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

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ABSTRACT

Ester analogs of (±)3-(4-(3-(bis(4-fluorophenyl)amino)propyl)piperazin-1-yl)-1-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 (K_i = 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 analogs of the more active *S*-enantiomer showed comparable binding affinities at both DAT and σ1 receptors with a maximal 16-fold DAT/σ1 selectivity.

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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 analogs 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 analogs 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 analogs, we identified compounds with varying affinities and selectivities for σ1 receptors and the DAT as potential in vivo probes.[4,10–12] 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 (Fig. 1).

JJC 2-010 (**1**) did not generalize in rats trained to discriminate 10 mg/kg cocaine from saline (Fig. 2). Moreover, JJC 2-010 (**1**), at 10 and 24 mg/kg, had no effect on the cocaine dose–effect curve

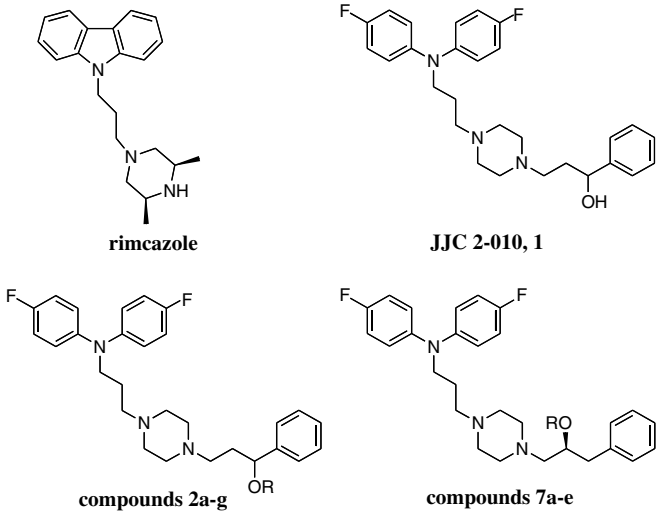

Figure 1. Dual DAT/σ1 receptor ligands.

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 analogs and cocaine, additional analogs were

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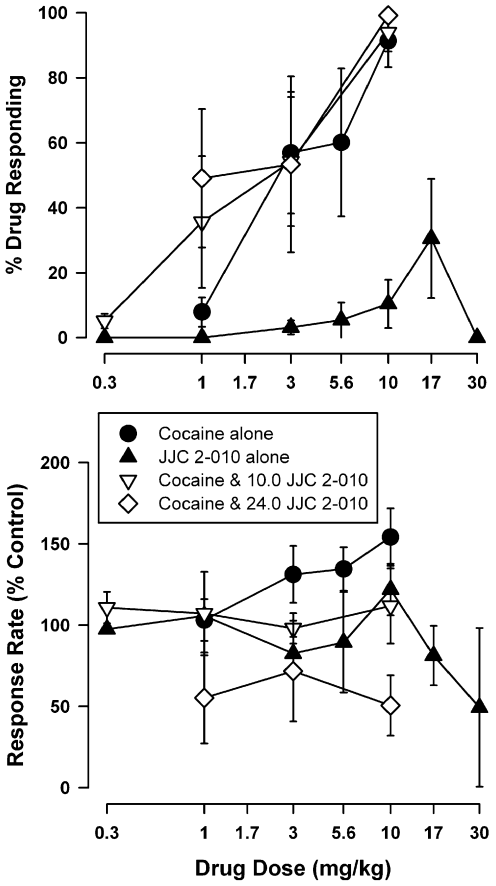


Figure 2. Discriminative stimulus effects of JJC 2-010 alone and with cocaine in rats trained to discriminate 10 mg/kg cocaine from saline (ip).

designed (Fig. 1). Using simple esterification of the linking chain OH group, steric tolerance could be explored.

In the present series, analogs 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)-3-phenylpropan-2-ol series to investigate enantioselectivity and then make ester analogs (**7a**–**e**) of the more active enantiomer (**6a**).

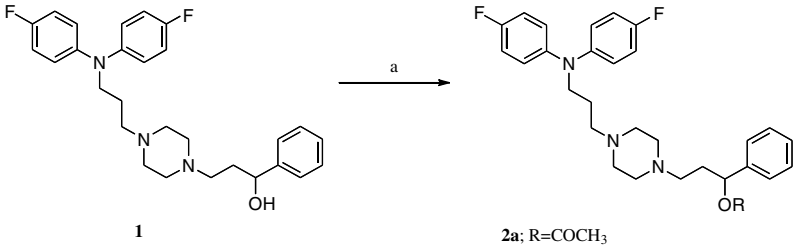
Compound **1** was prepared as previously described[11] and esterified (Scheme 1)[17] to give **2a**–**g**. In Scheme 2,[17] compounds **4a** and **4b** were synthesized via a regioselective epoxide ring opening using the Grignard reagent prepared from bromobenzene (**3**) as described previously.[15] 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 analogs (**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**, **6b,** and **7a**–**e** were determined and compared to those of 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 analogs 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 analogs. As mentioned above, the *S*-enantiomer **6a** showed slightly higher affinity (K_i = 1.72 nM) for DAT than its *R*-enantiomer **6b** (K_i = 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** (Table 1).

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

Analogs 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 σ 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 σ-receptor-mediated effects modulate the actions of cocaine. In addition, our previous results suggest that rimcazole analogs, including JJC 2-010, in contrast to cocaine analogs, 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.



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: (a) RCOCl, TEA, CH_2Cl_2.