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Dual DAT/σ1 receptor ligands based on 3-(4-(3-(bis(4-fluorophenyl)amino)propyl)piperazin-1-yl)-3-phenylpropan-1-ol

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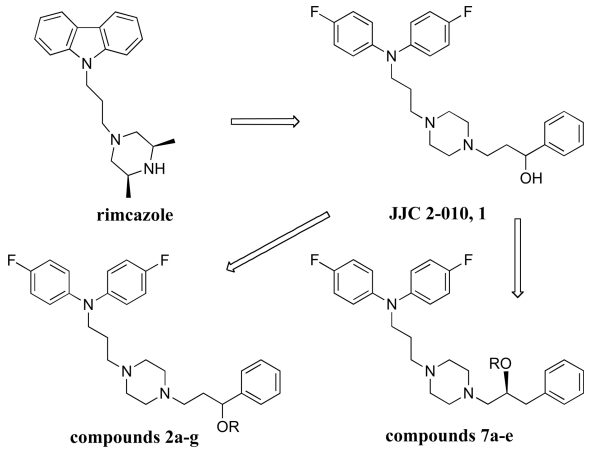
Abstract



Ester analogues of (±)3-(4-(3-(bis(4-fluorophenyl)amino)propyl)piperazin-1-yl)-3-phenylpropan-1-ol were synthesized and evaluated for binding at DAT, SERT, NET and σ1 receptors, and compared to GBR 12909 and several known σ1 receptor ligands. Most of these compounds demonstrated high affinity (Ki=4.3–51 nM) and selectivity for the DAT among the monoamine transporters. *S*- and *R*-1-(4-(3-(bis(4-fluorophenyl)amino)propyl)piperazin-1-yl)-3-phenylpropan-2-ol were also prepared wherein modest enantioselectivity was demonstrated at the DAT. However, no enantioselectivity at σ1 receptors was observed and most of the ester analogues of the more active *S*-enantiomer showed comparable binding affinities at both DAT and σ1 receptors with a maximal 16-fold DAT/σ1 selectivity.

Keywords

Dopamine transport inhibitors; sigma receptors; cocaine; rimcazole; GBR 12909

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Several lines of evidence have linked σ1 receptors to the attenuation of the behavioral effects of cocaine.[1] Rimcazole, a σ1-receptor antagonist,[2] also binds with moderate affinity to the dopamine transporter, (DAT)[3,4] but exhibits neither cocaine-like psychomotor stimulant nor cocaine discriminative stimulus effects in rodents.[5,6] Further, rimcazole attenuates cocaine-induced stimulation of locomotor activity,[6] convulsions,[7] and place conditioning;[8] actions that have been suggested to be mediated via blockade of σ1 receptors. However, as rimcazole and its analogues have similar σ1 and DAT binding affinities, a role of the DAT in these behavioral effects remains to be established. We have recently demonstrated that rimcazole and selected analogues bind the DAT in a conformation that differs from that for cocaine, which may be related to their unique *in vivo* effects.[9]

In earlier studies of rimcazole analogues, we identified compounds with varying affinities and selectivities for σ1 receptors and the DAT as potential *in vivo* probes.[4,10,11,12] The hydroxylated linking chain analogue, JJC 2-010 (**1**, (±)3-(4-(3-(bis(4-fluorophenyl) amino)propyl)piperazin-1-yl)-1-phenylpropan-1-ol) demonstrated high affinity and selectivity for the DAT over serotonin (SERT) and norepinephrine transporters (NET) and provided the template for the next generation of compounds (Figure 1).

JJC 2-010 (**1**) did not generalize in rats trained to discriminate 10 mg/kg cocaine from saline (Figure 2). Moreover, JJC 2-010 (**1**), at 10 and 24 mg/kg, had no effect on the cocaine dose-effect curve in this paradigm, suggesting that either this compound is an atypical dopamine uptake inhibitor[13,14] and/or its σ1 receptor antagonist actions affect the discriminative stimulus effects of cocaine. In order to further develop structure-activity relationships (SAR) in this series of compounds, and provide *in vivo* tools with which to characterize the roles of σ1 receptors and the DAT in the interactions of rimcazole analogues and cocaine, additional analogues were designed (Figure 1). Using simple esterification of the linking chain OH group, steric tolerance could be explored.

In the present series, analogues with an esterification of the –OH group in JJC 2-010 (**1**) were synthesized and tested for binding at σ1 receptors and the DAT, as well as the SERT and NET (**2a–g**). Further, additional SAR studies conducted on the GBR 12909 template have been reported recently[15,16] that led us to prepare the homologous 1-(4-(3-(bis(4-fluorophenyl)amino) propyl)piperazin-1-yl)-1-phenylpropan-2-ol series to investigate enantioselectivity and then make ester analogues (**7a–e**) of the more active enantiomer (**6a**).

Compound **1** was prepared as previously described[11] and esterified (Scheme 1)[17] to give **2a–g**. In Scheme 2,[17] compounds **4a** and **4b** were synthesized via a regioselective epoxide ring opening using the Grignard reagent prepared from bromobenzene (**3**) as described previously.[15] These chiral synthons (**4a** and **4b**) were then alkylated with the previously reported 4-fluoro-N-(4-fluorophenyl)-N-(3-(piperazin-1-yl)propyl)aniline[11] to give the *S*- and *R*- (**6a** and **6b**, respectively) enantiomers. These enantiomers were tested for binding at the DAT and it was discovered that the *S*-enantiomer had slightly higher affinity for the DAT, and thus ester analogues (**7a–e**) were prepared (Scheme 2) of the more active enantiomer (**6a**) only. Of note, similarly modest enantioselectivity was also observed in the GBR 12909 series[15] and did not inspire us to pursue the enantiomers of (±)**1**.

Binding affinities at σ1 receptors, as well as the DAT, SERT, and NET for **2a–g**, **6a,b** and **7a–7e** were determined and compared to those for rimcazole and JJC 2-010 (**1**), as well as GBR 12909 and several known σ1 receptor agonists. Note, binding affinities at DAT and σ1 for **1,** rimcazole and GBR 12909 are slightly higher than what was previously reported, due to slightly modified binding methods employed.[18] All the ester analogues of **1** demonstrated high affinity binding at the DAT, although the additional steric bulk of esters **2f** and **2g** reduced binding affinity ~10-fold. All compounds were uniformly less active at the SERT

and NET, but had similar affinities to **1** at σ1 receptors, again with a slight decrease in affinity for the sterically bulky analogues. As mentioned above, the *S*-enantiomer **6a** showed slightly higher affinity (Ki=1.72) nM) for DAT than its *R*-enantiomer **6b** (Ki=5.36 nM) and was the highest affinity compound in this series. Esterification of **6a** yielded esters **7a–e** that showed similar binding profiles to **2a–g**.

Selectivity profiles based on Ki ratios are displayed in Table 2. All of the new analogues were selective for DAT over SERT and NET, with compound **6a** showing the highest DAT selectivity ratios.

Analogues of rimcazole are of particular interest because they bind to the DAT but do not produce behavioral effects similar to those of cocaine.[6,11] Because sigma receptor antagonists have been reported to block several actions of cocaine, it has been proposed that these drugs block actions of cocaine mediated by sigma receptors, or that sigma-receptor mediated effects modulate the actions of cocaine. In addition, our previous results suggest that sigma receptor ligands, in contrast to cocaine analogues, bind the DAT in a manner that promotes its inward facing conformation.[9] Among the present compounds are several that have different degrees of selectivity for the DAT over σ1 receptors. Behavioral evaluation of selected ligands will prove useful in disentangling these molecular contributions to behavioral outcomes.

Thus this set of compounds will provide additional tools with which to explore the potential of compounds with dual actions at the DAT and σ1 receptors as leads for cocaine abuse medication discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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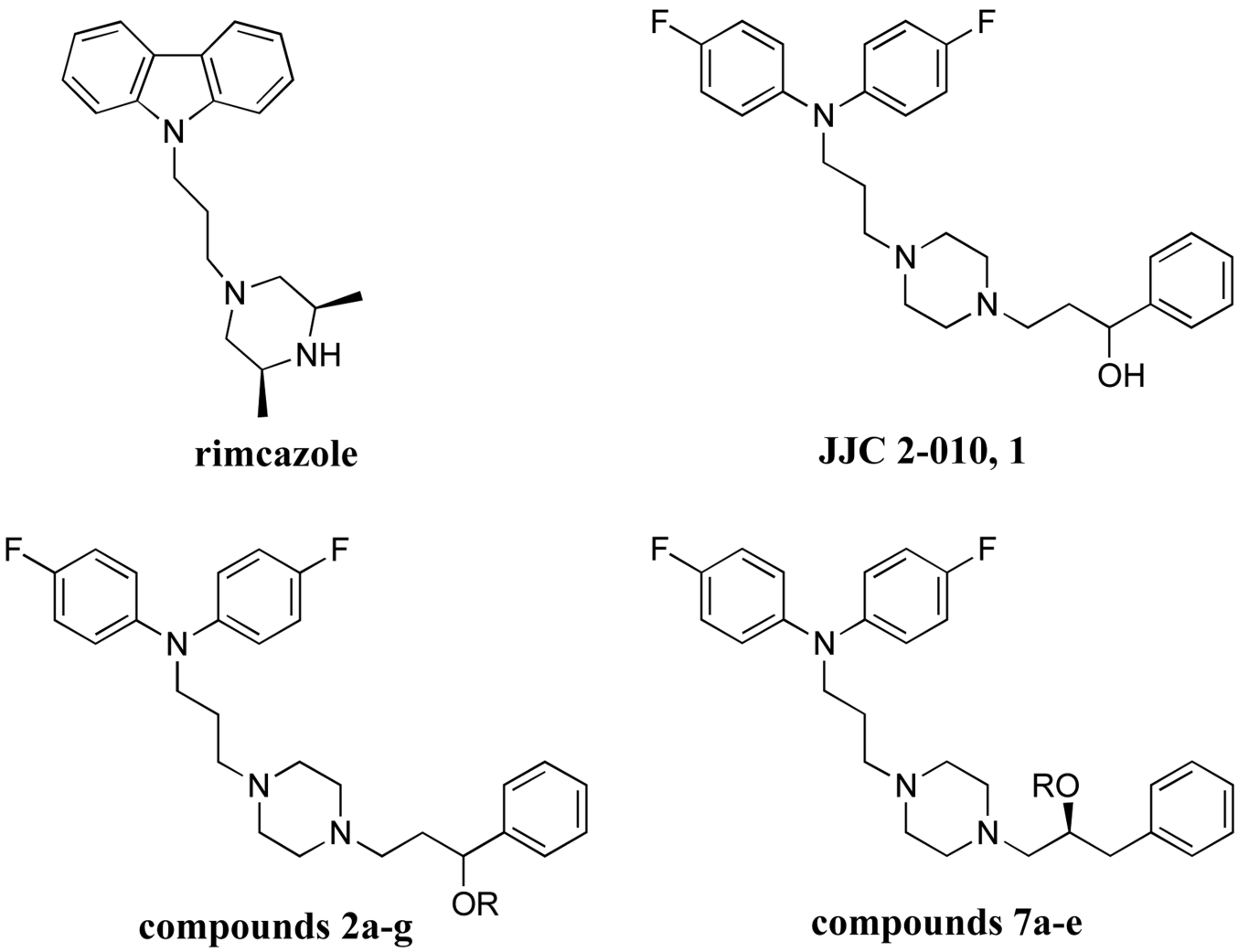


Figure 1.
Dual DAT/σ1 receptor ligands

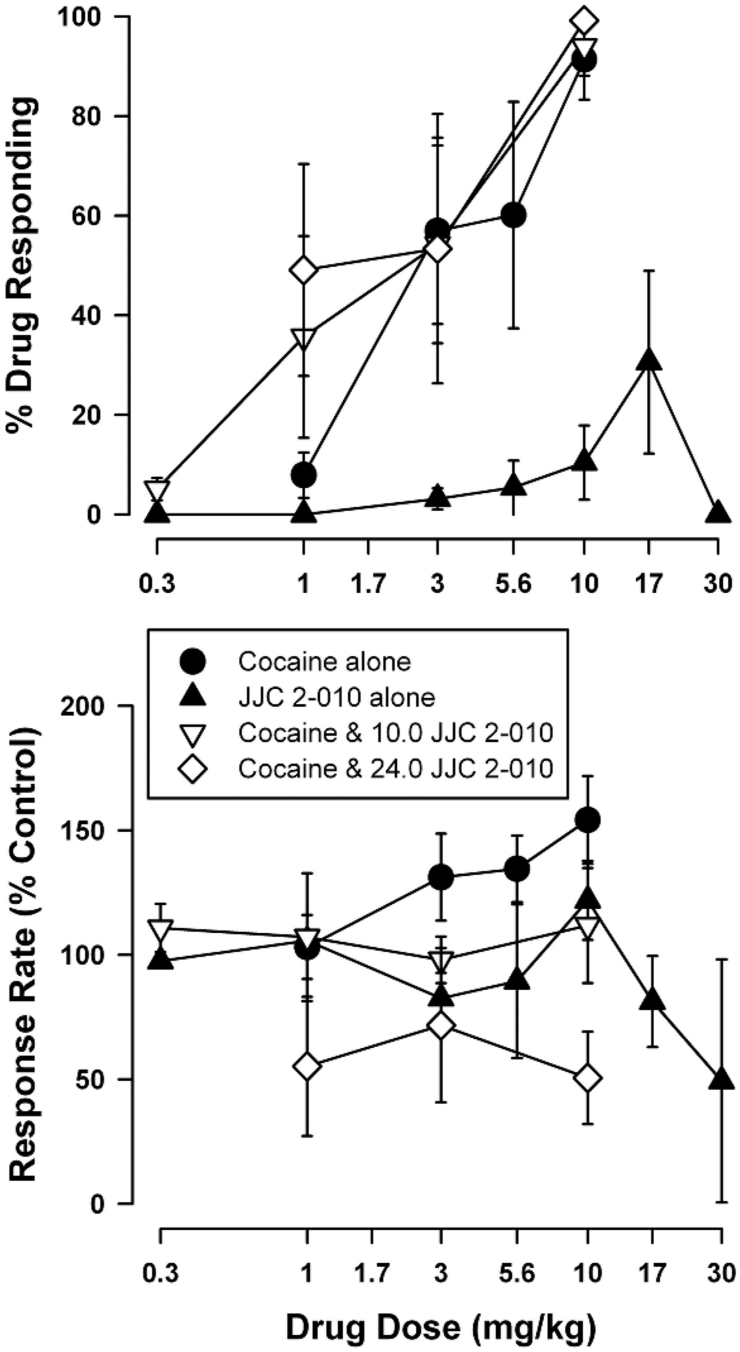
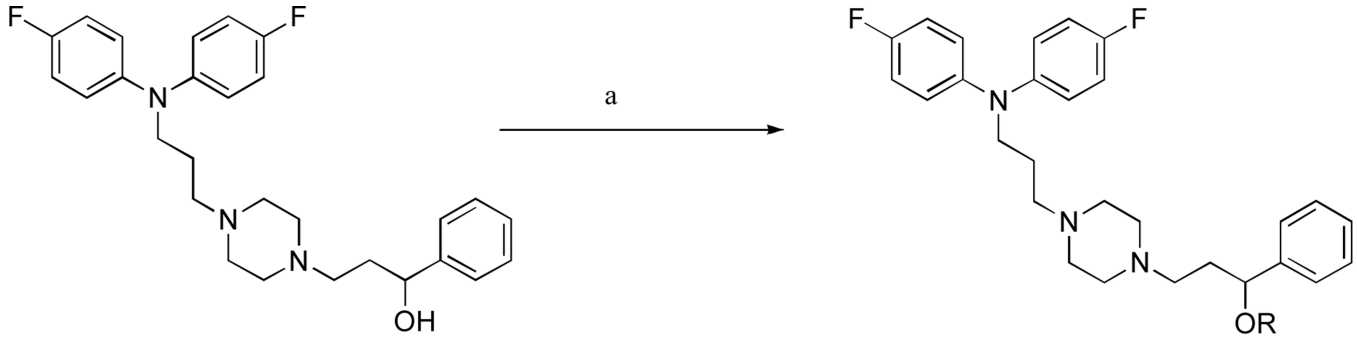


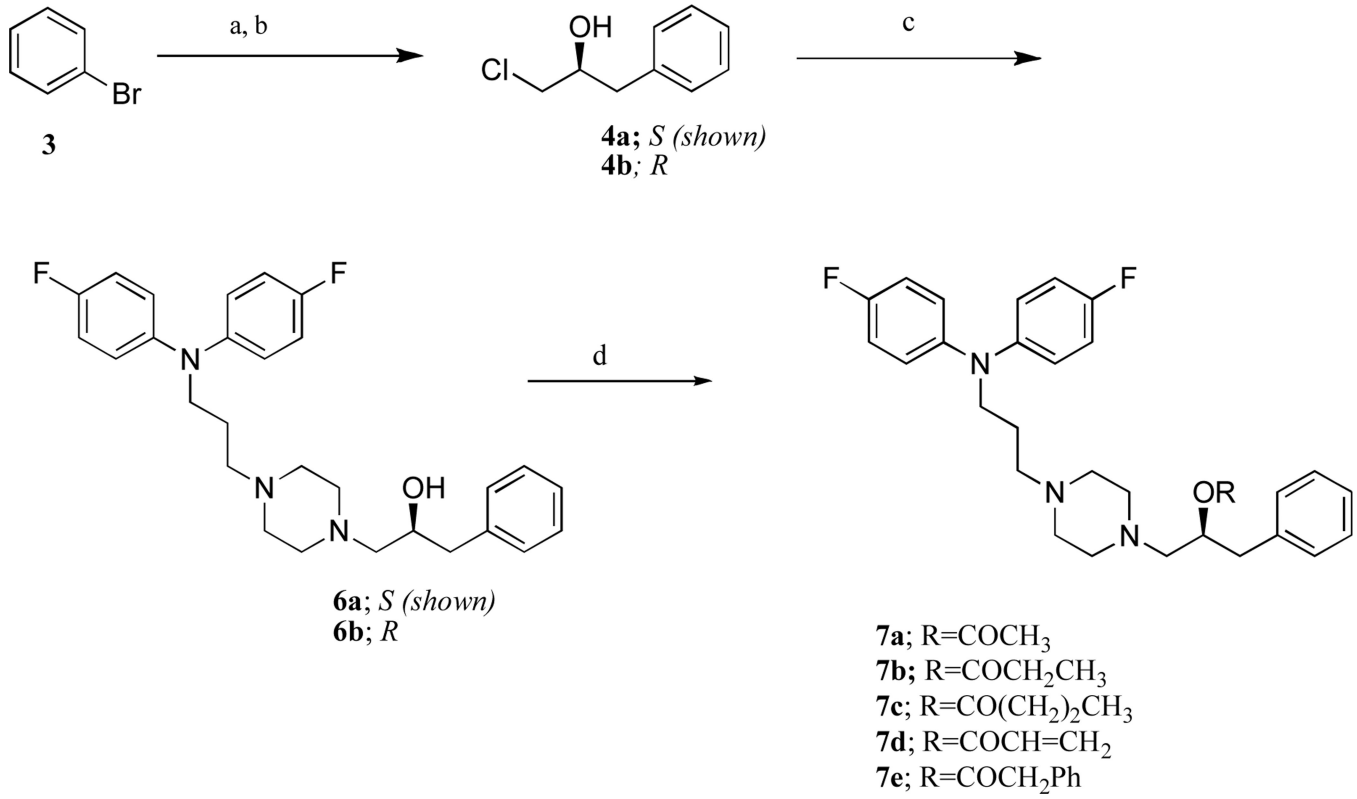
Figure 2.
Discriminative stimulus effects of JJC 2-010 alone and with cocaine in rats trained to discriminate 10 mg/kg cocaine from saline (i.p.)



1

2a; R=$COCH_3$
2b; R=$COCH_2CH_3$
2c; R=$COCH(CH_3)_2$
2d; R=$COCH{=}CH_2$
2e; R=$COCH_2Ph$
2f; R=$CO(CH_2)_2Ph$
2g; R=$CO(CH_2)_3Ph$

Scheme 1.
Reagents and conditions: (a) RCOCl, TEA, CH_2Cl_2



Scheme 2.

Reagents and conditions: (a) Mg, I_2, THF; (b) *R* or *S*-epichlorohydrin, CuI, THF; (c) **5** (4-fluoro-N-(4-fluorophenyl)-N-(3-(piperazin-1-yl)propyl)aniline,[11] K_2CO_3, MeOH; (d) RCOCl, TEA, CH_2Cl_2

Table 1

Binding data for DAT/σ1 compounds[a]

Compd#	DAT Ki, nM ± SEM	SERT Ki, nM ± SEM	NET Ki, nM ± SEM	σ1 Ki, nM ± SEM
1	3.45±0.410 8.5±0.8[1]	803±99.1[1]	1250±178 532±38[1]	45.0±6.51 372±21[1]
2a	4.28±0.552	204±15.2	990±48.1	56.6±2.89
2b	5.57±0.608	273±40.7	1500±128	76.0±4.86
2c	9.36±1.16	543±35.3	1520±141	88.3±6.49
2d	6.71±0.622	318±20.1	1950±194	87.3±9.47
2e	14.9±1.74	1230±50.8	2740±250	135±20.1
2f	36.6±4.00	1300±84.0	5350±584	235±28.8
2g	51.3±4.75	2190±292	>10,000	246±23.1
6a	1.72± 0.126	779 ± 85.2	766±112	28.1±1.3
6b	5.36±0.397	521±48.5	2110±266	33.4±4.77
7a	21.7±2.84	835±110	1050±121	75.0±9.26
7b	15.1±1.27	1040±103	1360±154	81.8±9.35
7c	33.5±3.04	1680±10.4	3460±509	292±38.1
7d	3.26±0.289	660±79.0	810±78.0	45.5±5.01
7e	6.92±0.884	1950 ±88.9	1680±190	87.4±7.42
NE-100	3620 ± 389	>10,000	ND	2.38±0.265
(+) pentazocine	NT	NT	NT	5.60±0.31
(−) pentazocine	NT	NT	NT	83.4±11.1
rimcazole	97.7±12	1711±71.5	NT	893±91.4 908±99[1]
GBR 12909	1.77±0.181	104 ±11.4	497±17.0	50.8±6.68 318 ± 18[2]

[a]DAT binding was performed with [^{3}H]WIN 35,428 in 0.32M sucrose, 10 mM phosphate buffer using previously frozen rat striatum for 120 min on ice. SERT binding was performed with [^{3}H]Citalopram in buffer containing 50 mM Tris, 5mM KCl and 120 mM NaCl using previously frozen rat brain stem for 60 minutes at 25 °C. NET binding was performed with [^{3}H]Nisoxetine in buffer containing 50 mM Tris, 5mM KCl and 120 mM NaCl using previously frozen rat frontal cortex for 180 minutes on ice. σ1 binding was performed with [^{3}H](+)-pentazocine in 50 mM Tris buffer using previously frozen guinea pig brain minus cerebellum for 120 min at 25 °C.

[1]ref. 11;

[2]ref. 4.

Table 2

Selectivity profiles based on Ki ratios

Compd#	SERT /DAT	NET /DAT	σ1/DAT
1	233	362	13
2a	48	231	13
2b	49	269	14
2c	58	162	9
2d	47	291	13
2e	83	184	9
2f	36	146	6
2g	43	248	5
6a	453	445	16
6b	97	393	6
7a	38	48	3
7b	69	90	5
7c	50	103	9
7d	202	248	14
7e	282	243	13
rimcazole	18	---	9