, and the furan-bearing derivative **26cc** was an even worse luciferase substrate. Attempts with a methyl group (compounds **26cd-cg**) followed pretty much the same pattern as the methoxy-bearing derivative **26ch** or the two analogs featuring a trifluoromethyl group **26ci-cj**, which all led to an almost complete loss of luminescence properties. We then focused on derivatives featuring a 2-fluorophenyl or a 3-fluorophenyl moiety on R^2 and a variety of substituents on R^3. For instance, the combination of a 2-fluorophenyl on R^2 and a 3-methylphenyl for compound **26ck** or a 3-methoxyphenyl for compound **26cl** both led to improved signals in comparison with the profiles listed in table 1 for compounds **26a** and **26g**. Such synergy on their bioluminescence properties was much less important (or not existing) for the analogues bearing a 3-fluorophenyl on R^2 when comparing compounds **26cq**, **26cr** and **26cs** with their phenyl homologues **26g**, **26m** and **8** listed in table 1. In any case, this prompted us to combine the alkylfuran groups on R^3 with a 2-fluorophenyl or a 3-fluorophenyl on R^2. For the four analogues featuring a 2-fluorophenyl group (compounds **26cm-cp**), tangible improvements (often in their initial intensity), were observed in comparison with their phenyl homologue furimazine (**5**), compounds **26ah**, **26ai** and **26an** listed in table 3. To a lesser extent this was also the case for derivatives with a 3-fluorophenyl group (compounds **26ct**, **26cu**, **26cv** and **26cw**) although the improvements were more tangible on their bioluminescence half-life than on their initial intensity.

Table 5. Some combined variations of R^2 and R^3



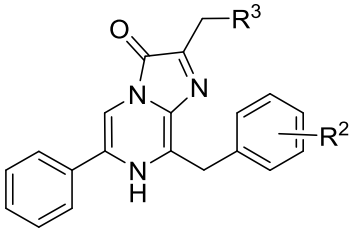
	R^2	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
5	C_6H_5	furan-2-yl	1	1	1	1
7	C_6H_5	C_6H_5	1.3	0.4	0.8	1.4
26ah	C_6H_5	5-Mefuran-2-yl	2.0	0.5	1.3	3.2
26bo	H	C_6H_5	<0.1	-	<0.1	-
26bp	THF-2-yl	C_6H_5	<0.1	1.8	0.1	<0.1
26bq	pyridin-3-yl	C_6H_5	0.3	1.1	0.3	0.1
26br[a]	2-HOC_6H_4	C_6H_5	<0.1	1.9	<0.1	-
26bs[a]	3-HOC_6H_4	C_6H_5	0.1	0.1	<0.1	-
26bt[a]	4-HOC_6H_4	C_6H_5	<0.1	-	<0.1	-
26bu	2-FC_6H_4	C_6H_5	1.2	0.4	0.7	1.4
26bv	3-FC_6H_4	C_6H_5	1.2	0.5	0.8	1.2
26bw	4-FC_6H_4	C_6H_5	0.1	1.0	0.1	0.2
26bx	4-FC_6H_4	furan-2-yl	<0.1	2.0	<0.1	<0.1
26by	2-ClC_6H_4	C_6H_5	0.8	0.5	0.5	1.0
26bz	2-ClC_6H_4	furan-2-yl	0.7	0.9	0.6	1.0
26ca	2-ClC_6H_4	5-Mefuran-2-yl	0.7	0.8	0.6	0.9
26cb	3-ClC_6H_4	C_6H_5	0.2	1.5	0.2	0.3
26cc	3-ClC_6H_4	furan-2-yl	<0.1	2.0	0.1	0.1
26cd	2-MeC_6H_4	C_6H_5	0.3	1.3	0.3	0.3
26ce	2-MeC_6H_4	furan-2-yl	0.2	1.3	0.3	0.3
26cf	3-MeC_6H_4	C_6H_5	0.1	1.0	0.1	0.1
26cg	3-MeC_6H_4	furan-2-yl	<0.1	1.8	<0.1	<0.1
26ch	2-$MeOC_6H_4$	C_6H_5	<0.1	1.5	<0.1	<0.1
26ci	2-$CF_3C_6H_4$	C_6H_5	<0.1	0.8	<0.1	<0.1
26cj	3-$CF_3C_6H_4$	C_6H_5	<0.1	2.0	<0.1	<0.1
26ck	2-FC_6H_4	3-MeC_6H_4	1.4	0.4	0.8	2.0
26cl	2-FC_6H_4	3-$MeOC_6H_4$	1.3	0.5	0.8	1.5
26cm	2-FC_6H_4	furan-2-yl	0.8	1.1	0.9	0.8
26cn	2-FC_6H_4	5-Mefuran-2-yl	2.2	0.5	1.4	3.3
26co	2-FC_6H_4	5-Etfuran-2-yl	2.3	0.5	1.4	4.6
26cp	2-FC_6H_4	4,5-Me_2furanyl	1.8	0.4	1.0	4.4
26cq	3-FC_6H_4	3-MeC_6H_4	1.2	0.7	1.0	1.2
26cr	3-FC_6H_4	3-$MeOC_6H_4$	1.0	0.8	0.9	1.2
26cs	3-FC_6H_4	4-FC_6H_4	1.0	0.5	0.7	1.5
26ct	3-FC_6H_4	furan-2-yl	0.9	1.3	1.0	1.1
26cu	3-FC_6H_4	5-Mefuran-2-yl	1.8	0.7	1.4	2.8
26cv	3-FC_6H_4	5-Etfuran-2-yl	2.0	0.7	1.5	5.0
26cw	3-FC_6H_4	4,5-Me_2furanyl	1.4	0.6	1.0	3.9

[a]: This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation.

These interesting effects of fluorine drove us to undertake the fairly systematic synthesis and bioluminescence evaluation of luciferins analogues bearing two fluorine atoms on the aryl R^2, depicted in table 6. However, in view of the appalling bioluminescence properties of compounds **26bw** and **26bx** listed in table 5, we avoided the synthesis and evaluation of analogues featuring a fluorine on the *para* position of R^2. The results are pointing out a

few tendencies. The most prominent one is that, out of the four groups of analogues made, the influence of these two fluorine atoms could be classed. The best luciferins featured a 2,3-difluorophenyl moiety (compounds **26dj-dr**) and this was followed by 2,6-difluorophenyl-bearing derivatives **26cx-da** and then the much less bioluminescent analogues **26db-de** and **26df-di**, respectively harboring a 3,5-difluorophenyl or a 2,5-difluorophenyl component. In every case, we studied the effect of small alkyls on the furan ring on R^3 and, within these four groups of difluorophenyl derivatives, a contribution pattern was recurrent. Indeed, a methyl and then an ethyl on carbon 5 of the furan provided the most improved initial intensity then, to a lesser degree, a 4,5-dimethylfuran had also a positive effect; all this in comparison with the compounds only featuring an unsubstituted furan ring. In view of the really strong bioluminescence improvement of the 2,3-difluorophenyl derivatives **26dl** and **26dm**, we also prepared further furan-bearing analogues with small alkyl substituents (**26do-dr**) but no additional improvement was secured and the same pattern observed in table 3 for the phenyl-bearing analogues **26ao-ar** was seen. Equally interesting was the profile of compounds **26db** or **26df**, which displayed only a third or a fifth of the initial intensity of furimazine (**5**) but had about twice its half-life. Finally, the poor bioluminescence of the last two analogues depicted in this table, the 2,3,5-triflurophenyl-bearing derivatives **26ds** and **26dt**, answered the question regarding a possible additive effect of a third fluorine atom.

Table 6. Poly-fluorinated substituents on R^2

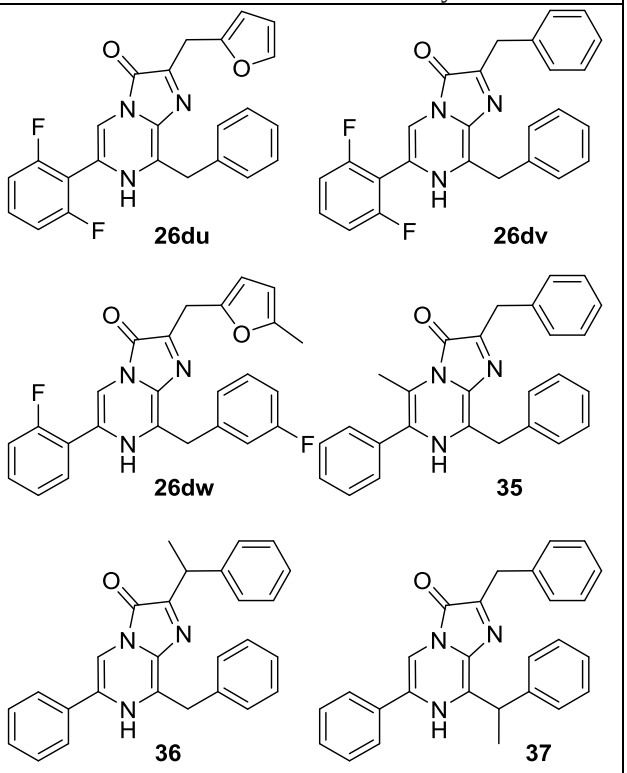


	R^2	R^3	I_{max}	$t_{1/2}$	S_{10}	S_{120}	S/B
5	H	furan-2-yl	1	1	1	1	1
26cx	2,6-F_2	furan-2-yl	0.7	0.8	0.6	0.6	0.6
26cy	2,6-F_2	5-Mefuran-2-yl	1.1	0.7	1.1	0.9	1.8
26cz	2,6-F_2	5-Etfuran-2-yl	1.2	0.6	1.2	0.9	2.3
26da	2,6-F_2	4,5-Me_2furan-2-yl	0.8	0.6	0.8	0.7	1.9
26db	3,5-F_2	furan-2-yl	0.3	1.9	0.3	0.4	0.3
26dc	3,5-F_2	5-Mefuran-2-yl	0.5	1.7	0.5	0.6	0.8
26dd	3,5-F_2	5-Etfuran-2-yl	0.8	1.1	0.8	0.8	1.7
26de	3,5-F_2	4,5-Me_2furan-2-yl	0.5	1.3	0.5	0.6	1.5
26df	2,5-F_2	furan-2-yl	0.2	1.9	0.2	0.2	0.2
26dg	2,5-F_2	5-Mefuran-2-yl	0.6	1.1	0.6	0.6	1.1
26dh	2,5-F_2	5-Etfuran-2-yl	0.8	0.8	0.8	0.7	2.2
26di	2,5-F_2	4,5-Me_2furan-2-yl	0.6	0.9	0.6	0.5	1.8
26dj	2,3-F_2	C_6H_5	1.4	0.3	1.3	0.6	1.8
26dk	2,3-F_2	furan-2-yl	1.1	1.0	1.1	1.1	1.1
26dl	2,3-F_2	5-Mefuran-2-yl	2.6	0.5	2.5	1.6	5.1
26dm	2,3-F_2	5-Etfuran-2-yl	2.2	0.4	2.2	1.1	4.9
26dn	2,3-F_2	4,5-Me_2furan-2-yl	2.1	0.4	2.0	1.1	5.9
26do	2,3-F_2	tetrahydrobenzofuranyl	0.8	0.3	0.7	0.3	1.6
26dp	2,3-F_2	4-Me-5-Etfuran-2-yl	1.2	0.4	1.1	0.6	3.1
26dq	2,3-F_2	4-Et-5-Mefuran-2-yl	1.2	0.4	1.2	0.6	3.4
26dr	2,3-F_2	4-Me-5-*i*-Prfuran-2-yl	0.6	0.3	0.6	0.2	1.3
26ds	2,3,5F_3	C_6H_5	0.1	1.4	0.1	0.1	0.1
26dt	2,3,5F_3	furan-2-yl	0.2	1.9	0.2	0.2	0.2

As depicted in table 7, we also investigated the bioluminescence properties of the difluorinated compounds **26du** and **26dv**, but no additional improvements were observed in comparison with the corresponding monofluorinated luciferins **26ax** and **26bk** of table 4. Moreover, as for other compounds bearing such a fluorine on R^1, the furan-bearing *O*-acetyl precursor of luciferin **26du** was not so stable and decomposed over few days. Similarly, the

difluorinated compound **26dw** did not display any enhanced bioluminescence in comparison with the mono-fluorinated analogues **26cu** or **26bm**. In a different approach, the effects of a methyl group on position 5 of the imidazo[1,2-*a*]pyrazin-3(7*H*)-one ring system (compound **35**) as well as on R^3 (compound **36**) or R^2 (compound **37**) were also studied. Interestingly, in every case this additional methyl had a strongly deleterious effect on the bioluminescence.

Table 7. Additional difluorinated or methylated luciferins



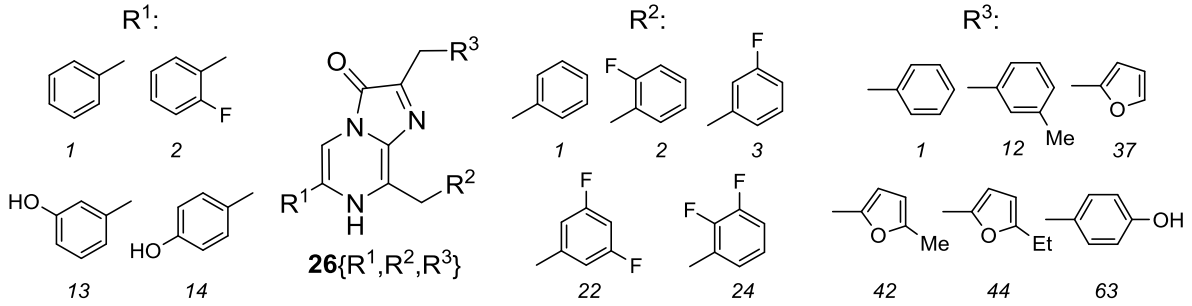
	I_{max}	$t_{1/2}$	S_{120}	S/B
5	1	1	1	1
26du[a]	-	-	-	-
26dv	1.1	0.4	0.6	2.6
26dw	1.9	0.6	1.5	3.6
35	0.1	0.9	0.1	< 0.1
36	< 0.1	< 0.1	< 0.1	< 0.1
37[b]	< 0.1	0.8	< 0.1	-

[a]: the O-acetylated derivative corresponding to this luciferin was not stable. [b]: this luciferin was assessed using the same experimental setting but in the course of another batch of evaluation.

As detailed in table 8; in an attempt to understand the reasons behind the bioluminescence improvements observed, we undertook the extensive enzymatic study of a selection of 18 luciferins, including furimazine (**5**). These experiments were done using a Berthold Centro LB 960 luminometer and the delay between the automated injection of the enzyme and the initiation of the bioluminescence monitoring was of exactly one second, shaking included. For this reason, some of the signal maximum intensity (I_{max}; in in $RLU \cdot s^{-1}$), half-life ($t_{1/2}$) and cumulated signal over two hours (S_{120}; in RLU) provided in table 8 may differ a bit from the normalized values listed in tables 1-7. Assuming again that the number of detected photons per consumed substrate molecule is constant whatever the substrate concentration, the use of a Michaelis-Menten model (and curve fitting calculations) as previously described,[11b] allowed us to determine the Michaelis constant (K_M), the maximal reaction rate (V_{max}) and the catalytic activity (k_{cat}) of nanoKAZ/NanoLuc for these substrates. A dissociation constant (K_I) was required for these curve fitting and is illustrating the fact that there is an inhibition of the luciferase by an excess of substrate through the binding of a second luciferin to the Michaelis' complex luciferin-luciferase. Accordingly, we suggest

the use of a 13 μM substrate concentration in experiments in order to secure the highest signal intensity. Moreover, a slow (or fast) irreversible inactivation of the luciferase by a reaction product followed a first order rate constant (k_{inact}) illustrating a stochastic mechanism. A far more extensive description of these experiments is available in the supplementary material. We could also, upon a complete consumption of the luciferin,[11b] determine the number of molecules consumed per photon detected by the luminometer in the condition of measurement (cpd·RLU^{-1}). This actually allows a comparison of the light emission efficacy for each the enzyme/substrates couples, even if the value provided is intrinsically luminometer-dependent. As seen in table 8, the nature of the luciferin used had very little effect on the wavelength at maximum emission (λ_{max}), as these turned out to be always close to 460 nm, as previously reported for furimazine (**5**).[9d] With these results, the luciferin could be classed in seven groups according to three criteria, namely the reaction rate (k_{cat}), the light emission efficiency (cpd·RLU^{-1}·s^{-1}) and the signal half-lifetime ($t_{1/2}$). It turns out that analogue **26dl**, is the only substrate featuring a high reaction rate (k_{cat} > 1000 mol·s^{-1}·mol$_{luc}^{-1}$), a high light emission efficiency (< 3000 cpd·RLU^{-1}) and a long half-lifetime (> 30 min). Analogue **26dw** is the only substrate studied with a high reaction rate, a low light emission efficiency and a long life whereas analogues **26ah**, **6**, and **1** are endowed with a high reaction rate, a low light emission efficiency and a short life. In this selection, quite a few substrates (furimazine (**5**), **26co**, **26cu**, **26cv**, **26db**, **26dc** and **26bh**) are displaying a low reaction rate, a high light emission efficiency and a long life. The analogs **26g** and **26cn** also have a low combustion rate and a high light emission efficiency but a rather short life. This in a relative opposition with the "isocoelenterazine" **26bj** which has low reaction rate and low light emission efficiency but a long life. Finally, the substrates bis-coelenterazine (**7**), **26bf** and **26bg** turn out to have a low reaction rate, a low light emission and a short life. Interestingly, none of the substrates studied here combined a high reaction rate, a high light emission and a short life. In any case, an actual molecular mechanism accounting for all these previously unreported behaviors remains elusive.

Table 8. Bioluminescence profiles, kinetic parameters and λ_{max} for a selection of luciferins



nb{*R*[1],*R*[2],*R*[3]}	I_{max} (10^6 RLU·s^{-1})	$t_{1/2}$ (min)	S_{120} (10^6 RLU)	cpd·RLU^{-1}	K_I (µM)	K_M (µM)	k_{cat} (mol·s^{-1}·mol_{luc}^{-1})	k_{inact} (10^{-4} s^{-1})	λ_{max} (nm) ± 3 nm
5{*1,1,37*}	1.7	74	85	1775	109	2.22	106	1.5	455
7{*1,1,1*}	3.3	19	81	4581	115	3.02	534	5.2	453
26ah{*1,1,42*}	5.9	24	151	4483	58	6.73	1200	4.4	453
26g{*1,1,12*}	3.0	28	82	2450	167	4.30	270	2.1	453
6{*14,1,1*}	2.0	3	6	12067	101	5.90	932	425	458
26bf{*14,1,37*}	3.1	0.3	12	4463	101	3.88	535	375	462
26cn{*1,2,42*}	6.0	38	216	2912	60	5.19	769	3.0	453
1{*14,1,63*}	0.2	21	6	101169	22	6.80	1500	3.8	465
26co{*1,2,44*}	4.2	68	128	1962	95	6.86	350	2.6	453
26cu{*1,3,42*}	3.4	94	173	2106	40	6.06	565	4.0	453
26cv{*1,3,44*}	3.4	101	177	2095	60	5.80	319	2.4	453
26db{*1,22,37*}	0.5	156	36	1836	140	2.20	30.8	1.3	463
26dw{*2,3,*42}	3.4	94	146	22032	63	5.53	3380	1.8	453
26dl{*1,24,42*}	5.3	39	178	2664	80	5.52	1420	4.5	455
26dc{*1,22,42*}	0.8	157	58	2834	64	3.30	96.1	1.4	458
26bh{*13,1,37*}	2.0	32	63	1804	84	3.30	140	4.5	458
26bj{*13,1,63*}	0.1	148	6	70020	35	2.94	362	3.1	460
26bg{*14,1,42*}	3.0	1.5	11	4677	121	3.88	874	280	460

Conclusion

This structure-bioluminescence activity investigation, very much reminiscent of a classic medicinal chemistry approach, involved the design and synthesis of many luciferins analogues in an iterative manner. Aside from the very intense but very short-lived bioluminescence profile we previously reported[11b] for a group of hydroxy-bearing luciferins such as **6** or **26bf**, we report here luciferins, such as **26cu** or **26dl**, which are endowed with a lasting as well as a much improved signal intensity in comparison with furimazine (**5**). Moreover, a third type of luciferins such as **26db**, which displays a more modest signal intensity but an inordinate stability over time, also emerged from this work. Concerning the emission wavelength observed with these compounds, all of them turned out to emit blue photon. However, the Gauss Gaussian nature of these photon emission wavelengths lead to a substantial wavelength spreading. Indeed, the strong intensity provided by furimazine (**5**), although not centered on a red wavelength, still provided an increased number of red photons which was found sufficient for *in vivo* studies.[19] Thus, the enhanced intensity observed here with the luciferin analogue **26dl** could provide some more advantage in comparison with furimazine (**5**) or with approaches based on "red-shifting" marine-based bioluminescence reporting systems.[20] Amongst avenues for further work, assessment of the signal profiles of this library of luciferins with other coelenterazine-using luciferases or the corresponding near infinite number of mutants, should provide many additional insights and further intensive for more structure-bioluminescence relationship studies.

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Supporting Information

Table of content

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and cross-coupling constants (*J*) are given in Hertz. Column chromatography were performed either on Merck silica gel 60 (0.035 - 0.070 mm) or neutral alumina containing 1.5% of added water using a solvent pump and an automated collecting system driven by a UV detector set to 254 nm unless required otherwise. Sample deposition was carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system or an Agilent 1200 series LC/MSD system using an Agilent Jet-Stream atmospheric electrospray ionization system and the high resolution mass spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source. As specified below, a Berthold Centro XS^3 luminometer or a Berthold Centro LB 960 were used for the bioluminescence experiments. The wavelengths at maximum emission (λ_{max}) were determined using a JASCO FP-6300 spectrofluorometer. When specified, the anhydrous solvents used were purchased. Unless stated otherwise, a purity of at least 95% was obtained for all the compounds by means of chromatography, recrystallization or distillation and this level of purity was established by TLC, LC/MS and NMR spectroscopy.

Numbering

The chemset numbering system recommended by the ACS for the description of chemical libraries prepared by combinatorial chemistry was adopted here to number most of the compounds described. The following tables are mirroring the tables 1-8 of in the main text and are featuring an additional column in order to provide a correspondence between this numbering system and the numbers used for the description of the luciferins in the main text.

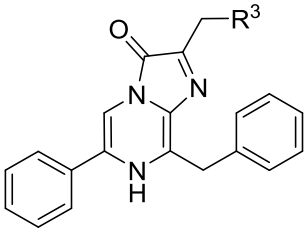
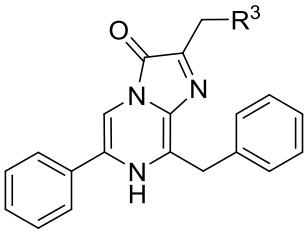
	Table 1. Variations on R^3					
						
		R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
26{*1,1,37*}	**5**	furan-2-yl	1	1	1	1
26{*1,1,1*}	**7**	C_6H_5	1.25	0.44	0.77	1.37
26{*1,1,2*}	**26a**	2-FC_6H_4	0.40	1.03	0.41	0.58
26{*1,1,3*}	**26b**	3-FC_6H_4	0.70	0.73	0.59	0.91
26{*1,1,4*}	**8**	4-FC_6H_4	1.17	0.37	0.61	1.50
26{*1,1,25*}	**26c**	2,4-$F_2C_6H_3$	1.02	0.32	0.50	1.52
26{*1,1,7*}	**26d**	4-ClC_6H_4	0.38	0.36	0.19	0.50
26{*1,1,20*}	**26e**	4-BrC_6H_4	0.34	0.24	0.13	0.46
26{*1,1,11*}	**26f**	2-MeC_6H_4	0.02	1.41	0.02	0.03
26{*1,1,12*}	**26g**	3-MeC_6H_4	1.29	0.62	0.97	1.60
26{*1,1,13*}	**26h**	4-MeC_6H_4	0.27	0.33	0.12	0.31
26{*1,1,8*}	**26i**	2-$CF_3C_6H_4$	0.07	0.94	0.06	0.17
26{*1,1,9*}	**26j**	3-$CF_3C_6H_4$	0.38	1.09	0.39	0.55
26{*1,1,10*}	**26k**	4-$CF_3C_6H_4$	0.16	0.44	0.09	0.22
26{*1,1,14*}	**26l**	2-$MeOC_6H_4$	0.40	0.47	0.24	0.39
26{*1,1,15*}	**26m**	3-$MeOC_6H_4$	1.15	0.68	0.93	1.26
26{*1,1,16*}	**26n**	4-$MeOC_6H_4$	0.74	0.33	0.34	0.86
26{*1,1,62*}	**26o**[a]	3-HOC_6H_4	0.22	0.05	0.03	-
26{*1,1,63*}	**26p**[a]	4-HOC_6H_4	0.09	0.10	0.03	-
26{*1,1,27*}	**26q**	3-*n*-PrC_6H_4	0.49	1.01	0.49	0.60
26{*1,1,29*}	**26r**	3-*c*-PrC_6H_4	0.55	0.85	0.50	0.62
26{*1,1,28*}	**26s**	4-*n*-PrC_6H_4	0.23	0.24	0.08	0.24
26{*1,1,31*}	**26t**	4-*i*-PrC_6H_4	0.27	0.41	0.13	0.26
26{*1,1,30*}	**26u**	4-*c*-PrC_6H_4	0.31	0.30	0.12	0.35
	[a] This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation					

Table 2. Further alterations of R^3



		R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
26{*1,1,37*}	**5**	furan-2-yl	1	1	1	1
26{*1,1,38*}	**26v**	tetrahydrofuran-2-yl	0.04	1.83	0.05	0
26{*1,1,39*}	**26w**	1,3-dioxolan-2-yl	0.03	1.73	0.04	0.01
26{*1,1,33*}	**26x**	cyclohexyl	0.01	1.83	0.02	0.01
26{*1,1,36*}	**26y**	cyclopentyl	0.01	1.83	0.02	0.01
26{*1,1,32*}	**26z**	benzyl	0.14	0.55	0.09	0.12
26{*1,1,34*}	**26aa**[a]	2-pyridyl	-	-	-	-
26{*1,1,40*}	**26ab**	furan-3-yl	0.47	0.94	0.46	0.14
26{*1,1,41*}	**26ac**	thiophene-2-yl	1.24	0.47	0.85	1.80
26{*1,1,56*}	**26ad**	3-Meisoxazol-5-yl	0.18	0.22	0.08	0.01
26{*1,1,57*}	**26ae**	3-Etisoxazol-5-yl	0.33	0.15	0.10	0.01
26{*1,1,58*}	**26af**[b]	5-Meoxazol-2-yl	0.20	1.76	0.24	-
26{*1,1,59*}	**26ag**	4,5-Me_2oxazol-2-yl	0.23	0.92	0.22	0.15

a: The corresponding *O*-acetyl derivative **25** decomposed over few days. [b] This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation

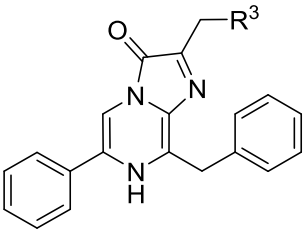
	Table 3. few analogues related to furimazine (**5**)					
						
		R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
26{*1,1,37*}	**5**	furan-2-yl	1	1	1	1
26{*1,1,42*}	**26ah**	5-Mefuran-2-yl	1.96	0.50	1.26	3.15
26{*1,1,44*}	**26ai**	5-Etfuran-2-yl	1.89	0.59	1.34	3.82
26{*1,1,47*}	**26aj**	5-*c*-Prfuran-2-yl	1.26	0.62	0.91	2.92
26{*1,1,45*}	**26ak**	5-*n*-Prfuran-2-yl	1.43	1.03	1.47	3.43
26{*1,1,46*}	**26al**	5-*n*-Pentfuran-2-yl	0.10	0.78	0.09	0.17
26{*1,1,43*}	**26am**	5-CF_3furan-2-yl	0.20	1.83	0.27	0.21
26{*1,1,48*}	**26an**	4,5-Me_2furan-2-yl	1.40	0.47	0.85	2.85
26{*1,1,49*}	**26ao**	tetrahydrobenzofuran-2-yl	0.59	0.51	0.35	1.16
26{*1,1,50*}	**26ap**	4-Me-5-Etfuran-2-yl	0.86	0.78	0.74	1.75
26{*1,1,51*}	**26aq**	4-Et-5-Mefuran-2-yl	0.86	0.41	0.43	2.15
26{*1,1,52*}	**26ar**	4-Me-5-*i*-Prfuran-2-yl	0.36	0.98	0.36	0.83
26{*1,1,41*}	**26as**	thiophene-2-yl	1.24	0.47	0.85	1.80
26{*1,1,53*}	**26at**	5-Etthiophen-2-yl	1.11	0.42	0.56	2.03
26{*1,1,54*}	**26au**	3-Methiophen-2-yl	0.15	1.83	0.20	0.22
26{*1,1,55*}	**26av**	4,5-Me_2thiophen-2-yl	0.54	1.11	0.55	1.04

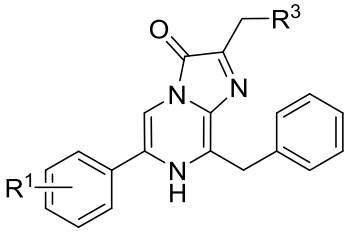
	Table 4. More elaborated analogues of furimazine						
							
		R^1	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
26{*1,1,37*}	**5**	H	furan-2-yl	1	1	1	1
26{*1,1,42*}	**26ah**	H	5-Mefuran-2-yl	1.96	0.50	1.26	3.15
26{*2,1,42*}	**26aw**[a]	2-F	5-Mefuran-2-yl	2.17	0.39	1.89	-
26{*2,1,37*}	**26ax**	2-F	furan-2-yl	1.35	0.80	1.18	1.15
26{*3,1,42*}	**26ay**	3-F	5-Mefuran-2-yl	1.65	0.49	1.11	3.62
26{*4,1,42*}	**26az**	4-F	5-Mefuran-2-yl	0.07	1.83	0.09	0.08
26{*5,1,42*}	**26ba**	3-Me	5-Mefuran-2-yl	0.41	1.15	0.44	0.71
26{*6,1,42*}	**26bb**	4-Me	5-Mefuran-2-yl	0	1.39	0	0
26{*7,1,37*}	**26bc**[a]	2-MeO	furan-2-yl	0.02	1.83	0.04	0
26{*8,1,42*}	**26bd**	3-MeO	5-Mefuran-2-yl	0.04	2.18	0.04	-
26{*9,1,42*}	**26be**	4-MeO	5-Mefuran-2-yl	0.01	1.83	0.01	0
26{*14,1,63*}	**1**	4-HO	4-HOC_6H_5	0.09	0.64	0.08	0.01
26{*14,1,37*}	**26bf**	4-HO	furan-2-yl	3.06	0.05	0.14	0.12
26{*14,1,42*}	**26bg**[b]	4-HO	5-Mefuran-2-yl	2.58	0	0.09	-
26{*14,1,1*}	**6**	4-HO	C_6H_5	0.52	0.03	0.04	0.09
26{*13,1,37*}	**26bh**	3-HO	furan-2-yl	0.92	0.80	0.80	1.19
26{*13,1,42*}	**26bi**	3-HO	5-Mefuran-2-yl	1.15	0.53	0.73	2.06
26{*13,1,63*}	**26bj**	3-HO	4-HOC_6H_5	0.04	1.93	0.05	0.04
26{*2,1,1*}	**26bk**	2-F	C_6H_5	1.32	0.41	0.75	2.55
26{*2,1,4*}	**26bl**	2-F	4-FC_6H_4	1.28	0.24	0.47	2.16
26{*2,1,44*}	**26bm**[a]	2-F	5-Etfuran-2-yl	2.59	0.35	2.33	-
26{*2,1,48*}	**26bn**[a]	2-F	4,5-Me_2furan-2-yl	2.13	0.28	1.97	-
	[a] The corresponding *O*-acetylated derivatives **25** were not stable over time, initial bioluminescence results only. [b] This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation.						

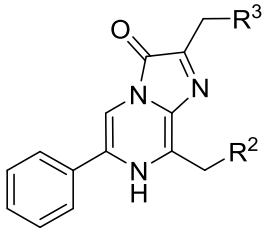
	Table 5. Some combined variations of R^2 and R^3						
							
		R^2	R^3	I_{max}	$t_{1/2}$	S_{120}	S/B
26{*1,1,37*}	**5**	C_6H_5	furan-2-yl	1	1	1	1
26{*1,1,1*}	**7**	C_6H_5	C_6H_5	1.25	0.44	0.77	1.37
26{*1,1,42*}	**26ah**	C_6H_5	5-Mefuran-2-yl	1.96	0.50	1.26	3.15
26{*1,60,1*}	**26bo**	H	C_6H_5	0.00	-	0.00	-
26{*1,38,1*}	**26bp**	THF-2-yl	C_6H_5	0.03	1.83	0.05	0
26{*1,35,1*}	**26bq**	pyridin-3-yl	C_6H_5	0.29	1.13	0.31	0.08
26{*1,61,1*}	**26br**[a]	2-HOC_6H_4	C_6H_5	0.01	1.90	0.02	-
26{*1,62,1*}	**26bs**[a]	3-HOC_6H_4	C_6H_5	0.05	0.05	0.02	-
26{*1,63,1*}	**26bt**[a]	4-HOC_6H_4	C_6H_5	0	-	0	-
26{*1,2,1*}	**26bu**	2-FC_6H_4	C_6H_5	1.19	0.38	0.66	1.37
26{*1,3,1*}	**26bv**	3-FC_6H_4	C_6H_5	1.17	0.52	0.81	1.17
26{*1,4,1*}	**26bw**	4-FC_6H_4	C_6H_5	0.13	0.97	0.13	0.17
26{*1,4,37*}	**26bx**	4-FC_6H_4	furan-2-yl	0.02	2.03	0.03	0.03
26{*1,5,1*}	**26by**	2-ClC_6H_4	C_6H_5	0.78	0.52	0.52	1.02
26{*1,5,37*}	**26bz**	2-ClC_6H_4	furan-2-yl	0.69	0.90	0.64	0.96
26{*1,5,42*}	**26ca**	2-ClC_6H_4	5-Mefuran-2-yl	0.68	0.75	0.57	0.89
26{*1,6,1*}	**26cb**	3-ClC_6H_4	C_6H_5	0.15	1.53	0.19	0.25
26{*1,6,37*}	**26cc**	3-ClC_6H_4	furan-2-yl	0.03	2.03	0.05	0.06
26{*1,11,1*}	**26cd**	2-MeC_6H_4	C_6H_5	0.26	1.26	0.29	0.28
26{*1,11,37*}	**26ce**	2-MeC_6H_4	furan-2-yl	0.23	1.31	0.25	0.28
26{*1,12,1*}	**26cf**	3-MeC_6H_4	C_6H_5	0.07	0.99	0.07	0.09
26{*1,12,37*}	**26cg**	3-MeC_6H_4	furan-2-yl	0.03	1.83	0.04	0.04
26{*1,14,1*}	**26ch**	2-$MeOC_6H_4$	C_6H_5	0.01	1.51	0.01	0
26{*1,8,1*}	**26ci**	2-$CF_3C_6H_4$	C_6H_5	0.02	0.80	0.02	0.03
26{*1,9,1*}	**26cj**	3-$CF_3C_6H_4$	C_6H_5	0	1.97	0	0
26{*1,2,12*}	**26ck**	2-FC_6H_4	3-MeC_6H_4	1.44	0.38	0.78	1.96
26{*1,2,15*}	**26cl**	2-FC_6H_4	3-$MeOC_6H_4$	1.26	0.49	0.84	1.54
26{*1,2,37*}	**26cm**	2-FC_6H_4	furan-2-yl	0.84	1.14	0.88	0.84
26{*1,2,42*}	**26cn**	2-FC_6H_4	5-Mefuran-2-yl	2.15	0.52	1.41	3.31
26{*1,2,44*}	**26co**	2-FC_6H_4	5-Etfuran-2-yl	2.27	0.49	1.44	4.63
26{*1,2,48*}	**26cp**	2-FC_6H_4	4,5-Me_2furan-2-yl	1.81	0.41	0.97	4.35
26{*1,3,12*}	**26cq**	3-FC_6H_4	3-MeC_6H_4	1.24	0.69	0.98	1.19
26{*1,3,15*}	**26cr**	3-FC_6H_4	3-$MeOC_6H_4$	1	0.76	0.85	1.16
26{*1,3,4*}	**26cs**	3-FC_6H_4	4-FC_6H_4	1	0.51	0.65	1.45
26{*1,3,37*}	**26ct**	3-FC_6H_4	furan-2-yl	0.87	1.33	0.98	1.05
26{*1,3,42*}	**26cu**	3-FC_6H_4	5-Mefuran-2-yl	1.84	0.66	1.42	2.82
26{*1,3,44*}	**26cv**	3-FC_6H_4	5-Etfuran-2-yl	1.98	0.68	1.54	5.02
26{*1,3,48*}	**26cw**	3-FC_6H_4	4,5-Me_2furan-2-yl	1.38	0.63	1.02	3.85
	[a] This luciferin was assessed using the same experimental setting but in the course of another batch of evaluation						

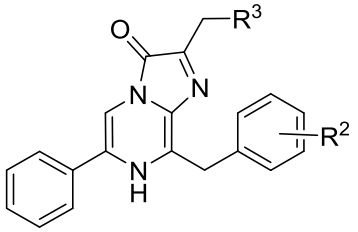
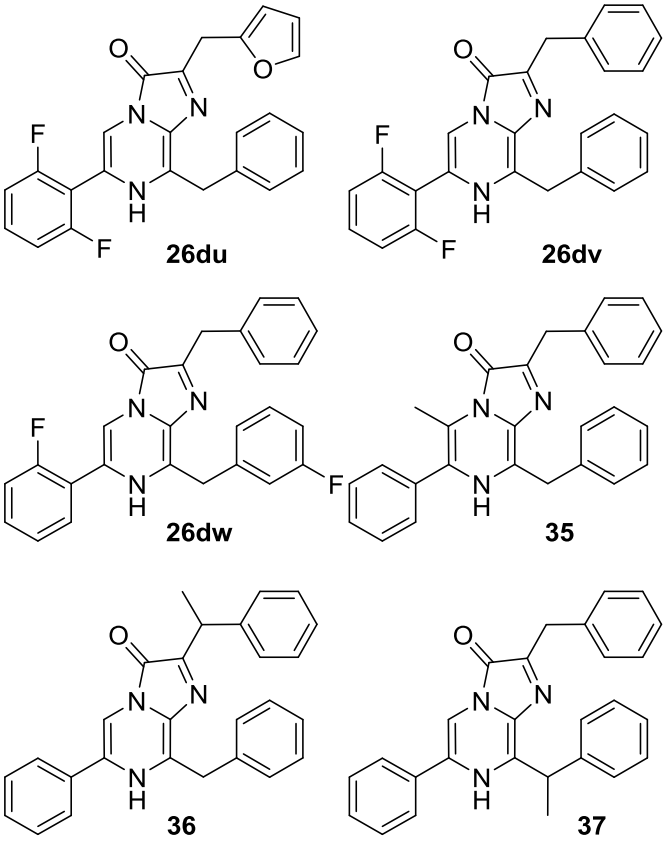
	Table 6. Poly-fluorinated substituents on R^2							
								
		R^2	R^3	I_{max}	$t_{1/2}$	S_{10}	S_{120}	S/B
26{*1,1,37*}	**5**	H	furan-2-yl	1	1	1	1	1
26{*1,21,37*}	**26cx**	2,6-F_2	furan-2-yl	0.65	0.78	0.64	0.57	0.56
26{*1,21,42*}	**26cy**	2,6-F_2	5-Mefuran-2-yl	1.12	0.68	1.10	0.91	1.80
26{*1,21,44*}	**26cz**	2,6-F_2	5-Etfuran-2-yl	1.18	0.64	1.16	0.91	2.33
26{*1,21,48*}	**26da**	2,6-F_2	4,5-Me_2furan-2-yl	0.84	0.64	0.81	0.65	1.92
26{*1,22,37*}	**26db**	3,5-F_2	furan-2-yl	0.28	1.91	0.27	0.37	0.25
26{*1,22,42*}	**26dc**	3,5-F_2	5-Mefuran-2-yl	0.49	1.70	0.47	0.61	0.77
26{*1,22,44*}	**26dd**	3,5-F_2	5-Etfuran-2-yl	0.81	1.05	0.76	0.82	1.71
26{*1,22,48*}	**26de**	3,5-F_2	4,5-Me_2furan-2-yl	0.48	1.34	0.46	0.55	1.52
26{*1,23,37*}	**26df**	2,5-F_2	furan-2-yl	0.17	1.90	0.17	0.21	0.17
26{*1,23,42*}	**26dg**	2,5-F_2	5-Mefuran-2-yl	0.60	1.05	0.59	0.61	1.05
26{*1,23,44*}	**26dh**	2,5-F_2	5-Etfuran-2-yl	0.81	0.83	0.79	0.73	2.17
26{*1,23,48*}	**26di**	2,5-F_2	4,5-Me_2furan-2-yl	0.59	0.88	0.56	0.54	1.76
26{*1,24,1*}	**26dj**	2,3-F_2	C_6H_5	1.36	0.32	1.29	0.64	1.77
26{*1,24,37*}	**26dk**	2,3-F_2	furan-2-yl	1.06	1.03	1.06	1.08	1.09
26{*1,24,42*}	**26dl**	2,3-F_2	5-Mefuran-2-yl	2.58	0.47	2.51	1.55	5.06
26{*1,24,44*}	**26dm**	2,3-F_2	5-Etfuran-2-yl	2.23	0.42	2.15	1.12	4.85
26{*1,24,48*}	**26dn**	2,3-F_2	4,5-Me_2furan-2-yl	2.05	0.44	2.00	1.14	5.88
26{*1,24,49*}	**26do**	2,3-F_2	tetrahydrobenzofuran-2-yl	0.76	0.34	0.72	0.31	1.64
26{*1,24,50*}	**26dp**	2,3-F_2	4-Me-5-Etfuran-2-yl	1.16	0.36	1.11	0.55	3.13
26{*1,24,51*}	**26dq**	2,3-F_2	4-Et-5-Mefuran-2-yl	1.24	0.37	1.18	0.59	3.41
26{*1,24,52*}	**26dr**	2,3-F_2	4-Me-5-*i*-Prfuran-2-yl	0.58	0.34	0.55	0.24	1.32
26{*1,26,1*}	**26ds**	2,3,5-F_3	C_6H_5	0.08	1.38	0.08	0.09	0.11
26{*1,26,37*}	**26dt**	2,3,5-F_3	furan-2-yl	0.17	1.85	0.17	0.22	0.17

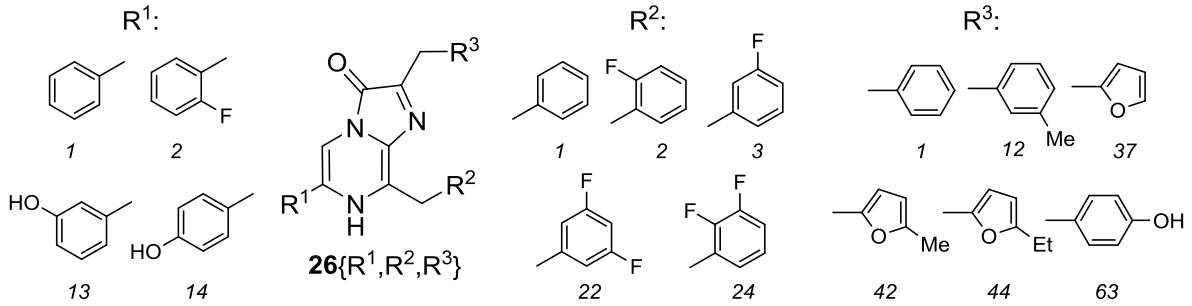
Table 7. Additional difluorinated or methylated luciferins



		I_{max}	$t_{1/2}$	S_{120}	S/B
26{*1,1,37*}	**5**	1	1	1	1
26{*10,1,37*}	**26du**[a]	-	-	-	-
26{*10,1,1*}	**26dv**	1.14	0.41	0.64	2.60
26{*2,3,37*}	**26dw**	1.94	0.64	1.48	3.61
35	**35**	0.05	0.88	0.05	0.04
36	**36**	0.01	0.01	0.01	0.01
37	**37**[b]	0.04	0.81	0.03	-

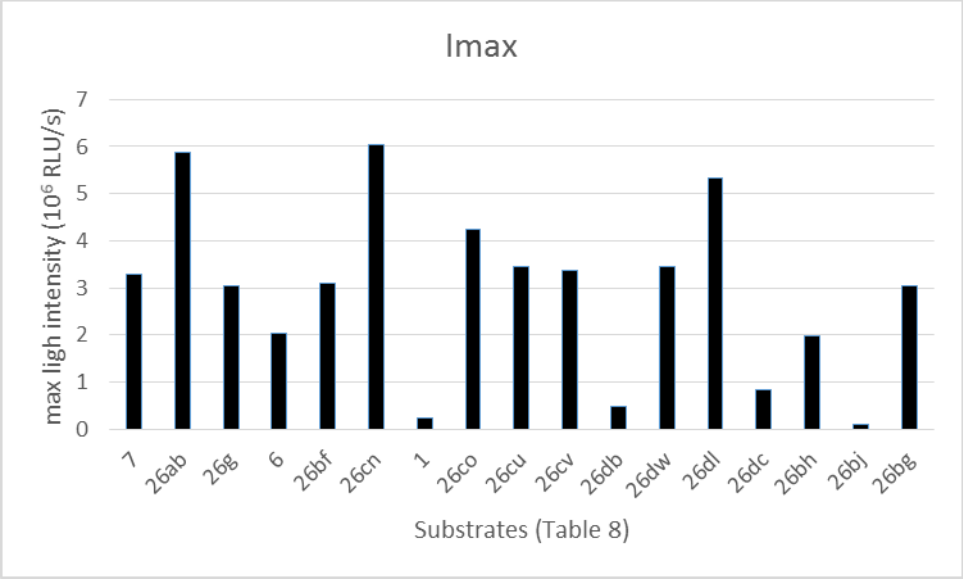
a: the O-acetylated derivative corresponding to this luciferin was not stable. b : this luciferin was assessed using the same experimental setting but in the course of another batch of evaluation.

Table 8. bioluminescence profiles, kinetic parameters and λ_{max} for a selection of luciferins



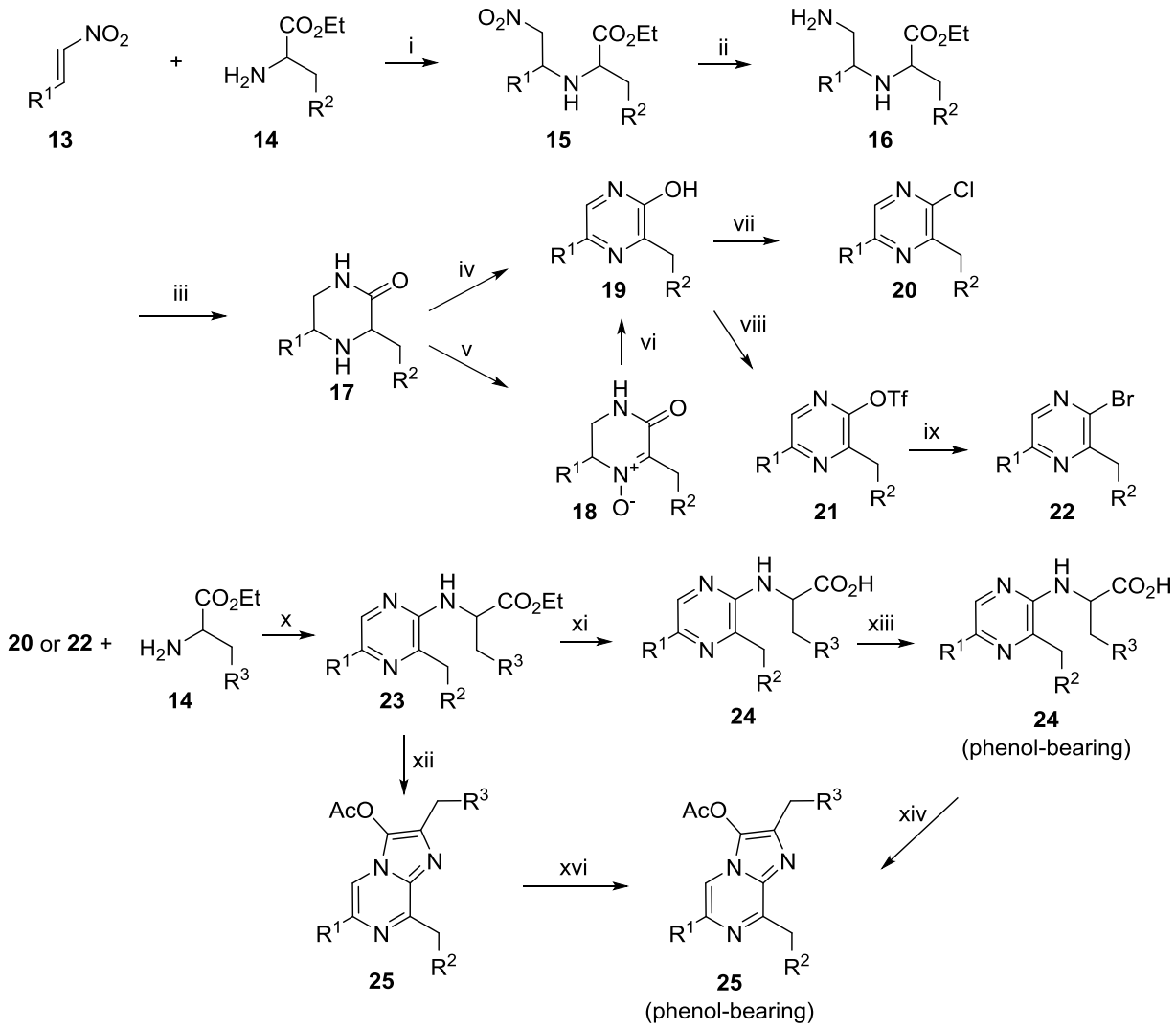
Names® of the O-acetylated precursor	{*R¹*,*R²*,*R³*}	I_{max} (10^6 RLU/s)	$t_{1/2}$ (min)	S_{120} (10^6 RLU)	cpd/RLU	K_I (10^{-6} M)	K_M (10^{-6} M)	k_{cat} (mol s^{-1} mol_{luc}^{-1})	k_{inact} (10^{-4}/s)	λ_{max} (nm)
Hikarazine-1	**5**{*1,1,37*}	1.7	74	85	1775	109	2.22	106	1.5	
Hikarazine-2	**7**{*1,1,1*}	3.3	19	81	4581	115	3.02	534	5.2	
Hikarazine-3	**26ah**{*1,1,42*}	5.9	24	151	4483	58	6.73	1200	4.4	
Hikarazine-14	**26g**{*1,1,12*}	3.0	28	82	2450	167	4.30	270	2.1	
Hikarazine-75	**6**{*14,1,1*}	2.0	3	6	12067	101	5.90	932	425	
Hikarazine-80	**26bf**{*14,1,37*}	3.1	0.3	12	4463	101	3.88	535	375	
Hikarazine-85	**26cn**{*1,2,42*}	6.0	38	216	2912	60	5.19	769	3.0	
Hikarazine-86	**1**{*14,1,63*}	0.2	21	6	101169	22	6.80	1500	3.8	
Hikarazine-96	**26co**{*1,2,44*}	4.2	68	128	1962	95	6.86	350	2.6	
Hikarazine-97	**26cu**{*1,3,42*}	3.4	94	173	2106	40	6.06	565	4.0	
Hikarazine-99	**26cv**{*1,3,44*}	3.4	101	177	2095	60	5.80	319	2.4	
Hikarazine-103	**26db**{*1,22,37*}	0.5	156	36	1836	140	2.20	30.8	1.3	
Hikarazine-105	**26dw**{*2,3,37*}	3.4	94	146	22032	63	5.53	3380	1.8	
Hikarazine-108	**26dl**{*1,24,42*}	5.3	39	178	2664	80	5.52	1420	4.5	
Hikarazine-113	**26dc**{*1,22,42*}	0.8	157	58	2834	64	3.30	96.1	1.4	
Hikarazine-149	**26bh**{*13,1,37*}	2.0	32	63	1804	84	3.30	140	4.5	
Hikarazine-150	**26bj**{*13,1,63*}	0.1	148	6	70020	35	2.94	362	3.1	
Hikarazine-162	**26bg**{*14,1,42*}	3.0	1.5	11	4677	121	3.88	874	280	

Nota: Hikari (光) means light in Japanese



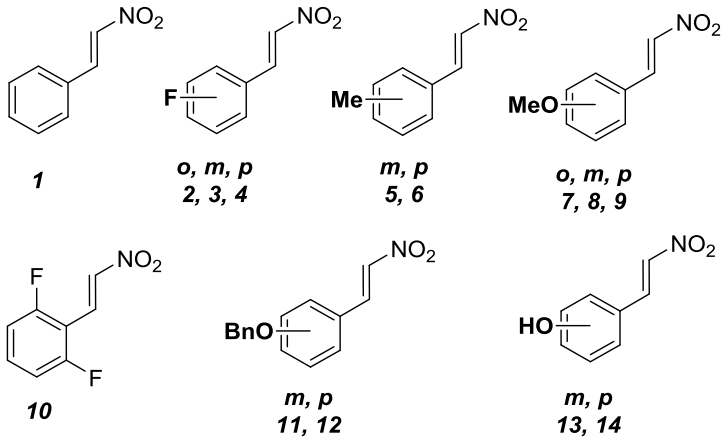
Bar graphs comparison of Imax for all the compounds listed in table 8.

General synthetic pathway used for synthesis of the O-acylated luciferins 25 (same numbering than in the main text):



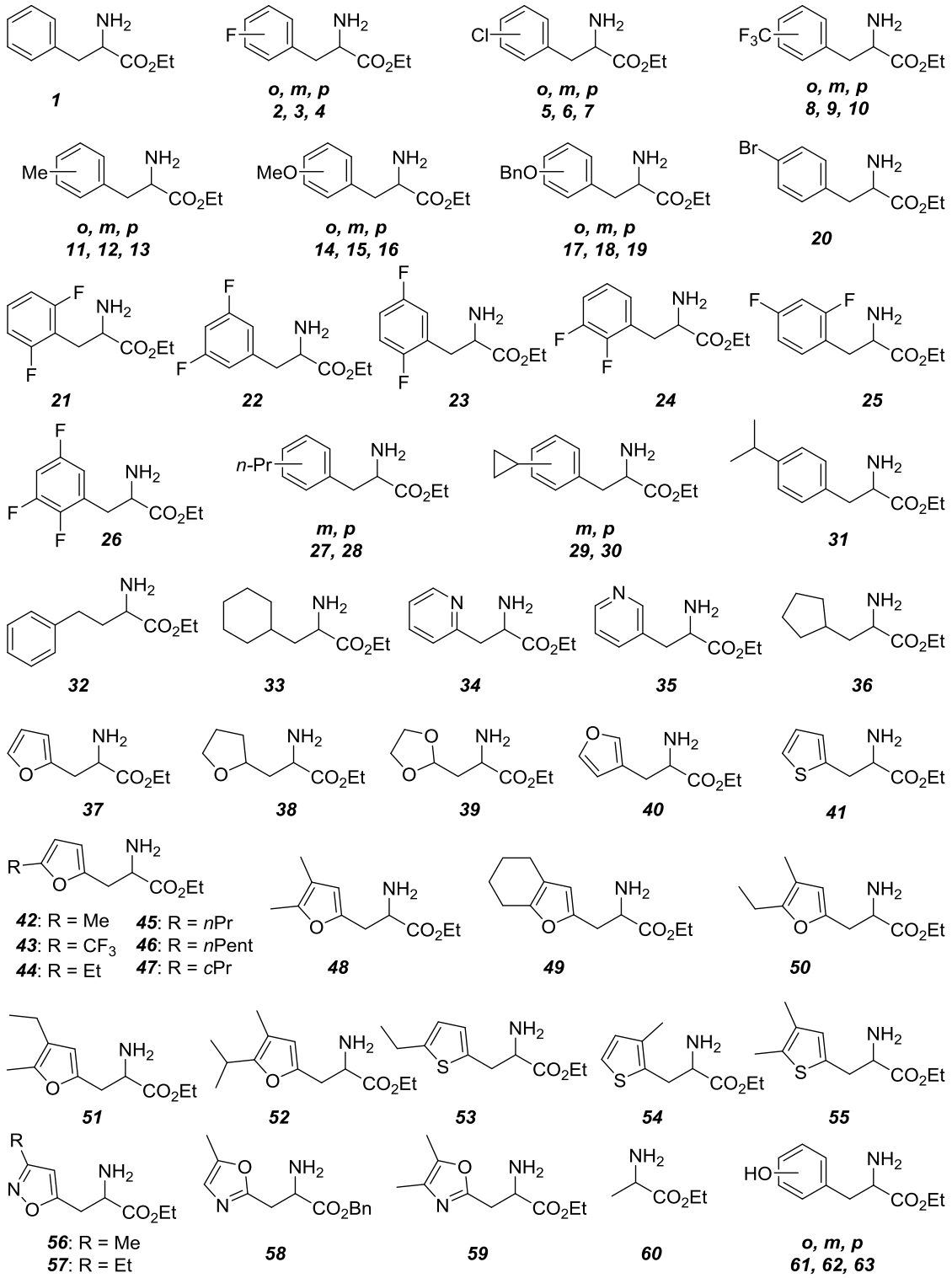
Scheme 1. i: neat, 20 °C, 10 min-12 h. ii: Zn, 37 % $H_3O^+Cl^-$, dioxane, 0-20 °C, 2 h. iii: neat, 140 °C, 3 h. iv: S_8, 1,3-$Cl_2C_6H_4$ or decaline, reflux, 10 h. v: AcOOH, AcOEt, 20 °C, 12 h. vi: NaOH, EtOH, 65 °C, 1 h. vii: $PhPOCl_2$, 100 °C, 12 h. viii: Tf_2O, NEt_3, CH_2Cl_2, 20 °C, 40 min. ix: NaBr, TfOH, DMF, 120 °C, 12 h. x: Cs_2CO_3, $Pd(OAc)_2$, BINAP, MeCN, 60 °C or toluene, 90 °C, 12 h. xi: a) NaOH, THF, 20 °C, 12 h, b) NH_4Cl, H_2O. xii: a) NaOH, THF, 20 °C, 12 h, b) Ac_2O, 20 °C, 2 h. xiii: Pd/C, $NH_4^+HCO_2^-$, EtOH, reflux, 90 min. xiv: Ac_2O, AcOEt, reflux, 30 min. xvi: H_2, Pd/C, AcOEt, AcOH, EtOH, 20 °C, 12 h.

Structure and numbering of the 12 nitrostyrenes 13 used. The last two were not used in the synthetic scheme depicted above but are provided for the convenient numbering of the phenol-bearing substrates prepared:

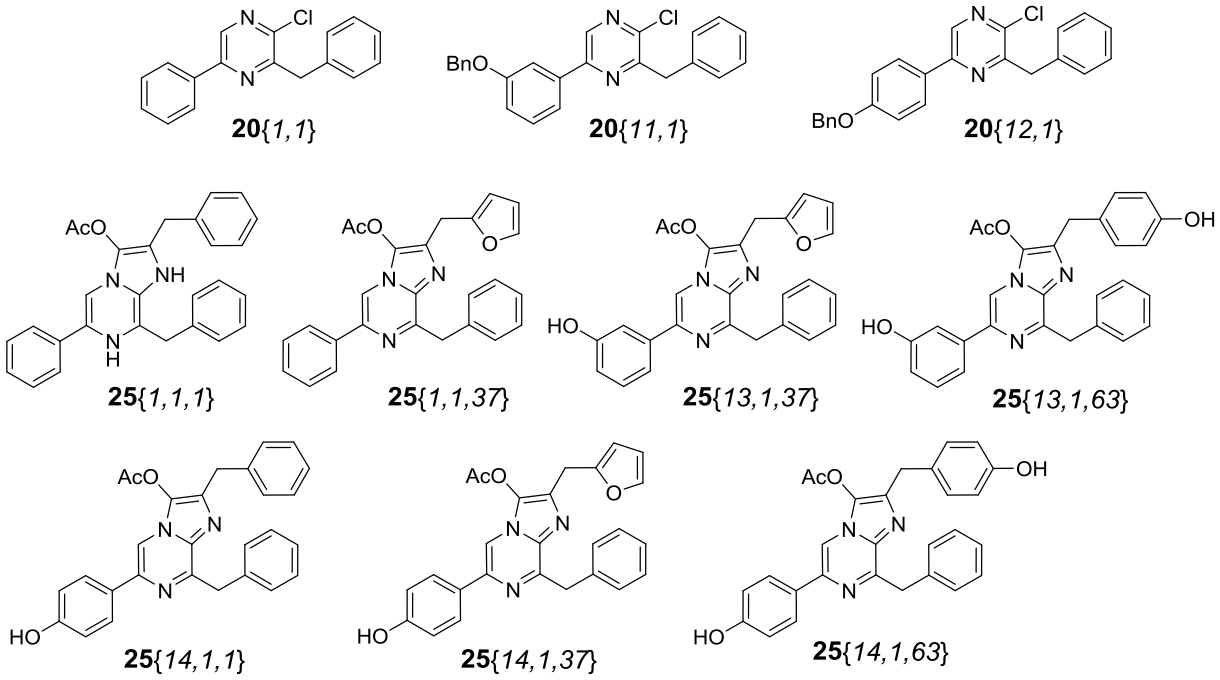


Note: these nitrostyrenes are commercially available and/or their preparations has been reported previously in the case of compound **13**{5},[1] and **13**{10}.[2]

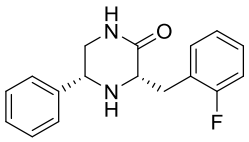
Structure and numbering of the α-amino esters[3] 14 used. The last four were not used in the synthetic scheme depicted above but are provided for the convenient numbering of substrates prepared.



Note: by using the synthetic scheme depicted above, we have previously reported[4] the preparations of the chloropyrazines **20**{*1,1*}, **20**{*11,1*} and **20**{*12,1*} as well as the O-acetylated luciferins **25**{1,1,1}, **25**{1,1,37}, **25**{13,1,37}, **25**{13,1,63}, **25**{14,1,1}, **25**{14,1,37}, **25**{14,1,63}:

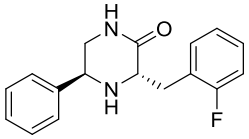


General preparation of piperazin-2-ones 17 via steps i-iii. Step i: the considered nitrostyrene **13** (0.1 mol) was added to a freshly extracted free base of α-amino ester **14** (0.1 mol) (see notes 1 and 2). Upon stirring on a rotatory evaporator at room temperature the suspension homogenized in sometime as quickly as 10 minutes to give the 1,4-adduct **15** as an oil (see note 3). Step ii: this oil was dispersed in a cold solution of dioxane (300 mL) and 37% hydrochloric acid (110 mL, 1.2 mol). Zinc dust (34.4 g, 0.4 mol, size < 10 µm) was promptly added portion-wise in the course of 10-15 minutes while cooling the reaction with an ice bath. The temperature was then allowed to rise back to room temperature and the suspension stirred for 2 hours. Most of the dioxane was removed (note 4) under vacuum and the residue was diluted in water, made basic with an excess of 22% ammonia and extracted with ethyl acetate. The organic layer was washed with 10% ammonia, brine, dried over sodium carbonate and concentrated to dryness to give the crude diamine **16** as an oil. Step iii: under an argon atmosphere, this oil was heated at 140 °C for 3 hours. The ethanol was removed under vacuum and the resulting solid was subjected to purification procedures as described below for each pair of diastereoisomers **17** (note 5). Concerning these diastereoisomers, their structure attribution was easily performed by checking for the existence (or not) of a nOe effect between H-3 and H-5. *Note 1*: In the course of this work, it was found that for step i, dissolving the reagents in a small amount of dichloromethane followed by a concentration to dryness insured their proper mixing. *Note 2*: Mixing the nitrostyrene **13**, the hydrochloride salt of the amino ester **14** and one equivalent of triethylamine in a small amount of dichloromethane prior to a concentration to dryness was also found possible, the resulting triethylamine hydrochloride did not interfere with the next step. *Note 3*: Ten minutes was found (by ^{1}H NMR) to be enough in some cases but the homogenous mixture was usually left to react overnight to ensure an almost complete 1,4-addition (as seen by ^{1}H NMR). *Note 4*: This concentration is not required on a smaller scale. *Note 5*: In some cases (mentioned below) this separation was not performed and the crude mixture of diastereoisomers was directly used in the next step, fairly often via step v, to prepare the nitrones **18**.

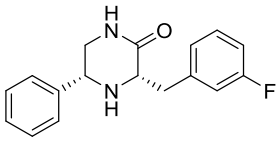


Cis-3-(2-fluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,2*} (YJ31070-020-5): This racemic isomer was obtained as a white powder (2.85 g, 31%) after a chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and a dispersion in boiling cyclohexane. ^{1}H NMR ($CDCl_3$): 7.35 (m, 6H), 7.21 (m, 1H), 7.07 (m, 2H), 6.60 (s (br), 1H), 4.08 (dd, 1H, *J* = 6.4, 8.3 Hz), 3.92 (dd, 1H, *J* = 3.1, 9.6 Hz), 3.65 (dd, 1H, *J* = 3.0, 14.0 Hz), 3.34 (m, 2H), 2.97 (dd, 1H, *J* = 9.6, 14.0 Hz), 1.78 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 170.9, 161.6 (246 Hz), 140.2, 131.7 (5 Hz), 128.7,

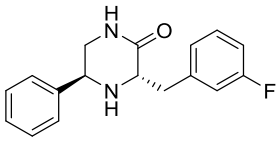
128.4 (8 Hz), 128.2, 126.8, 125.3 (15 Hz), 124.1 (3 Hz), 115.5 (22 Hz), 59.6, 57.7, 49.9, 31.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1412.



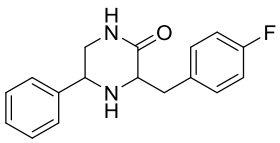
Trans-3-(2-fluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,2*} (YJ31070-020-6): This racemic isomer was obtained as a white powder (2.15 g, 23%) after a chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and a recrystallization of a sample in cyclohexane for analytical purposes. ^{1}H NMR ($CDCl_3$): 7.40-7.26 (m, 6H), 7.21 (m, 1H), 7.09 (m, 1H), 7.03 (m, 1H), 6.92 (s (br), 1H), 4.33 (dd, 1H, *J* = 3.9, 9.8 Hz), 3.92 (dd, 1H, *J* = 3.9, 10.6 Hz), 3.51-3.33 (m, 3H), 3.27 (dd, 1H, *J* = 4.0, 14.0 Hz), 1.72 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.7, 161.7 (244 Hz), 140.0, 131.4 (4 Hz), 128.7, 128.6 (8 Hz), 128.2, 127.0, 125.0 (15 Hz), 124.5 (3 Hz), 115.5 (22 Hz), 58.8, 51.7, 49.2, 31.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1410.



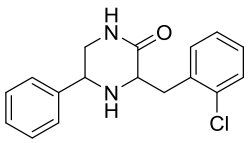
Cis-3-(3-fluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,3*} (YJ31070-152-1): This isomer was obtained as a powder (2.25 g, 13%) after a chromatography over silica gel (dichloromethane - ethanol 97.5/2.5) and a recrystallization in a mixture of toluene and cyclohexane. ^{1}H NMR ($CDCl_3$): 7.40-7.24 (m, 6H), 7.10 (m, 1H), 7.05 (m, 1H), 6.92 (m, 1H), 6.62 (s (br), 1H), 4.07 (m, 1H), 3.85 (dd, 1H, *J* = 2.9, 10.0 Hz), 3.55 (dd, 1H, *J* = 2.9, 13.5 Hz), 3.34 (m, 2H), 2.93 (dd, 1H, *J* = 10.0, 13.5 Hz), 1.74 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 170.8, 162.9 (245 Hz), 140.9 (7 Hz), 140.0, 130.0 (7 Hz), 128.7, 128.3, 126.8, 125.1 (2 Hz), 116.2 (21 Hz), 113.5 (21 Hz), 60.6, 57.7, 49.8, 38.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{19}FN_2O$: 285.1403, found: 285.1400.



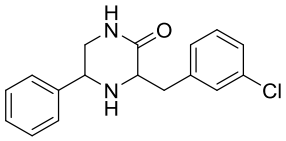
Trans-3-(3-fluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,3*} (YJ31070-151-5): This isomer was obtained as a powder (2.49 g, 15%) after a chromatography over silica gel (dichloromethane - ethanol 97.5/2.5). ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 7.26 (m, 3H), 6.70 (s (br), 1H), 4.21 (dd, 1H, *J* = 4.2, 9.3 Hz), 3.87 (dd, 1H, *J* = 3.8, 10.3 Hz), 3.54-3.41 (m, 2H), 3.30 (dd, 1H, *J* = 3.8, 14.0 Hz), 3.30 (dd, 1H, *J* = 10.3, 14.0 Hz), 1.77 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.5, 163.0 (245 Hz), 140.6 (7 Hz), 139.6, 130.2 (7 Hz), 128.8, 128.2, 126.9, 125.0 (2 Hz), 116.2 (21 Hz), 113.7 (21 Hz), 59.0, 51.8, 49.0, 37.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{19}FN_2O$: 285.1403, found: 285.1409.



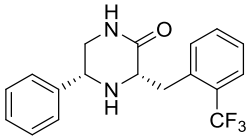
3-(4-fluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,4*} (YJ31067-121-3): This compound was obtained as white powder (0.9 g, 59% from nitrostyrene), as a mixture of diastereoisomers after a recrystallization in cyclohexane. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1408.



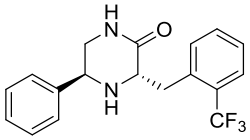
3-(2-Chlorobenzyl)-5-phenylpiperazin-2-one **17**{*1,5*} (EC31094-085-3): This compound was obtained a white powder containing a mixture of the two diastereoisomers after a recrystallization in cyclohexane (2.21 g, 45%). ^{1}H NMR ($CDCl_3$): 7.42-7.29 (m, 7H), 7.25-7.14 (m, 2H), 6.85 (s (br), 0.4H), 6.69 (s (br), 0.6H), 4.37 (dd, 0.4H, *J* = 9.8, 4.2 Hz), 4.10-3.98 (m, 1.4H), 3.83 (dd, 0.6H, *J* = 13.8, 3.4 Hz), 3.51-3.30 (m, 3H), 3.02 (dd, 0.6H, *J* = 13.8, 9.8 Hz). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}ClN_2O$: 301.1108; found, 301.1117.



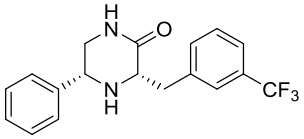
3-(3-Chlorobenzyl)-5-phenylpiperazin-2-one **17**{*1,6*} (VM32021-015-1): This mixture of isomers was obtained as an oil and used directly in the N-oxidation step v.



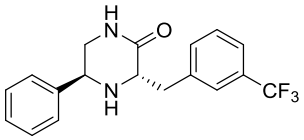
Cis-5-phenyl-3-(2-(trifluoromethyl)benzyl)piperazin-2-one **17**{*1,8*} (YJ 33067-99-4): This isomer was obtained as a powder (3.51 g, 35%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96.5/3.5) and a dispersion boiling cyclohexane. ^{1}H NMR (DMSO-d_6): 7.84 (m, 1H), 7.71 (m, 1H), 7.66 (m, 1H), 7.58 (m, 1H), 7.41-7.24 (m, 6H), 4.02 (m, 1H), 3.74 (m, 1H), 3.62 (m, 1H), 3.30 (dt, 1H, *J* = 4.1, 11.3 Hz), 3.17 (t, 1H, *J* = 11.5 Hz), 2.93 (dd, 1H, *J* = 9.8, 14.9 Hz), 2.49 (m, 1H). ^{13}C NMR (DMSO-d_6): 170.2, 141.7, 138.4 (2 Hz), 132.5, 132.3, 128.7, 128.1 (30 Hz), 127.8, 127.0, 126.9, 126.1 (6 Hz), 125.1 (274 Hz), 59.4, 56.6, 49.3, 34.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{18}F_3N_2O$: 335.1371, found: 335.1379.



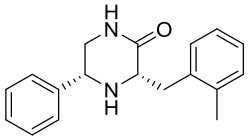
Trans-5-phenyl-3-(2-(trifluoromethyl)benzyl)piperazin-2-one **17**{*1,8*} (YJ 33067-99-3): This isomer was obtained as a powder (1.83 g, 18%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96.5/3.5). ^{1}H NMR (DMSO-d_6): 7.89 (m, 1H), 7.63 (m, 1H), 7.55 (m, 2H), 7.37 (m, 3H), 7.31 (m, 2H), 7.24 (m, 1H), 4.25 (m, 1H), 3.59 (m, 1H), 3.44 (dt, 1H, *J* = 3.9, 11.7 Hz), 3.35 (m, 1H), 3.23 (t, 1H, *J* = 10.9 Hz), 3.11 (dd, 1H, *J* = 10.7, 13.7 Hz), 2.67 (dd, 1H, *J* = 5.6, 8.8 Hz). ^{13}C NMR (DMSO-d_6): 171.1, 141.5, 138.5 (2 Hz), 133.1, 132.3, 128.7, 128.0 (30 Hz), 127.6, 127.1, 127.0, 126.0 (6 Hz), 125.1 (274 Hz), 58.0, 51.1, 48.6, 33.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{18}F_3N_2O$: 335.1371, found: 335.1369.



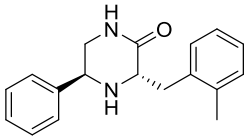
Cis-5-phenyl-3-(3-(trifluoromethyl)benzyl)piperazin-2-one **17**{*1,9*} (YJ 33067-101-4): This isomer was obtained as a powder (2.90 g, 32%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96.5/3.5) and a (slow) recrystallization in cyclohexane. ^{1}H NMR (DMSO-d_6): 7.75 (m, 2H), 7.61 (m, 1H), 7.51 (m, 2H), 7.40-7.24 (m, 5H), 4.02 (dt, 1H, *J* = 3.3, 10.4 Hz), 3.75 (m, 1H), 3.23 (dd, 1H, *J* = 4.0, 13.9 Hz), 3.62 (m, 1H), 3.17 (dt, 1H, *J* = 3.6 and 10.9 Hz), 3.04 (dd, 1H, *J* = 6.6, 14.4 Hz), 2.94 (t, 1H, *J* = 11.4 Hz), 2.77 (m, 1H). ^{13}C NMR (DMSO-d_6): 170.0, 141.8, 141.1, 134.4, 129.4, 128.9 (30 Hz), 128.7, 127.9, 127.1, 126.9 (6 Hz), 124.9 (271 Hz), 123.0 (3 Hz), 59.9, 56.7, 49.3, 37.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{18}F_3N_2O$: 335.1371, found: 335.1372.



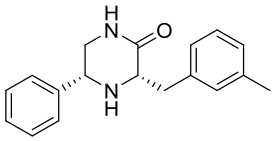
Trans-5-phenyl-3-(3-(trifluoromethyl)benzyl)piperazin-2-one **17**{*1,9*} (YJ 33067-101-3): This isomer was obtained as a powder (2.03 g, 22%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96.5/3.5). ^{1}H NMR (DMSO-d_6): 7.86 (m, 1H), 7.65 (m, 1H), 7.55 (m, 3H), 7.36 - 7.23 (m, 5H), 4.07 (m, 1H), 3.55 (m, 1H), 3.36 (dt, 1H, *J* = 3.7, 11.6 Hz), 3.24 (m, 1H), 3.14 (m, 2H), 2.71 (m, 1H). ^{13}C NMR (DMSO-d_6): 171.1, 141.5, 133.9, 129.7, 129.2 (30 Hz), 128.6, 127.1, 126.0 (4 Hz), 124.9 (274 Hz), 123.2 (4 Hz), 58.3, 51.2, 48.1, 37.5 (two signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{18}F_3N_2O$: 335.1371, found: 335.1371.



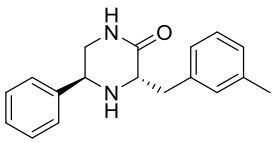
Cis-3-(2-methylbenzyl)-5-phenylpiperazin-2-one **17**{*1,11*} (YJ31070-175-4): This compound was obtained as a white powder (4.04 g, 26%) after a chromatography over silica gel (dichloromethane / ethanol 98/2 to 95/5) and a dispersion in boiling cyclohexane. ^{1}H NMR ($CDCl_3$): 7.40 – 7.27 (m, 6H), 7.14 (m, 3H), 6.58 (s (br), 1H), 4.03 (dd, 1H, *J* = 4.1, 10.5 Hz), 3.82 (d (br), 1H, *J* = 10.5 Hz), 3.68 (dd, 1H, *J* = 2.7, 14.0 Hz), 3.36 (m, 2H), 2.92 (dd, 1H, *J* = 10.8, 13.7 Hz), 2.45 (s, 3H), 1.77 (s, 1H). ^{13}C NMR ($CDCl_3$): 171.2, 140.3, 137.1, 136.6, 130.6, 129.9, 128.7, 128.2, 126.8, 126.7, 126.1, 60.0, 57.9, 50.0, 35.6, 19.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$, 281.1654; found: 281.1652.



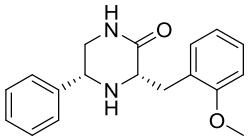
Trans-3-(2-methylbenzyl)-5-phenylpiperazin-2-one **17**{*1,11*} (YJ31070-175-5): This compound was obtained as a white powder (2.77 g, 17%) after a chromatography over silica gel (dichloromethane / ethanol 98/2 to 95/5) and a dispersion in boiling cyclohexane. ^{1}H NMR ($CDCl_3$): 7.41 – 7.30 (m, 5H), 7.14 (m, 4H), 6.80 (s (br), 1H), 4.35 (dd, 1H, *J* = 5.0, 9.8 Hz), 3.89 (dd, 1H, *J* = 3.3, 11.2 Hz), 3.43 (m, 2H), 3.39 (dd, 1H, *J* = 3.3, 13.9 Hz), 3.16 (dd, 1H, *J* = 11.2, 13.9 Hz), 2.40 (s, 3H), 1.76 (s, 1H). ^{13}C NMR ($CDCl_3$): 172.0, 139.9, 136.8, 136.2, 130.8, 130.0, 128.8, 128.2, 126.9, 126.8, 126.2, 58.2, 52.0, 49.4, 35.0, 19.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$, 281.1654; found: 281.1652.



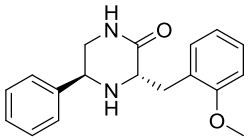
Cis-3-(3-methylbenzyl)-5-phenylpiperazin-2-one **17**{*1,12*} (YJ31070-177-4): This compound was obtained as a white powder (3.70 g, 26%) after a chromatography over silica gel (dichloromethane / ethanol 98/2 to 95/5) and a dispersion in boiling cyclohexane. ^{1}H NMR ($CDCl_3$): 7.40 – 7.28 (m, 5H), 7.20 (m, 1H), 7.13 (m, 2H), 7.04 (m, 1H), 6.72 (s (br), 1H), 4.05 (dd, 1H, *J* = 5.4, 9.5 Hz), 3.83 (d (br), 1H, *J* = 10.4 Hz), 3.58 (dd, 1H, *J* = 3.0, 13.6 Hz), 3.35 (m, 2H), 2.86 (dd, 1H, *J* = 10.4, 13.6 Hz), 2.34 (s, 3H), 1.80 (s, 1H). ^{13}C NMR ($CDCl_3$): 171.3, 140.2, 138.3, 138.2, 130.1, 128.7, 128.5, 128.1, 127.4, 126.8, 126.3, 60.9, 57.8, 49.9, 38.4, 21.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$, 281.1654; found: 281.1649.



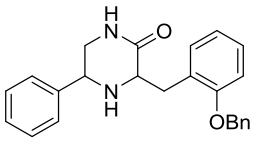
Trans-3-(3-methylbenzyl)-5-phenylpiperazin-2-one **17**{*1,12*} (YJ31070-177-5): This compound was obtained as a white powder (2.73 g, 19%) after a chromatography over silica gel (dichloromethane / ethanol 98/2 to 95/5) and a recrystallization in cyclohexane. ^{1}H NMR ($CDCl_3$): 7.39 – 7.30 (m, 5H), 7.19 (m, 1H), 7.05 (m, 3H), 6.81 (s (br), 1H), 4.26 (dd, 1H, *J* = 4.0, 9.9 Hz), 3.87 (dd, 1H, *J* = 3.8, 10.7 Hz), 3.45 (m, 2H), 3.28 (dd, 1H, *J* = 3.5, 13.7 Hz), 3.14 (dd, 1H, *J* = 10.7, 13.7 Hz), 2.31 (s, 3H), 1.81 (s, 1H). ^{13}C NMR ($CDCl_3$): 172.0, 139.9, 138.5, 137.8, 130.1, 128.7 (two signals), 128.2, 127.5, 127.0, 126.3, 59.3, 51.7, 49.1, 37.6, 21.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$, 281.1654; found: 281.1656.



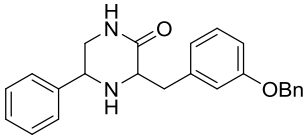
Cis-3-(2-methoxybenzyl)-5-phenylpiperazin-2-one **17**{*1,14*} (YJ31070-103-3): This isomer was obtained as a powder (4.03 g, still containing 5% of the aminoester) after a chromatography over silica gel (dichloromethane - ethanol 97.5/2.5). ^{1}H NMR ($CDCl_3$): 7.39-7.27 (m, 6H), 7.21 (m, 1H), 6.89 (m, 2H), 6.38 (s (br), 1H), 4.05 (dd, 1H, *J* = 5.3, 9.3 Hz), 3.92 (m, 1H), 3.84 (s, 3H), 3.75 (dd, 1H, *J* = 3.3, 13.7 Hz), 3.35 (m, 2H), 2.88 (dd, 1H, *J* = 10.3, 13.7 Hz), 1.81 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.5, 157.9, 140.5, 131.5, 128.6, 128.0, 127.9, 126.7, 126.6, 120.5, 110.4, 59.2, 57.8, 55.3, 50.1, 33.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1607.



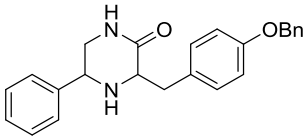
Trans-3-(2-methoxybenzyl)-5-phenylpiperazin-2-one **17**{*1,14*} (YJ31070-103-4): This isomer was obtained as a powder (2.23 g, 24%) after a chromatography over silica gel (dichloromethane - ethanol 97.5/2.5). ^{1}H NMR ($CDCl_3$): 7.39-7.30 (m, 5H), 7.21 (m, 2H), 6.92 (m, 1H), 6.82 (m, 1H), 6.70 (s (br), 1H), 4.36 (dd, 1H, *J* = 3.9, 9.9 Hz), 3.97 (dd, 1H, *J* = 3.9, 10.7 Hz), 3.68 (s, 3H), 3.46-3.32 (m, 4H), 3.26 (dd, 1H, *J* = 3.8, 13.5 Hz), 1.83 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 172.3, 158.0, 140.4, 131.3, 128.6, 128.1, 128.0, 127.0, 126.3, 120.9, 110.4, 59.0, 55.1, 52.0, 49.5, 32.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1604.



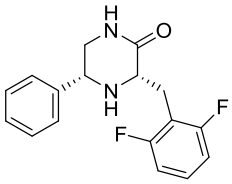
3-(2-(benzyloxy)benzyl)-5-phenylpiperazin-2-one **17**{*1,17*} (RB 32489-041): This mixture of isomers was obtained as an oil and used directly in the N-oxidation step v.



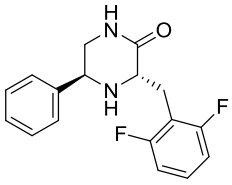
3-(3-(benzyloxy)benzyl)-5-phenylpiperazin-2-one **17**{*1,18*} (RB 32489-039): This mixture of isomers was obtained as an oil and used directly in the N-oxidation step v.



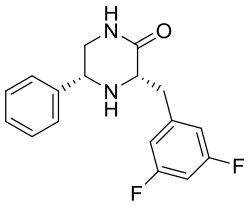
3-(4-(benzyloxy)benzyl)-5-phenylpiperazin-2-one **17**{*1,19*} (YJ 31776-031): This mixture of isomers was obtained as an oil and used directly in the N-oxidation step v.



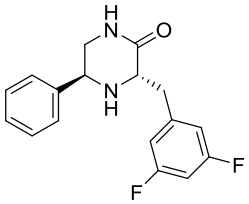
Cis-3-(2,6-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,21*} (EC31095-011-3): This isomer was obtained as a powder (1.73 g, 38%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96.5/3.5). ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 7.18 (m, 1H), 6.89 (m, 2H), 6.55 (s, 1H), 4.09 (dd, 1H, *J* = 9.4, 5.1 Hz), 3.95 (m, 1H), 3.64 (m, 1H), 3.38 (m, 2H), 3.09 (dd, 1H, *J* = 13.9, 10.3 Hz), 1.73 (s, 1H). ^{13}C NMR ($CDCl_3$): 170.7, 162.0 (248, 9 Hz), 140.2, 128.7, 128.3 (10 Hz), 128.2, 126.7, 114.2 (20 Hz), 111.2, 58.8, 57.6, 50.0, 25.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1301.



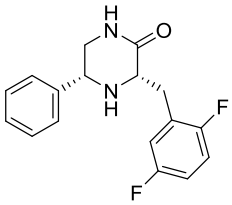
Trans-3-(2,6-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,21*} (EC31095-011-4): This isomer was obtained as a powder (1.05 g, 23%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96.5/3.5). ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 7.18 (m, 1H), 6.87 (m, 2H), 6.58 (s, 1H), 4.41 (dd, 1H, *J* = 10.1, 4.0 Hz), 3.96 (dd, 1H, *J* = 9.8, 5.4 Hz), 3.44 (m, 4H), 1.63 (s, 1H). ^{13}C NMR ($CDCl_3$): 171.3, 162.0 (247, 9 Hz), 128.7, 128.5 (10 Hz), 128.2, 127.0, 113.8 (20 Hz), 111.3, 57.6, 51.5, 49.3, 25.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1306.



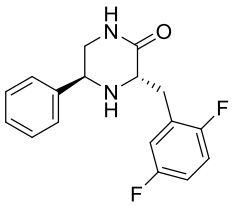
Cis-3-(3,5-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,22*} (EC31095-026-4): This isomer was obtained as a powder (1.52 g, 36%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96/4). ^{1}H NMR ($CDCl_3$): 7.36 (m, 5H), 6.87 (m, 3H), 6.68 (tt, 1H, *J* = 9.0, 2.3 Hz), 4.09 (dd, 1H, *J* = 8.4, 6.0 Hz), 3.87 (dd, 1H, *J* = 9.4, 3.0 Hz), 3.50 (dd, 1H, *J* = 13.8, 3.2 Hz), 3.35 (m, 2H), 2.94 (dd, 1H, *J* = 13.8, 9.5 Hz), 1.74 (s, 1H). ^{13}C NMR ($CDCl_3$): 170.6, 164.3 (13 Hz), 161.8 (13 Hz), 142.3 (9 Hz), 139.9, 128.8, 128.3, 126.8, 112.3, 102.2, 60.3, 57.7, 49.7, 38.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1302.



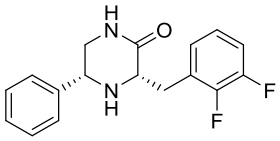
Trans-3-(3,5-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,22*} (EC31095-026-6): This isomer was obtained as a powder (1.05 g, 25%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96/4). ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 7.02 (s, 1H), 6.80 (m, 2H), 6.69 (tt, 1H, *J* = 9.0, 2.3 Hz), 4.19 (dd, 1H, *J* = 8.3, 4.6 Hz), 3.85 (dd, 1H, *J* = 10.1, 3.7 Hz), 3.49 (m, 2H), 3.27 (dd, 1H, *J* = 13.9, 3.6 Hz), 3.15 (dd, 1H, *J* = 13.9, 10.1 Hz), 1.76 (s, 1H). ^{13}C NMR ($CDCl_3$): 171.4, 164.4 (13 Hz), 161.9 (13 Hz), 142.2 (9 Hz), 139.5, 128.9, 128.3, 126.8, 112.2, 102.3 (25 Hz), 58.6, 51.9, 48.9, 37.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1306.



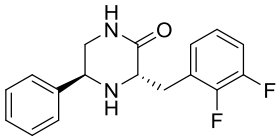
Cis-3-(2,5-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,23*} (EC31095-015-3): This isomer was obtained as a powder (1.58 g, 35%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96/4). ^{1}H NMR ($CDCl_3$): 7.34 (m, 5H), 7.05 (m, 2H), 6.89 (m, 1H), 6.66 (s, 1H), 4.10 (m, 1H), 3.93 (m, 1H), 3.57 (dd, 1H, *J* = 14.0, 2.4 Hz), 3.33 (dd, 2H, *J* = 6.8, 2.5 Hz), 2.99 (ddd, 1H, *J* = 14.0, 9.1, 0.8 Hz), 1.77 (s, 1H). ^{13}C NMR ($CDCl_3$): 170.6, 158.5 (242, 2 Hz), 157.6 (241, 2 Hz), 140.1, 128.8, 128.3, 127.1 (18, 8 Hz), 126.8, 118.0 (24, 5 Hz), 116.2 (25, 9 Hz), 114.6 (24, 9 Hz), 59.5, 57.7, 49.9, 31.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1304.



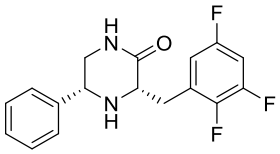
Trans-3-(2,5-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,23*} (EC31095-015-4): This isomer was obtained as a powder (1.17 g, 26%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96/4). ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 6.96 (m, 3H), 6.26 (s, 1H), 4.31 (dd, 1H, *J* = 9.7, 4.1 Hz), 3.91 (dd, 1H, *J* = 10.3, 4.1 Hz), 3.35 (m, 4H), 1.70 (s, 1H). ^{13}C NMR ($CDCl_3$): 171.0, 158.7 (240, 2 Hz), 157.6 (241, 2 Hz), 139.7, 128.8, 128.2, 127.0, 126.8 (18, 8 Hz), 117.6 (24, 5 Hz), 116.5 (26, 9 Hz), 114.9 (24, 9 Hz), 58.6, 51.8, 49.2, 31.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1306.



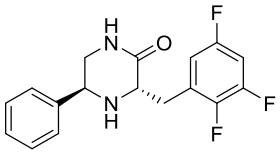
Cis-3-(2,3-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,24*} (EC31095-13-3): This isomer was obtained as a white powder (1.57 g, 36%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96/4). ^{1}H NMR ($CDCl_3$): 7.34 (m, 5H), 7.06 (m, 3H), 6.66 (s, 1H), 4.10 (t, 1H, *J* = 7.2 Hz), 3.94 (dd, 1H, *J* = 9.1, 3.2 Hz), 3.62 (ddd, 1H, *J* = 13.9, 3.4, 1.4 Hz), 3.33 (d, 2H, *J* = 8.5 Hz), 3.04 (dd, 1H, *J* = 14.0, 9.3 Hz), 1.77 (s, 1H). ^{13}C NMR ($CDCl_3$): 170.6, 150.7 (248, 13 Hz), 149.6 (247, 13 Hz), 140.1, 128.8, 128.3, 127.9 (12 Hz), 126.8, 126.3 (3 Hz), 123.9 (7, 5 Hz), 115.6 (17 Hz), 59.5, 57.7, 49.9, 31.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1308.



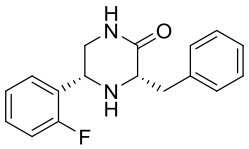
Trans-3-(2,3-difluorobenzyl)-5-phenylpiperazin-2-one **17**{*1,24*} (EC31095-13-3): This isomer was obtained as a white powder (1.21 g, 27%) after a chromatography over silica gel (dichloromethane - ethanol 98/2 to 96/4). ^{1}H NMR ($CDCl_3$): 7.36 (m, 5H), 7.05 (m, 3H), 6.58 (s, 1H), 4.32 (dd, 1H, *J* = 9.7, 4.0 Hz), 3.92 (dd, 1H, *J* = 10.2, 4.2 Hz), 3.38 (m, 4H), 1.70 (s, 1H). ^{13}C NMR ($CDCl_3$): 171.2, 150.7 (248, 13 Hz), 149.7 (247, 13 Hz), 139.7, 128.8, 128.2, 127.7 (12 Hz), 127.0, 125.9 (3 Hz), 124.3 (7, 5 Hz), 115.8 (17 Hz), 58.6, 51.8, 49.2, 31.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309; found, 303.1304.



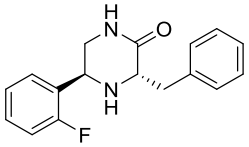
Cis-5-phenyl-3-(2,3,5-trifluorobenzyl)piperazin-2-one **17**{*1,26*} (YJ 33067-97-4): This isomer was obtained as a powder (1.45 g, 41%) after a chromatography over silica gel (dichloromethane - ethanol 97.5/2.5 to 96.5/3.5) and a dispersion in boiling cyclohexane. ^{1}H NMR (DMSO-d_6): 7.83 (m, 1H), 7.39-7.24 (m, 6H), 7.15 (m, 1H), 4.05 (m, 1H), 3.74 (m, 1H), 3.31 (dd, 1H, *J* = 4.0, 13.6 Hz), 3.22 (dt, 1H, *J* = 4.0, 11.5 Hz), 3.04 (t, 1H, *J* = 11.5 Hz), 2.93 (dd, 1H, *J* = 7.9, 14.1 Hz), 2.80 (m, 1H). ^{13}C NMR (DMSO-d_6): 169.8, 157.0 (244, 10 and 3 Hz), 149.8 (251, 12 and 14 Hz), 145.9 (243, 13 and 4 Hz), 141.7, 130.5 (9 and 15 Hz), 128.7, 127.8, 127.1, 113.5 (3 and 23 Hz), 103.9 (21 and 28 Hz), 59.1, 56.6, 49.3, 31.0.



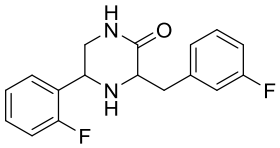
Trans-5-phenyl-3-(2,3,5-trifluorobenzyl)piperazin-2-one **17**{*1,26*} (YJ 33067-97-3): This isomer was obtained as a powder (0.77 g, 22%) after a chromatography over silica gel (dichloromethane - ethanol 97.5/2.5 to 96.5/3.5). ^{1}H NMR (DMSO-d_6): 7.87 (m, 1H), 7.38-7.23 (m, 6H), 7.09 (m, 1H), 4.18 (m, 1H), 3.55 (m, 1H), 3.40 (dt, 1H, *J* = 4.0, 11.0 Hz), 3.24 (m, 1H), 3.16 (dd, 1H, *J* = 4.6 and 13.9 Hz), 3.07 (dd, 1H, *J* = 10.3, 13.6 Hz), 2.83 (m, 1H). ^{13}C NMR (DMSO-d_6): 170.7, 157.1 (244, 10 and 3 Hz), 149.7 (251, 12 and 14 Hz), 145.9 (243, 13 and 4 Hz), 141.5, 130.8 (9 and 15 Hz), 128.7, 127.6, 127.1, 113.7 (3 and 23 Hz), 103.9 (21 and 28 Hz), 57.4, 50.9, 48.3, 31.0.



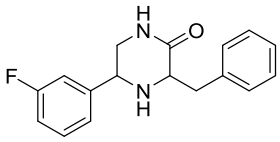
(3S,5R)-3-benzyl-5-(2-fluorophenyl)piperazin-2-one **17**{*2,1*} (YJ31134-014-3): This isomer was obtained as a white powder (4.06 g, 39%) after two chromatography over silica gel (dichloromethane - ethanol 96/4 to 94/6) and (cyclohexane - ethyl acetate 2/3 to 1/3) followed by a dispersion in boiling cyclohexane and extensive drying at 70 °C under vacuum. ^{1}H NMR ($CDCl_3$): 7.49 (m, 1H), 7.31 (m, 4H), 7.26 (m, 2H), 7.16 (m, 1H), 7.02 (m, 1H), 6.65 (s (br), 1H), 4.42 (m, 1H), 3.87 (m, 1H), 3.57 (dd, 1H, *J* = 3.3, 13.8 Hz), 3.29 (t, 1H, *J* = 10.9 Hz), 2.95 (dd, 1H, *J* = 9.1, 13.8 Hz), 1.73 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.0, 160.1 (246 Hz), 138.2, 129.4 (7 Hz), 129.3, 128.7, 127.4 (4 Hz), 127.1 (13 Hz), 126.7, 124.6 (4 Hz), 115.4 (22 Hz), 60.7, 50.4 (3 Hz), 48.4, 38.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1391.



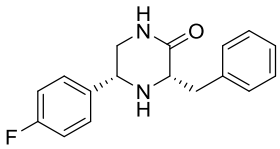
(3S,5S)-3-benzyl-5-(2-fluorophenyl)piperazin-2-one **17**{*2,1*} (YJ31134-013-4): This isomer was obtained as a white powder (2.16 g, 20%) after a chromatography over silica gel (dichloromethane - ethanol 96/4 to 94/6). ^{1}H NMR ($CDCl_3$): 7.44 (m, 1H), 7.27 (m, 6H), 7.13 (m, 1H), 7.08 (m, 1H), 6.74 (s (br), 1H), 4.65 (dd, 1H, *J* = 4.3, 9.1 Hz), 3.84 (dd, 1H, *J* = 3.5, 10.8 Hz), 3.48 (m, 2H), 3.34 (dd, 1H, *J* = 3.8, 13.7 Hz),), 3.15 (dd, 1H, *J* = 10.7, 13.7 Hz), 1.78 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.8, 160.5 (247 Hz), 137.9, 129.5 (9 Hz), 129.3, 128.8, 127.9 (3 Hz), 126.8 (13 Hz), 126.7, 124.5 (3 Hz), 115.6 (22 Hz), 59.2, 47.7, 44.9 (2 Hz), 37.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1367.



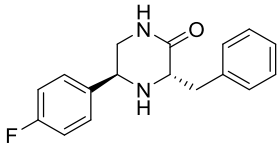
3-(3-Fluorobenzyl)-5-(2-fluorophenyl)piperazin-2-one **17**{*2,3*} (YJ 31068-119-1): This crude mixture of isomers was obtained as an oil and used directly in the N-oxidation step v.



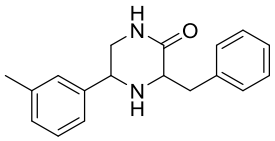
3-benzyl-5-(3-fluorophenyl)piperazin-2-one **17**{*3,1*} (YJ31067-006-2): This mixture of isomers was obtained as an oil, after washing it with cyclohexane to remove unreacted ethyl phenylalanine ester, and used directly in the aromatization step.



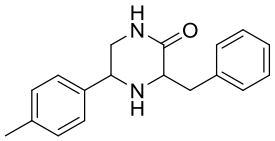
(3S,5R)-3-benzyl-5-(4-fluorophenyl)piperazin-2-one **17**{*4,1*} (YJ29794-192-7): This isomer was obtained as a white powder (2.03 g, 42%) after two chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and (cyclohexane - ethyl acetate 1/2 to 1/3). ^{1}H NMR ($CDCl_3$): 7.28 (m, 7H), 7.01 (m, 2H), 6.61 (s (br), 1H), 4.05 (t, 1H, *J* = 7.3 Hz), 3.82 (d, 1H, *J* = 9.3 Hz), 3.58 (dd, 1H, *J* = 3.0, 13.6 Hz), 3.31 (m, 2H), 2.89 (dd, 1H, *J* = 9.8, 13.6 Hz), 1.72 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 173.2, 164.7 (246 Hz), 140.4, 138.1, 131.6, 130.8, 130.6 (8 Hz), 128.8, 117.7 (21 Hz), 62.9, 59.2, 52.1, 40.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1342.



(3S,5S)-3-benzyl-5-(4-fluorophenyl)piperazin-2-one **17**{*4,1*} (YJ29794-192-8): This isomer was obtained as a white powder (1.32 g, 27%) after two chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and (ethyl acetate – ethanol 99/1). ^{1}H NMR ($CDCl_3$): 7.29 (m, 7H), 7.05 (m, 2H), 6.79 (s (br), 1H), 4.21 (dd, 1H, *J* = 4.5, 9.5 Hz), 3.86 (dd, 1H, *J* = 3.7, 10.6 Hz), 3.40 (m, 2H), 3.16 (dd, 1H, *J* = 10.7, 13.9 Hz), 1.74 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.8, 162.5 (247 Hz), 137.8, 135.6, 129.3, 128.9, 128.6 (8 Hz), 126.8, 115.6 (21 Hz), 59.2, 51.1, 49.2, 37.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{18}FN_2O$: 285.1403, found: 285.1315.

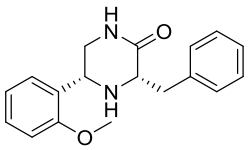


3-Benzyl-5-(m-tolyl)piperazin-2-one **17**{*5,1*} (YJ30367-057-3): An analytical sample of a mixture of the the two diastereoisomers was obtained by a recrystallization in cyclohexane but most of the solid and the filtrate were used directly in the in the aromatization step. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{20}N_2O$, 281.1654; found: 281.1645.

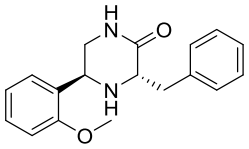


3-Benzyl-5-(p-tolyl)piperazin-2-one **17**{*6,1*} (YJ30367-027-3): This compound was obtained as a crude mixture of the two diastereoisomers (5.40 g) by dispersing the resulting solid in boiling cyclohexane and filtration at 20 °C

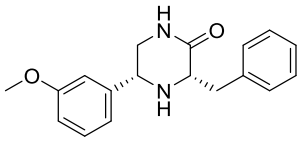
and was used directly in the aromatization step. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{20}N_2O$, 281.1654; found: 281.1649.



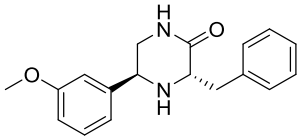
(3S,5R)-3-benzyl-5-(2-methoxyphenyl)piperazin-2-one **17**{*7,1*} (YJ29589-082-2): This isomer was obtained as a glass (1.06 g, 25%) after two chromatography over silica gel (dichloromethane - ethanol 96/4 to 95/5) and (cyclohexane - ethyl acetate 1/2 to 1/3). ^{1}H NMR ($CDCl_3$): 7.40-7.22 (m, 7H), 6.98 (m, 1H), 6.84 (m, 1H), 6.69 (s (br), 1H), 4.39 (dd, 1H, *J* = 3.7, 10.7 Hz), 3.74 (s, 3H), 3.85 (dd, 1H, *J* = 3.2, 9.2 Hz), 3.53 (dd, 1H, *J* = 3.5, 13.7 Hz), 3.44 (ddd, 1H, *J* = 4.0, 8.0, 11.0 Hz), 3.28 (t, 1H, *J* = 11.0 Hz), 3.01 (dd, 1H, *J* = 8.3, 13.7 Hz), 1.90 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.4, 156.6, 138.4, 128.8, 128.7, 128.6, 128.0, 126.7, 126.6, 120.9, 110.4, 60.8, 55.2, 51.6, 47.8, 38.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1591.



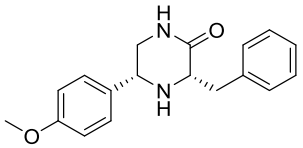
(3S,5S)-3-benzyl-5-(2-methoxyphenyl)piperazin-2-one **17**{*7,1*} (YJ29589-082-3): This isomer was obtained as a white solid (0.52 g, 12%) after two chromatography over silica gel (dichloromethane - ethanol 96/4 to 95) and (ethyl acetate - ethanol 1/0 to 99/1). ^{1}H NMR ($CDCl_3$): 7.36-7.20 (m, 7H), 6.94 (m, 1H), 6.88 (m, 1H), 6.65 (s (br), 1H), 4.64 (dd, 1H, *J* = 4.2, 8.1 Hz), 3.77 (s, 3H), 3.71 (dd, 1H, *J* = 3.3, 10.8 Hz), 3.59 (m, 1H), 3.47 (ddd, 1H, *J* = 1.0, 11.2 Hz), 3.36 (dd, 1H, *J* = 3.3, 13.7 Hz), 3.09 (dd, 1H, *J* = 10.8, 13.7 Hz), 2.08 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.9, 156.9, 138.2, 128.8, 128.6, 127.6, 129.3, 126.5, 127.2, 120.8, 110.4, 58.7, 55.2, 46.9, 46.0, 37.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1589.



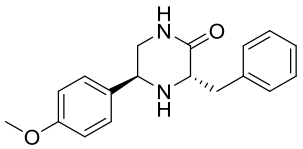
(3S,5R)-3-benzyl-5-(3-methoxyphenyl)piperazin-2-one **17**{*8,1*} (YJ29589-084-3): This isomer was obtained as a glass (1.33 g, 30%) after two chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and (cyclohexane - ethyl acetate 1/4). ^{1}H NMR ($CDCl_3$): 7.34-7.20 (m, 6H), 6.94 (m, 2H), 6.83 (m, 1H), 6.72 (s (br), 1H), 4.02 (dd, 1H, *J* = 6.3, 8.7 Hz), 3.83 (m, 1H), 3.81 (s, 3H), 3.58 (dd, 1H, *J* = 3.3, 13.4 Hz), 3.34 (m, 2H), 2.91 (dd, 1H, *J* = 10.3, 13.4 Hz), 1.90 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.2, 159.9, 141.8, 138.3, 129.7, 129.4, 128.6, 126.6, 119.1, 113.5, 112.5, 60.7, 57.6, 55.2, 49.8, 38.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1582.



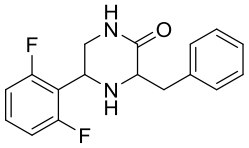
(3S,5S)-3-benzyl-5-(3-methoxyphenyl)piperazin-2-one **17**{*8,1*} (YJ29589-084-4): This isomer was obtained as a glass (0.84 g, 19%) after two chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and (ethyl acetate - ethanol 1/0 to 99/1). ^{1}H NMR ($CDCl_3$): 7.33-7.22 (m, 6H), 6.94 (m, 2H), 6.85 (m, 1H), 6.76 (s (br), 1H), 4.22 (dd, 1H, *J* = 4.1, 9.5 Hz), 3.88 (dd, 1H, *J* = 3.6, 10.6 Hz), 3.80 (s, 3H), 3.45 (m, 2H), 3.31 (dd, 1H, *J* = 3.6, 13.8 Hz), 3.16 (dd, 1H, *J* = 10.7, 13.8 Hz), 1.81 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.9, 159.9, 141.4, 137.9, 129.7, 129.3, 128.9, 126.6, 119.2, 113.6, 112.5, 59.3, 55.2, 51.7, 49.1, 37.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1584.



(3S,5R)-3-benzyl-5-(4-methoxyphenyl)piperazin-2-one **17**{*9,1*} (YJ29589-122-1): This isomer was obtained as a glass (1.37 g, 27%) after two chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and (cyclohexane - ethyl acetate 1/4). ^{1}H NMR ($CDCl_3$): 7.28 (m, 7H), 6.87 (m, 2H), 6.38 (s (br), 1H), 3.99 (dd, 1H, *J* = 4.3, 10.3 Hz), 3.82 (m, 1H), 3.80 (s, 3H), 3.58 (dd, 1H, *J* = 3.8, 13.6 Hz), 3.31 (m, 2H), 2.89 (dd, 1H, *J* = 10.2, 13.6 Hz), 1.90 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.1, 159.5, 138.4, 132.2, 129.4, 128.6, 127.9, 126.6, 114.1, 60.9, 57.1, 55.3, 50.0, 38.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1585.

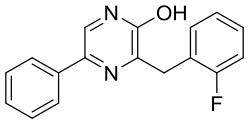


(3S,5S)-3-benzyl-5-(4-methoxyphenyl)piperazin-2-one **17**{*9,1*} (YJ29589-122-2): This isomer was obtained as a white powder (0.81 g, 16%) after two chromatography over silica gel (dichloromethane - ethanol 97/3 to 95/5) and (ethyl acetate - ethanol 1/0 to 99/1). ^{1}H NMR ($CDCl_3$): 7.28 (m, 7H), 6.81 (m, 2H), 6.73 (s (br), 1H), 4.19 (dd, 1H, *J* = 4.0, 9.8 Hz), 3.86 (dd, 1H, *J* = 3.6, 10.6 Hz), 3.80 (s, 3H), 3.44 (m, 1H), 3.31 (m, 2H), 3.36 (td, 1H, *J* = 3.8, 11.5 Hz), 3.30 (dd, 1H, *J* = 3.8, 13.9 Hz), 3.17 (dd, 1H, *J* = 10.6, 13.9 Hz), 1.85 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 171.9, 159.5, 137.9, 131.8, 129.3, 128.9, 127.1, 126.8, 114.1, 59.4, 55.3, 51.1, 49.2, 37.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 297.1603, found: 297.1533.

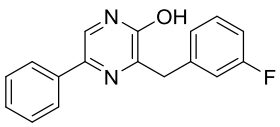


3-Benzyl-5-(2,6-difluorophenyl)piperazin-2-one **17**{*10,1*} (MM34284-016-1): This compound was obtained as a 1/1 mixture of diastereoisomers after a recrystallization in cyclohexane (1.97 g, 62%) and was used directly in the next step. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{17}F_2N_2O$: 303.1309, found: 303.1323.

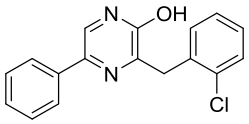
General preparation of pyrazin-2-ol 19 via steps iv. The considered piperazin-2-one **17** (0.011 mol, note 1) and sulfur (0.72 g, 0.0225 mol, note 2) were heated to reflux in 1,3-dichlorobenzene (40 mL, note 3) for 10 hours. This was concentrated to dryness and the residue purified as described below. Note 1: no difference was observed when starting from the pure diastereoisomers or from a mixture of both. Note: 2: an excess of sulfur is detrimental to the reaction yield, hence the importance of starting from purified piperazin-2-ones. Note 3: decahydronaphthalene can also be used as solvent.



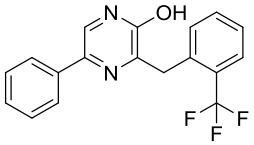
3-(2-Fluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,2*} (YJ31070-025-2): Obtained as a white powder (3.66 g, 88%) after a chromatography over silica gel (dichloromethane / ethanol 97.7:2.5). ^{1}H NMR (DMSO-d_6) 12.45 (s, 1H), 7.89 (s, 1H), 7.73 (m, 2H), 7.38-7.22 (m, 5H), 7.19-7.12 (m, 2H), 4.12 (s, 2H). ^{13}C NMR (DMSO-d_6): 161.2 (243 Hz), 156.1, 155.3, 136.4, 132.1 (5 Hz), 131.2, 129.0, 128.8 (8.2 Hz), 127.6, 125.1 (15 Hz), 124.8, 124.5 (3 Hz), 122.8, 115.4 (22 Hz), 32.4 (2 Hz). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O$: 281.1090; found, 281.1087.



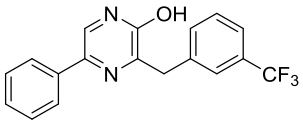
3-(3-Fluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,3*} (YJ31070-179-3): Obtained as a white powder (3.92 g, 88%) after a chromatography over silica gel (dichloromethane / ethanol 98:2). A sample was recrystallized in a mixture of cyclohexane and toluene for analytical purposes. ^{1}H NMR (DMSO-d_6) 12.45 (s (br), 1H), 7.89 (s, 1H), 7.82 (m, 2H), 7.41-7.26 (m, 4H), 7.17 (m, 2H), 7.04 (m, 1H), 4.10 (s, 2H). ^{13}C NMR (DMSO-d_6): 162.5 (242 Hz), 156.8, 155.4, 141.1 (7 Hz), 136.4, 131.4, 130.4 (8 Hz), 129.1, 127.7, 125.7 (3 Hz), 124.9, 123.1, 116.4 (21 Hz), 113.4 (21 Hz), 38.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O$: 281.1090; found, 281.1650.



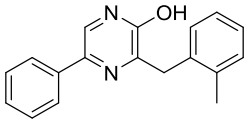
3-(2-Chlorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,5*} (EC31094-089-3): Obtained as a powder (2.06 g, 68%) after a chromatography over silica gel (dichloromethane / ethanol 98:2) and a dispersion in a boiling mixture of toluene and cyclohexane. ^{1}H NMR (DMSO-d_6): 12.47 (bs, 1H), 7.90 (s, 1H), 7.70 (m, 2H), 7.46 (m, 1H), 7.32 (m, 5H), 7.25 (m, 1H), 4.22 (s, 2H). ^{13}C NMR (DMSO-d_6): 156.1, 155.3, 136.4, 136.3, 134.1, 132.2, 131.2, 129.5, 129.0, 128.7, 127.6, 127.4, 124.8, 122.7, 36.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}ClN_2O$: 297.0795; found, 297.0795.



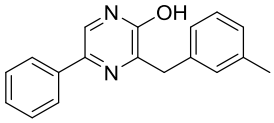
5-Phenyl-3-(2-(trifluoromethyl)benzyl)pyrazin-2-ol **19**{*1,8*} (YJ 33067-105-1): This compound was obtained as a powder (2.99 g, 60%) after two dispersions in boiling cyclohexane (100 mL each). ^{1}H NMR (DMSO-d_6): 12.49 (s, 1H), 7.90 (s, 1H), 7.3 (m, 1H), 7.66 - 7.61 (m, 3H), 7.48 (m, 2H), 7.24 (m, 2H), 7.20 (m, 1H), 4.29 (s, 2H). ^{13}C NMR (DMSO-d_6): 156.6, 155.2, 136.7 (2 Hz), 136.3, 133.1, 132.5, 131.1, 129.0 128.1 (30 Hz), 127.6, 127.4, 126.2 (6 Hz), 125.0 (273 Hz), 122.7, 35.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{14}F_3N_2O$: 331.1058; found, 331.1054.



5-Phenyl-3-(3-(trifluoromethyl)benzyl)pyrazin-2-ol **19**{*1,9*} (YJ 33067-107-3): Despite our efforts, was obtained as a solid (5.50 g) still containing some unidentified material out of which only the ^{1}H NMR could be properly described. ^{1}H NMR (DMSO-d_6): 12.47 (s, 1H), 7.90 (s, 1H), 7.81 (m, 2H), 7.74 (s, 1H), 7.65 (m, 1H), 7.55 (m, 2H), 7.39 (m, 2H), 7.26 (m, 1H), 4.19 (s, 2H). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{14}F_3N_2O$: 331.1058; found, 331.1053. This compound was then directly used in the next step.

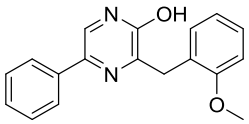


3-(2-Methylbenzyl)-5-phenylpyrazin-2-ol **19**{*1,11*} (YJ31070-183-3): This compound was obtained as a powder (5.65 g, 88%) after a chromatography over silica gel (dichloromethane - ethanol 99/1 – 98/2). ^{1}H NMR (DMSO-d_6) 12.40 (s, 1H), 7.87 (s, 1H), 7.77 (m, 1H), 7.37 (m, 2H), 7.24 (m, 2H), 7.16 (m, 1H), 7.10 (m, 1H), 4.08 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (DMSO-d_6): 157.3, 155.4, 137.0, 136.8, 136.4, 131.3, 130.3, 130.2, 129.0, 127.6, 126.8, 126.0, 124.8, 122.7, 36.6, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2ON$: 277.1341; found, 277.1392.

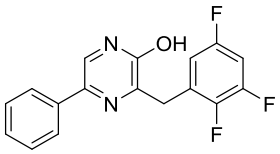


3-(3-Methylbenzyl)-5-phenylpyrazin-2-ol **19**{*1,12*} (YJ31070-185-3): This compound was obtained as a powder (5.52 g, 88%) after a chromatography over silica gel (dichloromethane - ethanol 99/1 – 98/2) and a sample (0.29 g)

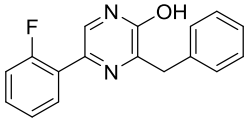
was recrystallized in a mixture of toluene and cyclohexane for analytical purposes (0.27 g). ^{1}H NMR (DMSO-d_6) 12.38 (s, 1H), 7.87 (s, 1H), 7.84 (m, 2H), 7.40 (m, 2H), 7.28 (m, 1H), 7.16 (m, 3H), 7.01 (m, 1H), 4.03 (s, 2H), 2.26 (s, 3H). ^{13}C NMR (DMSO-d_6): 157.4, 155.4, 138.3, 137.7, 136.4, 131.4, 130.1, 129.1, 128.6, 127.7, 127.3, 126.6, 124.9, 122.9, 39.2, 21.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2ON$: 277.1341; found, 277.1395.



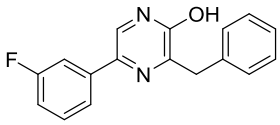
3-(2-Methoxybenzyl)-5-phenylpyrazin-2-ol **19**{*1,14*} (YJ31070-106-1): Obtained as a white powder (1.7 g, 30%) after a chromatography over silica gel (dichloromethane / ethanol 98.5:1.5 to 97.5:2.5) and a dispersion in a boiling mixture of cyclohexane and toluene. ^{1}H NMR (DMSO-d_6) 12.35 (s (br), 1H), 7.86 (s, 1H), 7.73 (m, 2H), 7.34 (m, 2H), 7.23 (m, 2H), 7.11 (m, 1H), 6.98 (m, 1H), 6.87 (m, 1H), 4.04 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (DMSO-d_6): 157.7, 157.3, 155.5, 136.5, 131.2, 130.6, 129.0, 128.0, 127.6, 126.6, 124.8, 122.4, 111.2, 55.9, 33.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found, 293.1280.



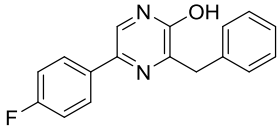
5-Phenyl-3-(2,3,5-trifluorobenzyl)pyrazin-2-ol **19**{*1,26*} (YJ 33067-103-2): Obtained as a powder (1.72 g, 90%) after a dispersion in boiling cyclohexane. ^{1}H NMR (DMSO-d_6): 12.54 (s, 1H), 7.92 (s, 1H), 7.70 (m, 2H), 7.43 - 7.34 (m, 3H), 7.25 (m, 1H), 7.11 (m, 1H), 4.17 (s, 2H). ^{13}C NMR (DMSO-d_6): 157.2 (242, 12 and 3 Hz), 155.2, 155.0, 149.9 (247 and 14 Hz), 145.7 (242, 12 and 4 Hz), 136.2, 131.2, 129.0, 128.9 (br), 127.7, 113.7 (3 and 24 Hz), 104.4 (21 and 28 Hz), 32.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}F_3N_2O$: 317.0902; found, 317.0910.



3-Benzyl-5-(2-fluorophenyl)pyrazin-2-ol **19**{*2,1*} (YJ31134-027-2): This compound was as a white powder (3.38 g, 62%) after a chromatography over silica gel (dichloromethane - ethanol 975/25) and a recrystallization in toluene. ^{1}H NMR (DMSO-d_6) 12.38 (s, 1H), 7.88 (m, 1H), 7.68 (s, 1H), 7.28 (m, 8H), 4.06 (s, 2H). ^{13}C NMR (DMSO-d_6): 159.5 (246 Hz), 158.1, 155.0, 138.2, 129.7 (9 Hz), 129.6, 129.4 (3 Hz), 129.3, 128.7, 128.6, 126.7, 126.4 (14 Hz), 125.1 (3 Hz), 116.5 (23 Hz), 39.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O$: 281.1090; found, 281.1050.

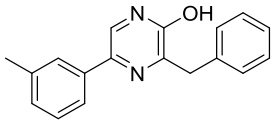


3-Benzyl-5-(3-fluorophenyl)pyrazin-2-ol **19**{*3,1*} (YJ31067-011-2): This compound was obtained as a 90% pure orange powder (1.69 g) after a chromatography over silica gel (dichloromethane – ethanol 98/2). ^{1}H NMR (DMSO-d_6) 12.50 (s, 1H), 7.98 (s, 1H), 7.69 (m, 1H), 7.64 (m, 1H), 7.42-7.17 (m, 6H), 7.08 (m, 1H), 4.07 (s, 2H). ^{13}C NMR (DMSO-d_6): 163.2 (244 Hz), 157.6, 155.5, 139.1 (8 Hz), 138.2, 131.0 (8 Hz), 129.6, 129.0, 128.7, 126.7, 123.7, 120.8 (3 Hz), 114.2 (22 Hz), 111.4 (22 Hz), 39.3. MS (*m/z*) = 281.

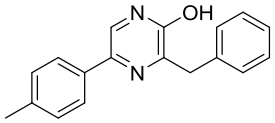


3-Benzyl-5-(4-fluorophenyl)pyrazin-2-ol **19**{*4,1*} (YJ29589-041-3): This compound was as a white powder (0.43 g, 72%) after a chromatography over silica gel (cyclohexane – ethyl acetate 1/1). ^{1}H NMR (DMSO-d_6) 12.4 (s,

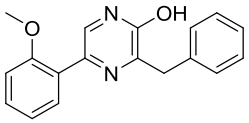
1H), 7.87 (m, 3H), 7.22 (m, 7H), 4.06 (s, 2H). ^{13}C NMR (DMSO-d_6): 162.2 (244 Hz), 157.4, 155.3, 138.3, 132.9 (9 Hz), 130.6, 129.5, 128.7, 128.7, 126.9 (8 Hz), 126.7, 122.9, 115.8 (21 Hz), 39.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O$: 281.1090; found, 281.1030.



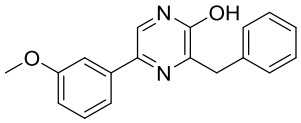
3-Benzyl-5-(m-tolyl)pyrazin-2-ol **19**{*5,1*} (YJ30367-063-3): A crude fraction was obtained by a filtration of the insoluble material formed in the course of the reaction followed by washing it with toluene. An analytical sample was obtained by a recrystallization in toluene of the concentrated filtrate. ^{1}H NMR (DMSO-d_6) 12.35 (s, 1H), 7.85 (s, 1H), 7.66 (m, 1H), 7.62 (m, 2H), 7.33-7.17 (m, 5H), 7.08 (m, 1H), 4.07 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (DMSO-d_6): 157.3, 155.4, 138.4, 138.1, 136.4, 131.6, 129.5, 129.0, 128.7, 128.3, 126.6, 125.5, 122.9, 122.1, 39.3, 21.6. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{16}N_2ONa$: 299.1160; found, 299.1172.



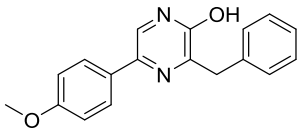
3-Benzyl-5-(p-tolyl)pyrazin-2-ol **19**{*6,1*} (YJ30367-029-2): A pure sample (1.48 g) of this compound was obtained as a white solid by a dispersion of the crude mixture in dichloromethane. The concentrated filtrate and most of this solid were used directly in the next step. ^{1}H NMR (DMSO-d_6) 12.35 (s, 1H), 7.82 (s, 1H), 7.72 (m, 2H), 7.40-7.17 (m, 7H), 4.06 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (DMSO-d_6): 157.2, 155.4, 138.4, 136.9, 133.7, 131.7, 129.6, 129.5, 128.7, 126.6, 124.9, 122.4, 39.3, 21.2. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{16}N_2ONa$: 299.1160; found, 299.1177.



3-Benzyl-5-(2-methoxyphenyl)pyrazin-2-ol **19**{*7,1*} (YJ31134-039-2): This compound was obtained as a powder (0.54 g, 79%) after a chromatography over silica gel (dichloromethane - ethanol 97/3). ^{1}H NMR ($CDCl_3$): 13.33 (s(br), 1H), 8.05 (s, 1H), 8.02 (dd, 1H, *J* = 7.7, 1.7 Hz), 7.51 – 7.42 (m, 2H), 7.37 – 7.28 (m, 3H), 7.25 – 7.19 (m, 1H), 7.08 (td, 1H, *J* = 7.7, 1.0 Hz), 7.02 – 6.94 (m, 1H), 4.27 (s, 2H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$): 157.1, 156.8, 156.5, 137.8, 131.2, 129.6 (2 signals), 129.1, 128.4, 126.5, 125.2, 124.6, 121.2, 111.3, 55.6, 39.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2$, 293.1290; found, 293.1253.

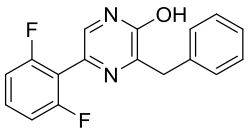


3-Benzyl-5-(3-methoxyphenyl)pyrazin-2-ol **19**{*8,1*} (YJ30367-079-1): An analytical sample of this compound was obtained as a white powder after a recrystallization of the resulting residue in toluene. ^{1}H NMR (DMSO-d_6) 12.41 (s, 1H), 7.90 (s, 1H), 7.41 (m, 8H), 6.85 (m, 1H), 4.07 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (DMSO-d_6): 160.1, 157.3, 155.5, 138.3, 137.9, 131.1, 130.1, 129.7, 128.6, 126.6, 123.1, 117.2, 113.4, 110.4, 55.5, 39.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found, 293.1279.



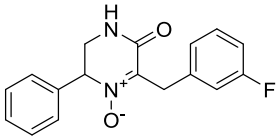
3-Benzyl-5-(4-methoxyphenyl)pyrazin-2-ol **19**{*9,1*} (YJ29793-047-3): This compound was obtained as a powder (0.9 g, 45%) after a chromatography over silica gel (dichloromethane - ethanol 98/2). ^{1}H NMR (DMSO-d_6) 12.30 (s, 1H), 7.77 (m, 3H), 7.30 (m, 2H), 7.27 (m, 2H), 7.21 (m, 1H), 6.96 (m, 2H), 4.06 (s, 2H), 3.77 (s, 3H). ^{13}C NMR

(DMSO-d_6): 159.2, 157.0, 155.3, 138.5, 131.8, 129.5, 129.0, 128.7, 126.6, 126.3, 121.9, 114.5, 55.6, 39.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1290; found, 293.1284.

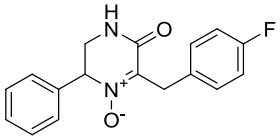


3-Benzyl-5-(2,6-difluorophenyl)pyrazin-2-ol **19**{*10,1*} (MM34284-020-3): This compound was obtained as a white powder (1.45 g, 83%) after a chromatography over silica gel (dichloromethane - ethanol 99/1). ^{1}H NMR (DMSO-d_6): 12.49 (s, 1H), 7.57 (s, 1H), 7.47 (m, 1H), 7.27 (m, 4H), 7.19 (m, 3H), 4.01 (s, 2H). ^{13}C NMR (DMSO-d_6): 162.4 (7, 244 Hz), 158.0, 138.1, 130.8 (10 Hz), 129.4, 128.7, 128.3, 126.7, 122.2, 114.8 (18 Hz), 112.3 (7, 18 Hz), 39.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}F_2N_2O$: 299.0996; found, 299.0994.

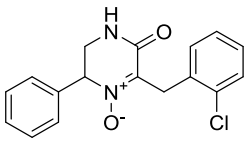
General preparation of 5-oxo-2,3,4,5-tetrahydropyrazine 1-oxides 18 via steps v. The considered piperazin-2-one **17** (0.015 mol) was dissolved in ethylacetate (80 mL) and the solution cooled to 0 °C with an ice bath. A 38% solution of peracetic acid in acetic acid (5.3 mL, 0.03 mol) was added (note 1 and 2). The ice bath was removed and the solution stirred overnight (note 3). This was concentrated to dryness and the residue purified as described below (note 3). Note 1: when starting from crude piperazin-2-one **17**, the amount of peracetic acid added was calculated as if the starting material was pure and was thus certainly larger than 2.0 equivalents but this had no ill effect on the reaction yield as 5-oxo-2,3,4,5-tetrahydropyrazine 1-oxides are quite resilient to further oxidation under these conditions. Note 2: since the title of a 36% peracetic acid solution in acetic acid steadily drops over time the use of aged solutions should take this into account to achieve a complete transformation. Note 3: the resulting 5-oxo-2,3,4,5-tetrahydropyrazine 1-oxide **18** can sometime precipitate in the course of the reaction. Note 4: initially, when possible, the resulting solutions were washed with water. Later on, we found out that most of the peracetic acid and acetic acid could be removed under vacuum.



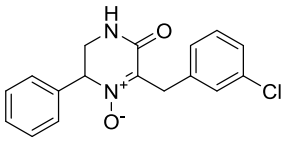
6-(3-fluorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,3*} (YJ 31068-153-3): Obtained as a solid (6.70 g, 48% from nitrostyrene) after a chromatography over silica gel (cyclohexane - ethyl acetate 2/3). ^{1}H NMR (DMSO-d_6): 8.36 (d (br), 1H, J = 3.7 Hz), 7.35-7.30 (m, 4H), 7.21-7.01 (m, 5H), 5.27 (t(br), 1H, *J* = 3.9 Hz), 3.99 (m, 3H), 3.57 (m, 1H). ^{13}C NMR (DMSO-d_6): 162.5 (242 Hz), 160.6, 140.6, 139.9 (8 Hz), 135.9, 130.4 (8 Hz), 128.9, 128.8, 127.1, 125.4 (3 Hz), 116.1 (21 Hz), 113.6 (21 Hz), 71.5, 42.6, 30.0. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{15}FN_2O_2Na$: 321.1015; found, 321.1015.



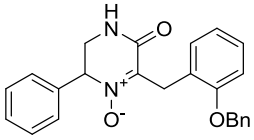
6-(4-Fluorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,4*} (YJ 33069-161-2): Obtained as a white powder (1.94 g, 36% from nitrostyrene) after a chromatography over silica gel (cyclohexane - ethyl acetate 3/2 to 1/1). ^{1}H NMR (DMSO-d_6) 8.32 (s (br), 1H), 7.35 (m, 5H), 7.16 (m, 2H), 7.10 (m, 2H), 5.25 (t(br), 1H, *J* = 3.7 Hz), 3.97 (m, 1H), 3.95 (s, 2H), 3.55 (ddd, 1H, *J* = 3.6, 4.7, 13.9 Hz). ^{13}C NMR (DMSO-d_6): 161.5 (242 Hz), 160.7, 141.0, 135.9, 133.2 (3 Hz), 131.3 (8 Hz), 128.9, 128.8, 127.0, 115.3 (21 Hz), 71.5, 42.7, 29.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{16}FN_2O_2$: 299.1196; found, 299.1202.



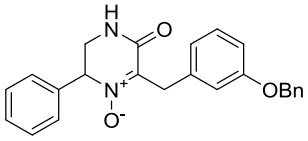
6-(2-Chlorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,5*} (YJ 33069-159-1): Obtained as a white powder (2.92 g, 50% from nitrostyrene) after a chromatography over silica gel (cyclohexane - ethyl acetate 3/2 to 1/1). ^{1}H NMR (DMSO-d_6) 8.41 (s (br), 1H), 7.44 - 7.37 (m, 4H), 7.31 (m, 2H), 7.24 (m, 2H), 7.17 (m, 1H), 5.31 (t(br), 1H, J = 4.0 Hz), 4.11 (d, 1H, J = 15.0 Hz), 4.02 (m, 2H), 3.64 (dt, 1H, J = 14.0, 4.1 Hz). ^{13}C NMR (DMSO-d_6): 160.6, 139.9, 135.7, 134.6, 133.4, 130.1, 129.6, 129.0, 128.9, 128.5, 127.5, 127.3, 71.8, 42.6, 28.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{16}ClN_2O_2$: 315.0900; found, 315.0923.



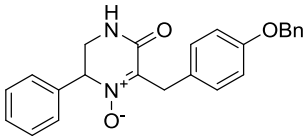
6-(3-Chlorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,6*} (YJ 33069-187-2): Obtained as a glass (3.12 g, 53% from nitrostyrene) after a chromatography over silica gel (cyclohexane - ethyl acetate 2/3). ^{1}H NMR (DMSO-d_6): 7.42 (s (br), 1H), 7.44 - 7.37 (m, 4H), 7.19 (m, 4H), 7.01 (s (br), 1H), 5.13 (t (br), J = 4.8 Hz), 4.08 (m, 2H), 4.02 (m, 1H), 3.68 (dt, 1H, J = 13.5, 4.2 Hz). ^{13}C NMR (DMSO-d_6): 161.1, 140.9, 137.9, 134.1, 134.0, 129.6, 129.5, 129.2, 129.0, 127.9, 127.0, 126.7, 71.9, 43.0, 30.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{16}ClN_2O_2$: 315.0900; found, 315.0892.



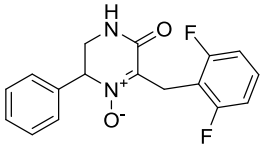
6-(2-(benzyloxy)benzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,17*} (RB32489-045-3): This compound was obtained as a pale yellow oil (3.51 g, 36% from nitrostyrene) after two chromatography over silica gel (cyclohexane – ethyl acetate 2/3) and (dichloromethane - ethanol 98/2). ^{1}H ($CDCl_3$): 7.45 – 7.29 (m, 8H), 7.22 (m, 3H), 7.09 (m, 1H), 7.04 (m, 1H), 6.85 (m, 1H), 5.10 (m, 1H), 5.02 (s, 2H), 4.11 (m, 2H), 3.95 (dd, 1H, J = 13.5, 5.0 Hz), 3.60 (dd, 1H, J = 13.5, 3.8 Hz). ^{13}C ($CDCl_3$): 161.2, 158.9, 141.5, 137.6, 137.1, 134.2, 129.4, 129.1, 129.0, 128.5, 127.9, 127.6, 126.7, 122.2, 115.9, 113.4, 71.8, 69.9, 42.9, 30.2. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{22}N_2O_3Na$: 409.1528; found, 409.1524.



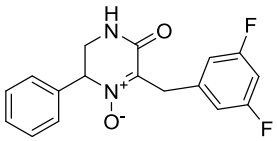
6-(3-(benzyloxy)benzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,18*} (RB32489-043-3): This compound was obtained as a pale yellow oil (4.49 g, 24% from nitrostyrene) after two chromatography over silica gel (cyclohexane – ethyl acetate 2/3) and (dichloromethane - ethanol 98/2). ^{1}H ($CDCl_3$): 7.49 (m, 2H), 7.40 – 7.16 (m, 10H), 6.91 (m, 2H), 6.28 (m, 1H), 5.09 (s, 2H), 5.02 (t, 1H, J = 3.9 Hz), 4.30 (d, 1H, J = 14.7 Hz), 4.12 (d, 1H, J = 14.7 Hz), 3.81 (dd, 1H, J = 13.5, 4.8 Hz), 3.48 (dt, 1H, , J = 13.3, 8.0, 3.7 Hz). ^{13}C ($CDCl_3$): 161.0, 156.5, 141.9, 137.2, 134.3, 130.3, 129.0, 128.9, 128.4, 127.9, 127.8, 127.7, 126.8, 125.0, 120.9, 111.8, 72.0, 70.3, 42.9, 26.1. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{22}N_2O_3Na$: 409.1528; found, 409.1526.



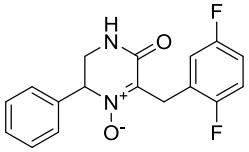
6-(4-(Benzyloxy)benzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,19*} (YJ 31776-033-2): Obtained as a white powder (3.40 g, 53% from nitrostyrene) after a chromatography over silica gel (cyclohexane - ethyl acetate 2/3). ^{1}H NMR ($CDCl_3$) 7.46 - 7.28 (m, 10H), 7.16 (m, 2H), 6.90 (m, 2H), 6.77 (s (br), 1H), 5.12 (t (br), J = 4.2 Hz), 5.05 (s, 2H), 4.06 (m, 2H), 4.01 (dd, 1H, J = 5.3, 13.3 Hz), 3.68 (dt, 1H, J = 4.0, 13.3 Hz). ^{13}C NMR ($CDCl_3$): 161.2, 157.7, 142.0, 137.2, 130.7, 129.1, 129.0, 128.5, 128.4, 127.9, 127.4, 126.6, 114.8, 71.8, 70.0, 43.1, 29.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$: 387.1709; found, 387.1710.



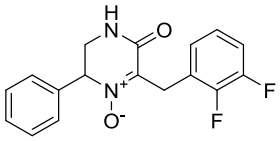
6-(2,6-Difluorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,21*} (EC31095-167-3): Obtained as a white solid (8.58 g, 30% from nitrostyrene) after chromatography over silica gel (cyclohexane–ethyl acetate 1:1). ^{1}H NMR (DMSO-d_6): 8.32 (d, 1H, J = 4.4 Hz), 7.38 (m, 3H), 7.28 (m, 3H), 7.03 (m, 2H), 5.24 (t, 1H, J = 4.1 Hz), 4.03 (s, 2H), 3.90 (ddd, 1H, J = 13.9, 4.8, 1.6 Hz), 3.55 (ddd, 1H, J = 13.9, 4.7, 3.4 Hz). ^{13}C NMR (DMSO-d_6): 161.5 (247, 8 Hz), 160.1, 139.3, 135.7, 129.0, 128.9, 128.8, 127.1, 112.8 (19 Hz), 111.7 (br), 71.8, 42.8, 18.9 (3 Hz). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{15}F_2N_2O_2$: 317.1102; found, 317.1105.



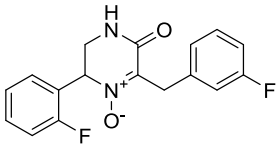
6-(3,5-difluorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,22*} (EC31095-167-3): Obtained as a white solid (4.82 g, 17% from nitrostyrene) after chromatography over silica gel (cyclohexane–ethyl acetate 1:1 to 1:2). ^{1}H NMR (DMSO-d_6): 8.39 (d, 1H, J = 4.3 Hz), 7.35 (m, 3H), 7.20 (m, 2H), 7.07 (tt, 1H, J = 9.5, 2.4 Hz), 6.99 (m, 2H), 5.29 (t, 1H, J = 4.2 Hz), 4.00 (m, 3H), 3.60 (ddd, 1H, J = 13.9, 4.6, 3.7 Hz). ^{13}C NMR (DMSO-d_6): 162.6 (246, 13 Hz), 160.5, 141.5 (10 Hz), 140.0, 135.8, 128.9, 128.9, 127.1, 112.5 (br), 102.4 (26 Hz), 71.5, 42.6, 30.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{15}F_2N_2O_2$: 317.1102; found, 317.1100.



6-(2,5-difluorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,23*} (YJ 31069-005-4): Obtained as a white solid (0.49 g, 11% from nitrostyrene) after chromatography over silica gel (cyclohexane–ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$) 7.38 (m, 3H), 7.26 (m, 2H), 7.21 (m, 1H), 6.98 (m, 2H), 6.88 (m, 1H), 5.15 (t (br), 1H, J = 4.8 Hz), 4.19 (d, 1H, J = 14.4 Hz), 4.06 (m, 2H), 3.73 (m, 1H). ^{13}C NMR ($CDCl_3$): 161.1, 158.5 (242 and 2 Hz), 157.0 (242 and 2 Hz), 154.4, 140.0, 133.9, 129.3, 129.0, 126.9, 126.0, 124.6 (18 and 8 Hz), 117.2 (21 and 4 Hz), 116.1 (25 and 8 Hz), 114.6 (24 and 9 Hz), 72.1, 42.9, 24.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{15}F_2N_2O_2$: 317.1102; found, 317.1101.

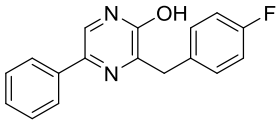


6-(2,3-difluorobenzyl)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*1,24*} (YJ 31069-011-4): Obtained as a white solid (2.56 g, 46% from nitrostyrene) after chromatography over silica gel (cyclohexane–ethyl acetate 1:2). ^{1}H NMR ($CDCl_3$) 7.38 (m, 3H), 7.26 (m, 2H), 7.11 - 6.93 (m, 4H), 5.15 (t (br), 1H, J = 4.5 Hz), 4.19 (d, 1H, J = 14.6 Hz), 4.06 (m, 2H), 3.73 (m, 1H). ^{13}C NMR ($CDCl_3$): 161.1, 150.7 (248 and 13 Hz), 149.2 (248 and 13 Hz), 140.0, 133.9, 129.3, 129.0, 126.8, 125.6 (22 and 6 Hz), 123.7 (7 and 5 Hz), 115.7, 115.5, 72.1, 42.9, 23.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{15}F_2N_2O_2$: 317.1102; found, 317.1100. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{15}F_2N_2O_2$: 317.1102; found, 317.1101.

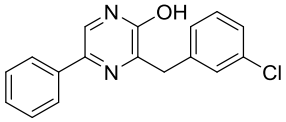


6-(3-fluorobenzyl)-2-(2-fluorophenyl)-5-oxo-2,3,4,5-tetrahydropyrazine 1-oxide **18**{*2,3*} (YJ 31068-149-2): Obtained as a solid (2.68 g, 50% from the nitrostyrene) after a chromatography over silica gel (cyclohexane - ethyl acetate 3/2 to 1/1). ^{1}H NMR (DMSO-d_6): 8.45 (s (br), 1H), 7.43 (m, 1H), 7.30 (m, 2H), 7.18 -7.01 (m, 5H), 5.55 (t(br), 1H, J = 5.0 Hz), 3.99 (m, 2H), 3.91 (m, 1H), 3.61 (m, 1H). ^{13}C NMR (DMSO-d_6): 162.5 (240 Hz), 160.6, 160.5 (247 Hz), 140.8, 139.8 (8 Hz), 131.3 (8 Hz), 130.5 (8 Hz), 129.1 (3 Hz), 125.4 (3 Hz), 125.0 (3 Hz), 122.5 (13 Hz), 116.3 (21 Hz), 116.1 (21 Hz), 113.6 (21 Hz), 66.8, 41.7, 30.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{15}F_2N_2O_2$: 317.1102; found, 317.1107.

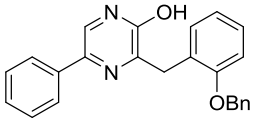
General preparation of pyrazin-2-ols 19 by dehydration of 5-oxo-2,3,4,5-tetrahydropyrazine 1-oxides 18 via step vi. The considered 5-oxo-2,3,4,5-tetrahydropyrazine 1-oxide **18** (0.09 mol) and sodium hydroxide (10.8 g, 0.27 mol) were dispersed in ethanol (40 mL) and stirred at 65 °C for one hour. This was diluted in water (200 mL) and made acid with 1N hydrochloric acid. The resulting precipitate was filtrated, washed with water and dried under vaccum at 60 °C to yield the hydroxypyrazine **19** as described below.



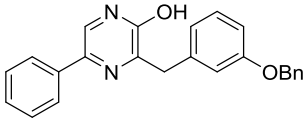
3-(4-Fluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,4*} (YJ 33069-169-2): Obtained as a white powder (1.50 g, 93%). ^{1}H NMR (CDCl3) 12.43 (s (br), 1H), 7.88 (s, 1H), 7.83 (m, 2H), 7.38 (m, 4H), 7.29 (m, 1H), 7.11 (m, 2H), 4.06 (s, 2H). ^{13}C NMR (CDCl3): 161.4 (242 Hz), 157.2, 155.4, 136.4, 134.4 (3 Hz), 131.4 (8 Hz), 129.0, 127.7, 124.9, 123.0, 115.3 (21 Hz), 38.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O_2$: 281.1085; found, 281.1096.



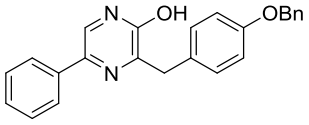
3-(3-Chlorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,6*} (YJ 33069-189-1): Obtained as a white powder (2.60 g, 88%). ^{1}H NMR (DMSO-d6) 12.46 (s (br), 1H), 7.90 (s, 1H), 7.83 (m, 2H), 7.42 - 7.26 (m, 6H), 4.09 (s, 2H). ^{13}C NMR (DMSO-d6): 156.7, 155.4, 140.8, 136.3, 133.2, 131.4, 130.5, 129.5, 129.1, 128.4, 127.7, 126.7, 124.9, 123.1, 38.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{14}ClN_2O_2$: 297.0795; found, 297.0794.



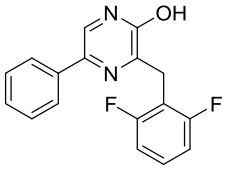
3-(2-(Benzyloxy)benzyl)-5-phenylpyrazin-2-ol **19**{*1,17*} (RB32489-049-1): Obtained as a white powder (3.01 g, 90%). ^{1}H NMR (DMSO-d_6): 12.41 (s (br), 1H), 7.89 (s, 1H), 7.85 (m, 2H), 7.43 – 7.26 (m, 8H), 7.21 (t, 1H, J = 7.9 Hz), 7.01 (m, 1H), 6.93 (m, 1H), 6.85 (m, 1H), 5.06 (s, 2H), 4.05 (s, 2H). ^{13}C NMR (DMSO-d_6): 158.8, 157.2, 155.4, 139.9, 137.6, 136.4, 131.5, 129.7, 129.1, 128.8, 128.2, 128.1, 127.7, 124.9, 123.0, 122.1, 116.2, 112.9, 69.6, 39.2. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{20}N_2O_2Na$: 391.1422; found, 391.1422.



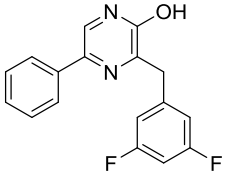
3-(2-(Benzyloxy)benzyl)-5-phenylpyrazin-2-ol **19**{*1,18*} (RB32489-047-1): Obtained as a white powder (4.00 g, 94%). ^{1}H NMR (DMSO-d_6): 12.36 (s (br), 1H), 7.86 (s, 1H), 7.72 (m, 2H), 7.37 – 7.18 (m, 10H), 7.03 (m, 1H), 6.90 (m, 1H), 5.10 (s, 2H), 4.13 (s, 2H). ^{13}C NMR (DMSO-d_6): 157.4, 156.7, 155.5, 137.8, 136.5, 136.4, 131.1, 129.0, 128.7, 128.0, 127.9, 127.5, 127.4, 127.0, 124.8, 122.4, 120.8, 112.5, 69.6, 33.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_2$: 369.1603; found, 369.1605.



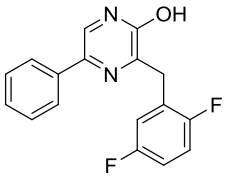
3-(4-(Benzyloxy)benzyl)-5-phenylpyrazin-2-ol **19**{*1,19*} (YJ 31776-035-1): Obtained as a white powder (2.88 g, 93%). ^{1}H NMR (DMSO-d_6): 12.36 (s (br), 1H), 7.86 (s, 1H), 7.84 (m, 2H), 7.39 (m, 6H), 7.28 (m, 4H), 6.93 (m, 2H), 5.06 (s, 2H), 4.00 (s, 2H). ^{13}C NMR (DMSO-d_6): 157.7, 157.4, 155.4, 137.7, 136.5, 131.4, 130.6, 130.5, 129.1, 128.9, 128.2, 128.0, 127.7, 124.9, 122.8, 115.1, 69.7, 31.1. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{20}N_2O_2Na$: 391.1422; found, 391.1421.



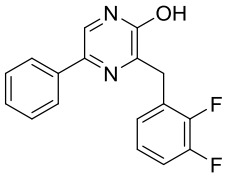
3-(2,6-Difluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,21*} (EC31095-171-1): Obtained as a white powder (8.27 g, 90%). ^{1}H NMR (DMSO-d6): 12.51 (s, 1H), 7.90 (s, 1H), 7.63 (m, 2H), 7.40 (m, 1H), 7.31 (m, 2H), 7.17 (m, 4H), 4.14 (s, 2H). ^{13}C NMR (DMSO-d6): 161.7 (246, 9 Hz), 155.2, 154.8, 136.3, 131.0, 129.3 (10 Hz), 129.0, 127.7, 124.6, 122.8, 113.7 (20 Hz), 111.5, 26.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}F_2N_2O$: 299.0996; found, 299.1000.



3-(3,5-difluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,22*} (EC31095-169-1): Obtained as a white powder (3.91 g, 86%). ^{1}H NMR (DMSO-d6): 12.50 (s, 1H), 7.91 (s, 1H), 7.81 (m, 2H), 7.39 (m, 2H), 7.28 (m, 1H), 7.07 (m, 3H), 4.11 (s, 2H). ^{13}C NMR (DMSO-d6): 162.6 (245, 13 Hz), 156.2, 155.4, 142.8 (10 Hz), 136.3, 131.4, 129.1, 127.7, 124.9, 123.3, 112.8, 102.2 (26 Hz), 38.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}F_2N_2O$: 299.0996; found, 299.1010.

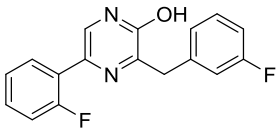


3-(2,5-difluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,23*} (YJ31069-007-1): Obtained as a white powder (0.37 g, 83%). ^{1}H NMR (DMSO-d_6) 12.50 (s(br), 1H), 7.91 (s, 1H), 7.72 (m, 2H), 7.35 (m, 2H), 7.24 (m, 3H), 7.14 (m, 1H), 4.11 (s, 2H). ^{13}C NMR (DMSO-d_6): 158.5 (240 and 2 Hz), 157.2 (240 and 2 Hz), 155.5, 155.2, 136.3, 131.2, 129.0, 127.7, 127.2 (8 Hz), 129.6 (19 and 9 Hz), 124.7, 123.0, 118.4 (25 and 5 Hz), 116.7 (25 and 9 Hz), 115.1 (24 and 9 Hz), 32.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}F_2N_2O$: 299.0996; found, 299.1001.



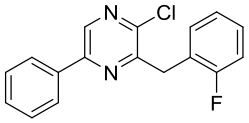
3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-ol **19**{*1,24*} (YJ31069-013-1): Obtained as a white powder (2.05 g, 85%). ^{1}H NMR (DMSO-d_6): 12.50 (s, 1H), 7.91 (s, 1H), 7.73 (m, 2H), 7.24 (m, 6H), 4.17 (s, 2H). ^{13}C NMR (DMSO-d_6): 155.5, 155.2, 150.2 (245, 13 Hz), 148.9 (245, 13 Hz), 136.3, 131.3, 129.0, 127.8 (13 Hz), 127.7, 127.2

(3 Hz), 124.7 (2 signals), 123.0, 115.9 (17 Hz), 32.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}F_2N_2O$: 299.0996; found, 299.1006.

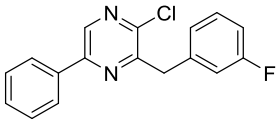


3-(3-Fluorobenzyl)-5-(2-fluorophenyl)pyrazin-2-ol **19**{*2,3*} (YJ 31068-157-1): Obtained as a white powder (2.14 g, 90%). ^{1}H NMR (DMSO-d_6) 12.44 (s(br), 1H), 7.85 (m, 1H), 7.43 (m, 1H), 7.69 (s, 1H), 7.34 (m, 2H), 7.26 (m, 2H), 7.16 (m, 1H), 7.04 (m, 1H), 4.09 (s, 2H). ^{13}C NMR (DMSO-d_6): 162.5 (240 Hz), 159.5 (246 Hz), 157.5, 155.0, 140.9 (8 Hz), 130.5 (8 Hz), 129.6 (8 Hz), 129.4 (3 Hz), 126.6, 126.5, 125.7 (3 Hz), 125.1 (3 Hz), 124.0 (13 Hz), 116.5 (21 Hz), 116.3 (21 Hz), 113.5 (21 Hz), 38.9. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{12}F_2N_2O$: 321.0815; found, 321.0810.

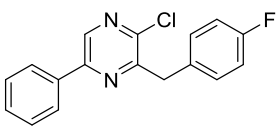
General procedure for the synthesis 2-chloropyrazines 20 via step vii. Under a calcium-protected atmosphere, the considered 2-hydroxypyrazine **19** (0.02 mol) was dispersed in phenylphosphonic dichloride (10 mL) and the suspension was heated at 100 °C for the indicated time. The resulting solution was diluted in ethyl acetate and poured onto an excess of crushed ice and stirred for 15 min (note 1). This was made basic with 22% ammonia and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The resulting residue was purified has described below. Note 1: stirring for a shorter time leads to the risk of generating a lot of an insoluble substance (probably *P*-phenylphosphonamidic acid) occurring upon the addition of ammonia on not yet fully hydrolyzed reactant.



2-Chloro-3-(2-fluorobenzyl)-5-phenylpyrazine **20**{*1,2*} (GG30532-114-3): Obtained as a white solid (3.01 g, 79%) after heating for 10 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 94/6). ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): 8.70 (s, 1H), 7.98-7.94 (m, 2H), 7.53-7.45 (m, 3H), 7.31-7.25 (m, 2H), 7.14-7.09 (m, 2H), 4.44 (s, 2H). ^{13}C NMR ($CDCl_3$): 161.1 (247 Hz), 152.5, 150.2, 146.8, 138.6, 135.2, 131.1 (4.2 Hz), 130.0, 129.0, 128.6 (8.2 Hz), 126.8, 124.1 (15.8 Hz), 124.0 (3.4 Hz), 115.4 (22.0 Hz), 34.2 (3.0 Hz). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}ClFN_2$, 299.0751; found, 299.0749.

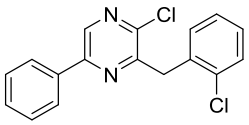


2-Chloro-3-(3-fluorobenzyl)-5-phenylpyrazine **20**{*1,3*} (YJ31067-131-2): Obtained as a white solid (0.71 g, 38% from 3-(3-fluorobenzyl)-5-phenylpiperazin-2-one) after heating for 12 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.69 (s, 1H), 8.03 (m, 2H), 7.52 (m, 3H), 7.29 (m, 1H), 7.18 (m, 1H), 7.12 (m, 1H), 6.96 (m, 1H), 4.39 (s, 2H). ^{13}C NMR ($CDCl_3$): 162.9 (243 Hz), 152.9, 150.5, 146.8, 139.4 (7Hz), 138.9, 135.2, 130.1, 129.9 (8 Hz), 129.1, 126.9, 124.8 (2 Hz), 116.1 (21 Hz), 113.7 (21 Hz), 40.9 (2 Hz). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}ClFN_2$, 299.0751; found, 299.0749.

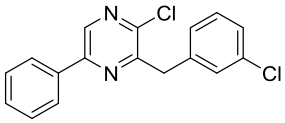


2-Chloro-3-(4-fluorobenzyl)-5-phenylpyrazine **20**{*1,4*} (YJ31067-133-2): Obtained as a solid (1.2 g, 77%) after heating for 10 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.68 (s, 1H), 8.02 (m, 2H), 7.52 (m, 3H), 7.36 (m, 2H), 7.02 (m, 2H), 4.36 (s, 2H). ^{13}C NMR ($CDCl_3$): 161.8 (246

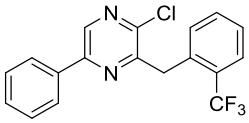
Hz), 153.4, 150.4, 146.7, 138.7, 135.2, 132.7 (3 Hz), 132.6 (8 Hz), 130.1, 129.1 (two signals), 126.8, 115.3 (21 Hz), 40.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}ClFN_2$, 299.0751; found, 299.0746.



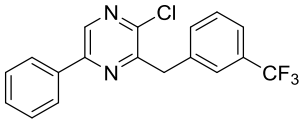
2-Chloro-3-(2-chlorobenzyl)-5-phenylpyrazine **20**{*1,5*} (EC31094-093-1): Obtained as a white solid (1.58 g, 73%) after heating for 12 hours and a recrystallization in ethanol. ^{1}H NMR ($CDCl_3$): 8.70 (s, 1H), 7.93 (m, 2H), 7.46 (m, 4H), 7.22 (m, 3H), 4.52 (s, 2H). ^{13}C NMR ($CDCl_3$): 152.4, 150.2, 147.0, 138.5, 135.2, 134.6, 131.0, 130.0, 129.5, 129.0, 128.2, 126.8, 126.7, 38.6. (One signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}Cl_2N_2$: 315.0456; found, 315.0466.



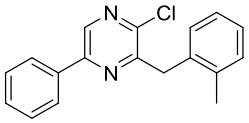
2-Chloro-3-(3-chlorobenzyl)-5-phenylpyrazine **20**{*1,6*} (YJ 31776-007-1): Obtained as a solid (2.28 g, 85%) after heating for 12 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.70 (s, 1H), 8.02 (m, 2H), 7.52 (m, 3H), 7.40 (m, 1H), 7.26 (m, 3H), 4.37 (s, 2H). ^{13}C NMR ($CDCl_3$): 152.8, 150.5, 146.8, 139.0, 138.9, 135.2, 134.3, 130.1, 129.7, 129.3, 129.1, 127.4, 127.0, 126.9, 40.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}Cl_2N_2$: 315.0456; found, 315.0452.



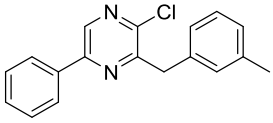
2-Chloro-5-phenyl-3-(2-(trifluoromethyl)benzyl)pyrazine **20**{*1,8*} (YJ 33067-109-2): Obtained as a solid (3.81 g, 68%) after heating for 12 hours and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.72 (s, 1H), 7.92 (m, 2H), 7.75 (m, 1H), 7.51 - 7.44 (m, 3H), 7.40 (m, 1H), 7.17 (m, 1H), 4.61 (s, 2H). ^{13}C NMR ($CDCl_3$): 152.5, 150.1, 146.9, 138.6, 135.6 (2 Hz), 135.1, 131.7, 131.3 129.1 (30 Hz), 129.0, 126.8, 126.7, 126.1 (4 Hz), 124.6 (273 Hz), 37.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{13}ClF_3N_2$: 349.0719; found, 349.0725.



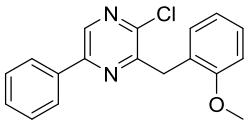
2-Chloro-5-phenyl-3-(3-(trifluoromethyl)benzyl)pyrazine **20**{*1,9*} (YJ 33067-111-2): Obtained as a solid (1.83 g, 35% from (YJ 33067-101-4) and (YJ 33067-101-3)) after heating for 12 hours and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.70 (s, 1H), 8.01 (m, 2H), 7.71 (s, 1H), 7.58 - 7.45 (m, 6H), 4.45 (s, 2H). ^{13}C NMR ($CDCl_3$): 152.6, 150.5, 146.7, 138.9, 137.8, 135.1, 132.6, 130.9 (30 Hz), 130.2.0, 129.1, 128.9, 128.8, 126.1 (6 Hz), 124.2 (273 Hz), 123.7 (4 Hz), 40.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{13}ClF_3N_2$: 349.0719; found, 349.0724.



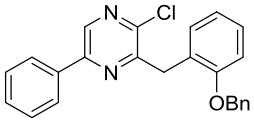
2-Chloro-3-(2-methylbenzyl)-5-phenylpyrazine **20**{*1,11*} (YJ31070-187-2): This compound was obtained as a solid (5.12 g, 89%) after heating for 12 hours and a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.69 (s, 1H), 7.98 (m, 2H), 7.50 (m, 3H), 7.20 (m, 4H), 4.39 (s, 2H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$): 153.5, 150.2, 147.0, 138.4, 136.8, 135.7, 135.3, 130.3, 130.0, 129.8, 129.5, 129.0, 126.9, 126.8, 125.9, 38.4, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2$, 295.1002; found, 295.1009.



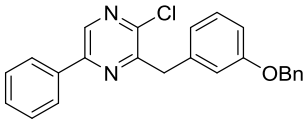
2-Chloro-3-(3-methylbenzyl)-5-phenylpyrazine **20**{*1,12*} (YJ31070-189-2): Obtained as a solid (5.03 g, 90%) after heating for 12 hours and a chromatography over silica gel (cyclohexane-ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.68 (s, 1H), 8.05 (m, 2H), 7.51 (m, 3H), 7.22 (m, 3H), 7.08 (m, 1H), 4.37 (s, 2H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$): 153.7, 150.4, 146.9, 138.6, 138.2, 137.0, 135.4, 130.0, 129.9, 129.0 (two signals), 127.5, 126.9 (two signals), 126.2, 41.2, 21.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2$, 295.1002; found, 295.0997.



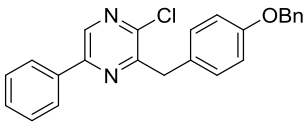
2-Chloro-3-(2-methoxybenzyl)-5-phenylpyrazine **20**{*1,14*} (YJ31070-109-1): Obtained as a white solid (0.73 g, 63%) after heating for 13 hours and a recrystallization in ethanol. ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): 8.66 (s, 1H), 7.96 (m, 2H), 7.48 (m, 3H), 7.27 (m, 1H), 7.14 (m, 1H), 6.93 (m, 2H), 4.40 (s, 2H), 3.83 (s, 2H). ^{13}C NMR ($CDCl_3$): 157.5, 153.8, 150.0, 147.1, 138.1, 135.5, 130.2, 129.8, 129.0, 128.0, 126.8, 126.0, 120.4, 110.4, 55.4, 35.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2O$, 311.0951; found, 311.0949.



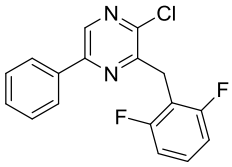
3-(2-(Benzyloxy)benzyl)-2-chloro-5-phenylpyrazine **20**{*1,17*} (RB32489-053-2): Obtained as a light yellow powder (2.67 g, 88%) after heating for 18 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.68 (s, 1H), 8.04 (m, 2H), 7.53 (m, 3H), 7.45 - 7.23 (m, 6H), 7.00 (m, 2H), 6.89 (m, 1H), 5.07 (s, 2H), 4.37 (s, 2H). ^{13}C NMR ($CDCl_3$): 158.9, 153.4, 150.4, 146.9, 138.7, 138.6, 137.0, 135.3, 130.0, 129.5, 129.1, 128.5, 127.9, 127.5, 126.9, 121.9, 116.0, 113.1, 70.1, 41.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{20}ClN_2O$ 387.1264; found, 387.1270.



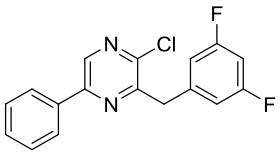
3-(3-(Benzyloxy)benzyl)-2-chloro-5-phenylpyrazine **20**{*1,18*} (RB32489-051-2): Obtained as a light yellow powder (3.67 g, 90%) after heating for 18 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.65 (s, 1H), 7.93 (m, 2H), 7.47 (m, 3H), 7.34 - 7.17 (m, 7H), 6.97 (m, 2H), 5.10 (s, 2H), 4.47 (s, 2H). ^{13}C NMR ($CDCl_3$): 156.6, 153.8, 150.0, 147.1, 138.1, 137.1, 135.4, 130.6, 129.8, 128.9, 128.4, 128.0, 127.7, 127.1, 126.8, 126.3, 120.7, 111.8, 70.1, 37.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{20}ClN_2O$ 387.1264; found, 387.1252.



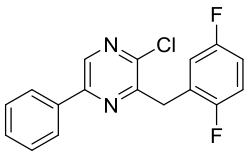
3-(4-(Benzyloxy)benzyl)-2-chloro-5-phenylpyrazine **20**{*1,19*} (YJ31776-037-2): Obtained as a yellow powder (2.00 g, 69%) after heating for 12 hours and a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.67 (s, 1H), 8.03 (m, 2H), 7.53 (m, 3H), 7.41 (m, 4H), 7.33 (m, 3H), 6.95 (m, 2H), 5.07 (s, 2H), 4.34 (s, 2H). ^{13}C NMR ($CDCl_3$): 157.8, 153.9, 150.4, 146.8, 138.5, 137.1, 135.4, 130.2, 130.0, 129.4, 129.1, 128.6, 127.9, 127.5, 126.9, 114.9, 70.1, 40.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{20}ClN_2O$ 387.1264; found, 387.1247.



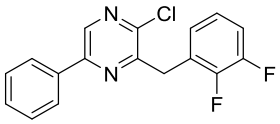
2-Chloro-3-(2,6-difluorobenzyl)-5-phenylpyrazine **20**{*1,21*} (EC31095-047-1): Obtained as a solid (7.5 g, 90%) after a heating for 12 hours and a chromatography over silica gel (cyclohexane–ethyl acetate 98:2). ^{1}H NMR ($CDCl_3$): 8.67 (m, 1H), 7.85 (m, 2H), 7.43 (m, 3H), 7.28 (m, 1H), 6.95 (m, 2H), 4.43 (s, 2H). ^{13}C NMR ($CDCl_3$): 161.8 (248, 8 Hz), 151.2, 150.0, 146.4, 138.3, 135.2, 129.9, 128.9, 128.6 (10 Hz), 126.7, 113.0 (20 Hz), 111.0, 28.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}ClF_2N_2$: 317.0657; found, 317.0650.



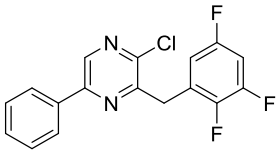
2-Chloro-3-(3,5-difluorobenzyl)-5-phenylpyrazine **20**{*1,22*} (EC31095-049-1): Obtained as a white solid (3.5 g, 90%) after heating for 12 hours and a chromatography over silica gel (cyclohexane–ethyl acetate 98:2). ^{1}H NMR ($CDCl_3$): 8.72 (s, 1H), 8.02 (m, 2H), 7.52 (m, 3H), 6.91 (m, 2H), 6.2 (tt, 1H, J = 9.0, 2.3 Hz), 4.36 (s, 2H). ^{13}C NMR ($CDCl_3$): 163.0 (dd, J = 248, 13 Hz), 152.2, 150.6, 146.8, 140.7 (t, J = 9 Hz), 139.1, 135.0, 130.2, 129.1, 126.9, 112.1, 102.4 (t, J = 25 Hz), 40.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}ClF_2N_2$: 317.0657; found, 317.0651.



2-Chloro-3-(2,5-difluorobenzyl)-5-phenylpyrazine **20**{*1,23*} (EC31095-049-1): Obtained as a white solid (1.16 g, 69%) after heating for 12 hours and a chromatography over silica gel (cyclohexane–ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.72 (s, 1H), 7.96 (m, 2H), 7.50 (m, 3H), 7.07 (m, 1H), 6.97 (m, 2H), 4.40 (s, 2H). ^{13}C NMR ($CDCl_3$): 158.5 (dd, J = 242, 2 Hz), 157.1 (dd, J = 242, 2 Hz), 151.7, 150.4, 146.7, 138.9, 135.1, 130.1, 129.1, 126.8, 125.7 (dd, J = 19, 8 Hz), 117.5 (dd, J = 24, 4 Hz), 116.2 (dd, J = 25, 9 Hz), 114.9 (dd, J = 24, 9 Hz), 34.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}ClF_2N_2$: 317.0657; found, 317.0658

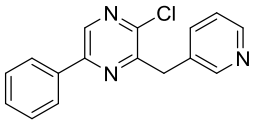


2-Chloro-3-(2,3-difluorobenzyl)-5-phenylpyrazine **20**{*1,24*} (GG30533-126-1): Obtained as a white solid (1.91 g, 80%) after a heating for 12 hours and a chromatography over silica gel (cyclohexane–ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.71 (s, 1H), 7.96 (m, 2H), 7.50 (m, 3H), 7.07 (m, 3H), 4.45 (s, 2H). ^{13}C NMR ($CDCl_3$): 151.8, 150.7 (dd, J = 248, 13 Hz), 150.3, 149.2 (dd, J = 248, 13 Hz), 146.7, 138.8, 135.1, 130.1, 129.1, 126.8, 126.6 (d, J = 13 Hz), 125.8 (t, J = 3 Hz), 123.8 (dd, J = 7, 5 Hz), 115.9 (d, J = 17 Hz), 34.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}ClF_2N_2$: 317.0657; found, 317.0651.

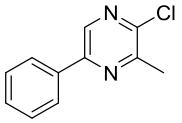


2-Chloro-5-phenyl-3-(2,3,5-trifluorobenzyl)pyrazine **20**{*1,26*} (YJ 33067-113-2): Obtained as a white solid (1.51 g, 72%) after a heating for 12 hours and a chromatography over silica gel (cyclohexane–ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.73 (s, 1H), 7.96 (m, 2H), 7.50 (m, 3H), 6.88 (m, 1H), 6.79 (m, 1H), 4.42 (s, 2H). ^{13}C NMR

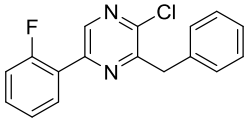
($CDCl_3$): 157.5 (242, 12 and 3 Hz), 151.1, 150.5, 150.3 (247, 13 and 15 Hz), 146.6, 145.8 (242, 12 and 4 Hz), 139.1, 134.9, 130.2, 129.1, 127.3 (9 and 14 Hz), 126.8, 112.2 (3 and 24 Hz), 104.2 (21 and 28 Hz), 34.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{11}ClF_3N_2$: 335.0563; found, 335.0556.



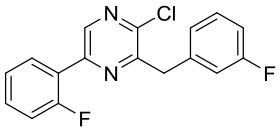
2-Chloro-5-phenyl-3-(pyridin-3-ylmethyl)pyrazine **20**{*1,35*} (YJ30367-031-2): Obtained as an oil (0.42 g, 83%) after heating for 10 hours and a chromatography over silica gel (dichloromethane - ethanol 98/2). ^1H NMR ($CDCl_3$): 8.70 (m, 1H), 8.69 (s, 1H), 8.52 (dd, 1H, *J* = 1.6, 4.9 Hz), 7.99 (m, 2H), 7.71 (m, 1H), 7.50 (m, 3H), 7.26 (ddd, 1H, *J* = 0.8, 4.9, 8.0 Hz), 4.38 (s, 2H). ^{13}C NMR ($CDCl_3$): 152.5, 150.6, 150.5, 148.3, 146.6, 139.0, 136.6, 135.0, 132.6, 130.2, 129.1, 126.8, 123.4, 38.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}ClN_3$, 282.0798; found, 282.0795.



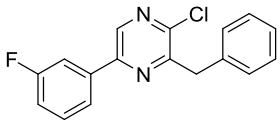
2-Chloro-3-methyl-5-phenylpyrazine **20**{*1,60*} (VHE30612-137-2): Obtained as a yellow solid (1.18 g, 74%) after heating only at 80 °C for 12 hours and a chromatography over silica gel (cyclohexane – dichloromethane 1/1). ^1H NMR ($CDCl_3$): 8.63 (s, 1H), 8.01 (m, 2H), 7.50 (m, 3H), 2.75 (s, 3H). ^{13}C NMR ($CDCl_3$): 152.2, 150.4, 147.1, 138.2, 135.5, 129.9, 129.0, 126.9, 22.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{10}ClN_2$, 205.0533; found, 205.0464.



3-Benzyl-2-chloro-5-(2-fluorophenyl)pyrazine **20**{*2,1*} (YJ31134-031-2): Obtained as a yellow solid (3.30 g, 67%) after heating for 16 hours and a chromatography over silica gel (cyclohexane-dichloromethane 2/1). ^1H NMR ($CDCl_3$): 8.78 (d, 1H, *J* = 2.2 Hz), 8.04 (dt, 1H, *J* = 7.6, 1.8 Hz), 7.30 (m, 8H), 4.40 (s, 2H). ^{13}C NMR ($CDCl_3$): 160.6 (250 Hz), 153.9, 147.1, 146.3 (3 Hz), 142.1 (13 Hz), 137.0, 131.6 (9 Hz), 130.9 (3 Hz), 129.2, 128.5, 126.8, 124.8 (3 Hz), 123.3 (12 Hz), 111.4 (22 Hz), 41.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}ClFN_2$, 299.0751; found, 299.0818.

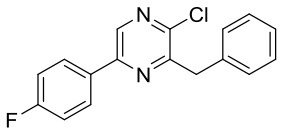


2-Chloro-3-(3-fluorobenzyl)-5-(2-fluorophenyl)pyrazine **20**{*2,3*} (YJ 31068-167-2): Obtained as a white solid (1.86 g, 84%) after heating for 14 hours and a chromatography over silica gel (cyclohexane-ethyl acetate 99/1 to 98.5/1.5). ^1H NMR ($CDCl_3$) 8.80 (d, 1H, *J* = 2.3 Hz), 8.04 (m, 1H), 7.47 (m, 1H), 7.30 (m, 2H), 7.22 (m, 1H), 7.16 (m, 1H), 7.10 (m, 1H), 6.96 (m, 1H), 4.39 (s, 2H). ^{13}C NMR ($CDCl_3$): 162.9 (246 Hz), 160.7 (250 Hz), 153.2, 147.0 (8 Hz), 142.3 (8 Hz), 139.3 (3 Hz), 131.6 (3 Hz), 130.9, 130.8, 129.9 (3 Hz), 124.9 124.8, 123.2 (11 Hz), 116.4 (21 Hz), 116.1 (21 Hz), 113.7 (21 Hz), 40.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}ClF_2N_2$, 317.0657; found, 317.0653.

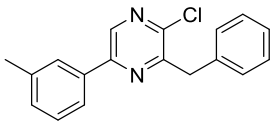


3-Benzyl-2-chloro-5-(3-fluorophenyl)pyrazine **20**{*3,1*} (YJ30367-115-2): Obtained as a solid after heating for 12 hours (0.98 g, 8% from 1-fluoro-3-(2-nitrovinyl)benzene). ^1H NMR ($CDCl_3$): 8.66 (s, 1H), 7.78 (m, 2H), 7.48 (m, 1H), 7.41-7.24 (m, 4H), 7.18 (m, 1H), 4.40 (s, 2H). ^{13}C NMR ($CDCl_3$): 163.4 (248 Hz), 153.9, 149.0 (2 Hz), 147.5,

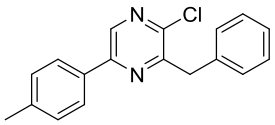
138.5, 137.6, 137.5 136.9, 130.6 (9 Hz), 129.2, 128.6, 126.8, 122.3 (3 Hz), 116.9 (21 Hz), 113.9 (23 Hz), 41.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}ClFN_2$, 299.0751; found, 299.0749.



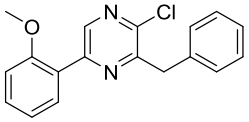
3-Benzyl-2-chloro-5-(4-fluorophenyl)pyrazine **20**{*4,1*} (YJ30531-117-1): Obtained as a white solid (0.84 g, 52%) after heating for 14 hours and a chromatography over silica gel (cyclohexane-dichloromethane 3/1). ^{1}H NMR ($CDCl_3$): 8.63 (s, 1H), 8.02 (m, 2H), 7.39 (m, 2H), 7.34 (m, 2H), 7.28 (m, 1H), 7.19 (m, 2H), 4.39 (s, 2H). ^{13}C NMR ($CDCl_3$): 164.1 (250 Hz), 153.7, 149.4, 146.8, 138.2 137.0, 131.4 (3 Hz), 129.2, 128.9, 128.8 (8 Hz), 126.8, 116.2 (22 Hz), 41.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}ClFN_2$, 299.0751; found, 299.0763.



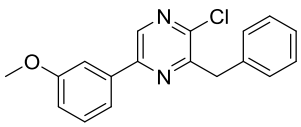
3-Benzyl-2-chloro-5-(m-tolyl)pyrazine **20**{*5,1*} (YJ30367-065-2): This compound was obtained as a white solid (3.02 g, 33% from 1-methyl-3-(2-nitrovinyl)benzene) after heating for 18 hours and a chromatography over silica gel (cyclohexane-ethyl acetate 96.5/3.5). ^{1}H NMR ($CDCl_3$): 8.66 (s, 1H), 7.84 (m, 1H), 7.82 (m, 2H), 7.43 – 7.24 (m, 6H), 4.40 (s, 2H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$): 153.5, 150.6, 146.8, 140.3, 138.8, 138.7, 137.1, 135.3, 130.8, 129.2, 129.0, 128.5, 127.5, 126.7, 124.0, 41.2, 21.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2$, 295.1002; found, 295.1014.



3-Benzyl-2-chloro-5-(p-tolyl)pyrazine **20**{*6,1*} (YJ30367-035-2): Obtained as a yellow solid (1.83 g, 22% from 1-methyl-4-(2-nitrovinyl)benzene) after heating for 12 hours and a chromatography over silica gel (cyclohexane-dichloromethane 3/2). ^{1}H NMR ($CDCl_3$): 8.64 (s, 1H), 7.94 (m, 2H), 7.48 – 7.23 (m, 7H), 4.39 (s, 2H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$): 153.5, 150.4, 146.4, 140.3, 138.3, 137.1, 132.6, 129.8, 129.2, .128.5, 126.8, 126.7, 123.0, 41.2, 21.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2$, 295.1002; found, 295.0999.

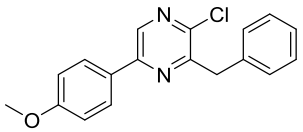


3-Benzyl-2-chloro-5-(2-methoxyphenyl)pyrazine **20**{*7,1*} (EC31092-035-2): Obtained as a yellow solid (1.82 g, 81%) after heating for 18 hours and a chromatography over silica gel (cyclohexane-dichloromethane 3/2). ^{1}H NMR ($CDCl_3$): 8.86 (s, 1H), 7.91 (dd, 1H, *J* = 7.6, 1.8 Hz), 7.48 – 7.36 (m, 3H), 7.34 – 7.28 (m, 2H), 7.26 – 7.18 (m, 1H), 7.11 (td, 1H, *J* = 7.6, 0.8 Hz), 7.03 (d, 1H, *J* = 8.3 Hz), 4.37 (s, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$): 157.4, 153.4, 149.4, 146.2, 143.3, 137.5, 131.3 (two signals), 129.3, 128.6, 126.8, 124.9, 121.4, 111.6, 55.7, 41.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2O$, 311.0951; found, 311.0965.

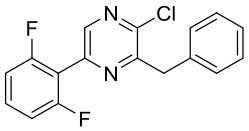


3-Benzyl-2-chloro-5-(3-methoxyphenyl)pyrazine **20**{*8,1*} (YJ30367-083-2): This compound was obtained as a white powder (0.4 g, 32% from piperazinone **17**{*8,1*}), after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.66 (s, 1H), 7.97 (m, 2H), 7.58 (m, 2H), 7.41 (m, 3H), 7.33 (m, 2H), 7.25 (m, 1H), 7.03 (m, 1H), 4.39 (s, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$): 160.2, 153.5, 150.1, 146.9, 138.6, 137.1, 136.7,

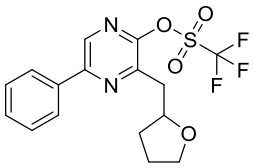
130.1, 129.2, 128.5, 126.7, 119.1, 115.8, 112.3, 55.4, 41.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2O$, 311.0951; found, 311.0962.



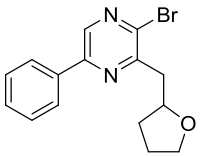
3-Benzyl-2-chloro-5-(4-methoxyphenyl)pyrazine **20**{*9,1*} (YJ29793-127-2): Obtained as a yellow solid (0.33 g, 35%) after heating for 12 hours and a chromatography over silica gel (cyclohexane-dichloromethane 3/2). ^{1}H NMR ($CDCl_3$): 8.61 (s, 1H), 7.97 (m, 2H), 7.40 (m, 2H), 7.31 (m, 2H), 7.27 (m, 1H), 7.02 (m, 2H), 4.37 (s, 2H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$): 161.3, 153.3, 150.2, 145.8, 137.9, 137.2, 129.2, 128.5, 128.3, 127.9, 127.7, 114.5, 55.4, 41.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2O$, 311.0951; found, 311.0955.



3-Benzyl-2-chloro-5-(2,6-difluorophenyl)pyrazine **20**{*10,1*} (MM34284-021-2): Obtained as a white solid (0.75 g, 56%) after heating for 12 hours and a chromatography over silica gel (cyclohexane-dichloromethane 3/1). ^{1}H NMR ($CDCl_3$): 8.44 (m, 1H), 7.43 (m, 3H), 7.27 (m, 2H), 7.25 (m, 1H), 7.05 (m, 2H), 4.40 (s, 2H). ^{13}C NMR ($CDCl_3$): 160.6 (6, 252 Hz), 154.3, 148.0, 143.2 (5 Hz), 143.1, 136.6, 131.3 (10 Hz), 129.2, 128.5, 126.8, 114.1 (18 Hz), 112.1 (6, 19 Hz), 41.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}ClF_2N_2$, 317.0657; found, 317.0648.



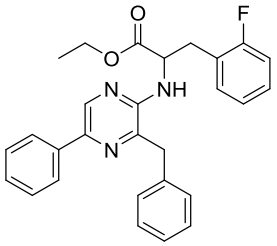
Synthesis, via step viii, of 5-phenyl-3-((tetrahydrofuran-2-yl)methyl)pyrazin-2-yl trifluoromethanesulfonate **21**{*1,38*} (YJ31134-135-2): Compound **19**{*1,38*} (0.56 g, 2.18 mmol) was dissolved in dry dichloromethane (30 mL, stabilized by amylene, dried over 4Å molecular sieve). Triethylamine (0.31 mL, 2.29 mmol) and triflic anhydride (0.37 mL, 2.22 mmol) were then added. The resulting solution was stirred for 40 minutes, diluted in ethyl acetate, washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane-dichloromethane 1/3) to yield compound **21**{*1,38*} as an oil (0.37 g, 43%). ^{1}H NMR ($CDCl_3$): 8.60 (s, 1H), 8.01 (m, 2H), 7.53 (m, 3H), 4.51 (m, 1H), 3.95 (m, 1H), 3.77 (m, 1H), 3.27 (dd, 1H, J = 7.8, 14.1 Hz), 3.10 (dd, 1H, J = 5.4, 14.1 Hz), 2.17 (m, 1H), 1.96 (m, 2H), 1.76 (m, 1H). ^{13}C NMR ($CDCl_3$): 153.3, 151.1, 146.5, 136.7, 135.0, 130.3, 129.1, 127.1, 118.6 (321 Hz), 77.3, 67.9, 38.2, 26.9, 25.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{16}F_3N_2O_4S$, 389.0783; found, 389.0808.



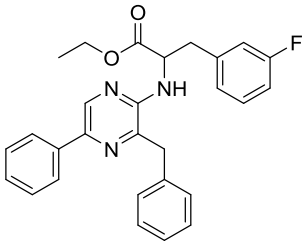
Synthesis, via step ix, of 2-bromo-5-phenyl-3-((tetrahydrofuran-2-yl)methyl)pyrazine **22**{*1,38*} (YJ31134-145-4): In a tube featuring a Teflon-coated screw cap, compound **21**{*1,38*} (0.37 g, 0.95 mmol) and dry sodium bromide (0.24 g, 2.38 mmol, flame-dried under vacuum) were dispersed in dry dimethylformamide (4 mL). Triflic acid (0.07 mL, 0.86 mmol) was added, the tube was closed and heated at 120 °C overnight. The resulting solution was diluted in diluted in ethyl acetate, washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane-dichloromethane 1/4 to dichloromethane – ethanol 99/1) to yield compound **22**{*1,38*} as an oil (0.19 g, 62%). ^{1}H NMR ($CDCl_3$): 8.62 (s, 1H), 8.02 (m, 2H), 7.50 (m, 3H), 4.57 (p, 1H, J = 6.7 Hz), 3.99 (m, 1H), 3.80 (m, 1H), 3.42 (dd, 1H, J = 6.7, 14.6 Hz), 3.14 (dd, 1H, J = 6.7, 14.6 Hz), 2.12 (m, 1H), 1.99 (m, 2H), 1.76 (m, 1H). ^{13}C NMR ($CDCl_3$): 154.3, 150.5,

140.2, 138.9, 135.4, 130.0, 129.0, 126.9, 77.4, 67.9, 42.1, 31.2, 25.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{16}BrN_2O$, 319.0446; found, 319.0464.

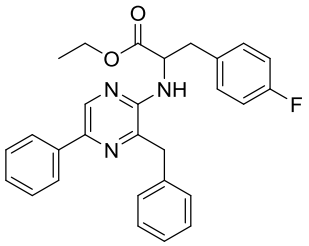
General procedure for the N-arylation of α-amino esters 14 by 2-halogenopyrazine 20 or 22, **preparation of compounds 23 via steps x.** In a 20 mL sealable vial (note 1), the considered 2-halogenopyrazine **20** or **22** (2.0 mmol), the considered amino ester **14** (2.05 mmol, either as a free base or as a hydrochloride salt), cesium carbonate (1.98 g 6.04 mmol), palladium acetate (0.022 g, 0.1 mmol) and 1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) (BINAP) (0.087 g, 0.14 mol) were weighted. The air was replaced by argon and, under an inert atmosphere, dry acetonitrile (8 mL) was injected (note 2). This was heated and stirred at 60 °C for 12 hours (note 3). The resulting dark red or black suspension was dispersed in ethyl acetate, filtered, rinsed with ethyl acetate and the filtrate was concentrated to dryness and the residue (note 4) subjected to further purification by a chromatography over silica gel as described below (note 5). Note 1: on larger scale, the use of standard glassware and rubber septum worked as fine. Note 2: as specified in some cases below, dry dimethylformamide at 60 °C or dry toluene at 90 °C were also used. Note 3: the occurrence of clumps of cesium hydrogen carbonate was observed to be detrimental to the reaction. A good stirring or an ultra sound bath (with a temperature regulation) were equally effective. Note 4: ^{1}H NMR spectra of this residue most often pointed out a complete or a well-advanced conversion. In some still unexplained (and fairly random) runs, no reaction occurred. However, starting the procedure described above again with this residue and fresh amount of cesium carbonate, palladium acetate and BINAP in the same solvent used often saved the day. Note 5: absorption of the residue on a small amount of silica gel prior to a chromatography was preferentially made under vacuum at 20 °C.



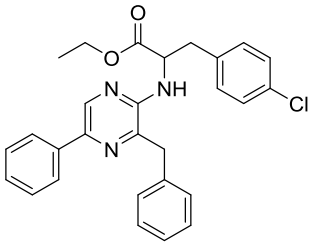
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(2-fluorophenyl)propanoate **23**{*1,1,2*} (EC31093-155-2): Obtained as an oil (0.32 g, 79%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.96 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.27 (m, 6H), 6.98 (m, 3H), 4.99 (m, 2H), 4.15 (m, 4H), 3.22 (dd, 1H, *J* = 13.9, 5.5 Hz), 3.16 (dd, 1H, *J* = 13.9, 6.3 Hz), 1.20 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 161.3 (246 Hz), 150.4, 141.2, 141.1, 137.5, 136.7 (25 Hz), 131.5 (5 Hz), 128.8, 128.7, 128.6, 128.6 (8 Hz), 127.8, 126.9, 125.7, 124.1, 124.0, 123.5 (16 Hz), 115.2 (22 Hz), 61.3, 54.3, 40.8, 31.2, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2084.



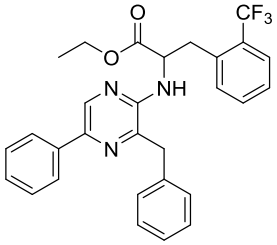
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-fluorophenyl)propanoate **23**{*1,1,3*} (YJ30367-011-2): Obtained as an oil (0.25 g, 64%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 7.32 – 7.23 (m, 5H), 7.17 (m, 1H), 6.92 (m, 1H), 6.73 (m, 1H), 4.98 (m, 2H), 4.16 (m, 4H), 3.18 (dd, 1H, *J* = 5.5, 13.8 Hz), 3.03 (dd, 1H, *J* = 5.1, 13.8 Hz), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 162.0 (242 Hz), 150.2, 141.2 (5 Hz), 138.8 (8 Hz), 137.4, 136.8, 136.4, 129.8 (8 Hz), 128.9, 128.8, 128.6, 127.8, 127.0, 125.6, 124.9, 124.8, 116.2 (21 Hz), 113.7 (20 Hz), 61.3, 54.7, 41.0, 37.6, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2065.



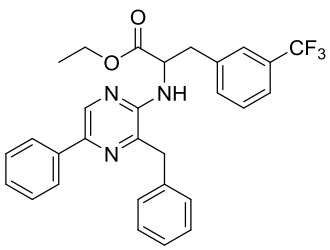
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-fluorophenyl)propanoate **23**{*1,1,4*} (EC31092-091-2): Obtained as an oil (0.45 g, 69%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.99 – 7.91 (m, 2H), 7.51 – 7.41 (m, 2H), 7.40 – 7.32 (m, 1H), 7.31 – 7.25 (m, 3H), 7.23 – 7.17 (m, 2H), 6.91 – 6.79 (m, 4H), 4.99 – 4.84 (m, 2H), 4.21 – 4.06 (m, 4H), 3.15 (dd, 1H, *J* = 13.9, 5.1 Hz), 3.03 (dd, 1H, *J* = 13.9, 5.5 Hz), 1.20 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 162.0 (245 Hz), 150.4, 141.3, 141.3, 137.6, 137.0, 136.6, 132.1 (3 Hz), 130.8 (8 Hz), 129.0, 128.9, 128.7, 128.0, 127.1, 125.8, 115.4 (21 Hz), 61.4, 55.0, 41.1, 37.0, 14.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2110.



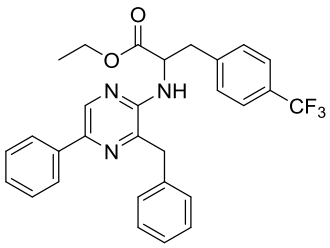
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-chlorophenyl)propanoate **23**{*1,1,7*} (CF34391-030-1): Obtained as an oil (0.38 g, 64%) after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3 to 96:4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H), 7.30 (m, 3H) 7.22 (m, 2H), 7.14 (m, 2H) 6.85 (m, 2H), 4.95 (m, 2H), 4.15 (m, 4H), 3.16 (m, 1H), 3.03 (m, 1H), 1.23 (t, 3H, *J* = 7.2 Hz,). ^{13}C NMR ($CDCl_3$): 172.1, 150.2, 141.2, 141.1, 137.4, 136.8, 136.4, 134.7, 132.7, 130.5, 128.9, 128.8, 128.6, 128.5, 127.9, 126.9, 125.7, 61.3, 54.6, 40.9, 37.0, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}ClN_3O_2$, 472.1792; found, 472.1782.



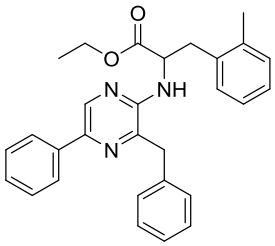
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(2-(trifluoromethyl)phenyl)propanoate **23**{*1,1,8*} (YJ30531-105-2): Obtained as an oil (0.08 g, 18%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.36 (s, 1H), 7.93 (m, 2H), 7.62 (m, 1H), 7.45 (m, 2H), 7.37 – 7.18 (m, 9H), 5.01 - 4.93 (m, 2H), 4.17 (s, 2H), 4.12 (m, 2H), 3.31 (m, 1H), 3.15 (m, 1H), 1.17 (m, 3H). ^{13}C NMR ($CDCl_3$): 172.4, 150.4, 141.3, 141.0, 137.4, 136.8, 136.6, 135.6, 131.6, 131.2, 128.9 (30 Hz), 128.8, 128.7, 128.6, 127.8, 126.9, 126.7, 125.9 (6 Hz), 125.6, 124.5 (275 Hz), 61.2, 54.8, 40.8, 34.7, 13.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{27}F_3N_3O_2$, 506.2055; found, 506.2053.



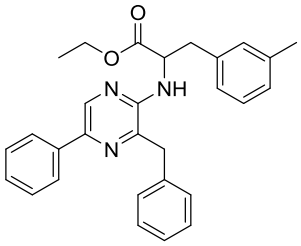
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-(trifluoromethyl)phenyl)propanoate **23**{*1,1,9*} (YJ30531-107-2): Obtained as an oil (0.14 g, 31%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.99 (m, 2H), 7.62 (m, 1H), 7.49 (m, 3H), 7.40 – 7.26 (m, 8H), 7.10 (m, 1H), 5.02 (m, 2H), 4.17 (s, 2H), 4.13 (m, 2H), 3.25 (m, 1H), 3.14 (m, 1H), 1.19 (m, 3H). ^{13}C NMR ($CDCl_3$): 171.9, 150.1, 141.3, 141.2, 137.5, 137.4, 136.8, 136.5, 132.7, 130.6 (32 Hz), 128.9, 128.8 (two signals), 128.6, 127.9, 127.0, 126.1 (6 Hz), 125.7, 124.1 (275 Hz), 123.6 (6Hz), 61.4, 54.7, 41.0, 37.7, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{27}F_3N_3O_2$, 506.2055; found, 506.2063.



Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-(trifluoromethyl)phenyl)propanoate **23**{*1,1,10*} (YJ30531-109-2): Obtained as an oil (0.12 g, 26%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.98 (m, 2H), 7.48 (m, 2H), 7.40 (m, 3H), 7.29 – 7.26 (m, 5H), 7.03 (m, 2H), 5.02 (m, 2H), 4.19 (m, 2H), 4.14 (s, 2H), 3.26 (dd, 1H, *J* = 5.6, 13.6 Hz), 3.14 (dd, 1H, *J* = 5.7, 13.6 Hz), 1.22 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.1, 141.3, 141.2, 137.4, 136.9, 136.4, 129.5, 129.2, 128.9, 128.9 (32 Hz), 128.8, 128.5, 127.9, 127.0, 126.9 (275 Hz), 125.7, 125.2 (4 Hz), 61.4, 54.6, 41.0, 37.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{27}F_3N_3O_2$, 506.2055; found, 506.2002.

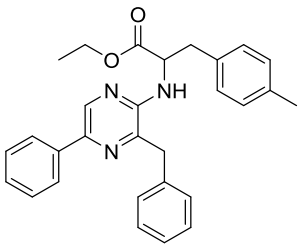


Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(o-tolyl)propanoate **23**{*1,1,11*} (YJ30367-157-2): Obtained as an oil (0.48 g, 90%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.94 (m, 2H), 7.48 – 7.42 (m, 2H), 7.38 – 7.24 (m, 6H), 7.15 (m, 2H), 7.06 (m, 1H), 6.93 (m, 1H), 4.92 (m, 2H), 4.16 (m,4H), 3.14 (dd, 1H, *J* = 6.1, 14.0 Hz), 3.02 (dd, 1H, *J* = 7.1, 14.0 Hz), 2.29 (s, 3H), 1.16 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.9, 150.5, 141.2, 141.1, 137.5, 136.8, 1367, 136.5, 134.7, 130.5, 129.8, 128.9, 128.7, 128.6, 127.8, 126.9, 125.9, 125.7 (two signals), 61.1, 54.3, 40.9, 35.7, 19.4, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_3O_2$, 452.2338; found, 452.2352.

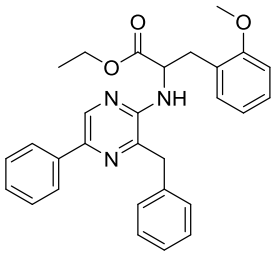


Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(m-tolyl)propanoate **23**{*1,1,12*} (EC31092-089-2): Obtained as an oil (0.28 g, 61%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 8.07 – 7.90 (m, 2H), 7.48 – 7.42 (m, 2H), 7.38 – 7.32 (m, 1H), 7.30 – 7.26 (m, 1H), 7.26 – 7.23 (m, 1H), 7.21 – 7.16 (m, 2H), 7.15 – 7.08 (m, 1H), 7.07 – 7.01 (m, 1H), 6.88 (s, 1H), 6.78 (d, 1H, *J* = 7.5 Hz), 4.93 (t, 1H, *J* = 5.9 Hz), 4.92 (t, 1H, *J* = 6.5 Hz), 4.88 – 4.79 (m, 2H), 4.11 (q, 2H, *J* = 7.1 Hz), 4.11 (q, 2H, *J* = 15.4 Hz), 3.11 (dd, 1H, *J* = 13.8, 5.5 Hz), 3.03 (dd, 1H, *J* = 13.8, 6.1 Hz), 2.30 (s, 3H), 1.17 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.7, 150.6, 141.3, 141.3, 138.1, 137.7, 137.0, 136.7, 136.3, 130.2, 128.9, 128.9, 128.8, 128.5, 127.9,

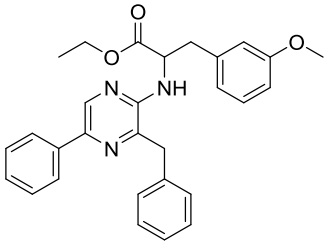
127.8, 127.0, 126.4, 125.8, 61.2, 55.1, 40.9, 38.0, 21.5, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_3O_2$, 452.2338; found, 452.2408.



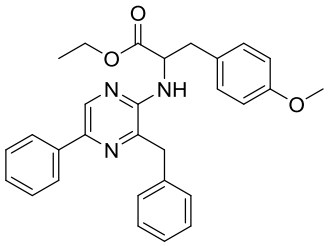
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(p-tolyl)propanoate **23**{*1,1,13*} (EC31093-153-2): Obtained as an oil (0.35 g, 87%) after a chromatography over silica gel (cyclohexane-ethyl acetate 94:6). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H), 7.28 (m, 3H), 7.22 (m, 2H), 7.04 (m, 2H), 6.89 (m, 2H), 4.93 (m, 2H), 4.15 (m, 4H), 3.15 (dd, 1H, *J* = 13.8, 5.2 Hz), 3.06 (dd, 1H, *J* = 13.8, 5.8 Hz), 2.35 (s, 3H), 1.21 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 150.4, 141.2, 141.1, 137.5, 136.8, 135.5, 135.4, 133.1, 129.2, 129.1, 128.8, 128.7, 128.6, 127.8, 126.8, 125.7, 61.1, 54.9, 40.8, 37.4, 21.1, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_3O_2$, 452.2338; found, 452.2325.



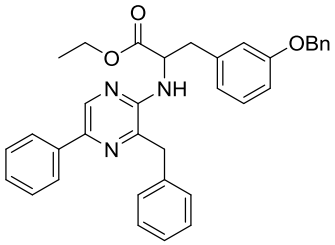
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(2-methoxyphenyl)propanoate **23**{*1,1,14*} (EC31093-157-2): Obtained as a yellow solid (0.32 g, 77%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.38 (s, 1H), 7.90 (m, 2H), 7.44 (m, 2H), 7.34 (m, 1H), 7.26 (m, 3H), 7.22 (m, 6H), 7.04 (dd, 1H, *J* = 7.4, 1.7 Hz), 6.88 (td, 1H, *J* = 7.4, 1.0 Hz), 6.83 (m, 1H), 5.30 (d, 1H, *J* = 7.0 Hz), 4.85 (m, 1H), 4.11 (m, 4H), 3.75 (s, 3H), 3.20 (dd, 1H, *J* = 13.6, 5.6 Hz), 3.15 (dd, 1H, *J* = 13.6, 7.6 Hz), 1.20 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 173.0, 157.6, 150.7, 140.9, 140.8, 137.6, 136.8, 136.7, 131.0, 128.7 (two signals), 128.4, 127.6, 126.7, 125.6, 125.2, 120.8, 110.6, 60.9, 55.4, 55.2, 40.2, 32.4, 14.2, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_3$, 468.2287; found, 468.2281.



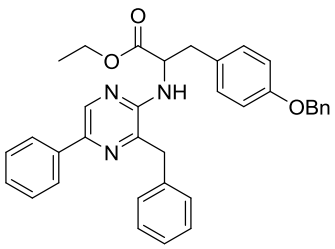
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-methoxyphenyl)propanoate **23**{*1,1,15*} (YJ31134-059-2): Obtained as an oil (0.30 g, 51%) containing 5% of an unidentified impurity after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.46 (m, 2H), 7.36 (m, 1H), 7.30 – 7.13 (m, 6H), 6.79 (m, 2H), 6.65 (m, 1H), 6.58 (m, 1H), 4.96 - 4.90 (m, 2H), 4.14 (m, 4H), 3.78 (s, 3H), 3.15 (dd, 1H, *J* = 5.6, 13.8 Hz), 3.07 (dd, 1H, *J* = 6.0, 13.8 Hz), 1.19 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 159.7, 150.4, 141.2, 141.1, 137.8, 137.5, 136.8, 136.5, 129.5, 129.3, 128.8, 128.6, 127.8, 126.8, 125.6, 121.6, 115.0, 112.3, 61.1, 55.1, 54.8, 40.8, 37.9, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_3$, 468.2287; found, 468.2301.



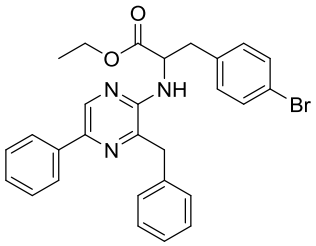
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-methoxyphenyl)propanoate **23**{*1,1,16*} (YJ30367-013-2): Obtained as an oil (0.16 g, 35%) after a chromatography over silica gel (cyclohexane – ethyl acetate 93/7). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.46 (m, 2H), 7.39-7.21 (m, 6H), 6.89 (m, 2H), 6.76 (m, 1H), 4.96 - 4.90 (m, 2H), 4.15 (m, 4H), 3.81 (s, 3H), 3.12 (dd, 1H, *J* = 4.8, 13.7 Hz), 3.03 (dd, 1H, *J* = 5.2, 13.7 Hz), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 159.7, 150.4, 141.2, 141.1, 137.8, 137.5, 136.8, 136.5, 129.5, 129.3, 128.8, 128.6, 127.8, 126.8, 125.6, 121.6, 115.0, 112.3, 61.1, 55.1, 54.8, 40.8, 37.9, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_3$, 468.2287; found, 468.2271.



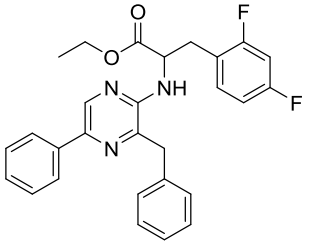
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-(benzyloxy)phenyl)propanoate **23**{*1,1,18*} (YJ 31776-183-1): Obtained as an oil (0.62 g, 77%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.50-7.34 (m, 8H), 7.35 (m, 4H), 7.26-7.16 (m, 6H), 7.28-7.14 (m, 6H), 6.88 (m, 1H), 6.74 (m, 1H), 6.61 (m, 1H), 5.04 (s, 2H), 4.95 (m, 2H), 4.13 (m, 4H), 3.16 (dd, 1H, *J* = 5.2, 13.6 Hz), 3.07 (dd, 1H, *J* = 6.0, 13.6 Hz), 1.20 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 158.9, 150.3, 141.3, 141.1, 137.8, 137.4, 137.0, 136.6, 136.4, 129.5, 128.8, 128.7, 128.6, 128.5, 128.0, 127.8, 127.4, 126.9, 125.6, 121.9, 116.0, 113.2, 69.9, 61.2, 54.9, 40.8, 37.9, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{34}N_3O_3$, 544.2600; found, 544.2607.



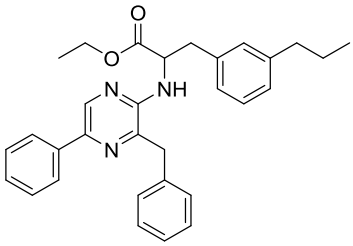
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-(benzyloxy)phenyl)propanoate **23**{*1,1,19*} (EC31093-059-2): Obtained as an oil (0.68 g, 70%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 8.00 – 7.86 (m, 2H), 7.50 – 7.16 (m, 13H), 6.90 – 6.84 (m, 2H), 6.84 – 6.79 (m, 2H), 5.05 (s, 2H), 4.99 – 4.84 (m, 2H), 4.12 (qd, 2H, *J* = 7.1, 0.6 Hz), 4.12 (s, 2H), 3.11 (dd, 1H, *J* = 13.9, 5.0 Hz), 3.01 (dd, 1H, *J* = 13.9, 5.5 Hz), 1.19 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.6, 157.9, 150.5, 141.2 (two signals), 137.7, 137.2, 137.0, 136.7, 130.4, 128.9 (two signals), 128.8, 128.7, 128.6, 128.1, 127.9, 127.6, 127.0, 125.8, 115.0, 70.2, 61.3, 55.1, 41.0, 37.1, 14.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{34}N_3O_3$, 544.2600; found, 544.2654.



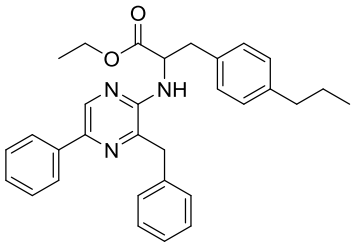
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-bromophenyl)propanoate **23**{*1,1,20*} (CF34391-28-1): Obtained as an oil (0.37 g, 57%) after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3 to 96:4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H), 7.29 (m, 5H), 7.22 (m, 2H), 6.79 (m, 2H), 4.95 (m, 2H), 4.15 (m, 4H), 3.16 (m, 1H), 3.03 (m, 1H), 1.23 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 150.2, 141.2, 141.1, 137.4, 136.8, 136.4, 135.2, 131.5, 130.9, 128.9, 128.8, 128.6, 127.9, 126.9, 125.7, 120.8, 61.3, 54.6, 40.9, 37.0, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}BrN_3O_2$, 516.1287; found, 516.1267.



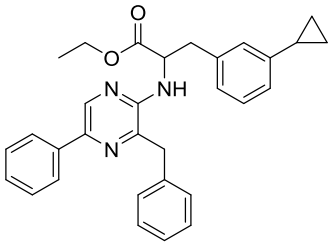
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(2,4-difluorophenyl)propanoate **23**{*1,1,25*} (YJ31067-053-2): Obtained as an oil (0.27 g, 61%) after a chromatography over silica gel (cyclohexane-ethyl acetate 96:4). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.96 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.27 (m, 5H), 6.98 (m, 1H), 6.70 (m, 2H), 4.97 (m, 2H), 4.16 (m, 4H), 3.22 (dd, 1H, *J* = 5.4, 14.3 Hz), 3.10 (dd, 1H, *J* = 6.1, 14.3 Hz), 1.22 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 161.9 (11 and 247 Hz), 161.2 (11 and 249 Hz), 150.2, 141.2, 141.1, 137.4, 136.8, 136.4, 132.0 (6 and 9 Hz), 128.8, 128.7, 128.6, 127.8, 126.9, 119.3 (4 and 16 Hz), 111.1 (3 and 21 Hz), 103.6 (25 Hz), 61.4, 54.1, 40.9, 30.6, 14.0 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}F_2N_3O_2$, 474.1993; found, 474.1988.



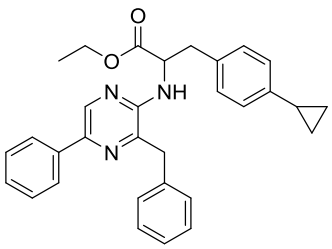
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-propylphenyl)propanoate **23**{*1,1,27*} (CF34204-036-1): Obtained as an oil (0.27 g, 79%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.26 (m, 5H), 7.16 (m, 1H), 7.07 (m, 1H), 6.92 (m, 1H), 6.82 (m, 1H), 4.93, (m, 2H), 4.14 (m, 4H), 3.15 (dd, 1H, *J* = 13.7, 5.6 Hz), 3.07 (dd, 1H, *J* = 13.7, 6.1 Hz), 2.56 (m, 2H), 1.63 (m, 2H), 1.18 (t, 3H, *J* = 7.2 Hz), 0.95 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 150.4, 142.8, 141.1 (2 signals), 137.5, 136.8, 136.5, 136.1, 129.4, 128.8, 128.7, 128.6, 128.4, 127.8, 127.1, 126.9, 126.6, 125.6, 61.1, 54.9, 40.8, 38.0, 37.9, 24.5, 14.1, 13.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{34}N_3O_2$, 480.2651; found, 480.2661.



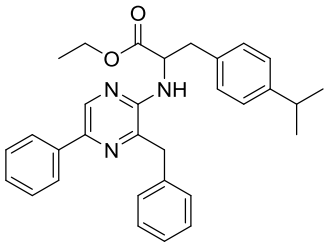
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-propylphenyl)propanoate **23**{*1,1,28*} (CF34204-044-1): Obtained as an oil (0.25 g, 73%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.96 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.26 (m, 5H), 7.05 (m, 2H), 6.91 (m, 2H), 4.93, (m, 2H), 4.13 (m, 4H), 3.14 (dd, 1H, *J* = 13.9, 5.5 Hz), 3.06 (dd, 1H, *J* = 13.9, 6.0 Hz), 2.59 (m, 2H), 1.65 (m, 2H), 1.19 (t, 3H, *J* = 7.2 Hz), 0.97 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 150.4, 141.2, 141.1, 141.0, 137.5, 136.9, 136.6, 133.3, 129.1, 128.8, 128.7, 128.6, 128.5, 127.8, 126.9, 125.6, 61.1, 54.9, 40.8, 37.7, 37.5, 24.5, 14.1, 13.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{34}N_3O_2$, 480.2651; found, 480.2671.



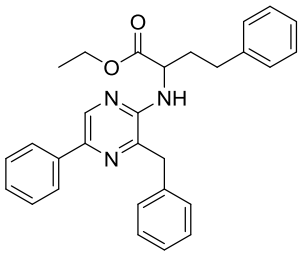
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-cyclopropylphenyl)propanoate **23**{*1,1,29*} (YJ30367-103-2): Obtained as an oil (0.46 g, 79%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 7.28-7.19 (m, 5H), 7.13 (m, 1H), 6.95 (m, 1H), 6.82 (m, 1H), 6.77 (m, 1H), 4.93, (m, 2H), 4.13 (m, 4H), 3.13 (dd, 1H, *J* = 5.5, 13.7 Hz), 3.05 (dd, 1H, *J* = 6.0, 13.7 Hz), 1.86 (m, 1H), 1.18 (t, 3H, *J* = 7.2 Hz), 0.96 (m, 2H), 0.67 (m, 2H). ^{13}C NMR ($CDCl_3$): 172.5, 150.4, 141.2, 141.1, 137.5, 136.8, 136.5, 136.2, 128.8, 128.7, 128.6 (two signals), 128.4, 127.8, 126.8, 126.3, 125.6, 124.1, 61.1, 54.9, 40.8, 37.9, 15.3, 14.1, 9.2, 9.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{32}N_3O_2$, 478.2495; found, 478.2480.



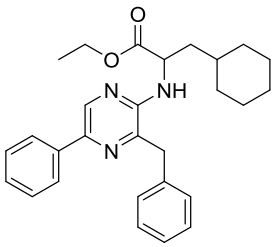
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-cyclopropylphenyl)propanoate **23**{*1,1,30*} (YJ30367-105-2): Obtained as an oil (0.46 g, 76%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.96 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 7.31-7.23 (m, 3H), 7.20 (m, 2H), 6.94 (m, 2H), 6.86 (m, 2H), 4.93, (m, 2H), 4.13 (m, 4H), 3.13 (dd, 1H, *J* = 5.3, 13.9 Hz), 3.04 (dd, 1H, *J* = 5.9, 13.9 Hz), 1.89 (m, 1H), 1.19 (t, 3H, *J* = 7.2 Hz), 0.98 (m, 2H), 0.69 (m, 2H). ^{13}C NMR ($CDCl_3$): 172.5, 150.4, 142.5, 141.1, 141.0, 137.5, 136.9, 136.5, 133.1, 129.1, 128.8, 128.7, 128.6, 127.7, 126.8, 125.8, 125.6, 61.1, 54.9, 40.8, 37.3, 15.1, 14.1, 9.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{32}N_3O_2$, 478.2495; found, 478.2487.



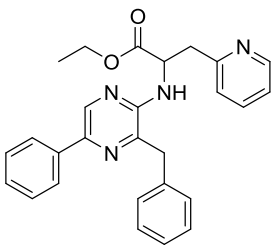
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-isopropylphenyl)propanoate **23**{*1,1,31*} (EC31093-091-2): Obtained as an oil (0.25 g, 73%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.97 – 7.90 (m, 2H), 7.49 – 7.40 (m, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 7.12 – 7.05 (m, 2H), 6.94 – 6.88 (m, 2H), 4.99 – 4.84 (m, 2H), 4.18 – 4.06 (m, 4H), 3.08 (qd, 2H, *J* = 13.8, 5.7 Hz), 2.96 – 2.84 (m, 1H), 1.25 (d, 6H, *J* = 6.9 Hz), 1.16 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.7, 150.6, 147.5, 141.3, 141.2, 137.7, 137.0, 136.7, 133.6, 129.3, 128.9, 128.9, 128.8, 127.9, 127.0, 126.6, 125.8, 61.2, 55.0, 41.0, 37.6, 33.9, 24.2, 24.1, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{34}N_3O_2$, 480.2683; found, 480.2690.



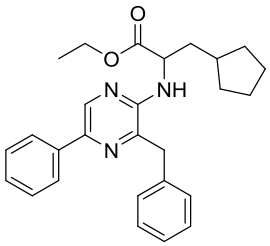
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-4-phenylbutanoate **23**{*1,1,32*} (YJ31070-127-2): Obtained as an oil (0.36 g, 80%) after a chromatography over silica gel (cyclohexane / ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.97 (m, 2H), 7.48 (m, 1H), 7.38 (m, 5H), 7.28 (m, 3H), 7.20 (m, 1H), 7.06 (m, 2H), 4.97 (d (br), 1H, *J* = 7.0 Hz), 4.73 (m, 1H), 4.27 (d, 1H, *J* = 15.4 Hz), 4.21 (d, 1H, *J* = 15.4 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 2.43 (m, 2H), 2.21 (m, 1H), 1.99 (m, 1H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 173.0, 150.5, 141.1, 141.0, 140.9, 137.5, 136.9, 136.8, 129.0, 128.8, 128.7, 128.4, 127.8, 127.1, 126.1, 125.7, 61.2, 53.6, 41.2, 33.6, 31.2, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_2$, 452.2338; found, 452.2335.



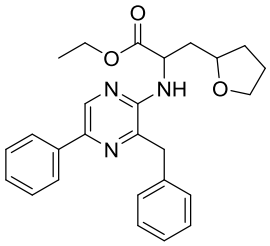
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-cyclohexylpropanoate **23**{*1,1,33*} (YJ31067-065-2): Obtained as an oil (0.36 g, 78%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.38-7.32 (m, 5H), 7.29-7.26 (m, 1H), 4.60 (m, 4H), 4.30 (d, 1H, *J* = 15.5 Hz), 4.20 (d, 1H, *J* = 15.5 Hz), 4.16 (m, 2H), 1.60 (m, 6H), 1.48 (m, 1H), 1.24 (t, 3H, *J* = 7.2 Hz), 1.08 (m, 4H), 0.86 (m, 2H). ^{13}C NMR ($CDCl_3$): 174.0, 150.8, 141.0, 140.9, 137.5, 137.0, 136.9, 129.0, 128.7, 128.6, 127.7, 127.1, 125.7, 60.9, 51.9, 41.2, 39.9, 33.9, 33.6, 32.4, 26.3, 26.0, 25.9, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{34}N_3O_2$, 444.2651; found, 444.2647.



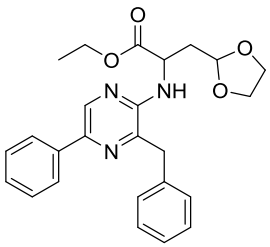
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(pyridin-2-yl)propanoate **23**{*1,1,34*} (EC31092-107-3): Obtained as an oil (0.45 g, 64%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5 to 75:25). ^{1}H NMR ($CDCl_3$): 8.42 – 8.39 (m, 1H), 8.38 (s, 1H), 7.95 – 7.89 (m, 2H), 7.52 (td, 1H, *J* = 7.6, 1.8 Hz), 7.47 – 7.39 (m, 2H), 7.36 – 7.29 (m, 3H), 7.29 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 7.11 (ddd, 1H, *J* = 7.6, 4.9, 1.0 Hz), 7.01 (d, 1H, *J* = 7.8 Hz), 6.30 (d, 1H, *J* = 7.3 Hz), 5.03 (dt, 1H, *J* = 7.3, 5.4 Hz), 4.20 (s, 2H), 4.08 (qd, 2H, *J* = 7.1, 1.1 Hz), 3.39 – 3.27 (m, 2H), 1.11 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 157.6, 150.8, 149.2, 141.3, 140.9, 137.8, 137.1, 136.9, 136.6, 128.9, 128.8, 128.7, 127.7, 126.7, 125.7, 123.8, 121.9, 61.0, 54.0, 40.6, 39.1, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_2$, 439.2134; found, 439.2152.



Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-cyclopentylpropanoate **23**{*1,1,36*} (YJ31067-067-2): Obtained as an oil (0.26 g, 58%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.38-7.32 (m, 5H), 7.29-7.26 (m, 1H), 4.78 (d, 1H, *J* = 7.4 Hz), 4.60 (m, 2H), 4.30 (d, 1H, *J* = 15.1 Hz), 4.21 (d, 1H, *J* = 15.1 Hz), 4.16 (q, 2H, *J* = 7.2 Hz), 1.83 (m, 1H), 1.70-1.39 (m, 7H), 1.24 (t, 3H, *J* = 7.2 Hz), 1.01 (m, 2H). ^{13}C NMR ($CDCl_3$): 173.8, 150.7, 141.0, 140.9, 137.6, 137.0, 136.9, 128.9, 128.7, 128.6, 127.7, 127.0, 125.6, 60.9, 53.7, 41.2, 38.3, 36.5, 32.8, 32.4, 25.0, 24.8, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_2$, 430.2495; found, 430.2485.

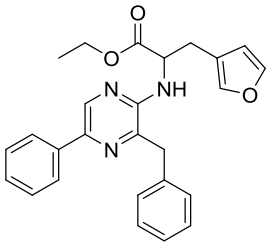


Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(tetrahydrofuran-2-yl)propanoate **23**{*1,1,38*} (YJ31134-043-3): Obtained as an oil (0.50 g, 60%) after a chromatography over silica gel (cyclohexane – ethyl acetate 9/1). ^{1}H NMR (diastereoisomeric mixture, 0.53 / 0.47 ratio) ($CDCl_3$): 8.39 (s, 1H), 7.96 (m, 2H), 7.45 (m, 2H), 7.35 (m, 5H), 7.25 (m, 1H), 4.78 (m, 0.6H), 4.59 (m, 0.4H), 4.20 (m, 4H), 3.81 (m, 1.6H), 3.70 (m, 1.4H), 2.1 (m, 1H), 1.88 (m, 4H), 1.46 (m, 1H), 1.25 (t, 1.4H, *J* = 7.2 Hz), 1.18 (t, 1.6H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 173.2/173.0, 150.9/150.5, 141.2/141.0, 140.7/140.6, 137.7/137.6, 137/137.0, 136.8/136.7, 128.9/128.8, 128.7/128.65, 128.6/128.5, 127.6/127.5, 126.7/126.6, 125.6, 76.6/76.5, 68.0/67.8, 61.0/60.9, 53.6/53.1, 40.5/40.4, 37.0/36.5, 31.9/31.8, 25.4/25.3, 14.2/14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{30}N_3O_2$, 432.2287; found, 432.2253.

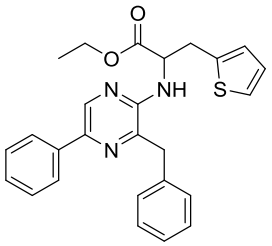


Ethyl 2-(3-benzyl-5-phenylpyrazin-2-ylamino)-3-(1,3-dioxolan-2-yl)propanoate **23**{*1,1,39*} (VHE30855-183-4): Obtained as an oil (0.61 g, 67%) after a chromatography over silica gel (cyclohexane – ethyl acetate 9/1 to 7/3). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.94 (m, 2H), 7.46 (m, 2H), 7.37 – 7.31 (m, 5H), 7.25 (m, 1H), 5.66 (m, 1H), 4.85 (t, 2H, *J* = 4.3 Hz), 4.77 (m, 1H), 4.23 (m, 2H), 4.18 (q, 2H, *J* = 7.1 Hz), 3.83 (m, 2H), 3.75 (m, 2H), 2.25 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 150.6, 141.0, 137.6, 136.9, 136.8, 128.8, 128.7, 128.6, 127.7,

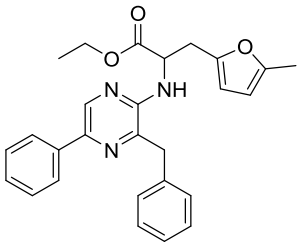
126.7, 125.6, 102.3, 64.9, 64.8, 61.1, 50.9, 40.5, 34.7, 26.9, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{28}N_3O_4$, 434.2080; found, 434.2117.



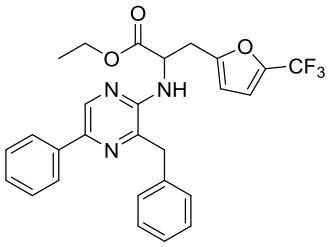
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(furan-3-yl)propanoate **23**{*1,1,40*} (VHE30855-181-3): Obtained as an oil (1.2 g, 89%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5 to 9/1). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.40 – 7.24 (m, 7H), 6.96 (m, 1H), 5.96 (m, 1H), 5.00 (m, 1H), 4.93 (m, 1H), 4.24 – 4.14 (m, 4H), 3.02 (dd, 1H, *J* = 5.1, 14.7 Hz), 2.95 (dd, 1H, *J* = 5.4, 14.7 Hz), 1.22 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 150.3, 142.9, 141.2, 141.1, 140.3, 137.5, 136.9, 136.5, 128.9, 128.7, 128.6, 127.8, 127.0, 125.6, 119.0, 111.1, 61.3, 53.8, 41.0, 27.2, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{26}N_3O_3$, 428.1974; found: 428.2006.



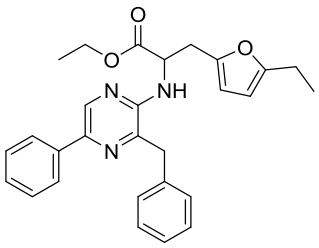
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(thiophen-2-yl)propanoate **23**{*1,1,41*} (EC31092-087-2): Obtained as an oil (0.51 g, 80%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 8.00 – 7.89 (m, 2H), 7.50 – 7.42 (m, 2H), 7.40 – 7.32 (m, 1H), 7.32 – 7.26 (m, 3H), 7.26 – 7.21 (m, 2H), 7.14 – 7.08 (m, 1H), 6.85 (dd, 1H, *J* = 5.2, 3.4 Hz), 6.58 – 6.50 (m, 1H), 5.12 (d, 1H, *J* = 7.1 Hz), 4.99 (dt, 1H, *J* = 7.1, 5.0 Hz), 4.17 (s, 2H), 4.14 (q, 2H, *J* = 7.1 Hz), 3.44 (dd, 1H, *J* = 14.6, 4.7 Hz), 3.37 (dd, 1H, *J* = 14.9, 4.9 Hz), 1.22 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.3, 141.5, 141.3, 137.8, 137.6, 137.0, 136.7, 129.0, 128.9, 128.9, 128.0, 127.0, 127.0, 126.7, 125.8, 124.7, 61.6, 54.7, 41.1, 32.0, 14.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{26}N_3O_2S$, 444.1746; found, 444.1766.



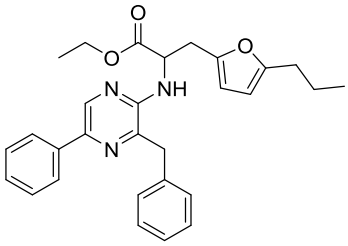
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,1,42*} (EC29990-157-2): Obtained as a yellow oil (0.69 g, 74%) after a chromatography over silica gel (dichloromethane). ^{1}H NMR ($CDCl_3$): 8.38 (s, 1H), 7.96 – 7.89 (m, 2H), 7.48 – 7.40 (m, 2H), 7.38 – 7.26 (m, 5H), 7.25 – 7.19 (m, 1H), 5.83 – 5.77 (m, 1H), 5.72 (d, 1H, *J* = 3.0 Hz), 5.11 (d, 1H, *J* = 7.5 Hz), 4.89 (dt, 1H, *J* = 7.5, 5.3 Hz), 4.21 – 4.08 (m, 4H), 3.12 (d, 2H, *J* = 5.3 Hz), 2.20 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 151.6, 150.5, 148.7, 141.3, 141.2, 137.7, 136.9, 136.8, 128.9, 128.9, 128.9, 127.9, 127.0, 125.8, 108.7, 106.3, 61.4, 53.4, 40.9, 30.7, 14.3, 13.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_3$, 442.2131; found, 442.2121.



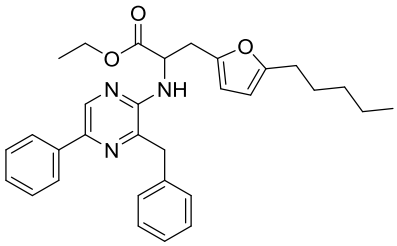
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-(trifluoromethyl)furan-2-yl)propanoate **23**{*1,1,43*} (EC31093-037-2): Obtained as an oil (0.17 g, 44%) after a chromatography over silica gel (cyclohexane-ethyl acetate 93/7). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.99 – 7.92 (m, 2H), 7.50 – 7.42 (m, 2H), 7.40 – 7.33 (m, 1H), 7.33 – 7.20 (m, 5H), 6.55 (dd, 1H, *J* = 3.3, 1.2 Hz), 5.74 (dd, 1H, *J* = 3.3, 0.6 Hz), 5.12 (d, 1H, *J* = 7.1 Hz), 4.98 (dt, 1H, *J* = 7.1, 5.2 Hz), 4.26 – 4.09 (m, 4H), 3.29 (dd, 1H, *J* = 15.2, 5.2 Hz), 3.19 (dd, 1H, *J* = 15.2, 5.2 Hz), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.6, 154.0, 150.0, 141.5 (23 Hz), 141.4 (15 Hz), 141.1 (43 Hz), 137.6, 136.9, 136.7, 129.0, 128.9, 128.8, 128.0, 127.1, 125.8, 119.2 (267 Hz), 112.5 (3 Hz), 108.8, 61.9, 52.9, 41.1, 30.6, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{25}F_3N_3O_3$, 496.1848; found, 496.1847.



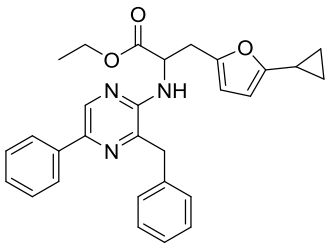
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-ethylfuran-2-yl)propanoate **23**{*1,1,44*} (EC31092-085-2): Obtained as a yellow solid (0.48 g, 74%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 7.96 – 7.89 (m, 2H), 7.50 – 7.40 (m, 2H), 7.37 – 7.26 (m, 4H), 7.26 – 7.20 (m, 2H), 5.80 (dd, 1H, *J* = 2.0, 1.0 Hz), 5.74 (d, 1H, *J* = 3.0 Hz), 5.09 (d, 1H, *J* = 7.5 Hz), 4.91 (dt, 1H, *J* = 7.5, 5.4 Hz), 4.22 – 4.08 (m, 4H), 3.14 (d, 2H, *J* = 5.3 Hz), 2.56 (qd, 2H, *J* = 7.5, 0.6 Hz), 1.21 (t, 3H, *J* = 7.3 Hz), 1.19 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 157.3, 150.5, 148.6, 141.3, 141.2, 137.7, 137.0, 136.8, 128.9 (three signals), 127.9, 127.0, 125.8, 108.5, 104.7, 61.4, 53.3, 40.9, 30.8, 21.5, 14.3, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_3$, 457.2319; found, 457.2314.



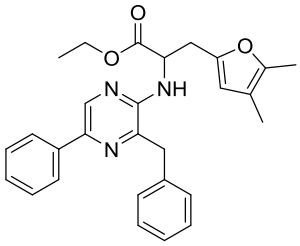
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-propylfuran-2-yl)propanoate **23**{*1,1,45*} (EC32712-117-1): This compound was obtained (using toluene at 90 °C) as an oil (0.30 g, 71%) after a chromatography over silica gel (cyclohexane–ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.31 (m, 6H), 5.83 (d, 1H, *J* = 3.0 Hz), 5.76 (d, 1H, *J* = 3.0 Hz), 5.12 (d, 1H, *J* = 7.5 Hz), 4.94 (dt, 1H, *J* = 7.5, 5.3 Hz), 4.18 (m, 4H), 3.16 (d, 2H, *J* = 5.3 Hz), 2.53 (t, 2H, *J* = 7.6 Hz), 1.65 (h, 2H, *J* = 7.4 Hz), 1.24 (t, 3H, *J* = 7.1 Hz), 0.97 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 155.7, 150.3, 148.4, 141.1, 141.0, 137.5, 136.8, 136.6, 128.8, 128.7, 127.7, 126.8, 125.6, 108.3, 105.5, 61.2, 53.2, 40.7, 30.6, 30.0, 21.3, 14.1, 13.7, (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_3$: 470.2444; found, 470.2445.



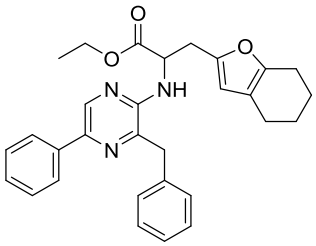
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-pentylfuran-2-yl)propanoate propanoate **23**{*1,1,46*} (YJ 31776-021-2): Obtained as an oil (0.30 g, 60%) after two chromatography over silica gel (cyclohexane-ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.94 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.38 - 7.23 (m, 5H), 5.82 (m, 1H), 5.75 (d, 1H, *J* = 3.1 Hz), 5.14 (d (br), *J* = 7.3 Hz), 4.93 (m, 1H), 4.17 (m, 4H), 3.16 (d, 2H, *J* = 5.3 Hz), 2.54 (t, 2H, *J* = 7.6 Hz), 1.62 (m, 2H), 1.34 (m, 4H), 1.24 (d, 3H, *J* = 7.0 Hz), 0.92 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 156.0, 150.2, 148.3, 141.3, 141.0, 137.4, 136.6, 136.5, 128.8, 128.7 (two signals), 127.8, 126.8, 125.6, 108.4, 105.3, 61.2, 53.2, 40.7, 31.3, 30.6, 28.0, 27.7, 22.4, 14.1, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{36}N_3O_3$: 498.2557; found, 498.2743.



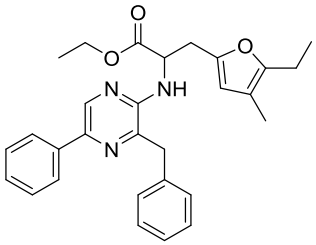
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-cyclopropylfuran-2-yl)propanoate **23**{*1,1,47*} (EC31093-075-2): Obtained as an oil (0.31 g, 67%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 7.97 – 7.90 (m, 2H), 7.48 – 7.41 (m, 2H), 7.38 – 7.20 (m, 6H), 5.78 (dd, 1H, *J* = 3.1, 0.5 Hz), 5.72 (d, 1H, *J* = 3.1 Hz), 5.08 (d, 1H, *J* = 7.6 Hz), 4.90 (dt, 1H, *J* = 7.6, 5.3 Hz), 4.20 – 4.11 (m, 4H), 3.12 (d, 2H, *J* = 5.3 Hz), 1.81 (tt, 1H, *J* = 8.5, 5.1 Hz), 1.22 (t, 3H, *J* = 7.1 Hz), 0.88 – 0.80 (m, 2H), 0.73 – 0.65 (m, 2H). ^{13}C NMR ($CDCl_3$): 172.2, 156.9, 150.5, 148.3, 141.3, 141.2, 137.7, 136.9, 136.7, 128.9 (three signals), 127.9, 127.0, 125.8, 108.7, 104.3, 61.4, 53.2, 40.9, 30.8, 14.3, 8.9, 6.6.HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_3$, 468.2287; found, 468.2291.



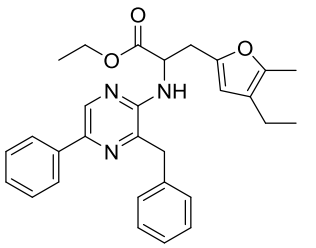
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethylfuran-2-yl)propanoate **23**{*1,1,48*} (EC31092-101-3): Obtained as an oil (0.20 g, 49%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 7.97 – 7.90 (m, 2H), 7.50 – 7.40 (m, 2H), 7.39 – 7.19 (m, 6H), 5.65 (s, 1H), 5.11 (d, 1H, *J* = 7.5 Hz), 4.88 (dt, 1H, *J* = 7.5, 5.4 Hz), 4.19 – 4.12 (m, 4H), 3.09 (d, 2H, *J* = 5.4 Hz), 2.12 (s, 3H), 1.87 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 150.6, 147.4, 146.8, 141.3, 141.2, 137.7, 137.0, 136.8, 128.9, 128.8, 127.9, 126.9, 125.8, 114.5, 111.2 (two signals), 61.3, 53.4, 40.8, 30.7, 14.2, 11.4, 10.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_3$, 456.2287; found, 456.2337.



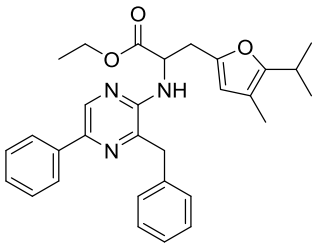
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4,5,6,7-tetrahydrobenzofuran-2-yl)propanoate **23**{*1,1,49*} (YJ 33068-073-2): Obtained as an oil (0.38 g, 73%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.95 (m, 2H), 7.46 (m, 2H), 7.36 (m, 1H), 7.32 - 7.23 (m, 5H), 5.68 (s, 1H), 5.17 (d (br), *J* = 7.6 Hz), 4.91 (m, 1H), 4.17 (m, 4H), 3.13 (m, 2H), 2.52 (m, 2H), 2.35 (m, 2H), 1.82 (m, 2H), 1.72 (m, 2H), 1.22 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 150.2, 150.1, 147.8, 141.3, 141.0, 137.4, 136.6, 136.5, 128.7 (three signals), 127.8, 126.8, 125.6, 117.4, 108.8, 61.2, 53.4, 40.7, 30.7, 23.1, 23.0 (two signals), 22.1, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{32}N_3O_3$, 482.2444; found, 482.2428.



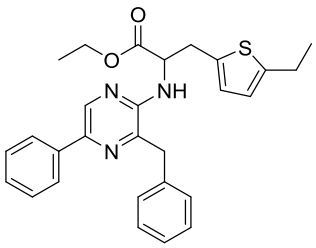
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-ethyl-4-methylfuran-2-yl)propanoate **23**{*1,1,50*} (YJ 33069-007-1): Obtained as an oil (0.63 g, 76%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.95 (m, 2H), 7.46 (m, 2H), 7.37 (m, 1H), 7.38 - 7.23 (m, 5H), 5.66 (s, 1H), 5.14 (d (br), *J* = 7.4 Hz), 4.92 (m, 1H), 4.18 (m, 4H), 3.13 (m, 2H), 2.52 (q, 2H, *J* = 7.5 Hz), 1.91 (s, 3H), 1.24 (t, 3H *J* = 7.1 Hz), 1.20 (t, 3H *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 151.9, 150.3, 147.2, 141.2, 141.0, 137.5, 136.6, 128.7 (four signals), 127.8, 126.8, 125.6, 113.5, 111.1, 61.2, 53.2, 40.7, 30.6, 19.3, 14.1, 12.9, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_3$, 470.2444; found, 470.2450.



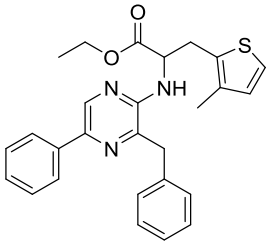
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-ethyl-5-methylfuran-2-yl)propanoate **23**{*1,1,51*} (YJ 33068-077-2): Obtained as an oil (0.32 g, 63%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.95 (m, 2H), 7.46 (m, 2H), 7.37 (m, 1H), 7.32 - 7.23 (m, 5H), 5.76 (s, 1H), 5.15 (d (br), *J* = 7.7 Hz), 4.91 (m, 1H), 4.17 (m, 4H), 3.11 (m, 2H), 2.30 (q, 2H, *J* = 7.6 Hz), 2.16 (s, 3H), 1.22 (d, 3H *J* = 7.0 Hz), 1.11 (d, 3H *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 150.3, 147.4, 145.9, 141.2, 141.0, 137.5, 136.6, 136.5, 128.7 (four signals), 127.8, 126.8, 125.6, 121.2, 109.5, 61.2, 53.3, 40.6, 30.7, 18.0, 14.9, 14.1, 11.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_3$, 470.2444; found, 470.2425.



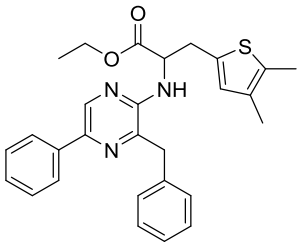
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-isopropyl-4-methylfuran-2-yl)propanoate **23**{*1,1,52*} (YJ 33068-095-1): Obtained as an oil (0.47 g, 85%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.94 (m, 2H), 7.46 (m, 2H), 7.37 (m, 1H), 7.38 - 7.23 (m, 5H), 5.63 (s, 1H), 5.10 (d (br), *J* = 7.4 Hz), 4.93 (m, 1H), 4.18 (m, 4H), 3.13 (m, 2H), 2.94 (sept, 1H, *J* = 6.5 Hz), 1.91 (s, 3H), 1.24 (d, 3H *J* = 7.0 Hz), 1.20 (d, 3H *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 154.9, 150.3, 146.8, 141.2, 141.0, 137.5, 136.5, 128.7 (four signals), 127.8, 126.8, 125.6, 112.3, 111.2, 61.2, 53.1, 40.6, 30.6, 26.1, 21.4, 21.3, 11.1, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{34}N_3O_3$, 484.2600; found, 484.2609.



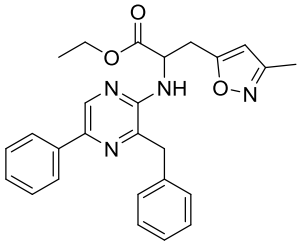
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-ethylthiophen-2-yl)propanoate **23**{*1,1,53*} (YJ30367-165-2): Obtained as an oil (0.47 g, 84%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.33 – 7.23 (m, 5H), 6.55 (m, 1H), 6.39 (m, 1H), 5.13 (d, 1H, *J* = 7.1 Hz), 4.91 (m, 1H), 4.17 (m, 4H), 3.34 (m, 2H), 2.79 (qd, 2H, *J* = 0.8, 7.5 Hz), 1.30 (t, 3H, *J* = 7.5 Hz), 1.24 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.2, 146.7, 141.3, 141.1, 137.5, 136.7, 136.6, 134.9, 128.8, 128,7 (two signals), 127.8, 126.8, 126.2, 125.6, 123.0, 61.3, 54.6, 40.8, 32.2, 23.4, 15.8, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_2S$, 472.2059; found, 472.2055.



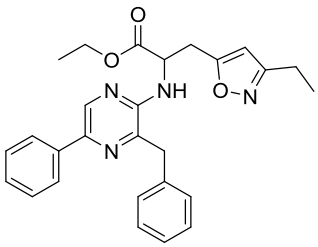
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-methylthiophen-2-yl)propanoate **23**{*1,1,54*} (YJ30367-167-2): Obtained as an oil (0.41 g, 76%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.97 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.33 – 7.23 (m, 5H), 7.05 (d, 1H, *J* = 4.8 Hz), 6.75 (d, 1H, *J* = 4.8 Hz), 5.15 (d, 1H, *J* = 7.1 Hz), 4.96 (m, 1H), 4.15 (m, 4H), 3.41 (dd, 1H, *J* = 5.1, 15.1 Hz), 3.31 (dd, 1H, *J* = 5.1, 15.1 Hz), 2.0 (s, 3H), 1.23 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 150.3, 141.4, 141.1, 137.5, 136.7, 136.5, 135.2, 131.2, 129.8, 128,8, 128.7 (two signals), 127.8, 126.8, 125.6, 122.8, 61.4, 54.7, 40.8, 29.8, 14.0, 13.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_2S$, 458.1902; found, 458.1910.



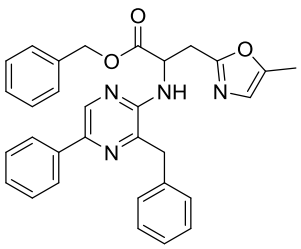
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethylthiophen-2-yl)propanoate **23**{*1,1,55*} (YJ31067-103-2): Obtained as an oil (0.24 g, 47%) after a chromatography over silica gel (cyclohexane-ethyl acetate 96:4). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 7.28 (m, 5H), 6.33 (s, 1H), 5.12 (d, 1H, *J* = 7.3 Hz), 4.92 (dt, 1H, *J* = 7.2, 5.0 Hz), 4.18 (m, 4H), 3.32 (dd, 1H, *J* = 4.7, 14.8 Hz), 3.26 (dd, 1H, *J* = 5.4, 14.8 Hz), 2.28 (s, 3H), 2.06 (s, 3H), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.3, 141.3, 141.1, 137.5, 136.7, 136.6, 132.6, 132.5, 132.0, 129.6, 128.8, 128.7, 127.8, 126.8, 125.6, 61.3, 54.6, 40.7, 32.0, 14.1, 13.5, 12.0 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_2S$, 472.2059; found, 472.2054.



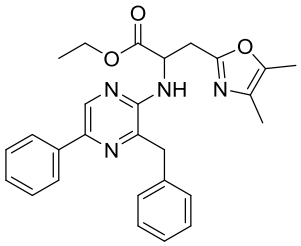
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-methylisoxazol-5-yl)propanoate **23**{*1,1,56*} (EC32712-027-2): Obtained as a yellow oil (0.17 g, 48%) after a chromatography over silica gel (cyclohexane–ethyl acetate 5:1). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.33 (m, 6H), 5.48 (s, 1H), 5.20 (d, 1H, *J* = 6.9 Hz), 5.01 (dt, 1H, *J* = 6.9, 5.2 Hz), 4.19 (m, 4H), 3.41 (dd, 1H, *J* = 15.4, 5.1 Hz), 3.28 (dd, 1H, *J* = 15.4, 5.3 Hz), 2.22 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.2, 167.9, 159.6, 149.9, 141.5, 141.4, 137.3, 136.7, 136.5, 128.9, 128.8, 128.7, 127.9, 126.9, 125.7, 103.2, 61.8, 52.4, 41.0, 29.0, 14.1, 11.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{27}N_4O_3$: 443.2083; found, 443.2092.



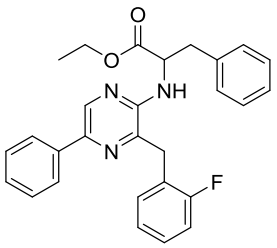
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-ethylisoxazol-5-yl)propanoate **23**{*1,1,57*} (EC32712-027-2): Obtained as a yellow oil (0.29 g, 50%) after a chromatography over silica gel (cyclohexane–ethyl acetate 5:1). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.96 (m, 2H), 7.48 (m, 2H), 7.33 (m, 6H), 5.57 (s, 1H), 5.20 (d, 1H, *J* = 7.0 Hz), 5.02 (dt, 1H, *J* = 7.0, 5.3 Hz), 4.17 (m, 4H), 3.40 (dd, 1H, *J* = 15.3, 5.1 Hz), 3.28 (dd, 1H, *J* = 15.3, 5.4 Hz), 2.62 (qd, 2H, *J* = 7.6, 1.7 Hz), 1.23 (m, 6H). ^{13}C NMR ($CDCl_3$): 171.3, 167.8, 165.0, 149.9, 141.5, 141.4, 137.3, 136.7, 136.5, 128.8, 128.8, 128.7, 127.9, 126.9, 125.7, 101.9, 61.8, 52.5, 40.9, 29.2, 19.5, 14.1, 12.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{29}N_4O_3$: 457.2240; found, 457.2244.



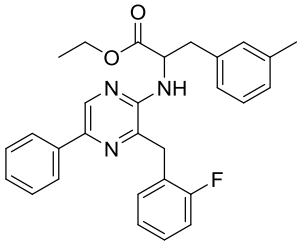
Benzyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(5-methyloxazol-2-yl)propanoate **23**{*1,1,58*} (YJ31776-087-2): Obtained a wax (0.37 g) still containing some BINAP after a chromatography over silica gel (cyclohexane–ethyl acetate 99:1 to 3/2). ^{1}H NMR ($CDCl_3$): 8.37 (s, 1H), 7.94 (m, 2H), 7.48 (m, 2H), 7.39 - 7.21 (m, 13H), 6.58 (m, 1H), 5.78 (d(br), 1H, J = 7.30 Hz), 5.16 (m, 3H), 4.19 (s, 2H), 3.37 (dd, 1H, *J* = 5.6, 15.8 Hz), 3.28 (dd, 1H, *J* = 5.2, 15.8 Hz), 2.22 (d, 3H, *J* = 1.0 Hz). This was used directly in the next step.



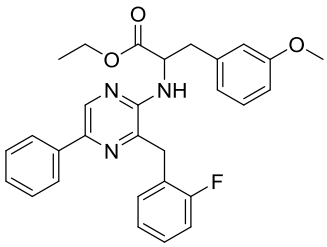
Ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethyloxazol-2-yl)propanoate **23**{*1,1,59*} (YJ31067-045-2): Obtained as an oil (0.20 g, 49%) after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3 to 3/1). ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 7.93 (m, 2H), 7.46 (m, 2H), 7.37 – 7.21 (m, 6H), 5.75 (d, 1H, *J* = 7.8 Hz), 5.07 (m, 1H), 4.20 (m, 2H), 4.15 (q, 2H, *J* = 7.1 Hz), 3.30 (dd, 1H, *J* = 5.6 and 15.3 Hz), 3.22 (dd, 1H, *J* = 5.4 and 15.3 Hz), 2.17 (s, 3H), 2.05 (s, 3H), 1.18 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.6, 157.8, 150.3, 143.2, 141.4, 141.2, 137.5, 136.8, 136.7, 130.4, 128.8, 128.7, 128.6, 127.7, 126.7, 125.6, 61.4, 52.0, 40.5, 30.4, 14.0, 11.1, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{29}N_4O_3$, 457.2240; found, 457.2234.



Ethyl (3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,2,1*} (GG30532-117-1): Obtained as an oil (0.19 g, 40%) after a chromatography over silica gel (cyclohexane-ethyl acetate 94/6). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.94-7.91 (m, 2H), 7.48-7.44 (m, 2H), 7.38-7.34 (m, 1H), 7.28-7.22 (m, 5H), 7.11-7.05 (m, 4H), 5.10-5.08 (m, 1H), 5.04-4.99 (m, 1H), 4.20-4.09 (m, 4H), 3.28-3.23 (m, 1H), 3.18-3.13 (m, 1H), 1.23-1.20 (t, 3H, *J* = 7.9 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 161.9, 159.5, 150.1, 141.1, 140.0, 137.4, 136.9, 136.3, 130.8, 129.2, 128.7, 128.6, 128.5, 128.4, 127.8, 126.9, 125.6, 124.4, 124.3, 123.5, 115.4, 61.2, 55.1, 38.0, 32.6, 30.2, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2096.

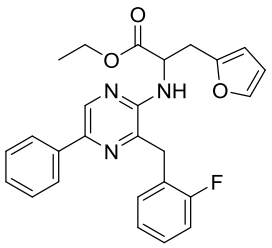


Ethyl 2-((3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(m-tolyl)propanoate **23**{*1,2,12*} (YJ31070-037-1): Obtained as an oil (0.34 g, 69%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.91 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.23 (m, 2H), 7.16-7.04 (m, 4H), 6.95 (m, 1H), 6.88 (m, 1H), 5.06 (d(br), 1H, *J* = 7.3 Hz), 4.97 (m, 1H), 4.15 (m, 4H), 3.20 (dd, 1H, *J* = 5.5, 13.7 Hz), 3.10 (dd, 1H, *J* = 6.7, 13.7 Hz), 2.31 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 160.7 (244 Hz), 150.2, 141.1, 139.9, 138.0, 137.4, 136.9, 136.2, 130.8 (4 Hz), 130.0, 128.7, 128.5 (8 Hz), 128.4, 127.8, 127.7, 126.2, 125.6, 124.3 (4 Hz), 123.5 (15 Hz), 115.3 (22 Hz), 61.1, 55.2, 37.9, 32.6 (3 Hz), 21.3, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}FN_3O_2$, 470.2244, found, 470.2253.

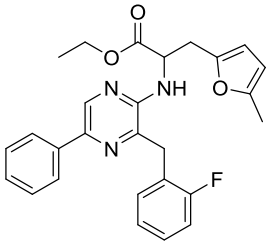


Ethyl 2-((3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(3-methoxyphenyl)propanoate **23**{*1,2,15*} (YJ31070-039-1): Obtained as an oil (0.32 g, 63%) after a chromatography over silica gel (cyclohexane-ethyl acetate 94/6). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.91 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.23 (m, 2H), 7.16 (m, 1H), 7.06 (m, 2H), 6.78 (m, 1H), 6.68 (m, 2H), 5.08 (d(br), 1H, *J* = 7.2 Hz), 4.99 (m, 1H), 4.16 (m, 4H), 3.77 (s, 3H), 3.23 (dd, 1H, *J* = 5.6, 13.9 Hz), 3.12 (dd, 1H, *J* = 6.4, 13.9 Hz), 1.22 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 160.7 (244 Hz), 159.6, 150.2, 141.1, 140.0, 137.9, 137.4, 136.9, 130.8 (4 Hz), 129.4, 128.7, 128.5 (8 Hz), 127.8, 127.8,

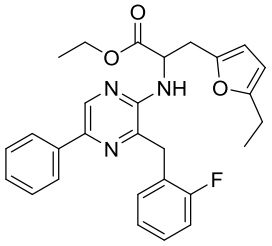
125.6, 124.3 (4 Hz), 123.4 (15 Hz), 121.5, 115.3 (22 Hz), 114.8, 112.4, 61.2, 55.1 (two signals), 38.0, 32.6 (3 Hz), 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}FN_3O_3$, 486.2193, found, 486.2182.



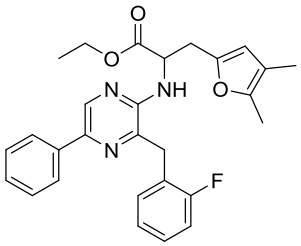
Ethyl 2-((3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,2,37*} (YJ31070-041-1): Obtained as an oil (0.29 g, 62%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.92 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.26 (m, 3H), 7.09 (m, 2H), 6.24 (dd, 1H, *J* = 1.9, 3.2 Hz), 5.95 (d, 1H, *J* = 3.1 Hz), 5.28 (d(br), 1H, *J* = 7.6 Hz), 5.01 (m, 1H), 4.19 (m, 4H), 3.77 (s, 3H), 3.26 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 160.8 (244 Hz), 150.6, 150.1, 142.0, 141.1, 140.0, 137.4, 136.8, 130.8 (4 Hz), 128.7, 128.5 (8 Hz), 127.8, 125.6, 124.3 (4 Hz), 123.5 (15 Hz), 115.3 (22 Hz), 110.3, 107.7, 61.3, 53.3, 32.6 (3 Hz), 30.5, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{25}FN_3O_3$, 446.1880, found, 446.1873.



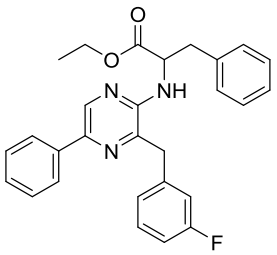
Ethyl 2-((3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,2,42*} (YJ31070-043-1): Obtained as an oil (0.23 g, 48%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.91 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.25 (m, 2H), 7.08 (m, 2H), 5.82 (m, 2H), 5.27 (d(br), 1H, *J* = 7.6 Hz), 4.97 (m, 1H), 4.19 (m, 4H), 3.77 (s, 3H), 3.20 (d, 2H, *J* = 5.8 Hz), 2.23 (s, 3H), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 160.8 (244 Hz), 151.5, 150.1, 148.6, 141.1, 139.9, 137.4, 136.8, 130.8 (4 Hz), 128.7, 128.5 (8 Hz), 127.8, 125.6, 124.3 (4 Hz), 123.6 (15 Hz), 115.3 (22 Hz), 108.5, 106.1, 61.2, 53.4, 32.5 (3 Hz), 30.6, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}FN_3O_3$, 460.2036, found, 460.2044.



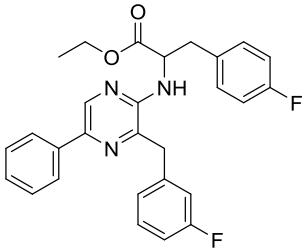
Ethyl 3-(5-ethylfuran-2-yl)-2-((3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)propanoate **23**{*1,2,44*} (YJ31068-011-1): Obtained an oil (0.19 g, 46%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.91 (m, 2H), 7.46 (m, 2H), 7.34 (m, 1H), 7.25 (m, 2H), 7.07 (m, 2H), 5.82 (m, 2H), 5.27 (d(br), 1H, *J* = 7.3 Hz), 4.97 (m, 1H), 4.20 (m, 4H), 3.77 (s, 3H), 3.20 (d, 2H, *J* = 5.1 Hz), 2.57 (q, 2H, *J* = 7.5 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.20 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 160.8 (244 Hz), 157.3, 150.1, 148.4, 141.1, 139.9, 137.4, 136.8, 130.8 (4 Hz), 128.7, 128.5 (8 Hz), 127.8, 125.6, 124.3 (4 Hz), 123.6 (15 Hz), 115.2 (22 Hz), 108.3, 104.5, 61.2, 53.4, 32.5 (3 Hz), 30.7, 21.3, 14.1, 12.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_3$, 474.2193, found, 474.2198.



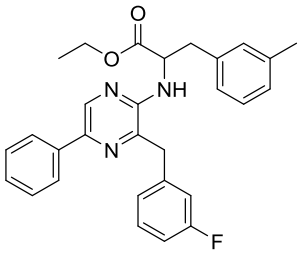
Ethyl 3-(4,5-dimethylfuran-2-yl)-2-((3-(2-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)propanoate **23**{*1,2,48*} (EC32712-113-1): Obtained an oil (0.32 g, 81%) after a chromatography over silica gel (cyclohexane-ethyl acetate 97/3).^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.91 (dd, 2H, *J* = 7.2, 1.6 Hz), 7.44 (m, 2H), 7.35 (m, 1H), 7.25 (m, 2H), 7.08 (m, 2H), 5.74 (s, 1H, 1H), 5.26 (d, *J* = 7.4 Hz), 4.94 (dt, 1H, *J* = 7.7, 5.5 Hz), 4.20 (m, 4H), 3.15 (d, 2H, *J* = 5.5 Hz), 2.13 (s, 3H), 1.88 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 160.8 (244 Hz), 150.2, 147.2, 146.7, 141.1, 139.9, 137.4, 136.9, 130.8 (4 Hz), 128.7, 128.4 (8 Hz), 127.7, 125.5, 124.2 (4 Hz), 123.7 (16 Hz), 115.2 (22 Hz), 114.4, 111.0, 61.2, 53.4, 32.5 (3 Hz), 30.6, 14.1, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_3$: 474.2193; found, 474.2194.



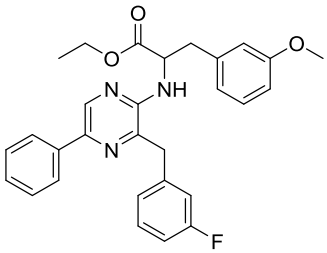
Ethyl (3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,3,1*} (YJ31067-149-1): Obtained as an oil (0.40 g, 57%) after a chromatography over silica gel (cyclohexane-ethyl acetate 94:6). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.95 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 7.36 – 7.21 (m, 4H), 7.10 - 6.92 (m, 5H), 5.02 (m, 1H), 4.85 (d(br), 1H, *J* = 7.5 Hz), 4.16 (q, 2H, *J* = 7.2 Hz), 4.11 (s, 2H), 3.21 (dd, 1H, *J* = 5.4, 13.8 Hz), 3.13 (dd, 1H, *J* = 5.9, 13.8 Hz), 1.22 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 163.0 (246 Hz), 150.3, 141.3, 140.3, 139.1 (7 Hz), 137.3, 137.1, 136.1, 130.1 (8 Hz), 129.2, 129.0, 128.4, 127.9, 127.0, 125.6, 124.2 (2 Hz), 115.5 (22 Hz), 113.9 (21 Hz), 61.2, 54.8, 40.3, 37.7, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2067.



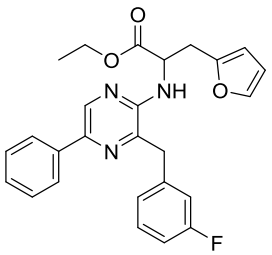
Ethyl 2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4-fluorophenyl)propanoate **23**{*1,3,4*} (YJ 31069-025-3): Obtained as an oil (0.42 g, 58%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$) 8.45 (s, 1H), 7.95 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 7.24 (m, 1H), 7.01 - 6.86 (m, 7H), 4.97 (m, 1H), 4.19 (d(br), 1H, J = 6.9 Hz), 4.16 (m, 4H), 3.20 (dd, 1H, J = 14.1 and 5.5 Hz), 3.09 (dd, 1H, J = 14.1 and 5.5 Hz), 1.24 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 163.0 (246 Hz), 161.9 (246 Hz), 150.1, 141.3, 139.0 (7 Hz), 137.2, 137.0, 131.8 (3 Hz), 130.6 (8 Hz), 130.3 (8 Hz), 128.8, 127.8, 125.7, 124.2 (2 Hz), 115.5 (21 Hz), 115.2 (21 Hz), 113.9 (21 Hz), 61.4, 54.8, 40.5, 36.8, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}F_2N_3O_2$: 474.1993; found, 474.1928.



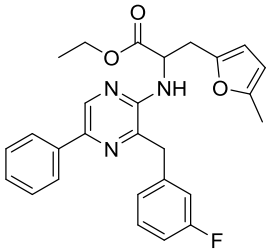
Ethyl 2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(m-tolyl)propanoate **23**{*1,3,12*} (YJ31068-041-1): Obtained as an oil (0.35 g, 74%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.94 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.23 (m, 1H), 7.14 (m, 1H), 7.07 (m, 1H), 6.93 (m, 3H), 6.81 (m, 1H), 4.96 (m, 1H), 4.82 (d(br), 1H, *J* = 7.4), 4.18 (m, 4H), 3.17 (dd, 1H, *J* = 5.5, 13.7), 3.09 (dd, 1H, *J* = 6.2, 13.7), 2.32 (s, 3H), 1.21 (t, 3H *J* = 7.1). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}FN_3O_2$: 470.2244; found, 470.2249.



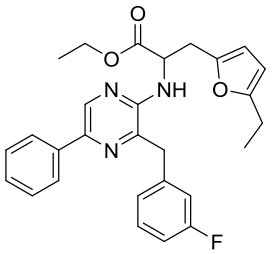
Ethyl 2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(3-methoxyphenyl)propanoate **23**{*1,3,15*} (YJ31068-043-1): Obtained as an oil (0.22 g, 45%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.94 (m, 2H), 7.47 (m, 2H), 7.36 (m, 1H), 7.19 (m, 2H), 6.93 (m, 3H), 6.79 (m, 1H), 6.60 (m, 2H), 4.97 (m, 1H), 4.81 (d(br), 1H, *J* = 7.7), 4.18 (m, 4H), 3.77 (s, 3H), 3.19 (dd, 1H, *J* = 5.7, 13.8), 3.10 (dd, 1H, *J* = 5.9, 13.8), 1.21 (t, 3H *J* = 7.1). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}FN_3O_3$: 486.2193; found, 486.2209.



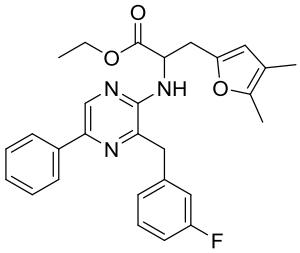
Ethyl 2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,3,37*} (YJ31070-031-2): Obtained as an oil (0.22 g, 57%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.95 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H), 7.28 (m, 2H), 7.06 (m, 1H), 6.96 (m, 2H), 6.24 (dd, 1H, *J* = 2.0, 3.2 Hz), 5.89 (dd, 1H, *J* = 0.7, 3.2 Hz), 5.08 (d(br), 1H, *J* = 7.5 Hz), 4.87 (m, 1H), 4.18 (m, 4H), 3.24 (d, 2H, *J* = 5.3 Hz), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 163.0 (246 Hz), 150.5, 150.2, 142.0, 141.3, 140.4, 139.1 (7 Hz), 137.3, 137.0, 130.1 (8 Hz), 128.7, 127.9, 125.6, 124.2 (2 Hz), 115.6 (22 Hz), 113.8 (21 Hz), 110.3, 107.8, 61.4, 53.2, 40.4, 30.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{25}FN_3O_3$, 446.1880; found, 446.1883.



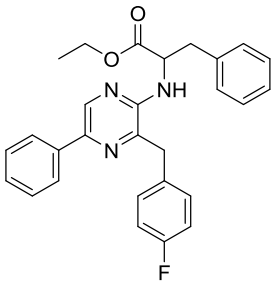
Ethyl 2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,3,42*} (YJ31068-013-1): Obtained as an oil (0.24 g, 57%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.93 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.28 (m, 1H), 7.06 (m, 1H), 6.96 (m, 2H), 5.82 (m, 1H), 5.78 (m, 1H), 5.06 (d(br), 1H, *J* = 7.9 Hz), 4.93 (m, 1H), 4.18 (m, 4H), 3.20 (d, 2H, *J* = 5.2 Hz), 2.22 (s, 3H), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 163.0 (244 Hz), 151.5, 150.3, 148.4, 141.2, 140.4, 139.1 (7 Hz), 137.3, 137.0, 130.1 (8 Hz), 128.8, 127.9, 125.6, 124.3 (2 Hz), 115.6 (22 Hz), 113.8 (21 Hz), 108.6, 106.2, 61.3, 53.2, 40.3 (2 Hz), 30.5, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}FN_3O_3$, 460.2036; found, 460.2039.



Ethyl 3-(5-ethylfuran-2-yl)-2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)propanoate **23**{*1,3,44*} (YJ31068-015-1): Obtained as an oil (0.20 g, 90% pure) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.94 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.27 (m, 1H), 7.06 (m, 1H), 6.96 (m, 2H), 5.82 (m, 1H), 5.78 (m, 1H), 5.06 (d(br), 1H, *J* = 7.7 Hz), 4.94 (m, 1H), 4.18 (m, 4H), 3.20 (d, 2H, *J* = 5.1 Hz), 2.57 (q, 2H, *J* = 7.6 Hz), 1.22 (m, 6H). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_3$, 474.2193; found, 474.2199.

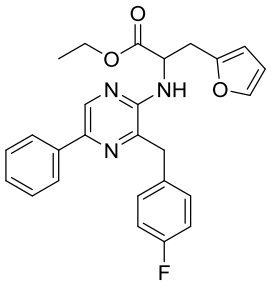


Ethyl 3-(4,5-dimethylfuran-2-yl)-2-((3-(3-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)propanoate **23**{*1,3,48*} (EC32712-115-1): Obtained as an oil (0.35 g, 88%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.94 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.27 (m, 1H), 7.07 (m, 1H), 6.97 (m, 2H), 5.70 (s, 1H), 5.08 (d, 1H, *J* = 7.6 Hz), 4.91 (dt, 1H, *J* = 7.6, 5.3 Hz), 4.19 (m, 4H), 3.14 (m, 2H), 2.13 (s, 2H), 1.89 (s, 2H), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 163.0 (246 Hz), 150.4, 147.1, 146.7, 141.2, 140.3, 139.2 (7 Hz), 137.4, 137.1, 130.1 (8 Hz), 128.7, 127.8, 125.6, 124.3 (3 Hz), 115.6 (22 Hz), 114.4, 113.7 (21 Hz), 111.1, 61.2, 53.2, 40.2 (2 Hz), 30.5, 14.1, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_3$: 474.2193; found, 474.2187.

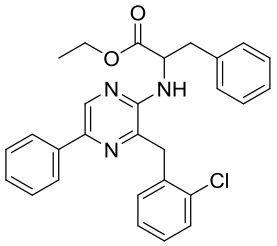


Ethyl (3-(4-fluorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,4,1*} (YJ31067-151-1): Obtained as an oil (0.12 g, 34%) after a chromatography over silica gel (cyclohexane-ethyl acetate 94:6). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.96 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 7.27 – 7.22 (m, 3H), 7.16 (m, 2H), 7.01 - 6.94 (m, 4H), 5.02 (m, 1H), 4.88 (d(br), 1H, *J* = 7.5 Hz), 4.16 (q, 2H, *J* = 7.0 Hz), 4.10 (s, 2H), 3.24 (dd, 1H, *J* = 5.5, 13.8 Hz), 3.14 (dd,

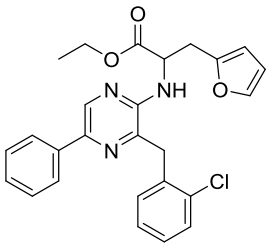
1H, *J* = 5.9, 13.8 Hz), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 161.8 (244 Hz), 150.3, 141.2, 140.9, 137.4, 137.0, 136.1, 132.1 (3 Hz), 130.1 (8 Hz), 129.2, 128.8, 128.5, 127.9, 126.9, 125.6, 115.6 (22 Hz), 61.2, 54.8, 39.9, 37.7, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2072.



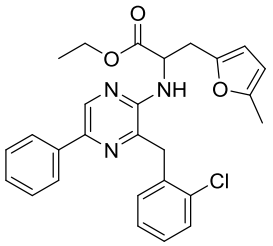
Ethyl 2-((3-(4-fluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,4,37*} (YJ 31776-005-1): Obtained as an oil (0.30 g, 71%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 96:4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.95 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.26 (m, 3H), 6.99 (m, 2H), 6.24 (m, 1H), 5.86 (d (br), 1H, *J* = 5.8 Hz), 5.09 (d (br), 1H, *J* = 7.8 Hz), 4.96 (m, 1H), 4.20 (m, 2H), 4.14 (s, 2H), 3.23 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 161.8 (244 Hz), 150.5, 150.0, 141.9, 141.2, 141.0, 137.3, 136.7, 132.1 (3 Hz), 130.1 (8 Hz), 128.8, 127.9, 125.6, 115.6 (22 Hz), 110.3, 107.8, 61.4, 53.2, 39.9, 30.3, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{25}FN_3O_3$, 446.1880; found, 446.1886.



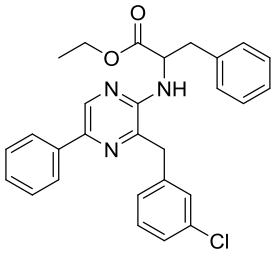
Ethyl (3-(2-chlorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,5,1*} (EC31094-099-2): Obtained as an oil (0.19 g, 68%) after a chromatography over silica gel (cyclohexane-ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.91 (m, 2H), 7.44 (m, 3H), 7.35 (m, 1H), 7.26-7.16 (m, 6H), 7.05 (m, 2H), 5.00 (m, 2H), 4.24 (m, 2H), 4.16 (dq, 2H, *J* = 7.2, 1.0 Hz), 3.22 (dd, 1H, *J* = 13.7, 5.4 Hz), 3.13 (dd, 1H, *J* = 13.7, 6.3 Hz), 1.22 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 150.3, 141.2, 140.0, 137.4, 136.9, 136.3, 134.5, 134.0, 130.4, 129.5, 129.2, 128.7, 128.5, 128.2, 127.8, 127.0, 126.9, 125.6, 61.2, 55.0, 38.0, 37.1, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}ClN_3O_2$: 472.1792; found, 472.1784.



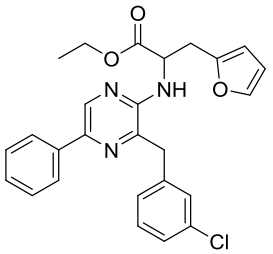
Ethyl 2-((3-(2-chlorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,5,37*} (EC31094-097-2): Obtained as an oil (0.44 g, 65%) after a chromatography over silica gel (cyclohexane-ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.91 (m, 2H), 7.45 (m, 3H), 7.35 (m, 1H), 7.25-7.15 (m, 4H), 6.22 (m, 1H), 5.92 (m, 1H), 5.18 (m, 1H), 5.00 (m, 1H), 4.28 (m, 2H), 4.19 (q, 2H, *J* = 7.1 Hz), 3.24 (d, 2H, *J* = 5.5 Hz), 1.24 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.6, 150.2, 142.0, 141.2, 140.0, 137.4, 136.9, 134.5, 134.1, 130.4, 129.5, 128.7, 128.2, 127.8, 127.0, 125.6, 110.3, 107.7, 61.3, 53.3, 37.1, 30.5, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{25}ClN_3O_3$: 462.1584; found, 462.1576.



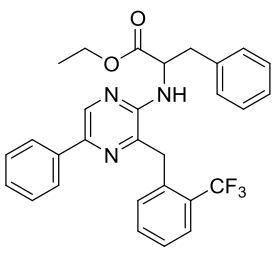
Ethyl 2-((3-(2-chlorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,5,42*} (YJ31068-009-1): Obtained as an oil (0.11 g, 36%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.91 (m, 2H), 7.43 (m, 3H), 7.35 (m, 1H), 7.20 (m, 3H), 6.22 (m, 1H), 5.80 (m, 2H), 5.19 (d (br), 1H, *J* = 7.6 Hz), 4.98 (m, 1H), 4.28 (m, 2H), 4.20 (m, 2H), 3.19 (m, 2H), 2.21 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 151.5, 150.3, 148.5, 141.1, 139.9, 137.4, 136.8, 134.6, 134.1, 130.4, 129.5, 128.7, 128.2, 127.8, 127.0, 125.5, 108.6, 106.2, 61.2, 53.3, 37.0, 30.6, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}ClN_3O_3$: 476.1741; found, 476.1744.



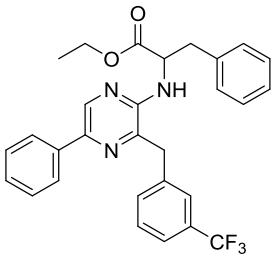
Ethyl (3-(3-chlorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,6,1*} (YJ 31776-015-1): Obtained as an oil (0.23 g, 55%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.94 (m, 2H), 7.47 (m, 2H), 7.37 (m, 1H), 7.22 (m, 6H), 7.07 (m, 1H), 7.00 (m, 1H), 5.01 (m, 1H), 4.84 (d (br), 1H, *J* = 7.6 Hz,), 4.18 (q, 2H, *J* = 7.2 Hz), 4.09 (s, 2H), 3.21 (dd, 1H, *J* = 5.7, 13.8 Hz), 3.12 (dd, 1H, *J* = 5.9, 13.8 Hz), 1.22 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 150.0, 141.2, 140.3, 138.5, 140.2, 138.7, 137.1, 136.7, 136.0, 134.6, 130.0, 129.2, 128.8, 128.7, 128.5, 128.0, 127.2, 127.0, 126.8, 125.7, 61.3, 54.9, 40.2, 37.7, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}ClN_3O_2$: 472.1792; found, 472.1789.



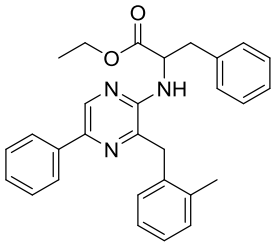
Ethyl 2-((3-(3-chlorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,6,37*} (EC31095-083-3): Obtained as a yellow oil (0.16 g, 36%) after a chromatography over silica gel (cyclohexane–ethyl acetate 97:3). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.94 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 7.27 (m, 2H), 7.24 (m, 2H), 7.16 (m, 1H), 6.25 (dd, 1H, *J* = 3.2, 1.9 Hz), 5.89 (dd, 1H, *J* = 3.2, 0.7 Hz), 5.06 (d, 1H, *J* = 7.6 Hz), 4.95 (m, 1H), 4.19 (m, 2H), 4.14 (d, 2H, *J* = 3.4 Hz), 3.24 (d, 2H, *J* = 5.2 Hz), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.5, 150.2, 142.0, 141.3, 140.2, 138.7, 137.3, 137.2, 134.6, 130.0, 128.8, 128.8, 127.9, 127.2, 126.9, 125.7, 110.3, 107.8, 61.4, 53.2, 40.3, 30.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{25}ClN_3O_3$: 462.1584; found, 462.1597.



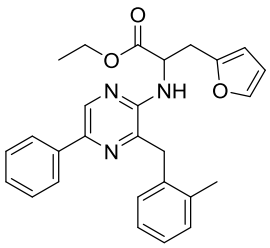
Ethyl (5-phenyl-3-(2-(trifluoromethyl)benzyl)pyrazin-2-yl)phenylalaninate **23**{*1,8,1*} (YJ 33067-119-1): Obtained as an oil (0.37 g, 85%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3 to 96/4). ^{1}H NMR ($CDCl_3$): 8.47 (s, 1H), 7.92 (m, 2H), 7.72 (m, 1H), 7.46 - 7.33 (m, 5H), 7.18 (m, 3H), 7.12 (m, 1H), 6.98 (m, 1H), 5.01 (m, 1H), 4.79 (d (br), *J* = 7.5 Hz), 4.32 (m, 2H), 4.15 (m, 2H), 3.18 (dd, 1H, *J* = 5.5 and 13.9 Hz), 3.08 (dd, 1H, *J* = 6.6 and 13.9 Hz), 1.20 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 150.1, 141.2, 139.8, 137.2, 136.8, 136.1, 135.2, 132.0, 130.2, 129.0, 128.8, 128.7 (30 Hz), 128.4, 127.9, 126.9, 126.8, 126.1 (4 Hz), 125.5, 124.5 (273 Hz), 61.2, 55.0, 37.9, 36.3, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{27}F_3N_3O_2$, 506.2055; found, 506.2053.



Ethyl (5-phenyl-3-(3-(trifluoromethyl)benzyl)pyrazin-2-yl)phenylalaninate **23**{*1,9,1*} (YJ 33067-121-1): Obtained as an oil (0.37 g, 85%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane-ethyl acetate 97:3 to 96/4). ^{1}H NMR ($CDCl_3$): 8.46 (s, 1H), 7.93 (m, 2H), 7.53 (m, 2H), 7.46 (m, 2H), 7.41 - 7.35 (m, 3H), 7.23 (m, 3H), 7.00 (m, 2H), 5.01 (m, 1H), 4.84 (d (br), *J* = 7.5 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 4.14 (s, 2H), 3.23 (dd, 1H, *J* = 5.7 and 13.9 Hz), 3.13 (dd, 1H, *J* = 6.0 and 13.9 Hz), 1.22 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 150.1, 141.3, 140.0, 137.5, 137.2, 137.0, 136.1, 132.0 131.0 (31 Hz), 129.2, 128.8, 128.5, 128.0, 127.0, 125.6, 125.4 (4 Hz), 124.0 (272 Hz), 123.8 (3 Hz), 61.3, 54.8, 40.0, 37.7, 14.1 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{27}F_3N_3O_2$, 506.2055; found, 506.2058.

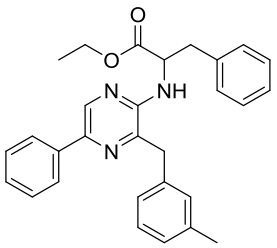


Ethyl (3-(2-methylbenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,11,1*} (YJ31068-017-1): Obtained as an oil (0.40 g, 86%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.92 (m, 2H), 7.43 (m, 2H), 7.35 (m, 1H), 7.20 (m, 5H), 7.11 (m, 1H), 6.98 (m, 3H), 5.01 (m, 1H), 4.86 (d (br), 1H, *J* = 7.1 Hz), 4.14 (m, 4H), 3.17 (dd, 1H, *J* = 5.6, 13.8 Hz), 3.07 (dd, 1H, *J* = 6.0, 13.8 Hz), 2.33 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 141.0, 140.9, 137.5, 137.0, 136.6, 136.3, 134.7, 130.6, 129.2, 128.7, 128.6, 128.4, 127.8, 127.0, 126.8, 126.3, 125.6, 61.1, 54.8, 38.6, 37.9, 19.9, 14.1 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_3O_2$, 452.2338; found, 452.2338.

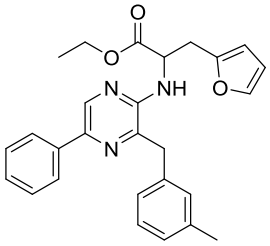


Ethyl 3-(furan-2-yl)-2-((3-(2-methylbenzyl)-5-phenylpyrazin-2-yl)amino)propanoate **23**{*1,11,37*} (YJ31068-019-1): Obtained as an oil (0.30 g, 71%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.93 (m, 2H), 7.47 (m, 2H), 7.35 (m, 1H), 7.20 (m, 3H), 7.13 (m, 1H), 7.06 (m, 1H), 6.21 (dd, 1H, *J* = 1.8, 3.1 Hz), 5.85 (m, 1H), 5.09 (d (br), 1H, *J* = 7.6 Hz), 4.98 (m, 1H), 4.18 (m, 4H), 3.20 (m, 2H), 2.39 (s, 3H), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 150.6, 150.4, 141.9, 141.1, 141.0, 137.4,

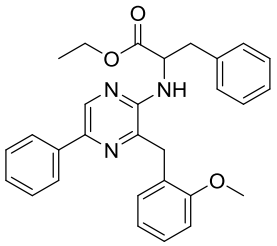
137.0, 136.5, 134.7, 130.6, 128.8, 128.7, 127.8, 127.0, 126.3, 125.6, 110.3, 107.7, 61.3, 53.2, 38.5, 30.5, 20.0, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_3$, 442.2131; found, 442.2137.



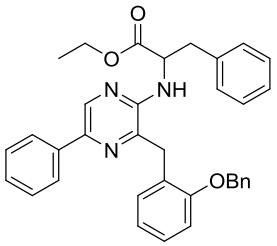
Ethyl (3-(3-methylbenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,12,1*} (YJ31068-021-1): Obtained as an oil (0.41 g, 89%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H), 7.21 (m, 4H), 7.08-6.96 (m, 4H), 4.97 (m, 2H), 4.14 (m, 4H), 3.17 (dd, 1H, *J* = 5.0, 13.7 Hz), 3.07 (dd, 1H, *J* = 5.7, 13.7 Hz), 2.31 (s, 3H), 1.20 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 150.4, 141.3, 141.0, 138.5, 137.5, 136.8, 136.4, 136.3, 129.3, 129.2, 128.7, 128.4, 127.7, 127.6, 126.8, 125.7, 61.1, 54.9, 40.9, 37.9, 21.4, 14.1 (two signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_3O_2$, 452.2338; found, 452.2337.



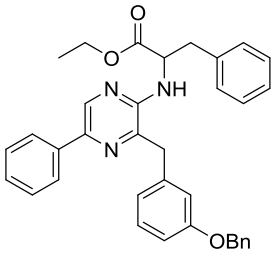
Ethyl 3-(furan-2-yl)-2-((3-(3-methylbenzyl)-5-phenylpyrazin-2-yl)amino)propanoate **23**{*1,12,37*} (YJ31068-023-1): Obtained as an oil (0.35 g, 75%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.96 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 7.21 (m, 2H), 7.08 (m, 3H), 6.22 (dd, 1H, *J* = 2.0, 3.3 Hz), 5.83 (m, 1H), 5.16 (d (br), 1H, *J* = 7.6 Hz), 4.96 (m, 1H), 4.17 (m, 4H), 3.21 (m, 2H), 2.33 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 150.6, 150.3, 141.8, 141.3, 141.1, 138.4, 137.5, 136.7, 136.4, 129.4, 128.7, 128.6, 127.8, 127.7, 125.8, 125.7, 110.2, 107.6, 61.3, 53.2, 40.9, 30.4, 21.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_3$, 442.2131; found, 442.2133.



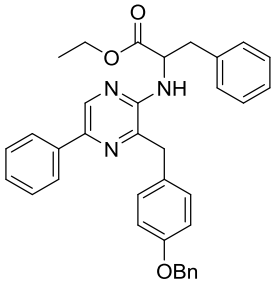
Ethyl (3-(2-methoxybenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,14,1*} (YJ31070-111-3): Obtained as an oil (0.1 g, 28%) after a chromatography over silica gel (cyclohexane-ethyl acetate 96:4). ^{1}H NMR ($CDCl_3$): 8.37 (s, 1H), 7.97 (m, 2H), 7.47 (m, 2H), 7.37 (m, 2H), 7.21 (m, 4H), 7.02 (m, 2H), 6.93 (m, 1H), 6.85 (m, 1H), 6.03 (d(br), 1H, *J* = 7.7 Hz), 5.08 (m, 1H), 4.17 (m, 4H), 3.72 (s, 3H), 3.20 (dd, 1H, *J* = 6.0, 13.9 Hz), 3.12 (dd, 1H, *J* = 6.2, 13.9 Hz), 1.21 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.4, 156.1, 150.1, 142.0, 140.5, 137.7, 136.7, 136.4, 130.8, 128.7, 128.3, 127.9, 127.6, 126.6, 125.6, 125.0, 121.1, 110.6, 61.0, 55.3, 55.0, 38.1, 33.2, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{29}N_3O_3$, 468.2287; found, 468.2298.



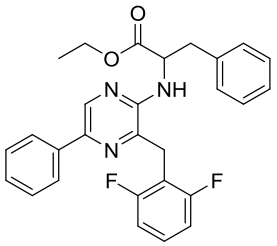
Ethyl (3-(2-(benzyloxy)benzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,17,1*} (RB32489-61-2): Obtained as an oil (0.54 g, 78%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H ($CDCl_3$, traces of EtOAc): 8.44 (s, 1H), 7.97 (m, 2H), 7.48 (m, 2H), 7.41-7.29 (m, 6H), 7.19 (m, 4H), 6.96 (m, 2H), 6.86 (m, 3H), 5.01 (s, 2H), 4.97 (m, 2H), 4.13 (q, 2H, *J* = 7.4 Hz), 4.12 (s, 2H), 3.16 (m, 1H), 3.07 (m, 1H), 1.20 (t, 3H, *J* = 7.4 Hz). ^{13}C ($CDCl_3$): 172.3, 159.2, 150.4, 141.1, 141.0, 138.1, 137.5, 137.0, 136.9, 136.3, 129.9, 129.2, 128.7, 128.5, 128.4, 127.9, 127.8, 127.5, 126.8, 125.7, 121.3, 115.0, 113.6, 69.9, 61.1, 54.9, 41.0, 37.8, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{34}N_3O_3$, 544.2600; found, 544.2605.



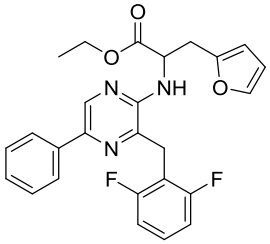
Ethyl (3-(3-(benzyloxy)benzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,18,1*} (RB32489-59-2): Obtained as an oil (0.57 g, 79%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H ($CDCl_3$): 8.37 (s, 1H), 7.93 (m, 2H), 7.49 – 7.29 (m, 9H), 7.23 (m, 1H), 7.17 (m, 3H), 6.96 (m, 4H), 5.66 (d, 1H, *J* = 7.5 Hz), 5.14 (d, 1H, *J* = 6.0, 14.0 Hz), 5.07 (d, 1H, *J* = 7.0, 12.4 Hz), 4.95 (q, 1H, *J* = 8.5 Hz), 4.24 (m, 2H), 4.09 (q, 2H, *J* = 7.3 Hz), 3.16 (dd, 1H, *J* = 6.0, 13.8 Hz), 3.07 (dd, 1H, *J* = 7.1, 13.8 Hz), 1.15 (t, 3H, *J* = 7.3 Hz). ^{13}C ($CDCl_3$): 172.5, 155.7, 150.3, 141.6, 140.7, 137.7, 137.0, 136.8, 136.5, 130.6, 129.2, 128.7, 128.6, 128.3, 128.0, 127.9, 127.6, 127.3, 126.6, 125.6, 125.5, 121.4, 112.4, 70.3, 60.9, 55.1, 38.0, 33.8, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{34}N_3O_3$, 544.2600; found, 544.2609.



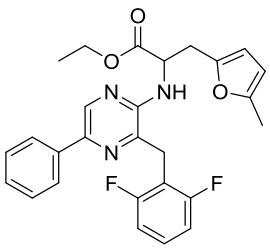
Ethyl (3-(2-(benzyloxy)benzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,19,1*} (RB32489-063-2): Obtained as an oil (0.57 g, 79%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H ($CDCl_3$): 8.42 (s, 1H), 7.98 (m, 2H), 7.49 – 7.31 (m, 8H), 7.22 (m, 3H), 7.12 (m, 2H), 6.96 (m, 2H), 6.90 (m, 2H), 5.07 (s, 2H), 4.95 (m, 2H), 4.15 (q, 2H, *J* = 7.0 Hz), 4.08 (s, 2H), 3.19 (dd, 1H, *J* = 5.4, 14.0 Hz), 3.09 (dd, 1H, *J* = 5.6, 14.0 Hz), 1.20 (t, 3H, *J* = 7.0 Hz). ^{13}C ($CDCl_3$): 172.4, 157.8, 150.3, 141.4, 141.0, 137.5, 137.1, 136.8, 136.3, 129.6, 129.3, 128.7, 128.6, 128.4, 128.0, 127.8, 127.4, 126.8, 125.7, 115.3, 70.0, 61.1, 54.9, 40.1, 37.8, 14.1, (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{34}N_3O_3$, 544.2600; found, 544.2609.



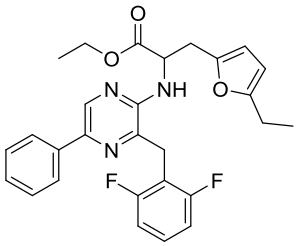
Ethyl (3-(2,6-difluorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,21,1*} (YJ 33069-165-1): Obtained as an oil (0.44 g, 91%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.80 (m, 2H), 7.39 (m, 2H), 7.39 (m, 2H), 7.33 - 7.24 (m, 5H), 7.17 (m, 2H), 6.94 (m, 2H), 5.17 (d (br), 1H, J = 7.0 Hz), 5.10 (m, 1H), 4.21 (q, 2H, J = 7.0 Hz), 4.07 (s, 2H), 3.33 (dd, 1H, J = 5.6, 13.8 Hz), 3.23 (dd, 1H, J = 6.1, 13.8 Hz), 1.26 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 161.8 (248, 8 Hz), 149.5, 140.9, 138.7, 137.1, 136.3, 136.0, 129.3, 128.6, 128.5, 128.3 (10 Hz), 127.8, 127.0, 125.4, 112.7 (20 Hz), 111.1 (7, 19 Hz), 61.3, 55.1, 37.9, 26.6, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}F_2N_3O_2$: 474.1993; found, 474.1995.



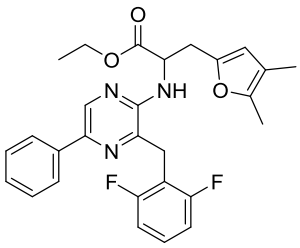
Ethyl 2-((3-(2,6-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,21,37*} (EC31095-077-2): Obtained as a white solid (0.40 g, 90%) after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3 to 96/4). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.80 (m, 2H), 7.39 (m, 2H), 7.35 (dd, 1H, *J* = 1.9, 0.8 Hz), 7.28 (m, 2H), 6.94 (m, 2H), 6.30 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.07 (dd, 1H, *J* = 3.2, 0.6 Hz), 5.34 (d, 1H, *J* = 7.4 Hz), 5.08 (dt, 1H, *J* = 7.5, 5.5 Hz), 4.25 (m, 2H), 4.12 (s, 2H), 3.34 (m, 2H), 1.29 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 161.8 (248, 8 Hz), 150.8, 149.7, 142.0, 140.9, 138.6, 137.3, 136.4, 128.6, 128.4 (10 Hz), 127.7, 125.4, 112.8 (20 Hz), 111.1, 110.3, 107.8, 61.4, 53.4, 30.6, 26.6, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}F_2N_3O_3$: 464.1786; found, 464.1798.



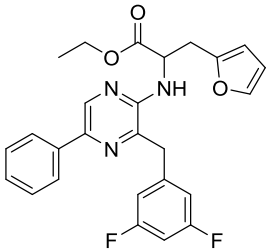
Ethyl 2-((3-(2,6-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,21,42*} (EC32712-083-2): Obtained as yellow solid (0.38 g, 83%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.80 (m, 2H), 7.38 (m, 2H), 7.29 (m, 2H), 6.95 (m, 2H), 5.96 (d, 1H, *J* = 3.0 Hz), 5.88 (dd, 1H, *J* = 3.0, 1.0 Hz), 5.36 (d, 1H, *J* = 7.5 Hz), 5.04 (dt, 1H, *J* = 7.5, 5.5 Hz), 4.25 (m, 2H), 4.12 (s, 2H), 3.27 (m, 2H), 2.27 (d, 3H, *J* = 1.0 Hz), 1.30 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 161.8 (247, 8 Hz), 151.6, 149.8, 148.8, 140.8, 138.5, 137.3, 136.4, 128.6, 128.4 (10 Hz), 127.7, 125.4, 112.8 (20 Hz), 111.1 (br), 108.6, 106.2, 61.3, 53.5, 30.7, 26.5 (2 Hz), 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{26}F_2N_3O_3$: 478.1942; found, 478.1951.



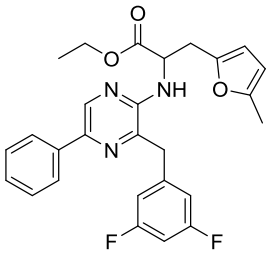
Ethyl 2-((3-(2,6-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-ethylfuran-2-yl)propanoate **23**{*1,21,44*} (EC32712-109-1): Obtained as an oil (0.28 g, 72%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.40 (s, 1H), 7.79 (m, 2H), 7.39 (m, 2H), 7.28 (m, 2H), 6.95 (m, 2H), 5.97 (d, 1H, *J* = 3.0 Hz), 5.88 (d, 1H, *J* = 3.0 Hz), 5.36 (d, 1H, *J* = 7.5 Hz), 5.05 (dt, 1H, *J* = 7.5, 5.5 Hz), 4.26 (m, 2H), 4.12 (s, 2H), 3.28 (m, 2H), 2.62 (qd, 2H, *J* = 7.6, 1.0 Hz), 1.30 (t, 3H, *J* = 7.1 Hz), 1.23 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 161.8 (248, 8 Hz), 157.4, 149.8, 148.7, 140.8, 138.5, 137.3, 136.4, 128.6, 128.4 (10 Hz), 127.7, 125.4, 112.8 (20 Hz), 111.1 (br), 108.4, 104.6, 61.3, 53.5, 30.7, 26.5, 21.4, 14.1, 12.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2103.



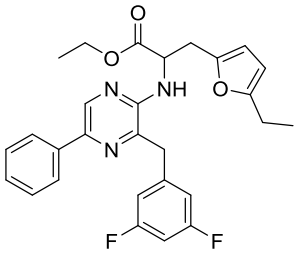
Ethyl 2-((3-(2,6-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethylfuran-2-yl)propanoate **23**{*1,21,48*} (EC32712-111-1): Obtained as an oil (0.33 g, 85%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 7.79 (d, 1H, *J* = 7.1 Hz), 7.38 (m, 2H), 7.29 (m, 3H), 6.94 (m, 2H), 5.86 (s, 1H), 5.37 (d, 1H, *J* = 7.4 Hz), 5.01 (dt, 1H, *J* = 7.4, 5.5 Hz), 4.25 (qd, 2H, *J* = 7.1, 4.6 Hz), 4.12 (s, 2H), 3.23 (m, 2H), 2.17 (s, 3H), 1.91 (s, 3H), 1.30 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 161.8 (248, 8 Hz), 149.8, 147.4, 146.8, 140.8, 138.5, 137.3, 136.4, 128.6, 128.4 (10 Hz), 127.6, 125.4, 114.5, 112.8 (20 Hz), 111.1, 111.0 (br), 61.3, 53.6, 30.6, 26.5 (br), 14.1, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2105.



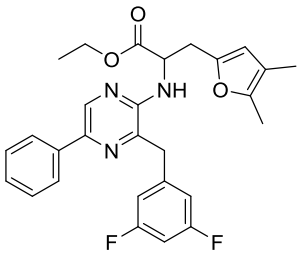
Ethyl 2-((3-(3,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,22,37*} (EC31095-081-3): Obtained as an oil (0.08 g, 18%) after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.46 (s, 1H), 7.95 (m, 2H), 7.48 (m, 2H), 7.39 (m, 1H), 7.29 (m, 1H), 6.81 (m, 2H), 6.71 (m, 1H), 6.26 (dd, 1H, *J* = 3.1, 1.9 Hz), 5.93 (d, 1H, *J* = 3.2 Hz), 5.04 (d, 1H, *J* = 7.6 Hz), 4.97 (dt, 1H, *J* = 7.5, 5.0 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 4.14 (s, 2H), 3.27 (d, 2H, *J* = 5.0 Hz), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 163.2 (249, 13 Hz), 150.5, 150.2, 142.1, 141.4, 140.6 (9 Hz), 139.6, 137.4, 137.2, 128.8, 128.0, 125.7, 111.6, 110.3, 107.9, 102.5 (25 Hz), 61.5, 53.2, 40.2, 30.3, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}F_2N_3O_3$: 464.1786; found, 464.1788.



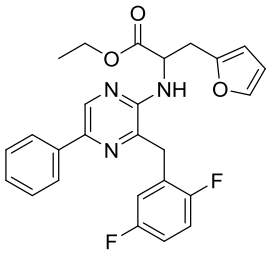
Ethyl 2-((3-(3,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,22,42*} (EC32712-005-2): Obtained as an oil (0.33 g, 68%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.93 (m, 2H), 7.48 (m, 2H), 7.38 (m, 1H), 6.79 (m, 2H), 6.70 (tt, 1H, *J* = 8.9, 2.3 Hz), 5.83 (m, 1H), 5.81 (m, 1H), 5.01 (d, 1H, *J* = 7.5 Hz), 4.93 (dt, 1H, *J* = 7.5, 5.1 Hz), 4.21 (m, 2H), 4.13 (s, 2H), 3.19 (m, 2H), 2.22 (d, 3H, *J* = 0.9 Hz), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 163.1 (249, 13 Hz), 151.7, 150.2, 148.3, 141.3, 140.6 (9 Hz), 139.5, 137.3, 137.2, 128.8, 128.0, 125.6, 111.6 (br), 108.7, 106.2, 102.4 (25 Hz), 61.4, 53.1, 40.1 (2 Hz), 30.5, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{26}F_2N_3O_3$: 478.1942; found, 478.1945.



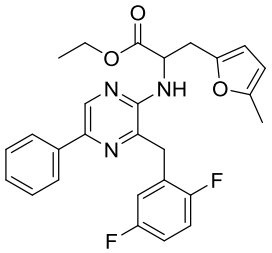
Ethyl 2-((3-(3,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-ethylfuran-2-yl)propanoate **23**{*1,22,44*} (EC32712-107-1): Obtained as an oil (0.31 g, 80%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.93 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 6.79 (m, 2H), 6.70 (m, 1H), 5.83 (m, 2H), 5.01 (d, 1H, *J* = 7.6 Hz), 4.95 (dt, 1H, *J* = 7.5, 5.1 Hz), 4.21 (m, 2H), 4.12 (s, 2H), 3.22 (m, 2H), 2.57 (qd, 2H, *J* = 7.5, 0.9 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.21 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 163.1 (249, 13 Hz), 157.4, 150.2, 148.2, 141.4, 140.6 (9 Hz), 139.5, 137.3, 137.2, 128.8, 127.9, 125.6, 111.6 (br), 108.5, 104.5, 102.4 (25 Hz), 61.4, 53.1, 40.0 (2 Hz), 30.5, 21.3, 14.1, 12.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2103.



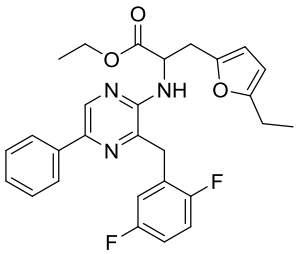
Ethyl 2-((3-(3,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethylfuran-2-yl)propanoate **23**{*1,22,48*} (EC32712-091-2): Obtained as an oil (0.24 g, 73%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.93 (m, 2H), 7.46 (m, 2H), 7.38 (m, 1H), 6.80 (m, 2H), 6.70 (m, 1H), 5.74 (s, 1H), 5.04 (d, 1H, *J* = 7.6 Hz), 4.92 (dt, 1H, *J* = 7.5, 5.2 Hz), 4.21 (m, 2H), 4.13 (s, 2H), 3.17 (m, 2H), 2.14 (s, 3H), 1.89 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 163.1 (249, 13 Hz), 150.3, 147.1, 146.9, 141.4, 140.7 (9 Hz), 139.5, 137.3, 137.2, 128.8, 127.9, 125.6, 114.5, 111.6 (br), 111.2, 102.3 (25 Hz), 61.3, 53.2, 40.0 (br), 30.4, 14.1, 11.2, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2087.



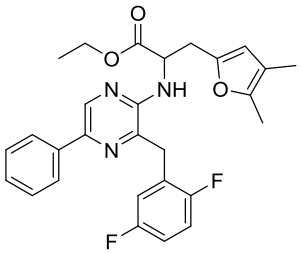
Ethyl 2-((3-(2,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,23,37*} (EC32712-015-3): Obtained as an oil (0.32 g, 53%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.91 (m, 2H), 7.46 (m, 2H), 7.37 (m, 1H), 7.28 (m, 1H), 7.06 (m, 1H), 6.94 (m, 2H), 6.25 (dd, 1H, *J* = 3.2, 1.9 Hz), 5.98 (dd, 1H, *J* = 3.2, 0.8 Hz), 5.22 (m, 1H), 5.01 (dt, 1H, *J* = 7.5, 5.4 Hz), 4.21 (qd, 2H, *J* = 7.1, 1.1 Hz), 4.14 (m, 2H), 3.28 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 158.7 (242, 2 Hz), 156.8 (240, 2 Hz), 150.6, 150.0, 142.0, 141.3, 139.2, 137.2, 137.2, 128.8, 127.9, 125.6, 125.4 (10, 8 Hz), 117.1 (24, 4 Hz), 116.2 (25, 9 Hz), 114.9 (24, 9 Hz), 110.3, 107.8, 61.4, 53.3, 32.5, 30.5, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}F_2N_3O_3$: 464.1786; found, 464.1783.



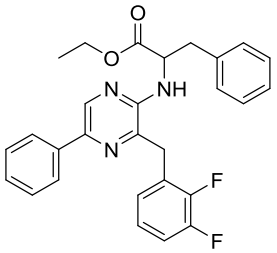
Ethyl 2-((3-(2,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,23,42*} (EC32712-041-2): Obtained as an oil (0.18 g, 47%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.90 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.05 (td, 1H, *J* = 8.9, 4.5 Hz), 6.94 (m, 2H), 5.86 (m, 1H), 5.82 (m, 1H), 5.21 (d, 1H, *J* = 7.5 Hz), 4.97 (dt, 1H, *J* = 7.5, 5.5 Hz), 4.21 (m, 2H), 4.13 (d, 2H, *J* = 1.5 Hz), 3.22 (d, 2H, *J* = 5.4 Hz), 2.23 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 158.7 (242, 2 Hz), 156.7 (240, 3 Hz), 151.6, 150.1, 148.5, 141.2, 139.1, 137.2, 137.1, 128.7, 127.9, 125.5, 125.5 (19, 8 Hz), 117.1 (24, 4 Hz), 116.2 (25, 9 Hz), 114.9 (24, 9 Hz), 108.6, 106.1, 61.3, 53.4, 32.4, 30.6, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{26}F_2N_3O_3$: 478.1942; found, 478.1940.



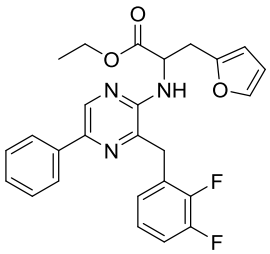
Ethyl 2-((3-(2,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-ethylfuran-2-yl)propanoate **23**{*1,23,44*} (EC32712-087-2): Obtained as an oil (0.50 g, 75%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.90 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.04 (m, 1H), 6.94 (m, 2H), 5.88 (d, 1H, *J* = 3.1 Hz), 5.83 (dt, 1H, *J* = 2.9, 0.9 Hz), 5.21 (m, 1H), 4.98 (dt, 1H, *J* = 7.6, 5.5 Hz), 4.21 (m, 2H), 4.13 (d, 2H, *J* = 2.2 Hz), 3.23 (d, 2H, *J* = 5.4 Hz), 2.58 (qd, 2H, *J* = 7.6, 0.9 Hz), 1.26 (t, 3H, *J* = 7.1 Hz), 1.21 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 158.7 (242, 2 Hz), 157.3, 156.8 (240, 2 Hz), 150.1, 148.4, 141.2, 139.1, 137.2, 137.1, 128.7, 127.9, 125.5, 125.4 (dd, *J* = 18, 8 Hz), 117.1 (24, 4 Hz), 116.2 (25, 9 Hz), 114.9 (24, 9 Hz), 108.4, 104.5, 61.3, 53.3, 32.4 (br), 30.6, 21.3, 14.1, 12.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2104.



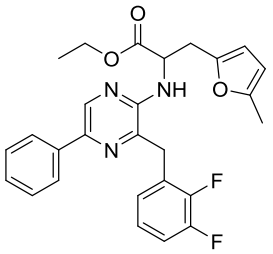
Ethyl 2-((3-(2,5-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethylfuran-2-yl)propanoate **23**{*1,23,48*} (EC32712-085-2): Obtained as an oil (0.25 g, 64%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.90 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.05 (m, 1H), 6.94 (m, 2H), 5.77 (s, 1H), 5.22 (d, 1H, *J* = 7.5 Hz), 4.95 (dt, 1H, *J* = 7.5, 5.5 Hz), 4.21 (m, 2H), 4.14 (d, 2H, *J* = 2.7 Hz), 3.17 (d, 2H, *J* = 5.5 Hz), 2.13 (s, 3H), 1.88 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 158.7 (241, 2 Hz), 156.8 (241, 2 Hz), 150.2, 147.2, 146.8, 141.2, 139.0, 137.2, 137.1, 128.7, 127.9, 125.5, 125.5 (19, 8 Hz), 117.1 (24, 4 Hz), 116.1 (25, 9 Hz), 114.8 (24, 9 Hz), 114.4, 61.3, 53.4, 32.4 (br), 30.5, 14.1, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2083.



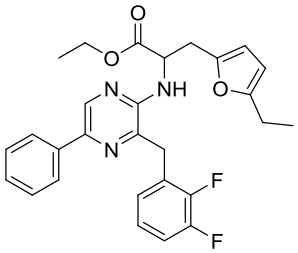
Ethyl (3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,24,1*} (YJ 33067-117-1): Obtained as an oil (0.37 g, 82%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3 to 96/4). ^{1}H NMR ($CDCl_3$): 7.91 (s, 1H), 7.90 (m, 2H), 7.45 (m, 2H), 7.35 (m, 1H), 7.24 (m, 3H), 7.07 (m, 3H), 6.95 (m, 1H), 5.02 (m, 2H), 4.18 (q, 2H, *J* = 7.3 Hz), 4.12 (m, 2H), 3.26 (dd, 1H, *J* = 5.6 and 14.1 Hz), 3.17 (dd, 1H, *J* = 6.0 and 14.1 Hz), 1.23 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 150.6 (248 and 13 Hz), 150.0, 148.9 (246, and 12 Hz), 141.3, 139.3, 137.1, 136.9, 136.1, 129.1, 128.7, 128.5, 127.9, 127.0, 126.0 (12 Hz), 125.6, 125.3 (3 Hz), 124.1 (4 and 6 Hz), 115.8 (18 Hz), 61.3, 55.0, 37.8, 32.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}F_2N_3O_2$: 474.1993; found, 474.1982.



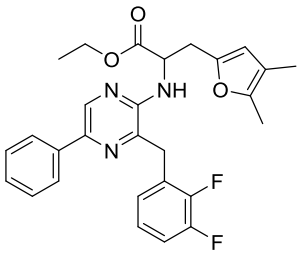
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*1,24,37*} (EC31095-125-4): Obtained as an oil (0.36 g, 66%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 92/8). ^{1}H NMR ($CDCl_3$): 8.44 (s, 1H), 7.91 (m, 2H), 7.45 (m, 2H), 7.37 (m, 1H), 7.29 (dd, 1H, *J* = 1.9, 0.8 Hz), 7.08 (m, 1H), 7.00 (m, 2H), 6.26 (dd, 1H, *J* = 3.2, 1.9 Hz), 5.98 (dd, 1H, *J* = 3.2, 0.8 Hz), 5.18 (d, 1H, *J* = 7.5 Hz), 5.01 (dt, 1H, *J* = 7.6, 5.4 Hz), 4.20 (m, 4H), 3.28 (d, , 2H *J* = 5.4 Hz), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 150.6 (248, 13 Hz), 150.5, 150.1, 148.9 (246, 13 Hz), 142.1, 141.3, 139.2 (1 Hz), 137.2, 137.1, 128.7, 127.9, 126.2 (d13 Hz), 125.6, 125.4 (3 Hz), 124.1 (7, 5 Hz), 115.7 (17 Hz), 110.3, 107.8, 61.4, 53.3, 32.4 (3 Hz), 30.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}F_2N_3O_3$: 464.1786; found, 464.1780.



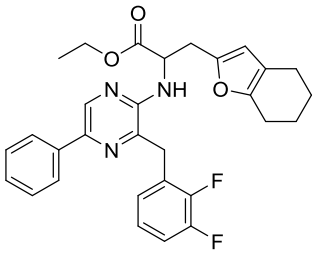
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*1,24,42*} (EC32712-039-2): Obtained as an oil (0.31 g, 80%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.90 (m, 2H), 7.45 (dd, 2H, *J* = 8.3, 6.9 Hz), 7.36 (m, 1H), 7.07 (m, 1H), 7.00 (m, 2H), 5.87 (d, 1H, *J* = 3.1 Hz), 5.83 (dd, 1H, *J* = 3.2, 1.2 Hz), 5.17 (d, 1H, *J* = 7.5 Hz), 4.97 (dt, 1H, *J* = 7.6, 5.4 Hz), 4.19 (m, 4H), 3.22 (d, 2H, *J* = 5.4 Hz), 2.23 (s, 3H), 1.27 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 151.6, 150.6 (248, 13 Hz), 150.1, 148.9 (246, 13 Hz), 148.4, 141.2, 139.2, 137.2, 137.0, 128.7, 127.9, 126.2 (12 Hz), 125.5, 125.4 (3 Hz), 124.0 (7, 5 Hz), 115.7 (17 Hz), 108.6, 106.1, 61.3, 53.3, 32.3, 30.6, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{26}F_2N_3O_3$: 478.1942; found, 478.1946.



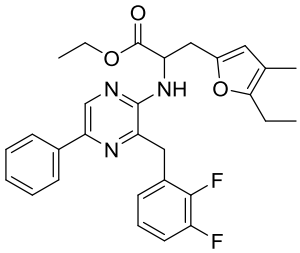
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-ethylfuran-2-yl)propanoate **23**{*1,24,44*} (EC32712-105-1): Obtained as an oil (0.45 g, 74%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.36 (m, 1H), 7.07 (m, 1H), 7.00 (m, 2H), 5.86 (m, 2H), 5.17 (d, 1H, *J* = 7.6 Hz), 4.98 (dt, , 1H *J* = 7.6, 5.4 Hz), 4.20 (m, 4H), 3.23 (d, 2H, *J* = 5.4 Hz), 2.57 (qd, 2H, *J* = 7.6, 1.0 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.21 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 157.4, 150.6 (248, 13 Hz), 150.0, 148.5 (246, 13 Hz), 148.3, 141.2, 139.2, 137.2, 137.0, 128.7, 127.9, 126.2 (13 Hz), 125.5, 125.4 (3 Hz), 124.0 (7, 5 Hz), 115.7 (17 Hz), 108.4, 104.5, 61.3, 53.3, 32.3, 30.6, 21.3, 14.1, 12.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2090.



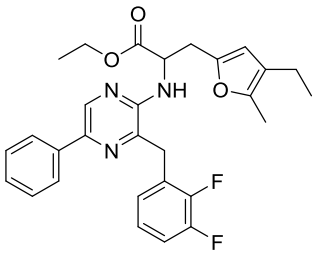
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4,5-dimethylfuran-2-yl)propanoate **23**{*1,24,48*} (EC32712-089-2): Obtained as an oil (0.21 g, 46%), using toluene at 60 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.36 (m, 1H), 7.08 (m, 1H), 7.00 (m, 2H), 5.77 (s, 1H), 5.20 (d, 1H, *J* = 7.6 Hz), 4.95 (dt, 1H, *J* = 7.6, 5.4 Hz), 4.21 (m, 4H), 3.18 (d, 2H, *J* = 5.4 Hz), 2.13 (s, 3H), 1.88 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 150.6 (248, 13 Hz), 150.1, 148.9 (246, 13 Hz), 147.1, 146.8, 141.2, 139.2, 137.2, 136.9, 128.7, 127.9, 126.2 (12 Hz), 125.5, 125.4 (Hz), 124.0 (7, 5 Hz), 115.7 (17 Hz), 114.4, 111.1, 61.3, 53.4, 32.3 (3 Hz), 30.5, 14.1, 11.2, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}F_2N_3O_3$: 492.2099; found, 492.2111.



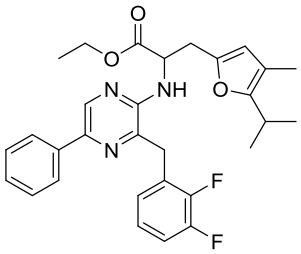
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4,5,6,7-tetrahydrobenzofuran-2-yl)propanoate **23**{*1,24,49*} (YJ 33068-075-2): Obtained as an oil (0.37 g, 56%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.42 (s, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.35 (m, 1H), 7.12 - 6.99 (m, 3H), 5.80 (s, 1H), 5.22 (d (br), *J* = 7.8 Hz), 4.96 (m, 1H), 4.21 (m, 4H), 3.20 (d, 2H, *J* = 5.5 Hz), 2.52 (m, 2H), 2.35 (m, 2H), 1.82 (m, 2H), 1.72 (m, 2H), 1.26 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 150.6 (13 and 248 Hz), 150.3, 150.1, 148.9 (13 and 248 Hz), 147.8, 141.2, 139.2, 137.2, 136.9, 128.7, 127.9, 126.2 (13 Hz), 125.5, 125.4 (4 Hz), 124.0 (4 and 7 Hz), 117.4, 115.6 (17 Hz), 108.8, 61.3, 53.5, 32.3, 30.7, 23.1, 23.0 (two signals), 22.0, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{30}F_2N_3O_3$: 518.2255; found, 518.2263.



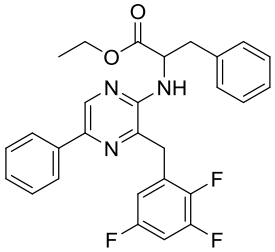
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-ethyl-4-methylfuran-2-yl)propanoate **23**{*1,24,50*} (YJ 33069-009-1): Obtained as an oil (0.59 g, 77%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.35 (m, 1H), 7.12 - 6.99 (m, 3H), 5.77 (s, 1H), 5.20 (d (br), *J* = 7.8 Hz), 4.96 (m, 1H), 4.22 (m, 4H), 3.19 (d, 2H, *J* = 5.5 Hz), 2.52 (q, 2H, *J* = 7.7 Hz), 1.90 (s, 3H), 1.27 (d, 3H *J* = 7.0 Hz), 1.15 (d, 3H *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 152.0, 150.6 (13 and 248 Hz), 150.1, 148.9 (13 and 248 Hz), 147.1, 141.2, 139.1, 137.2, 137.0, 128.7, 127.8, 126.2 (13 Hz), 125.5, 125.4 (4 Hz), 124.0 (4 and 7 Hz), 115.6 (17 Hz), 113.5, 111.2, 61.3, 53.3, 32.3, 30.6, 19.3, 14.1, 12.8, 9.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}F_2N_3O_3$: 505.2255; found, 505.2260.



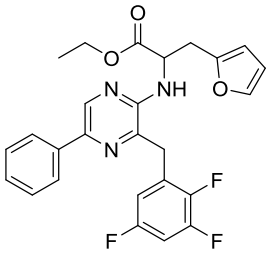
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(4-ethyl-5-methylfuran-2-yl)propanoate **23**{*1,24,51*} (YJ 33068-079-2): Obtained as an oil (0.45 g, 70%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.35 (m, 1H), 7.12 - 6.99 (m, 3H), 5.86 (s, 1H), 5.23 (d (br), *J* = 7.8 Hz), 4.97 (m, 1H), 4.21 (m, 4H), 3.18 (d, 2H, *J* = 5.5 Hz), 2.29 (q, 2H, *J* = 7.6), 2.15 (s, 3H), 1.26 (d, 3H *J* = 7.0 Hz), 1.10 (d, 3H *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 150.6 (13 and 248 Hz), 150.1, 148.9 (13 and 248 Hz), 147.3, 146.2, 139.1, 137.2, 136.9, 128.7, 127.8, 126.2 (13 Hz), 125.5, 125.4 (4 Hz), 124.0 (4 and 7 Hz), 121.2, 115.6 (17 Hz), 109.5, 61.3, 53.4, 32.3, 30.7, 17.9, 14.8, 14.1, 11.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}F_2N_3O_3$: 505.2255; found, 505.2257.



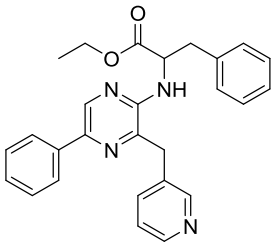
Ethyl 2-((3-(2,3-difluorobenzyl)-5-phenylpyrazin-2-yl)amino)-3-(5-isopropyl-4-methylfuran-2-yl)propanoate **23**{*1,24,52*} (YJ 33069-057-1): Obtained as an oil (0.54 g, 82%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.43 (s, 1H), 7.89 (m, 2H), 7.44 (m, 2H), 7.34 (m, 1H), 7.12 - 6.97 (m, 3H), 5.75 (s, 1H), 5.16 (d (br), *J* = 7.8 Hz), 4.99 (m, 1H), 4.22 (m, 4H), 3.21 (m, 2H), 2.94 (sept, 1H, *J* = 7.1), 1.91 (s, 3H), 1.28 (d, 3H *J* = 7.0 Hz), 1.19 (d, 3H *J* = 7.1 Hz), 1.18 (d, 3H *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 150.1, 150.6 (13 and 248 Hz), 150.1, 148.9 (13 and 248 Hz), 146.7, 141.1, 139.2, 137.2, 136.8, 128.7, 127.9, 126.2 (13 Hz), 125.5, 125.4 (4 Hz), 124.0 (4 and 7 Hz), 115.6 (17 Hz), 112.4, 111.3, 61.3, 53.3, 32.3, 30.6, 26.1, 21.3, 21.2, .3, 14.1, 9.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{32}F_2N_3O_3$: 520.2411; found, 520.2410.



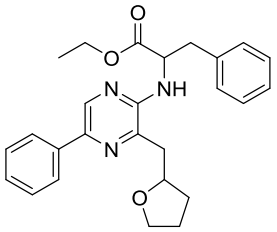
Ethyl (5-phenyl-3-(2,3,5-trifluorobenzyl)pyrazin-2-yl)phenylalaninate **23**{*1,26,1*} (YJ 33067-123-2): Obtained as an oil (0.13 g, 29%), using toluene at 60 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3 to 96/4). ^{1}H NMR ($CDCl_3$): 8.46 (s, 1H), 7.89 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 7.26 (m, 3H), 7.08 (m, 2H), 6.83 (m, 1H), 6.69 (m, 1H), 5.03 (m, 1H), 4.90 (d (br), *J* = 7.3 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 4.08 (m, 2H), 3.29 (dd, 1H, *J* = 5.6 and 13.8 Hz), 3.18 (dd, 1H, *J* = 6.3 and 13.8 Hz), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 157.5 (242, 12 and 3 Hz), 150.3 (247, 13 and 15 Hz), 149.9, 145.8 (242, 12 and 4 Hz), 141.4, 138.4, 137.3, 137.0, 136.1, 129.1, 128.8, 128.5, 128.0, 127.0, 126.9 (9 and 14 Hz), 125.5, 111.8 (3 and 24 Hz), 104.1 (21 and 28 Hz), 61.3, 55.0, 37.7, 32.2, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}F_3N_3O_2$: 492.1899; found, 492.1893.



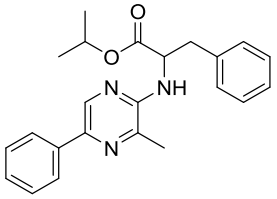
Ethyl 3-(furan-2-yl)-2-((5-phenyl-3-(2,3,5-trifluorobenzyl)pyrazin-2-yl)amino)propanoate **23**{*1,26,37*} (YJ 33067-125-2): Obtained as an oil (0.10 g, 23%), using toluene at 60 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.45 (s, 1H), 7.91 (m, 2H), 7.47 (m, 2H), 7.35 (m, 1H), 7.29 (m, 1H), 6.87 (m, 1H), 6.74 (m, 1H), 6.26 (m, 1H), 6.01 (m, 1H), 5.15 (d (br), *J* = 8.1 Hz), 5.03 (m, 1H), 4.22 (q, 2H, *J* = 7.1 Hz), 4.16 (m, 2H), 3.30 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 157.6 (242, 12 and 3 Hz), 150.5, 150.2 (247, 13 and 15 Hz), 145.4 (242, 12 and 4 Hz), 142.1, 141.4, 138.5, 137.2, 137.0, 128.8, 128.0, 127.1 (9 and 14 Hz), 125.6, 111.9 (3 and 24 Hz), 110.3, 107.8, 104.1 (21 and 28 Hz), 61.5, 53.3, 32.3, 30.39, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{23}F_3N_3O_3$: 482.1692; found, 482.1682.



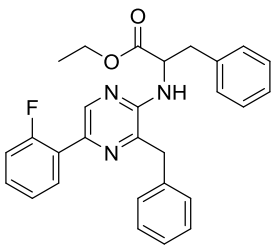
Ethyl (5-phenyl-3-(pyridin-3-ylmethyl)pyrazin-2-yl)phenylalaninate **23**{*1,35,1*} (YJ30367-037-3): Obtained as an oil (0.28 g, 62%) after a chromatography over silica gel (cyclohexane-ethyl acetate 2/1). ^{1}H NMR ($CDCl_3$): 8.52 (m, 3H), 8.44 (s, 1H), 7.90 (m, 2H), 7.46 (m, 3H), 7.35 (m, 1H), 7.26 (m, 3H), 7.19 (ddd, 1H, *J* = 0.9, 4.9, 5.6 Hz), 7.03 (m, 2H), 5.01 (m, 1H), 4.84 (d(br, 1H, *J* = 7.4 Hz), 4.17 (q, 2H, *J* = 7.0 Hz), 4.08 (s, 2H), 3.24 (dd, 1H, *J* = 5.9, 13.5 Hz), 3.16 (dd, 1H, *J* = 5.9, 13.6 Hz), 1.23 (t, 3H, *J* = 7.0 Hz).^{13}C NMR ($CDCl_3$): 172.4, 150.1, 150.0, 148.3, 141.4, 139.7, 137.2, 137.1, 136.2, 136.1, 132.2, 129.2, 128.8, 128.5, 127.9, 127.0 125.6, 123.4, 61.3, 54.8, 37.7, 37.3, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_2$, 439.2134; found, 439.2137.



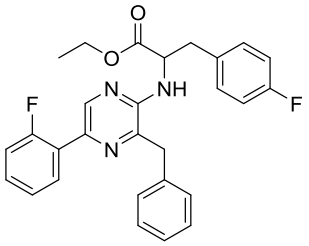
Ethyl (5-phenyl-3-((tetrahydrofuran-2-yl)methyl)pyrazin-2-yl)phenylalaninate **23**{*1,38,1*} (EC31093-017-3): Obtained as an oil (0.06 g, 21%) after a chromatography over silica gel (cyclohexane – ethyl acetate 93/7). ^{1}H NMR ($CDCl_3$; 1/1 mixture of diastereoisomers): 8.34 (s, 0.5H), 8.33 (s, 0.5H), 7.89 – 7.84 (m, 2H), 7.45 – 7.40 (m, 2H), 7.35 – 7.21 (m, 6H), 6.62 (d, 0.5H, *J* = 7.5 Hz), 6.44 (d, 0.5H, *J* = 7.1 Hz), 4.95 (dd, 0.5H, *J* = 13.0, 6.8 Hz), 4.86 (td, 0.5H, *J* = 7.4, 5.9 Hz), 4.37 – 4.30 (m, 0.5H), 4.30 – 4.23 (m, 0.5H), 4.22 – 4.13 (m, 2H), 3.89 – 3.79 (m, 0.5H), 3.77 – 3.58 (m, 1.5H), 3.31 – 2.88 (m, 4.5H), 2.17 – 2.00 (m, 1H), 1.92 – 1.61 (m, 3.5H), 1.22 (t, 1.5H, *J* = 7.1 Hz), 1.21 (t, 1.5H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 173.4, 173.1, 152.2, 152.0, 141.5, 141.2, 141.0, 140.9, 137.9, 137.8, 137.2, 137.0, 136.7, 129.6, 129.5, 128.8, 128.5 (two signals), 127.7, 126.9 (two signals), 125.8, 125.7, 79.1, 79.0, 68.2 (two signals), 61.1, 61.0, 55.8, 55.5, 41.0, 40.5, 38.4, 38.3, 31.5, 30.3, 26.0, 25.8, 14.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{30}N_3O_3$, 432.2287; found, 432.2273.



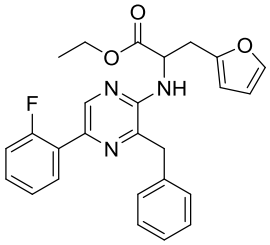
Isopropyl (3-methyl-5-phenylpyrazin-2-yl)phenylalaninate **23**{*1,60,1*} (VHE30855-051-5): Obtained as a solid after a chromatography over silica gel (cyclohexane - ethyl acetate 6/1). ^{1}H NMR ($CDCl_3$): 8.37 (s, 1H), 7.91 (m, 2H), 7.45 (m, 2H,), 7.25-7.37 (m, 4H), 7.20 (m, 2H), 4.99-5.10 (m, 2H), 4.89 (m, 2H), 3.29 (q, 1H, *J* = 13.8 Hz), 3.27 (q, 1H, *J* = 13.6 Hz), 2.43 (s, 3H), 1.28 (d, 3H, *J* = 6.3 Hz), 1.23 (d, 3H, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 150.5, 141.2, 139.6.2, 137.6, 136.4, 136.3, 129.4, 128.7, 128.5, 127.7, 127.0, 125.6, 69.1, 55.0, 37.8, 21.8, 21.7, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{26}N_3O_2$, 376.2025; found, 376.2027.



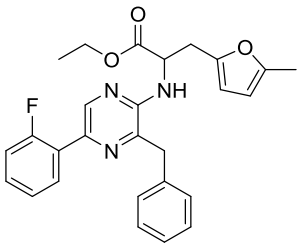
Ethyl (3-benzyl-5-(2-fluorophenyl)pyrazin-2-yl)phenylalaninate **23**{*2,1,1*} (YJ31134-033-2): Obtained as an oil (0.47 g, 81%) after a chromatography over silica gel (cyclohexane – ethyl acetate 91/9). ^{1}H ($CDCl_3$): 8.53 (d, 1H, *J* = 2.3 Hz), 8.04 (dt, 1H, *J* = 1.9, 7.9 Hz), 7.24 (m, 11H), 6.99 (m, 2H), 5.00 (m, 2H), 4.13 (m, 4H), 3.18 (dd, 1H, *J* = 5.1, 13.7 Hz), 3.10 (dd, 1H, *J* = 5.5, 13.7 Hz), 1.20 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.3, 160.2 (248 Hz), 150.2, 141.4, 140.6 (13 Hz), 136.7 (3 Hz), 136.4, 136.2, 130.0 (3 Hz), 129.3, 129.1 (8 Hz), 128.9, 128.6, 128.4, 126.3, 126.8, 125.3 (12 Hz), 124.5 (3 Hz), 116.1 (23 Hz), 61.2, 54.8, 40.8, 37.8, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}FN_3O_2$, 456.2087; found, 456.2079.



Ethyl 2-((3-benzyl-5-(2-fluorophenyl)pyrazin-2-yl)amino)-3-(4-fluorophenyl)propanoate **23**{*2,1,4*} (YJ30367-119-2): Obtained as a 90% pure oil (0.18 g, 59%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.53 (d, 1H, *J* = 2.3 Hz), 8.05 (dt, 1H, *J* = 1.9, 7.9 Hz), 7.37-7.14 (m, 8H), 6.88 (m, 2H), 6.86 (m, 2H), 4.99 (m, 2H), 4.15 (m, 4H), 3.16 (m, 1H), 3.07 (m, 1H), 1.20 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 161.9 (245 Hz), 160.2 (248 Hz), 150.1, 141.4, 140.5 (13 Hz), 136.8 (3 Hz), 136.4, 131.8 (3 Hz), 130.6 (8 Hz), 130.0 (3 Hz), 129.2 (8 Hz), 128.9, 128.6, 127.0, 124.5 (3 Hz), 116.1 (23 Hz), 115.2 (22 Hz), 61.3, 54.8, 40.9, 36.8, 14.1, one signal missing. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}F_2N_3O_2$, 474.1993; found, 474.1991.

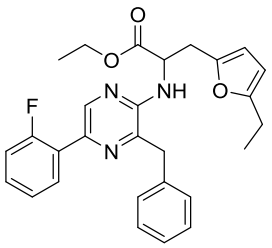


Ethyl 2-((3-benzyl-5-(2-fluorophenyl)pyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*2,1,37*} (YJ31134-087-2): Obtained as an oil (0.42 g, 72%) after a chromatography over silica gel (cyclohexane – ethyl acetate 91/9). ^{1}H NMR ($CDCl_3$): 8.52 (d, 1H, *J* = 2.3 Hz), 8.03 (dt, 1H, *J* = 1.9, 7.9 Hz), 7.41-7.24 (m, 8H), 7.17 (ddd, 1H, *J* = 1.3, 8.0, 11.4 Hz), 6.22 (dd, 1H, *J* = 1.8, 3.0 Hz), 5.84 (m, 1H), 5.19 (d(br), 1H, *J* = 7.6 Hz), 4.97 (m, 1H), 4.17 (m, 4H), 3.21 (m, 2H), 1.22 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 171.9, 160.1 (248 Hz), 150.5, 150.2, 141.9, 141.4, 140.5 (13 Hz), 136.8 (3 Hz), 136.5, 130.0 (3 Hz), 129.1 (8 Hz), 128.8, 128.7, 126.9, 125.3 (12 Hz), 124.4 (3 Hz), 116.1 (23 Hz), 110.3, 103.7, 61.3, 53.1, 40.8, 30.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{25}FN_3O_3$, 446.1880; found, 446.1870.

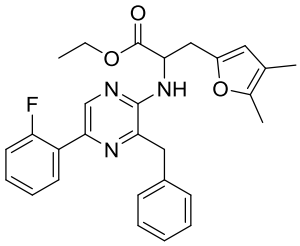


Ethyl 2-((3-benzyl-5-(2-fluorophenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*2,1,42*} (YJ30531-139-3): Obtained as an oil (0.11 g, 30%) after a chromatography over silica gel (cyclohexane – ethyl acetate 98/2 to 95/5). ^{1}H NMR ($CDCl_3$): 8.52 (d, 1H, *J* = 2.3 Hz), 8.03 (dt, 1H, *J* = 1.9, 7.8 Hz), 7.35-7.24 (m, 7H), 7.16 (ddd, 1H, *J* = 1.2, 8.1, 11.1 Hz), 5.82 (m, 1H), 5.75 (d, 1H, *J* = 3.0 Hz), 5.19 (d(br), 1H, *J* = 7.5 Hz), 4.95 (m, 1H), 4.18 (m, 4H), 3.16 (d, 2H, *J* = 5.4 Hz), 2.24 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 160.2 (248 Hz), 151.4, 150.3, 148.5, 141.4, 140.6 (13 Hz), 136.8 (3 Hz), 136.5, 130.0 (3 Hz), 129.2 (8 Hz), 128.8, 128.7,

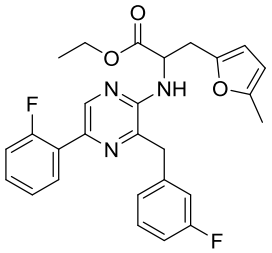
126.9, 125.3 (12 Hz), 124.4 (3 Hz), 116.1 (23 Hz), 108.6, 106.2, 61.3, 53.2, 40.7, 30.6, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}FN_3O_3$, 460.2036; found, 460.2039.



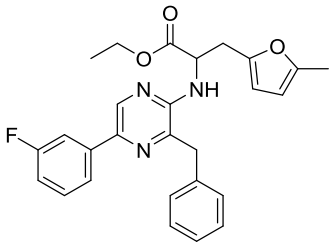
Ethyl 2-((3-benzyl-5-(2-fluorophenyl)pyrazin-2-yl)amino)-3-(5-ethylfuran-2-yl)propanoate **23**{*2,1,44*} (YJ30367-101-2): Obtained as an oil (0.2 g, 46%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.51 (d, 1H, *J* = 2.3 Hz), 8.03 (dt, 1H, *J* = 1.9, 7.8 Hz), 7.35-7.23 (m, 7H), 7.16 (ddd, 1H, *J* = 1.3, 8.1, 9.4 Hz), 5.82 (m, 1H), 5.75 (d, 1H, *J* = 3.0 Hz), 5.19 (d(br), 1H, *J* = 7.5 Hz), 4.95 (m, 1H), 4.18 (m, 4H), 3.15 (d, 2H, *J* = 5.3 Hz), 2.58 (q, 2H, *J* = 7.6 Hz), 1.24 (t, 3H, *J* = 7.2 Hz), 1.21 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 160.1 (248 Hz), 157.1, 150.2, 148.4, 141.4, 140.5 (13 Hz), 136.8 (3 Hz), 136.5, 130.0 (3 Hz), 129.2 (8 Hz), 128.8, 128.7, 126.9, 125.3 (12 Hz), 124.4 (3 Hz), 116.1 (23 Hz), 108.4, 104.6, 61.2, 53.1, 40.7, 30.6, 21.3, 14.1, 12.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_3$, 474.2193; found, 474.2186.



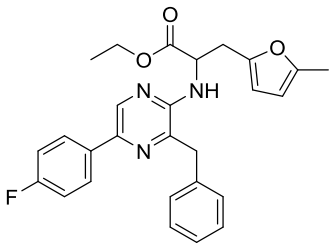
Ethyl 2-((3-benzyl-5-(2-fluorophenyl)pyrazin-2-yl)amino)-3-(4,5-dimethylfuran-2-yl)propanoate **23**{*2,1,48*} (YJ30367-171-2): Obtained as an oil (0.48 g, 86%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.51 (d, 1H, *J* = 2.4 Hz), 8.02 (dt, 1H, *J* = 1.9, 7.8 Hz), 7.35-7.23 (m, 7H), 7.16 (ddd, 1H, *J* = 1.3, 8.1, 9.4 Hz), 5.65 (s, 1H), 5.19 (d(br), 1H, *J* = 7.5 Hz), 4.92 (m, 1H), 4.16 (m, 4H), 3.11 (d, 2H, *J* = 5.1 Hz), 2.13 (s, 3H), 1.88 (s, 3H), 1.25 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 160.2 (248 Hz), 150.2, 147.1, 146.6, 141.4, 140.5 (13 Hz), 136.7 (3 Hz), 136.5, 130.0 (3 Hz), 129.2 (8 Hz), 128.8, 128.7, 126.8, 125.3 (12 Hz), 124.4 (3 Hz), 116.1 (23 Hz), 114.4, 111.1, 61.2, 53.2, 40.6, 30.5, 14.1, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{29}FN_3O_3$, 474.2193; found, 474.2203.



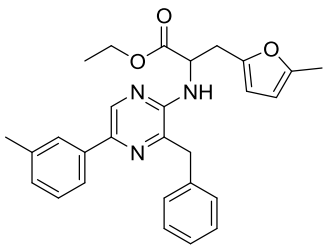
Ethyl 2-((3-(3-fluorobenzyl)-5-(2-fluorophenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*2,3,42*} (EC31095-109-2): Obtained as an oil (0.53 g, 80%), after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.53 (d, 1H, *J* = 2.3 Hz), 8.00 (td, 1H, *J* = 7.8, 1.9 Hz), 7.33 (m, 1H), 7.26 (m, 2H), 7.16 (m, 1H), 7.06 (dd, 1H, *J* = 7.6, 0.6 Hz), 6.96 (m, 2H), 5.82 (m, 1H), 5.77 (d, 1H, *J* = 3.0 Hz), 5.11 (d, 1H, *J* = 7.5 Hz), 4.95 (dt, 1H, *J* = 7.5, 5.3 Hz), 4.20 (m, 2H), 4.15 (s, 2H, *J* = 2.3 Hz), 3.18 (d, 2H, *J* = 5.3 Hz), 2.22 (d, 3H, *J* = 0.7 Hz), 1.25 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 163.1 (246 Hz), 160.2 (249 Hz), 151.5, 150.2, 148.4, 140.8 (13 Hz), 140.6, 139.1 (7 Hz), 136.9 (3 Hz), 130.2 (8 Hz), 130.0 (3 Hz), 129.2 (8 Hz), 125.2 (12 Hz), 124.5 (3 Hz), 124.3 (3 Hz), 116.1 (23 Hz), 115.6 (22 Hz), 113.9 (21 Hz), 108.7, 106.2, 61.3, 53.1, 40.2, 30.5, 14.1, 13.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{26}F_2N_3O_3$: 478.1942; found, 478.1935.



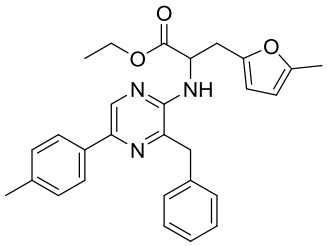
Ethyl 2-((3-benzyl-5-(3-fluorophenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*3,1,42*} (YJ30367-133-2): Obtained as a 90% pure oil (0.14 g, 36%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.73 (s, 1H), 7.70 (m, 2H), 7.45-7.23 (m, 6H), 7.02 (m, 1H), 5.82 (m, 1H), 5.74 (d(br), 1H, *J* = 3.1 Hz), 5.18 (d(br), 1H, *J* = 7.5 Hz), 4.92 (m, 1H), 4.17 (m, 4H), 3.15 (d, 2H, *J* = 5.5 Hz), 2.22 (m, 3H), 1.24 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.0, 163.1 (244 Hz), 151.4, 150.6, 148.4, 141.3, 139.8 (8 Hz), 139.6, 139.5, 136.9, 136.4, 130.1 (8 Hz), 128.7 (11 Hz), 126.9, 120.9 (2 Hz), 114.4 (20 Hz), 112.5 (23 Hz), 108.6, 106.2, 61.2, 53.2, 40.7, 30.5, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}FN_3O_3$, 460.2036; found, 460.2040.



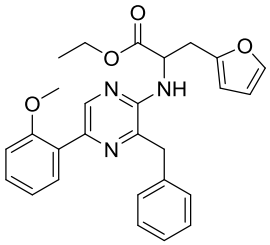
Ethyl 2-((3-benzyl-5-(4-fluorophenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*4,1,42*} (YJ30531-141-3): Obtained as an oil (0.12 g, 21%) after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR ($CDCl_3$): 8.36 (s, 1H), 7.91 (m, 2H), 7.34-7.23 (m, 5H), 7.15 (m, 2H), 5.82 (m, 1H), 5.75 (d, 1H, *J* = 3.0 Hz), 5.13 (d(br), 1H, *J* = 7.6 Hz), 4.92 (m, 1H), 4.17 (m, 4H), 3.15 (d, 2H, *J* = 5.3 Hz), 2.22 (s, 3H), 1.23 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 162.8 (246 Hz), 151.4, 150.3, 148.5, 141.2, 140.2, 136.5, 136.4, 133.7 (3 Hz), 128.8, 128.7, 127.3 (8 Hz), 126.9, 115.6 (21 Hz), 108.6, 106.2, 61.2, 53.2, 40.7, 30.6, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}FN_3O_3$, 460.2036; found, 460.2039.



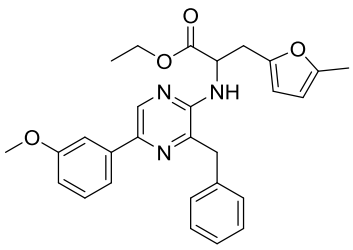
Ethyl 2-((3-benzyl-5-(m-tolyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*5,1,42*} (YJ30367-067-3): Obtained as an oil (0.20 g, 26%) after a chromatography over silica gel (cyclohexane-ethyl acetate 96:4). ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 7.77 (m, 1H), 7.72 (m, 1H), 7.37 – 7.23 (m, 6H), 7.17 (m, 1H), 5.81 (m, 1H), 5.74 (d, 1H, *J* = 3.0 Hz), 5.09 (d, 1H, *J* = 7.5 Hz), 4.91 (m, 1H), 4.17 (m, 4H), 3.12 (d, 2H, *J* = 5.3 Hz), 2.45 (s, 3H), 2.22 (s, 3H), 1.22 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 151.4, 150.3, 148.6, 141.3, 141.1, 138.3, 137.5, 136.9, 136.7, 128.8, 128.7, 128.6, 128.5, 126.8, 126.4, 122.8, 108.5, 106.2, 61.2, 53.2, 40.8, 30.6, 21.6, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_3$, 456.2287; found, 456.2253.



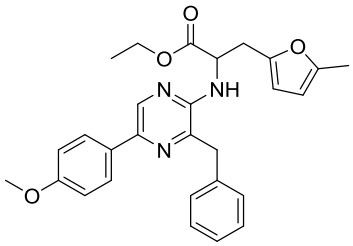
Ethyl 2-((3-benzyl-5-(p-tolyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*6,1,42*} (YJ30367-043-2): Obtained as an oil (0.23 g, 45%) after a chromatography over silica gel (cyclohexane-ethyl acetate 95:5). ^{1}H NMR ($CDCl_3$): 8.38 (s, 1H), 7.83 (m, 2H), 7.28 (m, 2H), 7.26 – 7.17 (m, 7H), 5.81 (m, 1H), 5.74 (d, 1H, *J* = 3.0 Hz), 5.07 (d, 1H, *J* = 7.9 Hz), 4.91 (m, 1H), 4.15 (m, 4H), 3.13 (d, 2H, *J* = 5.3 Hz), 2.41 (s, 3H), 2.22 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 151.4, 150.2, 148.6, 141.2, 141.0, 137.6, 136.7, 136.5, 134.8, 129.4, 128.8, 128.7, 126.8, 125.5, 108.5, 106.2, 61.2, 53.2, 40.7, 30.6, 21.2, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_3$, 456.2287; found, 456.2274.



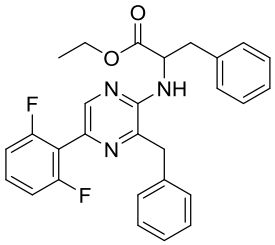
Ethyl 2-((3-benzyl-5-(2-methoxyphenyl)pyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*7,1,37*} (EC31092-049-2): Obtained as an oil (0.40 g, 64%) after a chromatography over silica gel (cyclohexane-ethyl acetate 90:10). ^{1}H NMR ($CDCl_3$): 8.58 (s, 1H), 7.87 (dd, 1H, *J* = 7.7, 1.8 Hz), 7.37 – 7.27 (m, 5H), 7.25 – 7.19 (m, 2H), 7.08 (td, 1H, *J* = 7.5, 1.0 Hz), 7.00 (dd, 1H, *J* = 8.3, 0.6 Hz), 6.20 (dd, 1H, *J* = 3.1, 1.8 Hz), 5.82 (dd, 1H, *J* = 3.1, 0.5 Hz), 5.07 (d, 1H, *J* = 7.6 Hz), 5.00 – 4.91 (m, 1H), 4.15 (s, 2H), 4.13 (qd, 2H, *J* = 7.1, 1.4 Hz), 3.89 (s, 3H), 3.19 (d, 2H, *J* = 5.3 Hz), 1.19 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 157.0, 150.8, 149.9, 142.0, 141.2, 141.1, 139.5, 137.0, 130.5, 129.1, 128.9 (two signals), 126.9, 121.3, 111.5, 110.4, 107.8, 61.4, 55.7, 41.0, 30.6, 27.1, 14.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_4$, 458.2080; found, 458.2083.



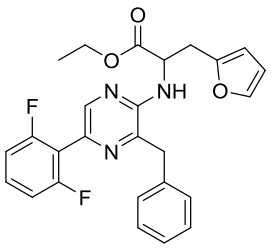
Ethyl 2-((3-benzyl-5-(3-methoxyphenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*8,1,42*} (YJ30367-093-3): Obtained as an oil (0.07 g, 20%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5 to 94/6). ^{1}H NMR ($CDCl_3$): 8.41 (s, 1H), 7.51 (m, 2H), 7.40-7.23 (m, 6H), 6.91 (m, 1H), 5.82 (m, 1H), 5.75 (d, 1H, *J* = 2.9 Hz), 5.06 (d(br), 1H, *J* = 7.3 Hz), 4.93 (m, 1H), 4.17 (m, 4H), 3.89 (s, 3H), 3.14 (d, 2H, *J* = 5.4 Hz), 2.23 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 160.1, 151.4, 150.4, 148.5, 141.1, 140.8, 139.0, 136.9, 136.6, 129.7, 128.8, 128.7, 126.8, 118.0, 113.6, 111.1, 108.6, 106.2, 61.2, 55.3, 53.2, 40.6, 30.6, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_4$, 472.2236; found, 472.2250.



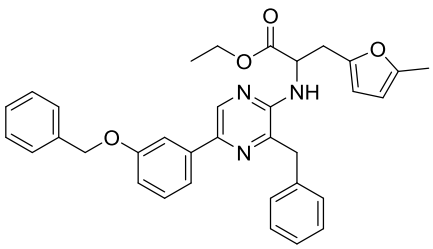
Ethyl 2-((3-benzyl-5-(4-methoxyphenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*9,1,42*} (YJ30531-175-3): Obtained, using DMF as the reaction solvant, as an oil (0.16 g, 44%) after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5 to 94/6). ^{1}H NMR ($CDCl_3$): 8.35 (s, 1H), 7.90 (m, 2H), 7.33-7.23 (m, 5H), 7.01 (m, 2H), 5.82 (m, 1H), 5.75 (d, 1H, *J* = 2.6 Hz), 5.06 (d(br), 1H, *J* = 7.5 Hz), 4.91 (m, 1H), 4.21 (m, 4H), 3.87 (s, 3H), 3.14 (d, 2H, *J* = 5.5 Hz), 2.22 (s, 3H), 1.23 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 159.6, 151.4, 149.9, 148.6, 141.1, 140.1, 136.7, 136.1, 130.3, 128.8, 128.7, 126.9, 126.8, 114.2, 108.5, 106.2, 61.2, 55.3, 53.2, 40.7, 30.6, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_4$, 472.2236; found, 472.2230.



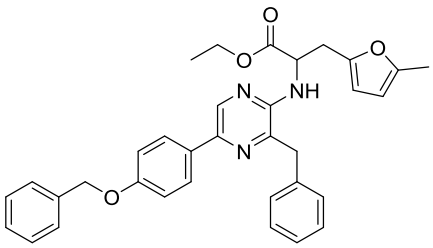
Ethyl (3-benzyl-5-(2,6-difluorophenyl)pyrazin-2-yl)phenylalaninate **23**{*10,1,1*} (MM34284-028-1): Obtained as an oil (0.24 g, 65%) after a chromatography over silica gel (cyclohexane – ethyl acetate 9/1). ^{1}H NMR ($CDCl_3$): 8.14 (s, 1H), 7.30-7.19 (m, 9H), 7.04 – 6.96 (m, 4H), 5.01 (m, 2H), 4.12 (m, 2H), 4.11 (s, 2H), 3.16 (dd, 1H, *J* = 5.2, 13.8 Hz), 3.08 (dd, 1H, *J* = 5.9, 13.8 Hz), 1.18 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.2, 160.7 (7, 250 Hz), 150.5, 150.2, 141.6 (3 Hz), 141.5, 136.2 (3 Hz), 132.4, 129.5 (10 Hz), 129.3, 128.9, 128.6, 128.4, 127.0, 126.8, 115.9 (20 Hz), 111.7 (7, 19 Hz), 61.2, 54.7, 40.8, 37.8, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}F_2N_3O_2$, 474.1993; found, 474.2011.



Ethyl 2-((3-benzyl-5-(2,6-difluorophenyl)pyrazin-2-yl)amino)-3-(furan-2-yl)propanoate **23**{*10,1,37*} (MM34284-030-1): Obtained as an oil (0.19 g, 52%) after a chromatography over silica gel (cyclohexane – ethyl acetate 9/1). ^{1}H NMR ($CDCl_3$): 8.13 (s, 1H), 7.36-7.19 (m, 7H), 7.04 – 6.98 (m, 2H), 6.23 (m, 1H), 5.84 (m, 1H), 5.22 (d, 1H, *J* = 7.3 Hz), 4.96 (m, 1H), 4.16 (s, 2H), 4.15 (m, 2H), 3.20 (d, 2H, *J* = 5.3), 1.12 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 171.8, 160.7 (7, 250 Hz), 150.5, 150.4, 141.9, 141.6, 141.5 (3 Hz), 136.3 132.4, 129.5 (10 Hz), 128.9, 128.6, 126.9, 115.8 (20 Hz), 111.7 (7, 19 Hz), 110.3, 107.7, 61.3, 53.0, 40.8, 30.4, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{23}F_2N_3O_3$, 464.1786; found, 464.1799.

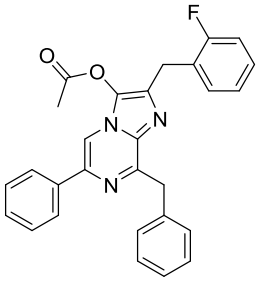


Ethyl 2-((3-benzyl-5-(3-(benzyloxy)phenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*11,1,42*} (RB32489-013-2): Obtained as an oil (0.50 g, 74%) after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3 to 96/4). ^{1}H ($CDCl_3$): 8.40 (s, 1H), 7.65 (m, 1H), 7.51 (m, 3H), 7.44-7.26 (m, 9H), 6.99 (dd, 1H, *J* = 8.1, 2.6 Hz), 5.82 (m, 1H), 5.76 (d, 1H, *J* = 3 Hz), 5.16 (s, 2H), 5.13 (m, 1H), 4.94 (m, 1H), 4.17 (m, 4H), 3.16 (m, 2H), 2.23 (s, 3H), 1.24 (t, 3H, *J* = 7.3 Hz). ^{13}C ($CDCl_3$) 172.1, 159.4, 151.4, 150.4, 148.5, 141.1, 140.7, 139.0, 137.2, 136.8, 136.6, 129.7, 128.8, 128.7, 128.6, 127.9, 127.6, 126.8, 118.2, 114.5, 112.1, 108.6, 106.2, 70.1, 61.2, 53.2, 40.7, 30.6, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{34}N_3O_4$, 548.2549; found, 548.2540.

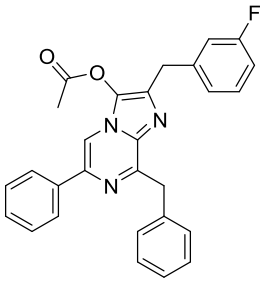


Ethyl 2-((3-benzyl-5-(4-(benzyloxy)phenyl)pyrazin-2-yl)amino)-3-(5-methylfuran-2-yl)propanoate **23**{*12,1,42*} (YJ 33069-163-1): Obtained as an oil (0.49 g, 82%), using toluene at 90 °C, after a chromatography over silica gel (cyclohexane – ethyl acetate 95/5). ^{1}H NMR ($CDCl_3$): 8.35 (s, 1H), 7.88 (m, 2H), 7.48 (m, 2H), 7.42 (m, 2H), 7.36 (m, 1H), 7.32-7.20 (m, 5H), 7.08 (m, 2H), 5.82 (m, 1H), 5.76 (d (br), 1H, *J* = 3.0 Hz), 5.15 (s, 2H), 5.07 (d(br), 1H, *J* = 7.6 Hz), 4.94 (m, 1H), 4.16 (m, 4H), 3.15 (d, 2H, *J* = 5.3 Hz), 2.23 (s, 3H), 1.23 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.1, 158.9, 151.4, 149.7, 148.5, 141.2, 141.0, 137.0, 136.6, 135.8, 130.4, 128.8, 128.7, 128.6, 127.9, 127.4, 126.9, 126.8, 115.2, 108.6, 106.2, 70.1, 61.2, 53.2, 40.7, 30.5, 14.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{34}N_3O_4$, 548.2549; found, 548.2556.

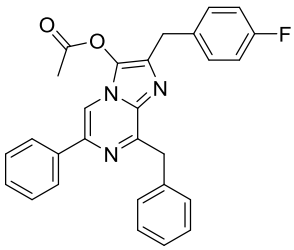
General procedure for the synthesis of the O-acetylated luciferins 25 via step xii. In a sealable vessel, the considered N-pyrazyl aminoester **24** (1.0 mmol) and sodium hydroxide (0.16 g, 4 mmol) were weighted. The air was replaced with argon and anhydrous THF (5 mL) was injected. This was stirred at 20 °C under an inert atmosphere overnight and acetic anhydride (1.41 mL, 15.0 mmol) was then injected. After stirring an additional two hours at room temperature, this was diluted in ethyl acetate, washed with water, brine and concentrated to dryness. The traces of acetic acid and acetic anhydride were removed by co-evaporation with toluene and then cyclohexane and the residue further purified as described below. Note: as mentioned in the main text, few of these compounds turned out to be unstable over at least a week. Most often an initial assessment of their bioluminescence properties could be made but this was not possible when, years later, we ran a second set of experiment with most of the compounds made. Although their analysis is provided in the following, these compounds are: **25**{*1,1,28*}, **25**{*2,1,42*, **25**{*7,1,37*}, **25**{*2,1,44*}, **25**{*2,1,48*} and **25**{*10,1,37*}.



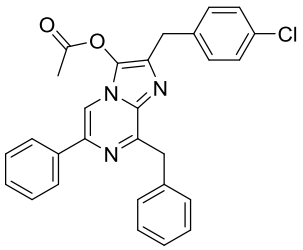
8-Benzyl-2-(2-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,2*} (YJ30367-149-1): Obtained as a white solid (0.22 g, 71%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.81 (s, 1H), 7.63 (m, 2H), 7.48 – 7.21 (m, 8H), 7.10 (m, 2H), 4.63 (s, 2H), 4.23 (s, 2H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 160.9 (244 Hz), 153.0, 139.1, 137.9, 136.8, 133.9 (32 Hz), 131.3 (4 Hz), 129.7 (two signals?), 128.7, 128.5, 128.4, 128.3, 128.2, 126.5, 126.4, 125.1 (16 Hz), 124.1 (4 Hz), 115.1 (21 Hz), 108.9, 39.5, 26.8 (4 Hz), 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774; found, 452.1769.



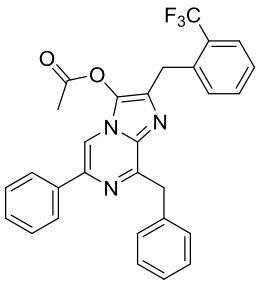
8-Benzyl-2-(3-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,3*} (YJ30367-017-1): Obtained as a white solid (0.13 g, 57%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.81 (s, 1H), 7.63 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.33 – 7.22 (m, 4H), 7.06 (m, 2H), 6.95 (m, 1H), 4.64 (s, 2H), 4.19 (s, 2H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (245 Hz), 153.0, 140.6 (7 Hz), 139.2, 137.8, 136.8, 134.4, 133.7, 129.8 (8 Hz), 129.7, 128.8, 128.7, 128.6, 128.3, 126.5, 126.4, 124.6 (3 Hz), 115.9 (21 Hz), 113.4 (20 Hz), 108.9, 39.5, 33.7, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774; found, 452.1778.



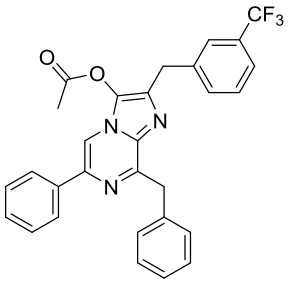
8-Benzyl-2-(4-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,4*} (EC31092-099-2): Obtained as a beige solid (0.31 g, 70%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.94 – 7.86 (m, 2H), 7.79 (s, 1H), 7.65 – 7.58 (m, 2H), 7.50 – 7.36 (m, 3H), 7.35 – 7.17 (m, 5H), 7.00 (dd, 2H, *J* = 9.8, 7.7 Hz), 4.62 (s, 2H), 4.15 (s, 2H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 161.8 (d, *J* = 244.6 Hz), 153.1, 139.3, 138.0, 136.9, 135.1, 133.9 (d, *J* = 3.3 Hz), 133.8, 130.6 (d, *J* = 7.9 Hz), 129.9, 128.9, 128.7, 128.4, 126.6, 126.6, 115.3 (d, *J* = 21.3 Hz), 109.0, 39.6, 33.4, 20.1 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774; found, 452.1776.



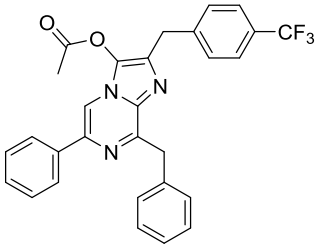
8-Benzyl-2-(4-chlorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,7*} (CF34391-037-1): Obtained as a white solid (0.23 g, 62%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.81 (s, 1H), 7.62 (m, 2H), 7.48 (m, 2H), 7.40 (m, 1H), 7.28 (m, 7H), 4.63 (s, 2H), 4.14 (s, 2H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 153.0, 139.2, 137.8, 136.8, 136.6, 134.6, 133.7, 132.3, 130.4, 129.7, 128.8, 128.6, 128.5, 128.3, 126.5, 126.4, 108.9, 39.5, 33.4, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}ClN_3O_2$, 468.1479; found, 468.1485.



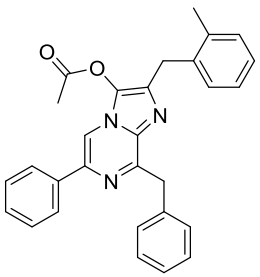
8-Benzyl-6-phenyl-2-(2-(trifluoromethyl)benzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,8*} (YJ30531-123-1): Obtained as wax (0.07 g, 95%). ^{1}H NMR ($CDCl_3$): 7.93 (m, 2H), 7.80 (s, 1H), 7.65 (m, 3H), 7.45 (m, 2H), 7.53 – 7.21 (m, 9H), 4.65 (s, 2H), 4.38 (s, 2H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 153.1, 139.2, 137.8, 136.8, 136.7, 133.9, 133.8, 131.8, 131.7, 129.7, 128.9, 128.7 (30 Hz), 128.6, 128.3, 126.6, 126.5, 126.4, 126.0, 125.7 (6 Hz), 124.5 (275 Hz), 109.1, 39.6, 29.7, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{23}F_3N_3O_2$, 502.1742; found, 502.1722.



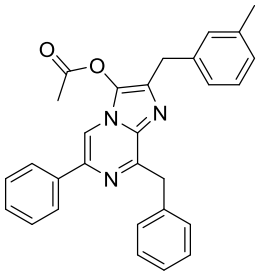
8-Benzyl-6-phenyl-2-(3-(trifluoromethyl)benzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,9*} (YJ30531-125-1): Obtained as a white solid after a recrystallization in n-heptane (0.08 g, 57%). ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.81 (s, 1H), 7.63 (m, 3H), 7.54-7.38 (m, 6H), 7.34 – 7.21 (m, 3H), 4.63 (s, 2H), 4.25 (s, 2H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 153.1, 139.3, 139.1, 137.8, 136.8, 134.2, 133.8, 132.5, 130.7 (31 Hz), 129.7, 128.9, 128.8, 128.7, 128.6, 128.3, 126.5, 126.4, 125.8 (6 Hz), 124.2 (275 Hz), 123.4 (6 Hz), 108.9, 39.5, 33.7, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{23}F_3N_3O_2$, 502.1742; found, 502.1795.



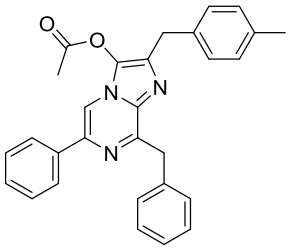
8-Benzyl-6-phenyl-2-(4-(trifluoromethyl)benzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,10*} (YJ30531-127-1): Obtained as a white solid after a recrystallization in n-heptane (0.08 g, 66%). ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.81 (s, 1H), 7.60 (m, 4H), 7.49-7.38 (m, 5H), 7.33 – 7.22 (m, 3H), 4.63 (s, 2H), 4.24 (s, 2H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 153.1, 142.3, 139.3, 137.7, 136.7, 134.1, 133.8, 129.7, 129.4, 128.9 (31 Hz), 128.8, 128.7, 128.6, 128.3, 126.5, 126.4, 125.3 (6 Hz), 124.3 (275 Hz), 108.9, 39.5, 33.7, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{23}F_3N_3O_2$, 502.1742; found, 502.1730.



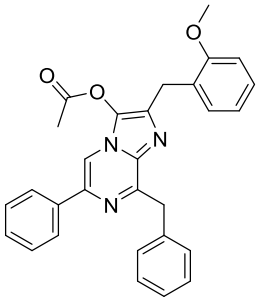
8-Benzyl-2-(2-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,11*} (YJ30367-179-1): Obtained as a white solid (0.44 g, 96%): ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.76 (s, 1H), 7.64 (m, 2H), 7.48 –7.18 (m, 10H), 4.64 (s, 2H), 4.24 (s, 2H), 2.32 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 152.8, 139.0, 137.9, 137.2, 136.9, 135.9, 135.5, 133.6, 130.3, 130.0, 129.7, 128.9, 128.8, 128.5, 128.3, 126.9, 126.5, 126.4, 125.9, 108.8, 39.4, 32.6, 26.9, 19.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2032.



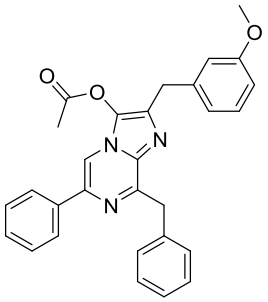
8-Benzyl-2-(3-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,12*} (EC31092-097-2): Obtained as a beige solid (0.17 g, 61%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 – 7.85 (m, 2H), 7.77 (s, 1H), 7.66 – 7.58 (m, 2H), 7.49 – 7.35 (m, 3H), 7.35 – 7.27 (m, 2H), 7.24 – 7.16 (m, 2H), 7.15 – 7.01 (m, 3H), 4.62 (s, 2H), 4.16 (s, 2H), 2.33 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 153.0, 139.2, 138.2, 138.1, 137.0, 135.5, 133.8, 130.0, 129.9, 129.0, 128.9, 128.7, 128.5, 128.4, 127.3, 126.6 (two signals), 126.2, 109.0, 39.6, 34.3, 21.5, 20.0 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2053.



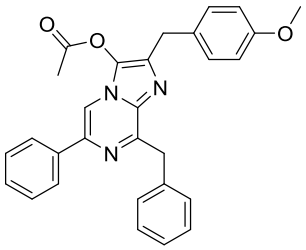
8-Benzyl-2-(4-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,13*} (YJ30367-147-1): Obtained as a white solid (0.21 g, 60%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.80 (s, 1H), 7.64 (m, 2H), 7.49 –7.13 (m, 10H), 4.65 (s, 2H), 4.18 (s, 2H), 2.36 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 152.9, 139.0, 137.9, 136.9, 135.9, 135.5, 134.9, 133.6, 129.8, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 126.5, 126.4, 108.8, 39.4, 33.8, 21.0, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2034.



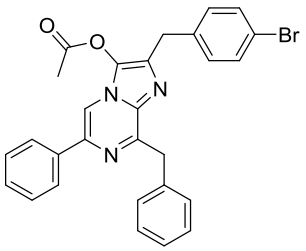
8-Benzyl-2-(2-methoxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,14*} (YJ30367-151-1): Obtained as a white solid (0.23 g, 72%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.78 (s, 1H), 7.64 (m, 2H), 7.46 (m, 2H), 7.39 (m, 1H), 7.32 (m, 2H), 7.24 (m, 3H), 6.92 (m, 2H), 4.63 (s, 2H), 4.22 (s, 2H), 3.82 (s, 3H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 157.6, 152.8, 138.9, 138.0, 137.0, 135.1, 133.6, 130.6, 129.8, 128.8, 128.7, 128.4, 128.2, 127.9, 126.4 (two signals), 126.3, 120.5, 110.4, 108.9, 55.4, 39.4, 28.5, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_3$, 464.1974; found, 464.1978.



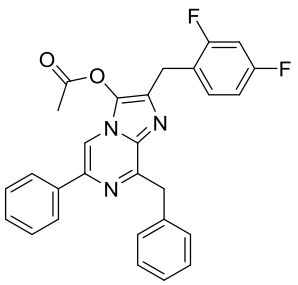
8-Benzyl-2-(3-methoxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,15*} (EC31092-127-2): Obtained as a white solid (0.20 g, 56%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 – 7.86 (m, 2H), 7.78 (s, 1H), 7.65 – 7.58 (m, 2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.34 (m, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.18 (m, 2H), 6.91 – 6.86 (m, 1H), 6.86 – 6.83 (m, 1H), 6.81 – 6.75 (m, 1H), 4.63 (s, 2H), 4.17 (s, 2H), 3.77 (s, 3H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 159.9, 153.1, 139.7, 139.2, 138.0, 137.0, 135.2, 133.8, 129.9, 129.6, 129.0, 128.9, 128.7, 128.4, 126.6 (two signals), 121.6, 114.7, 112.3, 109.0, 55.3, 39.5, 34.4, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_3$, 464.1974; found, 464.1982.



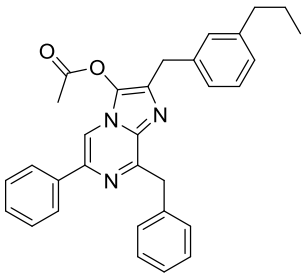
8-Benzyl-2-(4-methoxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,16*} (YJ30367-019-1): Obtained as a white solid (0.04 g, 28%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.80 (s, 1H), 7.63 (m, 2H), 7.45 (m, 2H), 7.40 (m, 1H), 7.33 (m, 3H), 7.23 (m, 2H), 6.87 (m, 2H), 4.63 (s, 2H), 4.17 (s, 2H), 3.77 (s, 3H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 158.3, 152.9, 139.0, 137.9, 136.9, 135.6, 133.6, 130.1, 130.0, 129.7, 128.7, 128.5, 128.3, 126.5, 126.4, 113.9, 108.4, 55.3, 39.4, 33.3, 19.9 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_3$, 464.1974; found, 464.1990.



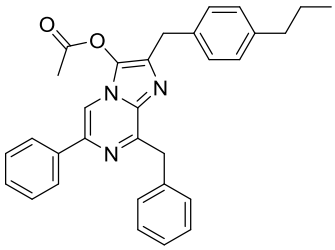
8-Benzyl-2-(4-bromobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,20*} (CF34391-035-1): Obtained as a white solid (0.18 g, 49%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.80 (s, 1H), 7.62 (m, 2H), 7.44 (m, 5H), 7.32 (m, 2H), 7.24 (m, 1H), 7.18 (m, 1H), 4.63 (s, 2H), 4.14 (s, 2H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 153.0, 139.2, 137.8, 137.1, 136.8, 134.5, 133.7, 131.5, 130.8, 129.7, 128.8, 128.6, 128.3, 126.5, 126.4, 120.4, 108.9, 39.5, 33.4, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}BrN_3O_2$, 512.0974; found, 512.0950.



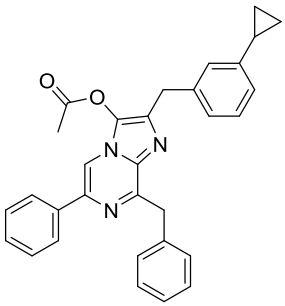
8-Benzyl-2-(2,4-difluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,25*} (YJ31067-055-1): Obtained as a white solid (0.13 g, 52%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.81 (s, 1H), 7.63 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 6.84 (m, 2H), 4.62 (s, 2H), 4.16 (s, 2H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.8 (11 and 247 Hz), 160.7 (11 and 247 Hz), 153.0, 139.2, 137.8, 136.8, 133.7, 131.8 (5 and 9 Hz), 129.7, 129.0, 128.8, 128.7, 128.6, 128.3, 126.5, 126.4, 121.0 (3 and 16 Hz), 111.1 (3 and 21 Hz), 108.9, 103.5 (26 Hz), 39.5, 26.8 (4 Hz), 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{22}F_2N_3O_2$, 470.1680; found, 470.1686.



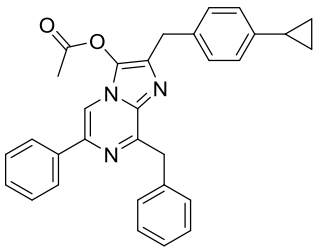
8-Benzyl-6-phenyl-2-(3-propylbenzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,27*} (CF34204-038-1): Obtained as a white solid (0.14 g, 54%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.80 (s, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.33 (m, 2H), 7.24 (m, 2H), 7.10 (m, 3H), 4.65 (s, 2H), 4.20 (s, 2H), 2.59 (m, 2H), 2.17 (s, 3H), 1.66 (m, 2H), 0.97 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 167.1, 152.9, 142.9, 139.1, 137.9, 137.8, 136.9, 135.4, 133.6, 129.7, 129.3, 128.9, 128.7, 128.5, 128.3, 128.2, 126.6, 126.5, 126.4, 126.3, 108.9, 39.4, 38.0, 34.3, 24.6, 19.9, 13.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{30}N_3O_2$, 476.2338; found, 476.2346.



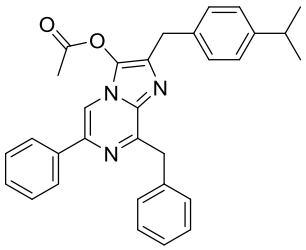
8-Benzyl-6-phenyl-2-(4-propylbenzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,28*} (CF34204-046-1): Obtained as a white solid (0.25 g, 73%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.80 (s, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.33 (m, 2H), 7.24 (m, 3H), 7.15 (m, 2H), 4.65 (s, 2H), 4.20 (s, 2H), 2.60 (m, 2H), 2.18 (s, 3H), 1.66 (m, 2H), 0.98 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 167.1, 152.9, 140.8, 139.0, 137.9, 136.9, 135.5, 135.2, 133.6, 129.8, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 126.4, 126.4, 108.8, 39.4, 37.7, 33.9, 24.6, 19.9, 13.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{30}N_3O_2$, 476.2338; found, 476.2332.



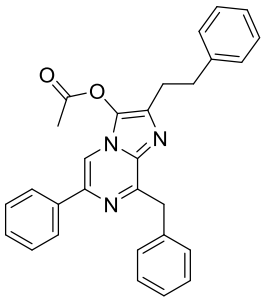
8-Benzyl-2-(3-cyclopropylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,29*} (YJ30367-109-1): Obtained as a white solid (0.29 g, 65%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.79 (s, 1H), 7.64 (m, 2H), 7.46 (m, 2H), 7.39 (m, 1H), 7.33 (m, 2H), 7.23 (m, 2H), 7.06 (m, 2H), 6.96 (m, 1H), 4.64 (s, 2H), 4.18 (s, 2H), 2.18 (s, 3H), 1.89 (m, 1H), 0.95 (m, 2H), 0.70 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.1, 152.9, 142.2, 139.0, 137.9, 137.8, 136.9, 135.3, 133.6, 129.7, 128.7, 128.5, 128.4, 128.3, 126.6, 126.5, 126.4, 126.1, 123.7, 108.8, 39.4, 34.3, 19.8, 15.3, 9.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{28}N_3O_2$, 474.2181; found, 474.2189.



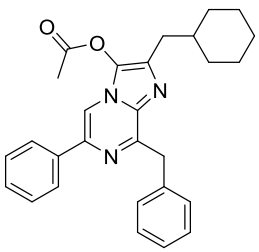
8-Benzyl-2-(4-cyclopropylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,30*} (YJ30367-107-1): Obtained as a white solid (0.29 g, 68%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.80 (s, 1H), 7.64 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 7.33 (m, 2H), 7.22 (m, 3H), 7.04 (m, 2H), 4.64 (s, 2H), 4.17 (s, 2H), 2.18 (s, 3H), 1.92 (m, 1H), 0.94 (m, 2H), 0.68 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.1, 152.9, 142.1, 139.0, 137.9, 136.9, 135.4, 134.9, 133.6, 129.7, 129.0, 128.8, 128.7, 128.5, 128.3, 126.5, 126.4, 125.8, 108.4, 39.4, 33.8, 19.9, , 15.0, 9.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{28}N_3O_2$, 474.2181; found, 474.2183.



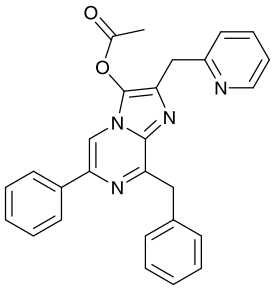
8-Benzyl-2-(4-isopropylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,31*} (E31093-093-2): Obtained as a white solid (0.16 g, 70%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.93 – 7.84 (m, 2H), 7.77 (s, 1H), 7.65 – 7.59 (m, 2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.33 (m, 1H), 7.33 – 7.28 (m, 2H), 7.24 – 7.14 (m, 5H), 4.62 (s, 2H), 4.17 (s, 2H), 2.90 (hept, 1H, J = 6.9 Hz), 2.13 (s, 3H), 1.25 (d, 6H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 167.2, 153.0, 147.2, 139.2, 138.0, 137.0, 135.6, 135.4, 133.8, 129.9, 129.2, 129.0, 128.9, 128.7, 128.4, 126.7, 126.6, 126.6, 109.0, 39.5, 34.1, 33.9, 24.2, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{30}N_3O_2$, 476.2338; found, 476.2337.



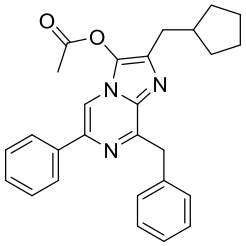
8-Benzyl-2-phenethyl-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,32*} (YJ31070-131-1): Obtained as a white powder after a recrystallization from n-heptane (0.22 g, 67%). ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.81 (s, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.35-7.21 (m, 8H), 4.65 (s, 2H), 3.12 (m, 4H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 141.5, 139.0, 138.0, 136.9, 136.0, 137.0, 133.7, 129.7, 128.8, 128.5, 128.4, 128.3, 128.2, 126.5, 126.4, 126.0, 108.9, 39.4, 34.7, 29.0, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2026.



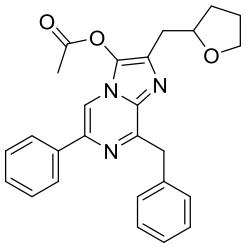
8-Benzyl-2-(cyclohexylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,33*} (YJ31067-071-1): Obtained as a powder (0.24 g, 72%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.80 (s, 1H), 7.65 (m, 2H), 7.47 (m, 2H), 7.39 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 4.63 (s, 2H), 2.78 (d, 2H, *J* = 7.2 Hz), 2.50 (s, 3H), 1.87 (m, 1H), 1.75 (m, 5H), 1.27 (m, 3H), 1.05 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.3, 152.7, 138.9, 138.0, 137.0, 136.0, 133.7, 129.8, 129.0, 128.7, 128.4, 128.2, 126.4, 126.3, 108.9, 39.4, 37.8, 34.5, 33.2, 26.5, 26.2, 20.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_2$, 440.2338; found, 440.2326.



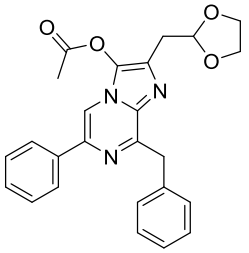
8-Benzyl-6-phenyl-2-(pyridin-2-ylmethyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,34*} (YJ31134-089-1): Obtained as an oil (0.41 g, 91%) which was evaluated without further purification. ^{1}H NMR ($CDCl_3$): 8.56 (m, 1H), 7.92 (m, 1H), 7.90 (m, 1H), 7.83 (s, 1H), 7.62 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 7.32 (m, 3H), 7.17 (m, 3H), 4.63 (s, 2H), 4.38 (s, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 158.4, 153.0, 149.1, 139.1, 137.8, 136.8, 136.5, 133.8, 133.7, 129.7, 129.2, 129.0, 128.8, 128.5, 128.2, 126.4, 123.4, 121.5, 108.9, 39.4, 36.6, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}N_4O_2$, 435.1821; found, 435.1823.



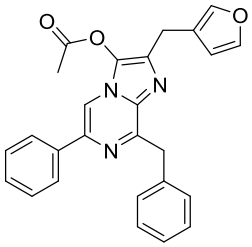
8-Benzyl-2-(cyclopentylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,36*} (YJ31067-073-1): Obtained as a powder (0.21 g, 88%) after a concentration to dryness. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.80 (s, 1H), 7.65 (m, 2H), 7.47 (m, 2H), 7.39 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 4.63 (s, 2H), 2.78 (d, 2H, *J* = 7.4 Hz), 2.50 (s, 3H), 2.38 (m, 1H), 1.80 (m, 2H), 1.64 (m, 4H), 1.29 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.3, 152.7, 138.9, 138.0, 137.0, 136.7, 133.6, 129.8, 128.7, 128.6, 128.5, 128.2, 126.4, 126.3, 108.9, 39.8, 38.4, 32.8, 32.5, 25.0, 20.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}N_3O_2$, 426.2181; found, 426.2180.



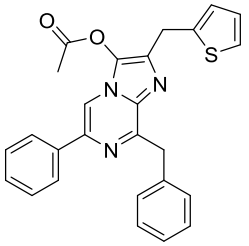
8-Benzyl-6-phenyl-2-((tetrahydrofuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,38*} (EC31092-129-2): Obtained as an oil (0.36 g, 81%) which was evaluated without further purification. ^{1}H NMR ($CDCl_3$): 7.93 – 7.87 (m, 2H), 7.82 (s, 1H), 7.62 – 7.57 (m, 2H), 7.48 – 7.41 (m, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.17 (m, 1H), 4.66 – 4.55 (m, 2H), 4.32 – 4.23 (m, 1H), 3.89 – 3.69 (m, 2H), 3.10 – 2.95 (m, 2H), 2.46 (s, 3H), 2.09 – 1.98 (m, 1H), 1.92 – 1.82 (m, 2H), 1.77 – 1.66 (m, 1H). ^{13}C NMR ($CDCl_3$): 167.5, 153.0, 139.1, 138.1, 137.1, 133.9, 133.8, 129.9, 129.7, 128.9, 128.6, 128.4, 126.6 (two signals), 109.2, 78.3, 68.2, 39.5, 33.5, 31.0, 25.8, 20.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{26}N_3O_3$, 428.1974; found, 428.1956.



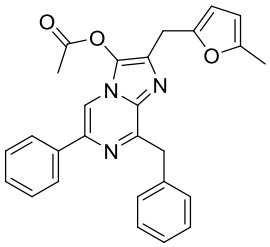
2-((1,3-Dioxolan-2-yl)methyl)-8-benzyl-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,39*} (VHE30855-189-2): Obtained as a white solid (0.46 g, 76%) after recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.85 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 5.29 (t, 1H, *J* = 4.5 Hz), 4.64 (s, 2H), 3.97 – 3.86 (m, 4H), 3.22 (d, 2H, *J* = 4.5 Hz), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$): 137.3, 153.0, 139.0, 137.9, 136.9, 133.8, 131.1, 130.0, 129.7, 128.7, 128.5, 128.2, 126.4 (two signals), 109.0, 103.1, 65.1, 39.3, 32.9, 20.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{24}N_3O_3$, 430.1767; found, 430.1762.



8-Benzyl-2-(furan-3-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,40*} (VHE30855-187-2): Obtained as a beige solid (0.74 g, 67%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.83 (s, 1H), 7.63 (m, 2H), 7.47 (m, 2H), 7.40 (m, 2H), 7.36 – 7.30 (m, 3H), 7.24 (m, 1H), 6.38 (m, 1H), 4.64 (s, 2H), 4.00 (m, 2H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 153.0, 142.9, 140.0, 139.1, 137.8, 136.8, 134.5, 133.6, 129.7, 128.8, 128.6, 128.3, 126.5, 126.4, 121.2, 111.5, 108.9, 39.4, 23.6, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{22}N_3O_3$, 424.1661; found, 424.1688.

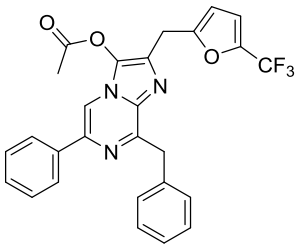


8-Benzyl-6-phenyl-2-(thiophen-2-ylmethyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,41*} (EC31092-095-2): Obtained as a white solid (0.37 g, 73%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 – 7.87 (m, 2H), 7.80 (s, 1H), 7.65 – 7.58 (m, 2H), 7.49 – 7.42 (m, 2H), 7.42 – 7.34 (m, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.19 (dd, 1H, *J* = 5.1, 1.3 Hz), 6.95 (dd, 1H, *J* = 5.1, 3.5 Hz), 6.93 – 6.88 (m, 1H), 4.62 (s, 2H), 4.38 (d, 2H, *J* = 0.8 Hz), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 153.1, 140.3, 139.2, 137.8, 136.8, 134.4, 133.5, 129.8, 128.8, 128.6 (two signals), 128.3, 126.8, 126.5, 126.4, 125.9, 124.3, 108.9, 39.4, 28.5, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{22}N_3O_2S$, 440.1433; found, 440.1486.

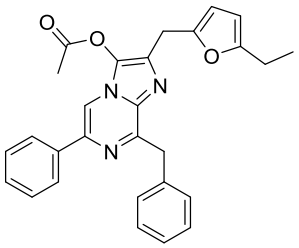


8-Benzyl-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,42*} (EC29990-164-1): Obtained as a white solid (0.14 g, 24%) after a chromatography over silica gel (cyclohexane-ethyl acetate 5:1) and a recrystallization from cyclohexane. ^{1}H NMR ($CDCl_3$): 7.93 – 7.86 (m, 2H), 7.82 (s, 1H), 7.64 – 7.57 (m,

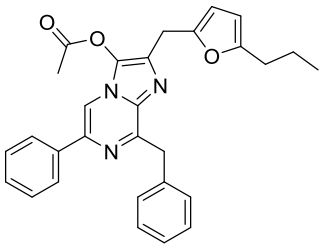
2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.16 (m, 1H), 6.03 – 5.97 (m, 1H), 5.93 – 5.86 (m, 1H), 4.62 (s, 2H), 4.17 (s, 2H), 2.34 (s, 3H), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 153.1, 151.3, 149.7, 139.3, 138.0, 137.0, 133.7, 133.0, 129.9, 129.1, 128.9, 128.7, 128.4, 126.6 (two signals), 109.0, 107.6, 106.3, 39.5, 27.5, 20.2, 13.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_3$, 438.1818; found, 438.1828.



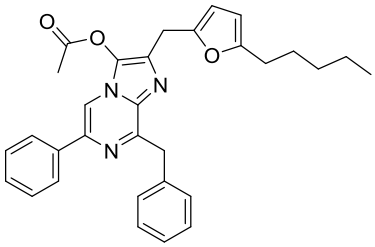
8-Benzyl-6-phenyl-2-((5-(trifluoromethyl)furan-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,43*} (EC31093-039-1): Obtained as a white solid (0.07 g, 43%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.94 – 7.87 (m, 2H), 7.83 (s, 1H), 7.63 – 7.57 (m, 2H), 7.49 – 7.42 (m, 2H), 7.42 – 7.35 (m, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 1H), 6.73 (dd, 1H, *J* = 3.3, 1.2 Hz), 6.21 (dd, 1H, *J* = 3.4, 0.7 Hz), 4.61 (s, 2H), 4.23 (s, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 154.9, 153.2, 140.9 (43 Hz), 139.4, 137.7, 136.7, 133.7, 131.2, 129.7, 129.0, 128.8, 128.7, 128.3, 126.5, 126.4, 119.2 (267 Hz), 112.6 (3 Hz), 109.0, 107.9, 39.5, 27.0, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{21}F_3N_3O_3$, 492.1535; found, 492.1566.



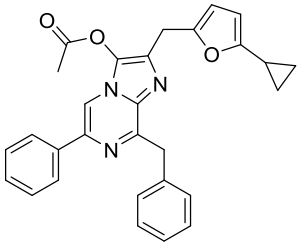
8-Benzyl-2-((5-ethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,44*} (EC31092-093-2): Obtained as a white solid (0.27 g, 57%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.93 – 7.86 (m, 2H), 7.81 (s, 1H), 7.64 – 7.57 (m, 2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 1H), 6.01 (d, 1H, *J* = 3.0 Hz), 5.93 – 5.87 (m, 1H), 4.62 (s, 2H), 4.17 (s, 2H), 2.61 (q, 2H, *J* = 7.5 Hz), 2.33 (s, 3H), 1.22 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 167.2, 157.2, 153.1, 149.5, 139.3, 138.0, 137.0, 133.7, 133.1, 129.9, 129.1, 128.9, 128.7, 128.4, 126.6 (two signals), 109.0, 107.4, 104.7, 39.5, 27.5, 21.5, 20.2, 12.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_3$, 452.1974; found, 452.2014.



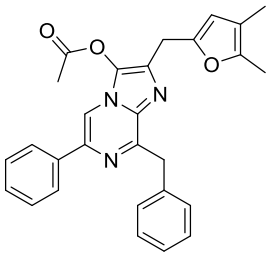
8-Benzyl-6-phenyl-2-((5-propylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,45*} (EC32712-133-2) Obtained as a white solid (0.15 g, 54%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.84 (s, 1H), 7.63 (m, 2H), 7.47 (m, 2H), 7.41 (m, 1H), 7.29 (m, 3H), 6.03 (d, 1H, *J* = 3.0 Hz), 5.93 (d, 1H, *J* = 3.0 Hz), 4.64 (s, 2H), 4.20 (s, 2H), 2.58 (t, 2H, *J* = 7.4 Hz), 2.35 (s, 3H), 1.67 (hept, 2H, *J* = 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 155.6, 153.0, 149.3, 139.1, 137.8, 136.8, 133.5, 132.9, 129.7, 128.9, 128.7, 128.5, 128.3, 126.4, 126.4, 108.8, 107.2, 105.4, 39.3, 30.1, 27.4, 21.4, 20.1, 13.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_3$: 466.2131; found, 466.2141.



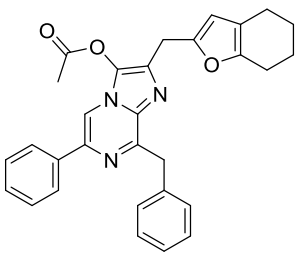
8-Benzyl-2-((5-pentylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,46*} (YJ 31776-029-1): Obtained as an oil which slowly solidified (0.18 g, 95%). ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.84 (s, 1H), 7.82 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 6.03 (m, 1H), 5.92 (d, 1H, *J* = 3.0 Hz), 4.65 (s, 2H), 4.21 (s, 2H), 2.59 (t, 2H, *J* = 7.5 Hz), 2.35 (s, 3H), 1.63 (m, 2H), 1.34 (m, 4H), 0.91 (m, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 155.9, 152.8, 149.0, 139.4, 137.6, 136.6, 133.4, 133.1, 132.6, 129.7, 128.9, 128.8, 128.7, 128.3, 126.5, 126.4, 108.8, 107.4, 105.3, 39.3, 31.4, 28.0, 27.7, 27.2, 22.4, 20.1, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{32}N_3O_3$: 494.2444; found, 494.2453.



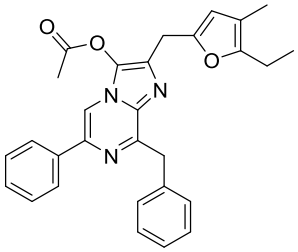
8-Benzyl-2-((5-cyclopropylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,47*} (EC31093-079-2): Obtained as a white solid (0.13 g, 42%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.93 – 7.86 (m, 2H), 7.81 (s, 1H), 7.64 – 7.57 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 1H), 5.98 (d, 1H, *J* = 3.1 Hz), 5.86 (d, 1H, *J* = 3.1 Hz), 4.61 (s, 2H), 4.15 (s, 2H), 2.34 (s, 3H), 1.84 (tt, 1H, *J* = 8.4, 5.1 Hz), 0.89 – 0.80 (m, 2H), 0.76 – 0.69 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.2, 156.8, 153.1, 149.3, 139.3, 138.0, 137.0, 133.7, 133.0, 129.9, 129.1, 128.9, 128.7, 128.4, 126.6, 126.6, 109.0, 107.6, 104.3, 39.5, 27.6, 20.2, 8.9, 6.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_3$, 464.1974; found, 464.1990.



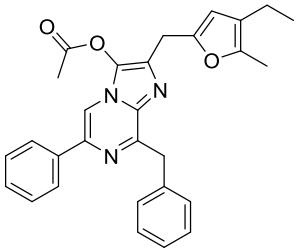
8-Benzyl-2-((4,5-dimethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,48*} (EC31092-103-2): Obtained as a beige solid (0.09 g, 45%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.94 – 7.86 (m, 2H), 7.82 (s, 1H), 7.65 – 7.58 (m, 2H), 7.50 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 1H), 5.90 (s, 1H), 4.62 (s, 2H), 4.13 (s, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 1.91 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 153.1, 148.4, 146.4, 139.2, 138.0, 137.0, 133.7, 133.2, 129.9, 129.0, 128.9, 128.7, 128.4, 126.6, 126.5, 114.7, 110.2, 109.0, 39.5, 27.4, 20.2, 11.4, 10.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_3$, 452.1974; found, 452.1990.



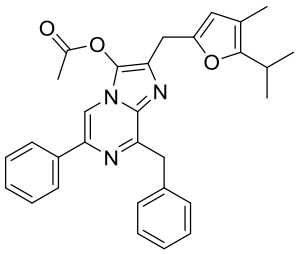
8-Benzyl-6-phenyl-2-((4,5,6,7-tetrahydrobenzofuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,49*} (YJ 33068-083-1): Obtained as a white solid (0.37 g, 47%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.84 (s, 1H), 7.82 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 5.96 (s, 1H), 4.64 (s, 2H), 4.18 (s, 2H), 2.58 (m, 2H), 2.40 (m, 2H), 2.37 (s, 3H), 1.84 (m, 2H), 1.73 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.0, 152.9, 149.8, 148.8, 139.2, 137.8, 136.7, 133.4, 132.9, 129.7, 128.9, 128.8, 128.6, 128.3, 126.5, 126.4, 117.5, 108.9, 107.8, 39.3, 31.9, 27.3, 23.2, 23.1 (two signals), 22.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{28}N_3O_3$, 478.2131; found, 478.2139.



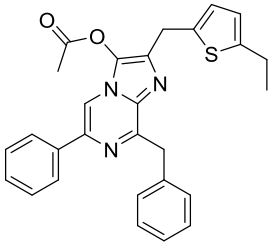
8-Benzyl-2-((5-ethyl-4-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,50*} (YJ 33069-011-1): Obtained as a white solid (0.41 g, 66%) after a recrystallization from cyclohexane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.84 (s, 1H), 7.63 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.24 (m, 1H), 5.91 (s, 1H), 4.65 (s, 2H), 4.16 (s, 2H), 2.57 (q, 2H, *J* = 7.3 Hz), 2.35 (s, 3H), 1.94 (s, 3H), 1.20 (t, 6H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 152.9, 151.6, 148.1, 139.2, 137.8, 136.7, 133.3, 132.9, 129.7, 128.9, 128.8, 128.6, 128.3, 126.5, 126.4, 113.7, 110.2, 108.9, 39.3, 27.2, 20.0, 19.3, 13.1, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_3$, 466.2131; found, 466.2127.



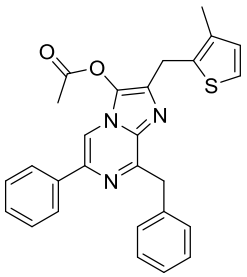
8-Benzyl-2-((4-ethyl-5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,51*} (YJ 33068-087-1): Obtained as a white solid (0.15 g, 52%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.84 (s, 1H), 7.82 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 5.97 (s, 1H), 4.64 (s, 2H), 4.16 (s, 2H), 2.36 (s, 3H), 2.33 (q, 2H, *J* = 7.4 Hz), 2.20 (s, 3H), 1.13 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 152.9, 148.3, 145.5, 139.2, 137.8, 136.8, 133.4, 132.9, 129.7, 128.9, 128.8, 128.6, 128.3, 126.5, 126.4, 121.3, 108.9, 108.4, 39.3, 27.3, 20.1, 18.1, 14.9, 11.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_3$, 466.2131; found, 466.2131.



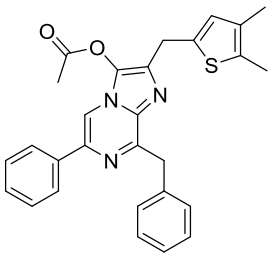
8-Benzyl-2-((5-isopropyl-4-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,52*} (YJ 33068-097-1): Obtained as a white solid (0.29 g, 62%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.83 (s, 1H), 7.82 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 5.87 (s, 1H), 4.64 (s, 2H), 4.15 (s, 2H), 2.97 (sept, 1H, *J* = 7.0 Hz), 2.34 (s, 3H), 1.95 (s, 3H), 1.24 (d, 6H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 154.6, 152.9, 147.8, 139.2, 137.8, 136.8, 133.4, 133.0, 129.7, 128.9, 128.8, 128.6, 128.3, 126.5, 126.4, 112.5, 110.2, 108.9, 39.3, 31.9, 27.2, 21.4, 14.1, 9.8. . HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{30}N_3O_3$, 480.2287; found, 480.2280.



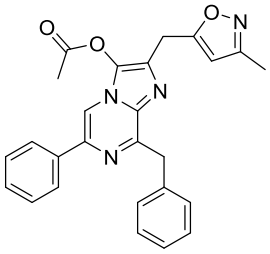
8-Benzyl-2-((5-ethylthiophen-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,53*} (YJ30367-173-1): Obtained as a white solid (0.25 g, 56%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.93 (m, 2H), 7.83 (s, 1H), 7.65 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.24 (m, 1H), 6.72 (m, 1H), 6.63 (m, 1H), 4.64 (s, 2H), 4.32 (s, 2H), 2.82 (q, 2H, *J* = 7.6 Hz), 2.33 (s, 3H), 1.31 (t, 3H, *J* = 7.6 Hz),. ^{13}C NMR ($CDCl_3$): 167.0, 153.1, 146.5, 139.1, 137.9, 137.5, 136.8, 134.6, 133.5, 129.8, 128.8, 128.6, 128.5, 128.3, 126.5, 126.4, 125.4, 122.8, 108.9, 39.4, 28.7, 23.5, 20.0, 16.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2S$, 468.1746; found, 468.1757.



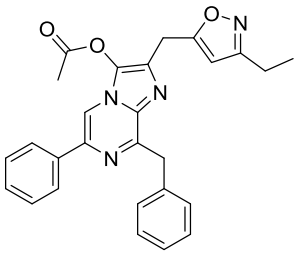
8-Benzyl-2-((3-methylthiophen-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,54*} (YJ30367-175-1): Obtained as a wax which solidified (0.37 g, 95%). ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.79 (s, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.39 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 7.10 (d, 1H, *J* = 5.2 Hz), 6.83 (d, 1H, *J* = 5.2 Hz), 4.64 (s, 2H), 4.32 (s, 2H), 2.27 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 153.0, 139.1, 137.8, 136.8, 134.5, 134.3, 133.4, 130.0, 130.0, 129.7, 128.8, 128.5, 128.3, 126.5, 126.4, 122.3, 108.9, 39.5, 26.8, 19.9, 13.8 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_2S$, 454.1589; found, 454.1591.



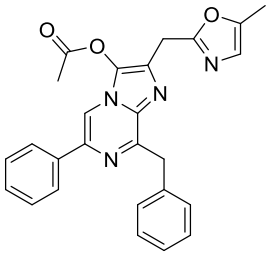
8-Benzyl-2-((4,5-dimethylthiophen-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,55*} (YJ310697-113-1): Obtained as a white solid (0.14 g, 59%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.82 (s, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.33 (m, 2H), 7.24 (m, 1H), 6.59 (s, 1H), 4.64 (s, 2H), 4.26 (s, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 153.1, 139.1, 137.9, 136.8, 135.2, 134.6, 133.5, 132.5, 131.4, 129.8, 128.8, 128.7, 128.5, 128.3, 126.5, 126.4, 108.9, 39.4, 31.9, 28.4, 20.0, 13.5, 12.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2S$, 468.1746; found, 468.1758.



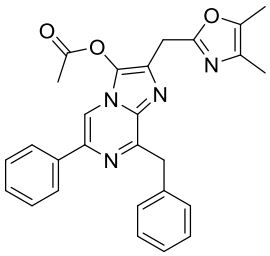
8-Benzyl-2-((3-methylisoxazol-5-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,56*} (EC32712-033-1): Obtained as a white solid (0.10 g, 59%) after a recrystallization from cyclohexane. ^{1}H NMR ($CDCl_3$): 7.93 (m, 2H), 7.86 (s, 1H), 7.61 (m, 2H), 7.48 (m, 2H), 7.42 (m, 1H), 7.32 (m, 2H), 7.25 (m, 1H), 5.94 (s, 1H), 4.63 (s, 2H), 4.27 (d, 2H, *J* = 0.9 Hz), 2.46 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): 168.9, 167.0, 160.0, 153.2, 139.4, 137.7, 136.6, 133.7, 130.6, 129.7, 129.0, 128.8, 128.7, 128.3, 126.5, 126.4, 109.0, 103.1, 39.5, 25.7, 20.1, 11.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{23}N_4O_3$: 439.1770; found, 439.1778.



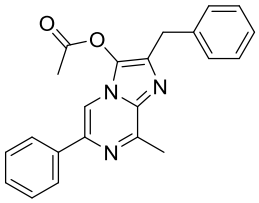
8-Benzyl-2-((3-ethylisoxazol-5-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,57*} (EC32712-035-1): Obtained as a white solid (0.12 g, 41%) after recrystallization in *n*–heptane. ^{1}H NMR ($CDCl_3$): 7.93 (m, 2H), 7.86 (s, 1H), 7.61 (m, 2H), 7.48 (m, 2H), 7.42 (m, 1H), 7.32 (m, 2H), 7.25 (m, 1H), 5.97 (s, 1H), 4.63 (s, 2H), 4.28 (d, 2H, *J* = 0.9 Hz), 2.68 (q, 2H, *J* = 7.6 Hz), 2.45 (s, 3H), 1.27 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 168.8, 167.0, 165.4, 153.2, 139.4, 137.7, 136.6, 133.7, 130.6, 129.7, 129.0, 128.8, 128.7, 128.3, 126.5, 126.4, 109.0, 101.8, 39.5, 25.7, 20.1, 19.6, 12.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_3$: 453.1927; found, 453.1938.



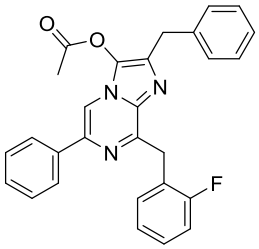
8-Benzyl-2-((5-methyloxazol-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,58*} (YJ 31776-096-2): Obtained as a white solid (0.01 g, 1.6% from 3-benzyl-2-chloro-5-phenylpyrazine) after a chromatography over silica gel (cyclohexane – ethyl acetate 1/1) and a recrystallization from cyclohexane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.86 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.23 (m, 1H), 6.67 (m, 1H), 4.64 (s, 2H), 4.33 (s, 2H), 2.43 (s, 3H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 159.4, 153.2, 149.2, 139.3, 137.7, 136.6, 133.5, 130.3, 129.7, 129.2, 128.8, 128.7, 128.3, 126.5, 126.4, 122.8, 108.9, 39.3, 27.7, 20.2, 10.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{23}N_4O_3$: 439.1770; found, 439.1778.



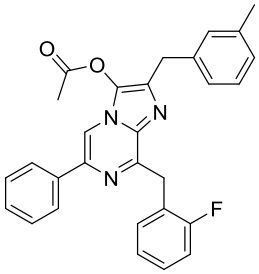
8-Benzyl-2-((4,5-dimethyloxazol-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,59*} (YJ31067-047-1): Obtained as a white crystals (0.1 g, 34%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.47 (m, 2H), 7.39 (m, 1H), 7.31 (m, 2H), 7.24 (m, 1H), 4.62 (s, 2H), 4.28 (s, 2H), 2.41 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 157.9, 153.2, 143.5, 139.2, 137.8, 136.7, 133.6, 130.5, 130.4, 129.7, 129.2, 128.8, 128.6, 128.3, 126.5, 126.4, 108.9, 39.4, 27.7, 20.2, 11.1, 9.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_3$, 453.1927; found, 453.1915.



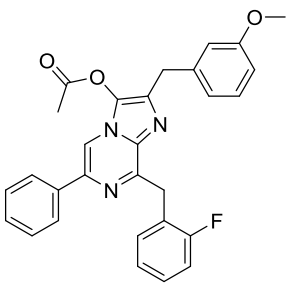
2-Benzyl-8-methyl-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,60,1*} (VHE30448-007-1): Obtained as a yellow solid (0.59 g, 88%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$7.91 (m, 2H), 7.80 (m, 1H), 7.48 (m, 2H), 7.41 (m, 1H), 7.35 – 7.23 (m, 5H), 4.21 (s, 2H), 2.96 (m, 3H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.6, 139.2, 137.9, 16.9, 134.9, 137.0, 129.0, 128.8, 128.7, 128.6, 128.5, 126.5, 108.9, 34.3, 20.3, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{20}N_3O_2$, 358.1556; found, 358.1544.



2-Benzyl-8-(2-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,1*} (GG30532-121-1): Obtained as a white solid (0.12 g, 61%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.86-7.83 (m, 3H), 7.52-7.48 (dt, 1H, *J* = 7.4, 1.9 Hz), 7.47-7.23 (m, 8H), 7.14-7.08 (m, 2H), 4.72 (s, 2H), 4.23 (s, 2H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.4 (247.0 Hz), 151.6, 138.9, 138.0, 136.7, 135.2, 133.7, 131.9 (4.3 Hz), 129.1, 128.9, 128.7, 128.6, 128.5, 128.3 (8.1 Hz), 126.5, 126.3, 124.7 (15.9 Hz), 123.7 (3.5 Hz), 115.2 (22.4 Hz), 108.8, 34.3, 32.2 (2.5 Hz), 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774, found, 452.1774.

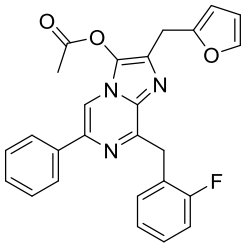


8-(2-Fluorobenzyl)-2-(3-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,12*} (YJ31070-047-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.18 g, 58%). ^{1}H NMR ($CDCl_3$): 7.84 (m, 2H), 7.83 (s, 1H), 7.50 (m, 1H), 7.42 (m, 2H), 7.36 (m, 1H), 7.23 (m, 2H), 7.13-7.06 (m, 5H), 4.72 (s, 2H), 4.19 (s, 2H), 2.35 (s, 3H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.4 (245 Hz), 151.6, 138.9, 138.1, 137.8, 136.7, 135.3, 133.6, 131.8 (4 Hz), 129.8, 128.8, 128.7, 128.5, 128.4, 128.2 (8 Hz), 127.2, 126.2, 126.1, 124.7 (16 Hz), 123.7 (4 Hz), 115.1 (22 Hz), 108.8, 34.3, 32.2 (2 Hz), 21.3, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_2$, 466.1931, found, 466.1938.

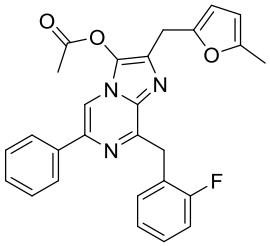


8-(2-Fluorobenzyl)-2-(3-methoxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,15*} (YJ31070-049-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.26 g, 87%). ^{1}H NMR ($CDCl_3$): 7.85 (m, 2H),

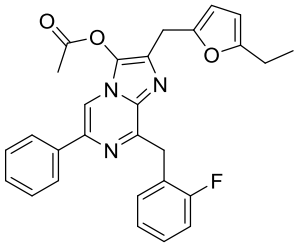
7.83 (s, 1H), 7.48 (m, 1H), 7.42 (m, 2H), 7.36 (m, 1H), 7.25 (m, 2H), 7.10 (m, 2H), 6.90 (m, 2H), 6.81 (m, 1H), 4.71 (s, 2H), 4.19 (s, 2H), 3.80 (s, 3H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.4 (245 Hz), 159.8, 151.6, 139.5, 138.9, 136.6, 135.1, 133.6, 131.8 (4 Hz), 129.4, 128.9, 128.7, 128.5, 128.3 (8 Hz), 126.3, 124.7 (16 Hz), 123.7 (4 Hz), 121.4, 115.1 (22 Hz), 114.6, 112.2, 108.8, 55.2, 34.2, 32.2 (2 Hz), 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_3$, 482.1880, found, 482.1873.



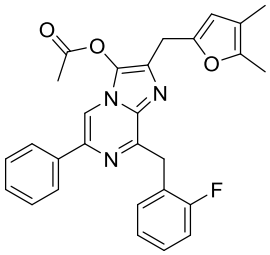
8-(2-Fluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,37*} (YJ31070-051-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.19 g, 73%). ^{1}H NMR ($CDCl_3$): 7.87 (s, 1H), 7.85 (m, 2H), 7.50-7.34 (m, 5H), 7.24 (m, 1H), 7.10 (m, 2H), 6.35 (dd, 1H, *J* = 1.9, 3.2 Hz), 6.17 (dd, 1H, *J* = 0.7, 3.2 Hz), 4.70 (s, 2H), 4.24 (s, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.4 (245 Hz), 151.7, 151.5, 141.7, 139.0, 136.6, 133.5, 131.8 (4 Hz), 128.9, 128.7, 128.6, 128.3 (8 Hz), 126.3, 124.6 (16 Hz), 123.7 (4 Hz), 115.1 (22 Hz), 110.5, 108.8, 106.8, 32.2 (2 Hz), 27.2, 20.1 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{21}FN_3O_3$, 442.1567, found, 442.1567.



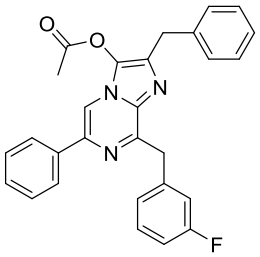
8-(2-Fluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,42*} (YJ31070-053-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.08 g, 38%). ^{1}H NMR ($CDCl_3$): 7.87 (s, 1H), 7.85 (m, 2H), 7.50-7.34 (m, 4H), 7.24 (m, 1H), 7.10 (m, 2H), 6.04 (d, 1H, *J* = 3.0 Hz), 5.91 (m, 1H), 4.70 (s, 2H), 4.19 (s, 2H), 2.37 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.4 (245 Hz), 151.7, 151.2, 149.5, 138.9, 136.6, 133.5, 132.8, 131.9 (4 Hz), 128.9, 128.7, 128.5, 128.2 (8 Hz), 126.2, 124.6 (16 Hz), 123.7 (4 Hz), 115.2 (22 Hz), 108.3, 107.5, 106.2, 32.2 (2 Hz), 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}FN_3O_3$, 456.1723, found, 456.1719.



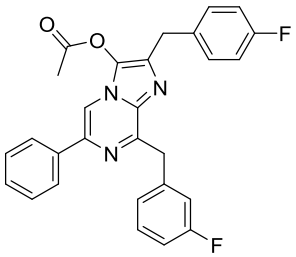
2-((5-Ethylfuran-2-yl)methyl)-8-(2-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,44*} (YJ31068-027-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.05 g, 28%). ^{1}H NMR ($CDCl_3$): 7.87 (s, 1H), 7.85 (m, 2H), 7.50-7.34 (m, 4H), 7.24 (m, 1H), 7.10 (m, 2H), 6.04 (d, 1H, *J* = 3.1 Hz), 5.92 (m, 1H), 4.70 (s, 2H), 4.20 (s, 2H), 2.64 (q, 2H, *J* = 7.2 Hz), 2.36 (s, 3H), 1.24 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 167.1, 161.4 (245 Hz), 151.7, 151.7, 149.3, 138.9, 136.6, 133.5, 132.8, 131.9 (4 Hz), 128.9, 128.7, 128.5, 128.2 (8 Hz), 126.3, 124.6 (16 Hz), 123.7 (4 Hz), 115.2 (22 Hz), 108.8, 107.5, 104.6, 32.2 (2 Hz), 27.3, 21.3, 20.1, 12.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}FN_3O_3$, 470.1880, found, 470.1881.



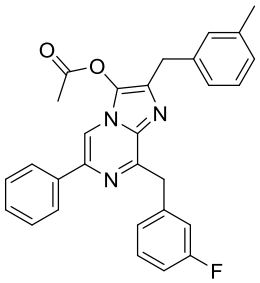
2-((4,5-Dimethylfuran-2-yl)methyl)-8-(2-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,2,48*} (EC32712-129-2): Obtained as a white solid after a recrystallization in *n*-heptane (0.19 g, 64%). ^{1}H NMR ($CDCl_3$): 7.87 (s, 1H), 7.85 (m, 2H), 7.43 (m, 4H), 7.25 (m, 1H), 7.10 (m, 2H), 5.93 (s, 1H), 4.70 (s, 2H), 4.15 (s, 2H), 2.38 (s, 3H), 2.19 (s, 3H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 161.4 (246 Hz), 151.7, 148.2, 146.3, 138.9, 136.6, 133.5, 132.9, 131.9 (4 Hz), 128.9, 128.7, 128.5, 128.2 (8 Hz), 126.2, 124.7 (16 Hz), 123.7 (Hz), 115.2 (22 Hz), 114.6, 110.1, 108.8, 32.2 (3 Hz), 27.2, 20.0, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}FN_3O_3$: 470.1880; found, 470.1870.



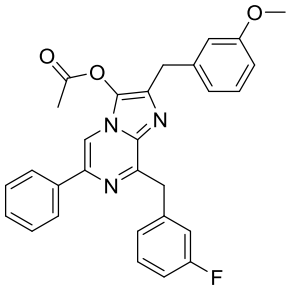
2-Benzyl-8-(3-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,1*} (YJ31067-161-1): Obtained as a solid (0.19 g, 50%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.82 (s, 1H), 7.47 (m, 2H), 7.42 - 7.25 (m, 9H), 6.95 (m, 1H), 4.63 (s, 2H), 4.22 (s, 2H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 162.8 (244 Hz), 152.2, 140.2 (8 Hz), 139.1, 137.9, 136.7, 135.4, 129.6 (8 Hz), 129.1, 128.9, 128.8, 128.6, 128.5, 126.5, 126.4, 125.4 (3 Hz), 116.6 (22 Hz), 113.3 (21 Hz), 109.0, 39.1, 34.2, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774; found, 452.1775.



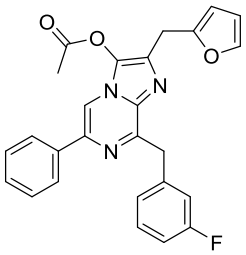
8-(3-Fluorobenzyl)-2-(4-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,4*} (YJ31069-031-1): (YJ 31069-31-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.34 g, 85%). ^{1}H NMR ($CDCl_3$) 7.90 (m, 2H), 7.83 (s, 1H), 7.48 (m, 2H), 7.48 (m, 2H), 7.38 (m, 3H), 7.27 (m, 3H), 7.02 (m, 2H), 6.93 (m, 1H), 4.63 (s, 2H), 4.17 (s, 2H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.7 (246 Hz), 161.7 (244 Hz), 152.2, 140.1 (7 Hz), 139.3, 136.6, 133.6 (3 Hz), 133.5, 130.4 (8 Hz), 129.6 (8 Hz), 128.8, 128.7, 126.4, 125.3 (2 Hz), 116.6 (21 Hz), 115.2 (21 Hz), 113.4 (21 Hz), 109.0, 39.1, 33.1, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{22}F_2N_3O_2$, 470.1680, found, 470.1676.



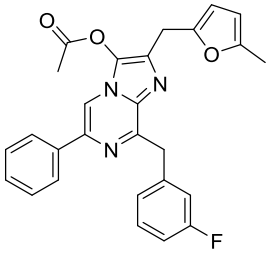
8-(3-Fluorobenzyl)-2-(3-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,12*} (YJ31068-045-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.16 g, 50%). ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.82 (s, 1H), 7.47 (m, 2H), 7.38 (m, 3H), 7.28 (m, 1H), 7.22 (m, 1H), 7.09 (m, 3H), 6.95 (m, 1H), 4.63 (s, 2H), 4.18 (s, 2H), 2.35 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 162.8 (244 Hz), 152.2, 140.2 (8 Hz), 139.1, 138.1, 137.8, 136.7, 135.6, 135.5, 129.8 129.6, (8 Hz), 128.9, 128.7, 128.6, 128.4, 127.2, 126.4, 126.1, 125.4 (3 Hz), 116.6 (22 Hz), 113.3 (21 Hz), 109.0, 39.1 (2 Hz), 34.1, 21.3, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_2$, 466.1931, found, 466.1926.



8-(3-Fluorobenzyl)-2-(3-methoxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,15*} (YJ31068-047-1): Obtained as a white solid after a recrystallization in *n*-heptane (0.12 g, 60%). ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.82 (s, 1H), 7.47 (m, 2H), 7.38 (m, 3H), 7.26 (m, 1H), 6.95 (m, 3H), 6.80 (m, 1H), 4.63 (s, 2H), 4.19 (s, 2H), 3.79 (s, 3H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 162.8 (244 Hz), 159.8, 152.2, 140.2(8 Hz), 139.5, 139.1, 136.7, 135.3, 133.5, 129.6 (8 Hz), 129.4, 128.9, 128.8, 128.6, 126.4, 125.4 (3 Hz), 121.4, 116.6 (22 Hz), 114.6, 113.3 (21 Hz), 112.2, 109.0, 55.2, 39.0, 34.2, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_3$, 482.1880, found, 482.1879.

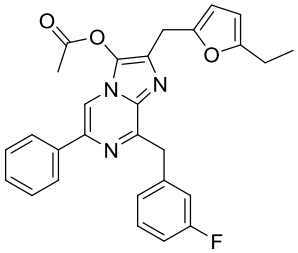


8-(3-Fluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,37*} (YJ31070-045-1): Obtained as a solid (0.13 g, 59%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.49 (m, 2H), 7.42 - 7.33 (m, 4H), 7.26 (m, 1H), 6.93 (m, 1H), 6.36 (dd, 1H, *J* = 2.0, 3.2 Hz), 6.17 (dd, 1H, *J* = 0.8, 3.2 Hz), 4.62 (s, 2H), 4.24 (s, 2H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 162.8 (244 Hz), 152.3, 151.4, 141.7, 140.2 (8 Hz), 139.2, 136.6, 133.5, 132.7, 129.6 (8 Hz), 129.0, 128.8, 128.7, 126.4, 125.3 (3 Hz), 116.6 (22 Hz), 113.3 (21 Hz), 110.5, 109.0, 106.9, 39.0, 27.2, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{21}FN_3O_3$, 442.1567; found, 442.1549.

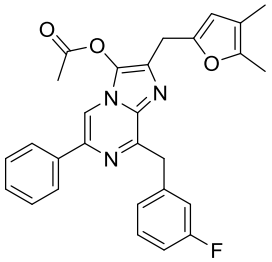


8-(3-Fluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,42*} (YJ31068-029-1): Obtained as a solid (0.10 g, 45%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.47 (m, 2H), 7.42 - 7.24 (m, 4H), 6.92 (m, 1H), 6.03 (d, 1H, *J* = 3.0 Hz), 5.91 (m, 1H), 4.62 (s, 2H), 4.18 (s, 2H), 2.37 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (244 Hz), 152.2, 151.2, 149.4, 140.2 (8 Hz), 139.2, 136.6, 133.4, 133.0, 129.6 (8 Hz), 129.0, 128.8, 128.6, 126.4, 125.3 (3 Hz), 116.6 (22

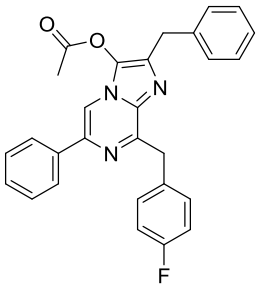
Hz), 113.3 (21 Hz), 109.0, 107.5, 106.2, 39.0, 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}FN_3O_3$, 456.1723; found, 456.1732.



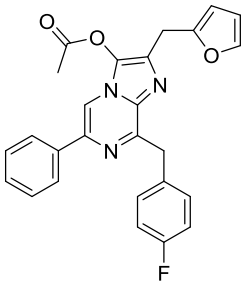
2-((5-Ethylfuran-2-yl)methyl)-8-(3-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,44*} (YJ31068-031-1): Obtained as a white solid (0.05 g, 11% from the 2-chloro-3-(3-fluorobenzyl)-5-phenylpyrazine) after a chromatography over silica gel (cyclohexane ethyl acetate 6/1) and recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.48 (m, 2H), 7.42 - 7.24 (m, 4H), 6.92 (m, 1H), 6.03 (d, 1H, *J* = 3.1 Hz), 5.92 (m, 1H), 4.62 (s, 2H), 4.19 (s, 2H), 2.63 (q, 2H, *J* = 7.5 Hz), 2.36 (s, 3H), 2.63 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (244 Hz), 157.1, 152.2, 149.3, 140.2 (8 Hz), 139.1, 136.7, 133.4, 133.1, 129.6 (8 Hz), 129.0, 128.8, 128.6, 126.4, 125.3 (3 Hz), 116.6 (22 Hz), 113.3 (21 Hz), 109.0, 107.3, 104.6, 39.0, 27.3, 21.3, 20.1, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}FN_3O_3$, 470.1880; found, 470.1888.



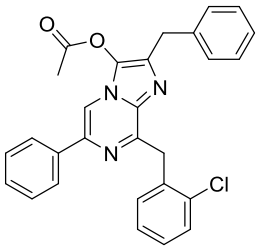
2-((4,5-Dimethylfuran-2-yl)methyl)-8-(3-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,3,48*} (EC32712-131-2): Obtained as a solid (0.18 g, 55%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.47 (m, 2H), 7.38 (m, 3H), 7.27 (m, 1H), 6.93 (m, 1H), 5.92 (s, 1H), 4.62 (s, 2H), 4.14 (s, 2H), 2.38 (s, 3H), 2.19 (s, 3H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.7 (d, *J* = 245 Hz), 152.2, 148.2, 146.3, 140.2 (d, *J* = 8 Hz), 139.1, 136.7, 133.4, 133.2, 129.6 (d, *J* = 8 Hz), 128.9, 128.8, 128.6, 126.4, 125.4 (d, *J* = 3 Hz), 116.6 (d, *J* = 22 Hz), 114.6, 113.4 (d, *J* = 21 Hz), 110.1, 109.0, 39.0 (d, *J* = 2 Hz), 27.2, 20.0, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}FN_3O_3$: 470.1880; found, 470.1880.



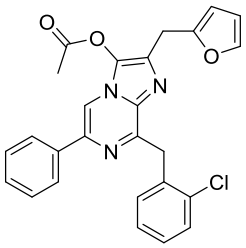
2-Benzyl-8-(4-fluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,4,1*} (YJ31067-163-1): Obtained as a solid in two crops (0.04 g, 33%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.81 (s, 1H), 7.58 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.36 – 7.24 (m, 5H), 7.00 (m, 2H), 4.60 (s, 2H), 4.21 (s, 2H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.7 (244 Hz), 139.1, 137.9, 136.7, 135.3, 133.5, 133.4 (3 Hz), 131.1 (7 Hz), 129.1, 128.9, 128.8, 128.6, 128.5, 126.5, 126.4, 115.0 (21 Hz), 108.9, 38.6, 34.2, 19.9 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774; found, 452.1789.



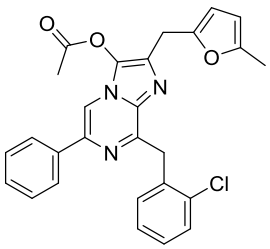
8-(4-Fluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,4,37*} (YJ 31776-011-1): Obtained as a solid (0.28 g, 95%) after dispertion of the reaction media in water, a filtration and drying under vacuum at 40°C. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.57 (m, 2H), 7.47 (m, 2H), 7.40 (m, 2H), 7.00 (m, 2H), 6.36 (m, 1H), 6.16 (m, 1H), 4.60 (s, 2H), 4.24 (s, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 161.7 (244 Hz), 152.7, 151.4, 141.7, 139.3, 136.6, 133.4 (3 Hz), 132.5, 131.1 (7 Hz), 129.0, 128.8, 128.7, 126.4, 115.0 (21 Hz), 110.5, 108.9, 106.9, 38.5, 27.1, 20.1 (one signal missing).



2-Benzyl-8-(2-chlorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,5,1*} (EC31094-105-1): Obtained as a white solid (0.12 g, 67%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.84 (s, 1H), 7.83 (m, 2H), 7.50-7.20 (m, 12H), 4.82 (s, 2H), 4.23 (s, 2H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.5, 138.8, 138.0, 136.6, 135.7, 135.1, 134.9, 133.7, 131.8, 129.3, 129.1, 128.8, 128.7, 128.5 (two signals), 127.9, 126.5 (two signals), 126.2, 108.8, 36.6, 34.3, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}ClN_3O_2$: 468.1479; found, 468.1489.

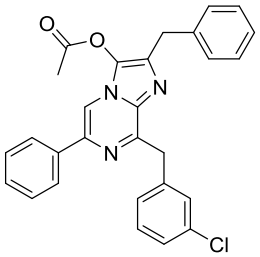


8-(2-Chlorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,5,37*} (EC31094-103-1): Obtained as a white solid after a recrystallization in n-heptane (0.27 g, 70%). ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.83 (m, 2H), 7.46-7.34 (m, 6H), 7.23 (m, 2H), 6.36 (m, 1H), 6.18 (m, 1H), 4.81 (s, 2H), 4.25 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.7, 151.5, 141.7, 138.9, 136.6, 135.6, 134.9, 133.7, 132.4, 131.8, 129.3, 128.9, 128.7, 128.6, 127.9, 126.5, 126.2, 110.5, 108.8, 106.9, 36.6, 27.3, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{20}ClN_3O_3$: 458.1271; found, 458.1266.

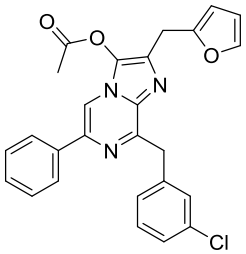


8-(2-Chlorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,5,42*} (YJ31068-025-1): Obtained as a solid (0.03 g, 27%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.83 (m, 2H), 7.46-7.33 (m, 5H), 7.21 (m, 2H), 6.04 (m, 1H), 5.91 (m, 1H), 4.81 (s, 2H), 4.19 (s, 2H), 2.38

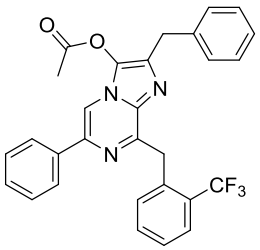
(s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.6, 151.2, 149.5, 138.9, 136.6, 135.6, 134.9, 133.6, 132.7, 131.8, 129.3, 128.9, 128.7, 128.5, 127.9, 126.5, 126.2, 108.8, 107.5, 106.2, 36.6, 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}ClN_3O_3$: 472.1428; found, 472.1408.



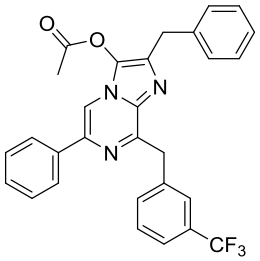
2-Benzyl-8-(3-chlorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,6,1*} (YJ 31776-019-1): Obtained as a solid (0.20 g, 90%) after dispertion of the reaction media in water, a filtration and drying under vacuum at 40°C. ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.81 (s, 1H), 7.64 (m, 1H), 7.47 (m, 3H), 7.42 - 7.20 (m, 8H), 4.62 (s, 2H), 4.22 (s, 2H). ^{13}C NMR ($CDCl_3$): 167.0, 152.0, 139.7, 139.2, 137.8, 136.6, 135.3, 134.0, 129.8, 129.5, 129.1, 128.9, 128.8, 128.7, 128.5, 128.0, 126.7, 126.5, 126.4, 109.3, 39.0, 34.1, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}ClN_3O_2$: 468.1479; found, 468.1480.



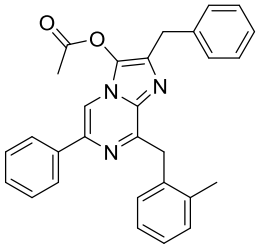
8-(3-Chlorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,6,37*} (EC31095-089-2): Obtained as a white solid (0.05 g, 30%) after a chromatography over silica gel (cyclohexane – ethyl acetate 6/1) and a recrystallization in *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.85 (s, 1H), 7.62 (m, 1H), 7.48 (m, 3H), 7.40 (m, 2H), 7.24 (m, 2H), 6.36 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.17 (m, 1H), 4.60 (s, 2H), 4.24 (s, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 152.2, 151.4, 141.7, 139.7, 139.2, 136.6, 134.0, 133.5, 132.7, 129.8, 129.5, 129.0, 128.8, 128.7, 127.9, 126.7, 126.4, 110.5, 109.1, 106.9, 38.9, 27.2, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{21}ClN_3O_3$: 458.1271; found, 458.1270.



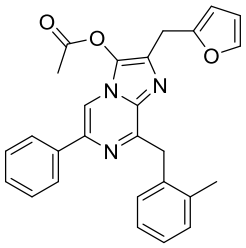
2-Benzyl-6-phenyl-8-(2-(trifluoromethyl)benzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,8,1*} (YJ 33067-129-1): Obtained as a white solid (0.24 g, 68%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.85 (s, 1H), 7.79 (m, 2H), 7.74 (m, 1H), 7.52 - 7.33 (m, 10H), 7.28 (m, 1H), 4.90 (s, 2H), 4.23 (s, 2H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.7, 138.8, 137.9, 136.5, 136.1 (1 Hz), 135.1, 133.7, 132.6 131.4, 129.4 (30 Hz), 129.2, 128.9, 128.7, 128.6, 128.5, 126.5, 126.1, 125.9 (4 Hz), 124.6 (273 Hz), 108.7, 35.7, 34.2, 19.8 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{23}F_3N_3O_2$: 502.1742; found, 502.1740.



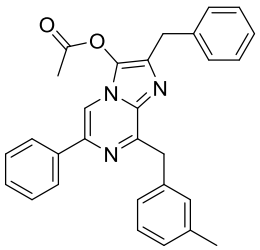
2-Benzyl-6-phenyl-8-(3-(trifluoromethyl)benzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,9,1*} (YJ 33067-131-1): Obtained as a white solid (0.12 g, 34%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.96 (s (br), 1H), 7.89 (m, 2H), 7.82 (s, 1H), 7.79 (m, 1H), 7.52 - 7.23 (m, 10H), 4.69 (s, 2H), 4.22 (s, 2H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 151.8, 139.2, 138.5, 137.8, 136.5, 135.4, 133.3, 133.2, 130.5 (31 Hz), 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 126.7 (4 Hz), 126.6, 126.4, 124.3 (272 Hz), 123.4 (3 Hz), 109.0, 39.0, 34.1, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{23}F_3N_3O_2$: 502.1742; found, 502.1735.



2-Benzyl-8-(2-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,11,1*} (YJ31068-033-1): Obtained as a white solid (0.29 g, 77%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.87 (m, 2H), 7.82 (s, 1H), 7.57 (m, 1H), 7.44 (m, 2H), 7.37 (m, 1H), 7.33 (m, 4H), 7.27 (m, 1H), 7.22 (m, 1H), 7.17 (m, 2H), 4.67 (s, 2H), 4.22 (s, 2H), 2.61 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 152.9, 138.9, 138.0, 137.4, 136.8, 136.3, 135.1, 133.7, 130.7, 130.1, 129.1, 128.8, 128.7, 128.5, 128.4, 126.6, 126.5, 126.2, 125.7, 108.7, 36.6, 34.2, 20.3, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$: 448.2025; found, 448.2031.

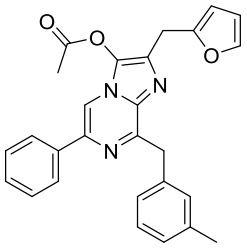


2-(furan-2-ylmethyl)-8-(2-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,11,37*} (YJ31068-035-1): Obtained as a white solid (0.18 g, 64%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (m, 2H), 7.85 (s, 1H), 7.54 (m, 2H), 7.45 (m, 2H), 7.38 (m, 2H), 7.23 (m, 1H), 7.16 (m, 2H), 6.36 (dd, 1H, J = 1.9, 3.4 Hz), 6.17 (m, 1H), 4.66 (s, 2H), 4.24 (s, 2H), 2.60 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 153.0, 151.6, 141.6, 139.0, 137.3, 136.7, 136.3, 133.7, 132.4, 130.6, 130.1, 128.8, 128.7, 128.5, 126.6, 126.3, 125.7, 110.5, 108.7, 106.8, 36.5, 27.2, 20.3, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_3$, 438.1818; found, 438.1823.

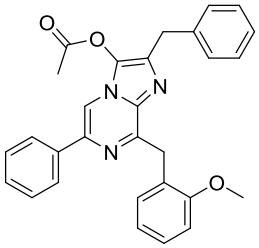


2-Benzyl-8-(3-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,12,1*} (YJ31068-037-1): Obtained as a white solid (0.27 g, 70%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.92 (m, 2H), 7.80 (s, 1H), 7.57 (m, 1H), 7.50-7.37 (m, 5H), 7.32 (m, 4H), 7.28-7.20 (m, 2H), 7.05 (m, 1H), 4.61 (s, 2H), 4.22 (s, 2H),

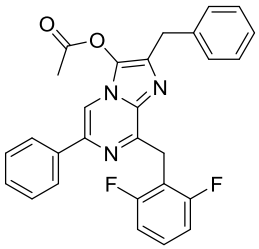
2.35 (s, 3H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 153.0, 139.1, 138.0, 137.8, 137.7, 136.9, 135.2, 133.7, 130.5, 129.1, 128.8, 128.7, 128.5, 128.4, 128.2, 127.2, 126.7, 126.5, 126.4, 108.8, 39.4, 34.2, 21.4, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$: 448.2025; found, 448.2026.



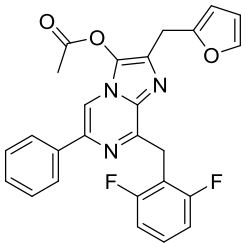
2-(Furan-2-ylmethyl)-8-(3-methylbenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,12,37*} (YJ31068-039-1): Obtained as a white solid (0.23 g, 70%) after a recrystallization in n-heptane. ^{1}H NMR ($CDCl_3$): 7.93 (m, 2H), 7.84 (s, 1H), 7.49-7.37 (m, 6H), 7.22 (m, 1H), 7.05 (m, 1H), 6.35 (dd, 1H, *J* = 1.7, 3.1 Hz), 6.16 (m, 1H), 4.60 (s, 2H), 4.24 (s, 2H), 2.36 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 153.1, 151.6, 141.6, 139.2, 137.8, 137.7, 136.8, 133.6, 132.5, 130.5, 128.9, 128.8, 128.6, 128.2, 127.2, 126.7, 126.4, 110.5, 108.9, 106.8, 39.3, 27.2, 21.4, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_3$, 438.1818; found, 438.1820.



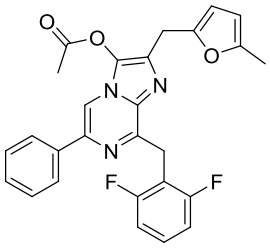
2-Benzyl-8-(2-methoxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,14,1*} (YJ31070-117-1): Obtained as a white solid (0.06 g, 70%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.84 (m, 2H), 7.82 (s, 1H), 7.43-7.23 (m, 10H), 6.93 (m, 2H), 4.69 (s, 2H), 4.22 (s, 2H), 3.83 (s, 3H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 157.8, 153.0, 138.8, 138.1, 136.8, 134.8, 133.9, 131.0, 129.1, 128.7, 128.5, 128.4, 127.7, 126.5, 126.4, 126.3, 120.3, 110.6, 108.5, 55.6, 34.2, 33.2, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_3$: 464.1974; found, 464.1983.



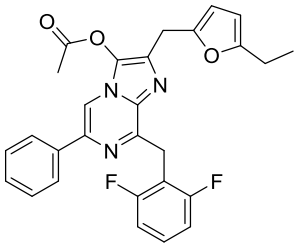
2-Benzyl-8-(2,6-difluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,21,1*} (YJ 33069-173-1): Obtained as a solid (0.40 g, 95%) after dispertion of the reaction media in water, a filtration and drying under vacuum at 40°C. ^{1}H NMR ($CDCl_3$): 7.84 (s, 1H), 7.75 (m, 2H), 7.34 (m, 9H), 6.97 (m, 2H), 4.77 (s, 2H), 4.24 (s, 2H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 161.8 (dd, J = 248, 8 Hz), 150.2, 140.9, 138.7, 137.8, 136.4, 134.8, 133.2, 129.1, 128.9, 128.6, 128.5, 128.3 (10 Hz), 126.5, 126.1, 113.2 (20 Hz), 110.8 (7, 19 Hz), 108.8, 34.2, 26.2, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{22}F_2N_3O_2$: 470.1680; found, 470.1680.



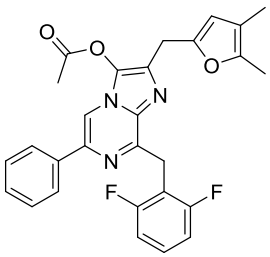
8-(2,6-Difluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,21,37*} (EC31095-085-2): Obtained as a solid (0.26 g, 69%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.75 (m, 2H), 7.35 (m, 5H), 6.96 (m, 2H), 6.36 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.19 (m, 1H), 4.75 (s, 2H), 4.26 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 162.1 (248, 8 Hz), 151.4, 150.3, 141.7, 138.6, 136.4, 133.4, 132.3, 128.9, 128.7, 128.5, 128.3 (10 Hz), 126.1, 113.1 (20 Hz), 110.9, 110.5, 108.8, 106.9, 27.3, 26.1, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{20}F_2N_3O_3$: 460.1473; found, 460.1469.



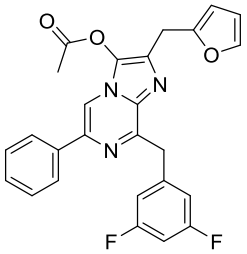
8-(2,6-Difluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,21,42*} (EC32712-093-2): Obtained as a solid (0.29 g, 82%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.75 (m, 2H), 7.34 (m, 4H), 6.96 (m, 2H), 6.05 (d, 1H, *J* = 3.0 Hz), 5.92 (dd, 1H, *J* = 3.0, 1.1 Hz), 4.75 (s, 2H), 4.21 (s, 2H), 2.38 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.1 (248, 8 Hz), 151.2, 150.2, 149.3, 138.7, 136.4, 133.1, 132.5, 128.9, 128.6, 128.5, 128.3 (10 Hz), 126.1, 113.1 (20 Hz), 110.8 (br), 108.8, 107.5, 106.2, 27.3, 26.2 (2 Hz), 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{22}F_2N_3O_3$: 474.1629; found, 474.1620.



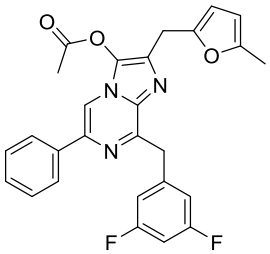
8-(2,6-Difluorobenzyl)-2-((5-ethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,21,44*} (EC32712-125-2): Obtained as a solid (0.18 g, 70%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.75 (m, 2H), 7.33 (m, 4H), 6.97 (m, 2H), 6.06 (d, 1H, *J* = 3.0 Hz), 5.93 (d, 1H, *J* = 3.0 Hz), 4.75 (s, 2H), 4.21 (s, 2H), 2.64 (q, 2H, *J* = 7.5 Hz), 2.37 (s, 3H), 1.24 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 162.1 (248, 9 Hz), 157.0, 150.3, 149.3, 138.5, 136.5, 133.3, 132.6, 128.9, 128.6, 128.5, 128.3 (10 Hz), 126.1, 113.2 (20 Hz), 110.8 (br), 108.8, 107.3, 104.6, 27.4, 26.1 (br), 21.4, 20.1, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1785



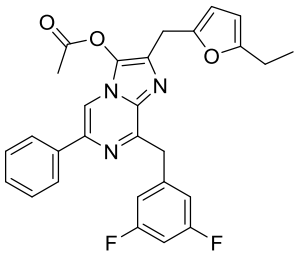
8-(2,6-Difluorobenzyl)-2-((4,5-dimethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,21,48*} (EC32712-127-2): Obtained as a solid (0.23 g, 75%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.75 (m, 2H), 7.34 (m, 4H), 6.96 (m, 2H), 5.95 (s, 1H), 4.75 (s, 2H), 4.16 (s, 2H), 2.38 (s, 3H), 2.19 (s, 3H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.1 (248, 9 Hz), 150.3, 148.2, 146.3, 138.5, 136.5, 133.3, 132.7, 128.9, 128.6, 128.5, 128.2 (10 Hz), 126.1, 114.6, 113.2 (20 Hz), 110.8 (br), 110.1, 108.8, 27.2, 26.1 (2 Hz), 20.0, 11.3, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1787.



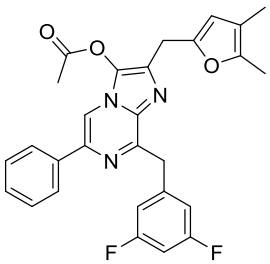
8-(3,5-Difluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,22,37*} (EC32712-007-1): Obtained as a solid (0.29 g, 61%) after a recrystallization from a mixture of *n*-heptane and cyclohexane (two crops). ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.87 (s, 1H), 7.48 (m, 2H), 7.43 (m, 1H), 7.38 (dd, 1H, *J* = 1.9, 0.9 Hz), 7.14 (m, 2H), 6.68 (tt, 1H, *J* = 9.1, 2.4 Hz), 6.36 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.17 (m, 1H), 4.59 (s, 2H), 4.24 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 162.8 (248, 13 Hz), 151.6, 151.3, 141.7, 141.4 (9 Hz), 139.2, 136.5, 133.4, 132.9, 129.0, 128.9, 128.8, 126.4, 112.5 (br), 110.5, 109.2, 106.9, 102.0 (25 Hz), 38.9 (2 Hz), 27.2, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{20}F_2N_3O_3$: 460.1473; found, 460.1473.



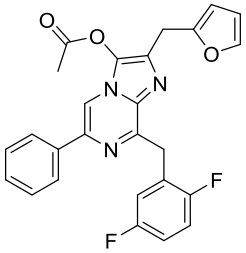
8-(3,5-Difluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,22,42*} (EC32712-011-1): Obtained as a solid (0.24 g, 81%) after a recrystallization from *n*-heptane.^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.87 (s, 1H), 7.48 (m, 2H), 7.42 (m, 1H), 7.14 (m, 2H), 6.68 (tt, 1H, *J* = 9.1, 2.3 Hz), 6.03 (d, 1H, *J* = 3.1 Hz), 5.92 (m, 1H), 4.59 (s, 2H), 4.18 (s, 2H), 2.38 (s, 3H), 2.28 (d, 3H, *J* = 1.0 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (248, 13 Hz), 151.5, 151.3, 149.3, 141.4 (9 Hz), 139.2, 136.5, 133.3, 133.2, 129.0, 128.9, 128.7, 126.4, 112.6 (br), 109.2, 107.5, 106.2, 102.0 (25 Hz), 38.9, 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{22}F_2N_3O_3$: 474.1629; found, 474.1631.



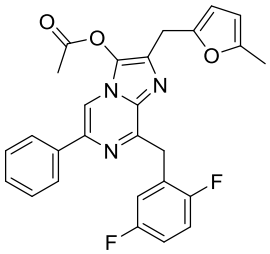
8-(3,5-Difluorobenzyl)-2-((5-ethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,22,44*} (EC32712-123-2): Obtained as a solid (0.13 g, 45%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.87 (s, 1H), 7.48 (m, 2H), 7.42 (m, 1H), 7.14 (m, 2H), 6.68 (tt, 1H, *J* = 9.1, 2.4 Hz), 6.04 (d, 1H, *J* = 3.2 Hz), 5.93 (dt, 1H, *J* = 3.2, 1.0 Hz), 4.60 (s, 2H), 4.19 (s, 2H), 2.63 (qd, 2H, *J* = 7.6, 1.0 Hz), 2.37 (s, 3H), 1.24 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (248, 13 Hz), 157.1, 151.5, 149.2, 141.4 (10 Hz), 139.2, 136.5, 133.4, 133.3, 129.0, 128.8, 128.7, 126.4, 112.6 (br), 109.2, 107.3, 104.6, 102.0 (25 Hz), 38.9 (2 Hz), 27.3, 21.3, 20.1, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1776.



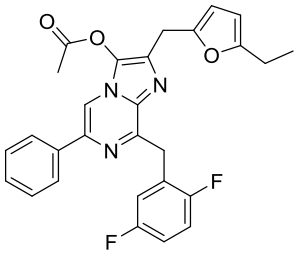
8-(3,5-difluorobenzyl)-2-((4,5-dimethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,22,48*} (EC32712-101-2): Obtained as a solid (0.15 g, 72%) after a chromatography over silica gel (cyclohexane – ethyl acetate 6/) and a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.91 (m, 2H), 7.87 (s, 1H), 7.46 (m, 3H), 7.15 (m, 2H), 6.68 (tt, 1H, *J* = 9.1, 2.4 Hz), 5.93 (s, 1H), 4.60 (s, 2H), 4.14 (s, 2H), 2.39 (s, 3H), 2.19 (s, 3H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (247, 13 Hz), 151.4, 148.0, 146.4, 141.4 (9 Hz), 139.3, 136.5, 133.3, 129.0, 128.8, 128.7, 126.4, 114.6, 112.5 (br), 110.1, 109.2, 102.0 (25 Hz), 38.9, 27.1, 20.0, 11.2, 9.8, (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1781.



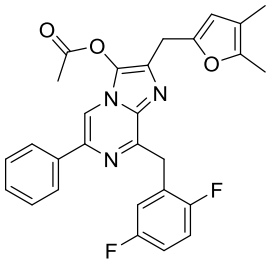
8-(2,5-Difluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,23,37*} (EC31095-141-1): Obtained as a solid (0.15 g, 54%) after a chromatography over silica gel (cyclohexane – ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H), 7.85 (m, 2H), 7.41 (m, 4H), 7.20 (ddd, 1H, *J* = 8.9, 5.7, 3.2 Hz), 7.05 (td, 1H, *J* = 8.9, 4.5 Hz), 6.93 (m, 1H), 6.35 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.18 (dd, 1H, *J* = 3.1, 0.9 Hz), 4.67 (s, 2H), 4.24 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 158.4 (241, 2 Hz), 157.3 (242, 2 Hz), 151.3, 151.0, 141.7, 139.1, 136.4, 133.5, 132.7, 128.8, 128.7, 126.3, 126.2 (18, 8 Hz), 118.2 (24, 4 Hz), 116.0 (25, 9 Hz), 114.5 (24, 8 Hz), 110.5, 109.0, 106.9, 32.2, 27.1, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{20}F_2N_3O_3$: 460.1473; found, 460.1477.



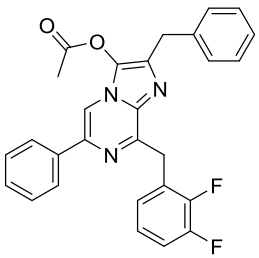
8-(2,5-Difluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,23,42*} (EC32712-045-1): Obtained as a solid (0.11 g, 65%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H), 7.85 (m, 2H), 7.44 (m, 2H), 7.39 (m, 1H), 7.21 (ddd, 1H, *J* = 8.9, 5.7, 3.2 Hz), 7.05 (td, 1H, *J* = 8.9, 4.6 Hz), 6.93 (m, 1H), 6.04 (d, 1H, *J* = 3.1 Hz), 5.92 (m, 1H), 4.67 (s, 2H), 4.19 (s, 2H), 2.38 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 158.4 (241, 2 Hz), 157.3 (242, 2 Hz), 151.2, 151.0, 149.4, 139.0, 136.5, 133.4, 133.0, 129.0, 128.8, 128.6, 126.3 (19, 8 Hz), 126.2, 118.2 (24, 5 Hz), 116.0 (25, 9 Hz), 114.5 (24, 8 Hz), 109.0, 107.5, 106.2, 32.1 (m), 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{22}F_2N_3O_3$: 474.1629; found, 474.1630.



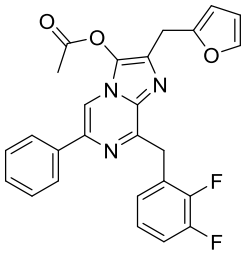
8-(2,5-Difluorobenzyl)-2-((5-ethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,23,44*} (EC32712-097-2): Obtained as a solid (0.08 g, 57%) after a chromatography over silica gel (cyclohexane – ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H), 7.85 (m, 2H), 7.43 (m, 3H), 7.21 (ddd, 1H, *J* = 8.9, 5.7, 3.2 Hz), 7.05 (td, 1H, *J* = 8.9, 4.5 Hz), 6.93 (m, 1H), 6.05 (d, 1H, *J* = 3.0 Hz), 5.92 (d, 1H, *J* = 2.9 Hz), 4.67 (s, 2H), 4.20 (s, 2H), 2.63 (q, 2H, *J* = 7.5 Hz), 2.37 (s, 3H), 1.24 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 158.4 (241, 2 Hz), 157.3 (243, 3 Hz), 157.1, 150.9, 149.1, 139.1, 136.4, 133.3, 132.9, 129.0, 128.8, 128.7, 126.3, 126.2 (19, 8 Hz), 118.2 (24, 4 Hz), 116.0 (25, 9 Hz), 114.5 (24, 8 Hz), 109.0, 107.4, 104.6, 32.2, 27.3, 21.3, 20.1, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1786.



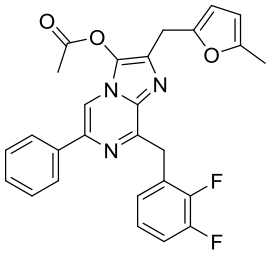
8-(2,5-Difluorobenzyl)-2-((4,5-dimethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,23,48*} (EC32712-095-2): Obtained as a solid (0.17 g, 71%) after a chromatography over silica gel (cyclohexane – ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H), 7.85 (m, 2H), 7.42 (m, 3H), 7.21 (m, 1H), 7.05 (m, 1H), 6.93 (m, 1H), 5.94 (s, 1H), 4.67 (s, 3H), 4.14 (s, 2H), 2.39 (s, 3H), 2.19 (s, 3H), 1.92 (s, 4H). ^{13}C NMR ($CDCl_3$): 167.0, 158.4 (241, 2 Hz), 157.3 (242, 2 Hz), 150.9, 148.0, 146.3, 139.0, 136.4, 133.3, 133.0, 129.0, 128.8, 128.7, 126.3 (19, 8 Hz), 126.3, 118.2 (24, 5 Hz), 116.0 (25, 9 Hz), 114.6, 114.5 (24, 8 Hz), 110.1, 109.0, 32.2, 27.1, 20.0, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1785.



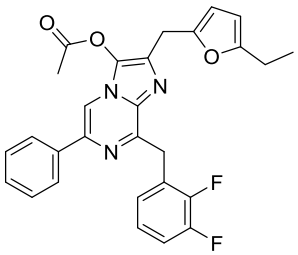
2-Benzyl-8-(2,3-difluorobenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,1*} (YJ 33067-127-1): Obtained as a solid (0.11 g, 65%) after a recrystallization from *n*-heptane. ^{1}H NMR (CDCl3): 7.85 (m, 3H), 7.45-722 (m, 9H), 7.03 (m, 3H), 4.73 (s, 2H), 4.22 (s, 2H), 2.02 (s, 3H). ^{13}C NMR (CDCl3): 167.1, 150.9, 150.7 (248 and 13 Hz), 149.5 (246, and 12 Hz), 139.0, 137.8, 136.5, 135.2, 133.4, 129.1, 128.9, 128.8, 128.6, 128.5, 127.1 (12 Hz), 126.6, 126.5 (m), 126.2, 123.5 (4 and 6 Hz), 115.5 (18 Hz), 109.0, 34.2, 32.1, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{22}F_2N_3O_2$: 470.1680; found, 470.1661.



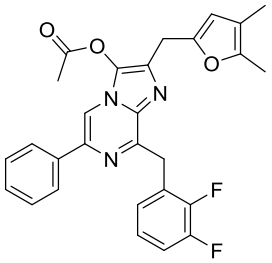
8-(2,3-Difluorobenzyl)-2-(furan-2-ylmethyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,37*} (EC32712-021-1): Obtained as a solid (0.24 g, 73%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.85 (m, 2H), 7.41 (m, 4H), 7.22 (tt, 1H, *J* = 6.1, 1.7 Hz), 7.05 (m, 2H), 6.36 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.18 (m, 1H), 4.72 (s, 2H), 4.25 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.4, 151.1, 150.7 (247, 13 Hz), 149.4 (248, 12 Hz), 141.7, 139.0, 136.4, 133.5, 132.6, 129.0, 128.8, 128.7, 127.1 (13 Hz), 126.5 (3 Hz), 126.2, 123.5 (7, 5 Hz), 115.5 (17 Hz), 110.5, 109.0, 106.9, 32.0 (2 Hz), 27.2, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{20}F_2N_3O_3$: 460.1473; found, 460.1473.



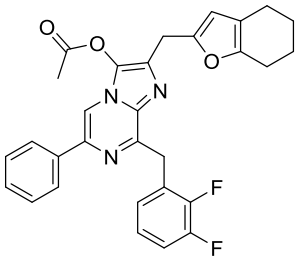
8-(2,3-Difluorobenzyl)-2-((5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,42*} (EC32712-043-1): Obtained as a solid (0.22 g, 73%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.85 (m, 2H), 7.43 (m, 2H), 7.38 (m, 1H), 7.23 (tt, 1H, *J* = 6.1, 1.7 Hz), 7.05 (m, 2H), 6.04 (d, 1H, *J* = 3.0 Hz), 5.92 (m, 1H), 4.72 (s, 2H), 4.19 (s, 2H), 2.38 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 151.2, 151.1 (247, 13 Hz), 151.0, 149.4 (248, 13 Hz), 149.4, 138.9, 136.5, 133.4, 133.0, 129.0, 128.8, 128.6, 127.1 (13 Hz), 126.5 (3 Hz), 126.2, 123.5 (7, 5 Hz), 115.5 (17 Hz), 109.0, 107.5, 106.2, 32.0 (2 Hz), 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{22}F_2N_3O_3$: 474.1629; found, 474.1629.



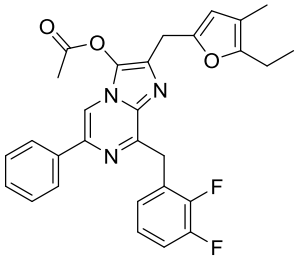
8-(2,3-Difluorobenzyl)-2-((5-ethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,44*} (EC32712-121-2): Obtained as a solid (0.32 g, 75%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.85 (m, 2H), 7.44 (m, 2H), 7.39 (m, 1H), 7.23 (m, 1H), 7.05 (m, 2H), 6.05 (d, 1H, *J* = 3.0 Hz), 5.93 (d, 1H, *J* = 3.0 Hz), 4.72 (s, 2H), 4.20 (s, 2H), 2.63 (q, 2H, *J* = 7.5 Hz), 2.37 (s, 3H), 1.24 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 157.1, 151.0, 150.7 (247, 13 Hz), 149.4 (248, 13 Hz), 149.2, 138.9, 136.5, 133.4, 133.0, 129.0, 128.8, 128.6, 127.1 (13 Hz), 126.5 (3 Hz), 126.2, 123.5 (7, 5 Hz), 115.5 (17 Hz), 109.0, 107.3, 104.6, 32.0 (m), 27.4, 21.4, 20.1, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1783.



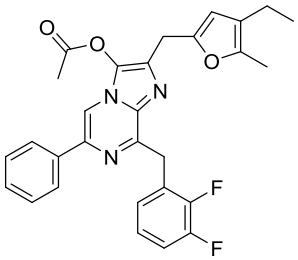
8-(2,3-Difluorobenzyl)-2-((4,5-dimethylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,48*} (EC32712-099-2): Obtained as a solid (0.14 g, 74%) after a chromatography over silica gel (cyclohexane – ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.85 (m, 2H), 7.41 (m, 3H), 7.22 (m, 1H), 7.05 (m, 2H), 5.94 (s, 1H), 4.72 (s, 2H), 4.15 (s, 2H), 2.39 (s, 3H), 2.19 (s, 3H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 150.9, 150.7 (247, 13 Hz), 149.4 (248, 13 Hz), 148.0, 146.3, 139.0, 136.4, 133.3, 133.0, 128.9, 128.8, 128.7, 127.1 (13 Hz), 126.5 (3 Hz), 126.2, 123.5 (7, 5 Hz), 115.5 (17 Hz), 114.6, 110.1, 109.0, 32.1 (2 Hz), 27.1, 20.0, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}F_2N_3O_3$: 488.1786; found, 488.1784.



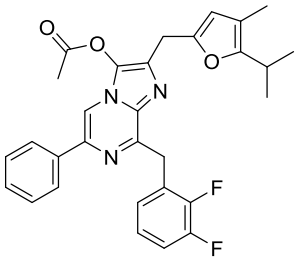
8-(2,3-difluorobenzyl)-6-phenyl-2-((4,5,6,7-tetrahydrobenzofuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,49*} (YJ 33068-085-1): Obtained as a solid (0.04 g, 12%) after a chromatography over silica gel (cyclohexane – ethyl acetate 6/1) and a recrystallization in *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.84 (m, 2H), 7.46-7.35 (m, 3H), 7.21 (m, 1H), 7.11 - 6.99 (m, 2H), 5.97 (s, 1H), 4.72 (s, 2H), 4.18 (s, 2H), 2.56 (m, 2H), 2.40 (m, 2H), 2.39 (s, 3H), 1.83 (m, 2H), 1.72 (m, 2H). ^{13}C NMR ($CDCl_3$): 167.1, 150.9, 150.7 (13 and 248 Hz), 149.8, 149.5 (13 and 248 Hz), 148.6, 139.1, 136.4, 133.2, 132.9, 129.9, 128.8, 128.7, 127.0 (13 Hz), 126.5 (4 Hz), 126.2, 123.5 (4 and 7 Hz), 117.6, 115.5 (17 Hz), 109.0, 107.8, . 32.1, 27.2, 23.2, 23.1 (two signals), 22.1, 22.1, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{26}F_2N_3O_3$: 514.1942; found, 514.1949.



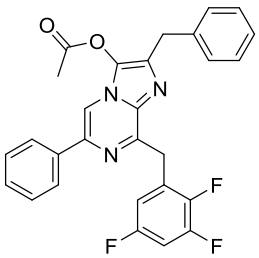
8-(2,3-Difluorobenzyl)-2-((5-ethyl-4-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,50*} (YJ 33069-013-1): Obtained as a solid (0.28 g, 47%) after a recrystallization from cyclohexane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.84 (m, 2H), 7.43 (m, 2H), 7.38 (m, 1H), 7.22 (m, 1H), 7.11 - 7.01 (m, 2H), 5.93 (s, 1H), 4.73 (s, 2H), 4.16 (s, 2H), 2.57 (q, 2H, J = 8.0 Hz), 2.37 (s, 3H), 1.94 (s, 3H), 1.19 (t, 3H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 151.7, 150.9, 150.7 (13 and 248 Hz), 149.5 (13 and 248 Hz), 147.9, 139.1, 136.4, 133.2, 132.9, 128.9, 128.8, 128.7, 127.0 (13 Hz), 126.5 (4 Hz), 126.2, 123.5 (4 and 7 Hz), 115.5 (17 Hz), 113.7, 110.2, 109.0, 32.1, 27.1, 20.0, 19.3, 13.1, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}F_2N_3O_3$: 502.1942; found, 502.1943.



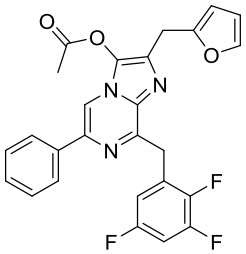
8-(2,3-Difluorobenzyl)-2-((4-ethyl-5-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,51*} (YJ33068-089-1): Obtained as a solid (0.54 g, 62%) after a chromatography over silica gel (cyclohexane – ethyl acetate 6/1) and a recrystallization in *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.83 (m, 2H), 7.46-7.35 (m, 3H), 7.21 (m, 1H), 7.11 - 6.99 (m, 2H), 5.99 (s, 1H), 4.72 (s, 2H), 4.16 (s, 2H), 2.38 (s, 3H), 2.33 (q, 2H, J = 7.4 Hz), 2.20 (s, 3H), 1.13 (t, 3H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 150.9, 150.7 (13 and 248 Hz), 148.2, 149.5 (13 and 248 Hz), 145.6, 139.0, 136.4, 133.3, 133.0, 129.0, 128.8, 128.6, 127.0 (13 Hz), 126.5 (4 Hz), 126.2, 123.5 (4 and 7 Hz), 121.3, 115.5 (17 Hz), 109.0, 108.4, 32.0, 27.2, 20.1, 18.1, 14.9, 11.3. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}F_2N_3O_3$: 502.1942; found, 502.1951.



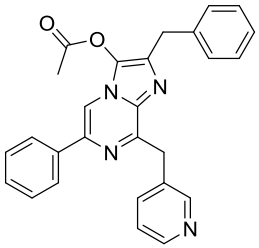
8-(2,3-Difluorobenzyl)-2-((5-isopropyl-4-methylfuran-2-yl)methyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,24,52*} (YJ 33069-063-1): Obtained as a solid (0.14 g, 26%) after a (slow) recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H), 7.85 (m, 2H), 7.43 (m, 2H), 7.38 (m, 1H), 7.22 (m, 1H), 7.11 - 7.01 (m, 2H), 5.90 (s, 1H), 4.73 (s, 2H), 4.16 (s, 2H), 2.99 (sept, 1H, J = 6.7 Hz), 2.36 (s, 3H), 1.95 (s, 3H), 1.23 (d, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 154.7, 150.9, 150.7 (13 and 248 Hz), 149.5 (13 and 248 Hz), 147.5, 139.1, 136.4, 133.2, 132.9, 128.9, 128.8, 128.7, 127.0 (13 Hz), 126.5 (4 Hz), 126.3, 123.5 (4 and 7 Hz), 115.5 (17 Hz), 112.6, 110.3, 108.9, 32.1, 27.1, 26.2, 21.4, 20.1, 9.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{28}F_2N_3O_3$: 516.2099; found, 516.2102.



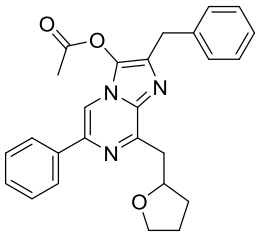
2-Benzyl-6-phenyl-8-(2,3,5-trifluorobenzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,26,1*} (YJ 33067-135-1): ^{1}H NMR ($CDCl_3$): Obtained as a solid (0.04 g, 28%) after a recrystallization from *n*-heptane. 7.85 (s, 1H), 7.84 (m, 2H), 7.43 - 7.26 (m, 9H), 7.02 (m, 1H), 6.84 (m, 1H), 4.70 (s, 2H), 4.21 (s, 2H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 157.1 (242, 12 and 3 Hz), 150.3 (247, 13 and 15 Hz), 150.1, 146.1 (242, 12 and 4 Hz), 139.1, 137.7, 136.3, 135.3, 133.2, 129.1, 129.0, 128.8, 128.7, 127.8 (9 and 14 Hz), 126.6, 126.3, 112.9 (3 and 24 Hz), 109.2, 103.8 (21 and 28 Hz), 34.1, 32.2, 19.8 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{21}F_3N_3O_2$: 488.1586; found, 488.1583.



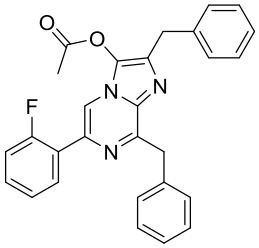
2-(Furan-2-ylmethyl)-6-phenyl-8-(2,3,5-trifluorobenzyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,26,37*} (YJ 33067-137-1): Obtained as a solid (0.41 g, 75%) after a recrystallization from a large amount of cyclohexane. ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H), 7.85 (m, 2H), 7.47 -7.36 (m, 4H), 7.02 (m, 1H), 6.85 (m, 1H), 4.69 (s, 2H), 4.23 (s, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 157.1 (242, 12 and 3 Hz), 151.2, 150.3 (247, 13 and 15 Hz), 150.2, 146.1 (242, 12 and 4 Hz), 141.7, 139.1, 136.3, 133.3, 132.8, 129.0, 128.8, 128.7, 127.8 (9 and 14 Hz), 126.2, 112.9 (3 and 24 Hz), 110.5, 109.2, 106.9, 103.8 (21 and 28 Hz), 32.1, 27.1, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{19}F_3N_3O_3$: 478.1378; found, 478.1374.



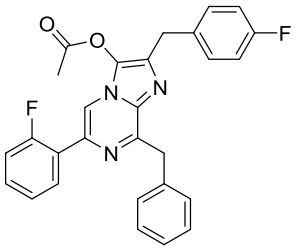
2-Benzyl-6-phenyl-8-(pyridin-3-ylmethyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,35,1*} (YJ30367-045-2): Obtained as a white solid (0.1 g, 37%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 8.87 (d, 1H, J = 2.0 Hz), 8.50 (dd, 1H, J = 1.7, 5.0 Hz), 7.92 (m, 1H), 7.87 (m, 2H), 7.82 (s, 1H), 7.48-7.22 (m, 9H), 4.63 (s, 2H), 4.21 (s, 2H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.1, 151.7, 150.9, 147.9, 139.1, 137.9, 137.2, 136.6, 135.5, 133.5, 133.3, 129.1, 129.0, 128.8, 128.7, 128.5, 126.3, 123.2, 109.1, 35.5, 34.2, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}N_4O_2$: 435.1821; found, 435.1805.



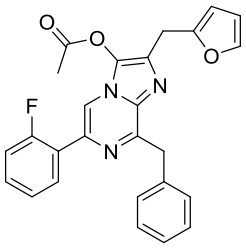
2-Benzyl-6-phenyl-8-((tetrahydrofuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,38,1*} (EC31093-023-1): Obtained as a solid (0.03 g, 30%) after a recrystallization from *n*-heptane and a small amount of toluene. ^{1}H NMR ($CDCl_3$): 7.90 (, 2H dt, J = 3.0, 1.8 Hz), 7.78 (s, 1H), 7.48 – 7.41 (m, 2H), 7.40 – 7.35 (m, 1H), 7.34 – 7.20 (m, 5H), 4.85 – 4.75 (m, 1H), 4.18 (s, 2H), 3.98 (td, 1H, J = 7.7, 6.2 Hz), 3.78 (td, 1H, J = 7.8, 6.1 Hz), 3.64 (dd, 1H, J = 14.3, 7.4 Hz), 3.38 (dd, 1H, J = 14.3, 6.1 Hz), 2.14 (s, 3H), 2.21 – 1.74 (m, 5H). ^{13}C NMR ($CDCl_3$): 167.2, 152.2, 139.2, 138.1, 137.1, 135.2, 134.2, 129.2, 128.9, 128.7, 128.6, 126.7, 109.0, 77.6, 68.0, 39.3, 34.5, 31.7, 25.7, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{26}N_3O_3$, 428.1974; found, 428.1936.



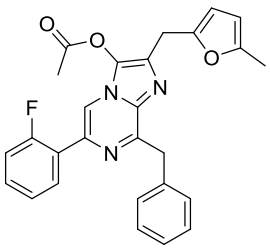
2,8-Dibenzyl-6-(2-fluorophenyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,1,1*} (YJ31134-091-1): Obtained as a solid (0.21 g, 45%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 8.20 (m, 1H), 8.05 (s, 1H), 7.62 (m, 2H), 7.32 (m, 10H), 7.15 (m, 1H), 4.63 (s, 2H), 4.22 (s, 2H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 160.0 (d, J = 248 Hz), 152.9, 138.0, 137.6, 135.4, 133.5, 133.3 (d, J = 2 Hz), 130.8 (d, J = 2 Hz), 129.8, 129.7, 129.1, 128.9, 128.5, 128.3, 126.5, 124.6 (d, J = 3 Hz), 124.3 (d, J = 11 Hz), 115.9 (d, J = 23 Hz), 112.9 (d, J = 16 Hz), 39.4, 34.2, 19.8 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{23}FN_3O_2$, 452.1774; found, 452.1838.



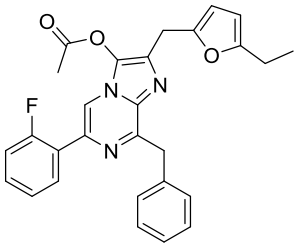
8-Benzyl-2-(4-fluorobenzyl)-6-(2-fluorophenyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,1,4*} (YJ30367-121-1): Obtained as a solid (0.1 g, 63%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 8.20 (dt, 1H, J = 2.0, 7.9 Hz), 8.06 (s, 1H), 7.60 (m, 2H), 7.38-7.21 (m, 7H), 7.15 (m, 1H), 7.01 (m, 2H), 4.62 (s, 2H), 4.16 (s, 2H), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 161.0 (243 Hz), 160.0 (248 Hz), 153.0, 137.7, 135.1, 133.7 (3 Hz), 133.5, 133.4 (2 Hz), 130.8 (2 Hz), 130.4 (8 Hz), 129.8 (9 Hz), 129.7, 128.8, 128.3, 126.5, 124.6 (3 Hz), 124.2 (11 Hz), 115.9 (23 Hz), 115.1 (22 Hz), 112.9 (16 Hz), 39.4, 33.2, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{22}F_2N_3O_2$, 470.1680; found, 470.1670.



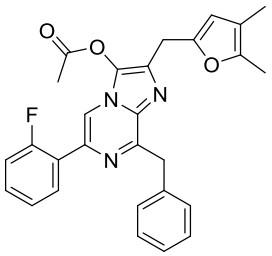
8-benzyl-6-(2-fluorophenyl)-2-(furan-2-ylmethyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,1,37*} (YJ31134-093-2): Obtained as a solid (0.15 g, 36%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 8.20 (m, 1H), 8.10 (s, 1H), 7.61 (m, 2H), 7.31 (m, 6H), 7.14 (m, 1H), 6.35 (m, 1H), 6.16 (m, 1H), 4.63 (s, 2H), 4.24 (s, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 160.1 (d, J = 248 Hz), 153.1, 151.5, 141.6, 137.7, 133.5, 133.4 (d, J = 2 Hz), 132.7, 130.8 (d, J = 2 Hz), 129.8 (d, J = 9 Hz), 129.7, 128.9, 128.3, 126.5, 124.6 (d, J = 3 Hz), 124.2 (d, J = 11 Hz), 115.9 (d, J = 23 Hz), 112.9 (d, J = 16 Hz), 110.5, 106.2, 39.3, 27.2, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{21}FN_3O_3$, 442.1567; found, 442.1631.



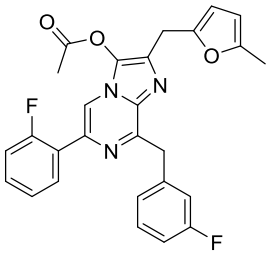
8-Benzyl-6-(2-fluorophenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,1,42*} (YJ30531-169-1): Obtained as a glass (0.08 g, 72%). ^{1}H NMR ($CDCl_3$): 8.19 (dt, 1H, J = 1.8, 7.8 Hz), 8.09 (s, 1H), 7.61 (m, 2H), 7.37-7.21 (m, 5H), 7.15 (ddd, 1H, J = 1.2, 8.1, 12.0 Hz), 6.02 (d, 1H, J = 3.0 Hz), 5.90 (m, 1H), 4.63 (s, 2H), 4.18 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 160.2 (248 Hz), 153.0, 151.2, 149.5, 137.7, 133.4 (2 Hz), 133.3, 133.0, 130.8 (2 Hz), 129.8 (9 Hz), 129.7, 128.9, 128.3, 126.5, 124.6 (3 Hz), 124.2 (11 Hz), 115.9 (23 Hz), 112.9 (16 Hz), 107.5, 106.2, 39.3, 27.2, 20.0, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}FN_3O_3$, 456.1723; found, 456.1734.



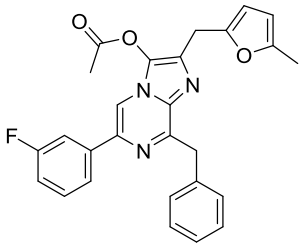
8-Benzyl-2-((5-ethylfuran-2-yl)methyl)-6-(2-fluorophenyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,1,44*} (YJ30367-111-1): Obtained as a wax (0.18 g, 95%). ^{1}H NMR ($CDCl_3$): 8.19 (dt, 1H, *J* = 1.8, 7.8 Hz), 8.10 (s, 1H), 7.62 (m, 2H), 7.39-7.22 (m, 5H), 7.15 (ddd, 1H, *J* = 1.2, 8.1, 12.0 Hz), 6.04 (d, 1H, *J* = 3.0 Hz), 5.93 (m, 1H), 4.64 (s, 2H), 4.21 (s, 2H), 2.65 (q, 2H, *J* = 7.6 Hz), 2.34 (s, 3H), 1.24 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$): 167.0, 160.1 (248 Hz), 157.0, 153.0, 149.3, 137.7, 133.4 (2 Hz), 133.3, 133.0, 130.8 (2 Hz), 129.8 (9 Hz), 129.7, 129.0, 128.3, 126.5, 124.6 (3 Hz), 124.2 (11 Hz), 115.9 (23 Hz), 112.9 (16 Hz), 107.3, 104.6, 39.3, 27.3, 21.3, 20.0, 12.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}FN_3O_3$, 470.1880; found, 470.1884.



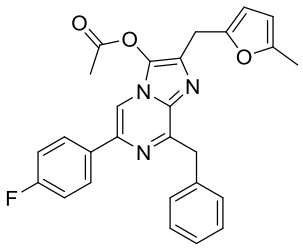
8-Benzyl-2-((4,5-dimethylfuran-2-yl)methyl)-6-(2-fluorophenyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,1,48*} (YJ30367-177-1): Obtained as a wax (0.44 g, 95%). ^{1}H NMR ($CDCl_3$): 8.20 (dt, 1H, *J* = 1.8, 8.0 Hz), 8.09 (s, 1H), 7.61 (m, 2H), 7.37 – 7.24 (m, 5H), 7.15 (ddd, 1H, *J* = 1.8, 8.1, 9.4 Hz), 5.91 (s, 1H), 4.63 (s, 2H), 4.41 (s, 2H), 2.35 (s, 3H), 2.19 (s, 3H), 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 160.0 (248 Hz), 153.0, 148.2, 146.3, 137.8, 133.4 (3 Hz), 133.3, 133.2, 130.8 (3 Hz), 129.8, 129.7 (three signals), 128.9, 128.3, 124.6 (3 Hz), 124.3 (11 Hz), 115.9 (22 Hz), 114.5, 112.9 (15 Hz), 110.1, 39.3, 27.3, 20.0, 11.2, 9.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{25}FN_3O_3$, 470.1880; found, 470.1890.



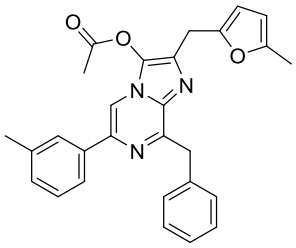
8-(3-fluorobenzyl)-6-(2-fluorophenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*2,3,42*} (EC31095-115-2): Obtained as a solid (0.35 g, 70%) after a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.17 (m, 2H), 7.32 (m, 5H), 7.16 (ddd, 1H, *J* = 11.9, 8.1, 1.2 Hz), 6.94 (m, 1H), 6.03 (d, 1H, *J* = 2.8 Hz), 5.92 (m, 1H), 4.62 (s, 2H), 4.19 (s, 2H), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 162.8 (245 Hz), 160.1 (248 Hz), 152.3, 151.2, 149.4, 140.1 (8 Hz), 133.4 (3 Hz), 133.3 (3 Hz), 130.7 (3 Hz), 129.9 (9 Hz), 129.6 (8 Hz), 129.0, 125.4 (3 Hz), 124.7 (3 Hz), 124.2 (11 Hz), 116.6 (22 Hz), 116.0 (23 Hz), 113.4 (21 Hz), 113.2, 113.0, 107.5, 106.2, 38.9 (2 Hz), 27.3, 20.0, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{22}F_2N_3O_3$: 474.1629; found, 474.1620.



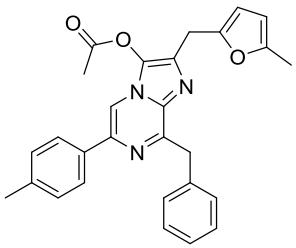
8-Benzyl-6-(3-fluorophenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*3,1,42*} (YJ30531-141-1): Obtained as white powder after a recrystallization in n-heptane (0.018 g, 14%). ^{1}H NMR ($CDCl_3$): 7.85 (s, 1H), 7.68 (m, 2H), 7.60 (m, 2H), 7.46-7.37 (m, 2H), 7.34-7.21 (m, 3H), 6.02 (d, 1H, *J* = 3.1 Hz), 5.90 (m, 1H), 4.62 (s, 2H), 4.18 (s, 2H), 2.37 (s, 3H), 2.26 (s, 3H). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}FN_3O_3$, 456.1723; found, 456.1732.



8-Benzyl-6-(4-fluorophenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*4,1,42*} (YJ30531-171-1): Obtained as a glass (0.1 g, 83%). ^{1}H NMR ($CDCl_3$): 7.88 (m, 2H), 7.78 (s, 1H), 7.59 (m, 2H), 7.34-7.12 (m, 6H), 6.02 (d, 1H, *J* = 3.0 Hz), 5.90 (m, 1H), 4.61 (s, 2H), 4.18 (s, 2H), 2.36 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 163.2 (248 Hz), 153.1, 151.2, 149.4, 138.3, 137.7, 133.4, 133.0, 132.9 (3 Hz), 129.7, 128.9, 128.2 (8 Hz), 128.1, 126.5 115.6 (21 Hz), 108.6, 107.5, 106.2, 39.3, 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}FN_3O_3$, 456.1723; found, 456.1721.

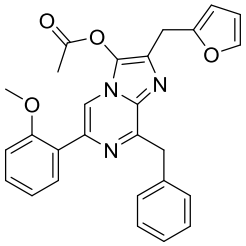


8-benzyl-2-((5-methylfuran-2-yl)methyl)-6-(m-tolyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*5,1,42*} (YJ30367-75-1) Obtained as a white solid (0.1 g, 53%) after a (slow) recrystallization from n-heptane. ^{1}H NMR ($CDCl_3$): 7.82 (s, 1H), 7.73 (m, 1H), 7.79 (m, 1H), 7.37 – 7.20 (m, 5H), 6.01 (d, 1H, *J* = 3 Hz), 5.91 (m, 1H), 4.62 (s, 2H), 4.18 (s, 2H), 2.45 (s, 3H), 2.36 (s, 3H), 2.28 (s, 2H). ^{13}C NMR ($CDCl_3$): 167.0, 152.9, 151.2, 149.5, 139.3, 138.4, 137.9, 136.8, 133.5, 132.8, 129.7, 129.3, 128.9, 128.7, 128.2, 127.1, 126.4, 123.5, 108.8, 107.4, 106.2, 39.4, 27.4, 21.5, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_3$, 452.1974; found, 452.1981.

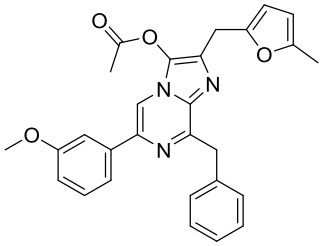


8-benzyl-2-((5-methylfuran-2-yl)methyl)-6-(p-tolyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*6,1,42*} (YJ30367-047-1): Obtained as a white solid (0.15 g, 70%) after a recrystallization from n-heptane. ^{1}H NMR ($CDCl_3$): 7.82 – 7.79 (m, 3H), 7.62 (m, 2H), 7.33 – 7.20 (m, 5H), 6.01 (d, 1H, *J* = 1 Hz), 5.90 (m, 1H), 4.62 (s, 2H), 4.17 (s, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 2.28 (s, 2H). ^{13}C NMR ($CDCl_3$): 167.0, 152.9, 151.1, 149.6, 139.2, 138.5, 137.9, 134.0, 133.5,

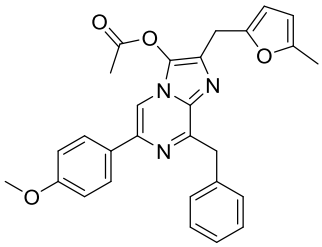
132.8, 129.7, 129.5, 128.8, 128.2, 126.4, 126.3, 108.4, 107.4, 106.2, 39.3, 27.3, 21.2, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_3$, 452.1974; found, 452.1960.



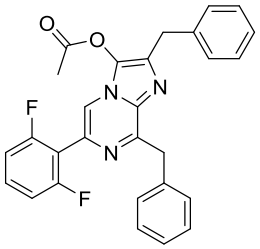
8-Benzyl-2-(furan-2-ylmethyl)-6-(2-methoxyphenyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*7,1,37*} (EC31092-057-3): Obtained as a beige solid (0.27 g, 68%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 8.21 (s, 1H), 8.05 (dd, 1H, *J* = 7.7, 1.8 Hz), 7.59 (dd, 2H, *J* = 7.9, 0.9 Hz), 7.39 – 7.27 (m, 4H), 7.23 – 7.18 (m, 1H), 7.09 (td, 1H, *J* = 7.6, 1.1 Hz), 6.99 (dd, 1H, *J* = 8.3, 0.9 Hz), 6.33 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.16 – 6.10 (m, 1H), 4.60 (s, 2H), 4.22 (s, 2H), 3.87 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 156.9, 152.5, 151.9, 141.7, 138.1, 135.6, 133.5, 132.4, 131.1, 129.9, 129.7, 128.8, 128.4, 126.5, 125.7, 121.4, 113.5, 111.7, 110.6, 106.9, 55.9, 39.5, 27.4, 20.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_4$, 454.1767; found, 454.1785.



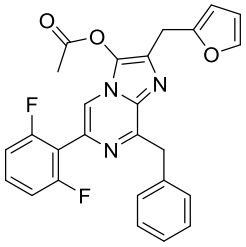
8-Benzyl-6-(3-methoxyphenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*8,1,42*} (YJ30367-113-1): Obtained as a wax (0.08 g, 95%). ^{1}H NMR ($CDCl_3$): 7.84 (s, 1H), 7.61 (m, 2H), 7.52 (m, 1H), 7.45 (m, 1H), 7.38-7.29 (m, 3H), 7.23 (m, 1H), 6.93 (m, 1H), 6.02 (d, 1H, *J* = 3 Hz), 5.91 (m, 1H), 4.63 (s, 2H), 4.18 (s, 2H), 3.88 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 160.1, 152.9, 151.2, 149.5, 138.8, 138.2, 137.8, 133.5, 132.9, 129.8, 129.7, 128.9, 128.2, 126.4, 118.5, 114.7, 112.3, 109.0, 107.5, 106.2, 55.3, 39.2, 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_4$, 468.1923; found, 468.1928.



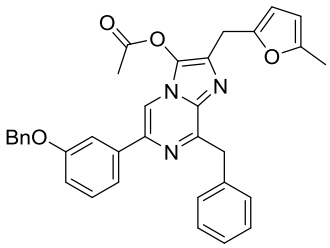
8-Benzyl-6-(4-methoxyphenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*9,1,42*} (YJ30531-183-2): Obtained as a white solid after a recrystallization in n-heptane (0.11 g, 69%). ^{1}H NMR ($CDCl_3$): 7.84 (m, 2H), 7.75 (s, 1H), 7.61 (m, 2H), 7.32 (m, 2H), 7.24 (m, 1H), 7.0 (m, 2H), 6.02 (m, 1H), 5.91 (m, 1H), 4.62 (s, 2H), 4.17 (s, 2H), 3.87 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 160.1, 152.8, 151.1, 149.6, 139.0, 137.9, 133.4, 132.7, 129.7, 129.4, 128.8, 128.2, 127.6, 126.4, 114.2, 107.8, 107.4, 106.2, 55.4, 39.3, 27.3, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_4$, 468.1923; found, 468.1919.



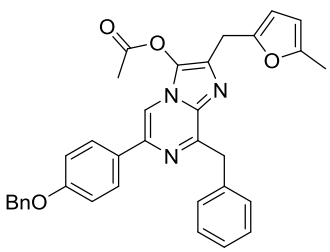
2,8-Dibenzyl-6-(2,6-difluorophenyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*10,1,1*} (MM34284-035-1): Obtained as a solid (0.16 g, 61%) after a recrystallization from *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.66 (s, 1H), 7.63 (m, 2H), 7.31 (m, 9H), 7.02 (m, 2H), 4.62 (s, 2H), 4.21 (s, 2H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 160.7 (6, 250 Hz), 153.3, 137.9, 137.6, 135.4, 133.3, 130.2 (10 Hz), 129.6, 129.5, 129.1, 128.7, 128.5, 128.2, 126.5, 126.4, 115.2 (18 Hz), 114.3, 111.8 (6, 19 Hz), 39.5, 34.2, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{21}F_2N_3O_2$, 470.1680; found, 470.1630.



8-Benzyl-6-(2,6-difluorophenyl)-2-(furan-2-ylmethyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*10,1,37*} (MM34284-038-1): Obtained as a wax (0.19 g, 95%). ^{1}H NMR ($CDCl_3$): 7.70 (s, 1H), 7.60 (m, 2H), 7.37-7.19 (m, 6H), 7.02 (m, 2H), 6.35 (m, 1H), 6.15 (m, 1H), 4.62 (s, 2H), 4.24 (s, 2H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.9, 160.7 (6, 250 Hz), 153.4, 151.4, 141.6, 137.5, 133.2, 132.8, 130.2 (10 Hz), 129.7, 129.6, 128.7, 128.2, 126.5, 115.2 (18 Hz), 114.3, 111.8 (6, 19 Hz), 110.4, 106.8, 39.4, 27.2, 20.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{19}F_2N_3O_3$, 460.1473; found, 460.1430.



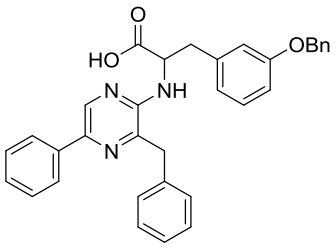
8-Benzyl-6-(3-(benzyloxy)phenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*11,1,42*} (RB32489-019-1): Obtained as an oil (0.46 g, still containing some AcOH, Ac_2O and EtOAc) which was used directly in the next step. ^{1}H ($CDCl_3$): 7.83 (s, 1H), 7.61 (m, 3H), 7.48 (m, 3H), 7.44-7.30 (m, 6H), 7.23 (m, 1H), 7.02 (m, 1H), 6.03 (d, 1H, J = 3.0 Hz), 5.91 (m, 1H), 5.14 (s, 2H), 4.64 (s, 2H), 4.20 (s, 2H), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C ($CDCl_3$) 176.3, 167.0, 159.3, 152.8, 151.2, 149.4, 138.8, 138.2, 137.7, 136.9, 133.4, 132.8, 129.8, 128.9, 128.6, 128.3, 128.0, 127.6, 126.5, 118.8, 115.0, 113.3, 109.0, 107.5, 106.2, 70.2, 39.3, 27.2, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{30}N_3O_4$, 544.2236; found, 544.2231.



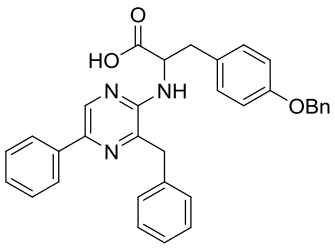
8-Benzyl-6-(4-(benzyloxy)phenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*12,1,42*} (YJ 33069-171-1): Obtained as a white solid (0.41 g, 91%) after diluting the THF solution in water, stirring for 15

minutes, a filtration and drying under vacuum at 40 °C. ^{1}H NMR ($CDCl_3$): 7.85 (m, 2H), 7.76 (s, 1H), 7.62 (m, 2H), 7.47 (m, 2H), 7.42 (m, 2H), 7.33 (m, 3H), 7.22 (m, 1H), 7.06 (m, 2H), 6.03 (d (br), 1H, *J* = 3.1 Hz), 5.91 (m, 1H), 5.15 (s, 2H), 4.64 (s, 2H), 4.20 (s, 2H), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$):. 167.0, 159.4, 152.7, 151.2, 149.3, 139.1, 137.7, 136.8, 133.1, 132.6, 129.7, 129.5, 128.8, 128.6, 128.3, 128.0, 127.7, 127.4, 126.5, 115.2, 107.9, 107.5, 106.2, 70.1, 39.3, 27.2, 20.1, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{30}N_3O_4$, 544.2236; found, 544.2232.

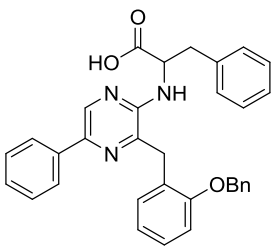
General procedure for the hydrolysis of esters 23 to prepare acids 24 via step xi. In a round bottomed flask, the considered ester **23** (1.0 mmol) and powdered sodium hydroxide (0.16 g, 4.0 mol) were mixed. The atmosphere was replaced with argon and dry tetrahydrofuran (5 mL) was added. This was stirred overnight under an inert atmosphere, neutralized with a solution of ammonium chloride (1.1 equivalent). The aqueous phase was saturated with sodium chloride, extracted with ethyl acetate, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness to yield the corresponding acids **24** as described below which were used directly in the next step.



2-((3-Benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-(benzyloxy)phenyl)propanoic acid **24**{*1,1,18*} (YJ 31777-035-1): ^{1}H NMR (DMSO-d_6, very badly resolved, containing AcOEt): 8.32 (s (br), 1H), 7.79 (m, 2H), 7.43 - 6.93 (m, 14H), 6.84 (s(br), 1H), 6.72 (m, 2H), 6.56 (s(br), 1H), 4.89 (s, 2H), 4.64 (s(br), 1H), 4.15 (s(br), 1H), 3.90 (m, 1H), 3.30 (m, 1H), 3.17 (m, 1H). ^{13}C NMR (DMSO-d_6): 158.5, 151.7, 141.7, 141.5, 138.1, 137.7, 137.6, 136.7, 129.4, 129.1, 129.0, 128.7, 128.6, 128.1, 128.0, 127.6, 126.5, 125.1, 122.4, 116.4, 112.2, 69.5, 57.4, 39.2, 37.5 (three signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{30}N_3O_3$: 516.2287; found, 516.2283.

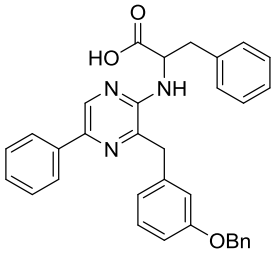


2-((3-Benzyl-5-phenylpyrazin-2-yl)amino)-3-(4-(benzyloxy)phenyl)propanoic acid **24**{*1,1,19*} (YJ 31777-037-1): ^{1}H NMR (DMSO-d_6, very badly resolved, containing AcOEt): 8.34 (s (br), 1H), 7.81 (m, 2H), 7.41 - 7.10 (m, 13H), 6.99 (m, 2H), 6.69 (m, 2H), 6.47 (s(br), 1H), 4.91 (s, 2H), 4.60 (s(br), 1H), 4.13 (s(br), 1H), 3.92 (m, 1H), 3.23 (m, 1H), 3.10 (m, 1H). ^{13}C NMR (DMSO-d_6): 157.0, 151.6, 141.6, 138.1, 137.7, 137.6, 136.8, 131.8, 130.8, 129.3, 129.0, 128.8, 128.7, 128.1, 128.0, 127.6, 126.6, 125.1, 114.5, 69.5, 57.4, 39.3, 36.5 (two signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{30}N_3O_3$: 516.2287; found, 516.2286.

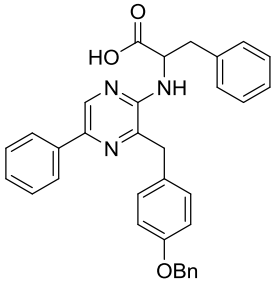


(3-(2-(Benzyloxy)benzyl)-5-phenylpyrazin-2-yl)phenylalanine **24**{*1,17,1*} (YJ31776-155-1): ^{1}H NMR (DMSO-d_6, very badly resolved, containing AcOEt): 8.38 (s (br), 1H), 7.86 (m, 2H), 7.41 - 7.25 (m, 8H), 7.12 - 6.97 (m, 6H),

6.93 (s(br), 1H), 6.82 (m, 2H), 6.48 (s(br), 1H), 5.07 (m, 2H), 4.62 (s(br), 1H), 4.02 (s(br), 2H), 3.29 (m, 1H), 3.10 (m, 1H). ^{13}C NMR (DMSO-d_6): 158.8, 151.6, 141.3, 139.7, 139.5, 138.1, 137.7, 137.6, 136.9, 129.9, 129.7, 129.4, 129.1, 128.8, 128.7, 128.2, 128.1, 128.0, 127.7, 126.0, 125.2, 115.9, 112.9, 69.6, 57.4, 39.3, 37.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{30}N_3O_3$: 516.2287; found, 516.2280.

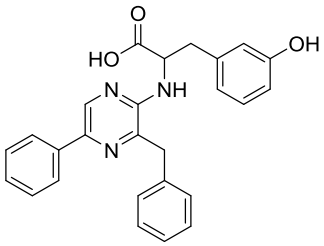


(3-(3-(Benzyloxy)benzyl)-5-phenylpyrazin-2-yl)phenylalanine **24**{*1,18,1*} (YJ31776-153-1) ^{1}H NMR (DMSO-d_6, very badly resolved, containing AcOEt): 8.40 (s (br), 1H), 7.79 (m, 2H), 7.37 - 7.14 (m, 9H), 7.02 (m, 7H), 6.81 (m, 1H), 6.29 (s(br), 1H), 5.00 (s, 2H), 4.52 (s(br), 1H), 4.12 (s(br), 1H), 3.94 (m, 1H), 3.28 (m, 1H), 3.13 (m, 1H). ^{13}C NMR (DMSO-d_6): 156.4, 151.5, 141.1, 139.5, 138.0, 137.8, 137.7, 136.5, 130.5, 130.0, 129.0, 128.7, 128.1, 128.0, 127.9, 127.6, 127.5, 126.2, 126.0, 121.0, 112.6, 69.6, 56.9, 37.4, 33.7 (two signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{30}N_3O_3$: 516.2287; found, 516.2297.



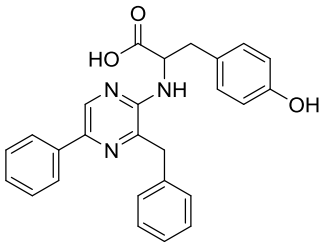
(3-(4-(Benzyloxy)benzyl)-5-phenylpyrazin-2-yl)phenylalanine **24**{*1,19,1*} (YJ31776-151-1) ^{1}H NMR (DMSO-d_6, very badly resolved, containing AcOEt): 8.36 (s (br), 1H), 7.86 (m, 2H), 7.44 - 7.27 (m, 9H), 7.12 (m, 2H), 7.05 (m, 5H), 6.83 (m, 2H), 6.43 (m, 1H), 5.02 (s, 2H), 4.54 (s(br), 1H), 4.07 (s(br), 1H), 3.90 (m, 1H), 3.28 (m, 1H), 3.12 (m, 1H). ^{13}C NMR (DMSO-d_6): 157.3, 151.5, 141.9, 139.7, 138.1, 137.7, 136.7, 130.2, 130.1, 129.8, 129.1, 128.9, 128.2, 128.1, 128.0, 127.6, 126.0, 125.2, 115.2, 115.1, 69.6, 57.3, 38.5, 37.3 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{30}N_3O_3$: 516.2287; found, 516.2288.

General procedure for the debenzylation of O-benzyl-bearing acids 24, preparation of the phenol-bearing acids 24 via step xiii. The considered O-benzyl derivative **24** (1.0 mmol) and ammonium formate (1.9 g, 30.0 mmol) were dissolved in ethanol (30 mL). To this was added 10% palladium over charcoal (0.10 g, 0.1 mmol) and the suspension was heated to reflux for 90 minutes. This was cooled, filtered washed with a small amount of water and ethanol and the filtrate was concentrated to dryness under high vacuum to remove any unreacted ammonium formate as much as possible. This gave the corresponding crude deprotected acids **24** as described below which were used without further purifications in the next step.

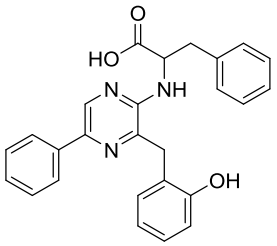


2-((3-Benzyl-5-phenylpyrazin-2-yl)amino)-3-(3-hydroxyphenyl)propanoic acid **24**{*1,1,62*} (YJ31777-045-1): ^{1}H NMR (DMSO-d_6, containing EtOH): 8.45 (s, 1H), 8.40 (s, 1H), 7.89 (m, 2H), 7.40 (m, 2H), 7.30 - 7.14 (m, 6H), 6.91 (m, 1H), 6.67 (m, 1H), 6.52 (m, 3H), 4.46 (s (br), 1H), 4.12 (d, 1H, J = 14.6 Hz), 3.94 (d, 1H, J = 14.6 Hz),

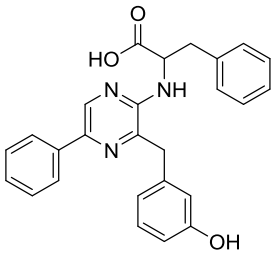
3.19 (dd, 1H, *J* = 4.8, 13.9 Hz), 3.06 (dd, 1H, *J* = 6.9, 13.9 Hz). ^{13}C NMR (DMSO-d_6): 157.5, 151.5, 141.6, 140.8, 138.2, 138.1, 137.7, 136.9, 129.4, 129.1, 128.9, 128.7, 127.7, 126.7, 125.2, 120.5, 116.9, 113.3, 57.0, 39.2, 37.2 (one signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_3$: 426.1818; found, 426.1820.



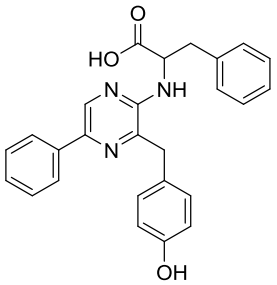
(3-Benzyl-5-phenylpyrazin-2-yl)tyrosine **24**{*1,1,63*} (YJ31777-047-1): ^{1}H NMR (DMSO-d_6, containing EtOH): 8.41 (s, 1H), 8.37 (s, 1H), 7.88 (m, 2H), 7.44 - 7.14 (m, 9H), 6.91 (m, 2H), 6.54 (m, 3H), 4.48 (s (br), 1H), 4.17 (d, 1H, *J* = 14.3 Hz), 3.95 (d, 1H, *J* = 14.3 Hz), 3.15 (m, 1H), 3.03 (m, 1H). ^{13}C NMR (DMSO-d_6): 156.0, 151.6, 141.6, 138.3, 138.1, 137.7, 136.8, 130.6, 129.4, 129.3, 129.1, 128.7, 127.6, 126.6, 125.2, 115.1, 57.3, 39.2, 36.4 (one signals missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_3$: 426.1818; found, 426.1816.



(3-(2-Hydroxybenzyl)-5-phenylpyrazin-2-yl)phenylalanine **24**{*1,61,1*} (YJ31776-157-1): ^{1}H NMR (DMSO-d_6, very badly resolved, containing EtOH): 8.43 (s (br), 1H), 7.89 (m, 2H), 7.43 (m, 2H), 7.29 (m, 2H), 7.12 - 6.98 (m, 6H), 6.70 (m, 2H), 6.60 (m, 1H), 6.40 (m, 1H), 4.53 (s(br), 1H), 4.07 (m, 1H), 3.82 (m, 1H), 3.25 (m, 1H), 3.09 (m, 1H). ^{13}C NMR (DMSO-d_6): 157.9, 151.4, 141.5, 139.4, 139.2, 138.3, 137.7, 136.8, 129.9, 129.7, 129.1, 128.1, 127.7, 126.1, 125.2, 119.9, 116.1, 113.9, 57.1, 39.2, 37.3 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_3$: 426.1818; found, 426.1821.

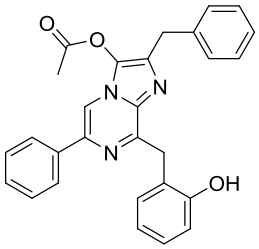


(3-(3-Hydroxybenzyl)-5-phenylpyrazin-2-yl)phenylalanine **24**{*1,62,1*} (YJ31776-159-1): ^{1}H NMR (DMSO-d_6, very badly resolved, containing EtOH): 8.39 (s (br), 1H), 7.89 (m, 2H), 7.39 (m, 3H), 7.28 (m, 2H), 7.18 - 7.01 (m, 6H), 6.92 (m, 1H), 6.69 (m, 2H), 4.63 (s(br), 1H), 4.03 (m, 2H), 3.28 (m, 1H), 3.04 (m, 1H). ^{13}C NMR (DMSO-d_6): 155.3, 151.5, 141.8, 140.8, 139.3, 138.3, 137.6, 136.5, 130.5, 129.8, 129.1, 128.2, 127.7, 126.2, 125.2, 123.9, 119.5, 115.9, 57.1, 37.9, 33.4 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_3$: 426.1818; found, 426.1821.

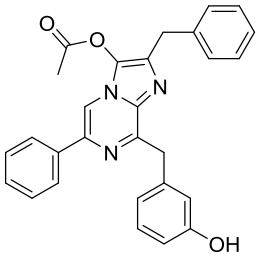


(3-(4-Hydroxybenzyl)-5-phenylpyrazin-2-yl)phenylalanine **24**{*1,63,1*} (YJ31776-161-1): ^{1}H NMR (DMSO-d_6, very badly resolved, containing EtOH): 8.40 (s (br), 1H), 7.89 (m, 2H), 7.39 (m, 2H), 7.29 (m, 2H), 7.14 - 7.01 (m, 7H), 6.64 (m, 2H), 4.63 (s(br), 1H), 4.01 (m, 2H), 3.84 (m, 2H), 3.24 (m, 1H), 3.12 (m, 1H). ^{13}C NMR (DMSO-d_6): 156.3, 151.4, 142.2, 139.5, 138.2, 137.7, 136.6, 130.1, 129.9, 129.1, 128.1, 127.9, 127.7, 126.1, 125.2, 115.6, 57.1, 38.6, 37.3 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_3$: 426.1818; found, 426.1822.

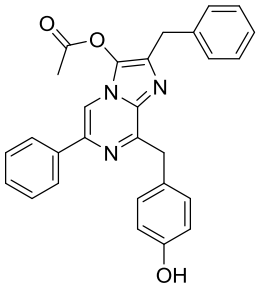
General protocol for the cyclization and mono-acetylation of OH-bearing acids 24, **preparation of phenol-bearing *O*-acetylated luciferins 25 via step xiv.** The considered deprotected acid (0.4 mmol) was dispersed in ethyl acetate (10 mL). To this was added acetic anhydride (0.095 mL, 0.8 mmol) and the mixture heated to reflux for 30 minutes. The resulting solution was adsorbed over a small amount of silica under vacuum, without any heating and purified by a chromatography over silica gel without delay as described below.



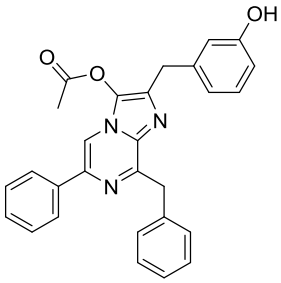
2-Benzyl-8-(2-hydroxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,61,1*} (YJ31777-013-2): Obtained as a yellow powder (0.06 g, 13% from **23**{*1,17,1*}) after a chromatography over silica gel (cyclohexane – ethyl acetate 3/1). ^{1}H NMR (DMSO-d_6): 9.30 (s, 1H), 8.73 (s, 1H), 8.08 (m, 2H), 7.51 (s, 2H), 7.40 (m, 1H), 7.30 (m, 4H), 7.22 (m, 1H), 7.08 (m, 1H), 6.91 (m, 2H), 6.62 (m, 1H), 4.40 (s, 2H), 4.11 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6): 168.5, 157.7, 152.2, 139.6, 138.9, 137.8, 136.7, 135.5, 133.5, 129.7, 129.3, 129.1, 128.9, 128.8, 126.7, 126.6, 120.4, 116.5, 113.9, 111.1, 39.2, 33.1, 20.7 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}N_3O_3$: 450.1818; found, 450.1812.



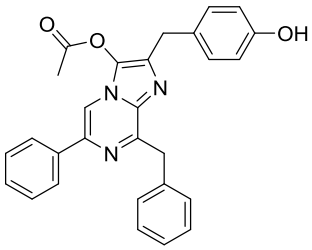
2-Benzyl-8-(3-hydroxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,62,1*} (YJ31777-015-1): Obtained as a pale pink powder (0.12 g, 25% from **23**{*1,18,1*}) after a chromatography over silica gel (cyclohexane – ethyl acetate 5/1) and a recrystallization in cyclohexane. ^{1}H NMR (DMSO-d_6): 9.66 (s, 1H), 8.74 (s, 1H), 8.00 (m, 2H), 7.46 (s, 2H), 7.40 (m, 1H), 7.30 (m, 4H), 7.22 (m, 2H), 7.08 (m, 1H), 6.84 (m, 1H), 6.74 (m, 1H), 4.45 (s, 2H), 4.09 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (DMSO-d_6): 168.6, 157.7, 152.4, 138.8, 137.8, 136.6, 135.2, 133.6, 131.1, 129.3, 129.2, 129.1, 128.9, 128.8, 128.2, 126.7, 126.5, 124.8, 119.5, 116.2, 111.1, 33.5, 33.0, 20.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}N_3O_3$: 450.1818; found, 450.1825.



2-Benzyl-8-(4-hydroxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,63,1*} (YJ31777-017-1): Obtained as a yellow powder (0.18 g, 38% from **23**{*1,19,1*}) after a chromatography over silica gel (cyclohexane – ethyl acetate 3/1) and a dispersion in boiling cyclohexane. ^{1}H NMR (DMSO-d_6): 9.20 (s, 1H), 8.70 (s, 1H), 8.07 (m, 2H), 7.49 (s, 2H), 7.40 (m, 1H), 7.31-7.19 (m, 7H), 6.67 (m, 2H), 4.36 (s, 2H), 4.09 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6): 168.5, 156.4, 152.8, 139.0, 137.8, 136.7, 135.4, 133.4, 130.6, 129.3, 129.2, 129.1, 128.9, 128.8, 128.4, 126.7, 126.5, 115.5, 111.0, 38.4, 33.0, 20.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}N_3O_3$: 450.1818; found, 450.1807.



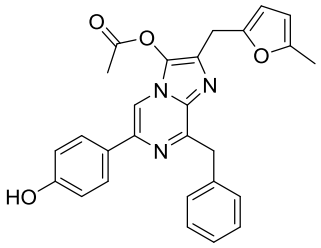
8-Benzyl-2-(3-hydroxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,62*} (YJ31777-051-1): Obtained as a yellow powder (0.21 g, 43% from **23**{*1,1,18*}) after a chromatography over silica gel (cyclohexane – ethyl acetate 3/1) and a dispersion in boiling cyclohexane. ^{1}H NMR ($CDCl_3$): 7.88 (m, 2H), 7.78 (s, 1H), 7.59 (m, 2H), 7.43 (m, 3H), 7.26 (m, 2H), 7.18 (m, 1H), 7.13 (m, 1H), 4.60 (s, 2H), 4.10 (s, 2H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.0, 156.8, 152.7, 139.5, 139.0, 137.5, 136.5, 134.8, 133.2, 129.7, 129.6, 129.0, 128.8, 128.7, 128.3, 126.5, 126.4, 120.7, 116.1, 114.2, 108.7, 39.2, 33.5, 19.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}N_3O_3$: 450.1818; found, 450.1814.



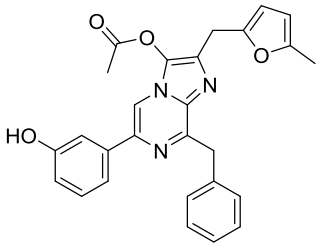
8-Benzyl-2-(4-hydroxybenzyl)-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate **25**{*1,1,63*} (YJ31777-049-1): Obtained as a yellow powder (0.14 g, 24% from **23**{*1,1,19*}) after a chromatography over silica gel (cyclohexane – ethyl acetate 3/1) and a dispersion in boiling cyclohexane. ^{1}H NMR (DMSO-d_6): 9.20 (s, 1H), 8.71 (s, 1H), 8.06 (m, 2H), 7.48 (s, 2H), 7.39 (m, 1H), 7.28 (m, 2H), 7.20 (m, 1H), 7.10 (m, 2H), 6.69 (m, 2H), 4.49 (s, 2H), 3.98 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6): 168.5, 156.2, 152.1, 138.3, 137.7, 136.7, 136.2, 133.4, 130.2, 129.7, 129.2, 129.1, 129.0, 128.9, 128.7, 126.9, 126.5, 115.5, 111.1, 39.2, 32.3, 20.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{24}N_3O_3$: 450.1818; found, 450.1814.

General procedure for the debenzylation of O-benzyl-bearing compound 25, preparation of the phenol-bearing O-acetylated luciferins 25 via step xvi. The considered O-acetylated luciferin **25** (1 mmol) was dissolved in a mixture of ethyl acetate (10 mL), ethanol (10 mL) and acetic acid (4 mL). To this was added 10% palladium over charcoal (0.1g, 0.1 mmol), the atmosphere was replaced with hydrogen and the reaction stirred for 13 hours. This was filtered, concentrated to dryness and the residue purified by a chromatography over silica gel as described

below (note 1). Note 1: the trace amount of palladium still present in the crude mixture, along with air, will over few hours, decompose the target luciferin. Similarly, adsorption of the residue over a small amount of silica should be done without any heating and the ensuing purification by chromatography undertaken without delay.

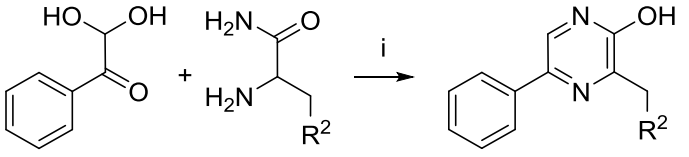


8-benzyl-6-(4-hydroxyphenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*14,1,42*} (YJ 31776-083-2): This compound was obtained as a beige powder (0.09 g, 27%) after a chromatography over silica gel (cyclohexane – ethyl acetate 4/1).^{1}H NMR (DMSO-d_6): 9.66 (s, 1H), 8.55 (s, 1H), 7.90 (m, 2H), 7.47 (m, 2H), 7.47 (m, 2H), 7.30 (m, 2H), 7.20 (m, 1H), 6.87 (m, 2H), 6.04 (d (br), 1H, J = 3.0 Hz), 5.97 (m, 1H), 4.47 (s, 2H), 4.07 (s, 2H), 2.40 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6): 168.3, 158.5, 152.0, 150.8, 150.0, 138.4, 138.3, 133.1, 132.8, 129.6, 129.2, 128.8, 127.9, 127.5, 126.8, 115.9, 109.3, 107.8, 106.8, 39.1, 26.6, 20.7, 13.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{54}N_3O_4$: 454.1767; found, 454.1766.



8-benzyl-6-(3-hydroxyphenyl)-2-((5-methylfuran-2-yl)methyl)imidazo[1,2-a]pyrazin-3-yl acetate **25**{*13,1,42*} (RB32489-025-2): This compound was obtained as a red powder (0.15 g, 41%) after a chromatography over silica gel (cyclohexane – ethyl acetate 4/1). ^{1}H ($CDCl_3$): 7.81 (s, 1H), 7.57 (m, 2H), 7.41 (m, 2H), 729-7.24 (m, 3H), 7.18 (m, 1H), 6.85 (m, 1H), 6.01 (d, 1H, J = 2.5 Hz), 5.89 (m, 1H), 4.61 (s, 2H), 4.19 (s, 2H), 2.34 (s, 3H), 2.25 (s (br), 3H). ^{13}C ($CDCl_3$) 167.0, 156.6, 152.8, 151.2, 149.3, 139.0, 138.1, 137.6, 133.4, 132.9, 129.9, 129.6, 129.0, 128.3, 126.5, 118.3, 115.9, 113.8, 109.1, 107.6, 106.2, 39.2, 27.2, 20.0, 13.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{54}N_3O_4$: 454.1767; found, 454.1760.

Synthetic scheme for the preparation of hydroxypyrazines 19{1,60}, 19{1,38}and 19{1,35}



27 **28a-c** **19a-c**

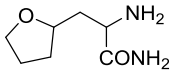
a: R^2 = H: 53%

b: R^2 = tetrahydrofuran-2-yl: 43 %

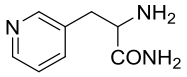
c: R^2 = pyridin-3-yl: 11 %

Scheme 3. i: a) NaOH, MeOH, -78 °C, b) $H_3O^+Cl^-$

Preparation of aminoamides 28 from □-amino esters. In a steel reactor, the considered □-amino ester (0.065 mol, free base, note 1) was dispersed in 7 N methanolic ammonia (50 mL). This was properly stirred and heated at 70 °C for 20 hours, concentrated to dryness as described below and used directly in the next step. Note 1: the hydrochloride salts were also used in other instances.

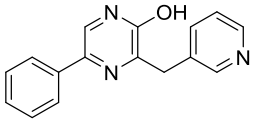


2-Amino-3-(tetrahydrofuran-2-yl)propanamide **28**{38} (YJ31134-019-1): Obtained as an oil which solidified (1.7 g, 93%). ^{1}H NMR ($CDCl_3$): mixture of isomer: 7.23 (s, 1H), 5.63 (s, 1H), 4.02 (m, 2H), 3.88 (m, 1H), 3.74 (m, 1H), 3.56 (m, 1H), 2.07 (m, 1H), 1.89 (m, 5H), 1.54 (m, 1H). ^{13}C NMR ($CDCl_3$): 178.3, 79.3, 68.0, 55.6, 40.3, 32.3, 25.2. HRMS (*m/z*): $[M+H]^+$ calcd for $C_7H_{15}N_2O$: 159.1134; found, 159.1122.

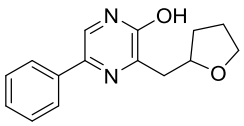


2-Amino-3-(pyridin-3-yl)propanamide **28**{35} (YJ30367-005-2): Obtained as an orange solid (3.46 g, 99%). ^{1}H NMR (DMSO-d_6): 8.42 (m, 1H), 8.40 (dd, 1H, *J* = 1.9, 4.6 Hz), 7.62 (m, 1H), 7.26 (m, 2H), 6.95 (s (br), 1H), 4.02 (m, 2H), 3.35 (dd, 1H, *J* = 5.3, 8.0 Hz), 2.90 (dd, 1H, *J* = 5.2, 13.6 Hz), 2.64 (dd, 1H, *J* = 8.0, 13.6 Hz), 1.75 (m, 2H). ^{13}C NMR (DMSO-d_6): 176.9, 150.9, 147.7, 137.2, 134.9, 123.6, 56.3, 38.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_8H_{12}N_3O$: 166.0980; found, 166.0984.

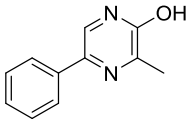
General procedure for the condensation between phenyl glyoxal 27 and amino amides 28. These compounds were prepared by following the protocols previously described.[5] Phenyl glyoxal hydrate **27** (1.33 g, 8.74 mmol) and the corresponding amino amide **28** (8.74 mmol) were dispersed in methanol (50 mL). This was cooled to -78 °C with a dry ice bath and sodium hydroxide (0.45 g, 11.36 mmol, note 1) dissolved in water (3 ml) was added drop-wise. The solution was stirred at – 78 °C for 15 minutes allowed to warm back to 0°C while stirring for 90 minutes and then further stirred at 20 °C for 30 minutes. This was made acid with 37% hydrochloric acid, diluted in water brought back to neutrality with solid sodium hydrogenocarbonate and filtered. When a precipitation occurred (note 2), the collected solid was washed with water and dry under vacuum ate 60 °C to yield the hydroxypyrazines **19** as described below. Note 1: if a hydrochloric salt of the aminoamide is used and additional equivalent of sodium hydroxide must be used. Note 2: see below for the isolation procedure of 5-phenyl-3-(pyridin-3-ylmethyl)pyrazin-2-ol (**19**{***1,35***}).



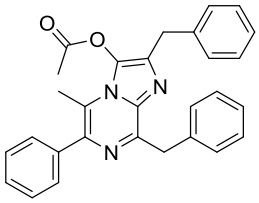
5-Phenyl-3-(pyridin-3-ylmethyl)pyrazin-2-ol **19**{*1,35*} (YJ30367-008-5): Obtained as a white solid (0.57 g, 11%) although an extraction of the reaction medium with ethyl acetate had to be made. The resulting residue was dispersed in dichloromethane and the insoluble material further purified by a chromatography over silica gel (dichloromethane – ethanol 95/5 to 9/1). ^{1}H NMR (DMSO-d_6): 12.47 (s(br), 1H), 8.57 (d, 1H, *J* = 1.7 Hz), 8.43 (dd, 1H, *J* = 1.7, 4.8 Hz), 7.89 (s, 1H), 7.92 (m, 2H), 7.74 (m, 1H), 7.40-7.25 (m, 4H), 4.10 (s, 2H). ^{13}C NMR (DMSO-d_6): 156.7, 155.3, 150.8, 147.9, 137.2, 136.3, 133.8, 131.4, 129.0, 127.7, 124.9, 123.8, 123.0, 36.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{14}N_3O$, 264.1137; found, 264.1122.



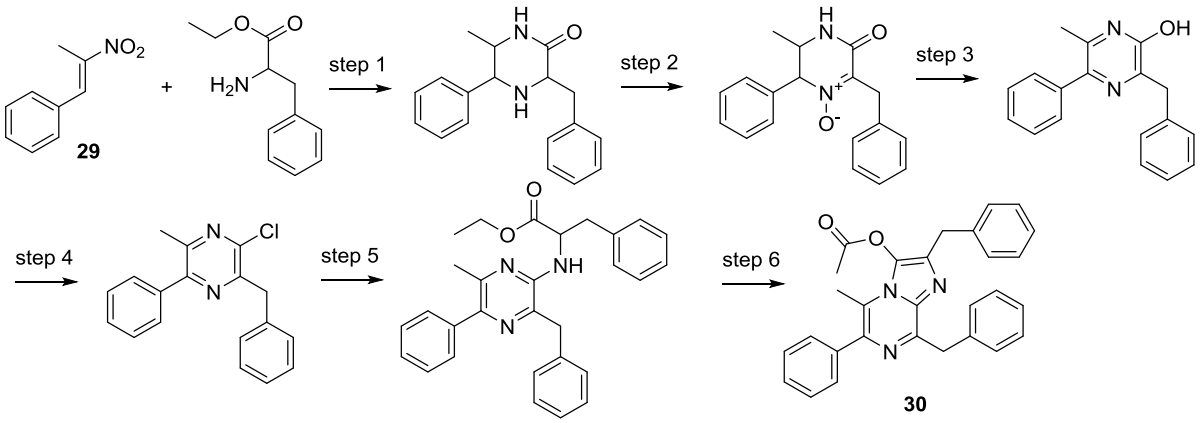
5-Phenyl-3-((tetrahydrofuran-2-yl)methyl)pyrazin-2-ol **19**{*1,38*} (YJ31134-061-1): Obtained as a pink solid (1.02 g, 45%) which was used without any further purification in the step viii described above. ^{1}H NMR ($CDCl_3$): 13.22 (s(br), 1H), 7.81 (m, 2H), 7.63 (s (br), 1H), 7.44 (m, 2H), 7.35 (m, 1H), 4.60 (p, 1H, *J* = 6.6 Hz), 3.99 (m, 1H), 3.80 (m, 1H), 3.30 (dd, 1H, *J* = 7.0, 14.8 Hz), 3.05 (dd, 1H, *J* = 6.1, 14.8 Hz), 2.17 (m, 1H), 1.98 (m, 2H), 1.76 (m, 1H). ^{13}C NMR ($CDCl_3$): 157.2, 156.8, 135.9, 134.4, 128.8, 128.0, 125.1, 120.3, 76.9, 67.8, 39.0, 31.4, 25.6. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_2$, 257.1290; found, 257.1281.



3-Methyl-5-phenylpyrazin-2-ol **19**{*1,60*} (VHE30612-133-2): This compound was obtained using alanine amide hydrochloride[6] as a light orange solid (4.08 g, 53%) which was used without any further purification in the step vii described above. ^{1}H NMR (DMSO-d_6) 12.31 (s, 1H), 7.83 (m, 3H), 7.39 (m, 2H), 7.28 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (DMSO-d_6): 156.3, 155.8, 136.5, 131.2, 129.0, 127.6, 124.9, 122.3, 20.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0871; found, 187.0808.



Preparation of 2,8-dibenzyl-5-methyl-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate (**30**), the following synthetic pathway was used:



First step, preparation of 3-benzyl-6-methyl-5-phenylpiperazin-2-one: By using the general protocol described above (steps i, ii and iii) for the synthesis compounds **17**, using compound **29** (5.94 g, 0.036 mol) and phenylalanine ethyl ester **14**{*1,1*} a crude mixture of the four possible diastereoisomers was obtained as an oil and used directly in the N-oxidation step. Note: in another trial, removal of unreacted phenylalanine ethyl ester was achieved under high vacuum at 180 °C and a chromatography over silica gel (dichloromethane – methanol 98/2 to 95/5) led to fractions containing unseparated mixture of these diastereoisomers. One of these fractions could be recrystallized in cyclohexane to give a single diastereoisomer (0.8 g, 7%) with an undetermined configuration. (GG 30532-125-1) ^{1}H NMR ($CDCl_3$): 7.38-7.28 (m, 7H), 7.24-7.20 (m, 3H), 6.62 (s, 1H), 3.90-3.87 (dd, 1H, J = 10.2, 3.8 Hz), 3.70-3.63 (m, 2H), 3.30-3.16 (m, 2H), 1.73 (s, 1H), 1.03-0.98 (m, 3H). ^{13}C NMR ($CDCl_3$): 172.0, 139.5, 138.0, 129.3, 128.9, 128.7, 128.4, 127.9, 126.8, 59.6, 59.5, 54.8, 37.7, 18.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_2O$: 281.1654, found: 281.1659.

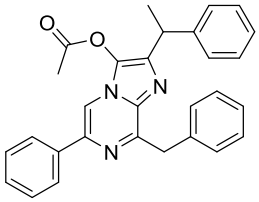
Second step, preparation of 6-benzyl-3-methyl-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrazine 1-oxide. By using the general protocol described above (steps v) for the synthesis compounds **18**, using the crude mixture of the four possible diastereoisomers described above (10.11 g), a 1/7 mixture of the two possible diastereoisomers (2.63 g, 24% from **29**) was obtained after after a chromatography over silica gel (cyclohexane – ethyl acetate 3/2 to 1/2). (YJ 31777-011-3) ^{1}H NMR ($CDCl_3$, minor isomer): 10.18 (s, 1H), 7.36-7.18 (m, 10H), 5.27 (d (br), 1H, J = 2.2 Hz), 4.08 (m, 1H), 4.01 (m, 2H), 1.35 (d, 3H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$): 157.3, 140.2, 136.9, 136.2, 129.1, 129.0, 128.8, 127.0, 126.8, 77.8, 59.5, 30.5, 17.0 (one signal missing). ^{1}H NMR ($CDCl_3$, major isomer): 8.47 (d (br), 1H, J = 3.9 Hz), 7.36-7.18 (m, 10H), 5.09 (d (br), 1H, J = 4.1 Hz), 3.98 (s, 2H), 3.84 (m, 1H), 1.21 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): 159.9, 140.4, 137.2, 136.1, 129.3, 128.9, 128.8, 1287, 127.3, 126.8, 77.0, 49.4, 30.1, 20.7. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_2$, 317.1266; found, 317.1262.

Third step, preparation of 3-benzyl-6-methyl-5-phenylpyrazin-2-ol: By using the general protocol described above (steps vi) for the synthesis compounds **19**, this compound was obtained as a pale-yellow solid (1.70 g, 70%) after a chromatography over silica gel (dichloromethane – ethanol 98/2). (YJ 31777-023-4) ^{1}H NMR (DMSO-d_6): 12.29 (s, 1H), 7.48 (m, 2H), 7.41 (m, 2H), 7.34-7.25 (m, 5H), 7.17 (m, 1H), 4.01 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6): 155.9, 154.3, 138.8, 138.1, 133.9, 131.0, 129.4, 129.3, 128.7, 128.5, 127.5, 126.6, 38.8, 17.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O$: 277.1341; found, 277.1344.

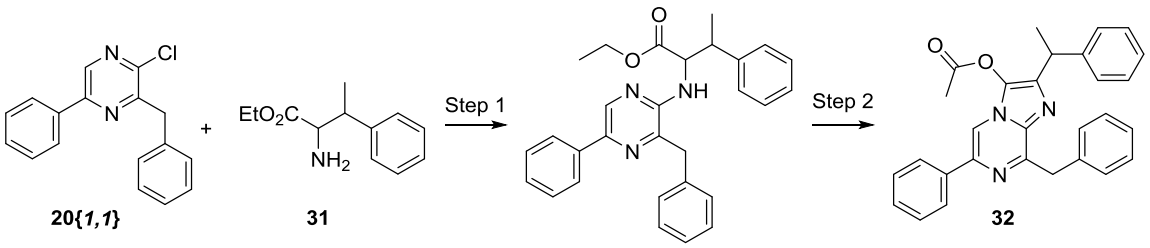
Fourth step, preparation of 2-benzyl-3-chloro-5-methyl-6-phenylpyrazine: By using the general protocol described above (steps vii) for the synthesis compounds **20**, and heating for 12 hours, this compound was obtained as an oil (0.83 g, 77%) after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). (YJ 31777-039-2) ^{1}H NMR ($CDCl_3$): 7.61 (m, 2H), 7.50 (m, 3H), 7.39 (m, 2H), 7.32 (m, 2H), 7.25 (m, 1H), 4.36 (s, 2H), 2.6 (s, 3H). ^{13}C NMR ($CDCl_3$): 151.5, 150.7, 149.3, 145.6, 137.6, 137.5, 129.1, 129.0, 128.9, 128.5, 128.4, 126.6, 43.7, 22.4. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2$, 295.1002; found, 295.1003.

Fifth step, preparation of ethyl (3-benzyl-6-methyl-5-phenylpyrazin-2-yl)phenylalaninate (GG30532-130-3): Obtained as an oil (0.4 g, 84%) using the N-arylation protocol (step x) described above for the preparation of compounds **23**, after a chromatography over silica gel (cyclohexane – ethyl acetate 94/6). ^{1}H NMR ($CDCl_3$): 7.60-7.57 (m, 2H), 7.48-7.44 (m, 2H), 7.39-7.35 (m, 1H), 7.31-7.20 (m, 8H), 7.03-7.00 (m, 2H), 5.00-4.95 (q, 1H, J = 7.0 Hz), 4.80-4.78 (m, 1H), 4.18-4.09 (m, 4H), 3.17-3.12 (m, 1H), 3.08-3.03 (m, 1H), 2.46 (s, 3H), 1.22-1.18 (t, 3H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): 172.7, 149.5, 146.3, 141.4, 139.7, 138.3, 137.0, 136.5, 129.3, 129.1, 128.8, 128.5, 128.4, 128.2, 127.3, 126.8 (two signals?), 61.0, 54.9, 40.4, 38.0, 22.4, 14.1. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_2$, 452.2338; found, 452.2347.

Sixth step, preparation of 2,8-dibenzyl-5-methyl-6-phenylimidazo[1,2-a]pyrazin-3-yl acetate (**30**) (GG30532-137-1): This compound was obtained as a red oil (0.30 g, 76%) after a using the general protocol described for the synthesis of compound **25** and a concentration to dryness. ^{1}H NMR ($CDCl_3$): 7.62 (m, 2H), 7.51-7.39 (m, 5H), 7.30 (m, 8H), 4.58 (s, 2H), 4.16 (s, 2H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$): 168.4, 150.8, 139.1, 138.4, 138.3, 138.1, 135.9, 134.6, 130.0, 129.9, 129.6, 129.1, 128.4, 128.3, 128.2, 127.9, 126.4, 126.3, 122.5, 34.1, 20.1, 14.8 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2020.

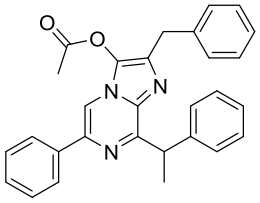


Synthesis of 8-benzyl-6-phenyl-2-(1-phenylethyl)imidazo[1,2-a]pyrazin-3-yl acetate (**32**), the following synthetic pathway was used:

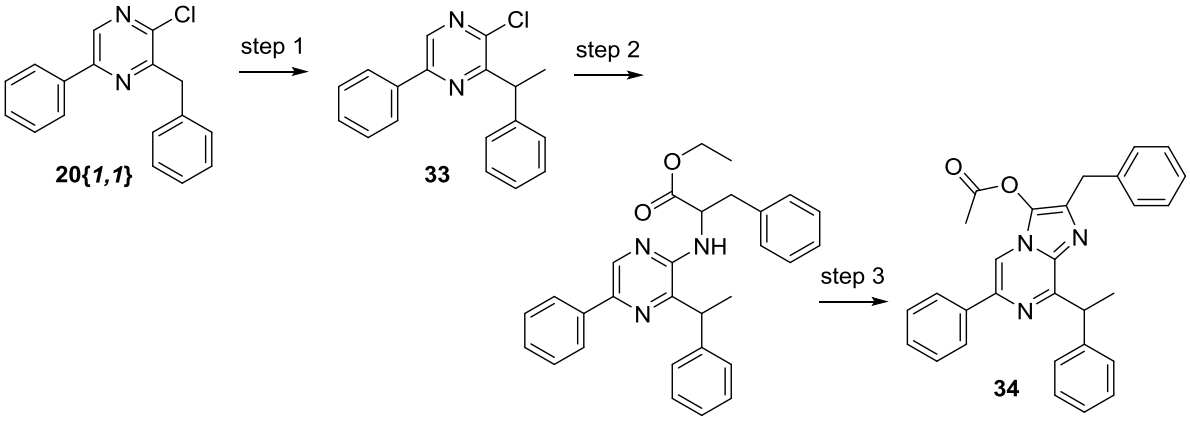


First step: preparation of ethyl 2-((3-benzyl-5-phenylpyrazin-2-yl)amino)-3-phenylbutanoate (YJ31067-019-2): This compound was obtained using the N-arylation protocol (step x) described above as an oil (0.3 g, 67%) after a chromatography over silica gel (cyclohexane – ethyl acetate 96/4). ^{1}H NMR (diastereoisomeric mixture, 0.6 / 0.4 ratio) ($CDCl_3$): 8.40 (s, 0.6H), 8.34 (s, 0.3H), 7.94 (m, 2H), 7.46 (m, 2H), 7.39-7.19 (m, 7H), 7.21 (m, 1H), 7.16 (m, 1H), 7.05 (m, 2H), 4.95 (m, 1H), 4.89 (d, 0.4H, J = 7.7 Hz), 4.69 (d, 0.6H, J = 8.3 Hz), 4.20 (m, 0.8H), 4.08 (m, 0.8H), 4.08 (m, 2.6H), 3.37 (m, 0.6H), 3.0 (m, 0.4H), 1.28 (d, 1.8H, J = 7.1 Hz), 1.24 (d, 0.8H, J = 7.3 Hz), 1.16 (t, 1.8H, J = 7.5 Hz), 1.08 (t, 0.8H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): too many signal overlaps. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_2$, 452.2338; found, 452.2378.

Second step: preparation of 8-Benzyl-6-phenyl-2-(1-phenylethyl)imidazo[1,2-a]pyrazin-3-yl acetate (**32**) (YJ31067-23-1): This compound was obtained using the cyclization/O-acetylation protocol described above (step xii) as a white powder after a recrystallization from n-heptane (0.12 g, 44%). ^{1}H NMR ($CDCl_3$): 7.90 (m, 2H), 7.74 (s, 1H), 7.68 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 7.33 (m, 5H), 7.25 (m, 2H), 4.68 (d, 1H, *J* = 13.8 Hz), 4.63 (d, 1H, *J* = 13.8 Hz), 4.34 (q, 1H, *J* = 6.7 Hz), 2.14 (s, 3H), 1.83 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 167.1, 153.0, 143.9, 139.5, 139.0, 138.0, 137.0, 133.4, 129.8, 128.7, 128.5, 128.4, 128.2, 127.8, 126.4 (three signals), 108.9, 39.6, 38.5, 20.7, 19.8. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2031.



Preparation of 2-benzyl-6-phenyl-8-(1-phenylethyl)imidazo[1,2-a]pyrazin-3-yl acetate (**34**), the following synthetic pathway was used:



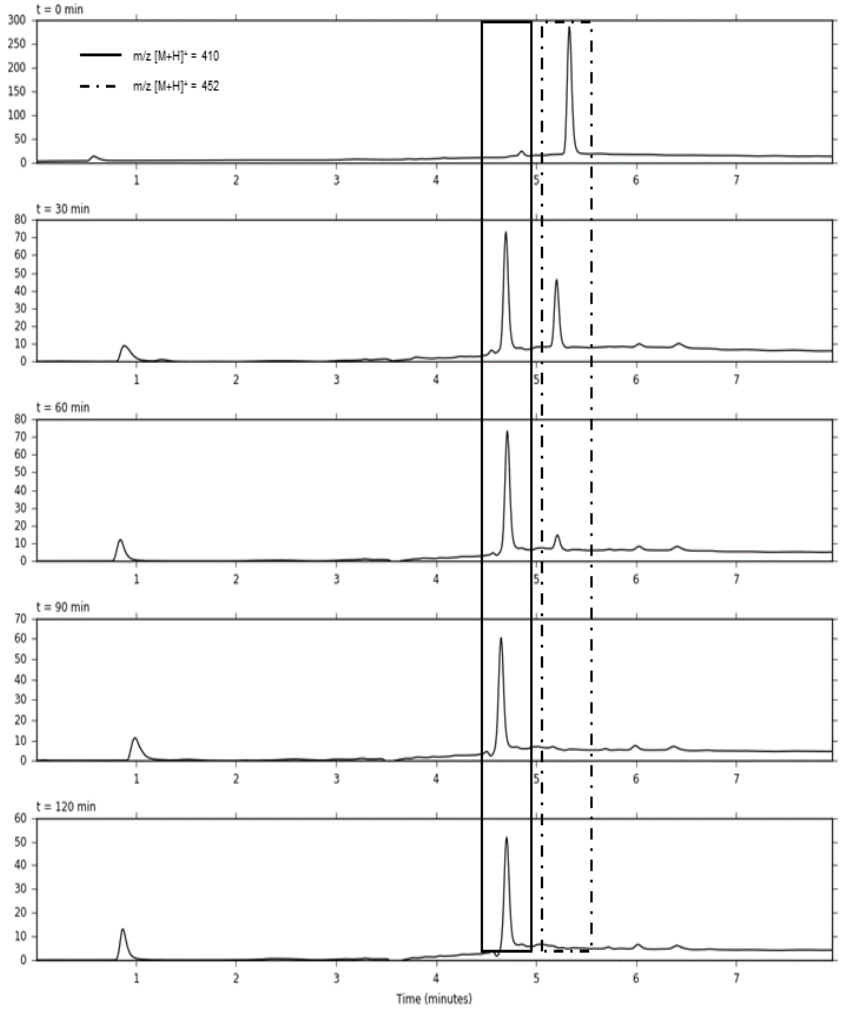
Step 1, preparation of 2-chloro-5-phenyl-3-(1-phenylethyl)pyrazine (**33**) (YJ 31777-025-2): Under an argon-protected atmosphere, compound **20**{*1,1*} (0.94 g, 3.34 mmol) was dissolved in dry tetrahydrofuran (15 mL). This was cooled to -78 °C, and a 2M solution of lithium diisopropylamide (2 mL, 4.02 mmol, in THF, *n*-heptane and ethylbenzene) was injected. This was stirred at -78 °C for 10 minutes (immediate blackening of the solution) and methyl iodide (0.27 mL, 4.35 mmol) was then injected. This was stirred for 10 minutes at -78 °C and allowed to warm back to room temperature for 20 minutes. The resulting solution was diluted in water and ethyl acetate, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane – dichloromethane 3/1) to yield compound **33** as a solid (0.73 g, 73%). ^{1}H NMR ($CDCl_3$): 8.67 (s, 1H), 8.11 (m, 2H), 7.54 (m, 3H), 7.42 (m, 2H), 7.33 (m, 2H), 7.22 (m, 1H), 4.76 (q, 1H, *J* = 7.0 Hz), 1.81 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 156.5, 150.0, 146.7, 143.0, 138.1, 135.6, 130.0, 129.1, 128.5, 128.0, 126.8, 126.7, 43.0, 20.9. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{16}ClN_2$, 295.1002; found, 295.1006.

Step 2, preparation of ethyl (5-phenyl-3-(1-phenylethyl)pyrazin-2-yl)phenylalaninate (YJ 31777-041-1): By using the general N-arylation protocol described above for the preparation of compounds **23** (step x), this compound was obtained as an oily 1/1 mixture of two diastereoisomers (0.33 g, 52%) using toluene as a solvent and a chromatography over silica gel (cyclohexane – ethyl acetate 97/3). ^{1}H NMR ($CDCl_3$): 8.44 (s, 0.5H), 8.42 (s, 0.5H), 8.06 (m, 2H), 7.49 (m, 2H), 7.38 (m, 1H), 7.40-7.11 (m, 9H), 6.81 (m, 1H), 4.95 (m, 3H), 4.81 (d (br), 1H, *J* = 8.0 Hz), 4.20-3.97 (m, 3H), 3.19 (dd, 0.5H, *J* = 5.9, 13.6 Hz), 3.09 (m, 1H), 2.99 (dd, 0.5H, *J* = 5.5, 13.6 Hz), 1.77 (m, 3H), 1.25 (t, 1.5H, *J* = 7.1 Hz), 1.09 (t, 1.5H, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 172.5, 172.3, 149.8, 149.6, 144.1, 143.7, 143.1, 142.9, 140.4, 140.3, 137.7, 136.5, 135.8, 135.7, 129.4, 129.1, 129.0, 128.9, 128.7, 128.5,

128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.5, 126.9, 126.7, 125.5, 61.2, 61.0, 55.0, 54.8, 42.9, 42.8, 37.9, 21.0, 20.8, 14.1, 14.0. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_2$, 452.2338; found, 452.2332.

Step 3, preparation of 2-benzyl-6-phenyl-8-(1-phenylethyl)imidazo[1,2-a]pyrazin-3-yl acetate (**34**) (YJ 31777-053-1): By using the general protocol described above for the preparation of compounds **25**, this *O*-acetylated luciferin was obtained as a white cotton (0.10 g, 32%) after a recrystallization in *n*-heptane. ^{1}H NMR ($CDCl_3$): 7.99 (m, 2H), 7.79 (s, 1H), 7.71 (m, 2H), 7.50 (m, 2H), 7.42 (m, 1H), 7.35-7.28 (m, 6H), 7.26-7.19 (m, 2H), 5.30 (q, 1H, J = 7.1 Hz), 4.22 (s, 2H), 2.16 (s, 3H), 1.91 (d, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 167.1, 156.2, 143.5, 139.0, 137.9, 136.9, 134.6, 133.0, 129.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 126.5, 126.3, 108.4, 41.2, 34.1, 20.2, 19.8 (one signal missing). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_2$, 448.2025; found, 448.2038.

General hydrolysis protocol of O-acetylated luciferins 25, to generate solutions of the luciferins 26 (or **35-37**) **via step xv.** In a closed plastic vial (even closed 50 mL falcon tubes were fine on large scale), the considered O-acetylated luciferin (1 mg) was dissolved in DMSO (0.2 mL) and then diluted by adding a solution of acidic ethanol (0.3 ml) made from the addition of 37% hydrochloric acid (100µl) on 100% ethanol (12 mL). This 0.5 mL solution was incubated at 50 °C for 2 hours to give a stock solution which was then stored at -20 °C. As depicted in the figure below, the LC/MS monitoring of the hydrolysis of the *O*-acetylated luciferin **25**{1,1,44} into the corresponding luciferin **26**{1,1,44} under these conditions was complete and fairly clean in less than two hours.



HPLC profiles over time for the acetyl hydrolysis of proluciferin **25**{1,1,44} into the corresponding luciferin **26**{1,1,44}. Obtained on an Agilent apparatus, with a 3.5 µm XDB-C18 column and a water / methanol gradient (containing 5 mM ammonium formate, from 95-5 to 5-95 in 3.5 min and then 3.5 min back at 5-95) UV monitoring set at 254 nM.

Note: in general, the resulting acid solution of these luciferins can be used within few hours or should be stored at -20°C to avoid their relatively slow decay (see below for more extensive LC/MS monitoring). On the other hand, upon dilution in buffers, the resulting solutions are decaying much faster and should be used within a short time frame.

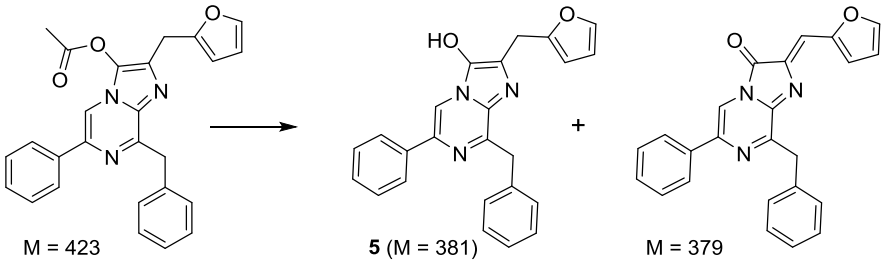
HPLC/MS monitoring of the hydrolysis products of the O-acetylated luciferins 25 described in table 8.

The hydrolysis of each of the proluciferins (hikarazines) **25** listed in table 8 and leading to 5 mM solution of the corresponding luciferins **26** was undertaken following the protocols described above for**.**

An initial LC/MS analysis was run on diluted (1/10 in DMSO) samples of the solutions right after the hydrolysis step, a second one was done16 hours after and a third one 14 days after all this while keeping the stock solutions at 18°C.

As depicted below, we provide in each cases the reaction involved along with, when relevant, hypothetical structures corresponding to some additional mass peak detected. This is followed by the HPLC profiles, as detected by UV at 254 nm, and the TIC profile (mass between 180 and 800) along with the corresponding spectra obtained from the main HPLC peak as well as the lesser one. The first set corresponds to the analysis right after the hydrolysis, the second corresponds to the same analysis but after leaving the mother solution standing at 18°C for 16 hours.
The HPLC profile were obtained on an Agilent 1200 series LC/MSD system using an Agilent Jet-Stream atmospheric electrospray ionization system, with a 3.5 µm XDB-C18 column and a water / acetonitrile gradient (containing 5 mM ammonium formate, from 95-5 to 5-95 in 3.5 min and then 3.5 min back at 5-95) UV monitoring set at 254 nM.

Hydrolysis products of hikarazine-1 (**25{*1,1,37*}**)



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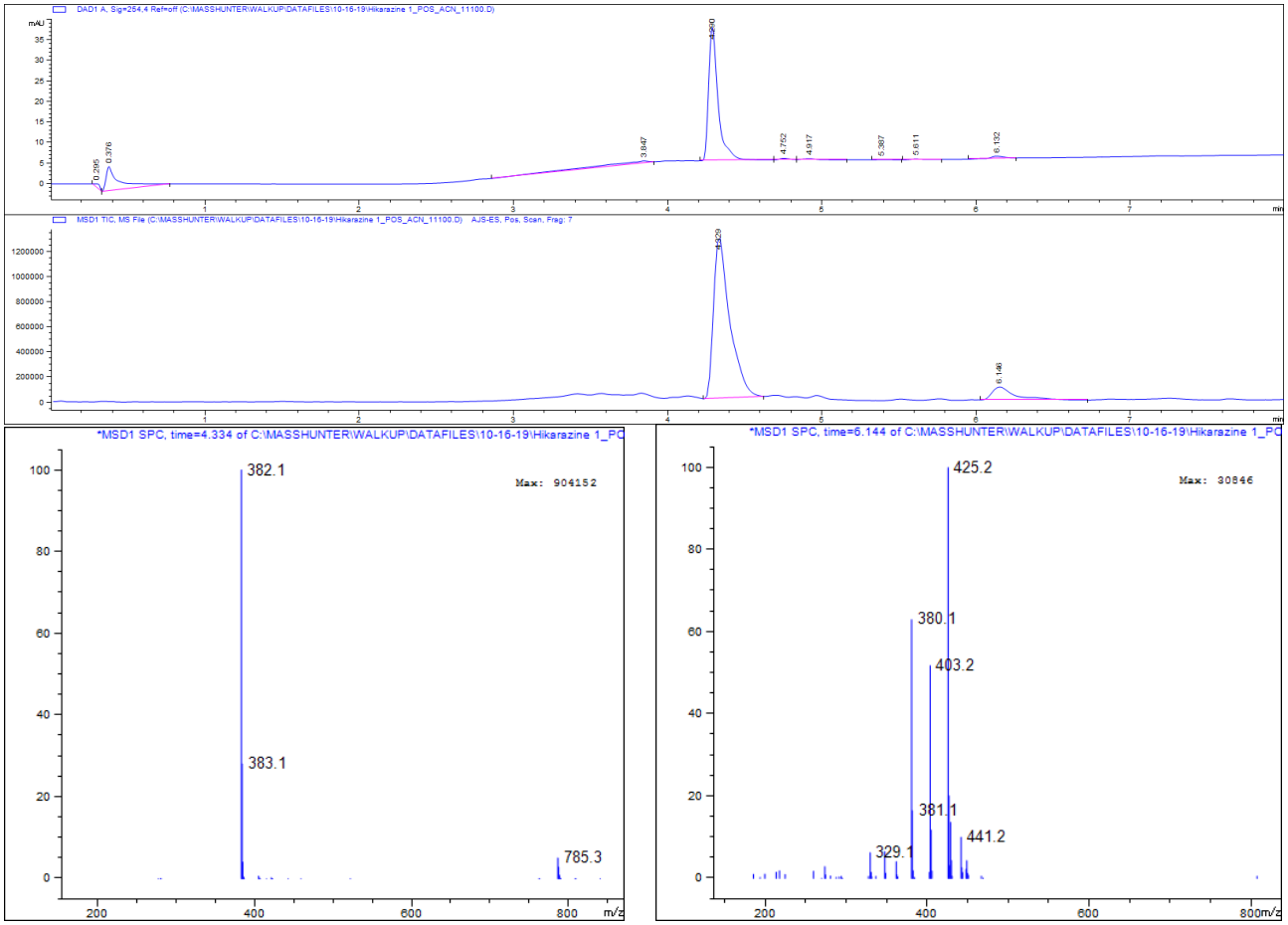
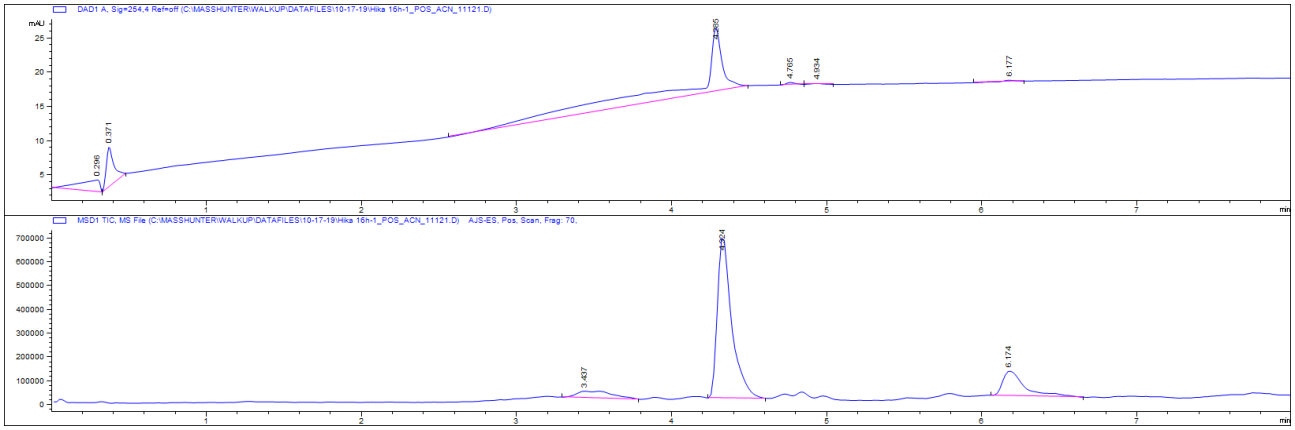


t = 16h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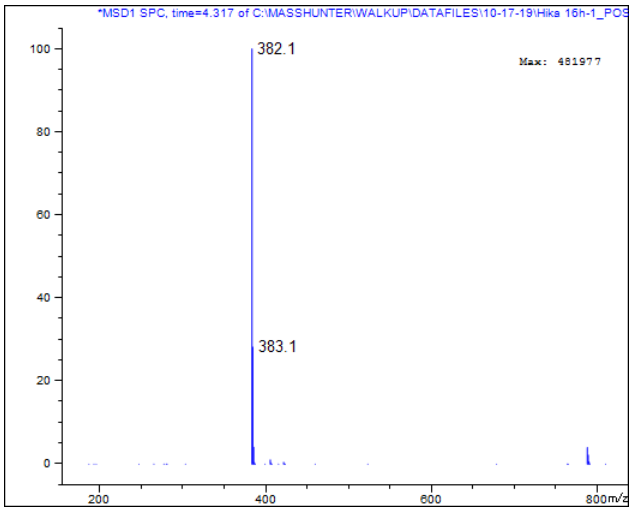
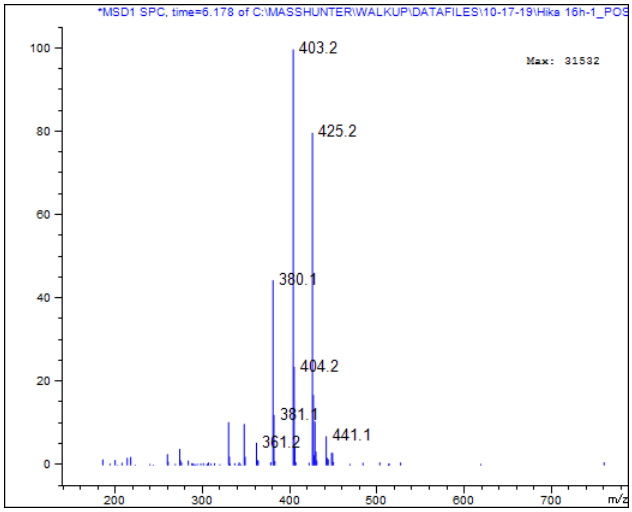
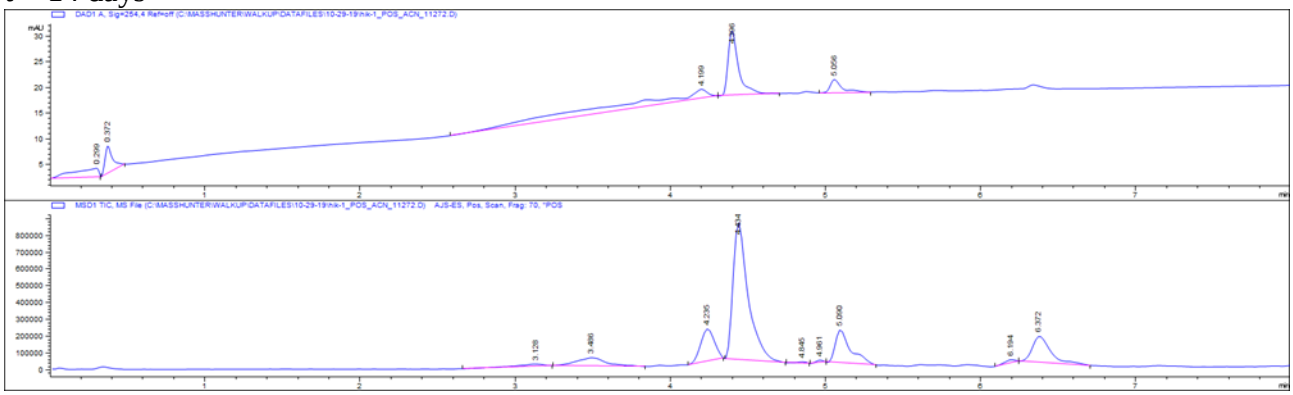
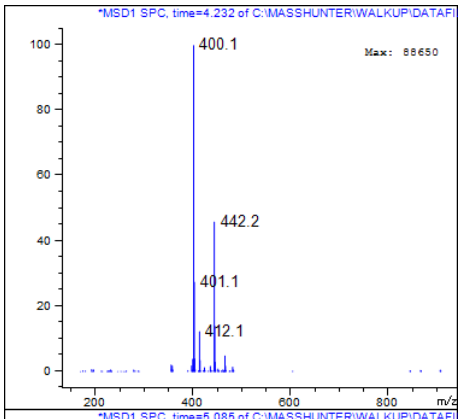
mAU
0.296
0.371
4.765
4.934
6.177
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-1_POS_ACN_11121.D) AJS-ES, Pos, Scan, Frag: 70.
3.427
6.174
min


*MSD1 SPC, time=4.317 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-1_POS
382.1
Max: 481977
383.1
m/z


*MSD1 SPC, time=6.178 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-1_POS
403.2
Max: 31532
425.2
380.1
404.2
381.1
361.2
441.1
m/z

t = 14 days

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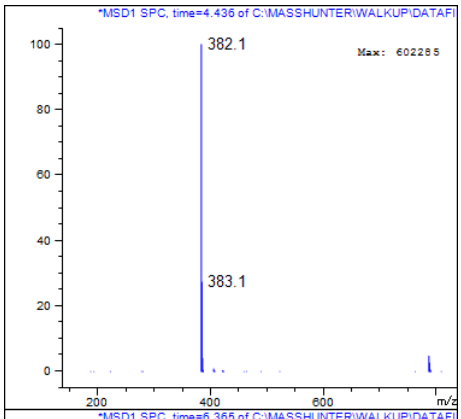
400.1
Max: 88650
442.2
401.1
412.1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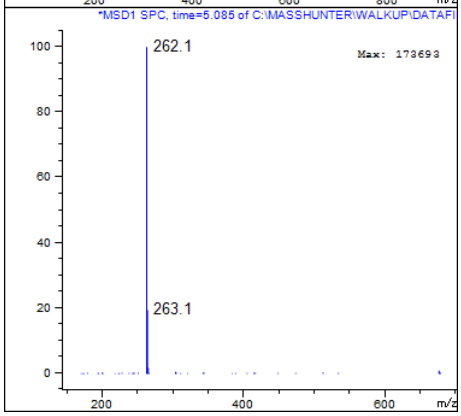
382.1
Max: 602285
383.1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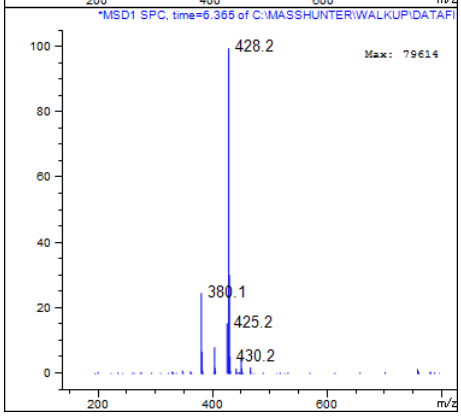
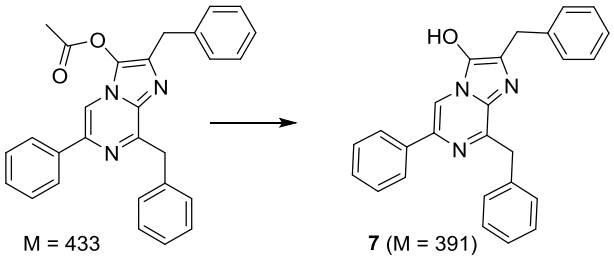
262.1
Max: 173693
263.1

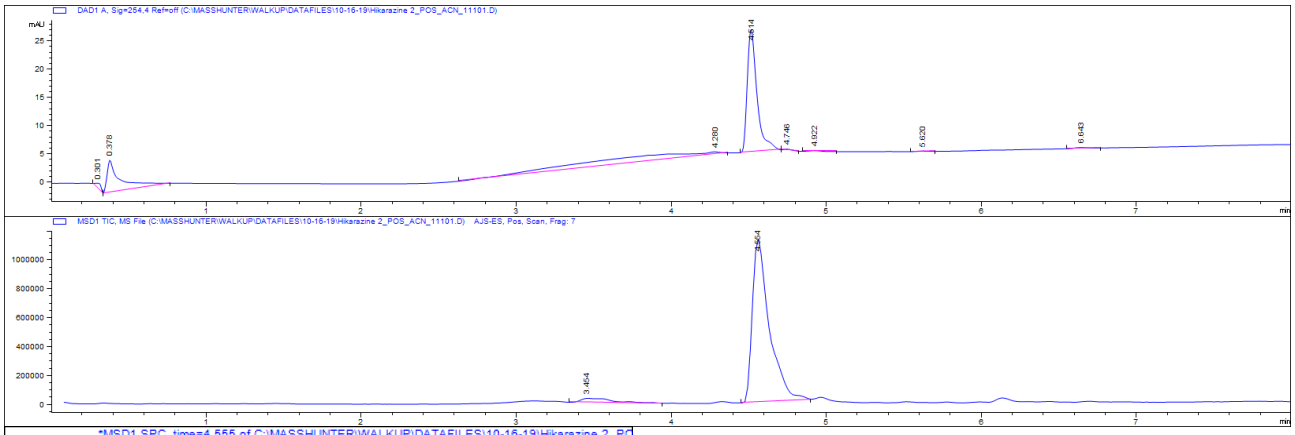

*MSD1 SPC, time=6.365 of C:\MASSHUNTER\WALKUP\DATAFI
428.2
Max: 79614
380.1
425.2
430.2

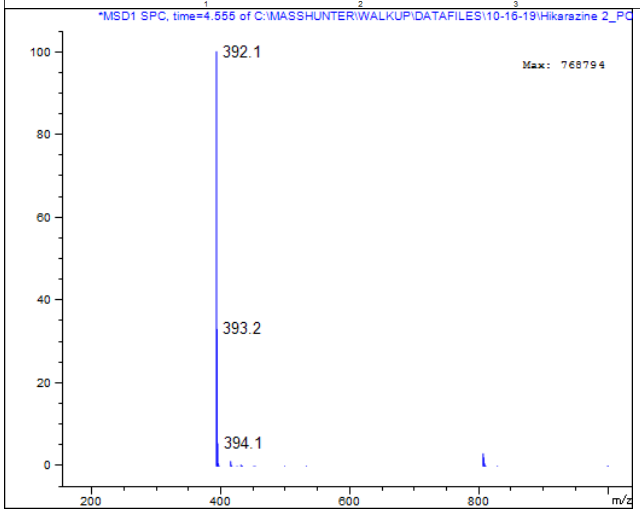
Hydrolysis products of hikarazine-2 (**25{*1,1,1*}**)



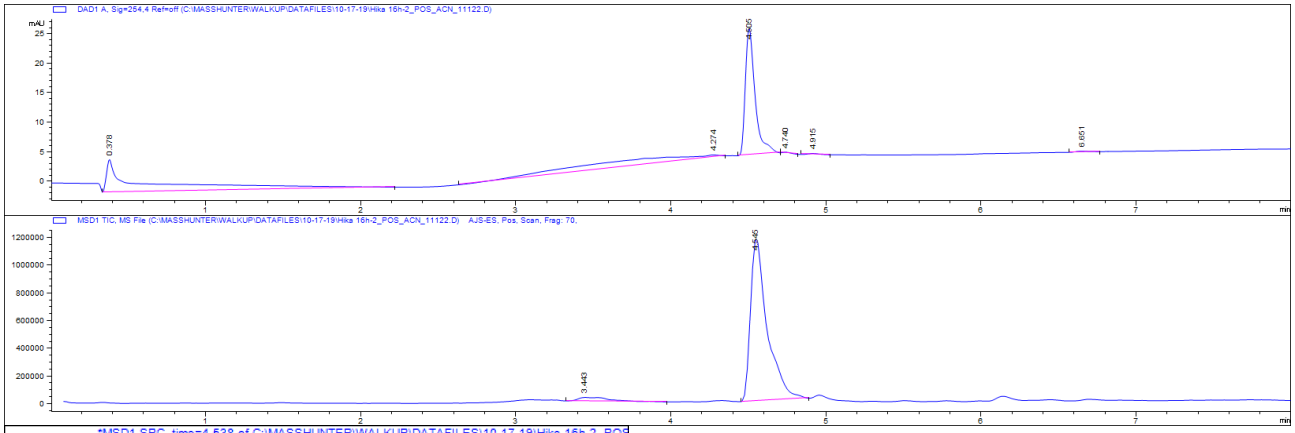
M = 433 **7** (M = 391)

t = 0





t = 16h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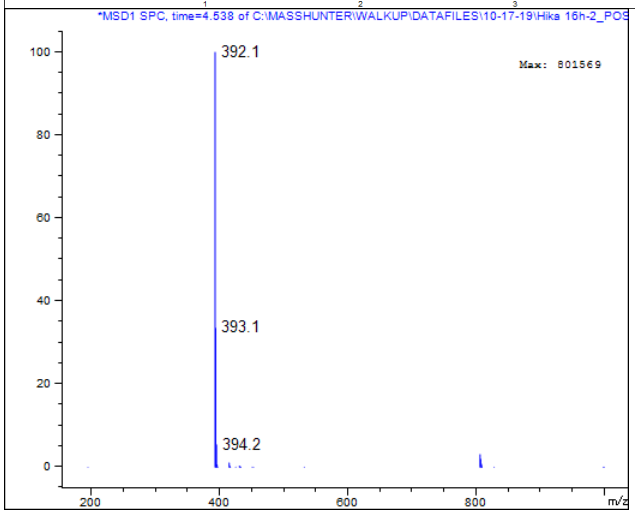
mAU
0.378
4.274
4.505
4.740
4.915
6.661
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-2_POS_ACN_11122.D) AJS-ES, Pos, Scan, Frag: 70.
3.443
4.545
min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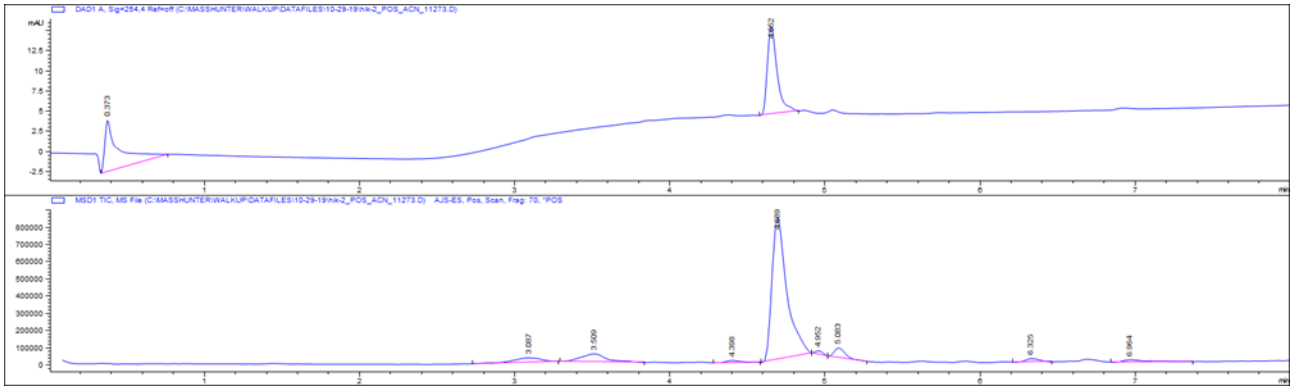
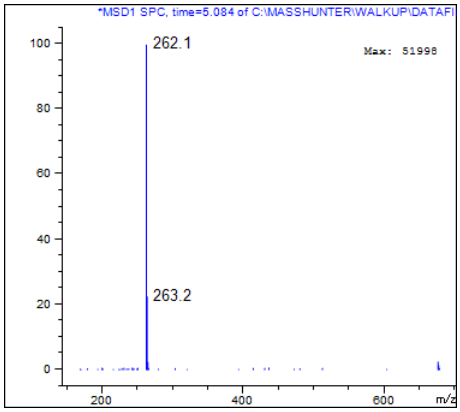
Max: 801569
392.1
393.1
394.2
m/z

t = 14 days

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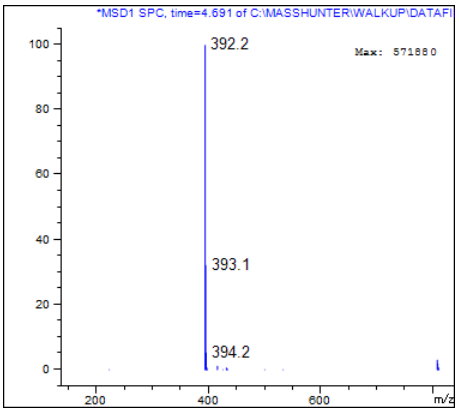
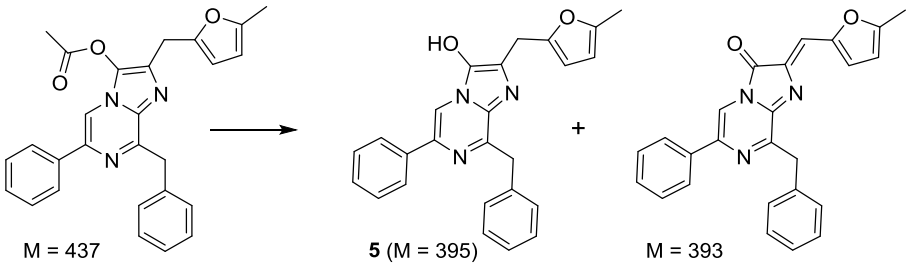
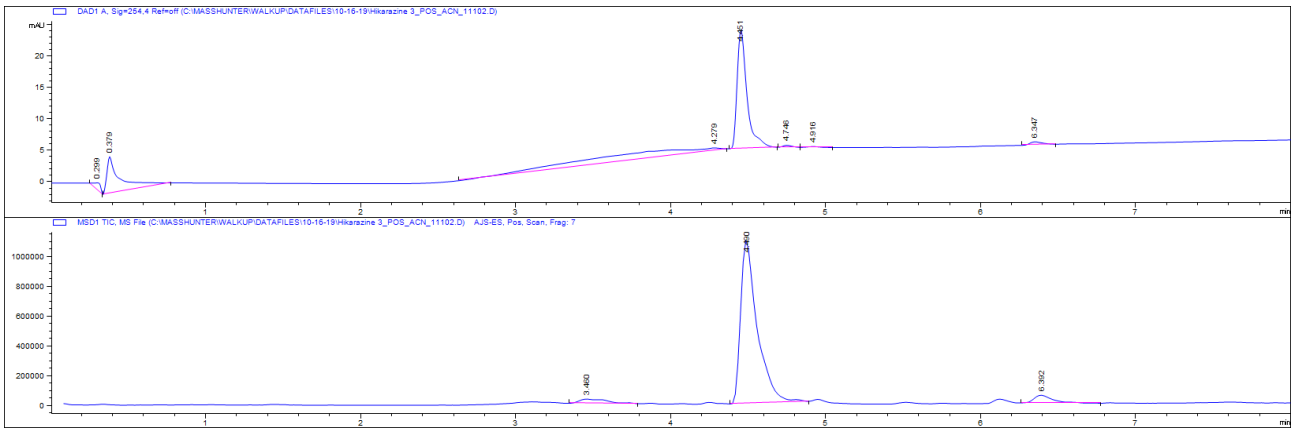
262.1
Max: 51998
263.2
100
80
60
40
20
0
200
400
600
m/z

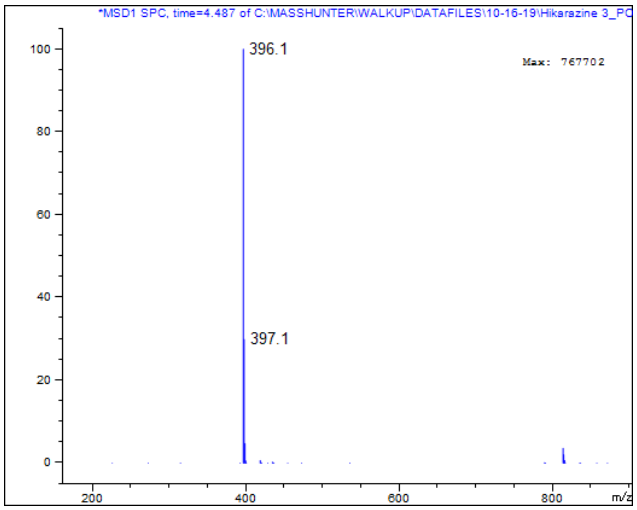

*MSD1 SPC, time=4.691 of C:\MASSHUNTER\WALKUP\DATAFI
392.2
Max: 571880
393.1
394.2
100
80
60
40
20
0
200
400
600
m/z

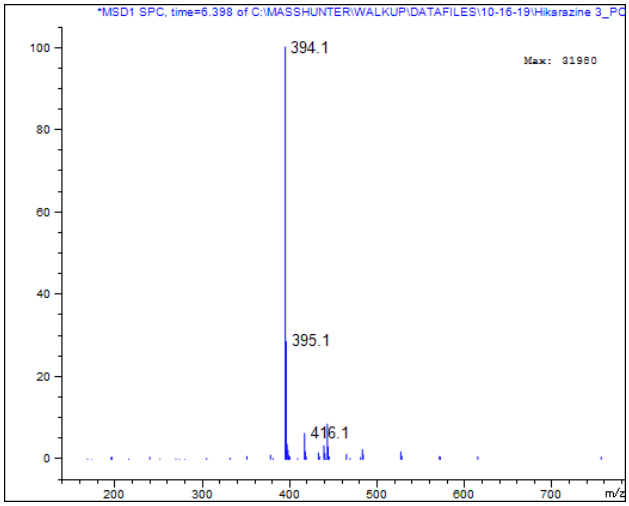
Hydrolysis products of hikarazine-3 (**25{*1,1,42*}**)



t = 0







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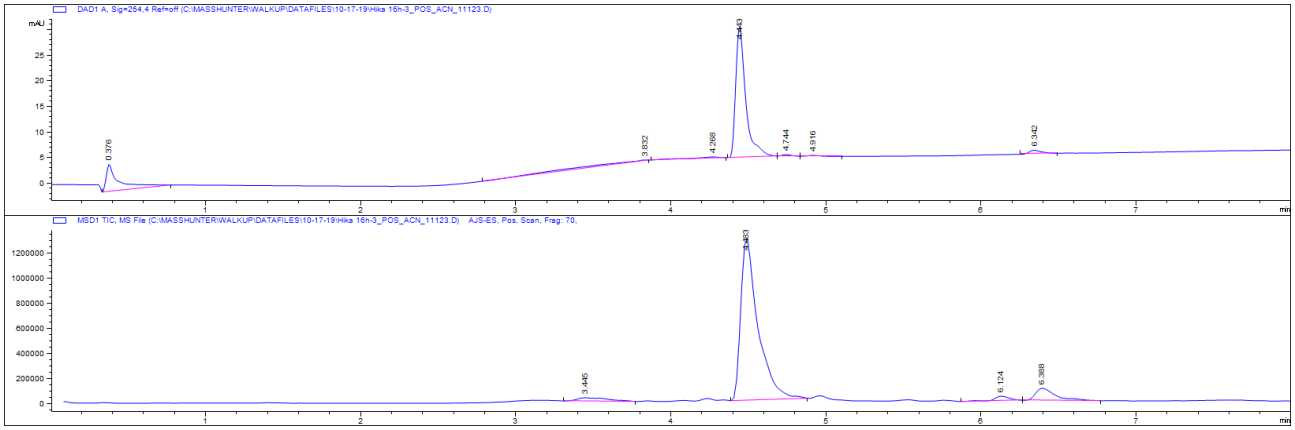
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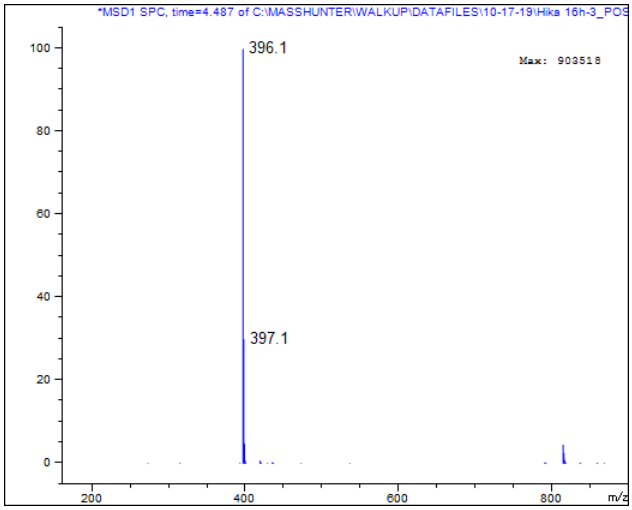
mAU
0.376
3.832
4.268
4.443
4.744
4.916
6.342
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-3_POS_ACN_11123.D) AJS-ES, Pos, Scan, Frag: 70.
3.445
4.453
6.124
6.388
min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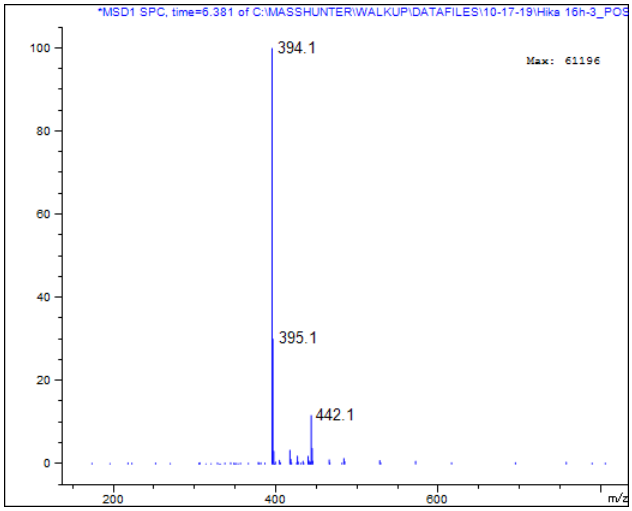
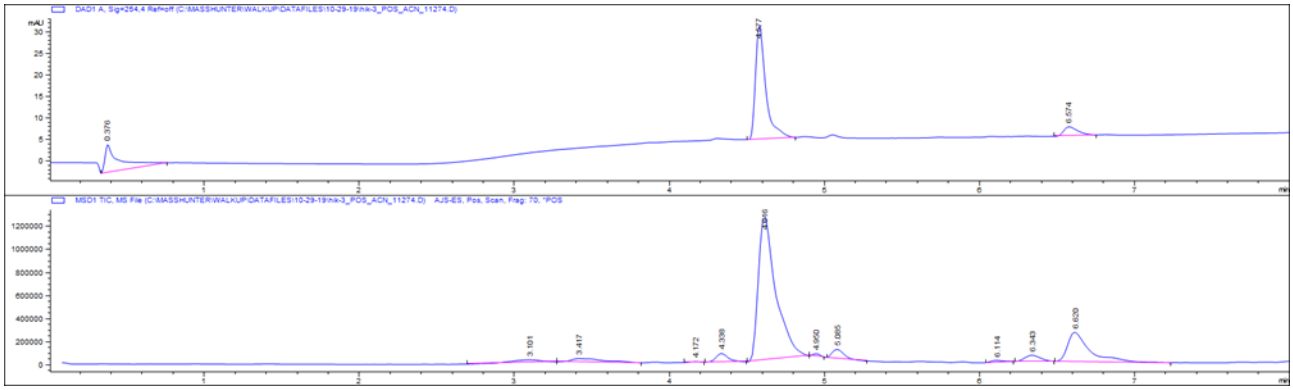
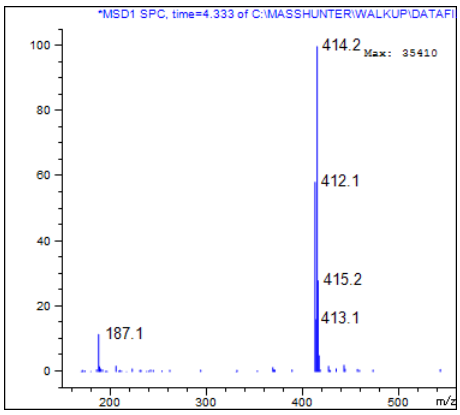
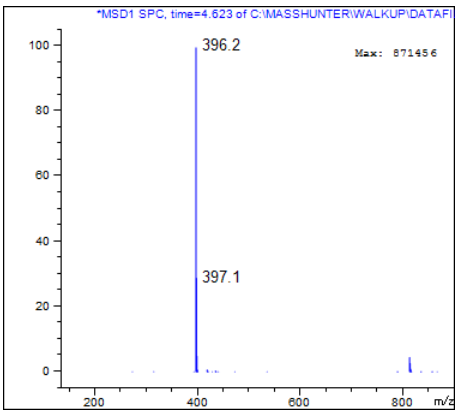
396.1
397.1
m/z

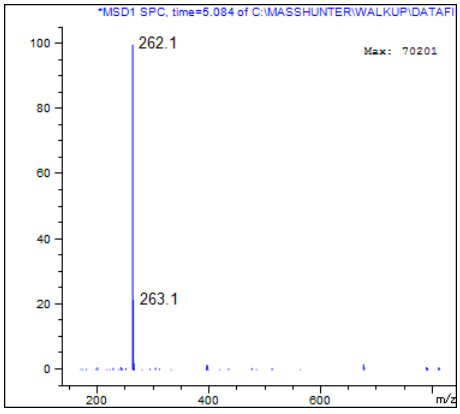

*MSD1 SPC, time=6.381 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-3_POS
Max: 61196
394.1
395.1
442.1
m/z

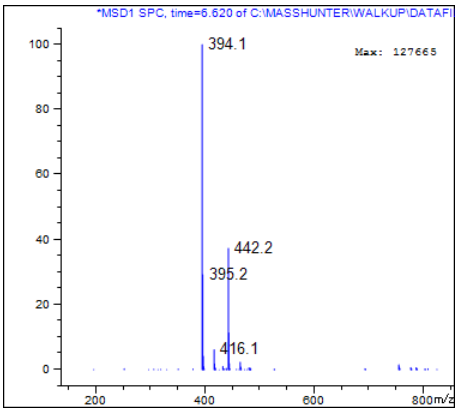
t = 14 days



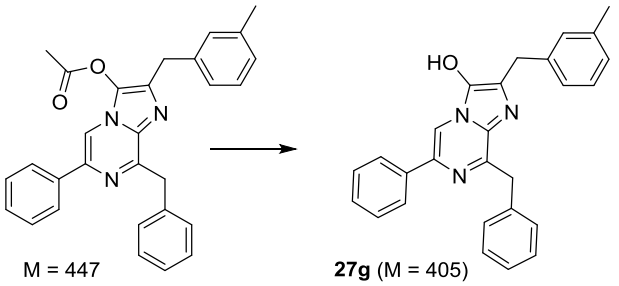

*MSD1 SPC, time=4.333 of C:\MASSHUNTER\WALKUP\DATAFI
414.2
Max: 35410
412.1
415.2
413.1
187.1
m/z


*MSD1 SPC, time=4.623 of C:\MASSHUNTER\WALKUP\DATAFI
396.2
Max: 871456
397.1
m/z


*MSD1 SPC, time=5.084 of C:\MASSHUNTER\WALKUP\DATAFI
262.1
Max: 70201
263.1
m/z

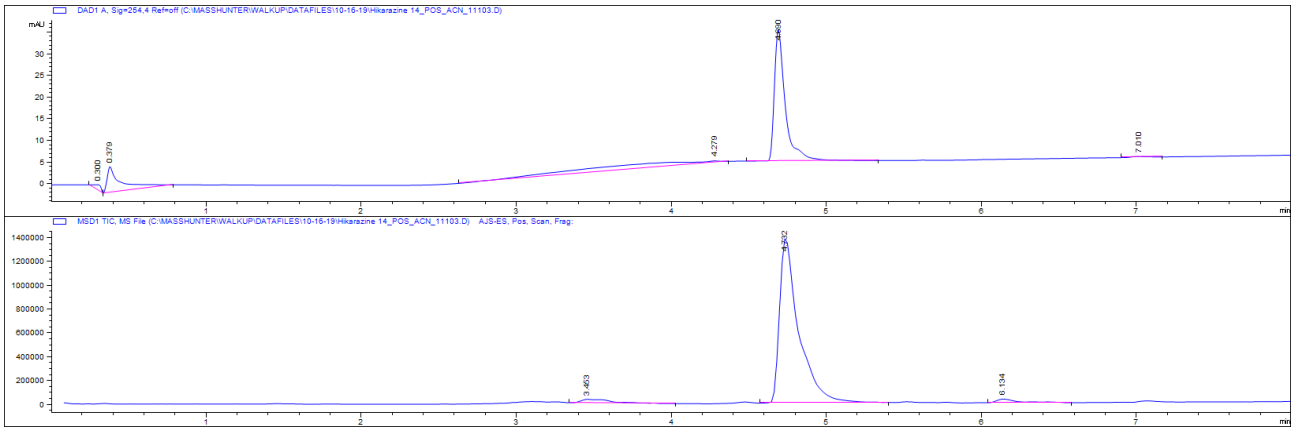

*MSD1 SPC, time=6.620 of C:\MASSHUNTER\WALKUP\DATAFI
394.1
Max: 127665
442.2
395.2
416.1
m/z

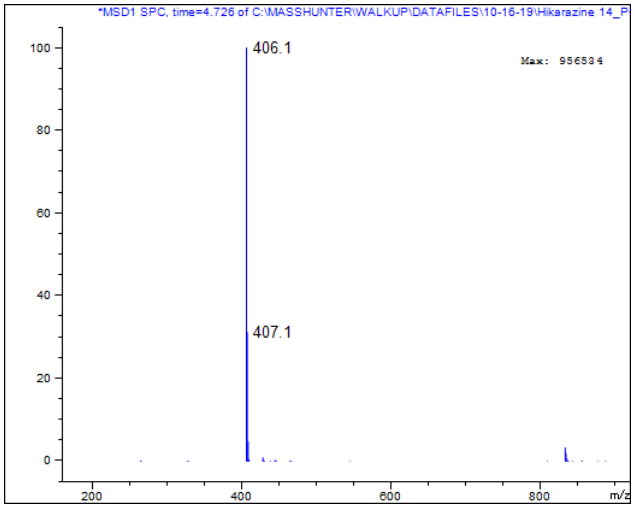
Hydrolysis products of hikarazine-14 (**25{*1,1,12*}**)



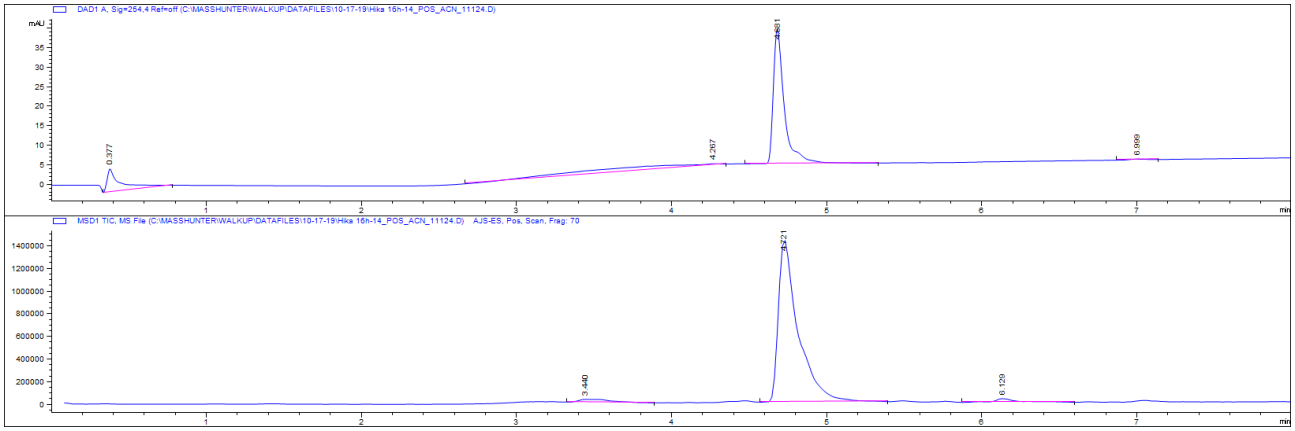
M = 447 **27g** (M = 405)

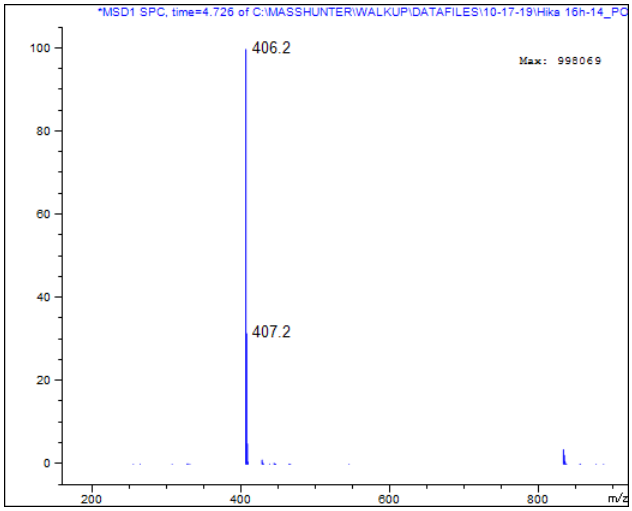
t = 0



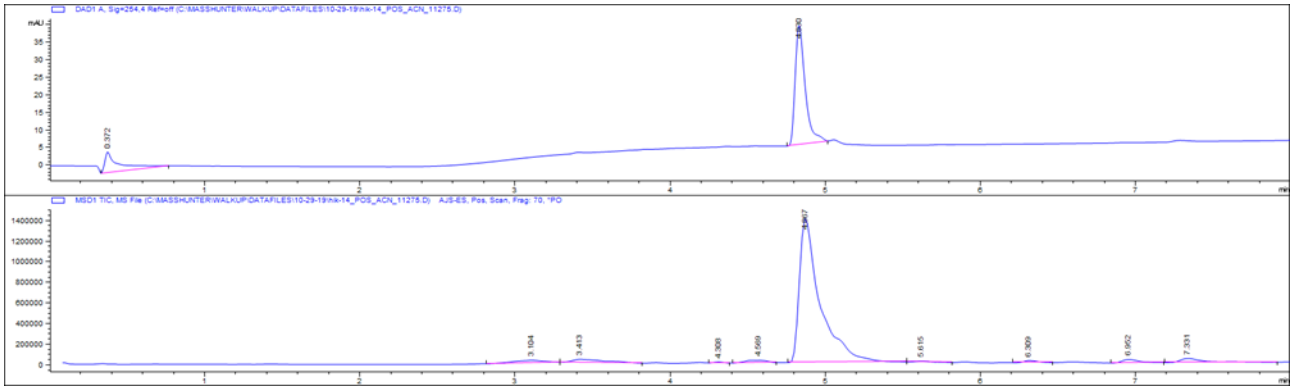


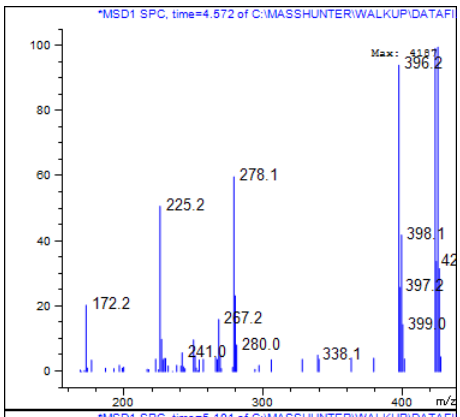
t = 16h

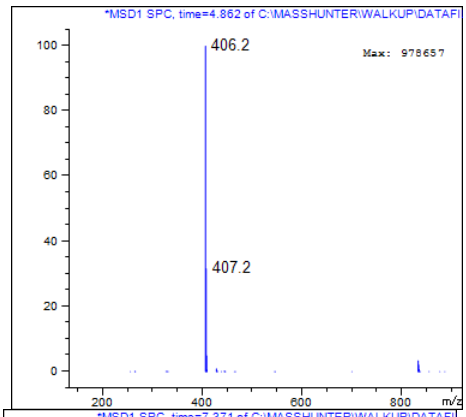

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-14_POS_ACN_11124.D)
mAU
0.377
4.267
4.681
6.999
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-14_POS_ACN_11124.D) AJS-ES, Pos, Scan, Frag: 70
3.440
4.721
6.129
min

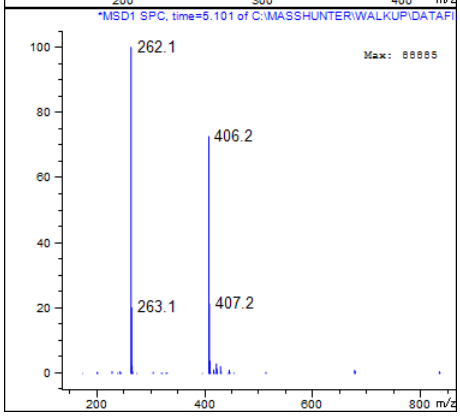

*MSD1 SPC, time=4.726 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-14_PO
406.2
Max: 998069
407.2
m/z

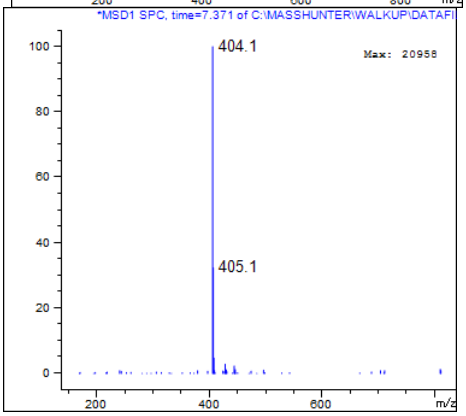
t = 14 days



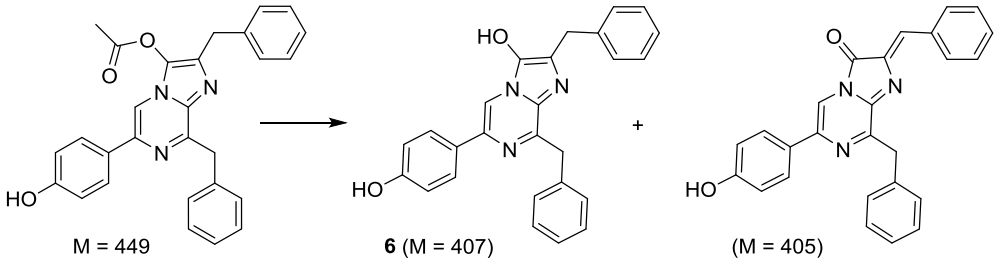

*MSD1 SPC, time=4.572 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 4187
396.2
278.1
225.2
398.1
397.2
399.0
172.2
267.2
280.0
241.0
338.1
m/z


*MSD1 SPC, time=4.862 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 978657
406.2
407.2
m/z


*MSD1 SPC, time=5.101 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 88885
262.1
406.2
263.1
407.2
m/z

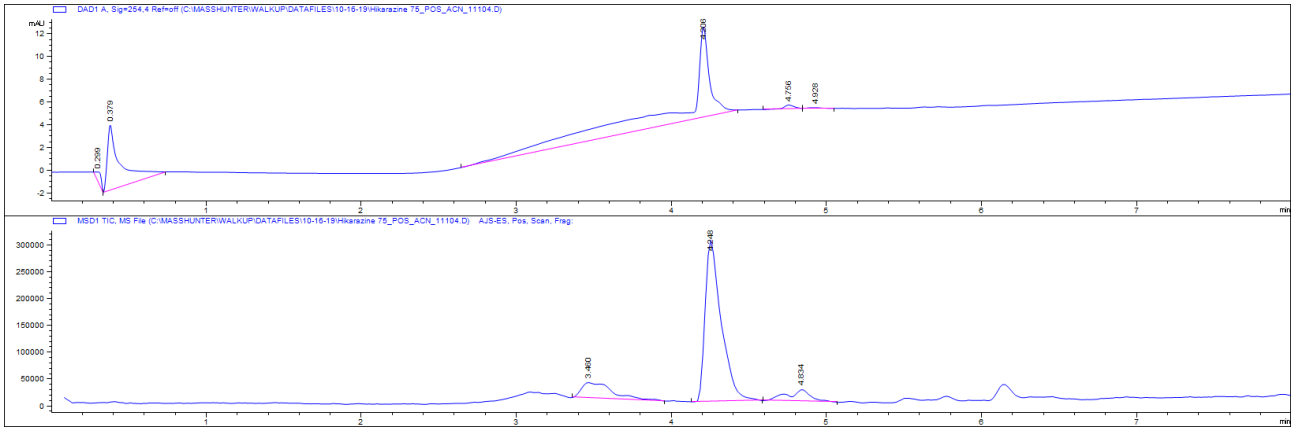

*MSD1 SPC, time=7.371 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 20958
404.1
405.1
m/z

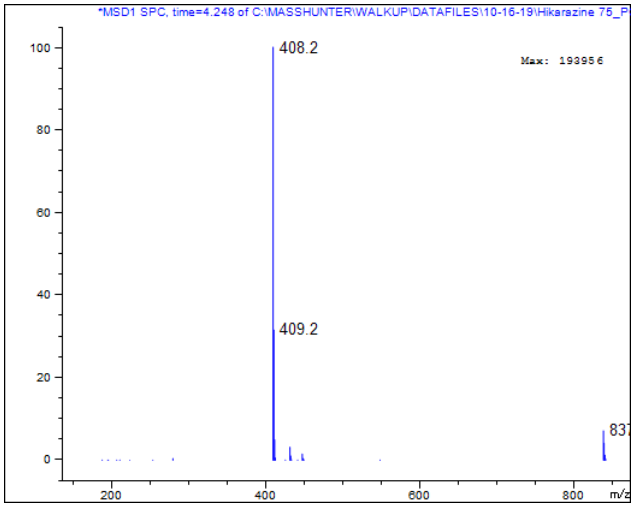
Hydrolysis products of hikarazine-75 (**25{*14,1,1*}**)



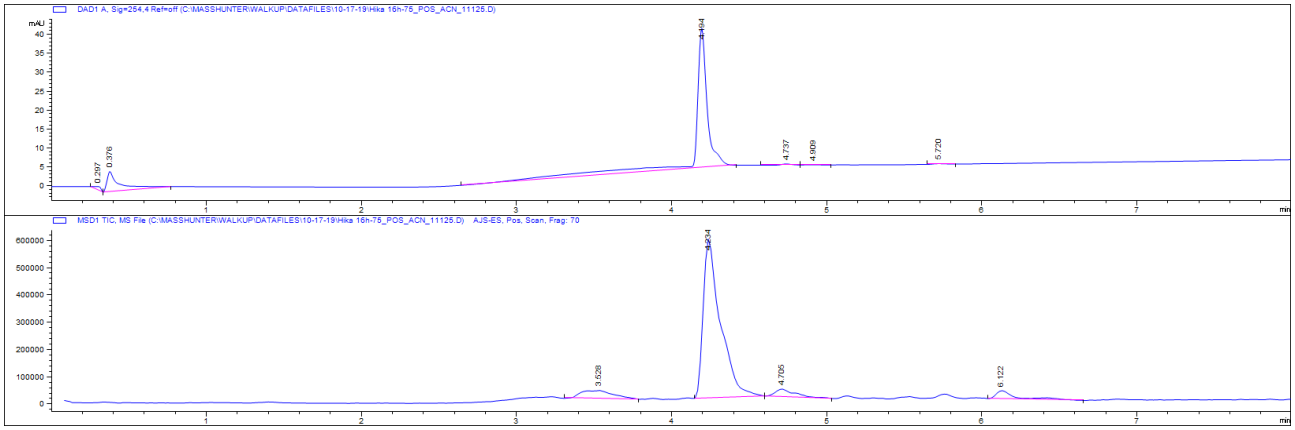
M = 449 **6** (M = 407) (M = 405)

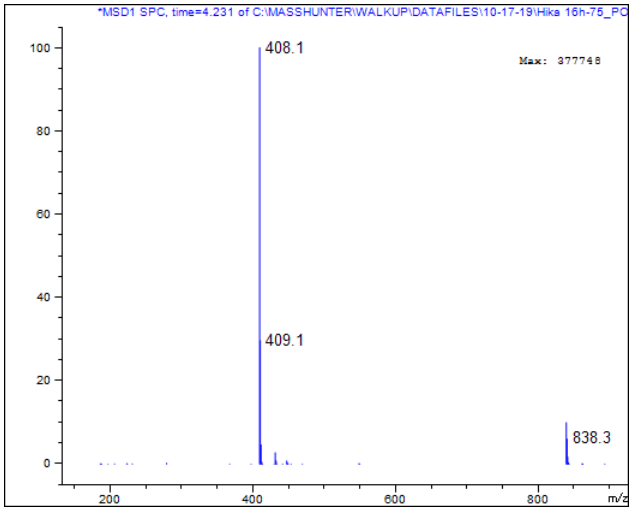
t = 0

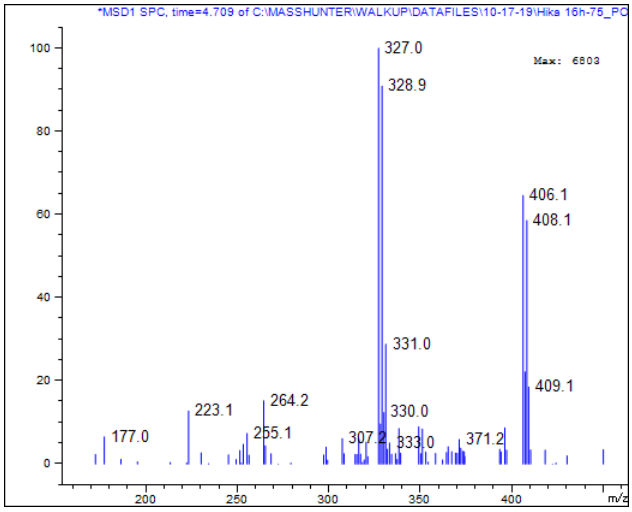




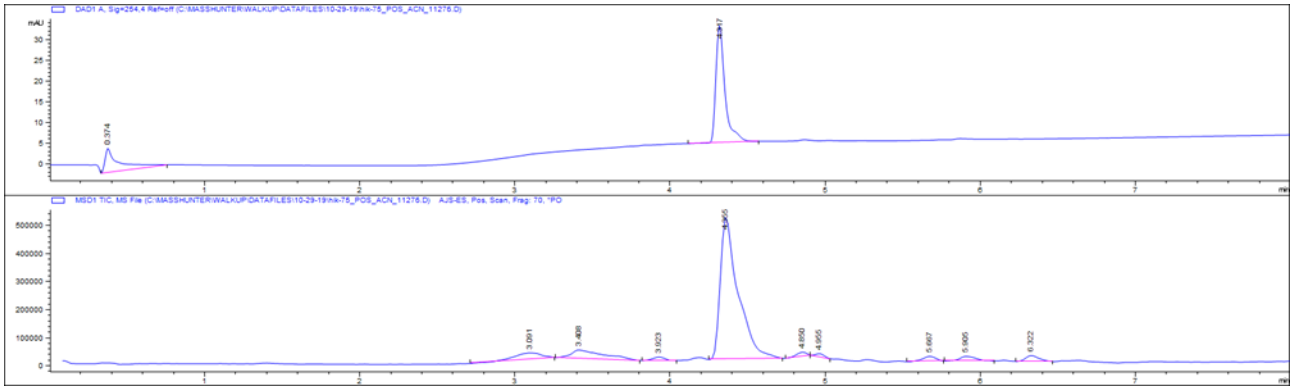
t = 16h

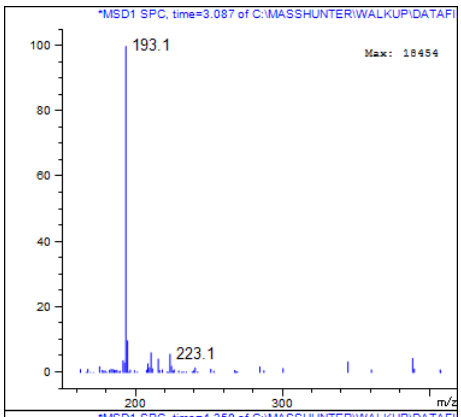

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hka 16h-75_POS_ACN_11125.D)
mAU
0.297
0.376
4.737
4.909
5.720
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hka 16h-75_POS_ACN_11125.D) AJS-ES, Pos, Scan, Frag: 70
3.528
4.705
6.122
min

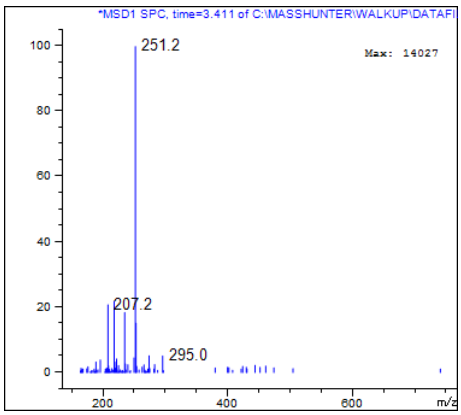

*MSD1 SPC, time=4.231 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hka 16h-75_PC
Max: 377748
408.1
409.1
838.3
m/z

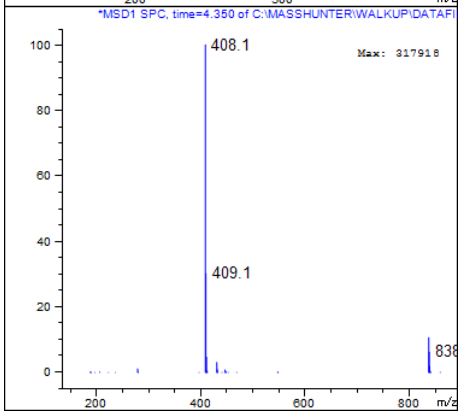

*MSD1 SPC, time=4.709 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hka 16h-75_PC
Max: 6803
327.0
328.9
406.1
408.1
331.0
409.1
223.1
264.2
330.0
177.0
255.1
307.2
333.0
371.2
m/z

t = 14 days

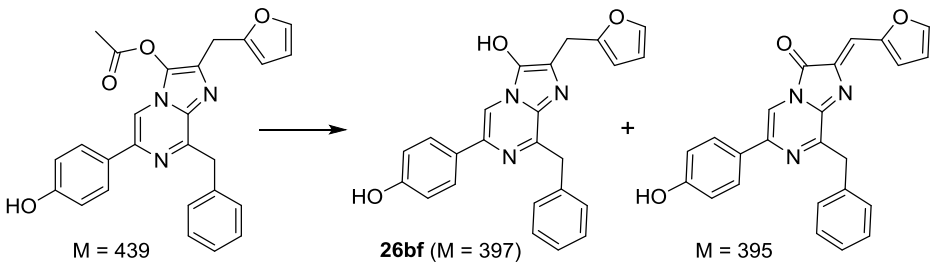



*MSD1 SPC, time=3.087 of C:\MASSHUNTER\WALKUP\DATAFI
193.1
Max: 18454
223.1
m/z

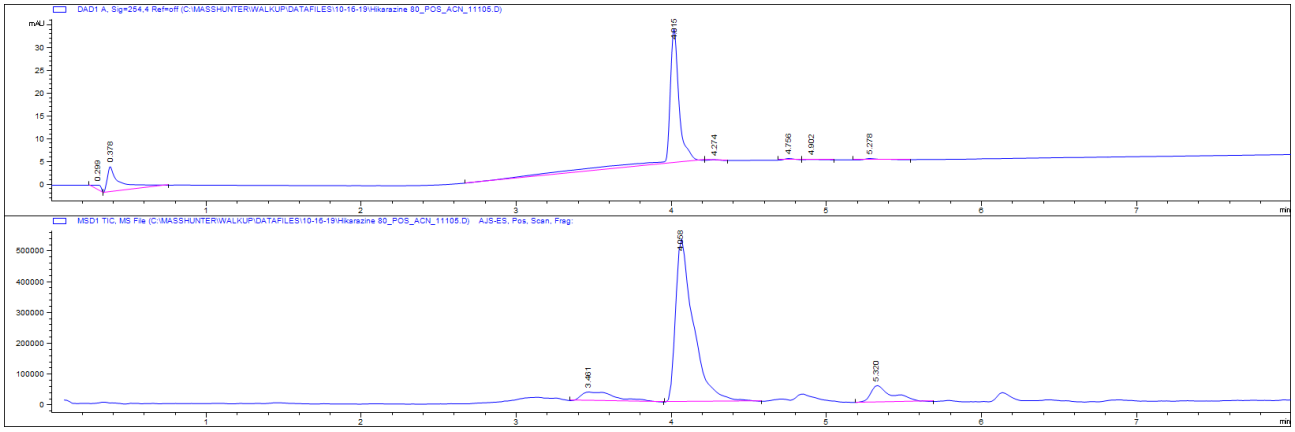

*MSD1 SPC, time=3.411 of C:\MASSHUNTER\WALKUP\DATAFI
251.2
Max: 14027
207.2
295.0
m/z

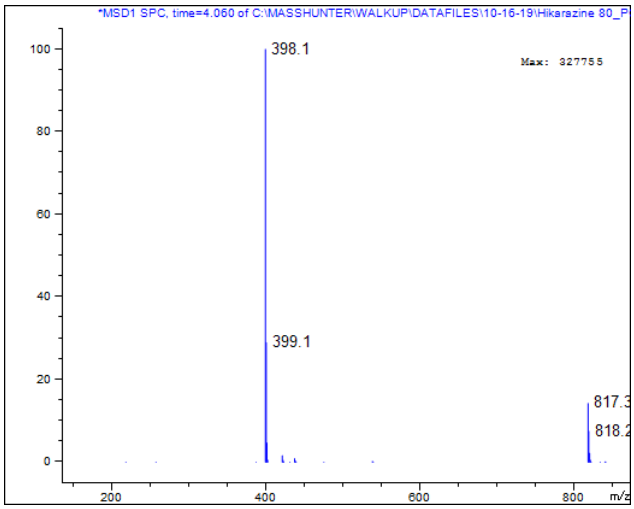

*MSD1 SPC, time=4.350 of C:\MASSHUNTER\WALKUP\DATAFI
408.1
Max: 317918
409.1
m/z

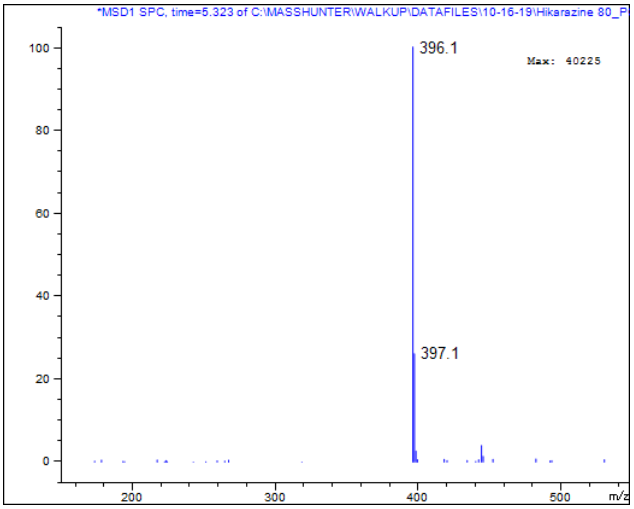
Hydrolysis products of hikarazine-80 (**25{*14,1,37*}**)



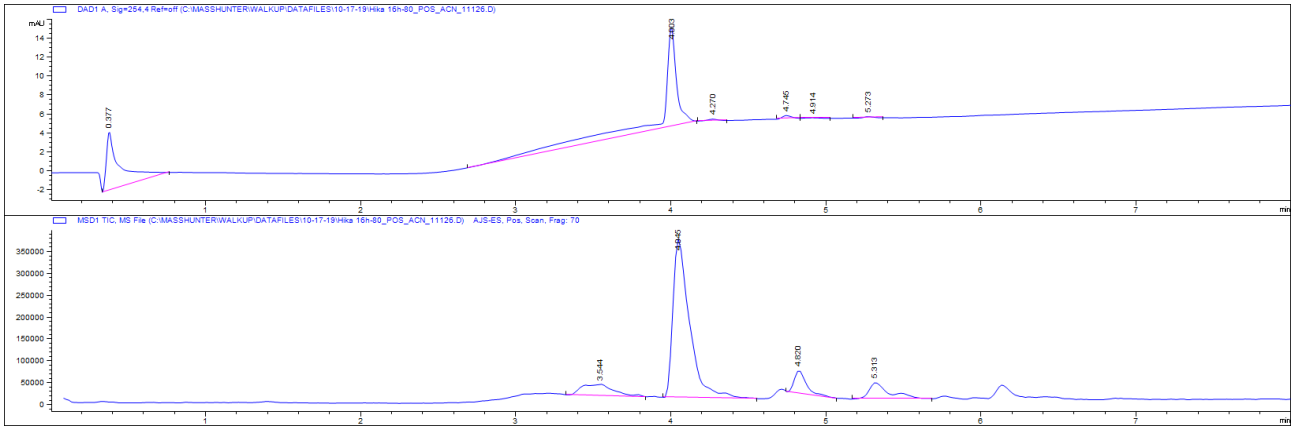
t = 0

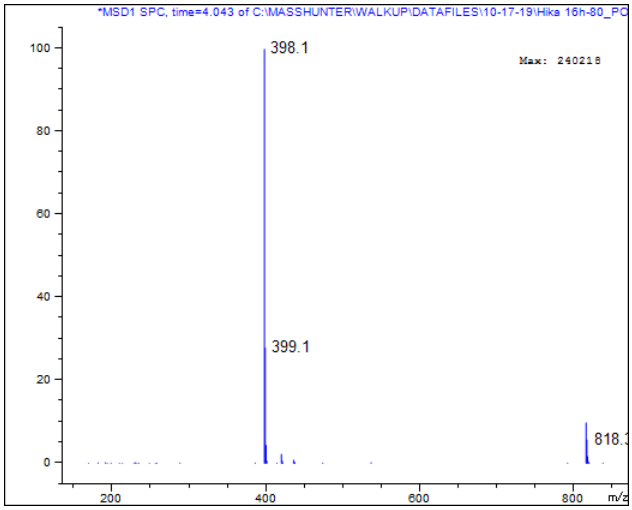


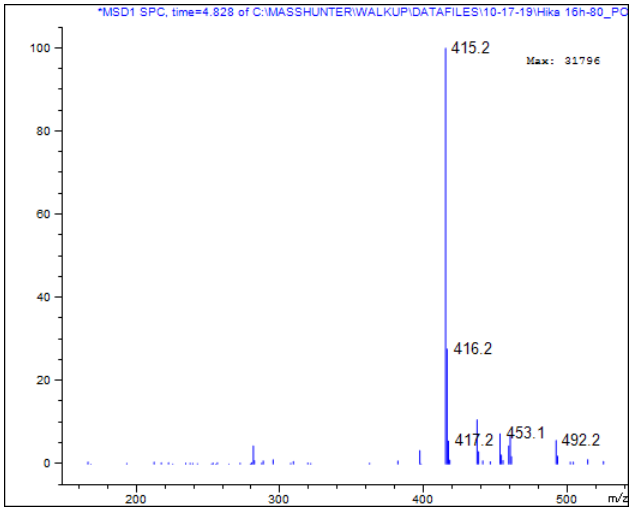


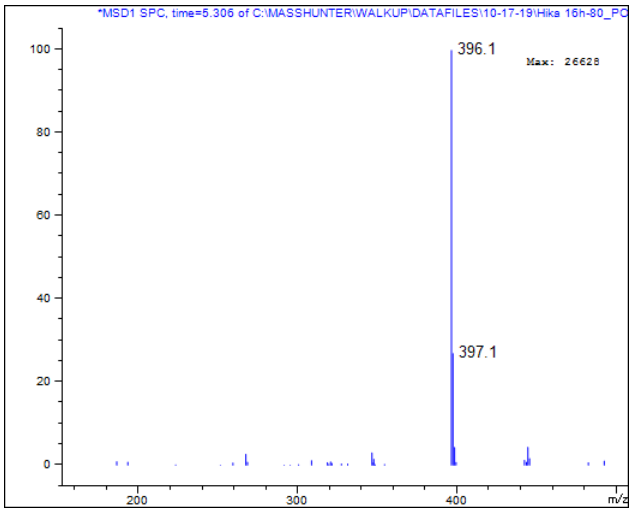


t = 16h

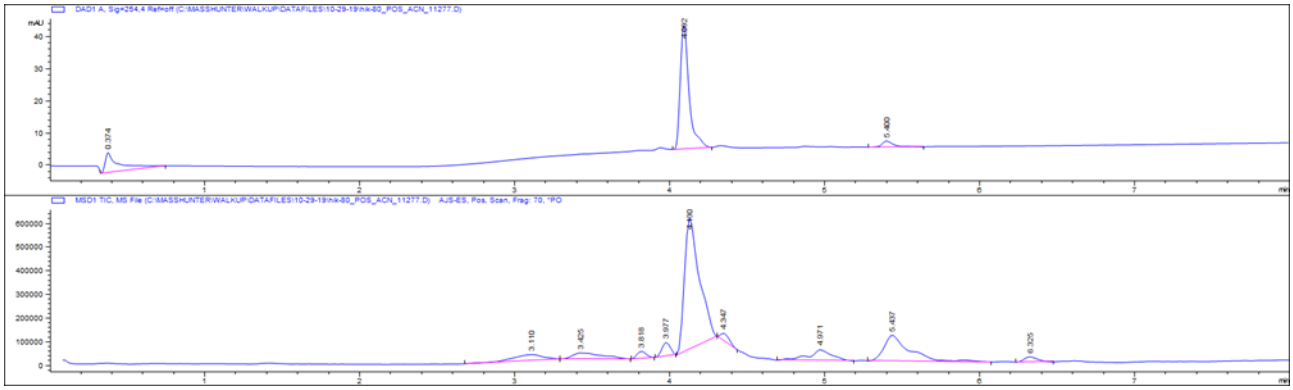

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-80_POS_ACN_11126.D)
mAU
0.377
4.270
4.745
4.914
5.273
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-80_POS_ACN_11126.D) AJS-ES, Pos, Scan, Frag: 70
3.544
4.620
5.313
min

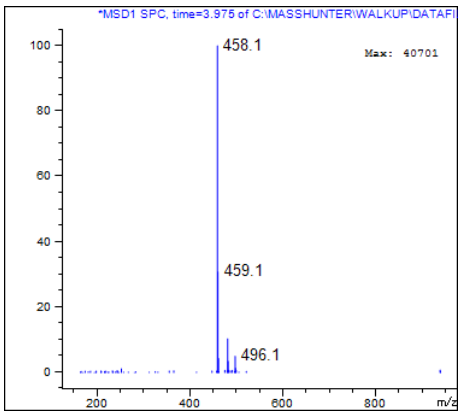

*MSD1 SPC, time=4.043 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-80_PC
Max: 240218
398.1
399.1
818.1
m/z

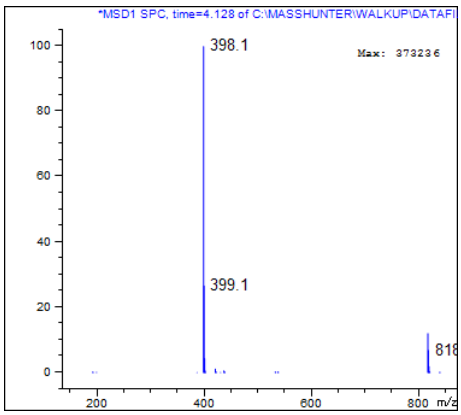

*MSD1 SPC, time=4.828 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-80_PC
Max: 31796
415.2
416.2
417.2
453.1
492.2
m/z

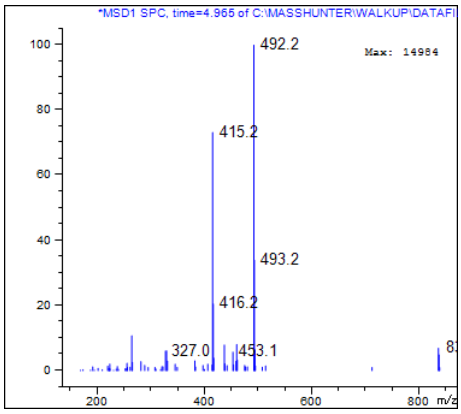

*MSD1 SPC, time=5.306 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-80_PC
Max: 26628
396.1
397.1
m/z

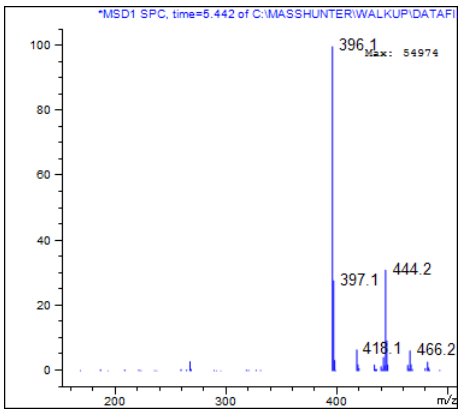
t = 14 days



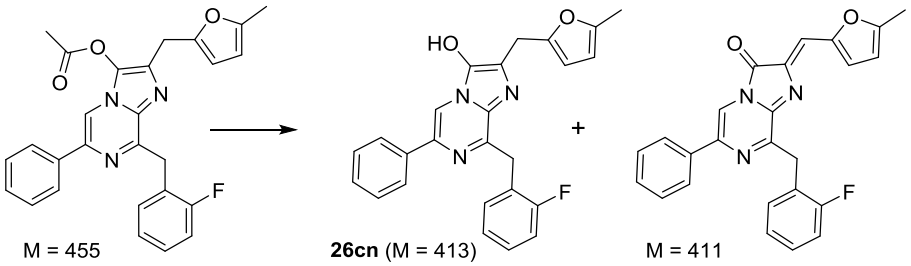

*MSD1 SPC, time=3.975 of C:\MASSHUNTER\WALKUP\DATAFI
458.1
Max: 40701
459.1
496.1


*MSD1 SPC, time=4.128 of C:\MASSHUNTER\WALKUP\DATAFI
398.1
Max: 373236
399.1

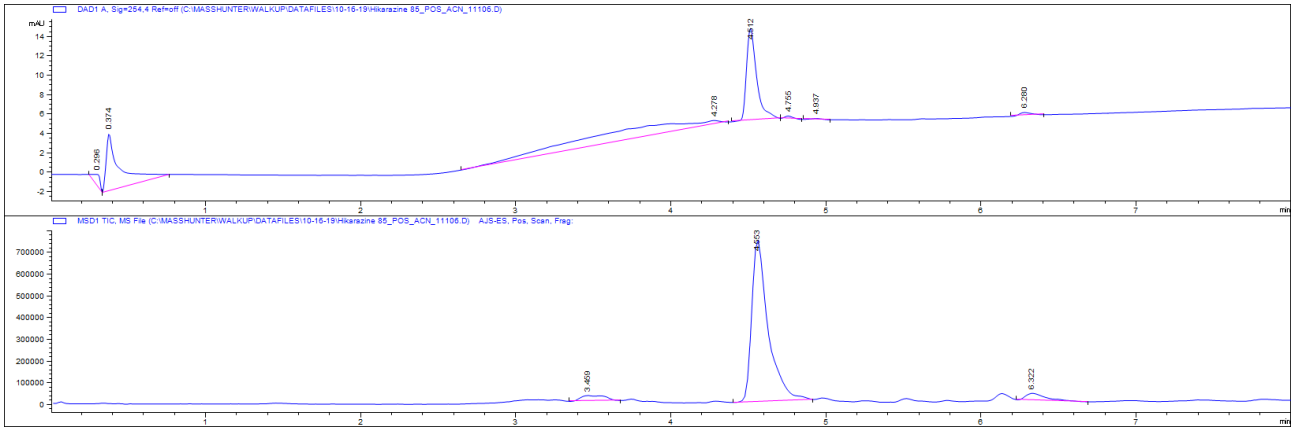

*MSD1 SPC, time=4.965 of C:\MASSHUNTER\WALKUP\DATAFI
492.2
Max: 14984
415.2
493.2
416.2
327.0
453.1

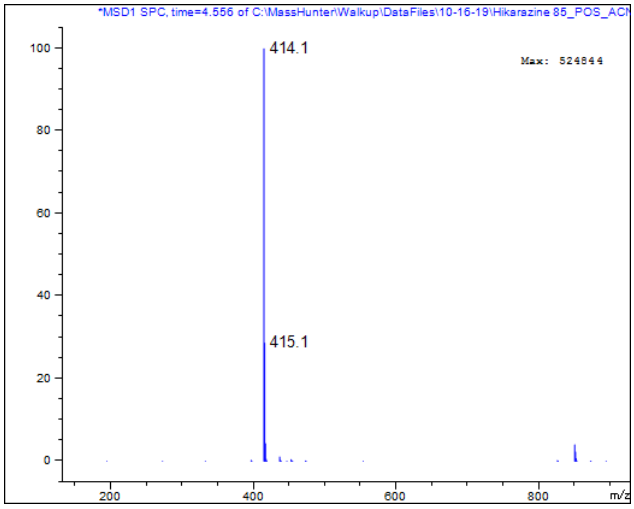

*MSD1 SPC, time=5.442 of C:\MASSHUNTER\WALKUP\DATAFI
396.1
Max: 54974
397.1
444.2
418.1
466.2

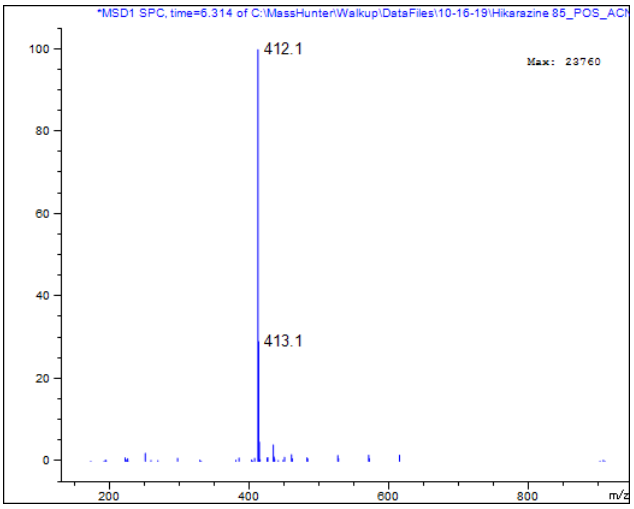
Hydrolysis products of hikarazine-85 (**25**{*1,2,42*})



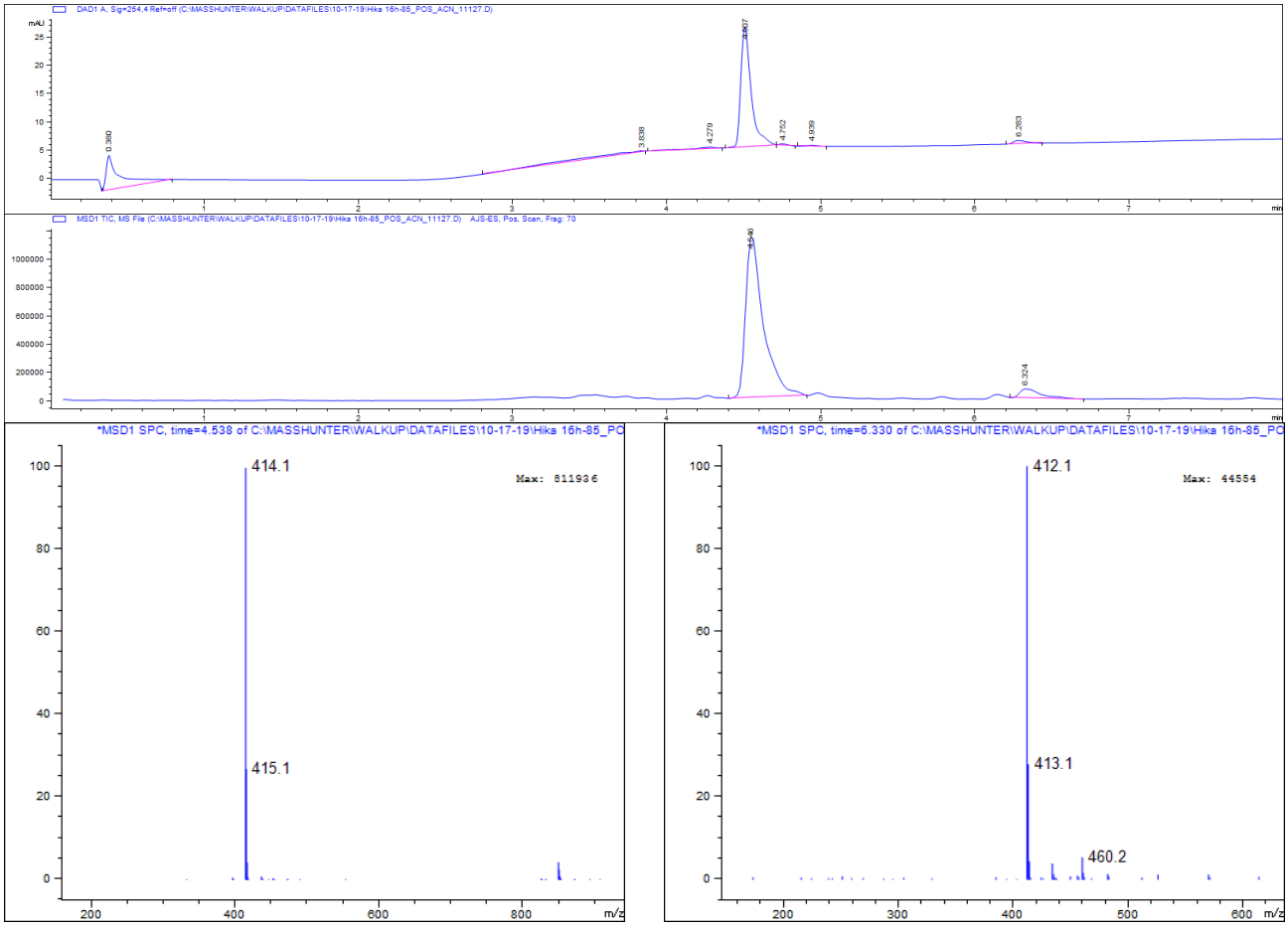
t = 0



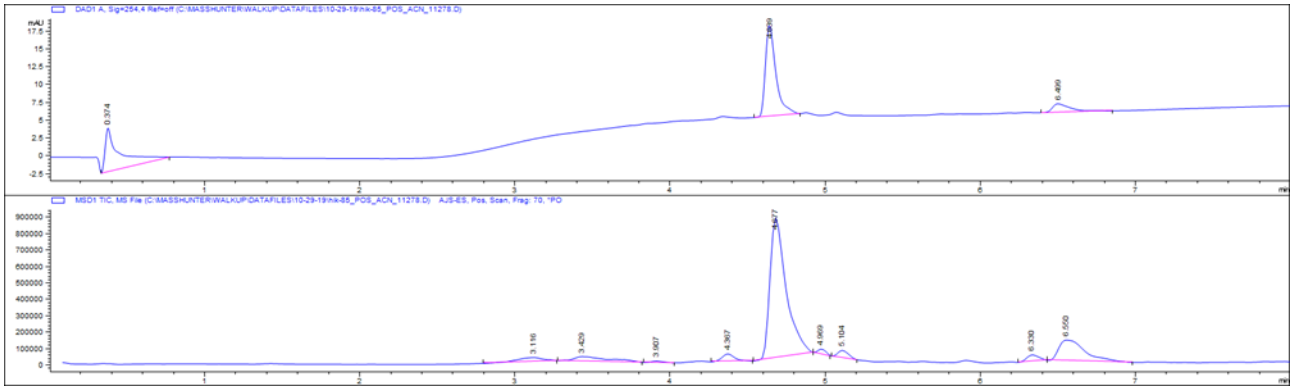


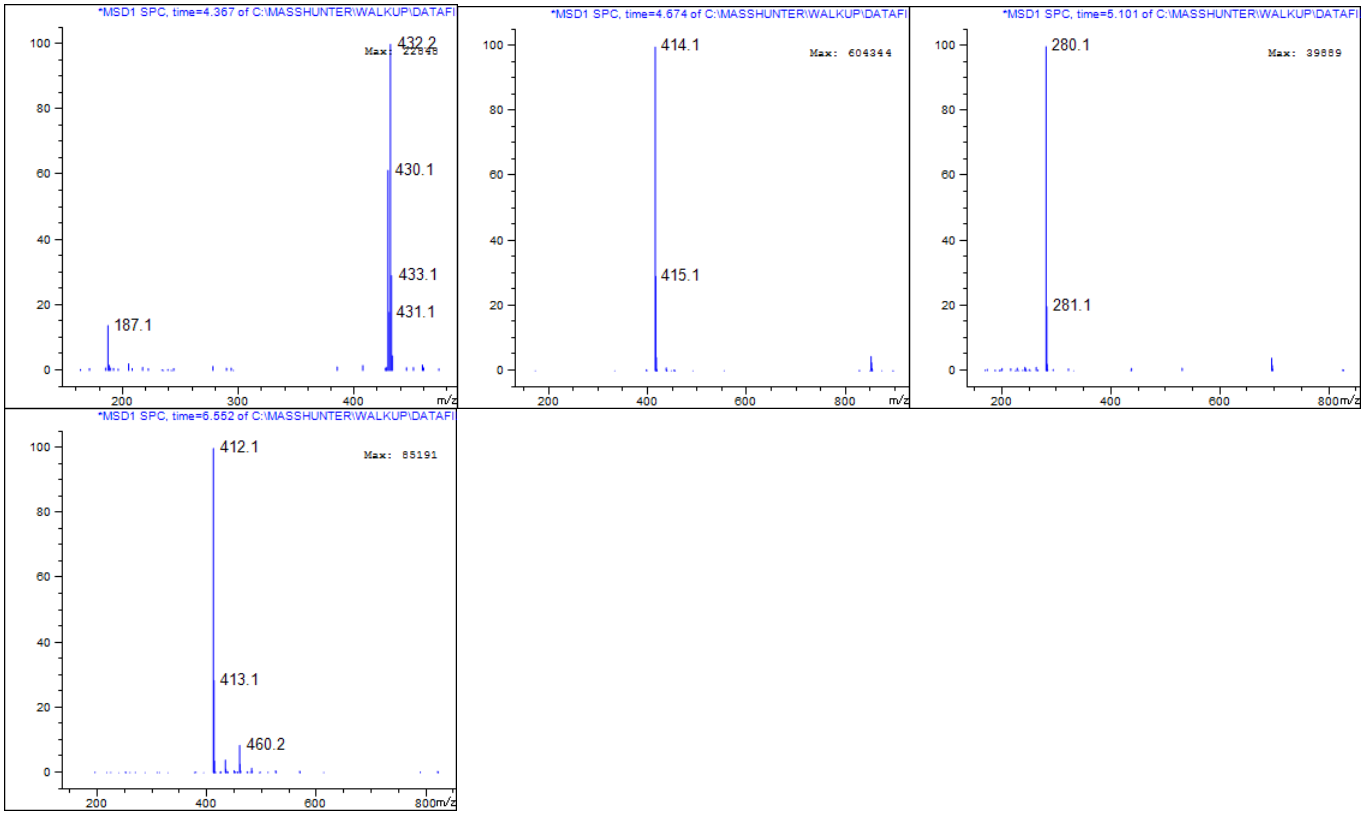


t = 16h

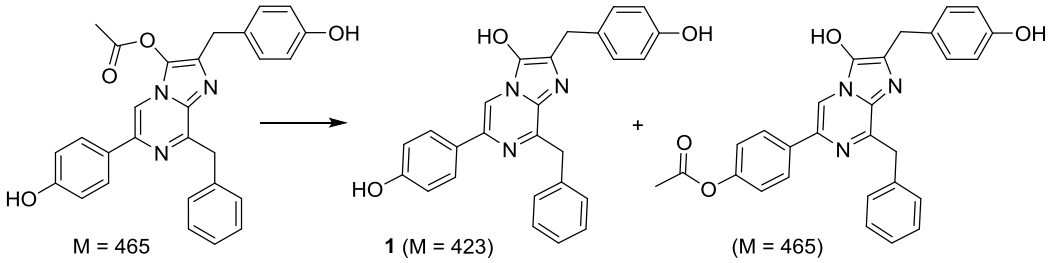

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-85_POS_ACN_11127.D)
mAU
0.360
3.838
4.279
4.907
4.752
4.939
6.263
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-85_POS_ACN_11127.D) AJS-ES, Pos, Scan, Frag: 70
4.546
6.324
*MSD1 SPC, time=4.538 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-85_PC
414.1
Max: 811936
415.1
m/z
*MSD1 SPC, time=6.330 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-85_PC
412.1
Max: 44554
413.1
460.2
m/z

t = 14 days

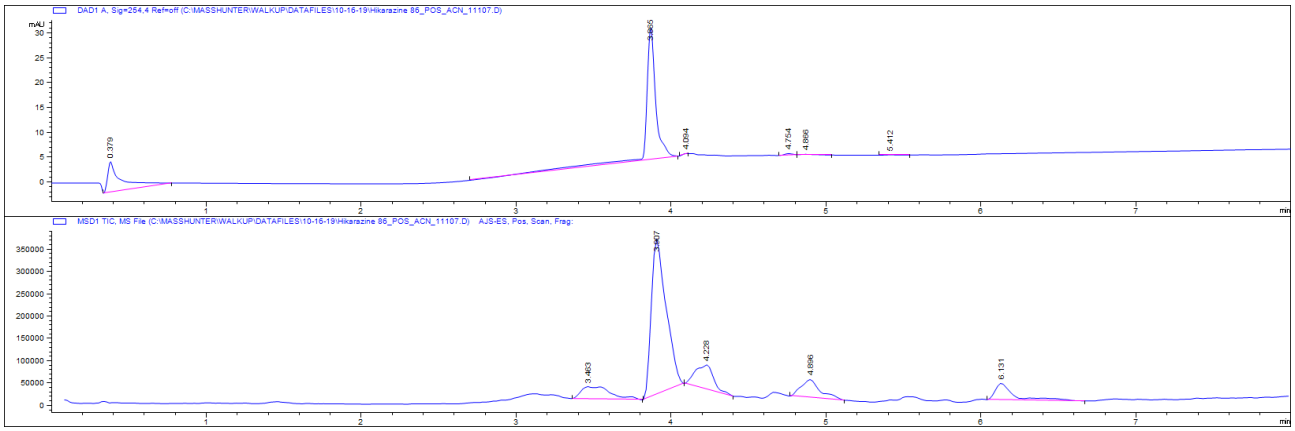


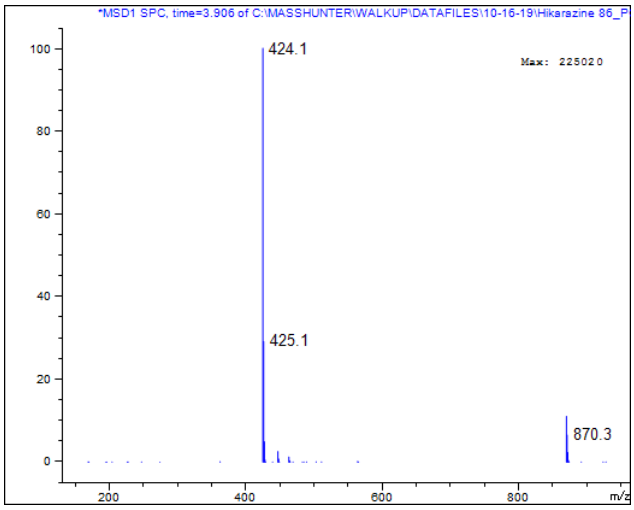

*MSD1 SPC, time=4.367 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 225945
432.2
430.1
433.1
431.1
187.1
*MSD1 SPC, time=4.674 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 604344
414.1
415.1
*MSD1 SPC, time=5.101 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 39889
280.1
281.1
*MSD1 SPC, time=6.552 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 85191
412.1
413.1
460.2

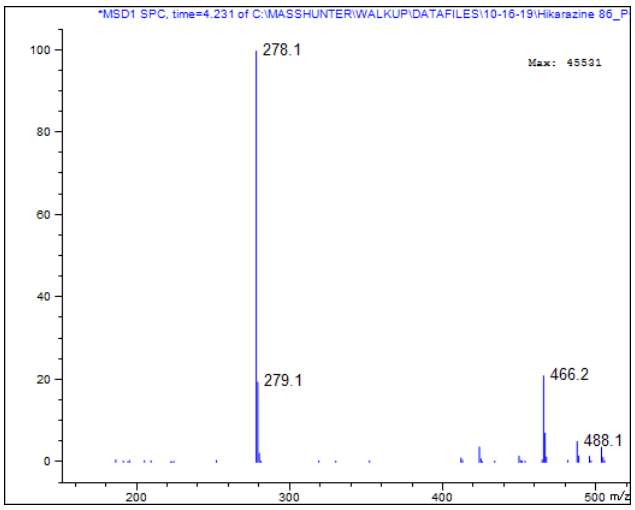
Hydrolysis products of hikarazine-86 (**25**{*14,1,63*})



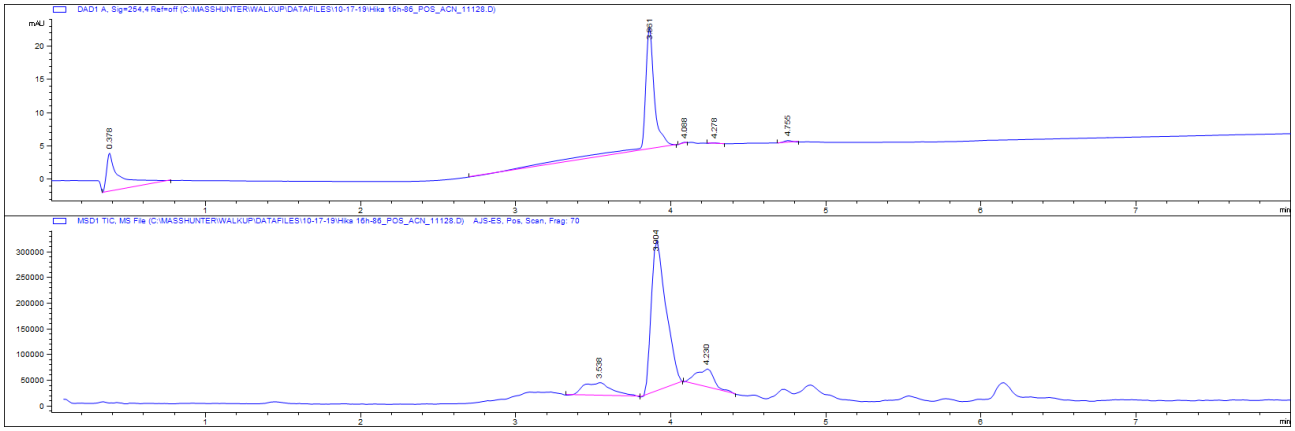
t = 0

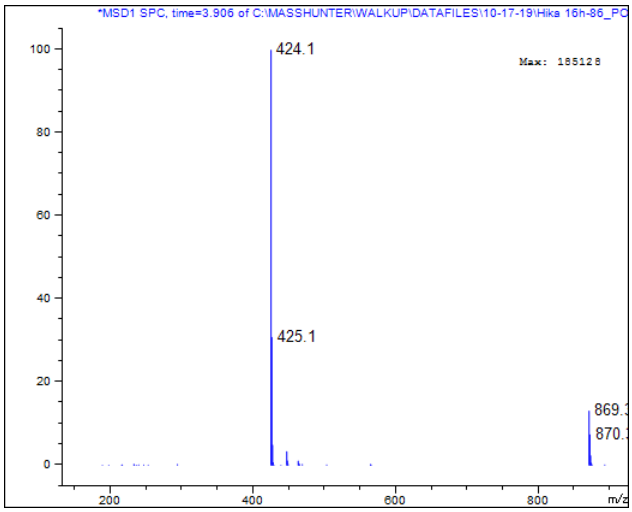




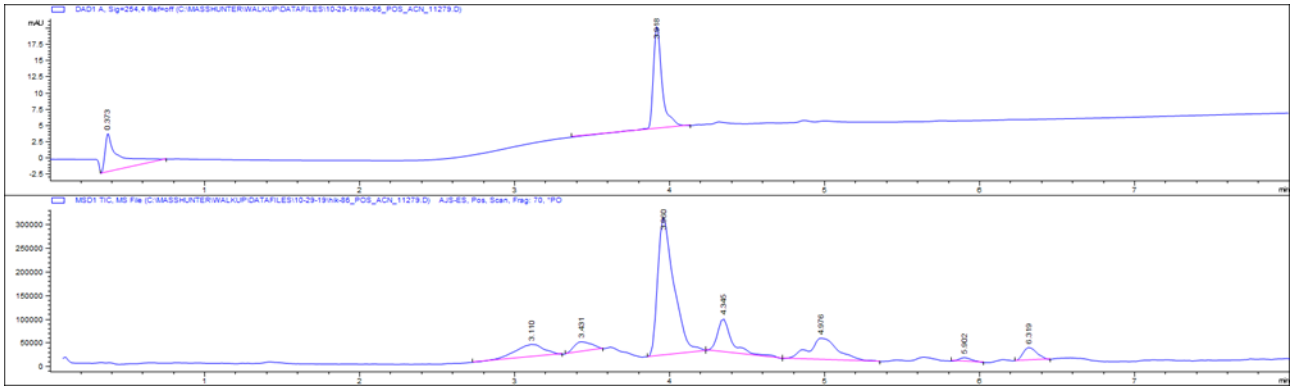


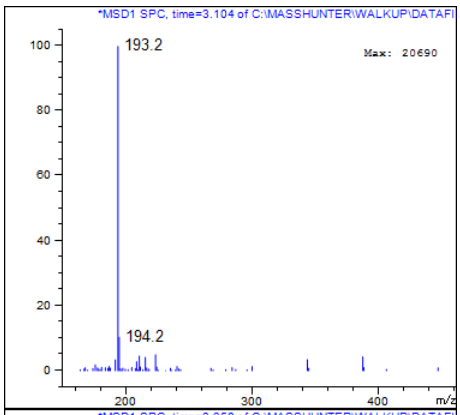
t = 16h

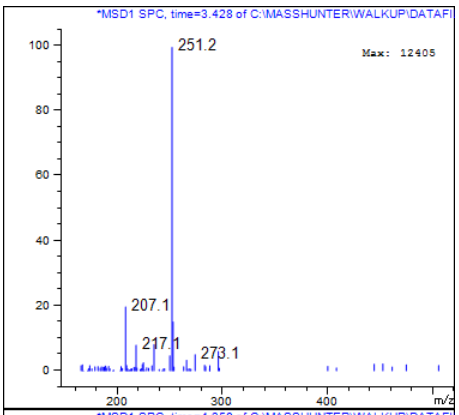

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-86_POS_ACN_11128.D)
mAU
0.376
3.861
4.088
4.278
4.755
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-86_POS_ACN_11128.D) AJS-ES, Pos, Scan, Frag: 70
3.904
3.636
4.230
min

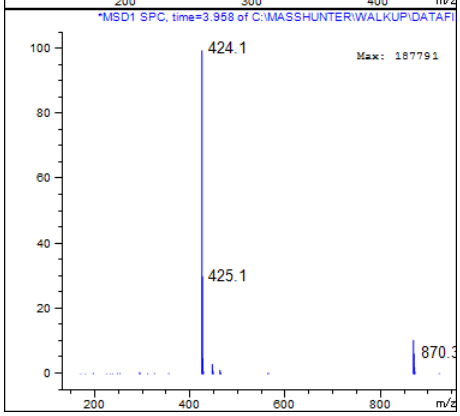

*MSD1 SPC, time=3.906 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-86_PO
Max: 185128
424.1
425.1
869.1
870.1
m/z

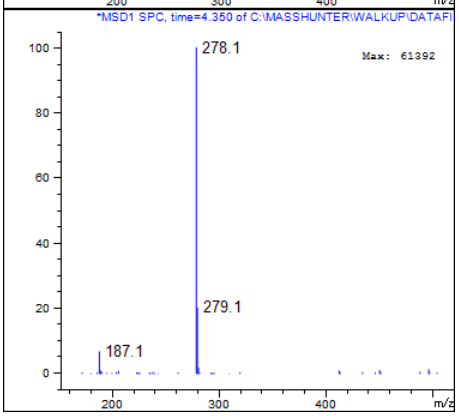
t = 14 days

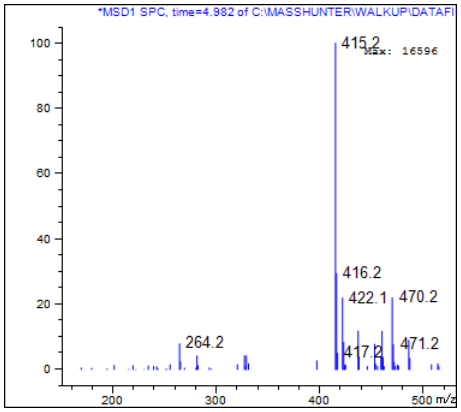



*MSD1 SPC, time=3.104 of C:\MASSHUNTER\WALKUP\DATAFI
193.2
Max: 20690
194.2

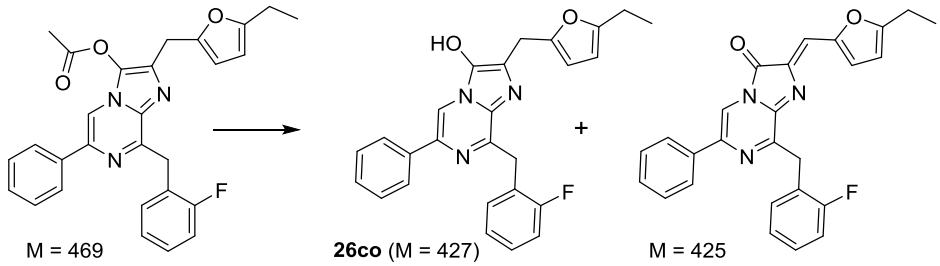

*MSD1 SPC, time=3.428 of C:\MASSHUNTER\WALKUP\DATAFI
251.2
Max: 12405
207.1
217.1
273.1


*MSD1 SPC, time=3.958 of C:\MASSHUNTER\WALKUP\DATAFI
424.1
Max: 187791
425.1

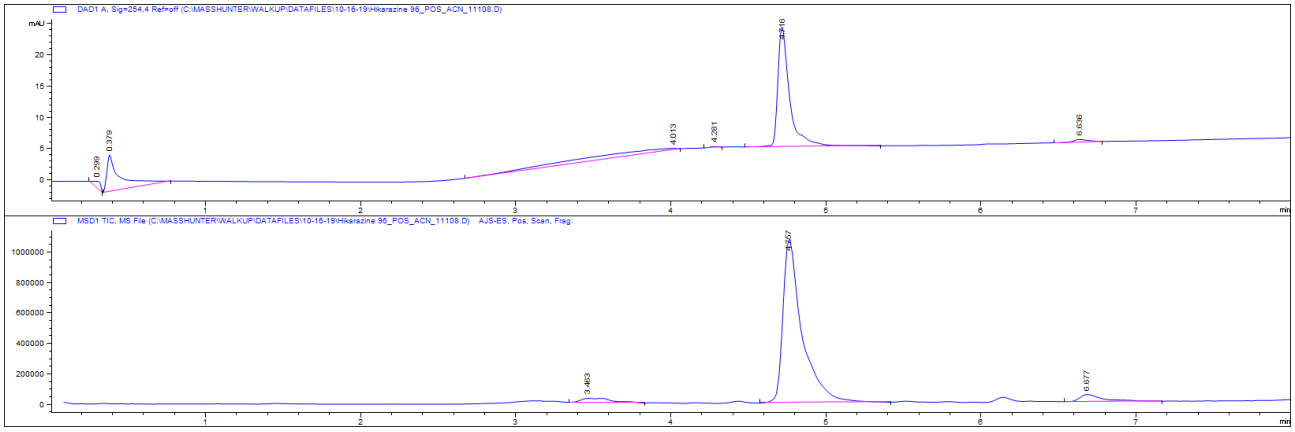

*MSD1 SPC, time=4.350 of C:\MASSHUNTER\WALKUP\DATAFI
278.1
Max: 61392
279.1
187.1

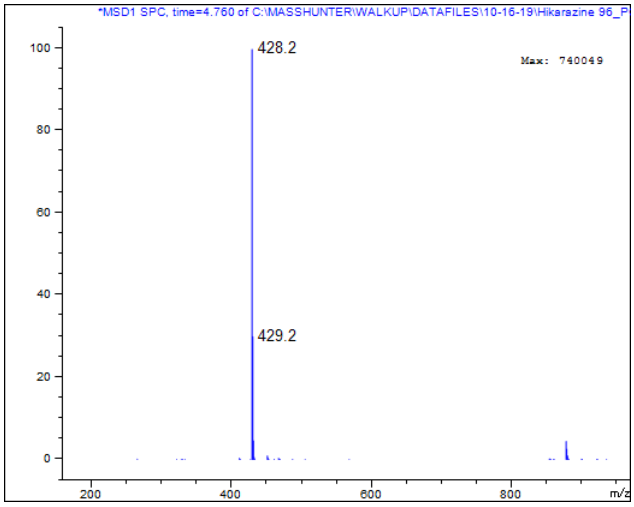

*MSD1 SPC, time=4.982 of C:\MASSHUNTER\WALKUP\DATAFI
415.2
Max: 16596
416.2
422.1
470.2
264.2
417.2
471.2

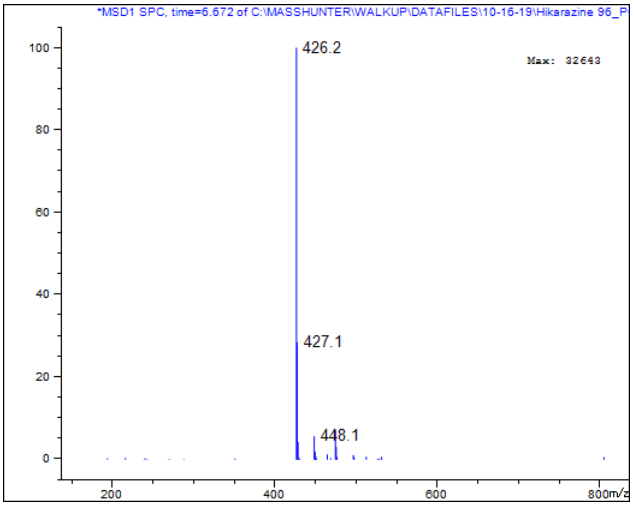
Hydrolysis products of hikarazine-96 (**25**{*1,2,44*})



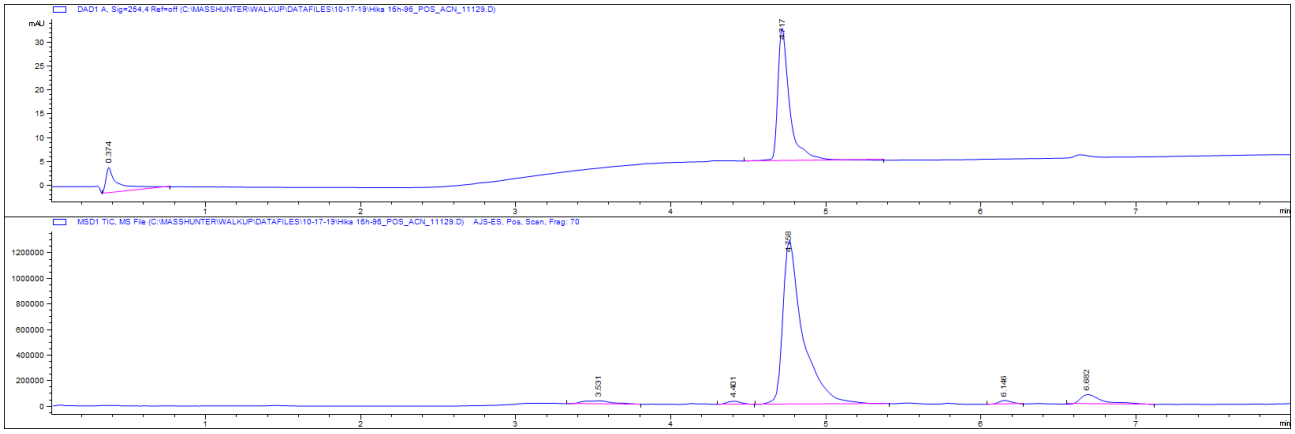
t = 0

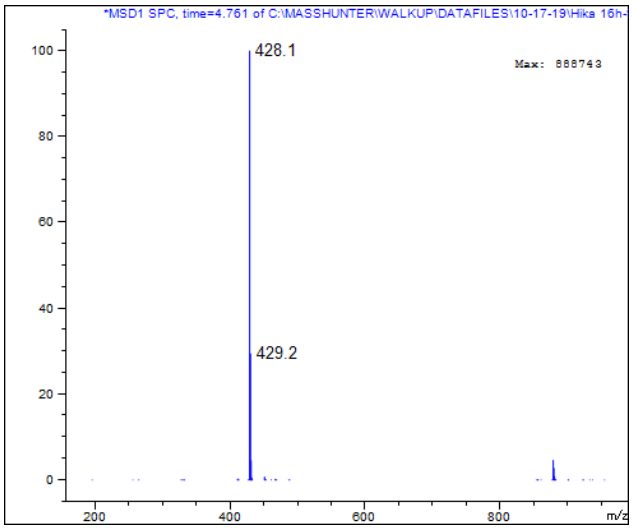


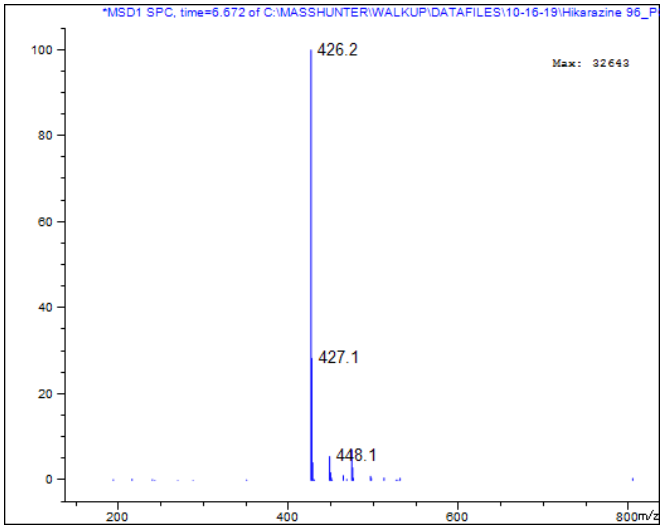




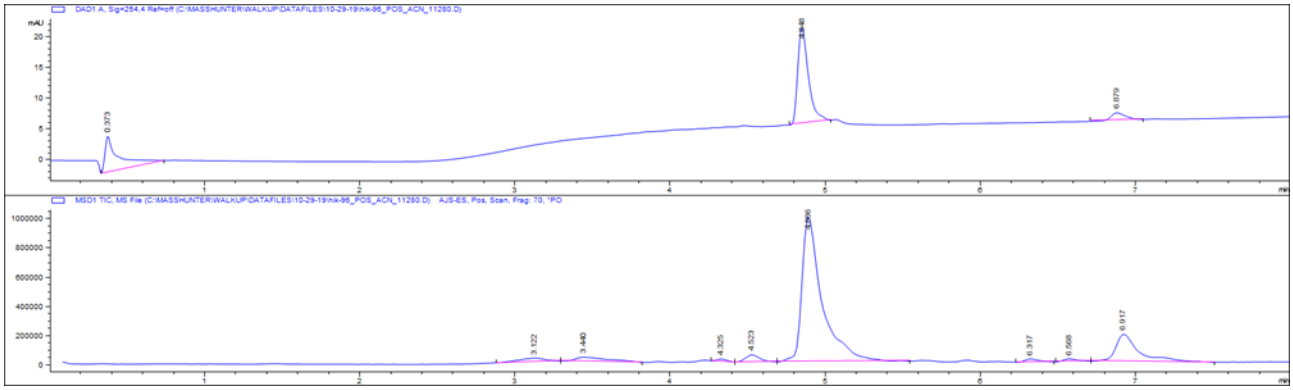
t = 16h

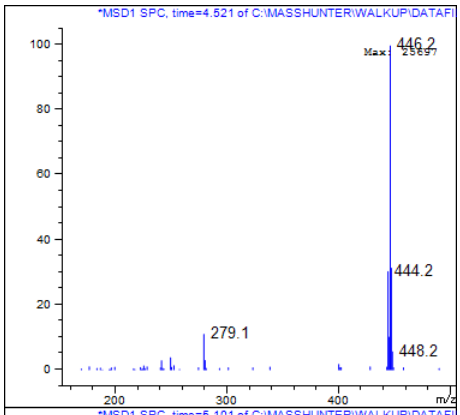

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-96_POS_ACN_11129.D)
mAU
0.374
4.417
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-96_POS_ACN_11129.D) AJS-ES, Pos, Scan, Frag: 70
4.458
3.531
4.401
6.146
6.682
min

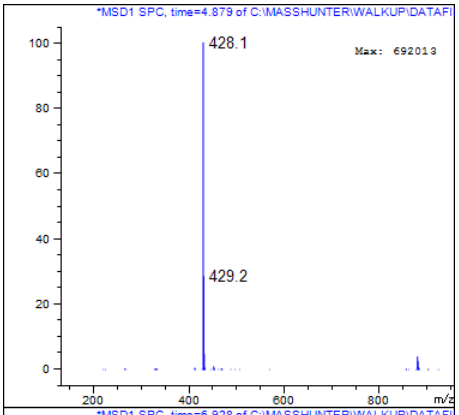

*MSD1 SPC, time=4.761 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 888743
428.1
429.2
m/z

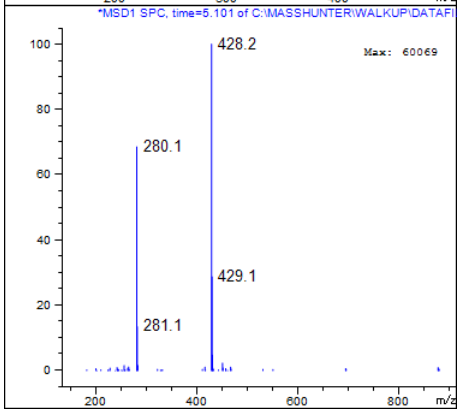

*MSD1 SPC, time=6.672 of C:\MASSHUNTER\WALKUP\DATAFILES\10-16-19\Hikarazine 96_P
Max: 32643
426.2
427.1
448.1
m/z

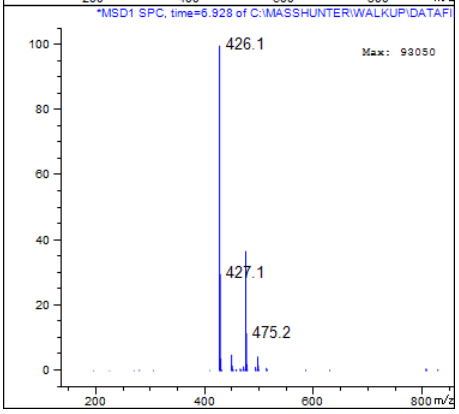
t = 14 days



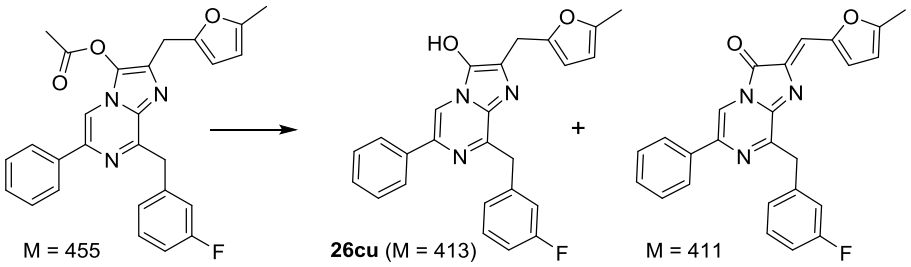

*MSD1 SPC, time=4.521 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 25697
446.2
444.2
279.1
448.2


*MSD1 SPC, time=4.879 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 692013
428.1
429.2

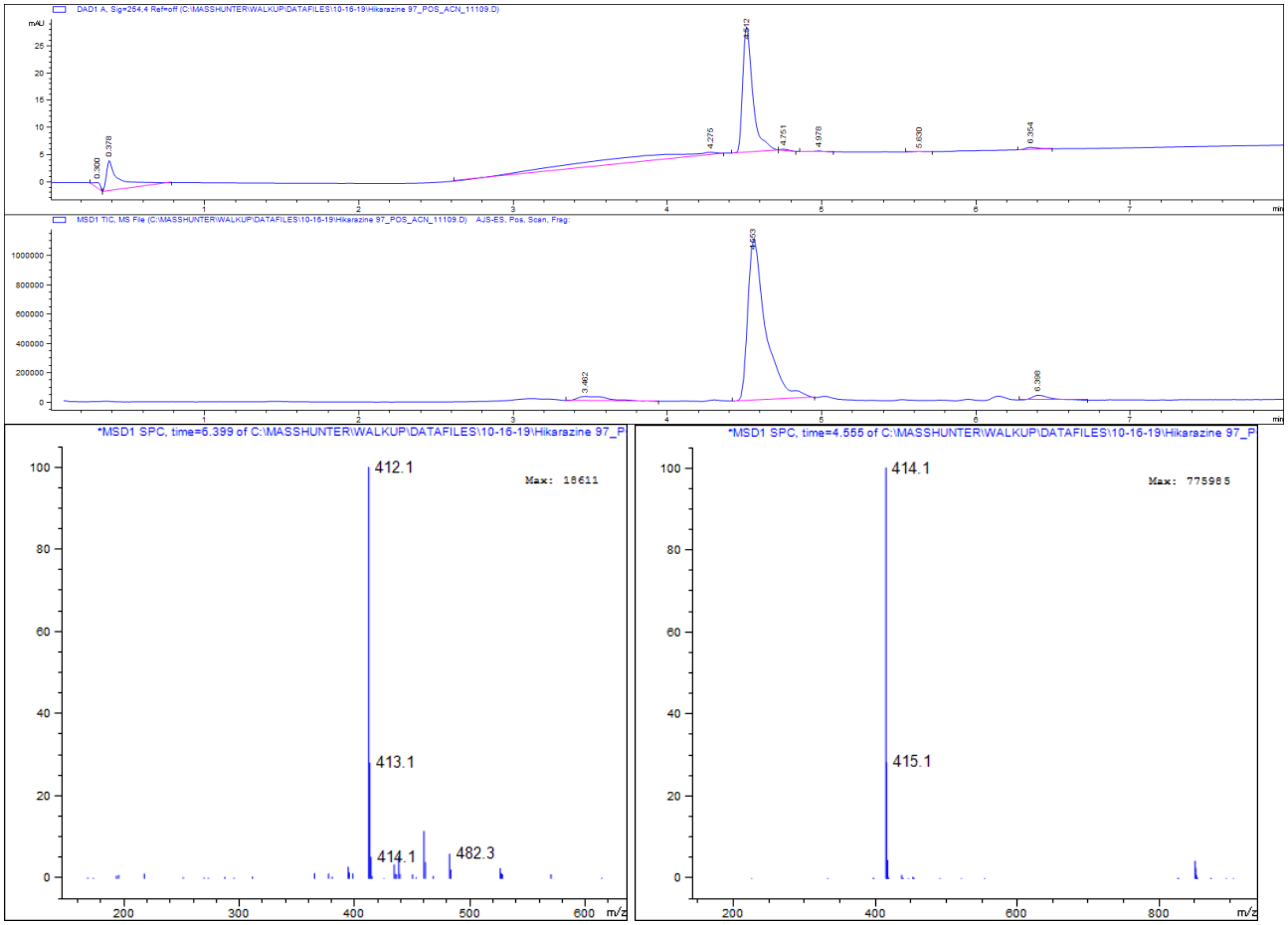

*MSD1 SPC, time=5.101 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 60069
428.2
280.1
429.1
281.1


*MSD1 SPC, time=6.928 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 93050
426.1
427.1
475.2

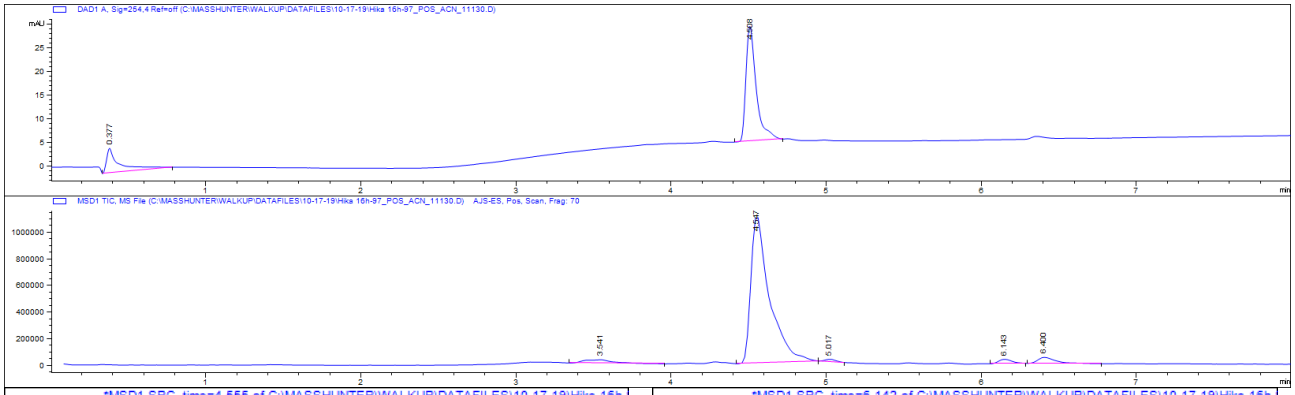
Hydrolysis products of hikarazine-97 (**25{*1,3,42*}**)

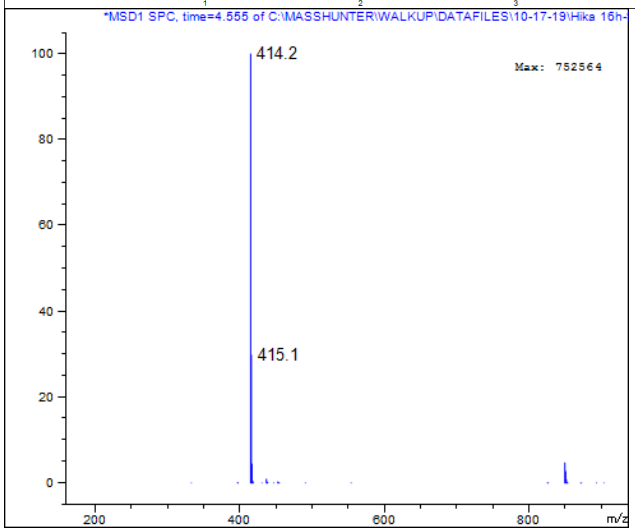


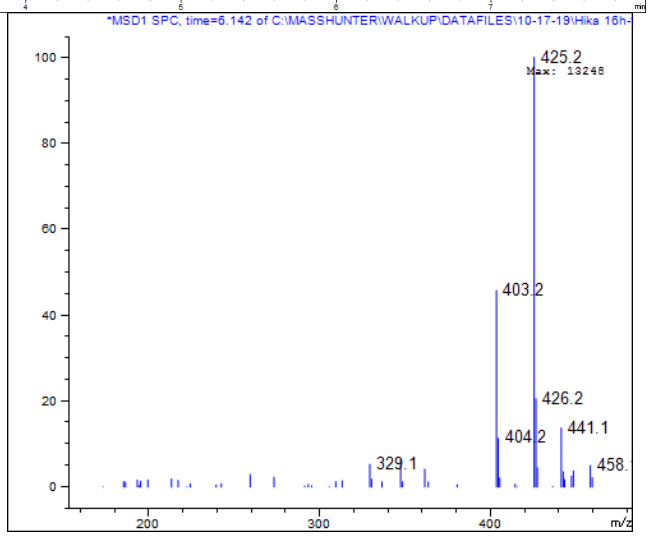
t = 0

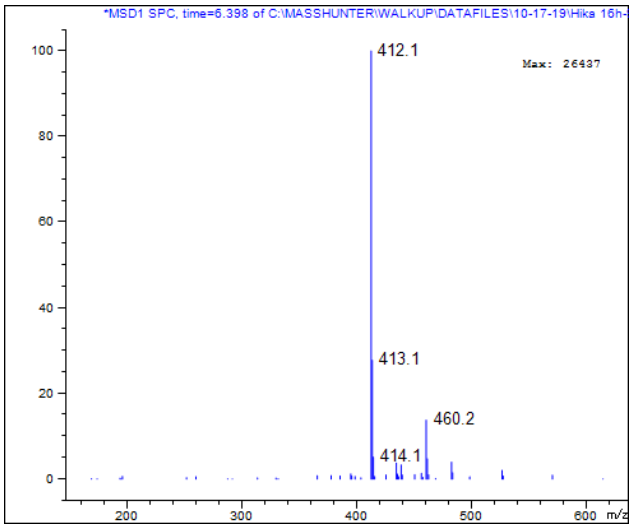


t = 16h

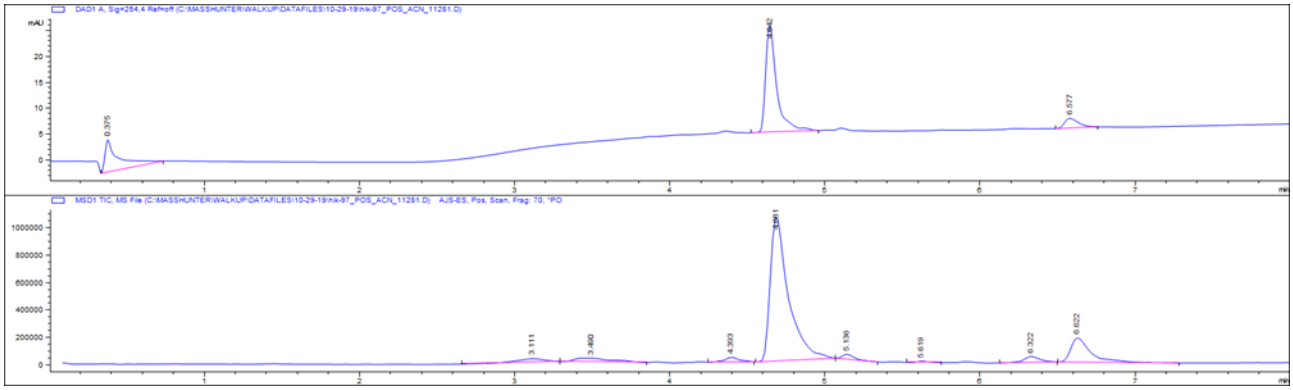

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-97_POS_ACN_11130.D)
mAU
0.377
3.908
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-97_POS_ACN_11130.D) AJS-ES, Pos, Scan, Frag: 70
3.541
3.647
5.017
6.143
6.400
min

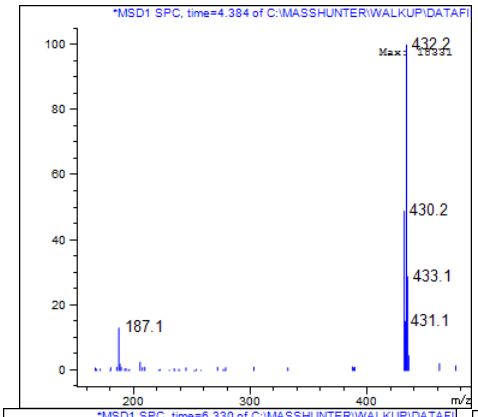

*MSD1 SPC, time=4.555 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
414.2
Max: 752564
415.1
m/z

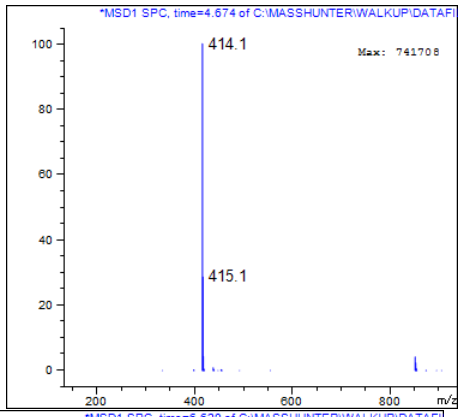

*MSD1 SPC, time=6.142 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
425.2
Max: 13248
403.2
426.2
441.1
404.2
329.1
458.
m/z

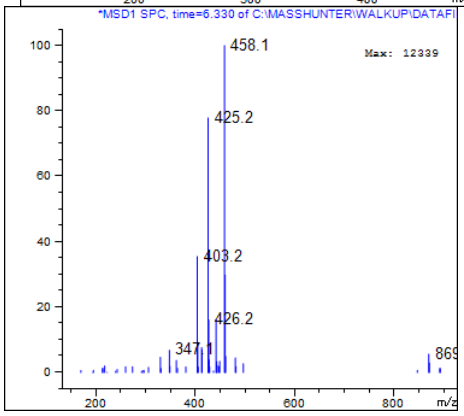

*MSD1 SPC, time=6.398 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
412.1
Max: 26437
413.1
460.2
414.1
m/z

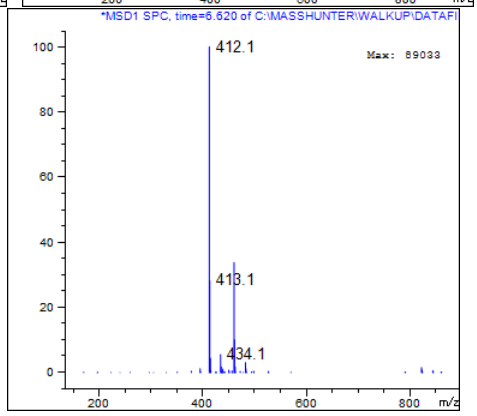
t = 14 days



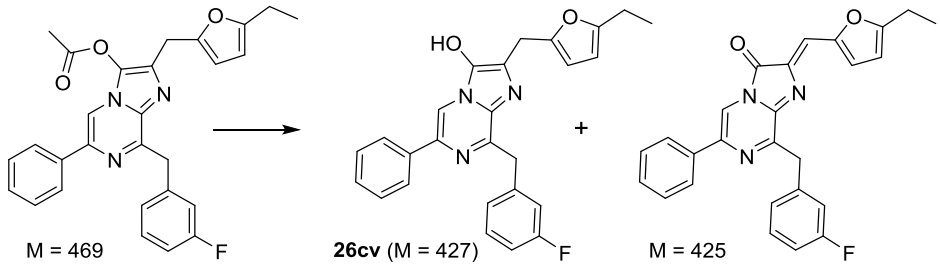

*MSD1 SPC, time=4.384 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 18931
432.2
430.2
433.1
431.1
187.1


*MSD1 SPC, time=4.674 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 741708
414.1
415.1

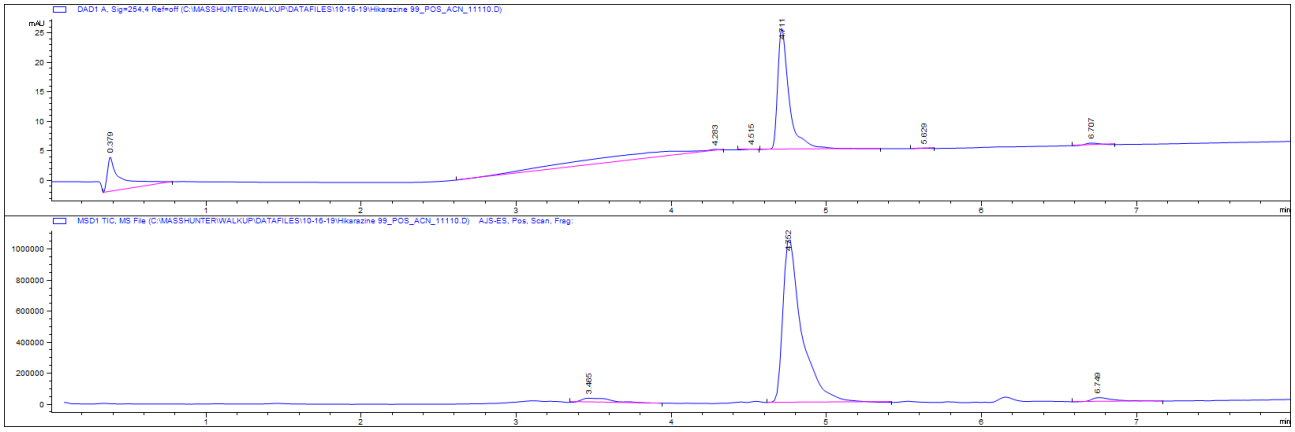

*MSD1 SPC, time=6.330 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 12339
458.1
425.2
403.2
426.2
347.1

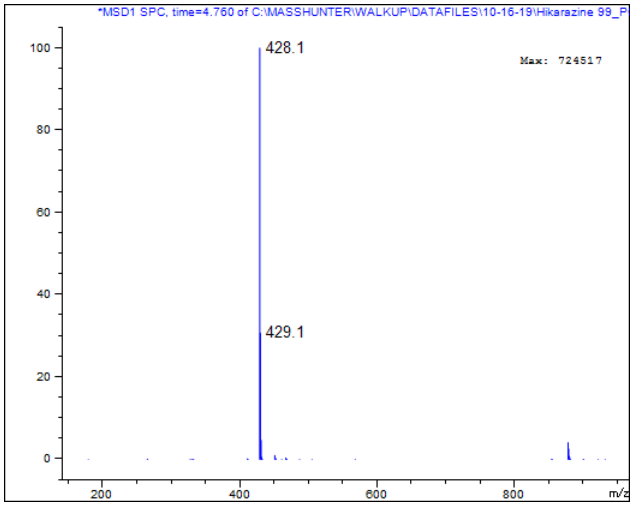

*MSD1 SPC, time=6.620 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 89033
412.1
413.1
434.1

Hydrolysis products of hikarazine-99 (**25**{*1*,*3*,*44*})

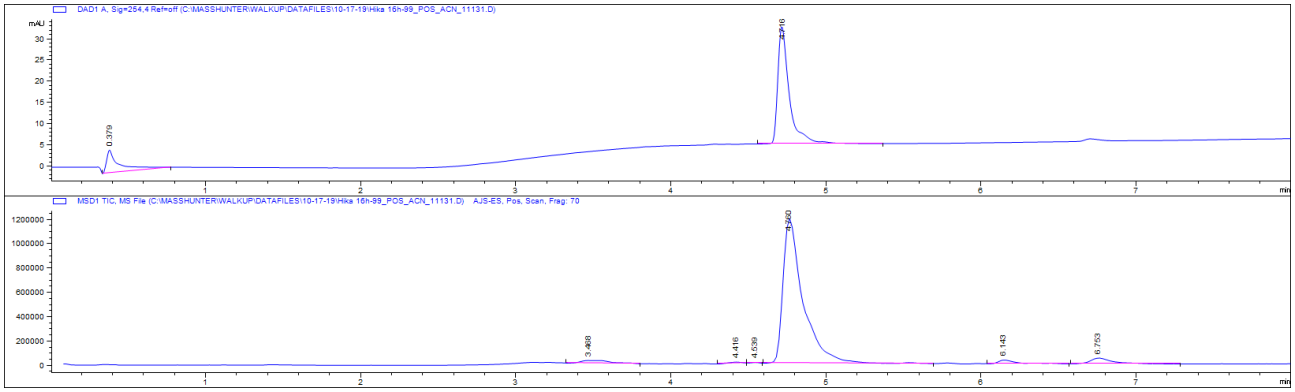


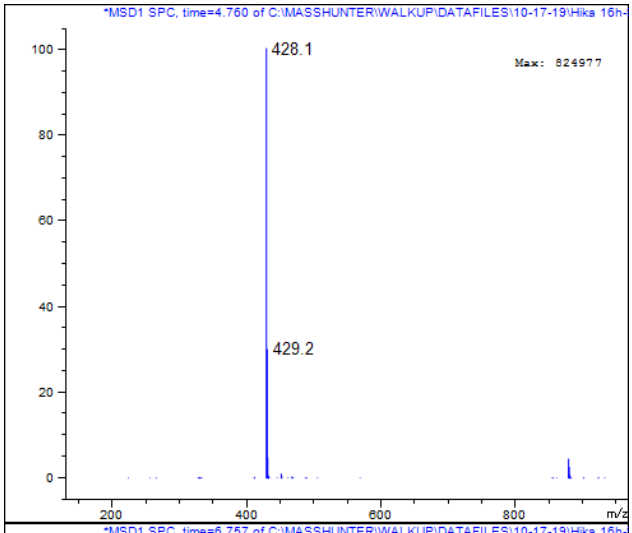
t = 0

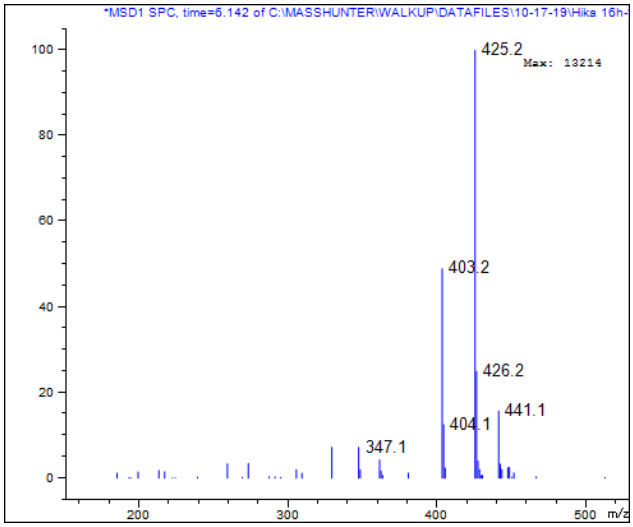


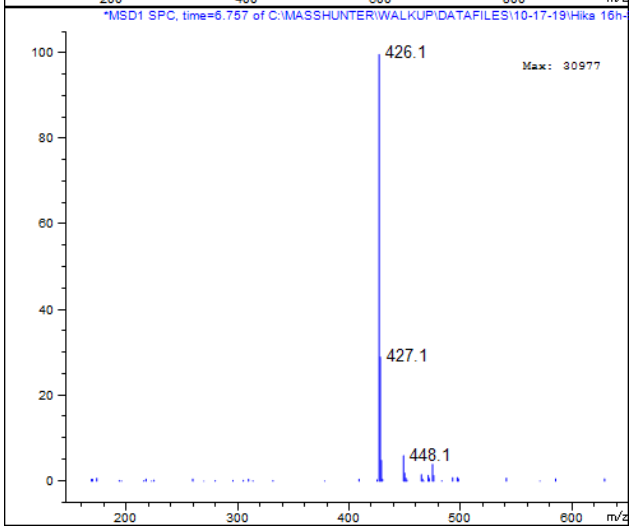


t = 16h

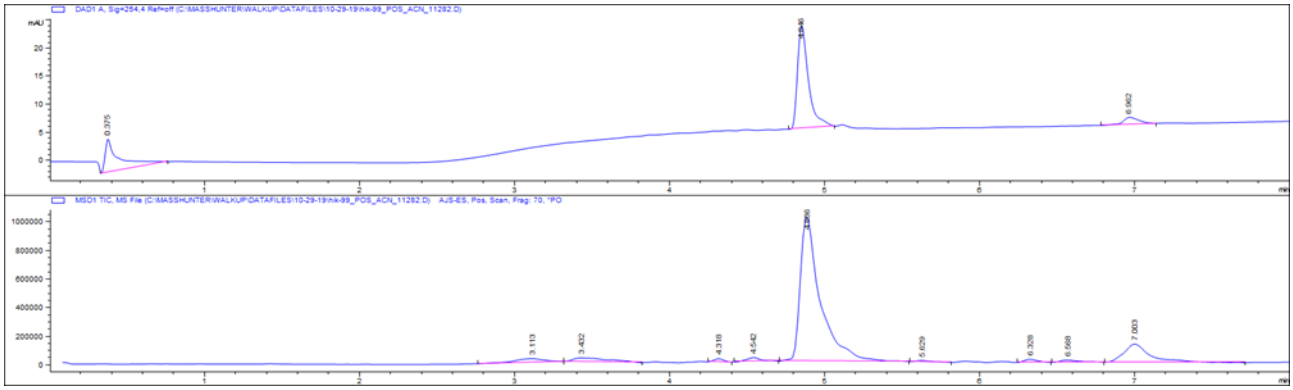

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-99_POS_ACN_11131.D)
mAU
0.379
4.746
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-99_POS_ACN_11131.D) AJS-ES, Pos, Scan, Frag: 70
4.760
3.468
4.416
4.539
6.143
6.753
min

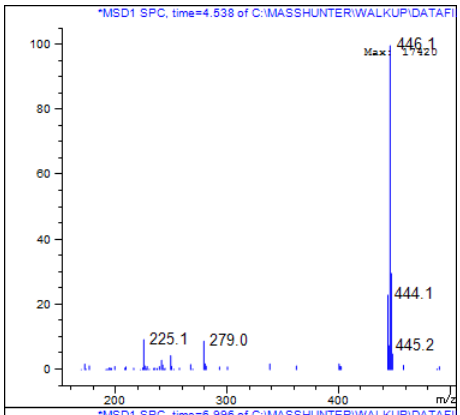

*MSD1 SPC, time=4.760 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
428.1
Max: 824977
429.2
m/z

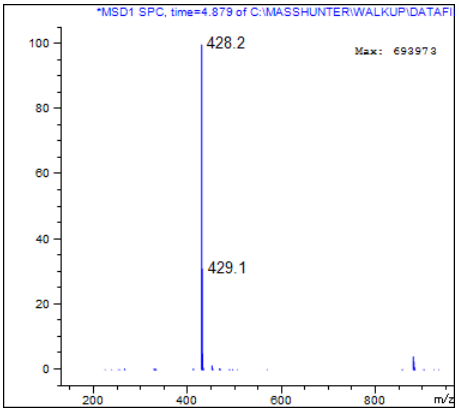

*MSD1 SPC, time=6.142 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
425.2
Max: 13214
403.2
426.2
441.1
404.1
347.1
m/z

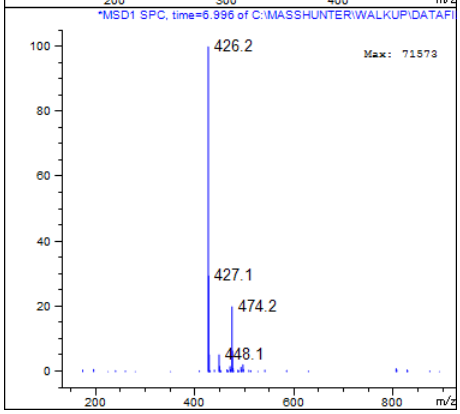

*MSD1 SPC, time=6.757 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
426.1
Max: 30977
427.1
448.1
m/z

t = 14 days

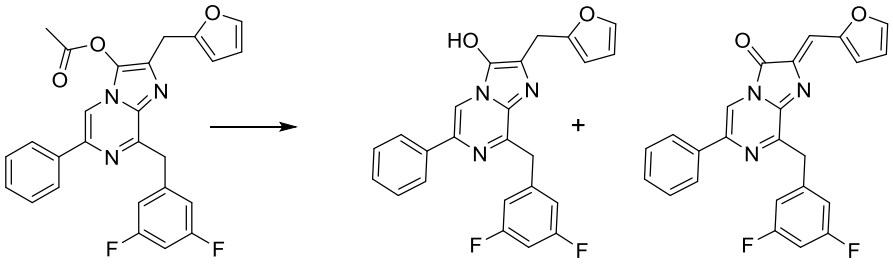



*MSD1 SPC, time=4.538 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 17420
446.1
444.1
445.2
225.1
279.0


*MSD1 SPC, time=4.879 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 693973
428.2
429.1

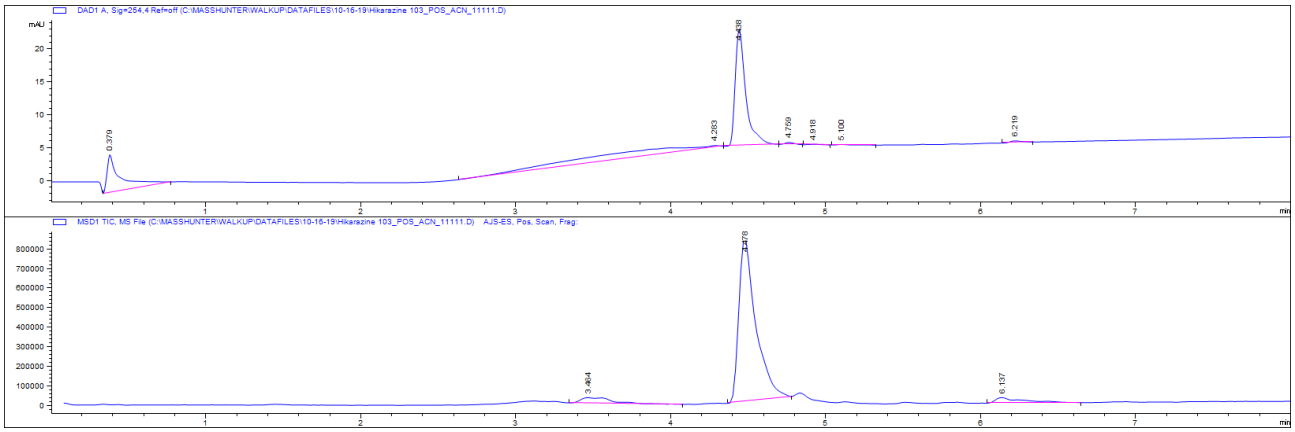

*MSD1 SPC, time=6.996 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 71573
426.2
427.1
474.2
448.1

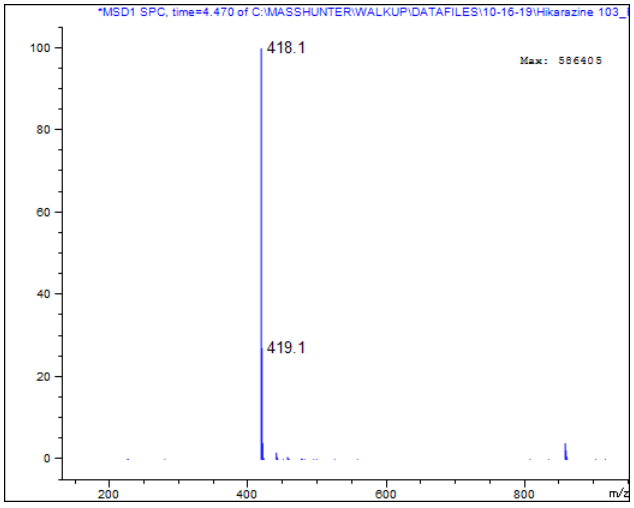
Hydrolysis products of hikarazine-103 (**26db**{*1,22,37*})



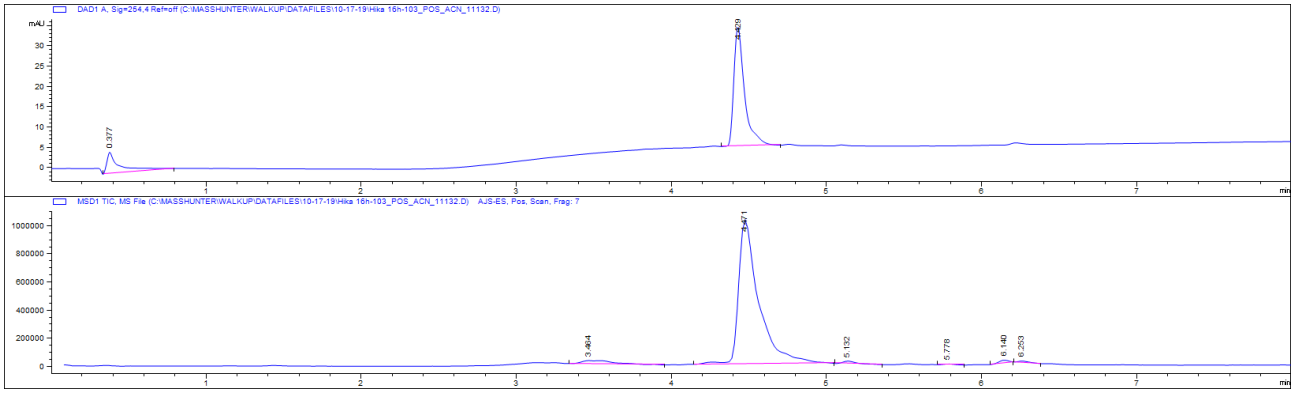
M = 459 **26db** (M = 417) M = 415

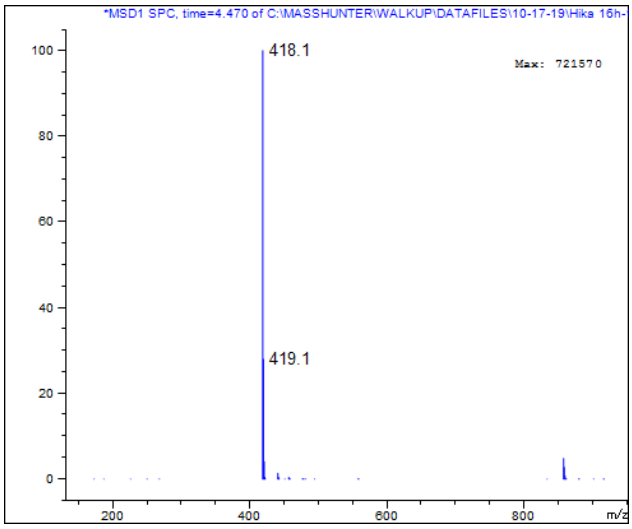
t = 0

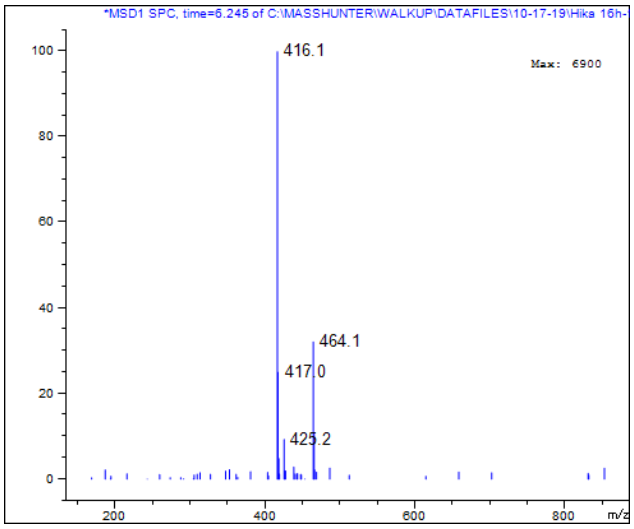




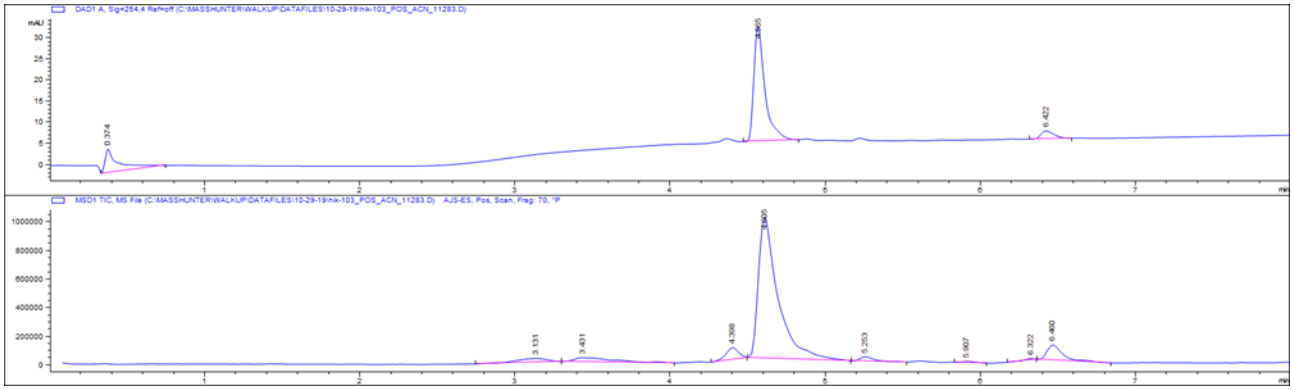
t = 16h

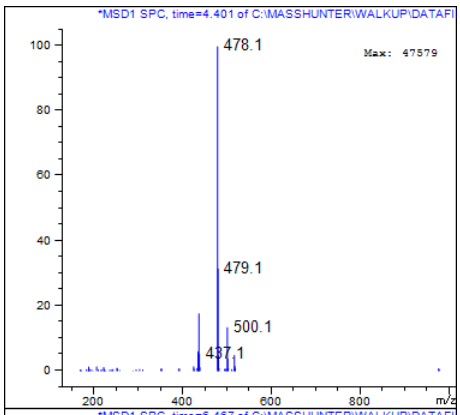

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-103_POS_ACN_11132.D)
mAU
0.377
4.459
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-103_POS_ACN_11132.D) AJS-ES, Pos, Scan, Frag: 7
4.471
3.464
5.132
5.778
6.140
6.293
min

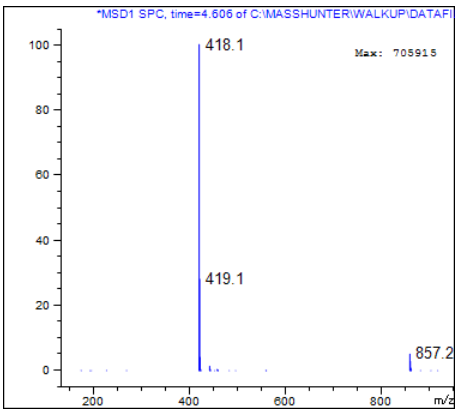

*MSD1 SPC, time=4.470 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
418.1
Max: 721570
419.1
m/z

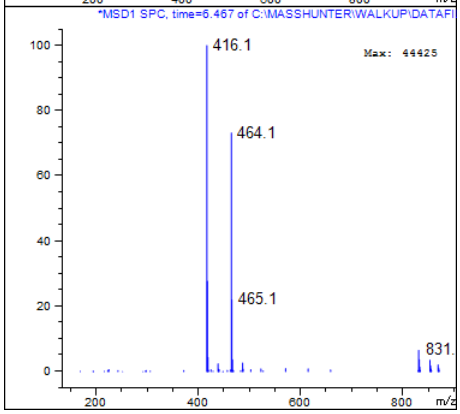

*MSD1 SPC, time=6.245 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
416.1
Max: 6900
464.1
417.0
425.2
m/z

t = 14 days

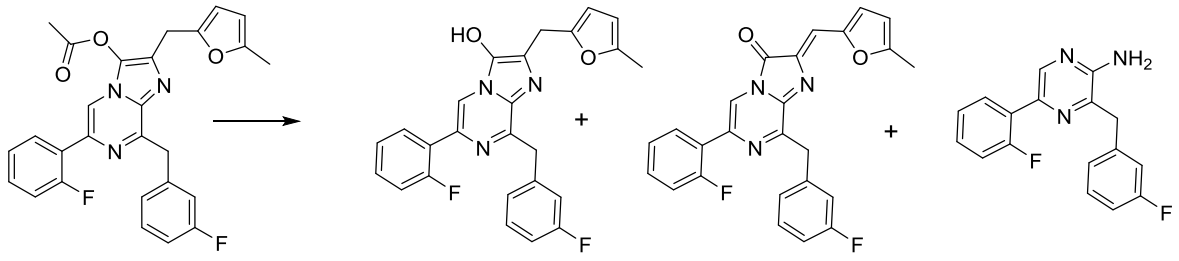



*MSD1 SPC, time=4.401 of C:\MASSHUNTER\WALKUP\DATAFI
478.1
Max: 47579
479.1
500.1
437.1


*MSD1 SPC, time=4.606 of C:\MASSHUNTER\WALKUP\DATAFI
418.1
Max: 705915
419.1
857.2

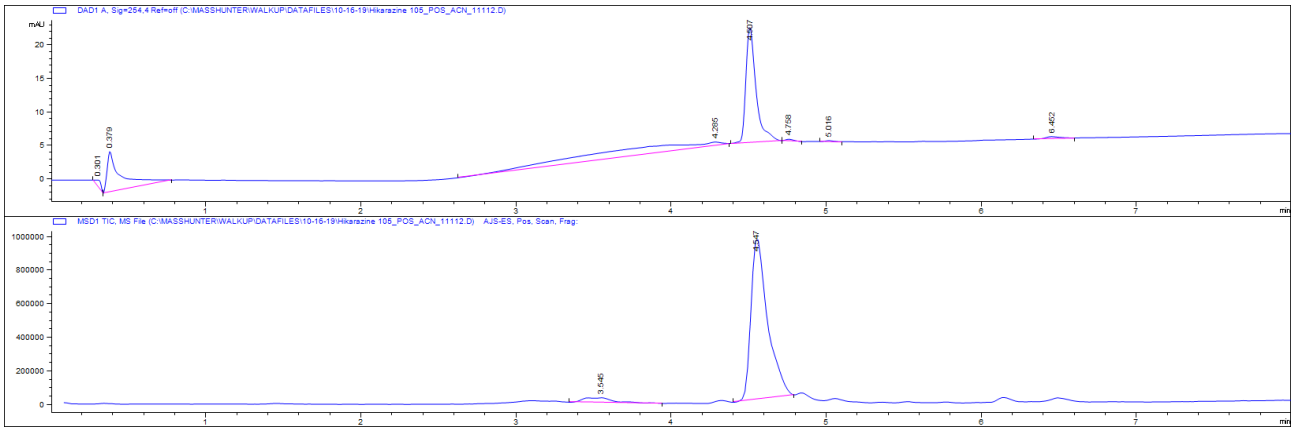

*MSD1 SPC, time=6.467 of C:\MASSHUNTER\WALKUP\DATAFI
416.1
Max: 44425
464.1
465.1
831.

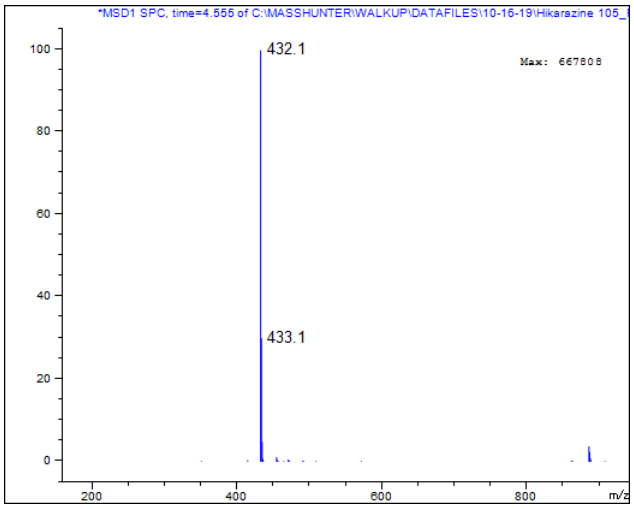
Hydrolysis products of hikarazine-105 (**26dw**{*2*,*3*,42})



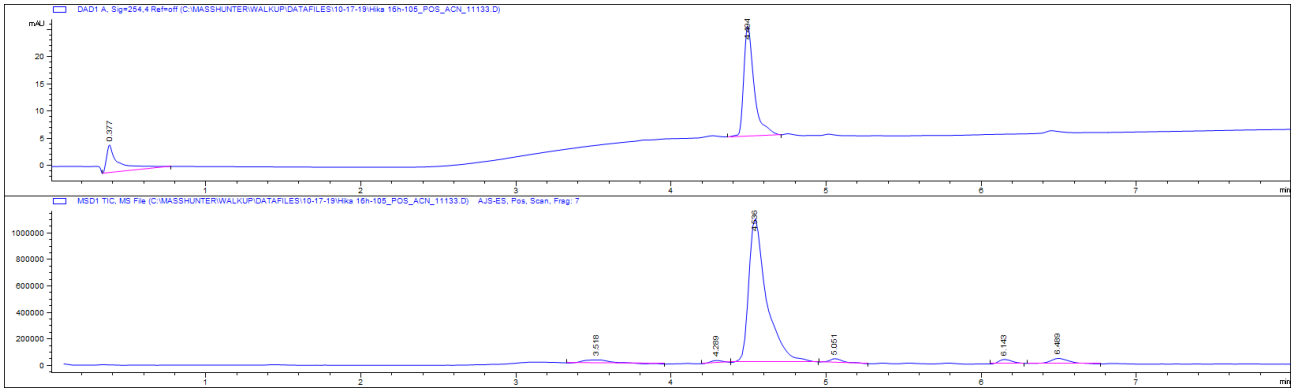
M = 473 | **26dw** (M = 431) | M = 429 | M = 297

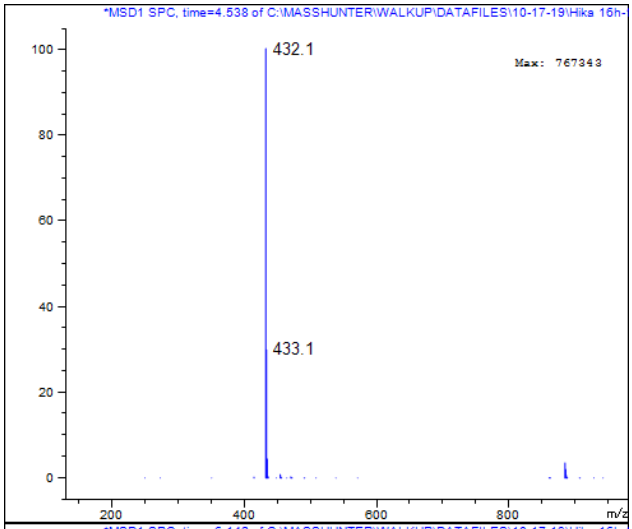
t = 0

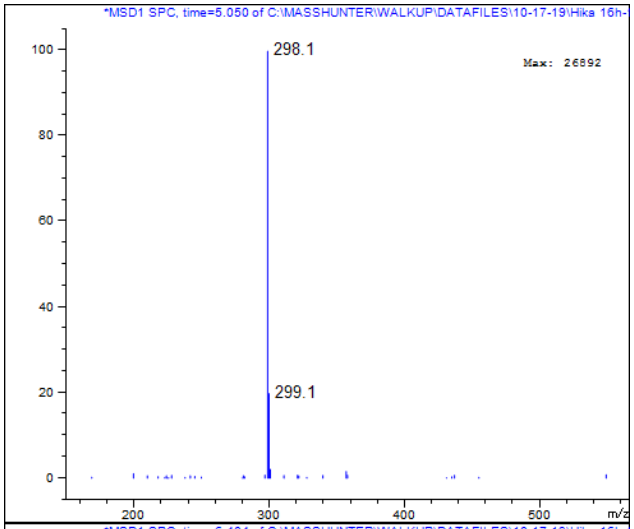


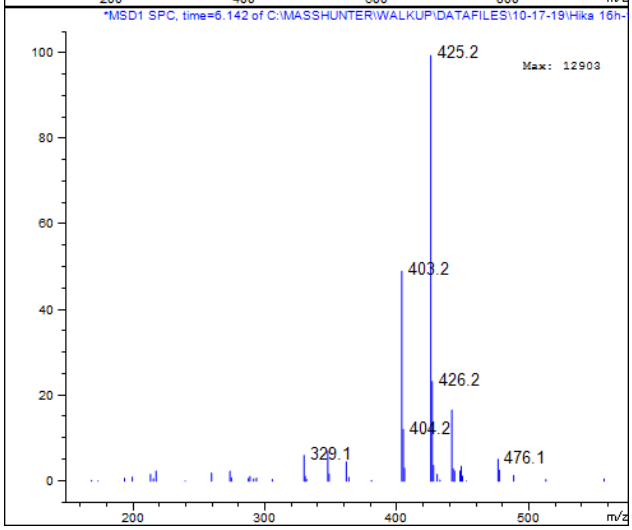


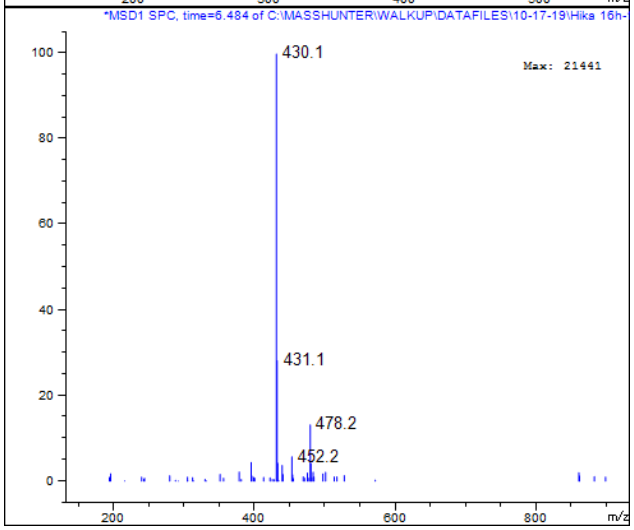
t = 16h


DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-105_POS_ACN_11133.D)
mAU
0.377
5.484
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-105_POS_ACN_11133.D) AJS-ES, Pos, Scan, Frag: 7
5.536
3.518
4.289
6.051
6.143
6.489
min

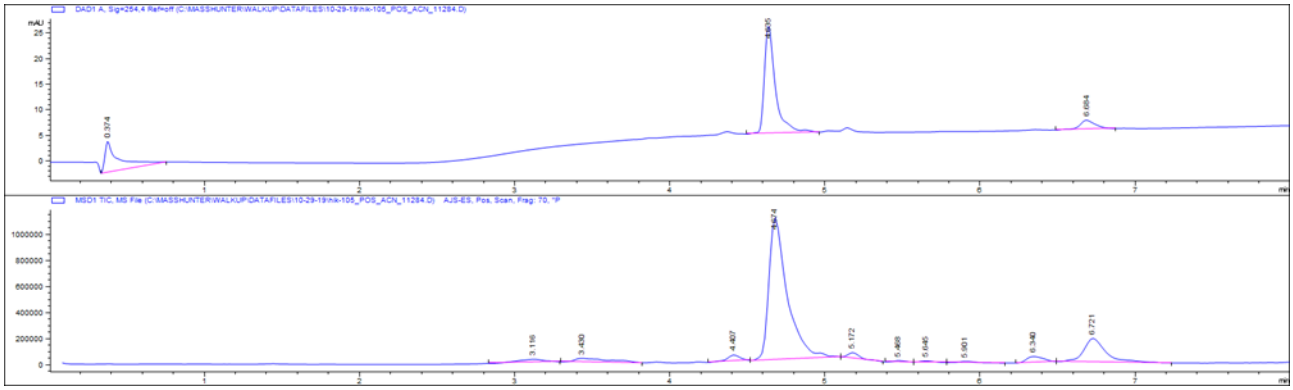

*MSD1 SPC, time=4.538 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
432.1
Max: 767343
433.1
m/z

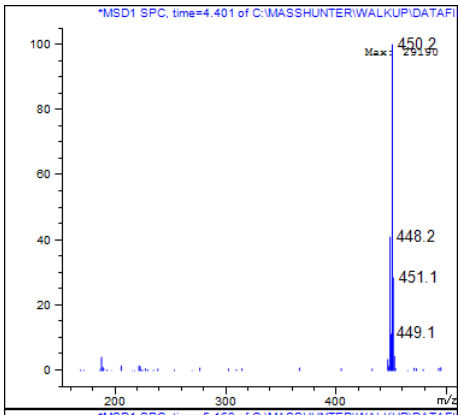

*MSD1 SPC, time=5.050 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
298.1
Max: 26892
299.1
m/z

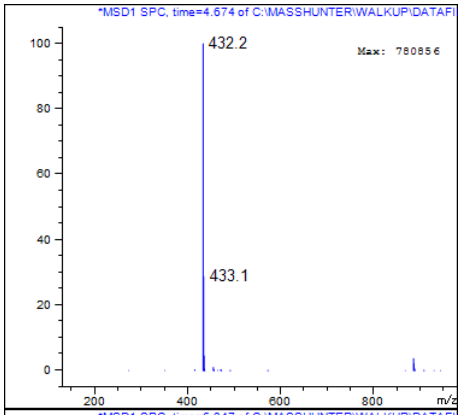

*MSD1 SPC, time=6.142 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
425.2
Max: 12903
403.2
426.2
404.2
329.1
476.1
m/z

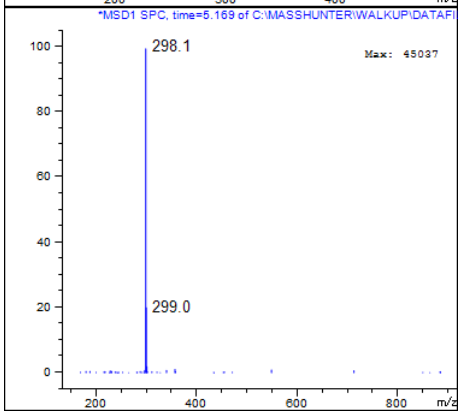

*MSD1 SPC, time=6.484 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
430.1
Max: 21441
431.1
478.2
452.2
m/z

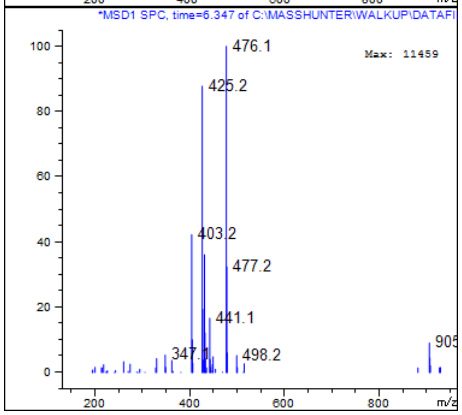
t = 14 days

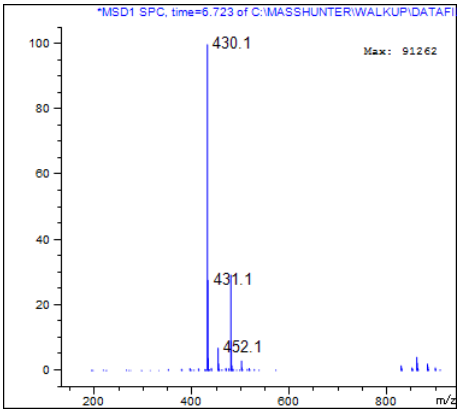



*MSD1 SPC, time=4.401 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 29190
450.2
448.2
451.1
449.1

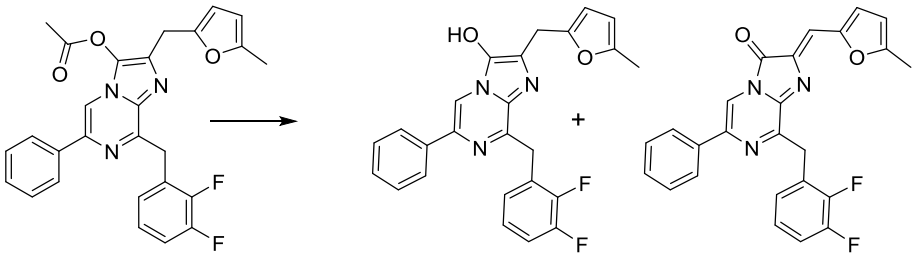

*MSD1 SPC, time=4.674 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 780856
432.2
433.1


*MSD1 SPC, time=5.169 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 45037
298.1
299.0


*MSD1 SPC, time=6.347 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 11459
476.1
425.2
403.2
477.2
441.1
498.2

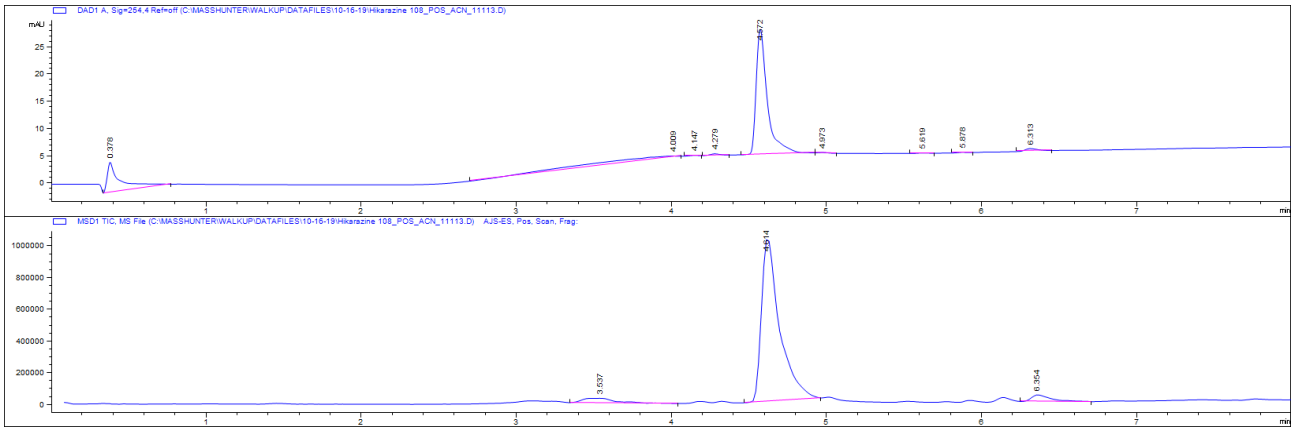

*MSD1 SPC, time=6.723 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 91262
430.1
431.1
452.1

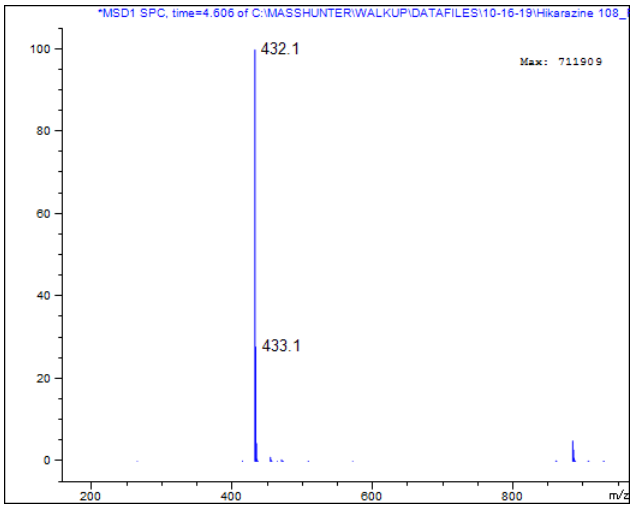
Hydrolysis products of hikarazine-108 (**25**{*1,24,42*})



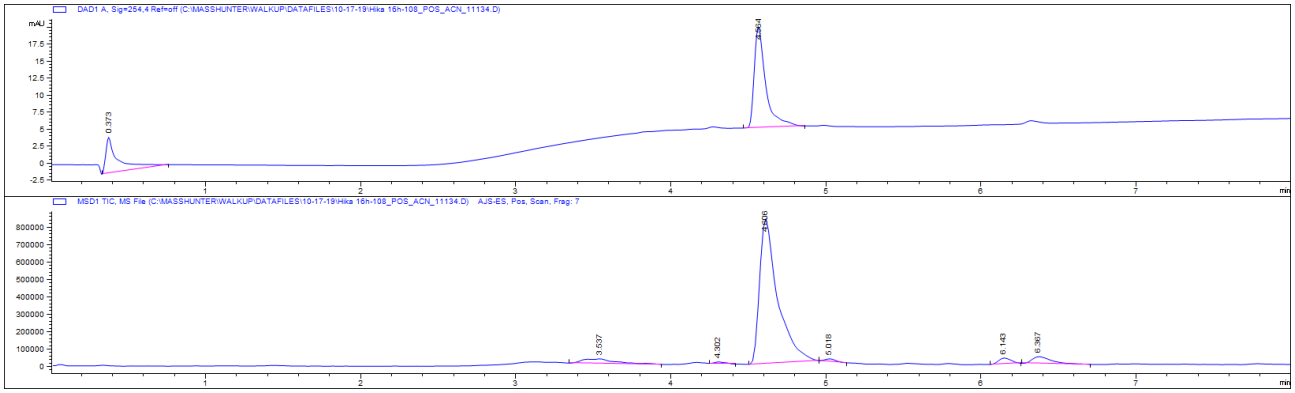
M = 473 **26dl** (M = 431) M = 429

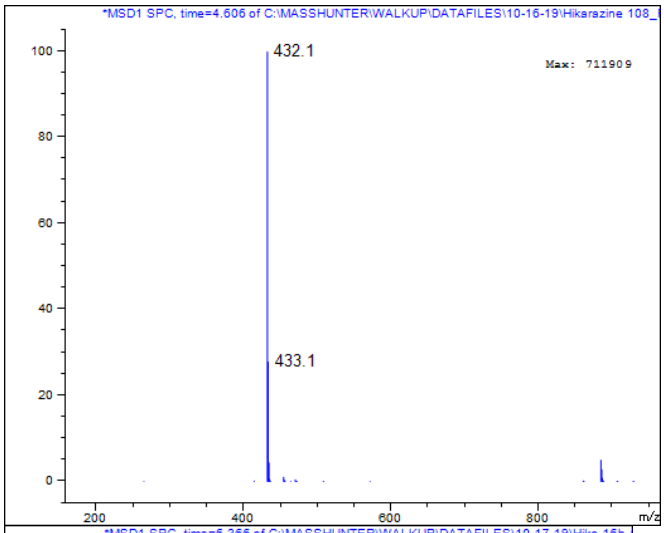
t = 0

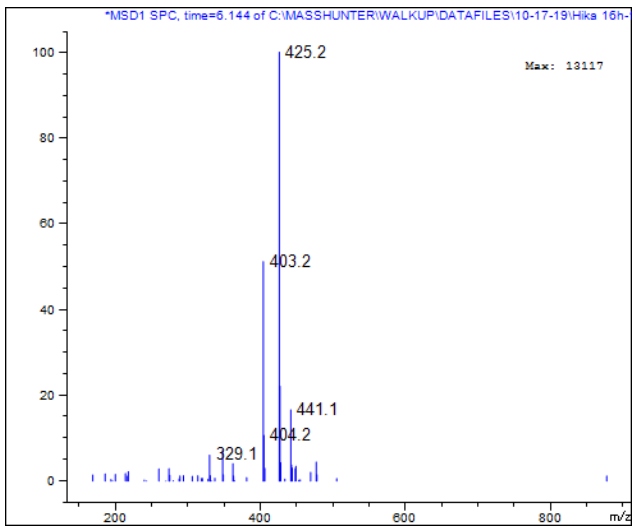


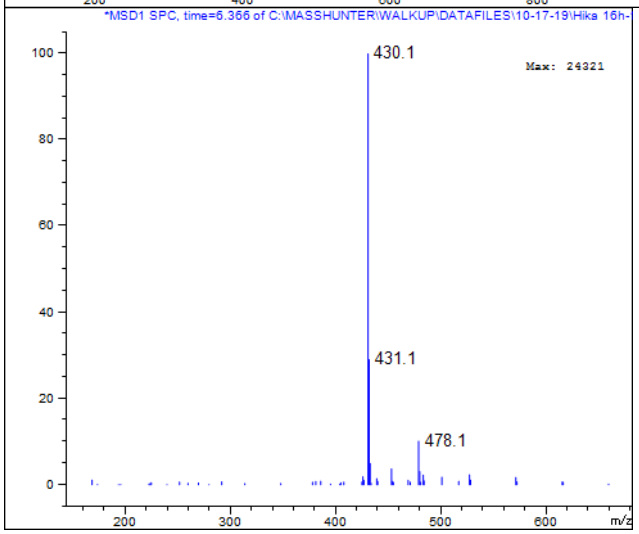


t = 16h

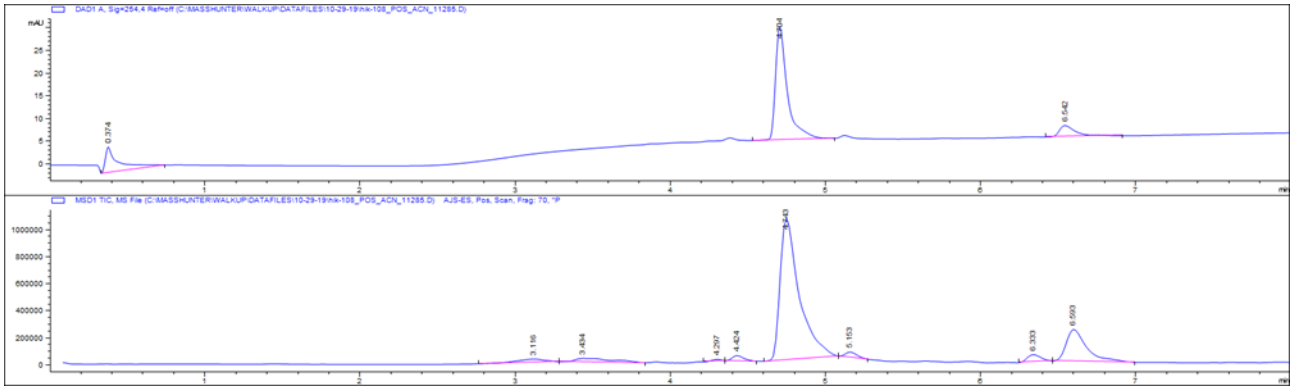

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-108_POS_ACN_11134.D)
0.373
4.604
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-108_POS_ACN_11134.D) AJS-ES, Pos, Scan, Frag: 7
4.609
3.637
4.302
5.018
6.143
6.367
min

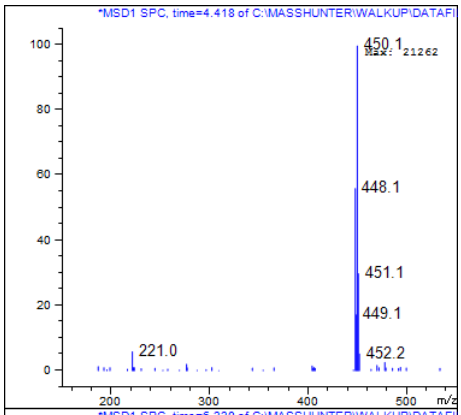

*MSD1 SPC, time=4.606 of C:\MASSHUNTER\WALKUP\DATAFILES\10-16-19\Hikarazine 108_
Max: 711909
432.1
433.1
m/z

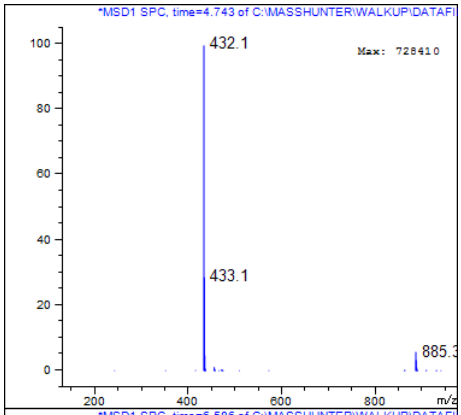

*MSD1 SPC, time=6.144 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 13117
425.2
403.2
441.1
404.2
329.1
m/z

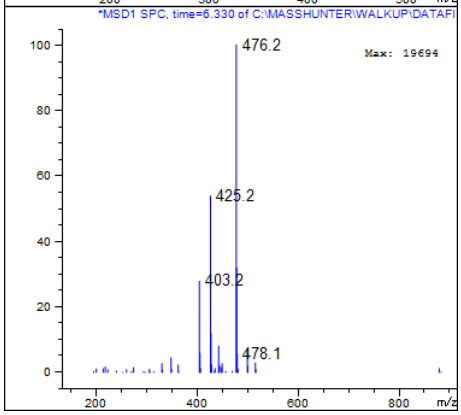

*MSD1 SPC, time=6.366 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 24321
430.1
431.1
478.1
m/z

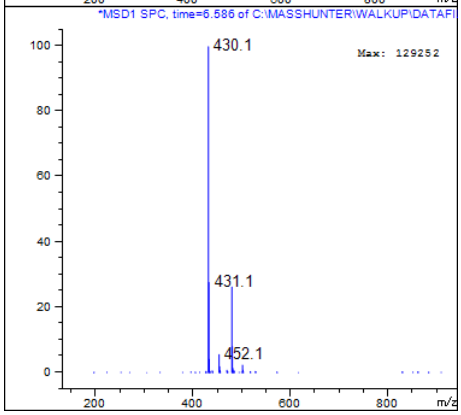
t = 14 days



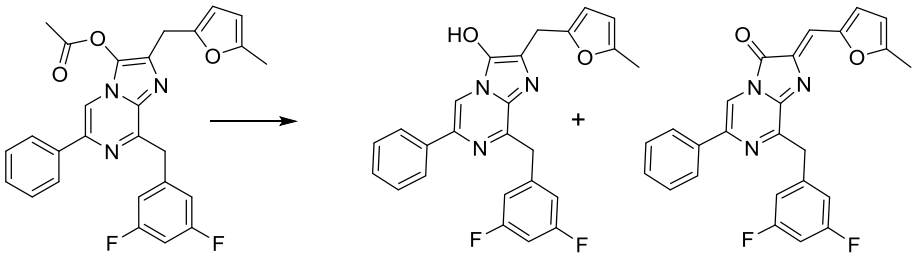

*MSD1 SPC, time=4.418 of C:\MASSHUNTER\WALKUP\DATAFI
450.1
Max: 21262
448.1
451.1
449.1
452.2
221.0


*MSD1 SPC, time=4.743 of C:\MASSHUNTER\WALKUP\DATAFI
432.1
Max: 728410
433.1
885.3


*MSD1 SPC, time=6.330 of C:\MASSHUNTER\WALKUP\DATAFI
476.2
Max: 19694
425.2
403.2
478.1

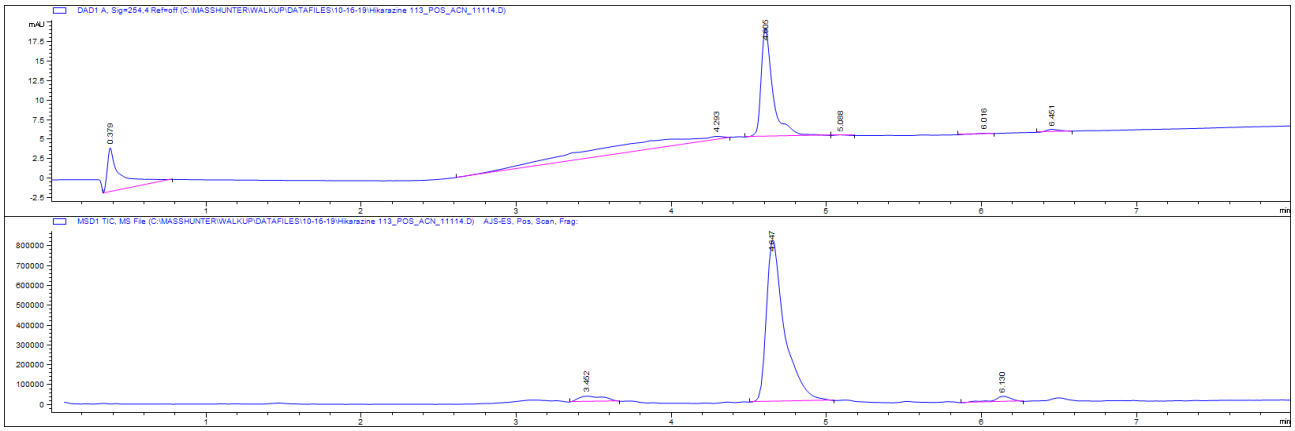

*MSD1 SPC, time=6.586 of C:\MASSHUNTER\WALKUP\DATAFI
430.1
Max: 129252
431.1
452.1

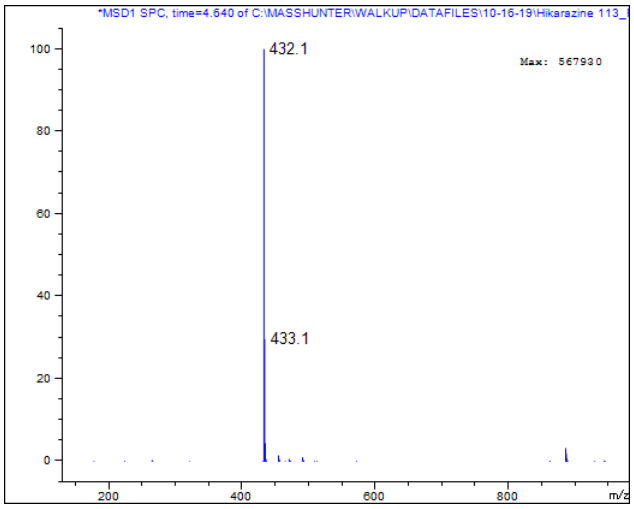
Hydrolysis products of hikarazine-113 (**25**{*1,22,42*})



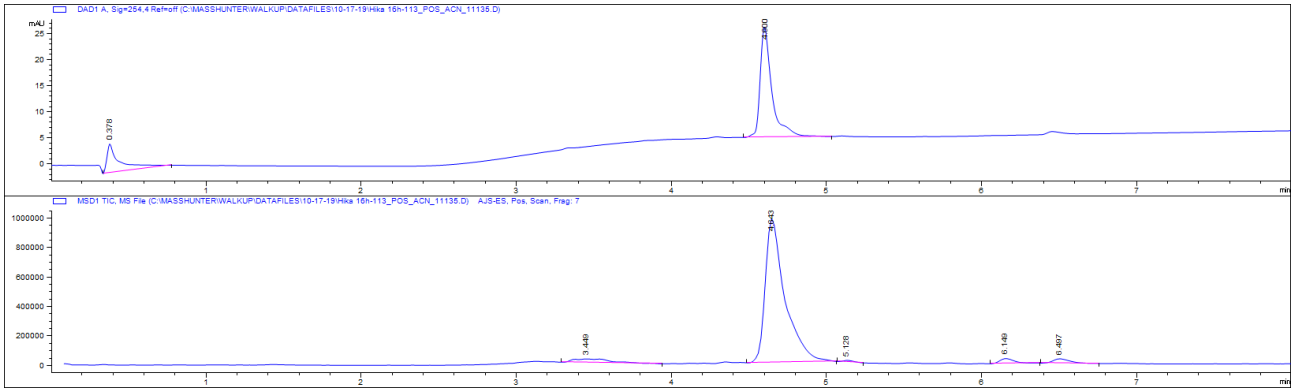
M = 473 **26dc** (M = 431) M = 429

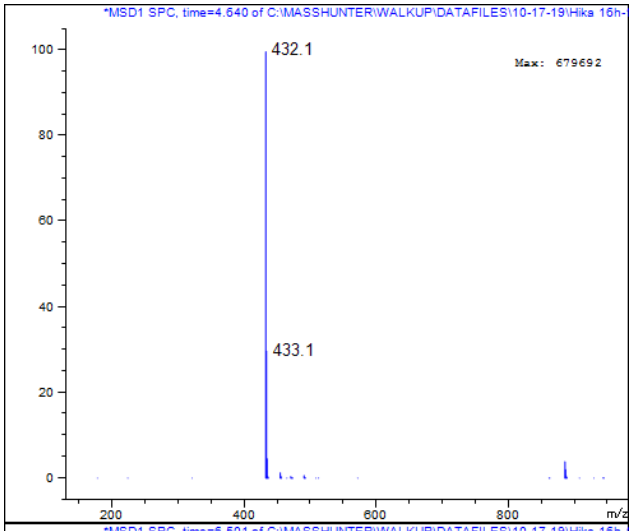
t = 0

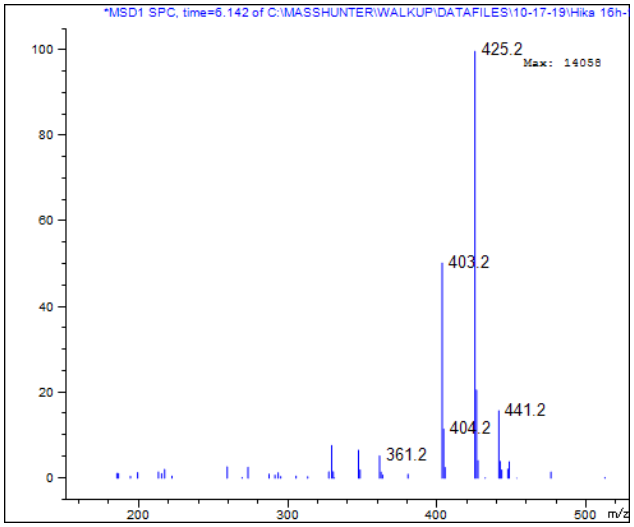


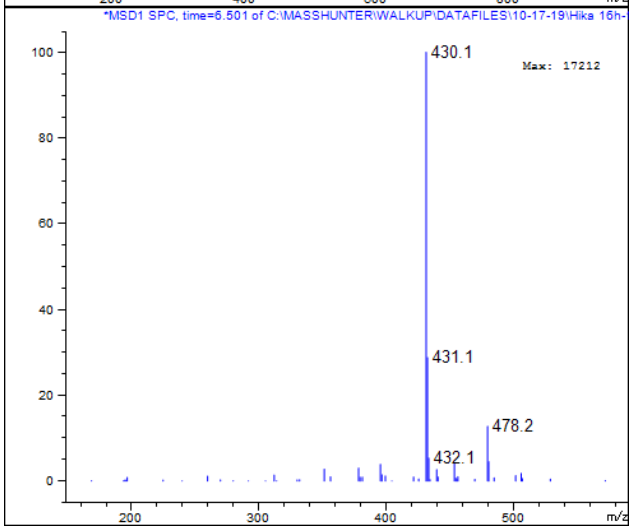


t = 16h

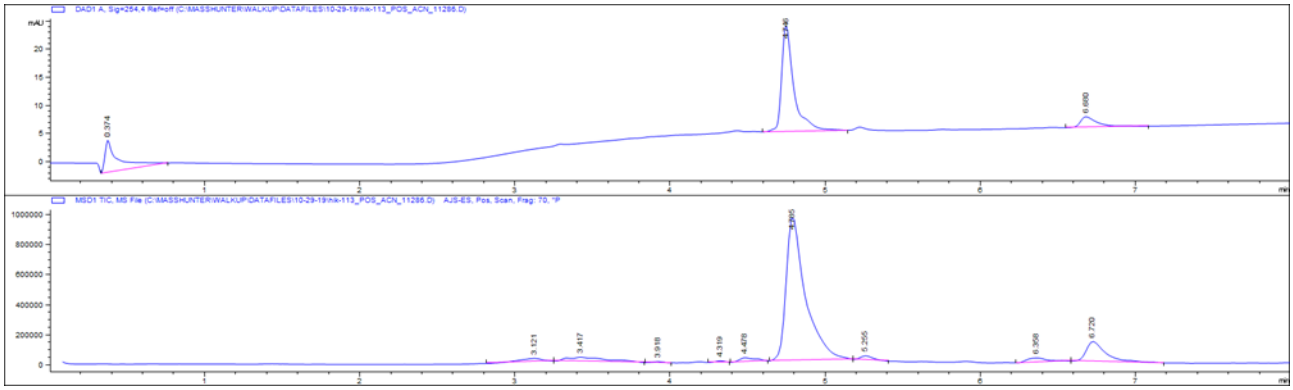

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-113_POS_ACN_11135.D)
mAU
0.378
4.900
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-113_POS_ACN_11135.D) AJS-ES, Pos, Scan, Frag: 7
4.643
3.449
5.128
6.149
6.497
min

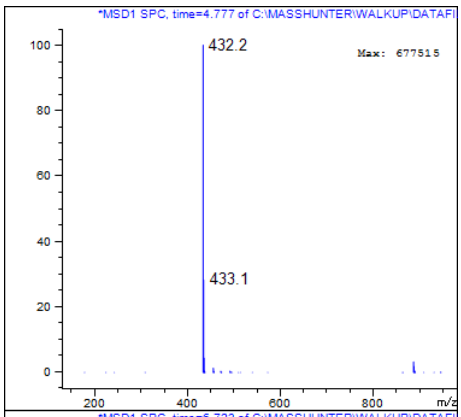

*MSD1 SPC, time=4.640 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 679692
432.1
433.1
m/z

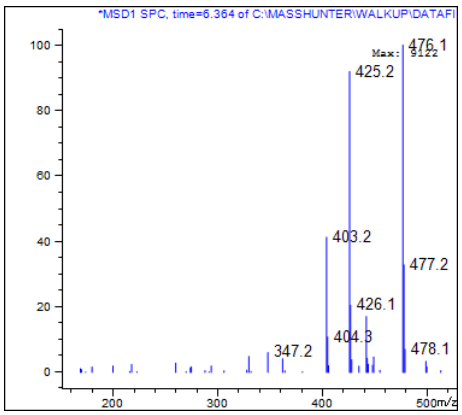

*MSD1 SPC, time=6.142 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 14058
425.2
403.2
441.2
404.2
361.2
m/z

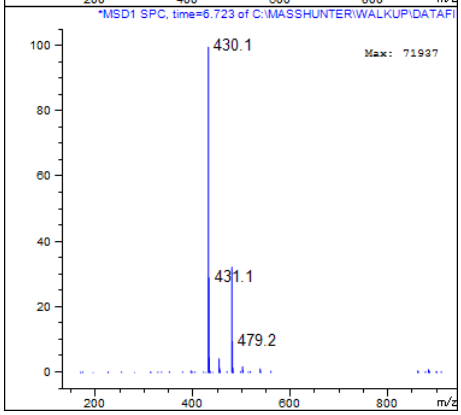

*MSD1 SPC, time=6.501 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 17212
430.1
431.1
478.2
432.1
m/z

t = 14 days

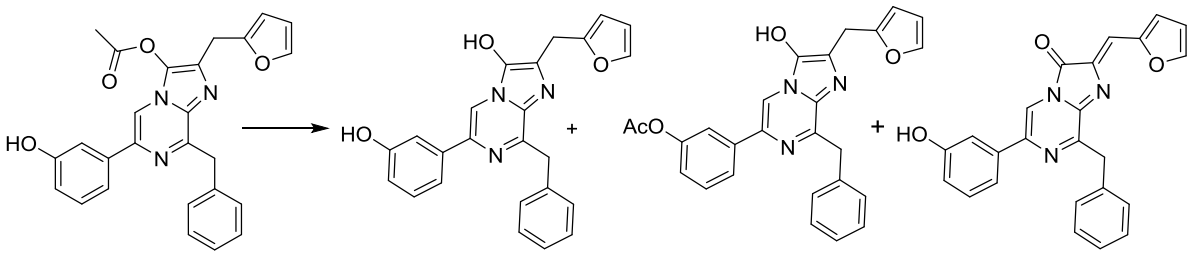



*MSD1 SPC, time=4.777 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 677515
432.2
433.1


*MSD1 SPC, time=6.364 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 5122
476.1
425.2
403.2
477.2
426.1
404.3
347.2
478.1

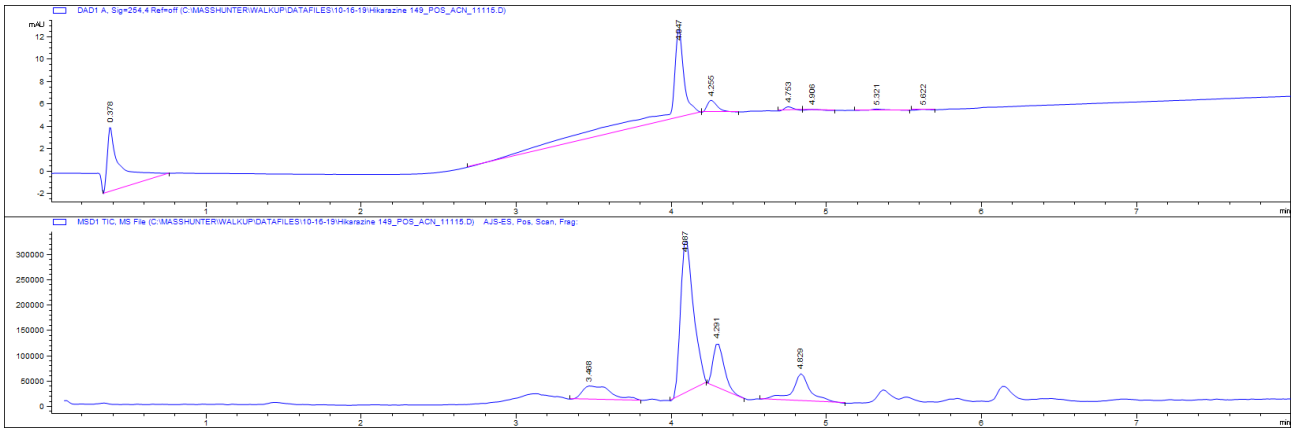

*MSD1 SPC, time=6.723 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 71937
430.1
431.1
479.2

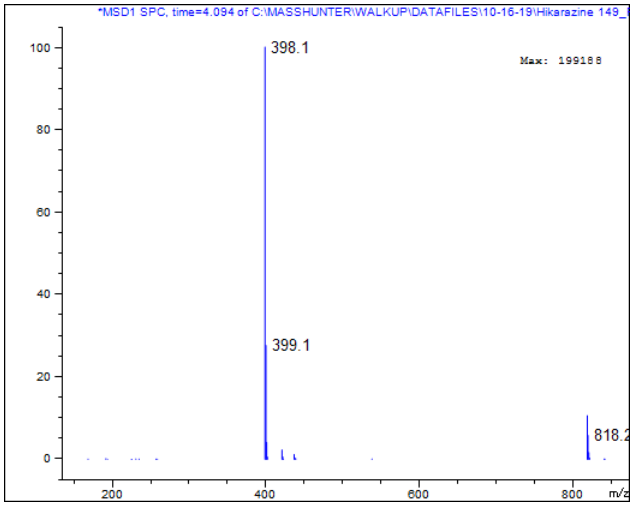
Hydrolysis products of hikarazine-149 (**25**{*13,1,37*})

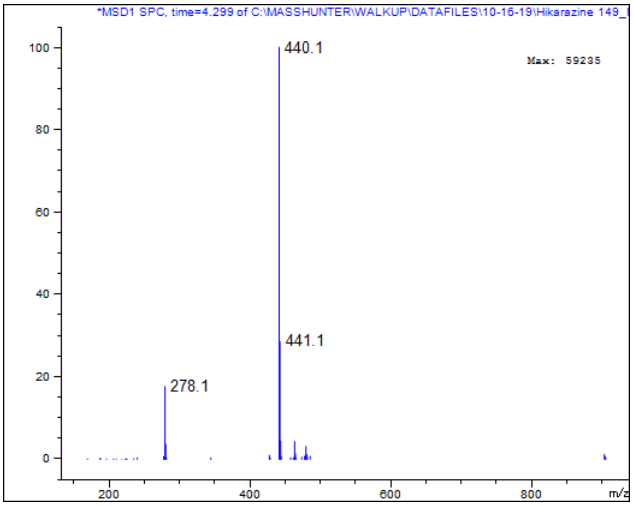


M = 439 **26bh** (M =397) M = 439 M = 395

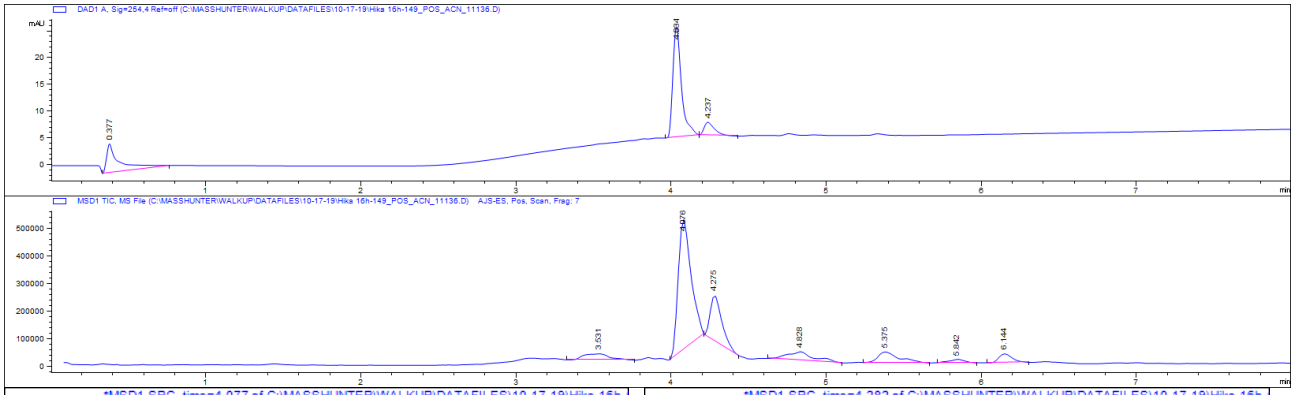
t = 0

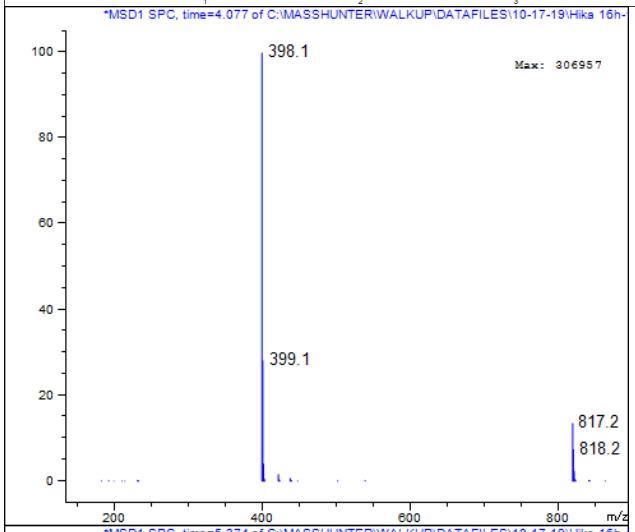


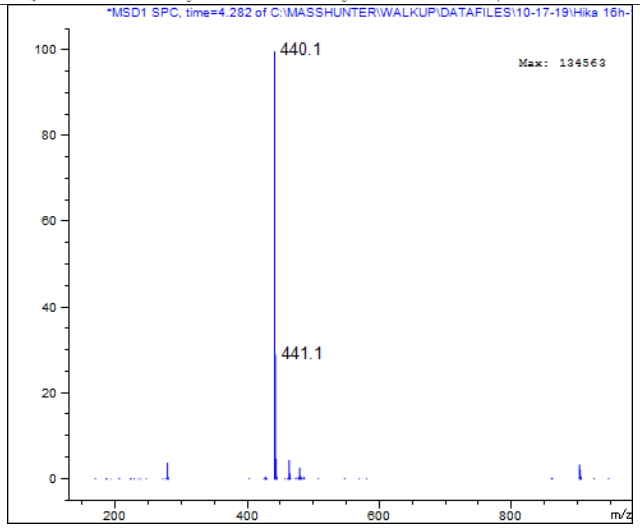


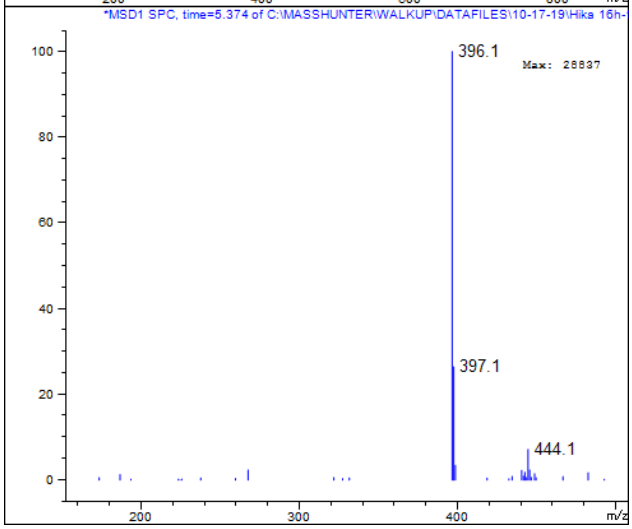


t = 16h

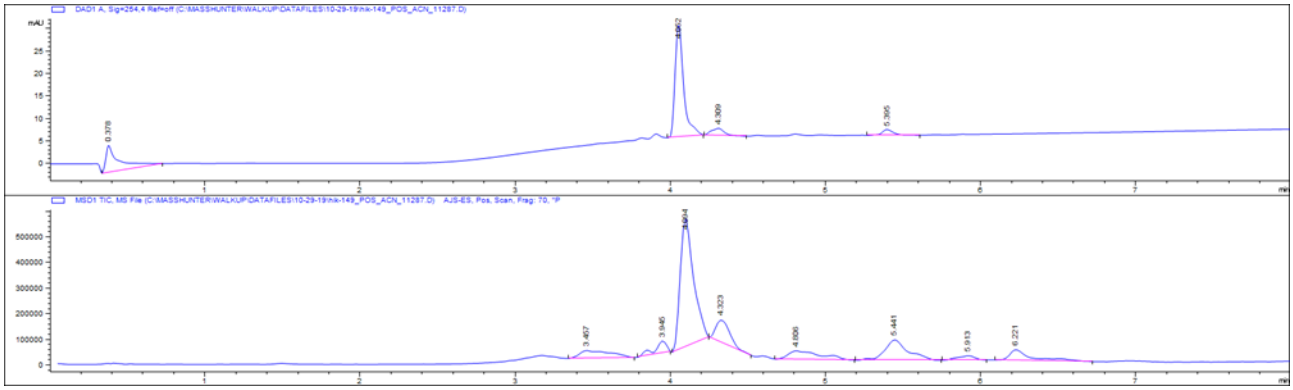

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-149_POS_ACN_11136.D)
mAU
0.377
4.237
min
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-149_POS_ACN_11136.D) AJS-ES, Pos, Scan, Frag: 7
3.531
4.275
4.828
5.375
5.842
6.144
min

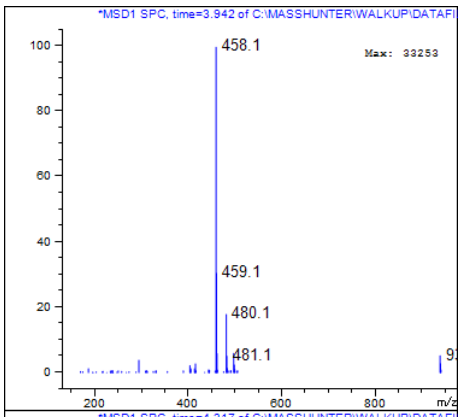

*MSD1 SPC, time=4.077 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 306957
398.1
399.1
817.2
818.2
m/z

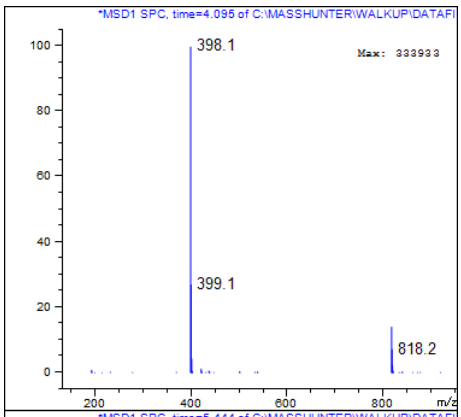

*MSD1 SPC, time=4.282 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 134563
440.1
441.1
m/z

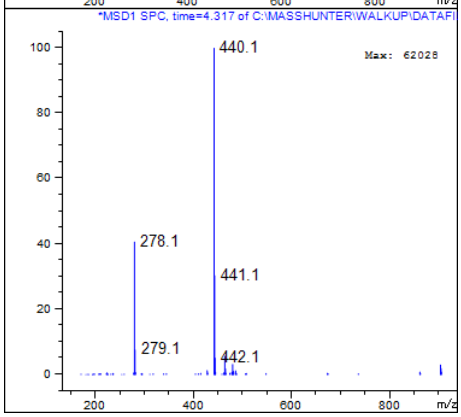

*MSD1 SPC, time=5.374 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 28837
396.1
397.1
444.1
m/z

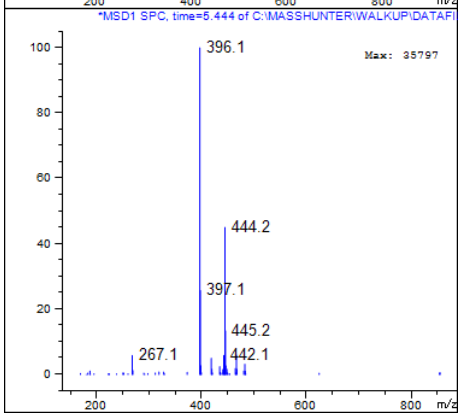
t = 14 days

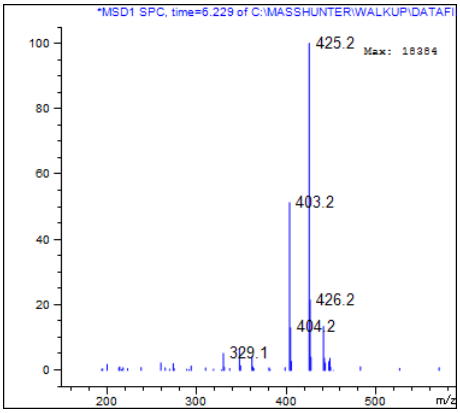



*MSD1 SPC, time=3.942 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 33253
458.1
459.1
480.1
481.1

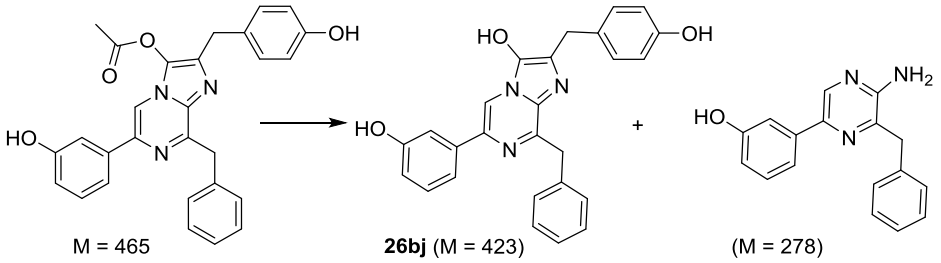

*MSD1 SPC, time=4.095 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 333933
398.1
399.1
818.2


*MSD1 SPC, time=4.317 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 62028
440.1
278.1
441.1
279.1
442.1


*MSD1 SPC, time=5.444 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 35797
396.1
444.2
397.1
445.2
267.1
442.1

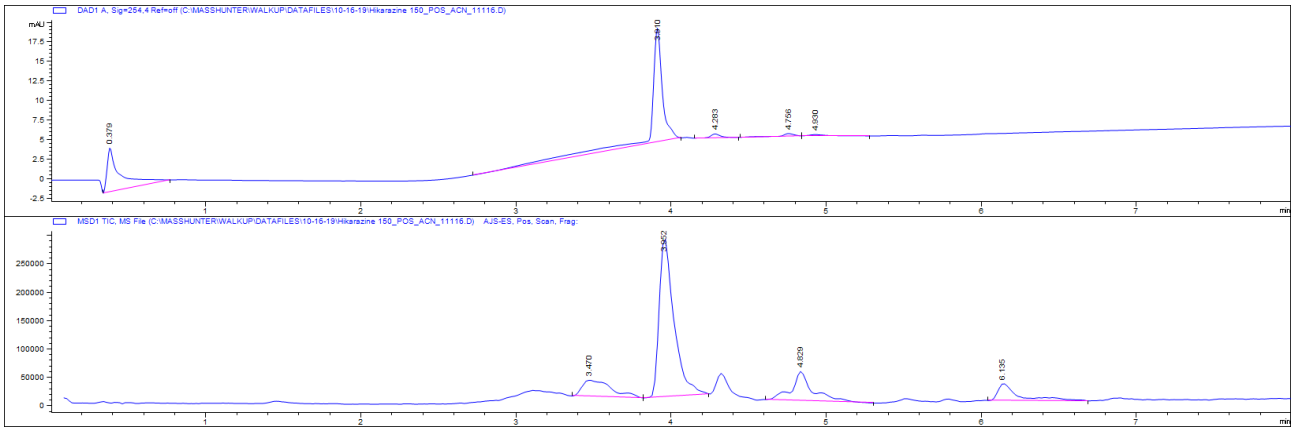

*MSD1 SPC, time=6.229 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 18384
425.2
403.2
426.2
404.2
329.1

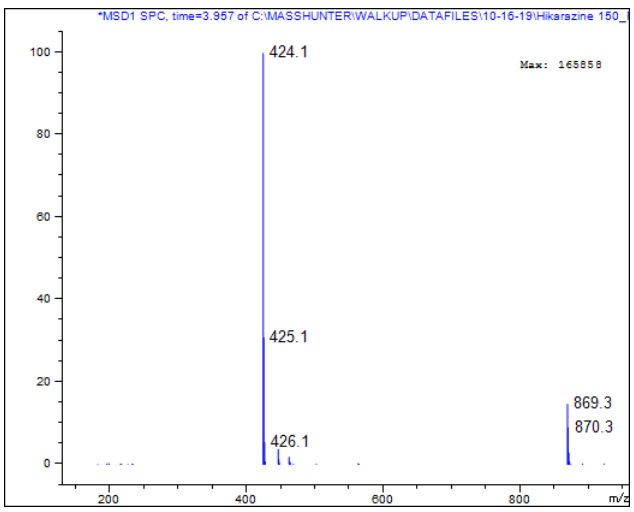
Hydrolysis products of hikarazine-150 (**25**{*13,1,63*})

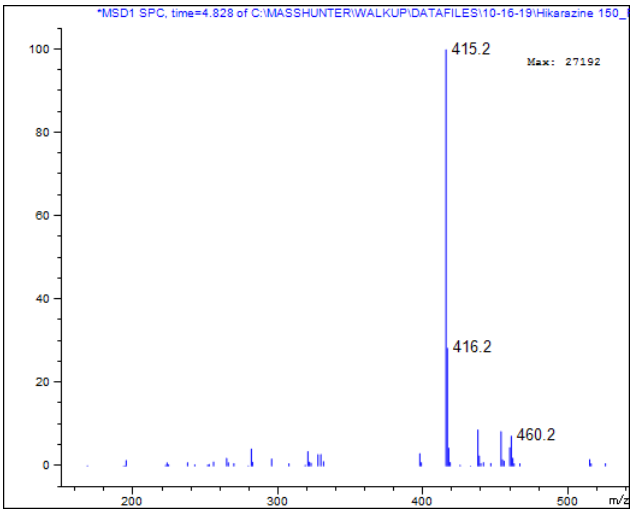


M = 465 **26bj** (M = 423) (M = 278)

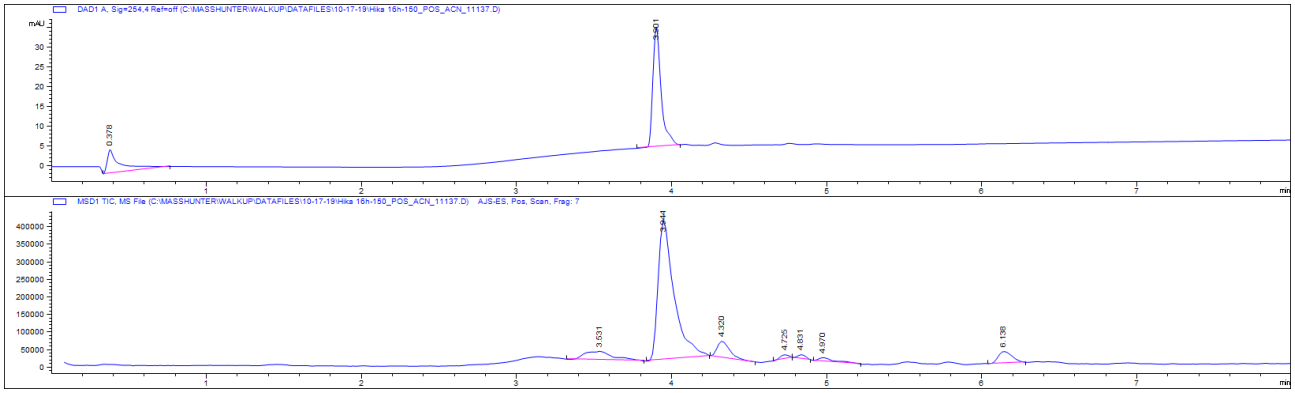
t = 0

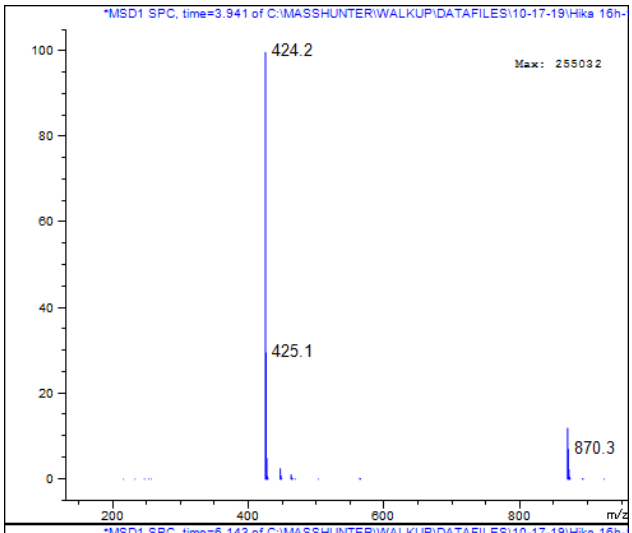


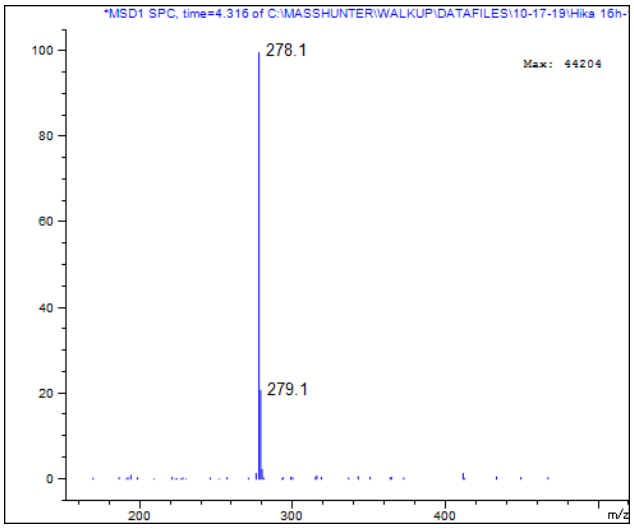


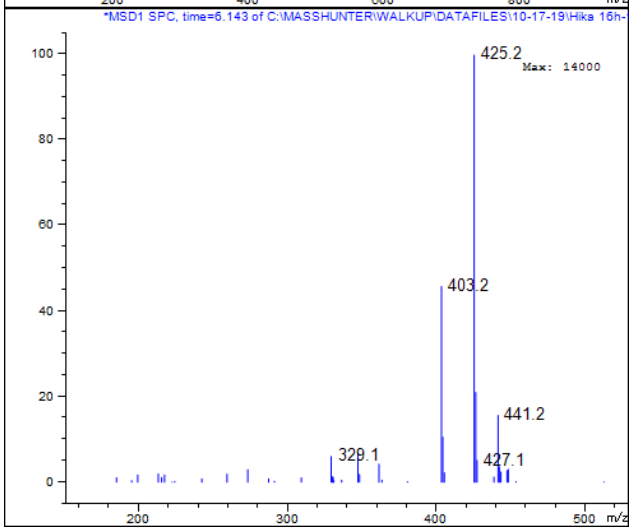


t = 16h

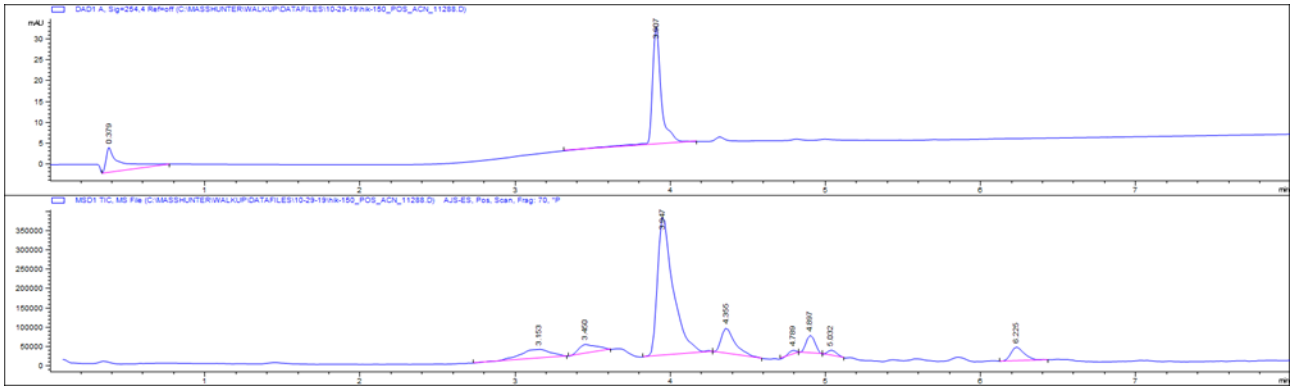

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-150_POS_ACN_11137.D)
mAU
0.378
3.941
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-150_POS_ACN_11137.D) AJS-ES, Pos, Scan, Frag: 7
3.631
3.944
4.320
4.725
4.831
4.970
6.138
min

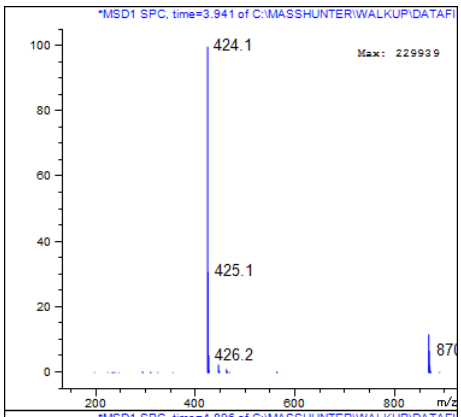

*MSD1 SPC, time=3.941 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 255032
424.2
425.1
870.3
m/z

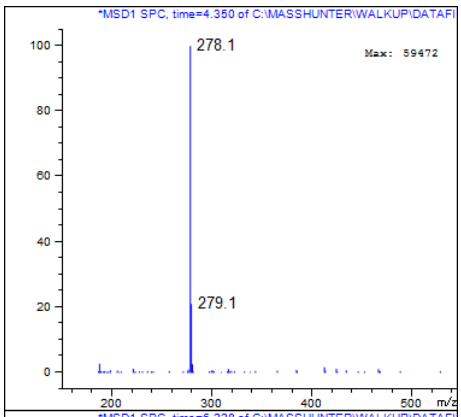

*MSD1 SPC, time=4.316 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 44204
278.1
279.1
m/z

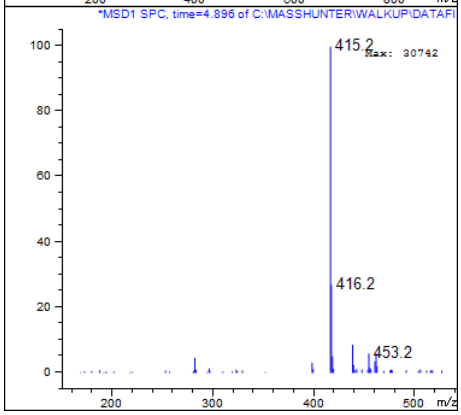

*MSD1 SPC, time=6.143 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
Max: 14000
425.2
403.2
441.2
427.1
329.1
m/z

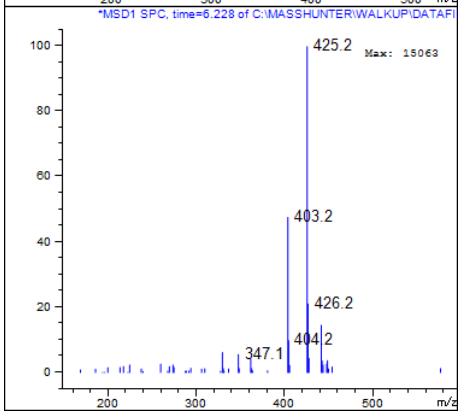
t = 14 days



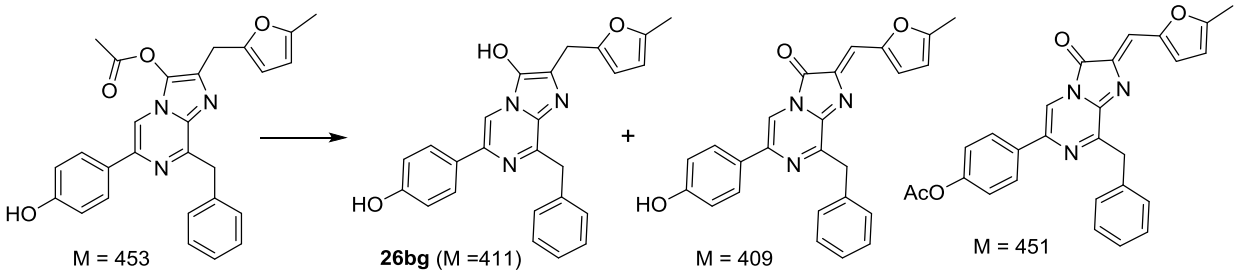

*MSD1 SPC, time=3.941 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 229939
424.1
425.1
426.2


*MSD1 SPC, time=4.360 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 59472
278.1
279.1

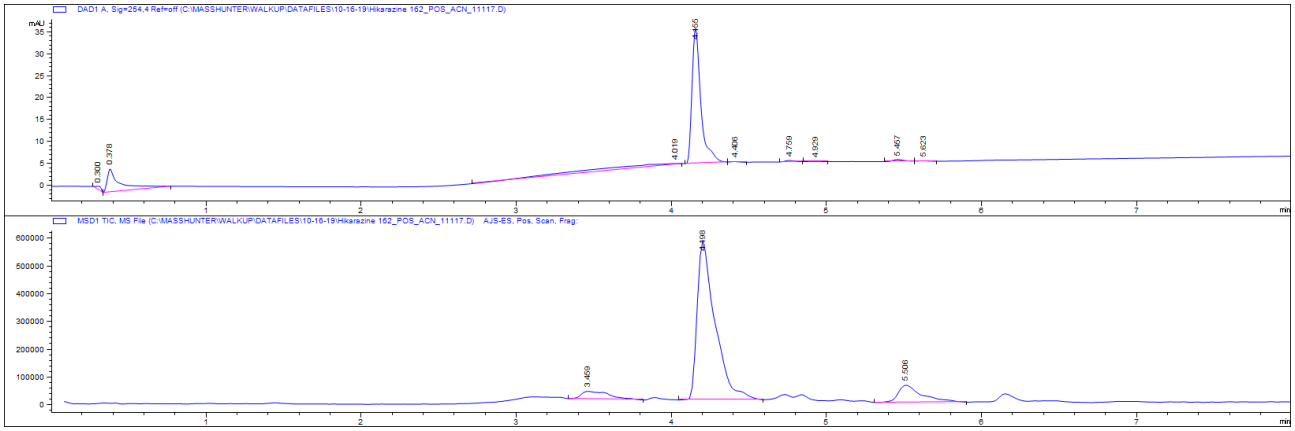

*MSD1 SPC, time=4.896 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 30742
415.2
416.2
453.2

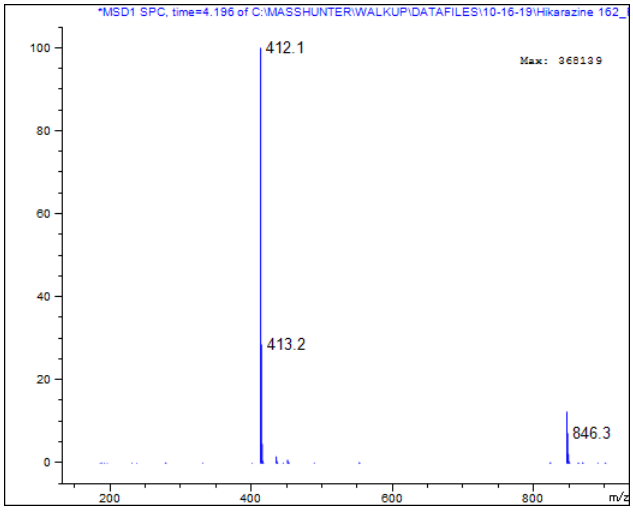

*MSD1 SPC, time=6.228 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 15063
425.2
403.2
426.2
404.2
347.1

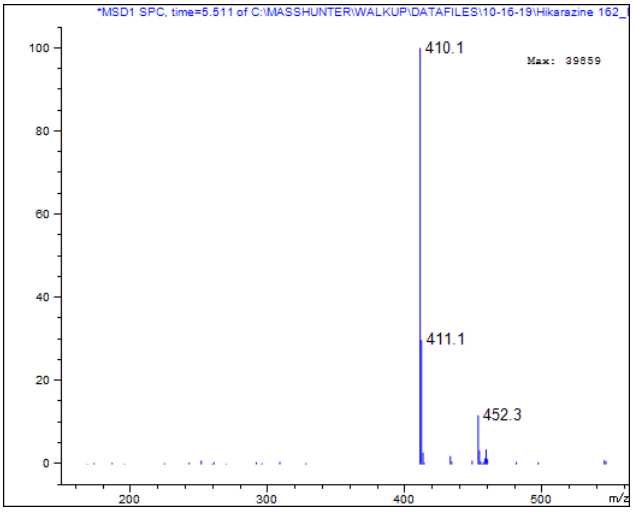
Hydrolysis products of hikarazine-162 (**25**{*14,1,42*})



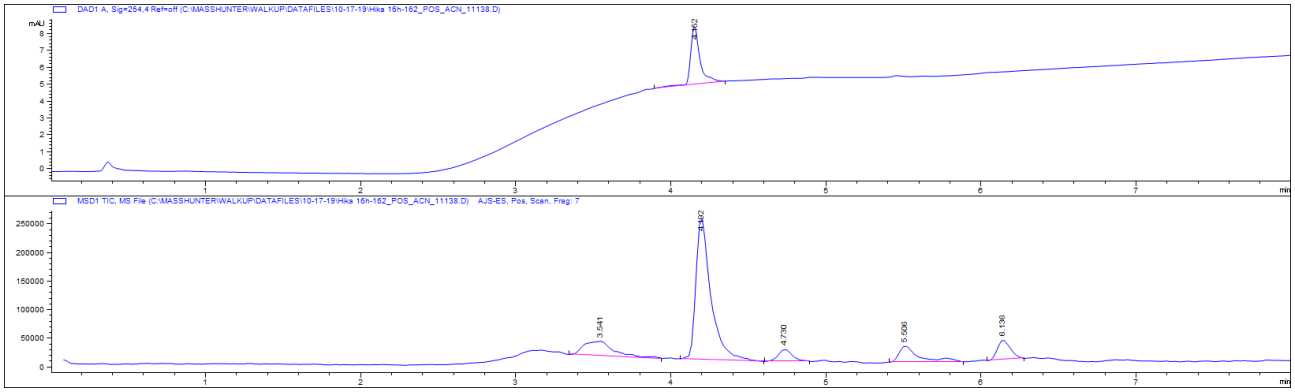
t = 0

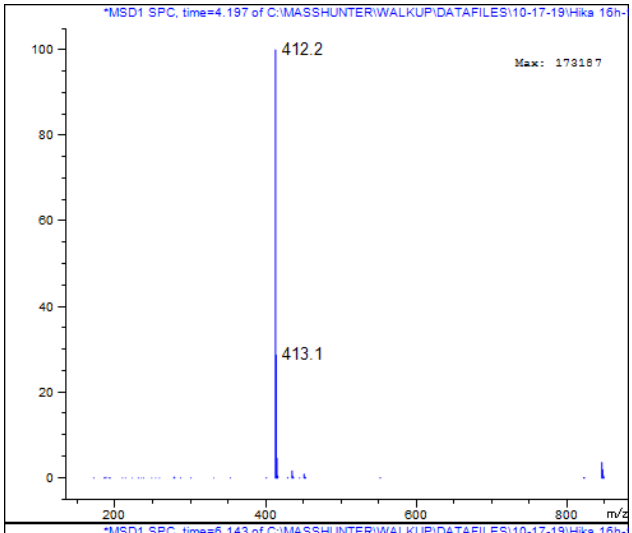


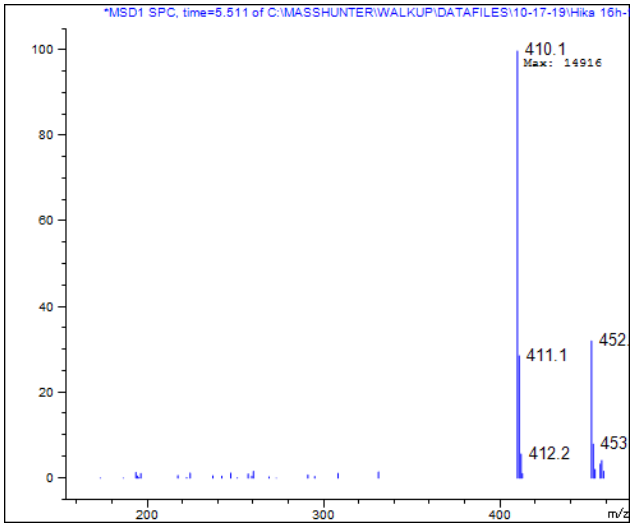


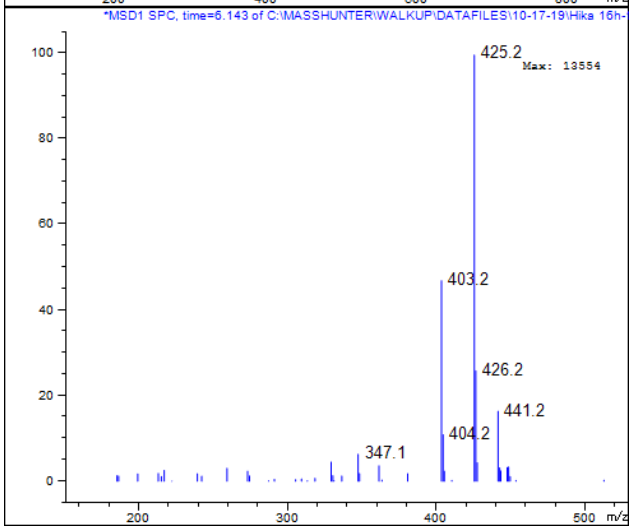


t = 16h

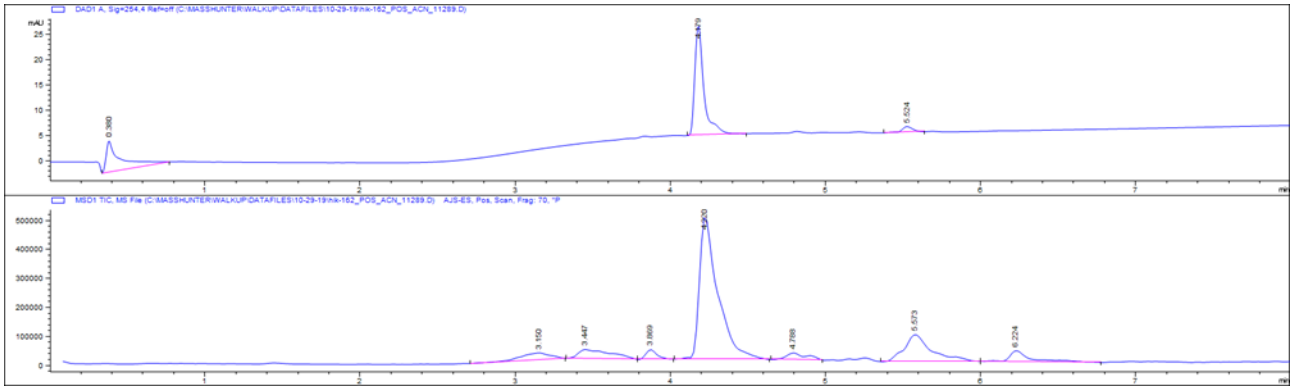

DAD1 A, Sig=254,4 Ref=off (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-162_POS_ACN_11138.D)
mAU
MSD1 TIC, MS File (C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-162_POS_ACN_11138.D) AJS-ES, Pos, Scan, Frag: 7
3.541
4.730
5.506
6.136
min

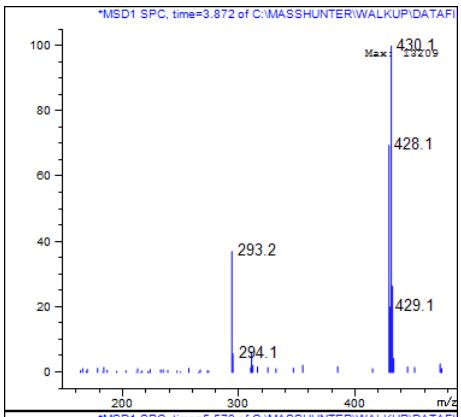

*MSD1 SPC, time=4.197 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
412.2
Max: 173187
413.1
m/z

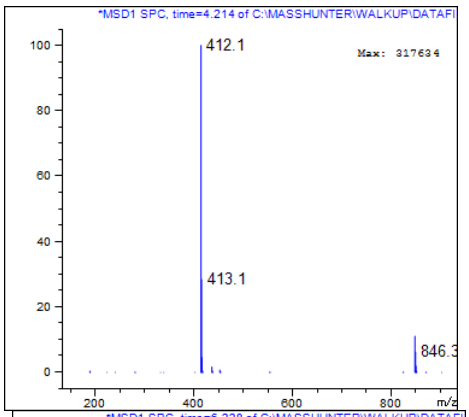

*MSD1 SPC, time=5.511 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
410.1
Max: 14916
411.1
412.2
452
453
m/z


*MSD1 SPC, time=6.143 of C:\MASSHUNTER\WALKUP\DATAFILES\10-17-19\Hika 16h-
425.2
Max: 13554
403.2
426.2
441.2
404.2
347.1
m/z

t = 14 days




*MSD1 SPC, time=3.872 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 19209
430.1
428.1
293.2
429.1
294.1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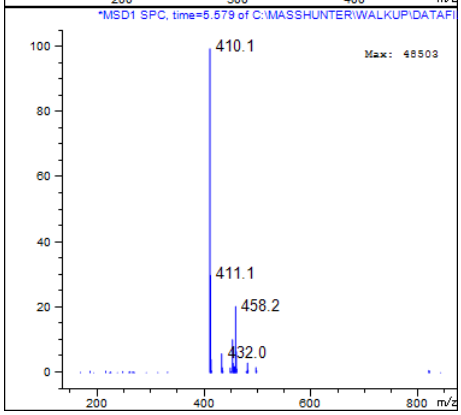
Max: 317634
412.1
413.1
846.3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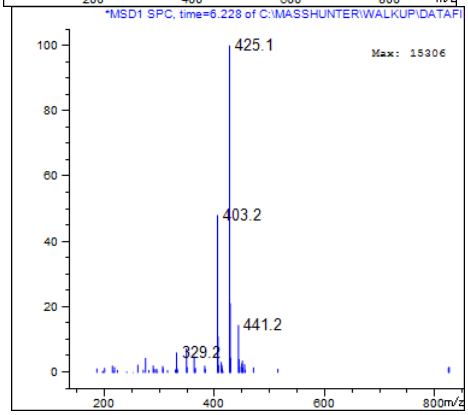
Max: 48503
410.1
411.1
458.2
432.0


*MSD1 SPC, time=6.228 of C:\MASSHUNTER\WALKUP\DATAFI
Max: 15306
425.1
403.2
441.2
329.2

Recombinant nanoKAZ/NanoLuc was produced as described before.[4]

Bioluminescence assays

- Protocol for the results described in tables 1-7 (a Berthold CentroXS3 luminometer was used for these experiments).

Buffer A: Dulbecco's Phosphate-Buffer Saline (DPBS) 1X, no calcium, no magnesium + 0.1%v/v Tween® 20.

1. Preparation of 96-well daughter plates and deprotection of O-acetylated luciferins **35**
- Move 96-well mother plates containing 10 mM stock solutions of preluciferins in DMSO from 20 °C to room temperature.
- Pipette 5 µL from mother plates into wells of polypropylene V-shaped 96-well daughter plates.
- Pipette 5 µL from a stock 0.84%v/v ethanolic solution of 37% hydrochloric acid (leading to a 0.1 M HCl concentration) into wells of daughter plates.
- Thermo-seal daughter plates, centrifuge 60 seconds at 2000 rpm, and store overnight at room temperature to allow deprotection of preluciferins.
- Store daughter plates at -20 °C until use. Note: the luciferins being intrinsically unstable, it is advised to immediately use daughter plates, or to minimize as much as possible the storage duration.

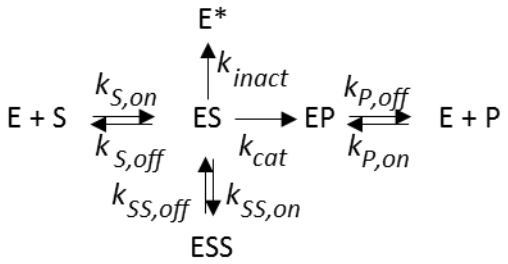
2. Dilutions for bioluminescence assays
- Move prepared 96-well daughter plates containing 5 mM solutions of luciferins in DMSO/ethanol/HCl from -20 °C to room temperature.
- Dilute luciferins 1:20 by adding 190 µL of Buffer A into wells and mixing, leading to 250 µM solutions of luciferins.
- Pipette 10 µL of the 250 µM solutions of luciferins into white polystyrene flat-bottomed 96-well plates (e.g. Greiner Lumitrac® 200). This plate P1 will be used for determination of the autoluminescence of luciferins in Buffer A.
- Pipette 10 µL of the 250 µM solutions of luciferins into white polystyrene flat-bottomed 96-well plates (e.g. Greiner Lumitrac® 200). This plate P2 will be used for determination of the luminescence of luciferins with the desired luciferase.

3. Bioluminescence Assays
- For autoluminescence measurements, dilute luciferins 1:10 adding 90 µL of Buffer A into wells of P1 and mixing.
- Measure autoluminescence signal over 5 minutes, integrating 1 s/well.
- For luminescence measurements, dilute luciferins 1:10 adding 90 µL of enzyme solution into wells of P2.
Note: in our case, the nanoKAZ solution (at 50 ng/L) was prepared diluting 1:2.000.000 adding 2 µL of a 0.1 g/L solution in 198 µL Buffer A, mixing, then adding 2 µL of this 1 mg/L solution in 198 µL Buffer A, mixing, then adding 100 µL of this 10 µg/L solution in 19.9 mL Buffer A.
- Shake 10 seconds, then measure luminescence signal over 2 hours, integrating 0.5 s/well.
The bioluminescence assays were carried out two times, starting from the same mother plate. Data were normalized to multiple wells containing furimazine, then averaged over the two runs. The final concentrations were 25 µM for each substrate and 45 ng/L for the nanoKAZ luciferase.

Given the design of the experiment, the first measurement of luminescence occurred between 30 seconds and 1 minute after addition of the luciferase; maximum intensities can thus be under-estimated for extremely fast-decaying substrates. For most of the substrates, however, the maximum of intensity was reached after 2 to 4 minutes.

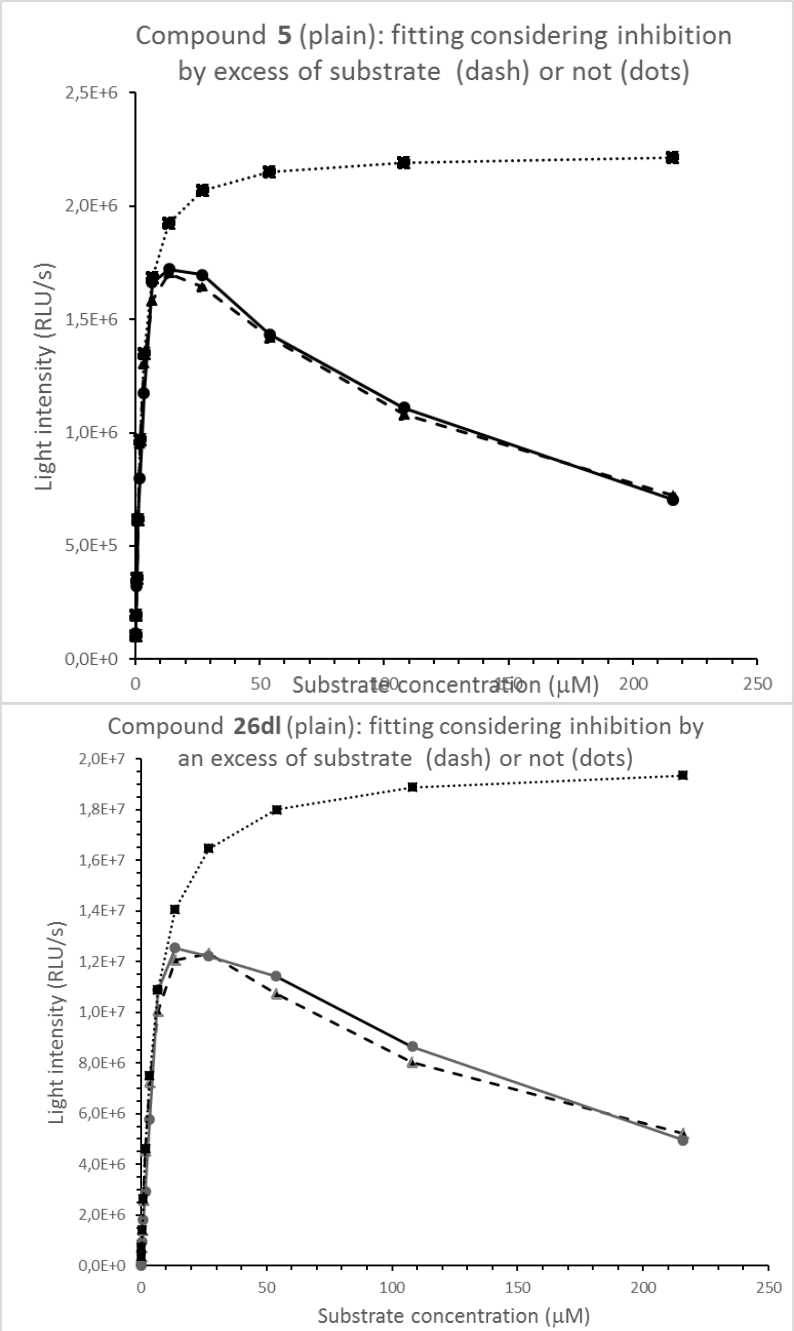
Kinetics analysis described in table 8.

In these experiments and as described before,[5] a Berthold Centro LB 960 luminometer was used. In order to get the maximum intensities for extremely fast-decaying substrates, the kinetics were acquired individually for each of substrates for 4 minutes, starting 1 second after the direct injection of the enzyme in the well of the plate already inside the plate reader and a one second period of shaking.
The apparent reaction rate (v') is given by the measured light intensity (RLU/s) reflecting counted photons/s, depending on the real catalytic rate (k_{cat}) and the yield of the measurement (ρ, the number of molecules catalyzed per collected RLU). The kinetics have been fitted with Michaelis-Menten model drawn below considering 1) the luciferins (S) as the limiting substrates and O_2 as saturating substrate in the experimental assay conditions (100 µL) in a 6 mm-diameter well of multi-well plates, 2) the inhibition of the enzyme E by excess of substrate through the binding of a second substrate (ESS) on the Michaelis' complex (ES) with the dissociation constant K_I and the on ($k_{SS,on}$) and off ($k_{SS,off}$) binding constants, and 3) the stochastic inactivation of the enzyme (E*) along the reaction turn over decreasing exponentially the active enzyme population with the kinetic constant k_{inact}. K'_M is the apparent constant of Michaelis and V'_{max} the apparent maximal reaction velocity.

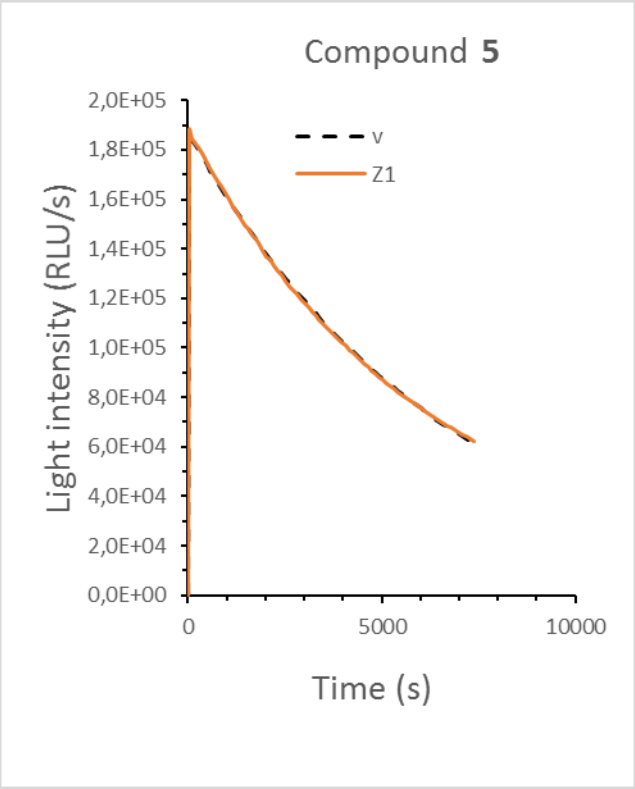


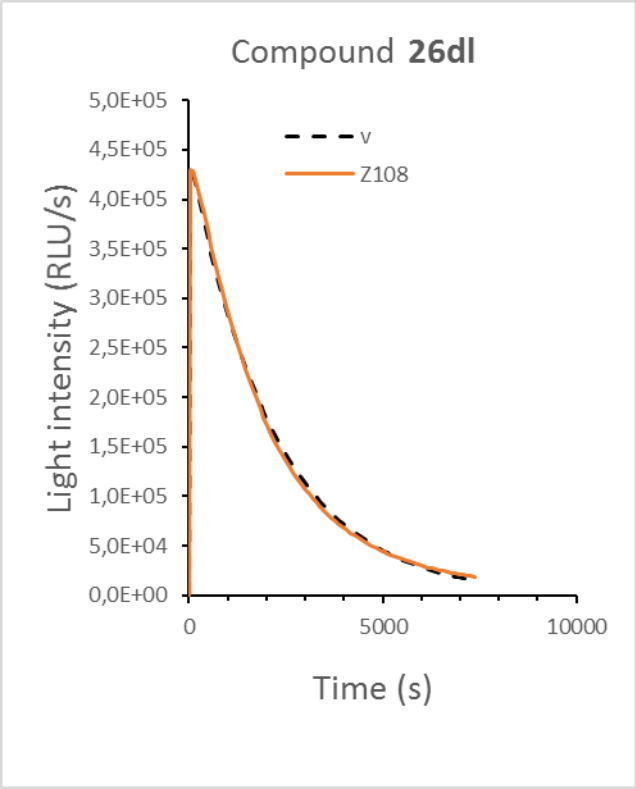
with
$d[ES]/dt = [E]\,[S]\,k_{S,on} - [ES]\,k_{S,off} - [ES]\,k_{cat} - [ES]\,[S]\,k_{SS,on} + [ESS]\,k_{SS,off} - [ES]\,k_{inact}$
$K_I = k_{SS,off} / k_{SS,on}$ in M
$K_M = (k_{S,off} + k_{cat})/ k_{S,on} = K_M' / (1+ [S]^2/K_I)$ expressed in M
$V_{max} = [E_0]\,[S]\,k_{cat} = V'_{max}\,([S] + K_M + ([S]^2/K_I)) / [S]$ expressed in mol/s
$v' = [E]\,[S]\,k_{cat} / ([S] + K_M + ([S]^2/K_I))$ expressed in RLU/s
$[E] = [E_0]\,e^{-t \cdot k_{inact}}$ with k_{inact} expressed in s^{-1} and the time t in s.
$v = v' \rho$ in mol/s
$\rho = [S]\,N_a\,vol / \Sigma I$ in molecules/RLU with $N_a = 6.02 \cdot 10^{23}$ and the sample volume vol in L

As an illustration of the inhibition of reaction by an excesses of substrates, the two figures below are providing the curves obtained (in plain) for compounds **5** and **26dl** as well as the fitting with calculated curves taking in account (or not) this inhibition. Time frame of these experiences was of four minutes.



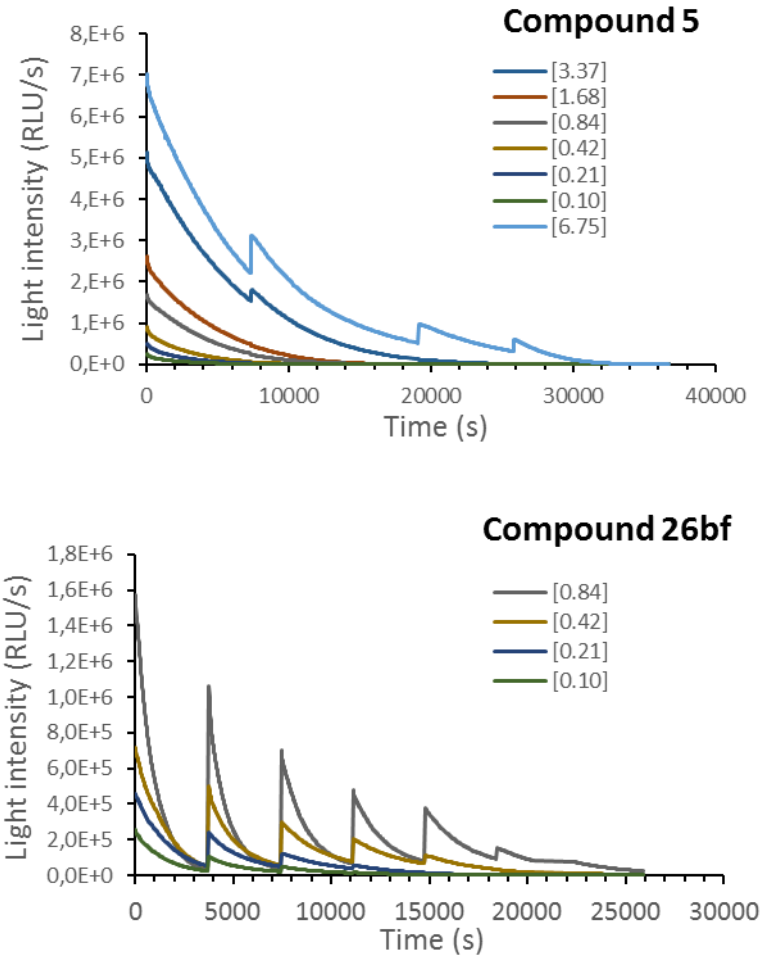
As an illustration of the irreversible inhibition over time, the two following figure are depicting the kinetics (plain) and their fit (dash), again for compound **5** and **26dl**, when taking account an enzyme inactivation. The first point was measured after one second.





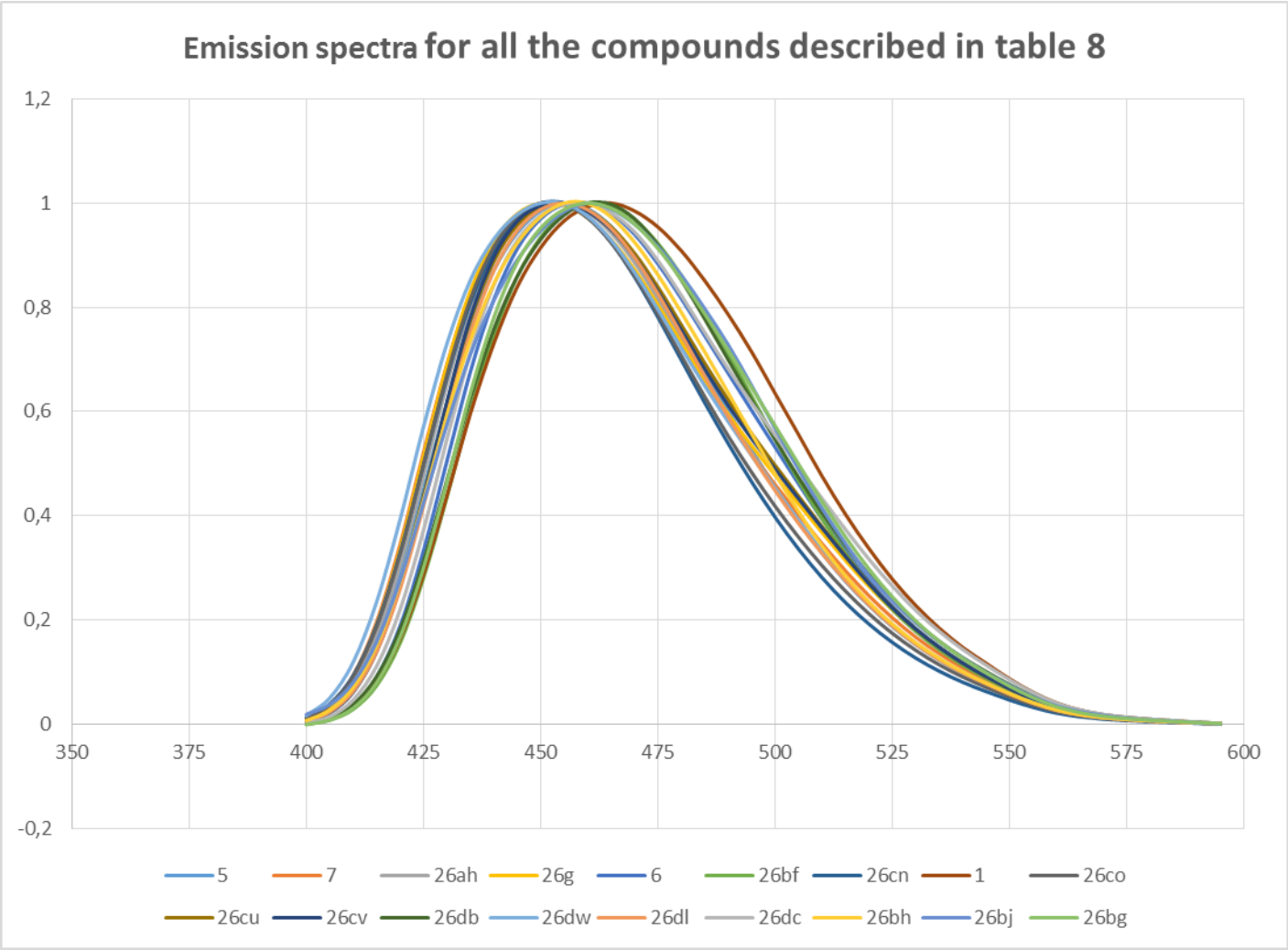
Enzyme inactivation kinetics. The kinetics are plotted versus time with the same enzyme concentration and the same substrate concentration. These plots compare the fitting of the experimental data (red plain line) with the theoretical reaction velocity computed according to the described Michaelis-Menten model taking into consideration the irreversible inactivation of the enzyme (dashed black lines).

Finally, as another illustration of this enzyme death over time, we provide in the following the signal profile over time for compound **5** and for the flashy compound **26bf** (which we have already published[4]). Each of the intensity increases marks the addition of fresh enzyme in the reaction media.



Light emission intensity decreases with time: steeply for the "flashy" compound **26bf** and much more slowly for compound **5** a "glow" substrates. To check if the reaction rate indicated by the photon emission (RLU/s) decreases with time, the same enzyme amount ($62 \cdot 10^{-18}$ mol) was added as seen by the intensity increases for different concentrations of substrates (in µM) as indicated in the legend between brackets.

The wavelengths at maximum emission (λ_{max}) were determined using a JASCO FP-6300 spectrofluorometer, the following pictures is depicting the superposition of the 18 compounds listed in table 8, their intensities were normalized to compare the wavelength max as well as the spread.



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