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Discovery and Characterization of ML398, a Potent and Selective Antagonist of the D_4 Receptor with *in Vivo* Activity

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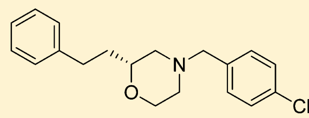
Supporting Information

ABSTRACT: Herein, we report the structure−activity relationship of a chiral morpholine-based scaffold, which led to the identification of a potent and selective dopamine 4 (D_4) receptor antagonist. The 4-chlorobenzyl moiety was identified, and the compound was designated an MLPCN probe molecule, ML398. ML398 is potent against the D_4 receptor with IC_{50} = 130 nM and K_i = 36 nM and shows no activity against the other dopamine receptors tested (>20 μM against D_1, D_{2S}, D_{2L}, D_3, and D_5). Further *in vivo* studies showed that ML398 reversed cocaine-induced hyperlocomotion at 10 mg/kg.



ML398
D_4 IC_{50} = 130 nM
D_4 K_i = 36 nM
Selectivity D_1, D_{2S}, D_{2L}, D_3, D_5 > 20 μM
B:P = 2.0

KEYWORDS: *Dopamine 4 receptor antagonist, ML398, addiction, MLPCN*

Dopamine receptors are members of the Class A G-protein coupled receptors (GPCRs) superfamily. GPCRs, also known as seven-transmembrane domain receptors (7TM receptors), are protein receptors that mediate most of the physiological responses to many hormones, neurotransmitters, etc., and constitute the largest class of drug targets. The dopamine receptors are further divided into five subtypes, included in two families. The D_1-like family of receptors contains D_1 and D_5, while the D_2-like family contains D_2, D_3, and D_4.[1,2] The dopamine receptors are associated with numerous neurological processes including memory, learning, motivation, pleasure, and cognition; and as such, they are familiar drug targets.[2] Included in the list of disorders linked to dysfunction of dopaminergic signaling is schizophrenia,[3−5] attention-deficit hyperactivity disorder (ADHD),[6−8] Parkinson's disease,[9,10] and drug[2,11] and alcohol[12,13] dependence. Recently there has been mounting evidence linking elevations in synaptic dopamine levels with the reinforcing effects of cocaine and hence its abuse potential.[14−16]

Cocaine is a powerful stimulant made from the leaves of the coca plant and produces short-term euphoria and energy bursts. According to the National Survey on Drug Use and Health (NSDUH), there are ~2 M current cocaine users in the US with young adults (18−25 years old) representing the largest population of users. Unfortunately, there are no approved treatments for cocaine dependence.[17] Cocaine does not directly bind to the D_1 and D_2 receptors, but rather binds to the dopamine transporter, thereby increasing synaptic levels of dopamine and its downstream effects on D_1 and D_2 receptors that enables the cocaine reinforcement effects. The involvement of D_4 receptors as another potential target for cocaine reinforcement/dependence is due to its tissue distribution in the limbic and cortical brain regions implicated in cocaine addiction.[3,18] In fact, the dopamine D_4 receptor has been coined the "adventure gene" due to the higher novelty seeking scores in individuals grouped by the long, polymorphic repeat region in exon III of the D4DR (L-D4DR) gene.[19,20] Although the notion of the adventure gene has been questioned,[21,22] further data has suggested that D4 has a role in severity of dependence.[23] While there have been numerous studies on the role of dopamine D4, the field has been hampered by the lack of selective D_4 receptor antagonists.[2] Herein, we report the discovery and characterization of a potent and selective dopamine D_4 receptor antagonist, ML398.

Recently we reported an enantioselective synthesis of a chiral morpholine analogue via an organocatalytic α-chlorination of aldehydes followed by cyclization to form the morpholine scaffold.[24] As part of the previous report, we synthesized a known dopamine D_4 antagonist, **1**, in order to confirm the stereochemistry of the active enantiomer (Figure 1).[25] Biological evaluation of **1** revealed the (*R*)-enantiomer was the active isomer with a D_4 IC_{50} = 180 nM and K_i = 70 nM. (*R*)-**1** was inactive against dopamine D_1 and D_2 (>100 μM) and weakly active against D_3 (IC_{50} = 46.2 μM and K_i = 15.7 μM).

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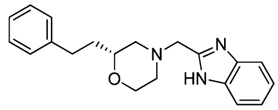

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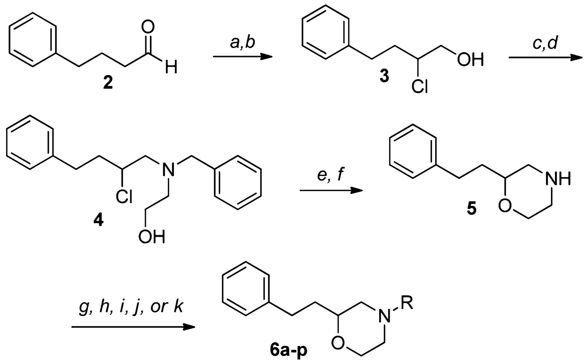
Receptor		(±)-1	(*S*)-1	(*R*)-1
D_1	K_i	>100	>100	>100
	IC_{50}	>100	>100	>100
D_2	K_i	>100	>100	>100
	IC_{50}	>100	>100	>100
D_3	K_i	10.8	25.9	15.7
	IC_{50}	31.8	76.4	46.2
D_4	K_i	0.14	>100	0.07
	IC_{50}	0.36	>100	0.18

Figure 1. Structure and activity of initial hit, (*R*)-**1**. K_i and IC_{50} values are in μM.

The (*S*)-**1** was inactive against D_4 (>100 μM), and the racemic-**1** was less active (IC_{50} = 360 nM and K_i = 140 nM). On the basis of the activity and binding of (*R*)-**1**, we embarked on a medicinal chemistry campaign to explore the structure−activity relationship (SAR) around the benzimidazole portion of the molecule.

In an effort to evaluate a number of compounds, the racemic phenethyl morpholine was synthesized and then rapidly analogued and assayed at D_4. Active compounds would then be assayed in enantiopure form. The racemic synthesis of the initial analogues for the SAR evaluation is outlined in Scheme 1

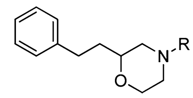
Scheme 1. Synthesis of Racemic Morpholine D_4 Receptor Antagonists[a,24]

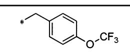
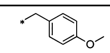
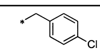
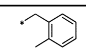
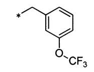
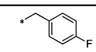
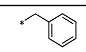
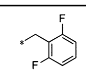
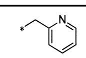
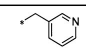
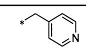
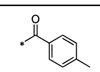
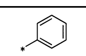
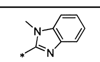
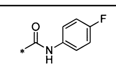
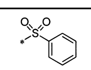


[a]Reagents and conditions: (a) DL-proline (10 mol %), NCS, CH_2Cl_2, 0 °C; (b) $NaBH_4$, MeOH; 86%; (c) Tf_2O, lutidine, DCM, −78 °C; (d) $BnNHCH_2CH_2OH$, DCM, −78 °C → rt; 78%; (e) KOfBu, CH_3CN, −20 °C; 54%; (f) H_2, Pd/C, MeOH; (g) R-Br, K_2CO_3, CH_3CN, rt; (h) DIPEA, acid chloride, DMF, rt, 1 h; (i) $Pd_2(dba)_3$, XANTPHOS, Cs_2CO_3, aryl bromide, 1,4-dioxane, 100 °C, 18 h; (j) aryl isocyanate, THF, rt, 1 h; (k) DIPEA, sulfonyl chloride, DMF, 40 °C, 1 h

and is identical to the previous work, except for the organocatalyst.[24] The racemic synthesis utilizes DL-proline as the catalyst to obtain the racemic α-chloro aldehyde, **3**. Next, the alcohol was activated (Tf_2O, lutidine) and displaced with the amino alcohol to yield **4**. Next, the morpholine ring was formed via an intramolecular cyclization and then the benzyl protecting group was removed to yield the common intermediate, **5**. The benzylic analogues in Table 1 were synthesized by alkylation of the morpholine nitrogen (R-Br, K_2CO_3). The amide analogues were synthesized via the corresponding acid chloride (DIPEA, DMF, rt, 1 h), the direct aryl compounds were synthesized via a palladium catalyzed cross-coupling ($Pd_2(dba)_3$, XANTPHOS, Cs_2CO_3, and 1,4-dioxane), the urea analogues were made via the aryl isocyanate (THF, rt, 1 h), and the sulfonamides were made via reaction with the appropriate sulfonyl chloride (DIPEA, DMF, 40 °C, 1 h).

Table 1. SAR Evaluation of the *N*-Morpholine Substituent[a]



Entry	R	D_4 (% inh. @ 10 μM)
6a		94
6b		98
6c		97
6d		54
6e		88
6f		88
6g		74
6h		51
6i		23
6j		35
6k		13
6l		17
6m		5
6n		17
6o		5
6p		2

[a]All assays were performed on the human D_4 receptor.[26]

The first set of analogues were substituted benzyl analogues (**6a**−**6h**), which all showed varying degrees of dopamine D_4 receptor inhibition (51−98% at 10 μM) (Table 1). Interestingly, the pyridyl analogues (2-, 3-, and 4-pyridylmethyl) were all inactive (**6i**−**6k**). Introduction of an amide group (thus changing the linker group from a methylene to a carbonyl) was not tolerated and led to inactive compounds (**6l**). Deletion of the linker group (direct arylation of the morpholine) was also not tolerated (**6m** and **6n**). Lastly, the urea analogue (**6o**) and sulfonamides (**6p**) were also inactive, potentially suggesting the need for a flexible or rotatable bond between the morpholine and the right-hand substituent (See Supplemental Table 1 for full SAR).

Next, the active benzyl analogues were progressed into the IC_{50} and K_i determinations, and clear SAR trends emerged (Table 2). First, ortho substituents were less tolerated than the

Table 2. IC_{50} and K_i Evaluation of the Racemic and Enantiomerically Pure Benzyl Analogues

compd	D_4 (% inh. @ 10 μM)[a]	IC_{50} (μM)	K_i (μM)
(±)-**6a**	94	0.16	0.043
(*R*)-**6a**	96	0.23	0.065
(±)-**6b**	98	0.17	0.046
(*R*)-**6b**	86	0.10	0.028
Selectivity Profile[a]: >20 μM against D_1, D_{2S}, and D_5			
D_{2L}, IC_{50} = 16.5 μM; K_i = 5.5 μM			
D_3, IC_{50} = 8.17 μM; K_i = 2.77 μM			
(±)-**6c**	97	0.29	0.081
(*R*)-**6c**	96	0.13	0.036
Selectivity Profile[a]: >20 μM against D_1, D_{2S}, D_{2L}, D_3, and D_5			
(±)-**6d**	54	3.68	1.02
(±)-**6e**	88	0.39	0.11
(±)-**6f**	88	1.14	0.32
(±)-**6g**	74	1.48	0.41
(±)-**6h**	51	3.88	1.07

[a]All assays were performed on the human receptor.[26]

meta- and *para*-substituents (even the small fluorine analogues) (**6d** and **6h**). Second, the *para*-fluoro (**6f**) and unsubstituted benzyl (**6g**) were less active. Lastly, the most potent compounds contained a *meta*- or *para*-trifluoromethoxybenzyl group (**6a**, **6e**), a *para*-methoxybenzyl group (**6b**), or a *para*-chlorobenzyl group (**6c**). On the basis of these results, both enantiomers of **6a**−**c** were synthesized using the previously published route.[24] Both the (*R*)- and (*S*)-enantiomers were evaluated, and as previously determined, the (*S*)-enantiomers were inactive. All three of the compounds tested were potent antagonists of the dopamine D_4 receptor with high binding affinities ((*R*)-**6a**, IC_{50} = 230 nM, K_i = 65 nM; (*R*)-**6b**, IC_{50} = 100 nM, K_i = 28 nM; (*R*)-**6c**, IC_{50} = 130 nM, K_i = 36 nM). On the basis of these results, we further profiled (*R*)-**6b** and (*R*)-**6c** for their selectivity against the other dopamine receptors, and (*R*)-**6c** was inactive (>20 μM) against all of the dopamine receptors tested. Thus, on the basis of potency, binding, and selectivity profile, (*R*)-**6c** was declared an MLPCN probe (ML398).

ML398 was further profiled in a battery of Tier 1 *in vitro* DMPK assays (Table 3). The intrinsic clearance was assessed in hepatic microsomes (rat and human), and ML398 was shown to be unstable to oxidative metabolism and predicted to display high clearance in both species. In addition, using an equilibrium dialysis approach, the protein binding of ML398 was evaluated, and it was shown to have good free fraction in both species (6.1% in human and 3.9% in rat). ML398 was evaluated for its inhibition of the cytochrome P450 (CYP) enzymes using a cocktail approach in human liver microsomes as a screen for potential drug−drug interaction liability. ML398 displayed no significant activity against the panel of CYPs. ML398 was also profiled in an *in vivo* tissue distribution study (plasma and brain levels). Because of the predicted high clearance, ML398 was dosed at a single dose via intraperitoneal (IP) route of

Table 3. *In Vitro* and *in Vivo* PK Properties of ML398

	ML398	(*R*)-**1**
In Vitro PK Properties		
microsome predicted hepatic clearance (mL/min/kg)		
rat CL_{HEP}	67.5	65.1
human CL_{HEP}	15.7	17.9
plasma unbound fraction (F_u)		
human	0.061	0.012
rat	0.039	0.133
CYP inhibition (IC_{50}, μM)		
1A2	>30	13.1
2C9	>30	4.8
2D6	18.0	12.0
3A4	>30	15.6
plasma exposure in SD Rat		
10 mg/kg, intraperitoneal, 0.25 hr sample		
plasma (nM)	482	1935
brain (nM)	987	3558
Brain:Plasma	2.0	1.8

administration with a suspension formulation and then evaluated at a single time point. ML398 readily crosses the blood−brain barrier with a B/P ratio of ∼2 and total brain concentrations of ∼1 μM. Lastly, ML398 was tested using EuroFins Lead Profiling screen (radioligand binding assay panel of 68 GPCRs, ion channels, and transporters screened at 10 μM). ML398 was found to not significantly interact with 63 of the 68 assays performed (<50% binding at 10 μM) (See Supporting Information). ML398 did have activity against five targets (adrenergic, α_1A (77%); histamine, H_1 (93%); sigma, σ_1 (99%); dopamine transporter, DAT (72%); norepinephrine transporter, NET (68%).

Having identified a potent, selective, and brain penetrant D_4 antagonist, we wanted to test its ability to reverse hyperlocomotion induced by cocaine. It is believed that cocaine increases locomotor activity by increasing synaptic concentrations of dopamine by blocking dopamine reuptake or by enhancing the release of dopamine. This, in turn, increases stimulation of postsynaptic dopamine receptors. The increased locomotor activity can be blocked by selective dopamine antagonists as well as haloperidol.[27] The cocaine-induced hyperlocomotion assay is used to establish PK/PD relationship. The effects of both (*R*)-**1** and ML398 were evaluated in this assay, and the results are shown in Figure 2. Cocaine was

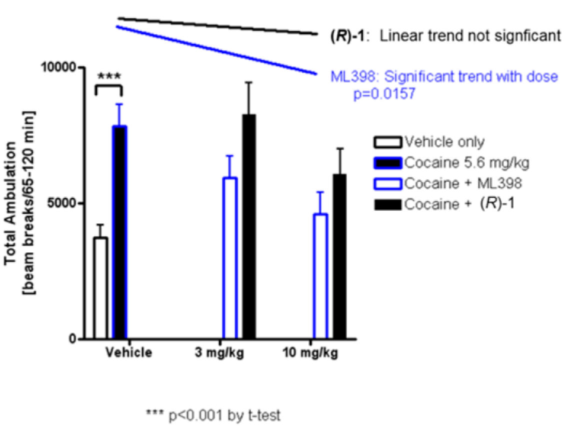


Figure 2. Effects of ML398 and (*R*)-**1** on reversing cocaine-induced hyperlocomotion in rats.

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shown to significantly induce hyperactivity in rats, which is characterized by an increase in the number of beam breaks using the SmartFrame open field activity chambers. Both test compounds were dosed via IP administration at doses of 3 mg/kg and 10 mg/kg. Although (*R*)-**1** showed a linear trend of reversal, the data was not significant. However, ML398 did show a statistically significant reversal of cocaine-induced hyperlocomotion at the highest dose tested (10 mg/kg).

In conclusion, we have identified a new, potent, and selective dopamine D_4 antagonist based on a chiral morpholine scaffold. As many of the previous D_4 antagonists contain a piperidine moiety, the reduced basicity of the morpholine may help contribute to the unprecedented selectivity. The SAR studies showed that the benzylic substitution is optimal as the amides, ureas, and arylation analogues were all inactive. In addition, the (*R*)-enantiomer was confirmed as the active isomer within this series. ML398 is >100-fold selective versus the other dopamine receptors and is highly brain penetrant. ML398 also was shown to reverse cocaine-induced hyperlocomotion in rats. Further optimization studies are ongoing in an effort to discover an improved molecular probe for biological study as well and development of a radioligand for the D_4 receptor.

■ ASSOCIATED CONTENT

Supporting Information

General methods for the synthesis and characterization of all compounds. General methods for the *in vitro* and *in vivo* DMPK protocols and *in vivo* pharmacology. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

⊥J.P.H. and J.A.W. contributed equally to this work. C.B.B., M.B., C.K.J., C.W.L., J.S.D., and C.R.H. drafted/corrected the manuscript. C.B.B., J.P.H., and J.A.W. performed the chemical synthesis. C.W.L. and C.R.H. oversaw the target selection and interpreted the biological data. C.W.L. and J.S.D. performed the *in vitro* DMPK experiments. M.B. and C.K.J. performed the *in vivo* experiments. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DIPEA, diisopropyl ethyl amine; DMF, dimethylformamide; THF, tetrahydrofuran; NCS, *N*-chlorosuccinimide; DCM, dichloromethane

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