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Original Citation:

Availability:

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Published version:

DOI:10.1039/c6ra07071j

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This is the author's final version of the contribution published as:

Calcio Gaudino, E.; Tagliapietra, S.; Martina, K.; Palmisano, G.; Cravotto, G.
Recent advances and perspectives in the synthesis of bioactive coumarins.
RSC ADVANCES. 6 (52) pp: 46394-46405.
DOI: 10.1039/c6ra07071j

The publisher's version is available at:

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Recent advances and perspectives in the synthesis of bioactive coumarins

E. Calcio Gaudino^a, S. Tagliapietra^a, K. Martina^a, G. Palmisano^b, G. Cravotto ^{*a}

The impressive pharmacological properties shown by a number of coumarins have lead to extraordinarily large emphasis being placed on the design of more efficient and greener synthetic procedures to produce them. The increasing use of enabling technologies, such as microwaves, ultrasound, new heterogeneous catalysts and greener solvents in recent years has made access to coumarin derivatives much simpler. This review will highlight the most recent synthetic advances that make use of non-conventional methods and energy sources and some perspectives for the future.

1 Introduction

Naturally occurring coumarins and their synthetic derivatives are well known for their significant biological and pharmacological properties, which include anticoagulant, antimicrobial, antitumor, anti-HIV, anti-inflammatory and antioxidant activities.¹ Coumarins have found widespread applications in several fields,²⁻⁸ including drugs, cosmetics, pesticides and fluorescent dyes,⁹ to such an extent that not even a book, never mind a review, would be sufficient to describe them completely. The impressive molecular diversity found in coumarins has lead to a number of excellent surveys according to chemical structure,¹⁰ such as prenyloxycoumarins,¹¹ furocoumarins¹² and hydroxycoumarins.¹³ Recent reviews have highlighted the progress of coumarin derivatives in drug development. Examples include antioxidant,^{14,15} anticoagulant,¹⁶ anticancer,¹⁷⁻²⁰ antituberculosis²¹ and anti-inflammatory agents.^{22,23} The coumarin skeleton is at the core of important antibiotics, such as novobiocin, coumermycin A1 and chlorobiocin,²⁴ and remains a valuable source of lead compounds for the design and development of effective antimicrobial and antifungal therapy drugs.²⁵

Coumarin derivatives are usually prepared via the chemical modification of the benzopyran ring. Classic coumarin preparation makes use of the von Pechmann,²⁶ Perkin, Knoevenagel,²⁷ Reformatski, Kostanecki-Robinson, Wittig and Baylis-Hillman reactions as well as the Baker-Venkataraman rearrangement and the intramolecular Claisen condensation.

Most synthetic procedures are costly, time consuming, not environmentally friendly, give relatively poor yields,

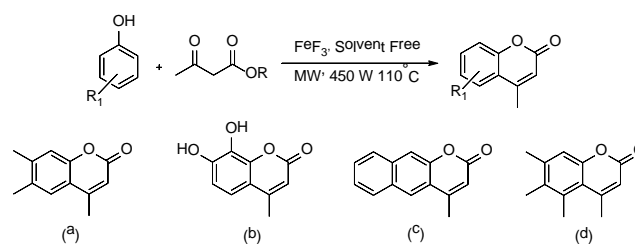
incompatible with other functional groups and require laborious purification. However, the last two decades have seen new, efficient and green methods that use non-conventional energy sources, such as microwaves (MW)²⁸ and ultrasound irradiation,²⁹ being developed.^{30, 31}

In this work, we present an overview of recent literature and technical advances in this research field in order to provide insight into modern approaches to the synthesis of bioactive coumarins.

The review is made up of four main paragraphs which are subdivided according to coumarin structure and functionalization: 1) simple coumarins, 2) pyranocoumarins, 3) furocoumarins and 4) hybrid coumarin derivatives. This review covers the literature from January 2013 to the end of 2015. Earlier papers that are nonetheless relevant and had not previously been reviewed are cited in some cases.

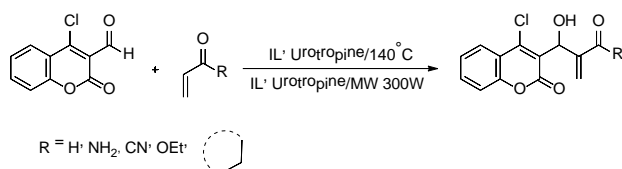
1.1. Simple coumarins

Multi-functionalized coumarins bare at least two substituents with different functional groups.³² Several efficient synthetic procedures for these have recently been reported in the literature. Vahabi *et al.* (2014),³³ have described a rapid solvent-free, one-pot synthesis of coumarin derivatives via the von Pechmann condensation of phenols with ethyl acetoacetate using FeF₃ as an acid catalyst under MW irradiation (Scheme 1). The best results were obtained in solvent-free conditions at 110 °C (MW power 450 W) and 1 bar (95% yield). The same reaction entailed longer reaction times and gave lower yields when carried out in solution (dimethylformamide, acetonitrile, dioxane, water). The antimicrobial and antifungal activity of all products was screened (*Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger* and *Helminthosporium oryzae*) using penicillin and griseofulvin as standard reference drugs. Good activity against both bacteria and fungi was found in all compounds, but especially in (a), (b), (c) and (d) (Scheme 1).



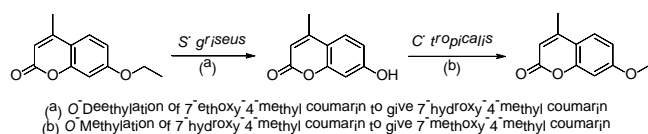
Scheme 1. FeF₃ catalyzed von Pechmann reaction.

Chandramouli *et al.* (2013),³⁴ have reported the synthesis of coumarin derivatives in the presence of catalytic amounts of urotropine in ionic liquids (i.e. [BMIM]BF₄ and [BIPIM]BF₄). The Baylis-Hillman reaction gave good yields under MW irradiation (76–84% yields) (Scheme 2). The antibacterial activity of all compounds (*Bacillus subtilis*, *Bacillus sp.*, *Pseudomonas putida* and *E. coli*) proved to be moderate compared to streptomycin.



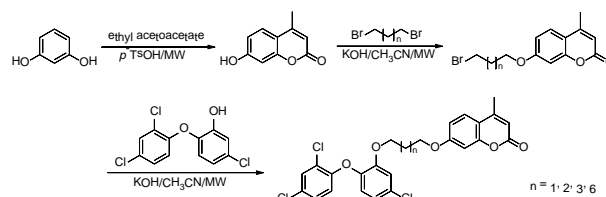
Scheme 2. Synthesis of Baylis-Hillman adducts.

Microbial biotransformation has also been used for these synthetic aims. Nigam *et al.* (2013),³⁵ have described a new microbial transformation of the benzopyran ring system via the functional group transferring action of various fungi and bacteria (Scheme 3). The *O*-deethylation of 7-ethoxy-4-methylcoumarin by *Streptomyces griseus* and *O*-methylation to the 7-methoxy analogue by *Candida tropicalis* occurred in very poor yields (4.2% after 72 h and 5.5% after 5 d, respectively). Although conversion and purification still require considerable improvement, 7-hydroxy-4-methylcoumarin showed interesting inhibitory activity (*B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa*).



Scheme 3. Microbial biotransformation of coumarin ring system.

Four chalcone-triclosan, chromone-triclosan and coumarin-triclosan hybrid compounds have been synthesized by Otero *et al.* (2014),³⁶ and tested for their cytotoxic and leishmanicidal activities. Initially, 7-hydroxy-4-methylcoumarin (obtained from the MW-assisted von Pechmann reaction between resorcinol and ethyl acetoacetate) was alkylated with 1, ω -dibromoalkanes (ω = 3, 4, 5, 8) in the presence of KOH, which gave the respective bromoalkyl derivatives in significantly rapid times. These compounds were then coupled with triclosan to produce the corresponding coumarin hybrids in 50–80% yields (Scheme 4). All compounds showed higher leishmanicidal activity than cytotoxicity. This high leishmanicidal activity and low cytotoxicity meant that these compounds were found to be promising candidates as drug development templates. SAR studies had previously established that a short chain improves selectivity.



Scheme 4. Synthetic pathway for triclosan-coumarins.

The orphan G-protein-coupled receptor, GPR55, which is activated by 1-lysophosphatidylinositol and interacts with cannabinoid (CB) receptor ligands, has been proposed as a new potential drug target for the treatment of diabetes, Parkinson's disease, neuropathic pain and cancer. The development of coumarin derivatives as novel ligands for CB (cannabinoid) receptors has recently been reported.³⁷ The properties of 7-alkyl-3-benzylcoumarins have been compared with those of GPR55 antagonists (G-protein-coupled receptor), Δ^9 -tetrahydrocannabivarin (a), and cannabidivarin (b), a cannabidiol analogue, which were isolated from *Cannabis sativa*, and are depicted in Figure 1.

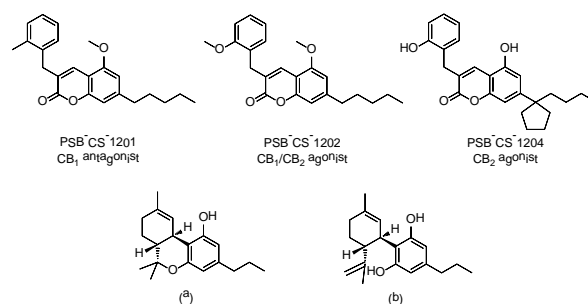
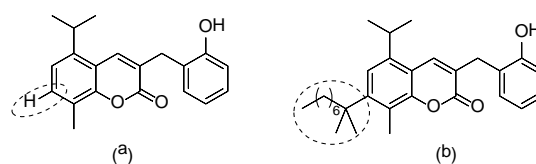


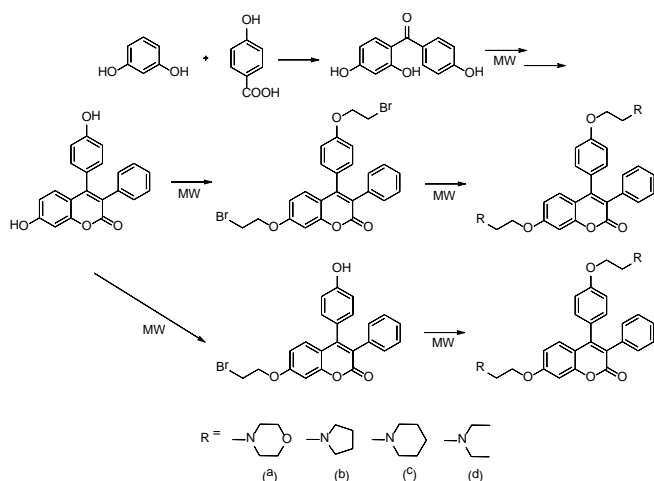
Figure 1. Structural comparison of cannabinoid receptor antagonists (PSB-CS-1201) and agonist (PSB-CS-1202, PSB-CS-1204) with the GPR55 antagonists Δ^9 -tetrahydrocannabivarin (a) and cannabidivarin (b).

Müller *et al.* (2013),³⁷ have established a straightforward coumarin synthesis for these derivatives; a one-pot procedure from suitably substituted salicylaldehydes and α,β -unsaturated aldehydes under MW irradiation (110 °C for 50 min, 200 W). Selective and competitive GPR55 antagonists were identified among the 7-unsubstituted coumarins produced. These include 3-(2-hydroxybenzyl)-5-isopropyl-8-methyl-2*H*-chromen-2-one (a), that has derivatives with long alkyl chains in the 7 position which are potent, possibly allosteric, GPR55 antagonists with ancillary CB receptor affinity (b) (Scheme 5).



Scheme 5. Coumarin GPR55 antagonist (a) and allosteric antagonist (b).

Chen *et al.* (2013),³⁸ have designed and synthesized novel diphenylethylene–coumarin derivatives, containing varying numbers of amino side chains, in good yields under MW radiation. 3,4-Diphenyl coumarins were synthesized by reacting resorcinol with 4-hydroxybenzoic acid to yield benzophenone under Fries reaction conditions. The treatment of benzophenone with phenyl acetic acid mainly gave the acylated 3,4-diaryl coumarin derivative via the Perkin reaction route. The acetyl groups of these compounds were removed in acidic solution and provided free phenol –OH, whose derivatization with 1,2-dibromoethane yielded the mono- and di-O-alkyl bromo derivatives. The S_N2 substitution of bromine with a variety of amines provided the final products which either contained two amino alkyl chains or one side chain at the 7-position (Scheme 6). The triaminoalkyl derivatives were obtained in the same way from the corresponding 3-methosiphenol. MW irradiation efficiently improved the Perkin reaction and nucleophilic substitution. Of those prepared and tested, four compounds containing two amino alkyl chains [(a): R = morpholinyl, (b): R = pyrrolidinyl, (c): R = piperidinyl, (d): R = NEt_2] proved themselves to possess superior anti-proliferative activity to the positive controls against five cancer cell lines.



Scheme 6. Diphenylethylene–coumarin derivative synthesis.

1.2. Pyranocoumarin derivatives

Pyrano fused heterocyclic compounds (pyranocoumarins) are an important class of structural motif which possesses a wide range of biological activity and are present in many natural products and synthetic drugs (Figure 2). They exhibit antifungal, insecticidal, anticancer, anti-HIV, anti-inflammatory and antibacterial activity. More specifically, pyrano[3,2-c]coumarins have become attractive synthetic targets for medicinal chemistry applications because of the broad spectrum of biological properties they display and relative natural abundance.

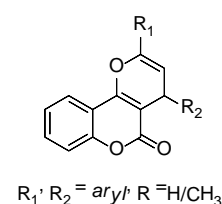
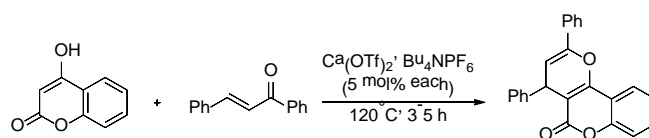
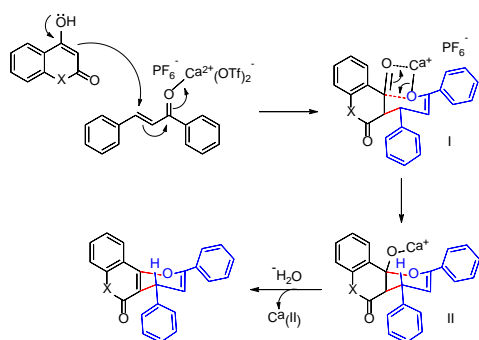


Figure 2. Representative structures of pyrano[3,2-c]coumarin.

The most common pyranocoumarin synthesis starts with the cyclization of 4-hydroxycoumarin (nucleophile) with electrophiles, such as α,β -unsaturated carbonyls (generally chalcones), 1,3-diaryllallylic compounds, propargylic alcohols etc., while cyclohexane-1,3-diones are generally used as nucleophiles for benzopyran synthesis. Although some of these methods are efficient, most of them suffer from limitations, including long reaction times, expensive catalysts, strongly acidic and non-benign conditions, regioselectivity issues and poor yields. In view of their biological importance, Yaragorla *et al.* (2015),³⁹ have developed a $Ca(OTf)_2$ catalyzed, one-pot conjugate addition and annulation of various nucleophiles to the α,β -unsaturated carbonyl compounds for the synthesis of bioactive pyranocoumarins. The solvent-free reaction of 4-hydroxycoumarin and chalcone with 5 mol % of $Ca(OTf)_2$ and Bu_4NPF_6 (5 mol %) at 120 °C was performed on the gram scale. 2,4-diphenylpyrano[3,2-c]chromen-5(4H)-one was obtained in a 92% yield (Scheme 7). As shown in scheme 8, the oxygen of the enone complexed $Ca(II)$ and thus facilitated the conjugate addition (Michael type) of 4-hydroxycoumarin to intermediate I. In the second step, the oxyanion of Ca-enolate underwent intramolecular nucleophilic addition to intermediate (II). This was followed by Ca-catalyzed, thermodynamic annulation which delivered the final product.

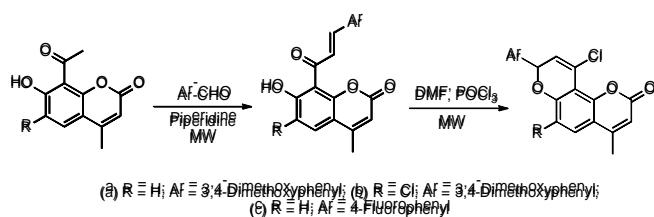


Scheme 7. Gram scale cascade, one-pot reaction of 4-hydroxycoumarin with chalcone for the synthesis of pyranocoumarins.



Scheme 8. Plausible mechanism for Ca(II)-catalyzed cascade conjugate addition and annulation in the synthesis of pyranocoumarins.

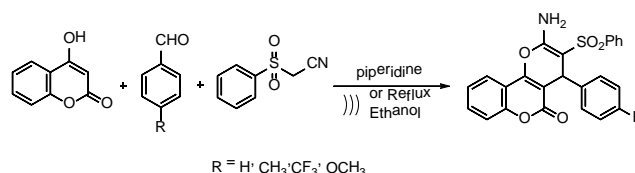
Ashok *et al.* (2015),⁴⁰ have synthesized hybrid pyranocoumarins in order to access the potential antimicrobial activity of coumarin scaffolds. The condensation of 8-acetyl-7-hydroxy-4-methyl coumarin with aromatic or (het)aromatic aldehydes gave substituted (*E*)-1-(7-hydroxy-4-methyl-8-coumarinyl)-3-(het)aryl-2-propen-1-ones in excellent yields in the presence of piperidine, under MW irradiation.⁴¹ The cyclization of these chalcones to substituted 4-chloro-8-methyl-2-(het)aryl-1,5-dioxo-2*H*-phenanthren-6-ones was accomplished via treatment with the Vilsmeier-Haack reagent (POCl₃-DMF). MW irradiation (160 W) gave excellent results (80-85% yield) in short reaction times (4-5 min) (Scheme 9). The antibacterial and antifungal activity of these novel compounds against Gram + (*B. subtilis* and *S. aureus*), and Gram- bacteria (*Klebsiella pneumoniae* and *E. coli*), as well as against *Fusarium oxysporum*, *A. niger* and *A. flavus* was evaluated. Compounds A, B and C showed significant action against the tested bacterial strains compared to the standard drug, gatifloxacin.



Scheme 9. Synthesis of substituted 4-chloro-8-methyl-2-phenyl-1,5-dioxo-2*H*-phenanthren-6-ones.

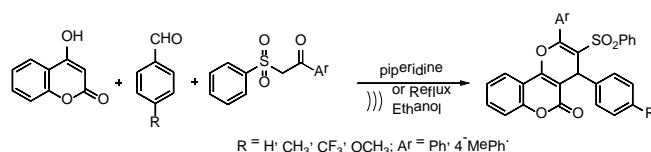
The same compounds also showed moderate to high antifungal activity compared to the standard drug, clotrimazole. As stated earlier, coumarin derivatives are versatile molecules that can be transformed into new active heterocyclic products. In addition, sulfone groups that are strategically positioned in heterocyclic compounds can play important roles in drug design. Accordingly, pyrrolyl aryl sulfones (PASS) have been reported,⁴² as a new class of human immunodeficiency virus type 1 (HIV-1) RT inhibitors which act on the non-nucleoside binding site of this enzyme. Al-bogami (2015),⁴² has made use of the sonochemistry concept for the rapid and efficient synthesis of some novel pyrano[3,2-*c*]coumarins which contain

the sulfone moiety with the aim of synthesizing new heterocyclic compounds for biological screening. Each reaction of 4-hydroxy coumarin, aromatic aldehydes and 2-(phenylsulfonyl)-acetonitrile in EtOH, in the presence of catalytic piperidine under ultrasonic irradiation at room temperature, afforded a single product identified as the corresponding 2-amino-3-phenylsulfonyl-4-aryl-4*H*-pyrano[3,2-*c*]coumarin (Scheme 10), in excellent yields (88-94%) and shorter reaction times (30-45 min) than under conventional conditions (reflux) (74-79%, 10 h).



Scheme 10. Synthesis of 2-amino-3-phenylsulfonyl-4-aryl-4*H*-pyrano [3,2-*c*]coumarin derivatives.

In a similar procedure, β -ketosulfones were reacted uneventfully with 4-hydroxy coumarin and aromatic aldehyde derivatives under ultrasonic irradiation (room temperature, 45 min) to provide 2,4-diaryl-3-(phenylsulfonyl)pyrano[3,2-*c*]coumarin derivatives in virtually quantitative yields (Scheme 11).



Scheme 11. Synthesis of 2,4-diaryl-3-(phenylsulfonyl)pyrano[3,2-*c*]coumarin derivatives.

1.3. Furocoumarin derivatives

Furocoumarins are another structural motif found in numerous pharmaceutically active compounds. A number of excellent reviews⁴³⁻⁴⁷ exist on this subject. However, for the sake of brevity, we shall only deal with compounds that bear the furo[3,2-*c*]coumarin ring system in this review. Some of these molecules have successfully been used for the treatment of skin diseases, such as cancer and psoriasis. In particular, neotanshinlactone and coumestrol exhibit high anti-tumour tissue-type as well as anti-breast cancer cell line selectivity (Fig. 3). For this reason, considerable effort has been invested in designing efficient synthetic methods of furocoumarin synthesis. The main features of a modern and straightforward furocoumarin synthetic protocol are: good atom-economy, mild conditions, low cost, green solvents and high regioselectivity. In this regard, Tan *et al.* (2015),⁴⁸ have developed the successful Pd(CF₃COO)₂ catalyzed aerobic oxidative alkoxylation of 4-hydroxycoumarins and alkenes in a cascade sequence to afford furo[3,2-*c*]coumarins in good yields (70-85%).

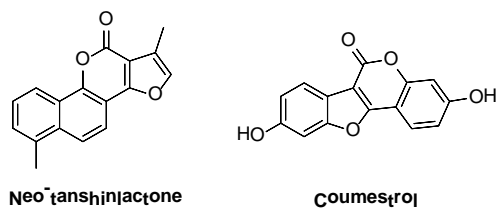
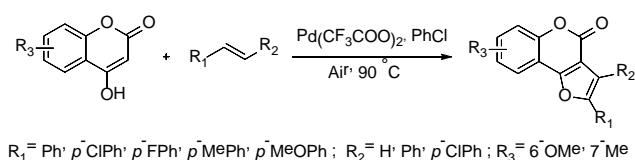


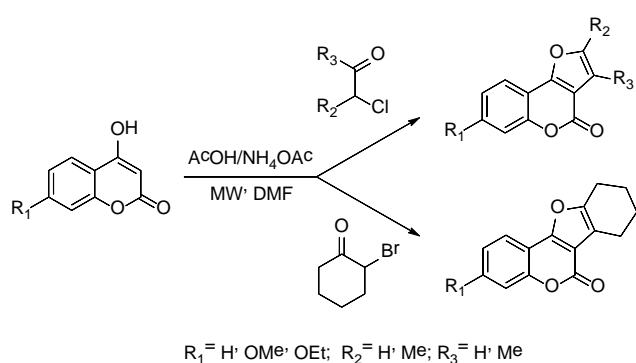
Figure 3. Furo[3,2-c]coumarins with high anti-tumour activity.

The best reaction conditions were described as follows; 90 °C, 20 mol% of $\text{Pd}(\text{CF}_3\text{COO})_2$ catalyst and 1:1 (4-hydroxycoumarin:alkenes) molar ratio. The desired products (Scheme 12) were obtained in 4 h in higher yields from electron-rich than from electron-poor alkenes.



Scheme 12. Synthesis of substituted furo[3,2-c]coumarins from 4-hydroxycoumarins and alkenes.

Zhang *et al.* (2014),⁴⁹ described the fast, MW-assisted synthesis of new furo and benzofuro coumarins. In particular, furo[3,2-c]chromen-4-one and 7,8,9,10-tetrahydro-6H-benzofuro[3,2-c]chromen-6-one derivatives (30 min, 400 W) (Scheme 13) were obtained in relatively good yields (50-65%) from 4-hydroxycoumarin and a variety of α -chloroketones and α -bromocyclohexanones.



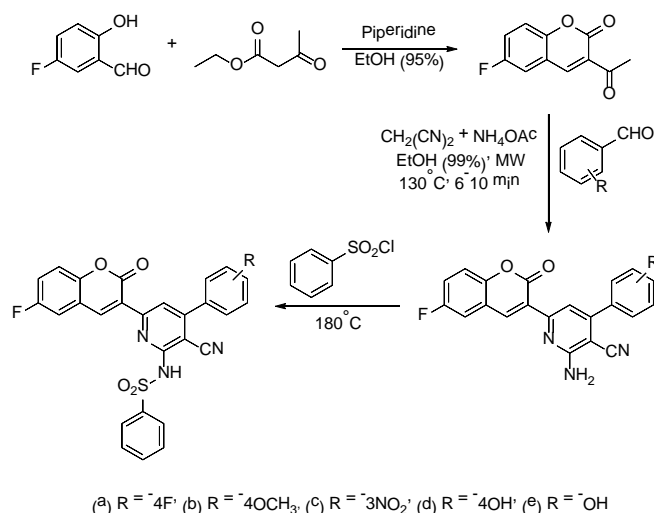
Scheme 13. Synthesis of polysubstituted furo[3,2-c]chromen-4-ones and 7,8,9,10-tetrahydro-6H-benzofuro[3,2-c]chromen-6-ones.

All of the reported furo and benzo furo coumarins were tested against *Colletotrichum capsica*, *Rhizoctoria solani* and *Botrytis cinerea* showing very good activity relative to osthol which was used as the reference fungicidal drug. Moreover, the antifungal

data reveal that the coumarin C-7 substituents and the furano ring were the two major structural reasons for their antifungal bioactivity.

1.4. Hybrid coumarin derivatives

Combining two pharmacological agents into a single molecule, a hybrid molecule, is an emerging strategy in medicinal chemistry and drug discovery.^{50,51} Hybrid structures may display dual activity but do not necessarily act on the same biological target. Desai *et al.* (2013)⁵² have reported on the conventional and MW assisted syntheses of new coumarin-based 3-cyanopyridine scaffolds [*i.e.* 3-(2-pyridyl)coumarins and 3-(3-pyridyl)coumarins], which bear a sulfonamide group, and have evaluated their antibacterial and antifungal properties. The coumarin nucleus in these compounds is attached at the C-3 position by pyridine moieties and the second pyridine ring position has been linked with the phenyl ring by a sulphonamide group. The pyridine ring was *de novo* synthesized via a 4-component [2+2+1+1] reaction between 3-acetyl-6-fluoro-2H-chromen-2-one 3, malononitrile, aromatic aldehydes and ammonium acetate to give 2-amino-6-(6-fluoro-2-oxo-2H-chromen-3-yl)-4-(aryl) nicotinonitriles which were, in turn, *N*-sulfonylated to the target compounds (Scheme 14). The MW assisted method was much more efficient and gave the best yields (66-82 %) in shorter reaction times (6-10 min).



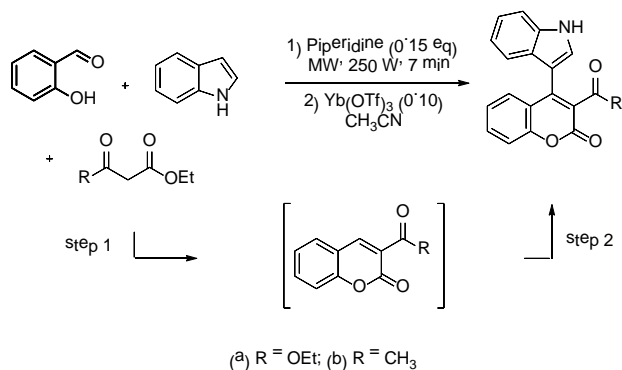
Scheme 14. Synthetic pathway.

Furthermore, the new compounds were all tested for their antibacterial and antifungal activities against *E. coli*, *S. aureus*, *P. aeruginosa*, *S. pyogenes*, *C. albicans*, *A. niger* and *A. clavatus*. Compounds reported on Scheme 14 showed excellent activity, but others reported by Desai *et al.* had just moderate or weak activity.

The presence of indole rings in a number of bioactive compounds means that novel methods for the preparation of polyfunctionalized indole derivatives are of great interest. The combined use of a Lewis acid catalysis and MW irradiation provided Viola *et al.* (2014),⁵³ with satisfactory results in the

Yonemitsu-type trimolecular condensation of indoles with aldehydes and 1,3-dicarbonyl compounds (malonates or acetoacetates), and yielded novel indole-coumarin compounds (Scheme 15). The main advantage of this procedure is the use of a catalytic amount of Lewis acid and the great reduction in reaction times (7 min), given by MW activation (250 W). The procedure was applied to aliphatic and aromatic aldehydes, as well as to substituted indoles. The optimization of the conditions for malonate and acetoacetate gave satisfactory results for both substrates, providing efficient access to a new class of indole-coumarin derivatives of potential biological interest.

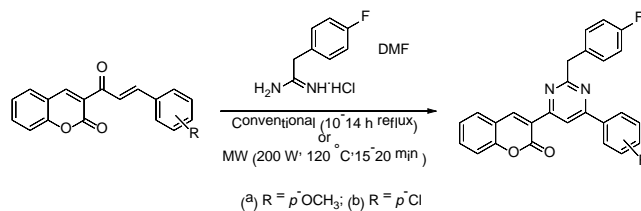
Fluorine-containing organic compounds have provided a long contribution to medicinal chemistry. The unique properties of fluorine mean that the incorporation of an atom or fluorinated group into drugs is often accompanied by higher binding affinity, enhanced metabolic stability and improved bioavailability, which can all critically influence both the pharmacodynamic and pharmacokinetic properties of drugs.



Scheme 15. Yonemitsu-type trimolecular condensation for indole-coumarin synthesis.

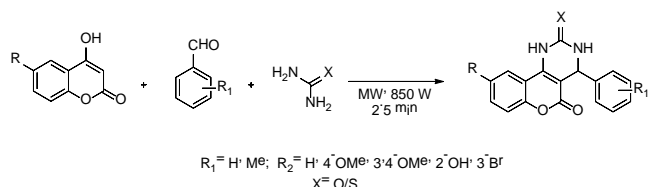
Encouraged by the reported bioactive significance of coumarin (in its interactions with numerous enzymes and receptors) and pyrimidine derivatives (anticancer properties) in combination with the fluorine moiety (enhancement of activity), Hosamani *et al.* (2015)⁵⁴ integrated these subunits into a single structural frame. These hybrid compounds may well exhibit high anticancer activity as a result of the synergetic effect of the combined units. Efficient synthetic entry to 3-(2-(4-fluorobenzyl)-6-(substituted phenyl) pyrimidin-4-yl)-2H-chromen-2-one derivatives under MW irradiation from substituted-enone coumarin derivatives (synthesized via the Claisen–Schmidt condensation reaction) was described in this work. Their subsequent heterocyclization with 2-(4-fluorophenyl) acetamidine hydrochloride in DMF afforded the desired 3-(2-(4-fluorobenzyl)-6-(substituted phenyl) pyrimidin-4-yl)-2H-chromen-2-one derivatives (Scheme 16).

Excellent yields were described in the presence of *para* or *meta*-substituted chalconated coumarins, while lower yields were reported in the presence of the *ortho* substituted moieties, due to steric hindrance.



Scheme 16. Synthesis of fluorinated coumarin–pyrimidine hybrids.

Compound yields and reaction times were drastically improved under MW irradiation with respect to conventional methods (74–91%, 15–20 minutes). All fluorinated coumarin–pyrimidine hybrid compounds were screened for *in vitro* anti-cancer activity against two human cancer cell lines, A-549 (human lung carcinoma) and MDAMB-231 (human adenocarcinoma mammary gland), by MTT assay and were further evaluated for their CT-DNA cleavage using the agarose gel electrophoresis method. The results revealed that compounds (a) and (b) exhibit cytotoxicity against the two cancer cell lines tested which was comparable or longer than that of standard cisplatin. Tuberculosis (TB) is the world's second leading cause of death by infectious disease, after acquired immune deficiency syndrome (AIDS), and as such, special effort is needed to find and develop new leads against the many validated TB targets.⁵⁵ The fact that coumarins have antitubercular properties while benzopyranopyrimidines show antifungal and antibacterial activity has lead to Ambre *et al.* (2014)⁵⁶ formulated hypothesis that their fusion would bring synergism to the individual antitubercular activities. They then synthesized and tested 16 new compounds that contained 4-(substituted)phenyl-1,2,3,4-tetrahydro-benzopyrano [4,3-*d*]pyrimidine-2,5-dione, 4-(substituted) phenyl-2-thioxo-1,2,3,4-tetrahydro-benzopyrano[4,3-*d*]pyrimidin- 5-ones and 2-thiopyrimidone nuclei. The syntheses of these hybrid compounds were carried out via a 3-component Biginelli reaction which involved reactions between a substituted aldehyde, 6-substituted-4-hydroxy coumarin and urea (or thiourea) in the presence of an acid catalyst (*p*-toluenesulfonic acid (PTSA)). The reaction was also successfully performed under MW irradiation (850 W, 2.5 min, 90 % yields) in the absence of solvents (Scheme 17). The new structures were assayed against *Mycobacterium tuberculosis* using rifampicin as the standard. The described hybrid coumarin and pyrimidin-2,5-dione structures are divided into two classes according to their structures; 2-thioxo-5-one (class A) and 2,5-dione (class B) functionality. The majority of class A molecules are non-cytotoxic, as based on human virulent cell line evaluations, although they possess relatively good antitubercular activity. While the molecules of class B inhibit the growth of *Mycobacterium tuberculosis*, they have high cytotoxicity profiles.



Scheme 17. 3-Component Biginelli reaction for synthesis of hybrid coumarins which include pyrimidine with 2-thioxo-5-one (class A) and 2,5-dione (class B) functionality.

Siddiqui and Khan (2014),⁵⁷ have recently reported a solvent-free, environmentally benign and simple one-pot multi-component protocol for the synthesis of novel bis-Biginelli compounds (Fig. 4) in excellent yields using HClO_4 -modified PEG-6000 as a biodegradable and reusable solid acid catalyst at ambient temperature.

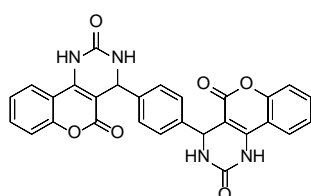
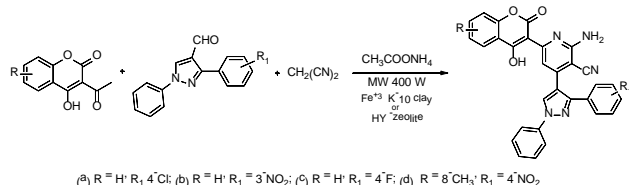


Figure 4. Bis-Biginelli compound structure.

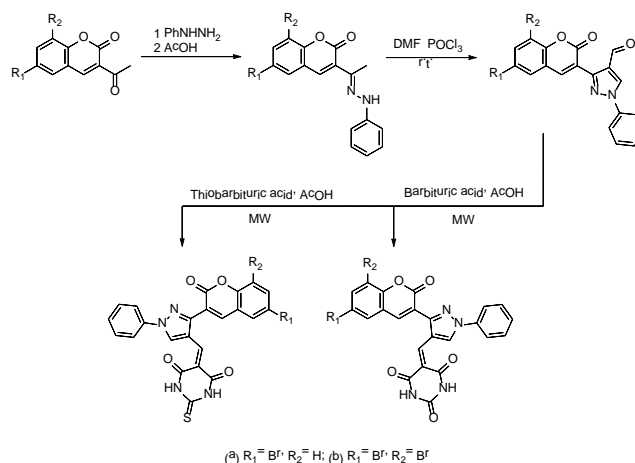
Cyanopyridines and triazolopyridines have also played an important role as members of the wide variety of heterocycles in medicinal chemistry. Thakrar *et al.* (2014),⁵⁸ have reported the synthesis of 2-amino 3-cyano pyridine derivatives, which contain both coumarin and pyrazole moieties, via the multicomponent reaction of 3-acetyl 4-hydroxy coumarin, 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde, malononitrile and ammonium acetate in the presence of acid catalysts under MW irradiation (Scheme 18).



Scheme 18. Synthetic pathway for 2-amino 3-cyano pyridine derivatives.

Two solid acids, Fe(III) montmorillonite K10 clay and HY-zeolite were efficiently used as cheap, recyclable and easily-available catalysts. The main advantages of this environmentally friendly procedure are the short reaction times (4-9 min), easy work up and good reaction yields. The newly synthesized 2-amino 3-cyano pyridine derivatives were screened for their antibacterial activity (vs. *S. typhi*, *Streptococcus pyogenus* and *Vibrio cholera*) and antifungal activity against *C. albicans*.

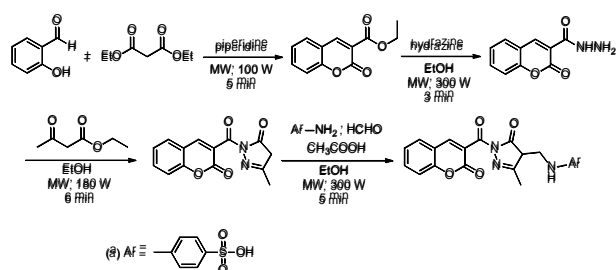
A SAR study into these compounds has shown that EW-groups attached to coumarin rings increase potency (compounds (a), (b), (c), (d)), whereas hydrophobic groups lower potency against antibacterial species. All compounds exhibited less potency against *C. albicans*. In addition to the compounds mentioned above, pyrazole and isoxazole derivatives have also exhibited well documented biological properties (bacteriostatic, antidiabetic, anti-inflammatory, antimicrobial and anticancer properties) as have thiobarbituric acid (TBA) and barbituric acid (BA), which are generally used as sedatives and antibacterial, antidiabetic, antiviral and anticancer agents. In this regard, Laxmi *et al.* (2013),⁵⁹ have reported the MW-assisted synthesis of a new class of pyrazole-barbiturate coumarin derivative and have assessed their antimicrobial activity. In particular, this series of 5-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and dihydro-5-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-thioxo pyrimidine-4,6(1*H*,5*H*)-dione derivatives were synthesized via the Knoevenagel condensation of 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde with barbituric acid and thiobarbituric acid in acetic acid under MW irradiation, giving excellent yields (75-85%) in shorter times (5-10 min) than conventional heating (5-10 h) (Scheme 19).



Scheme 19. Synthesis of pyrazole-barbiturate coumarin derivatives.

The substituted 3-acetyl coumarins were treated with phenyl hydrazine in methanolic acetic acid under reflux (30 min) to afford the corresponding phenyl hydrazones that were subsequently transformed to the corresponding 1*H*-pyrazole-4-carbaldehyde derivatives using the Vilsmeier formylation. The newly synthesized compounds were then evaluated for their antibacterial activity against *B. subtilis*, *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa* and *K. pneumoniae*. All compounds were found to be moderately active against the microorganisms, while compounds (a) and (b) exhibited good antifungal activity against *A. niger*.

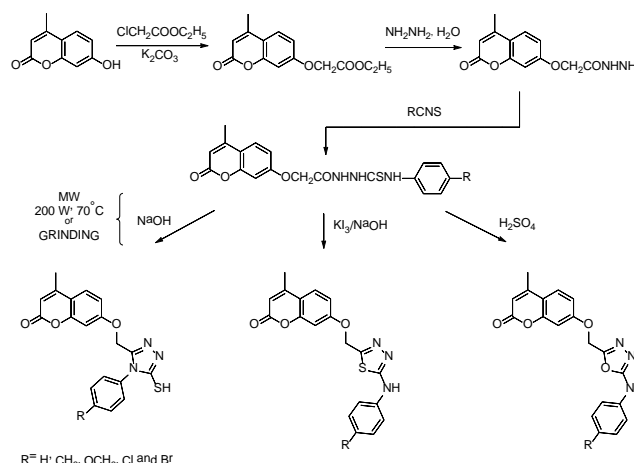
The antioxidant effects of coumarins have also attracted intense interest in recent years. These properties permit coumarins to quench active free radicals, such as O_2^\bullet , OH^\bullet and lipid peroxy radicals LOO^\bullet , while the core pyrazolone structure has generally been of interest because of its large range of activity. In view of these observations, Sivakumar *et al.* (2014),⁶⁰ have reported the synthesis of Mannich base pyrazolone-coumarin derivatives, (using both conventional and eco-friendly dielectric heating), which have been found to possess interesting anti-inflammatory and analgesic activity coupled with a significant reduction in their ulcerogenic potential. The synthetic pathway for these hybrid compounds is displayed below (Scheme 20). Ethyl 2-oxo-2H-chromene-3-carboxylate was prepared via the cyclization of salicylaldehyde with diethylmalonate in the presence of catalytic piperidine.⁶¹ The subsequent reaction with hydrazine hydrate, followed by heterocyclization with ethyl acetoacetate in glacial acetic acid, provided the corresponding pyrazolone. The condensation of pyrazolone with formaldehyde (40%) and various aromatic primary amines resulted in a set of Mannich bases. MW assisted techniques were found to be more effective in terms of impact on the environment, reaction time, high yields, ease of work-up and product isolation (78-88% vs 55-69% yields).



Scheme 20. Synthetic pathway for the Mannich base pyrazolone-coumarin derivatives.

The newly synthesized compounds, which combined both pyrazolone-linked coumarins, were screened for anti-inflammatory, analgesic, antioxidant and antibacterial activity and their effects were compared with those of standard drugs. Of the compounds studied, (a) displayed anti-inflammatory and analgesic activity which was nearly equipotent to the standard drug indomethacin, along with a minimal ulcerogenic index. The substitution of EW-groups at the para/ortho position of the phenyl ring imparted significant anti-inflammatory and analgesic activity to the resulting compounds. The compounds screened for their *in vitro* antimicrobial activity against Gram-positive (*Micrococcus luteus*, *S. aureus*) and Gram-negative bacteria (*E. coli* and *K. pneumoniae*) displayed better activity (especially in the presence of electron donating (ED) groups at the para position in the Mannich base phenyl ring) against Gram-negative than against Gram-positive bacteria. However, starting from this positive finding all the other compounds demonstrated weak to moderate activity compared to ciprofloxacin.

It has been well established that the presence of the 7-hydroxy-4-methyl-2-coumarin moiety is an important structural feature of a wide variety of synthetic drugs. The additional presence of heterocyclic moieties such as 1,3,4-triazole, -thiadiazole and -oxadiazole further extend this wide range of therapeutic properties. As a result, the preparation of novel compounds that fuse these azoles onto a coumarin structure has been reported by Surendra Babu *et al.* (2014).⁶² In this procedure, the key intermediate, ethyl-2-(4-methyl-2-oxo-2-coumarin-7-yloxy)acetate, was prepared via the reaction of 7-hydroxy-4-methyl coumarin in the presence of anhydrous K_2CO_3 with ethyl chloroacetate in boiling acetone. This compound was readily converted to 2-(4-methyl-2-oxo-2H-chromen-4-yloxy)acetohydrazide via treatment with hydrazine hydrate. The resulting hydrazide was reacted with substituted aryl isothiocyanates to form thiosemicarbazide compounds. The 1-(2-(4-methyl-2-oxo-2-coumarin-7-yloxy)acetyl)-4-aryl thiosemicarbazides underwent cyclization with different reagents under conventional, MW and grinding conditions to furnish coumarin derivatives that bore triazoles (in the presence of NaOH), thiadiazoles (in the presence of conc. H_2SO_4), and oxadiazoles (in the presence of NaOH/ KI_3), respectively (Scheme 21).

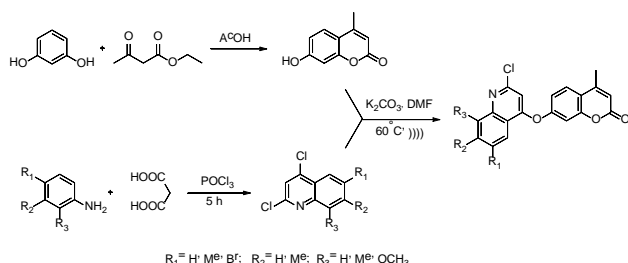


Scheme 21. Triazole, oxadiazole, thiadiazole-coumarin hybrid structures.

In this case, MW- and grinding-assisted procedures provided advantages in terms of reaction time and yields. The MW irradiation method, in particular, gave products in less time and better yields (2-3 min, 70–85%). The synthesized compounds were screened for their antibacterial activities against *K. pneumonia* and *E. coli* bacterial strains and antifungal activity against *A. niger*, *A. fumigates* and *A. terreus*. All compounds showed moderate to good activity against all the tested organisms.

With an eye to the relevance of both quinoline (antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive and anticancer activity) and coumarin as pharmacophoric units, Balaji *et al.* (2013),⁶³ have reported the synthesis of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-

chromen-2-one derivatives and their *in vitro* antibacterial, antioxidant and molecular docking studies. Quinoline-based coumarin derivatives were synthesized via the one-pot alkylation of 2,4-dichloroquinolines with 7-hydroxy-4-methyl-2*H*-chromen-2-one in the presence of catalytic amounts of K₂CO₃ under ultrasonic irradiation (60 °C, 20 min) (Scheme 22).

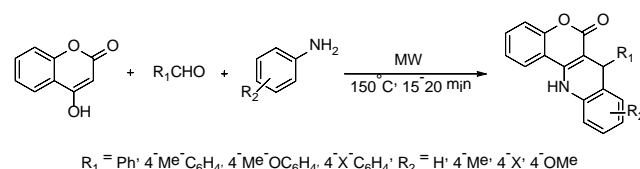


Scheme 22. Synthesis of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2*H*-chromen-2-one derivatives.

While the observed reactivity of the halogen atoms in the various quinolines varied widely, kinetic studies underlined the fact that the chlorine atom on the C-4 of 2,4-dichloroquinolines showed doubled reactivity towards nucleophilic reactions (making this a highly regioselective procedure), which predominantly take place via a σ^x complex in an addition-elimination mechanism. All synthesized compounds were screened for antibacterial (*E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*) and antioxidant activities. Some of these quinoline-based coumarin hybrids were found to be equipotent or even more potent than the standard drug, streptomycin.

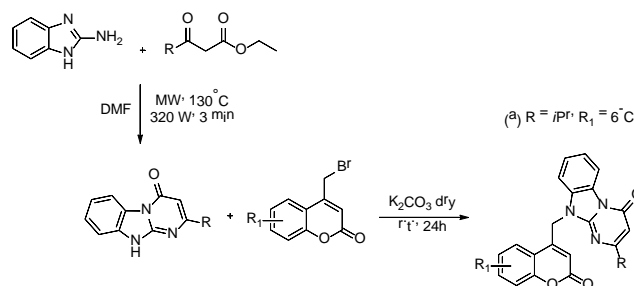
Multicomponent reactions (MCRs) have proven themselves to be valuable tools in medicinal chemistry and drug design because of their simplicity, efficiency and high selectivity. Such processes have the advantages of intrinsic atom economy, time and energy savings, as well as significant environmental benignity. In this regard, Chen *et al.* (2013)⁶⁴ have reported the synthesis of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolone derivatives via a three-component condensation of 4-hydroxycoumarin with different aldehydes and aromatic amines in water. The best results (80-94 % yields) were described under MW irradiation (150 °C, 15-20 min), and using a sulfonic acidic ionic liquid [*L*-2-(hydroxymethyl)-1-(4-sulfobutyl)pyrrolidinium hydrogen sulfate] ([HYSBPI]-HSO₄) as catalyst, which enhanced reactant water solubility (Scheme 23). The dimeric product, obtained together with 7,12-dihydro-6*H*-chromeno [4,3-*b*] quinoline, is not unexpected as the reaction of 4-hydroxycoumarin with aldehydes is fully regio- and chemoselective, affording 3,3'-alkylidene-4,4-dihydroxybis [2*H*-1-benzopyran-2-ones].⁶⁵

Since chromeno[4,3-*b*]quinolone derivatives showed moderate cytotoxic capacity and very low calcium channel antagonist activity, the antitumor activities of all the synthesized compounds were assessed on two different human cancer cell lines (A-549 and MCF-7). The results showed that these compounds had weak-to-good antitumor activities.



Scheme 23. Synthesis of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinoline derivatives.

Shivashankar *et al.* (2013),⁶⁶ have optimized a simple protocol which produced a new class of dihydrobenzo[4,5]imidazo [1,2-*a*]pyrimidin-4-one substituted coumarin using MW irradiation in an effort to discover novel antimicrobial and anticancer agents. In this procedure, the dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones were first obtained in short reaction times and excellent yields (74-94%) via β -keto ester and 2-aminobenzimidazole condensation under MW irradiation. These molecules were then reacted with various substituted 4-bromomethylcoumarins (synthesized via the von Pechmann cyclization of phenols with 4-bromoethylacetoacetate in the presence of conc. H₂SO₄, used as a cyclizing agent) to yield this new series of substituted coumarins (Scheme 24). All the newly synthesized compounds were screened for their antibacterial and antifungal activity giving better antifungal than antibacterial properties. The *in vitro* cell cytotoxicity of these new coumarin substituted dihydrobenzo[4,5]imidazo [1,2-*a*]pyrimidin-4-ones was also determined and the (a) structure was found to be the most potent cytotoxic compound (88%) against Dalton's ascitic lymphoma cell line.



Scheme 24. Dihydrobenzo[4,5]imidazo [1,2-*a*]pyrimidin-4-one substituted coumarin synthesis.

It is now well known that chromene derivatives exhibit a wide range of biological activity, including antimicrobial, antioxidant, and antitumor properties. Rao *et al.* (2015),⁶⁷ have therefore reported an eco-friendly and catalyst-free synthesis of novel hybrid chromene - coumarin derivatives (Scheme 25). The pivotal C-C bond formation was carried out in aqueous medium under MW irradiation, providing high conversion and high regio-selectivity in a short reaction time. A number of solvents were tested, but "in water" reactions were the most effective in terms of time and yields (78%, 105 °C).



The versatile, medicinal and chemical properties of benzofuran and its derivatives have attracted considerable interest over recent years. Puttaraju *et al.* (2014),⁶⁸ have therefore reported the synthesis of novel 4-(3-hydroxy-benzofuran-2-yl)coumarins and have evaluated them for their potential biological activity. Starting 4-bromomethylcoumarins were first obtained via the von Pechmann cyclization; 4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)-benzoic acid methyl ester was synthesized by reacting 4-bromomethyl-6-methylcoumarin and methyl salicylate in the presence of anhydrous K₂CO₃. These intermediates did not yield benzofuranyl coumarins in the presence of DBU and DMF under conventional thermal conditions (benzofuran cyclization does not occur), but only under MW irradiation (Scheme 26).

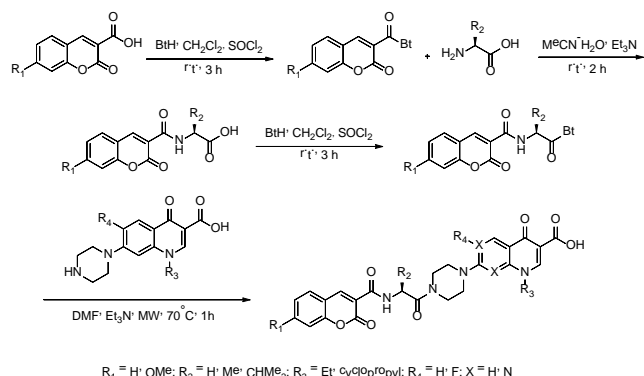


Nucleosides and modified nucleosides are another significant class of bioactive compound that can boast of very interesting biological activity, including antiviral, antimetabolic and anticancer properties. This has led to Kallitsakis *et al.* (2013),⁶⁹ describing a new series of modified nucleosides, which combine coumarin and purine moieties to act as free-radical scavengers (Scheme 27). Coumarin-skeleton-modified acyclic purine N-nucleosides were obtained via the cross metathesis (CM) reaction of 9-butenylpurines with 4-butenyloxycoumarins (a) and 4-allyloxycoumarins (b) in the presence of Grubbs 2nd generation catalyst under MW irradiation (100 °C, 3h). They were obtained in moderate to high yields (50-86%) without producing purine homodimers. Analogous derivatives obtained from the CM reaction of 9-butenyl-6-piperidinylpurine with 6-coumarinyl acrylate were also described (c). These compounds were tested as possible lipoxygenase (LOX) inhibitors, hydroxyl radical (HO•) scavengers and potential inhibitors of lipid peroxidation and thrombin. Significant antioxidant activity was observed mostly in (a), (b) and (c), while only (b) and (c) showed any noteworthy interaction with the stable free-radical molecule 2,2-diphenyl-1-picrylhydrazyl (DPPH) and high scavenging potency against HO• radicals.



Substituted (coumarin-3-yl carbonyl)benzotriazoles were prepared via the reaction of the corresponding carboxylic acids, (1H-benzotriazole (BtH), thionyl chloride CH_2Cl_2 , r.t.) and were subsequently coupled with amino acids in the presence of TEA at r.t. to give the required amino acid conjugates. These reactive intermediates were coupled with quinolone antibiotics using the same methodology (TEA, 70 °C, under MW irradiation) to give the target compounds in good yields (65-78%) (Scheme

28). These reactions were also carried out under conventional heating.



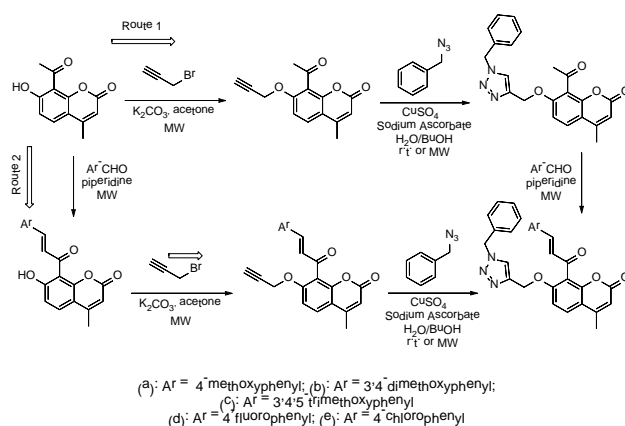
Scheme 28. Quinolone antibiotics linked by amino acid residues to fluorescent coumarins.

However, the reactions did not complete even after a number of hours. The photophysical properties of all the fluorescent-labelled antibiotic conjugates synthesized were also investigated. Encouraged by the biological importance of coumarins, chalcones and triazoles, Dongamanti *et al.* (2014),⁷¹ have described the efficient, practical and high-yielding MW-assisted synthesis of a new series of hybrid coumarin-based compounds which contain both 1,2,3-triazole and chalcone. The synthesis of the desired product was accomplished using two synthetic strategies which are both shown in scheme 29. MW furnished shorter reaction times (5-10 min vs 24 h) and higher yields than under conventional conditions in both routes.

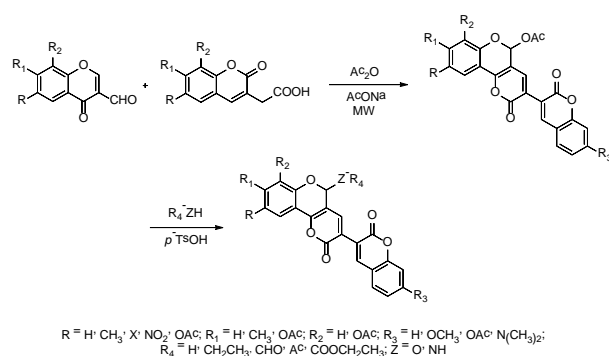
All compounds were investigated for their *in vitro* antimicrobial activity against Gram -positive and -negative bacteria as well as fungi. The reported compounds ((a), (b), (c), (d) and (e)) showed good antimicrobial activity against selected microorganisms (*S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*) and fungi (*A. niger*, *Penicillium italicum*) as compared with reference drugs (amoxicillin and mycostatin).

Finally, coumarin derivatives are also versatile synthons for the synthesis of a different set of rearranged products and new heterocyclic systems. Key 3-(2-oxo-2H-chromen-3-yl)-2-oxo-2H,5H-pyrano[3,2-c]chromen-5-yl acetates have been synthesized in high yields (72-87%) via the cyclocondensation of 4-oxo-4H-chromen-3-carbaldehydes with coumarin-3-acetic acids under MW irradiation (10 min at 400 W) by Gašparová *et al.* (2013).⁷²

The reaction pathway (Scheme 30) involves aldol condensation and subsequent intramolecular lactonization to afford the 2-oxo-2H,5H-pyrano[3,2-c]chromene skeleton. Further treatment of 3-(2-oxo-2H-chromen-3-yl)-2-oxo-2H,5H-pyrano[3,2-c]chromen-5-yl acetates with alcohols, water or nitrogen containing compounds led to 5-alkoxy-, 5-hydroxy- or 5-acylamino-2H,5H-pyrano[3,2-c]chromen-2-ones via the nucleophilic substitution of acetoxy group at C-5.

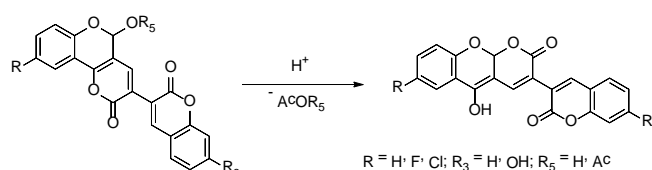


Scheme 29. Hybrid coumarin-based compounds containing both 1,2,3-triazole and chalcone.



Scheme 30. Synthesis of 5-alkoxy-, 5-hydroxy- or 5-acylamino-2H,5H-pyrano[3,2-c]chromen-2-ones.

Acetates and hydroxyl derivatives undergo facile rearrangement in an acid medium to yield 5-hydroxypyrano[2,3-b]chromen-2(10aH)-ones (Scheme 31).



Scheme 31. Rearrangement to 5-hydroxypyrano[2,3-b]chromen-2(10aH)-ones.

The antineoplastic activities of twelve prepared compounds were evaluated on 60 human tumour cell lines. The results confirmed the role of 3-(2-oxo-2H-chromen-3-yl)-2H,5H-pyrano[3,2-c]chromen-2-one as a new leading skeleton and one which is worthy of further antitumor activity study.

2 Conclusion

The synthesis of coumarins and their derivatives has drawn the attention of organic and medicinal chemists over the decades.

Recent years have seen a greener approach being taken while the use of MW-assisted enabling technologies, sonochemical conditions and heterogeneous catalysis have made access to these heterocyclic compounds much simpler. This review summarizes the most recent advances in the synthesis of bioactive coumarins and some perspectives in the application of non-conventional methods and energy sources.

Acknowledgements

This work has been supported by the University of Turin (fondi Ricerca locale 2014).

Keywords: Bioactive coumarins • Pyranocoumarins • Furocoumarins • Microwave-assisted synthesis • Ultrasound-assisted synthesis • Green chemistry

Notes and references

- P. K.;Monga, S. Dipak, D. Arti, *E-Int. Sci. Res. J.*, 2012, **4**(1), 16.
- R. O'Kennedy, R. D. Thornes, *Coumarins: Biology Applications and Mode of Action*. Wiley: Chichester, 1997.
- A. M. Katsori, D. Hadjiipavlou-Litina, *Expert. Opin. Ther. Pat.*, 2014, **24**, 1323.
- M. E. Riveiro, N. De Kimpe, A. Moglioni, R. Vasquez, F. Monczor, C. Shayo, C. Davio, *Curr. Med. Chem.*, 2010, **17**, 1325.
- X. M. Peng, G. L. Damu, C. Zhou, *Curr. Pharm. Des.*, 2013, **19**, 3884.
- K. N. Venugopala, V. Rashmi, B. Odhav, *Biomed. Res. Int.*, 2013, 2013:963248.doi:10.1155/2013/963248.
- P. O. Patil, S. B. Bari, S. D. Firke, P. K. Deshmikh, S. T. Donda, D. A. Patil, *Biorg. Med. Chem.*, 2013, **21**, 2434.
- M. Asif, *Am. J. Curr. Org. Chem.*, 2015, **1**, 1.
- M. Zabradnik, *The Production and Application of Fluorescent Brightening Agents*. Wiley: New York, 1992.
- For an exhaustive survey on the chemistry of coumarins, see: R.S. Bezwada, *Chemistry of coumarins*, INDOFINE Chem Co, Hillsborough, NJ, USA, 2008.
- M. Curini, G. Cravotto, F. Epifano, G. Giannone, *Curr. Med. Chem.*, 2006, **13**, 763.
- R. Gambari, I. Lampronti, N. Bianchi, C. Zuccato, G. Viola, D. Vedaldi, F. Dall'Acqua, *Top. Heterocycl. Chem.*, 2007, **9** (Bioactive Heterocycles III), 265.
- J.-C. Jung, O.-S. Park, *Molecules*, 2009, **14**(11), 4790.
- G. B. Bubols, R. Vianna Dda, A. Medina-Ramon, G. von Poser, R.M. Lamuela-Ramentos, V.L. Eifler-Lima, S.C. Garcia, *Mini Rev. Med. Chem.*, 2013, **13**, 318.
- I. Najmanová, M. Dosedel, R. Hrdina, P. Anzenbacher, T. Filipsky, M. Riha, P. Mladenka, *Curr. Top. Med. Chem.*, 2015, **15**, 830.
- M. E. Riveiro, N. De Kimpe, A. Moglioni, R. Vasquez, F. Monczor, C. Shayo, C. Davio, *Curr. Med. Chem.*, 2010, **17**, 1325.
- A. Thakur, R. Singla, V. Jaitak, *Eur. J. Med. Chem.*, 2015, **101**, 476.
- K. Venkatasairam, B. M. Gurupadayya, R. S. Chandan, D. K. Nagesha, B. Vishwanathan, *Curr. Drug Deliv.*, 2015, **12**, doi:10.2174/1567201812666150702102800.
- S. Emami, S. Dadashpour, *Eur. J. Med. Chem.*, 2015, **102**, 611.
- M. Kaur, S. Kohli, S. Sandhu, Y. Bansal, G. Bansal, *Anticancer Agents Med. Chem.*, 2015, **15**, 1032.
- R. S. Keri, B. S. Sasidhar, B. M. Nagaraja, M. A. Santos, *Eur. J. Med. Chem.*, 2015, **100**, 257.
- J. Grover, S. M. Jachak, *RSC Adv.*, 2015, **5**(49), 38892.
- G. Kayal, K. Jain, S. Malviya, A. Kharia, *Int. J. Pharm. Sci. Res.*, 2014, **5**(9), 3577.
- A. Bryskier, M. Klich, *Antimicrobial Agents*; Bryskier, M.D. A Ed., ASM Press: Washington, 2005; pp. 816-825.
- R. Kharb, M. Kaur, A.K. Sharma, *Int. J. Pharm. Sci. Rev. Res.*, 2013, **20**(1), 87.
- M. M. Heravi, S. Khaghaninejad, M. Mostofi, *Advances in Heterocyclic Chemistry*, Elsevier (Academic Press), 2014, Vol. 112, pp. 1-44.
- R. H. Vekariya, H. D. Patel, *Synth. Commun.*, 2014, **44**, 2756.
- P. K. Monga, D. Sharma, A. Dubey, *J. Chem. Pharm. Res.*, 2012, **4**(1), 822.
- G. Cravotto, G. M. Nano, G. Palmisano, S. Tagliapietra, *Synthesis*, 2003, **2003**(8), 1286.
- For a green approach to coumarins, see: M.B. Gawande, V. D. B. Bonifacio, R. Luque, P. S. Branco, R. S. Varma, *Chem. Soc. Rev.*, 2013, **42**, 5522.
- Brahmachari, G. *Green synthetic approaches for biologically relevant heterocycles*, Elsevier, 2015.
- M. Kale, K. Patwardhan, *J. Curr. Pharma Res.*, 2014, **4**, 1150.
- V. Vahabi, F. Hatamjafari, *Molecules*, 2014, **19**, 13093.
- A. S. Kumar, S. Kanakaraju, B. Prasanna, G. V. P. Chandramouli, *Chem. Sci. Trans.*, 2013, **2**(2), 561.
- S. Nigam, J. V. Rao, B. S. Jayashree, *Indian J. Biotechnol.*, 2013, **12**, 379.
- E. Otero, S. Vergara, S. M. Robledo, W. Cardona, M. Carda, I.D. Vélez, C. Rojas, F. Otálvaro, *Molecules*, 2014, **19**, 13251.
- V. Rempel, N. Volz, F. Gläser, M. Nieger, S. Bräse, C. E. Müller, *J. Med. Chem.*, 2013, **56**, 4798.
- H. Chen, S. Li, Y. Yao, L. Zhou, J. Zhao, Y. Gu, K. Wang, X. Li, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4785.
- S. Yaragorla, P. L. Saini, G. Singh, *Tetrahedron Lett.*, 2015, **56**, 1649.
- D. Ashok, B. Vijaya Lakshmi, S. Ravi, A. Ganesh, *Med. Chem. Res.*, 2015, **24**, 1487.
- M. K. Paramjeet, S. Dipak, D. Art, *J. Chem. Pharm. Res.*, 2012, **4**, 822.
- A. S. Al-bogami, *Res. Chem. Intermed.*, 2015, **41**, 93.
- L. Santana, E. Uriarte, F. Roleira, N. Milhazes, F. Borges, *Curr. Med. Chem.*, 2004, **11**, 3239.
- V. F. Traven, *Molecules*, 2004, **9**, 50.
- R. Gambari, I. Lampronti, N. Bianchi, C. Zuccato, G. Viola, D. Vedaldi, F. Dall'Acqua, *Top. Heterocycl. Chem.*, 2007, **9**, 265.
- N. Kitamura, S. Kohtani, R. Nakagaki, *J. Photochem. Photobiol. C: Photochem. Rev.*, 2005, **6**(2-3), 168.
- X. M. Peng, G. L. Damu, C. Zhou, *Curr. Pharm. Des.*, 2013, **19**(21), 3884.
- X. Tan, H. Zhao, Y. Pan, N. Wu, H. Wang, Z. Chen, *RSC Adv.*, 2015, **5**, 4972.
- R. Zhang, Z. Xu, W. Yin, P. Liu, W. Zhang, *Synth. Comm.*, 2014, **44**(22), 3257.
- S. Sandhu, Y. Bansal, O. Silakari, G. Bansal, *Bioorg. Med. Chem.*, 2014, **22**, 3806.
- F. G. Medina, J. G. Marrero, M. Macías-Alonso, M. C. Gonzalez, I. Cordova-Guerrero, A. G. Teissier Garcia, S. Osegueda-Robles, *Nat. Prod. Rep.*, 2015, **32**, 1472.
- N. C. Desai, H. M. Satodiya, K. M. Rajpara, H. V. Vaghani, *Indian. J. Chem. B.*, 2013, **52**, 904.
- A. Viola, L. Ferrazzano, G. Martelli, S. Ancona, L. Gentilucci, A. Tolomelli, *Tetrahedron*, 2014, **70**, 6781.
- K. M. Hosamani, D. S. Reddy, H. C. Devarajegowda, *RSC Adv.*, 2015, **5**, 11261.
- R. S. Keri, B. S. Sasidhar, B. M. Nagaraja, M. A. Santos, *Eur. J. Med. Chem.*, 2015, **100**, 257.

- 56 K. A. Premlata, R. S. P. Raghuvir, D. W. Ravindra, S. S. Mushtaque, M. K. Vijay, W. Baojie, G. F. Scott, C. C. Evans, *Med. Chem. Res.*, 2014, **23**, 2564.
- 57 Z. N. Siddiqui, T. Khan, *RSC Adv.*, 2014, **4**, 2526.
- 58 S. Thakrar, A. Bavishi, A. Radadiya, H. Vala, S. Parekh, D. Bhavsar, R. Chaniyara, A. Shah, *J. Heterocyclic Chem.*, 2014, **51**, 555.
- 59 S. Vijaya Laxmi, B. Suresh Kuarm, B. Rajitha, *Med. Chem. Res.*, 2013, **22**, 768.
- 60 K. K. Sivakumar, A. Rajasekaran, P. Senthilkumar, P. P. Wattamwar, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2940.
- 61 B. F. Abdel-Wahab, H. A. Mohamed, A. A. Farhat, *Org. Commun.*, 2014, **7**, 1.
- 62 K. R. Reddy, R. Mamatha, M. S. S. Babu, K. Shiva Kumar, G. Narayanaswamy, *J. Heterocyclic Chem.*, 2014, **51**, 132.
- 63 G. L. Balaji, K. Rajesh, R. Priya, P. Iniyavan, R. Siva, V. Vijayakumar, *Med. Chem. Res.*, 2013, **22**, 3185.
- 64 Z. Chen, J. Bi, W. Su, *Chinese J. Org. Chem.*, 2013, **31**, 507.
- 65 G. Appendino, G. Cravotto, S. Tagliapietra, S. Ferraro, G. M. Nano, G. Palmisano, *Helv. Chim. Acta.*, 1991, **74**, 1451.
- 66 K. B. Puttaraju, K. Shivashankar, C. M. Mahendra, V. P. Rasal, P. N. Venkata Vivek, K. Rai, M. B. Chanu, *Eur. J. Med. Chem.*, 2013, **69**, 316.
- 67 L. Chandrasekhara Rao, N. Satish Kumar, V. Dileepkumar, U.S.N. Murthy, H.M. Meshram, *RSC Adv.*, 2015, **5**, 28958.
- 68 P. Boregowda, S. Kalegowda, V. P. Rasal, J. Eluru, E. Koyye, *Org. Chem. Int.*, 2014, ID 297586.
- 69 M. G. Kallitsakis, D. J. Hadjipavlou-Litina, K. E. Litinas, *J. Enzym. Inhib. Journal of Med. Chem.*, 2013, **28**(4), 765.
- 70 A. D. Tiwari, S. S. Panda, A. M. Asiri, C. D. Hall, A. R. Katritzky, *Synthesis*, 2014, **46**(18), 2430.
- 71 A. Dongamanti, V. L. Bommidi, G. Arram, R. Sidda, *Heterocycl. Commun.*, 2014, **20**(5), 293.
- 72 R. Gašparová, P. Koiš, M. Láčová, S. Kováčová, A. Boháč, *Cent. Eur. J. Chem.*, 2013, **11**, 502.