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Synthesis and Biological Evaluation of *N*-Fluoroalkyl and 2-Fluoroalkoxy Substituted Aporphines: Potential PET Ligands for Dopamine D_2 Receptors

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Abstract

The 2-fluoroalkoxy substituted catechol-aporphines **6, 8a-f** and 11-monohydroxyaporphines **11a-e** were synthesized and found to have high in vitro affinity and selectivity for the dopamine D_2 receptors. The catechol aporphines, **8b** and **8d**, and the monohydroxy aporphines, **11a-d**, were identified as candidates for development as potential PET ligands.

Keywords

aporphine; D_2 agonist; neurological disorders; positron emission tomography; dopamine receptors

Dopamine is unarguably one of the most important neurotransmitters in the brain. Disturbances in the dopaminergic system, and especially irregularities in dopamine D_2 receptor function, have been implicated in many different neurological and psychiatric disorders, including Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit-hyperactivity disorder, Tourette's syndrome, restless leg syndrome, and addiction.1 Early diagnosis of these disorders is desirable, as early treatment would allow for a better outcome for the patient, either by slowing the progression of the disease or lessening the severity of the symptoms or future episodes. Physical symptoms tend to manifest themselves much later, after significant changes occur in the brain. Thus, identification of subtle changes in the brain early in the course of the disease, before a clinical diagnosis from physical symptoms can be made, would offer the best opportunity for early treatment.

Noninvasive imaging of molecular and biological processes in living subjects with positron emission tomography (PET)2 and single photon emission computed tomography (SPECT)3 are invaluable tools for the investigation of human neurochemistry and neuropharmacology in vivo. 4 Thus, extensive research efforts have been directed toward the development of PET radioligands suitable for probing the dopaminergic system. For example, the PET ligands [^{18}F]-DOPA and the dopamine transporter ligand, [^{11}C]-PE2I, have been used to quantify the presynaptic dopamine levels in patients suffering from Parkinson's disease.2 However, these radioligands do not elucidate the postsynaptic dopamine functions in neurological disorders. In order to gain more insight into dopamine D_2 receptor function,

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Supporting Information Available: Experimental details and characterization of all compounds, biological methods. This material is available free of charge via the Internet at http://pubs.acs.org.

several different D_2 receptor radioligands have been developed to date. These include radioligands for striatal D_2 binding, [^{11}C]methylspiperone, [^{11}C]raclopride; and high affinity ligands for extrastriatal binding, [^{11}C]FLB457, [^{11}C]cyclopropyl-FLB457, and [^{18}F]fallypride (see Figure 1 for structures).5

Although these radioligands are invaluable tools for studying or diagnosing diseases, they have certain limitations. As mentioned above, the presynaptic radioligands do not directly provide information on postsynaptic dopamine function. Of the D_2 radioligands discussed above, [^{11}C]raclopride binding is reduced when synaptic dopamine concentration is high. For others, selectivity may be an issue. For example, [^{11}C]methylspiperone also has $5HT_2$ affinity, while the higher affinity ligands [^{11}C]FLB457, and [^{18}F]fallypride do not discriminate between D_2 and D_3 sites.6 It has been hypothesized that, in schizophrenia and other DA-dependent neurological disorders, more D_2 receptors exist in the D_2^{high} state,7,8 and that D_2^{high} is the primary and common target for the antiparkinson action of dopamine agonists.9 However, all of the D_2 radioligands discussed above are based on benzamide D_2 antagonists, which do not discriminate between high affinity (D_2^{high}) and low affinity (D_{2low}) states of the D_2 receptor. Therefore, it is anticipated that an agonist tracer would be more sensitive to endogenous DA concentration changes than that of an antagonist tracer, and thus, will serve as a superior probe for quantifying endogenous DA concentration.10 There have been very few attempts to develop D_2 agonist radiotracers to date. The agonist tracer [^{18}F]F-PHNO was recently reported to have high binding affinities to D_2 and D_3 receptors *in vitro* as well as good brain penetration; however, in contrast to [^{3}H]-(+)-PHNO (Figure 1), it did not perform well *ex vivo*.11a However, [^{11}C](+)PHNO proved to be a nonselective D_2/D_3 receptor agonist tracer with good brain uptake and favorable kinetics for PET in humans.11b,c As an alternative, aporphines exhibiting D_2 receptor activity in the brain have been considered as potential agonist PET tracers. Several ^{11}C and ^{18}F labeled apomorphine analogues have been investigated for their in vivo binding potency to the D_2 receptors and their distribution in brain and peripheral tissues of rats or monkey, such as *N*-[^{11}C]methylnorapomorphine, 12 *N*-*n*-3-[^{18}F]fluoropropylnorapomorphine, 13 a,b *N*-*n*-2-[^{18}F]fluoroethylnorapomorphine,13b *N*-[^{11}C]-propylnorapomorphine (NPA),13c 2-[^{11}C]methoxy-NPA,13d,e and 2-chloro-N-[^{11}C-propyl]norapomorphine.13f

A need for even more potent dopamine ligands, with higher selectivity and oral availability, has led to the development of many novel aporphines. 14 Furthermore, substituents in the 2-position of aporphines have been demonstrated to modulate the dopaminergic receptor potency and D_2/D_1 selectivity.15 In this report, several novel 2-fluoroalkoxy aporphines were synthesized and tested for dopamine receptor affinities and selectivities.

The synthesis of the twelve target molecules (**6, 8a-f** and **11a-e**) is shown in Scheme 1. 3-Deoxynormorphine **4** was prepared from morphine according to our published procedure in 4 steps.16 *N*-Alkylation of **4** with 1-bromo-3-fluoropropane led to the *N*-substituted-3-deoxynormorphine **5**. Acid-catalyzed rearrangement of **5** with methanesulfonic acid at 90-100 °C yielded the target compound 11-hydroxy-*N*-(3-fluoropropyl)aporphine **6**. Starting from thebaine, *N*-ethyl and -propyl nororipavines **7b,c** were prepared in 4 steps using our previously reported procedure.17 Acid-catalyzed rearrangement of oripavine **7a** or nororipavines **7b,c** with methanesulfonic acid at 90-95 °C18 in the presence of 2-fluoroethanol or 3-fluoropropanol yielded the corresponding fluorinated compounds **8a-f**. *N*-*n*-Alkyl-3-*O*-[(trifluoromethyl)sulfonyl]nororipavines **9b-c** were prepared in 5 steps from thebaine according the published procedure.19 3-*O*-[(trifluoromethyl)sulfonyl] oripavine **9a** was obtained in one step from oripavine.19 Acid-catalyzed rearrangement of **9a-c** with methanesulfonic acid at 90-100 °C in the presence of either fluoroethanol or fluoropropanol yielded **10a-e**. Pd/C catalyzed reduction of the latter with Mg metal in MeOH at rt in the presence of NH_4OAc19 provided the target compounds 2-(fluoroalkoxy)-11-hydroxy-*N*-*n*-

alkylnoraporphines **11a-e**. Alternatively, triflates **10a-e** could be reduced using a Pd-triethylhydrosilane system to furnish 11-hydroxy aporphine derivatives **11a-e**.20

The receptor affinities of the twelve novel compounds **6, 8a-f** and **11a-e** at D_1 and D_2 dopamine receptors were assessed using competitive radioreceptor binding assays with membrane-containing homogenates of rat corpus striatum tissue. Affinities to the D_3 receptor were assessed using human D_3 clones following procedures previously reported in detail9b (see Supporting Information for details). However, the receptor affinities at D_3 dopamine receptors for compounds **11a-d** were assessed using rat clones following procedures reported in detail21 (see Supporting Information for details). The results are summarized in Table 1.

From the binding data shown in Table 1, we observed that the cold compounds **6, 8a-f** and **11a-e** showed good to high affinity at D_2^{high} site, high selectivity of D_2 versus D_1 and, in contrast to [^{11}C]-(+)PHNO11 and [^{18}F]fallypride6, exhibited low affinity or no affinity at all to the D_3 site. N-fluoropropyl aporphine **6** retained a similar binding affinity as N-propyl analog **3b** to D_2^{high} (6.9 and 4.9 nM, respectively). However, it has been previously shown that increasing the length of the N-substituent beyond three carbons causes D_2 binding affinity to drop, thereby limiting the potential for improving binding affinity and selectivity by varying the labeled N-substituent.23 Placing a fluoroalkoxy group at position 2 would allow for more flexibility with respect to ligand design. Thus, a series of different N-*n*-propyl, ethyl, and methyl aporphines were systematically synthesized and evaluated, while varying the fluoropropanoxy and fluoroethoxy chains at position 2 (see Table 1). Likewise, the corresponding 10,11-dihydroxy (**8a-f**) and 11-hydroxy analogs (**11a-e**), all aimed at achieving the best combination of binding affinity, selectivity, and lipophilicity, were also evaluated.

We began by focusing on N-*n*-propyl catechol-aporphines, since these have been shown to have consistently higher D_2 binding affinities and selectivities over their N-ethyl and N-methyl counterparts.23 Unfortunately, the 2-fluoropropanoxy analog **8a** exhibited a loss of D_2^{high} affinity compared to NPA (**2a**), 2-MeO-NPA (**2b**),22 and 2-F-NPA (**2c**) (27 nM vs. 5.1 to 2.7 nM range). However, in comparison, we found that by removing one carbon from the 2-substituent, 2-fluoroethoxy analog (**8b**) restored D_2^{high} affinity (3.7 nM) without compromising the remaining DA receptor binding affinity profile.

We next focused our attention on N-ethyl analogs, with the expectation that we may be able to improve D_2^{high} binding affinities. In comparison to the N-propyl catechol-aporphine analog **8a**, the N-ethyl-2-fluoropropanoxy catechol-aporphine **8c** afforded about a 4-fold increase in D_2^{high} affinity while simultaneously showing higher selectivity against D_3. The 2-fluoroethoxy analog (**8d**) afforded a more than 2-fold improvement in D_2^{high} binding affinity while retaining a similar binding affinity profile among the other dopamine receptors tested.

Encouraged by these findings, we investigated the N-methyl series. It was found that the 2-fluoropropanoxy catechol aporphine **8e** exhibited a D_2^{high} affinity consistent with **8a**, although, unlike **8a** or even **8c**, it did not exhibit any D_3^{high} affinity. The 2-fluoroethoxy analog **8f** afforded further improvement in D_2^{high} binding over the N-propyl and N-ethyl analogs **8b** and **8d**, again with no appreciable affinity to D_3.

Finally, we investigated the series of 11-monohydroxy aporphines in order to determine the effect of the absence of the 10-hydroxy group on D_2^{high} binding affinities. It was reasoned that, although 11-monohydroxyaporphines exhibited reduced D_2^{high} binding affinities compared to the 10,11-dihydroxy analogs (see **3a, 3b**, and **6** compared to **1, 2a, 2b**, and **2c**, Table 1), they were also far less prone to oxidation than the catechol-aporphines, and may

thus be a viable consideration for development of imaging agents. Since catechol-aporphine **8f** exhibited the highest D_2^{high} binding affinity among the catechol-aporphine derivatives, we began by synthesizing and testing its 11-monohydroxy analog, **11e**. We expected to obtain a more stable analog, hopefully without significantly sacrificing D_2^{high} binding. We were pleased to find that the binding profile of analog **11e** exceeded our expectations, having a binding affinity to the D_2^{high} receptor in the same range as **8f**. Encouraged by this promising result, we proceeded to synthesize and test other fluorinated 11-monohydroxy aporphines, which we hypothesized might also have analogous relationships in binding affinities to their parent catechol-aporphines as the **8f – 11e** pair. Another advantage to developing N-alkyl aporphines is that they are predicted to be more lipophilic than N-methyl derivatives, which may make them better candidates as potential PET ligands. Next, we tested N-propyl-2-fluoroethoxy-11-monohydroxy aporphine **11b**, the analog of catechol-aporphine **8b**, and found that, indeed, as in the **8f – 11e** pair, the D_2^{high} binding affinity was about the same. We were pleased to find that the N-ethyl 11-monohydroxy analog **11d** was found to have binding affinity on the order of 1 nM and exhibiting an improved binding affinity than its 10,11-dihydroxy analog **8d**. Next we tested N-ethyl-2-fluoropropanoxy-11-monohydroxy aporphine **11c**. As expected, it also exhibited an overall improved binding affinity to D_2^{high} compared to its 10,11-dihydroxy analog **8c**. Unexpectedly, the last analog, N-propyl-2-fluoropropanoxy-11-monohydroxy aporphine **11a**, had the highest D_2^{high} binding affinity of any of the aporphines tested in this study. It was measured to have an average K_i value of 0.54 nM, which is at minimum an order of magnitude higher than its dihydroxy analog **8a**. Our goal of finding a fluorinated aporphine with high binding affinity and high selectivity to D_2^{high} was achieved. Having a series of fluorinated aporphines derivatives in hand which exhibit binding affinities in the 0-2 nM range (**8b,d,f; 11a-e**), we can proceed with radiolabelling and *in vivo* PET studies.

Conclusion

A series of aporphines containing different N-substituents, substituents at the 2-position, 10,11-dihydroxy-, and 11-monohydroxy- groups have been systematically synthesized and tested for dopamine receptor binding affinity. Some conclusions could be made from the obtained binding data. It was found that 2-fluoroethoxy catechol-aporphines generally tended to have higher affinity to D_2^{high} than the 2-fluoropropanoxy analogs. In contrast to the generally accepted trend for nitrogen substituents in the aporphine series, smaller substituents on nitrogen (Me>Et>*n*Pr) allowed for improved D_2^{high} binding and selectivity. Contrary to our expectations, removal of the 10-hydroxy group generally *enhanced* the binding affinity to the D_2^{high} site. This is an especially attractive characteristic since the 11-hydroxy aporphines are more resistant to oxidation and are orally active24 compared to their 10,11-dihydroxy counterparts. Two of the 11-hydroxy aporphines, **11a** and **11d**, were found to have average subnanomolar affinity to the D_2^{high} binding site. Unlike the series of catechol-aporphines, no clear structure-activity relationships between the substituents and binding affinities could be concluded in the 11-monohydroxy aporphine series. Finally, this new class of fluorinated aporphines could potentially prove to be valuable as therapeutics or as PET ligands. Such studies are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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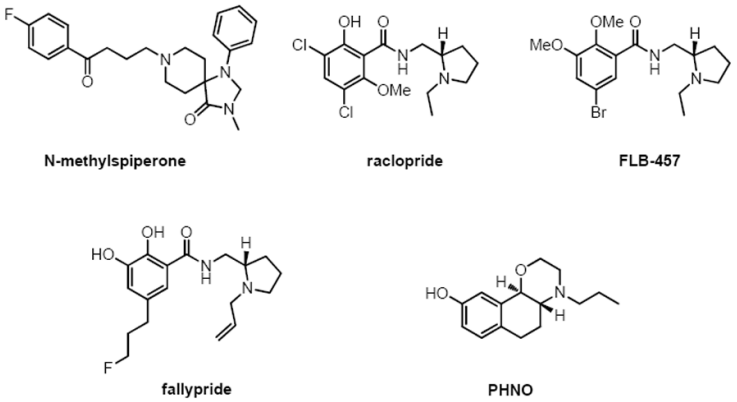
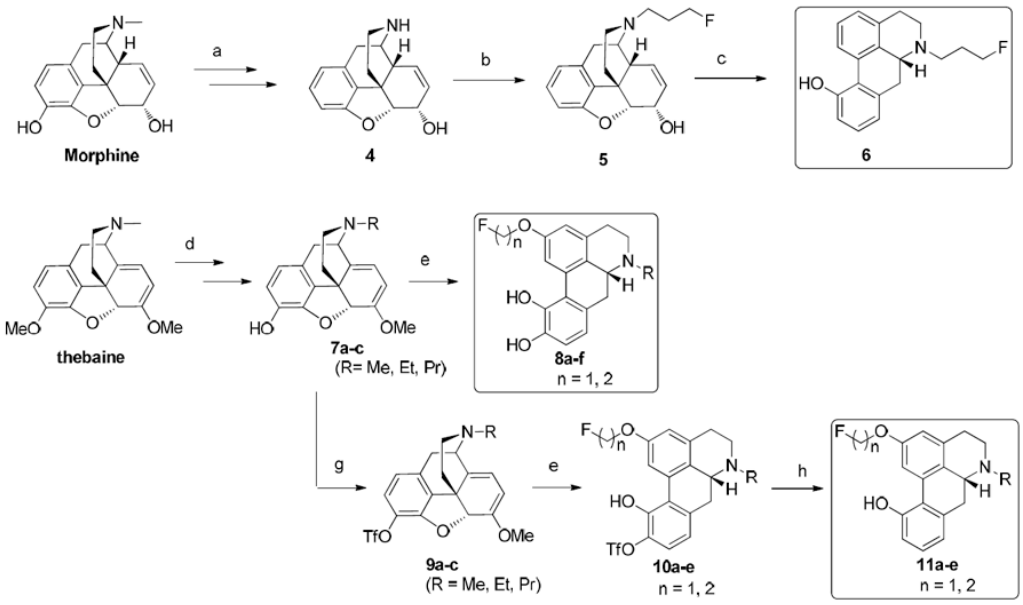


Figure 1.
High affinity D_2 ligands used in PET imaging.



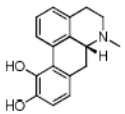
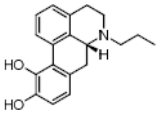
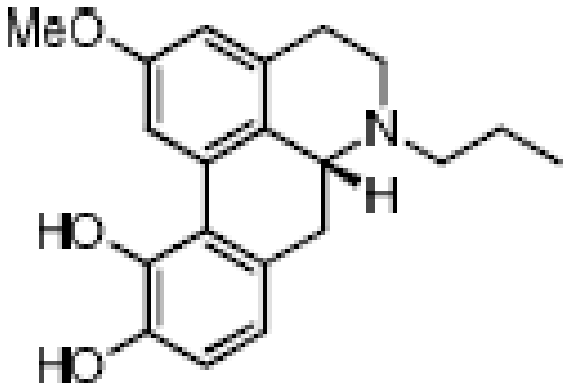
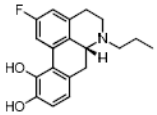
Scheme 1.

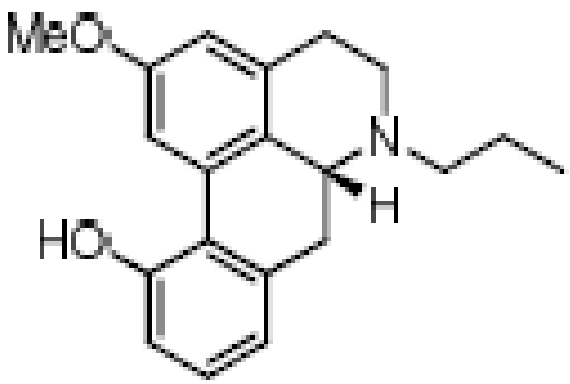
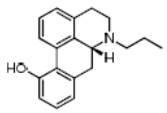
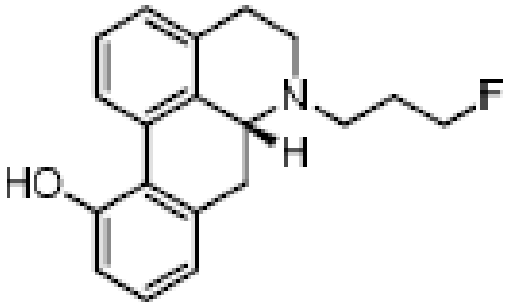
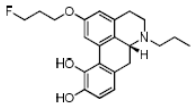
Synthesis of aporphine analogs **6, 8a-f**, and **11a-e**

a) ref. 16. b) 1-bromo-3-fluoropropane, $NaHCO_3$, EtOH/reflux; c) $MeSO_3H$, 95 °C; d) ref. 17. e) ROH, $MeSO_3H$, 95 °C; f) NaI, acetone, reflux; g) $PhNTf_2$, Et_3N, CH_2Cl_2; h) Pd/c, Mg, NH_4OAc, MeOH.

Table 1

Affinities (K_i) at Dopamine D_2 and D_3 receptors[b]

Compound		K_i (nM)[a,b]			
		D_2^{low} [^{3}H] domperidone	D_2^{high} [^{3}H] domperidone	D_3 [^{3}H] domperidone	CLogP[c]
	**1 (APO)**	98±40 [d]	1.8±0.9 [d]	2.6 [e]	2.49
	**2a (NPA)**	54±20 [d]	0.18±0.03 [d]	0.44 [g]	3.55
	**2b[f] (2-OMe-NPA)**	810±140	5.1±1.3	1.02 [g]	3.51
	**2c (2-F-NPA)**	1800±340	2.7±1.3	>10μM [h]	3.77

Compound		K_i (nM)[a,b]			
		D_2^{low} [^{3}H] domperidone	D_2^{high} [^{3}H] domperidone	D_3 [^{3}H] domperidone	CLogP[c]
	**3a (MCL-509)**	1400±370	20±6	>10μM [h]	4.10
	**3b (11-OH-NPa)**	1410±220	4.9±1.2	1700±250[h]	4.15
	**6 (MCL-517)**	860±170	6.9±2.1	>10μM	3.57
	**8a (MCL-526)**	3000	28±15	430±64[h]	3.99

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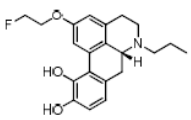
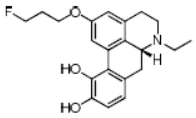
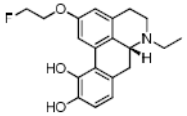
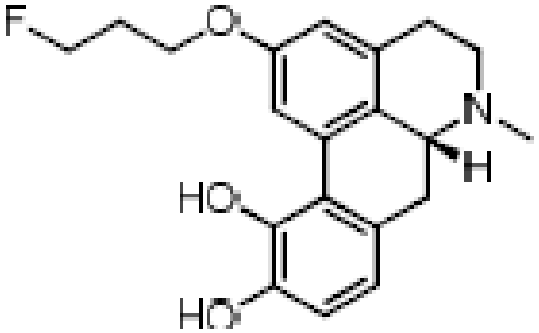
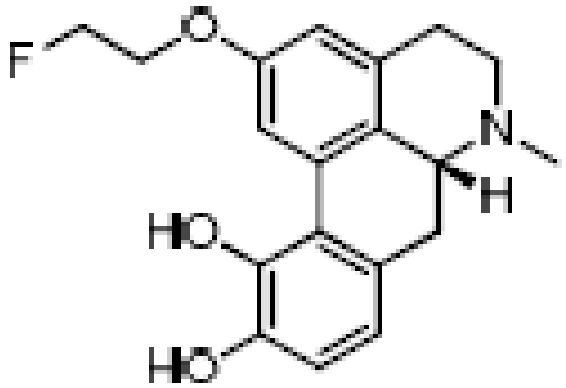
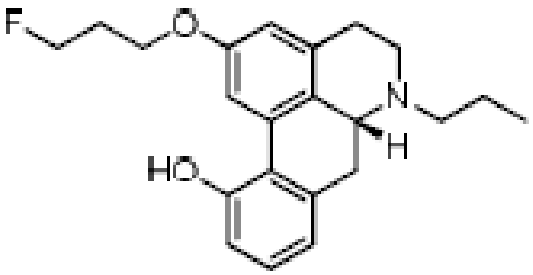
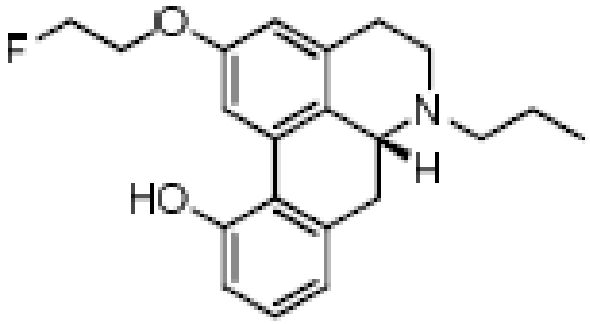
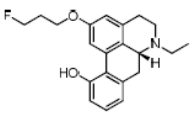
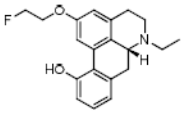
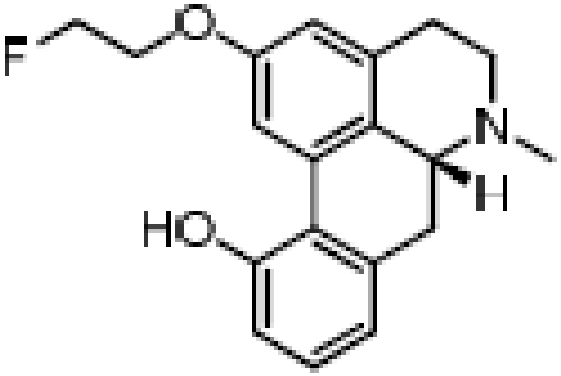
Compound		K_i (nM)[a,b]			
		D_2^{low} [^{3}H] domperidone	D_2^{high} [^{3}H] domperidone	D_3 [^{3}H] domperidone	CLogP[c]
	**8b (MCL-524)**	990±35	3.7±1.2	2200±330[h]	3.77
	**8c (MCL-527)**	1600±780	6.1±3	>10μM [h]	3.47
	**8d (MCL-528)**	2400±1500	2.5±0.8	>10μM [h]	3.24
	**8e (MCL-531)**	>10,000	31 ± 9	>10μM	2.94

Compound		K_i (nM)[a,b]			
		D_2^{low} [^{3}H] domperidone	D_2^{high} [^{3}H] domperidone	D_3 [^{3}H] domperidone	CLogP[c]
	**8f (MCL-530)**	620±260	2.0±0.96	>10μM	2.71
	**11a (MCL-536)**	490 ±280	0.54±1.6	100±14[i]	4.58
	**11b (MCL-522)**	56 ±37	3.5±2.0	410±62 [i]	4.35

Compound		K_i (nM)[a,b]			
		D_2^{low} [^{3}H] domperidone	D_2^{high} [^{3}H] domperidone	D_3 [^{3}H] domperidone	CLogP[c]
	**11c (MCL-537)**	400±290	3.2±2.2	240±33 *i*	4.05
	**11d (MCL-538)**	750±560	0.83±0.60	550±89 *i*	3.82
	**11e (MCL-534)**	480±130	1.2±0.4	890±130	3.29

[a] Source and radioligands: D_1: rat striatum [^{3}H]SCH23390; D_2: rat striatum [^{3}H] domperidone. D_3: human D_3 clone [^{3}H]domperidone; errors are expressed as standard deviations.

[b] Compounds in Table 1 have been tested and found to have low affinity to D_1 (K_i>5000) except for the following: **1** (K_i = 650±310 nM), **2a** (K_i = 490±220 nM), **3b** (K_i = 4300±250 nM), **8f** (K_i = 3700±1200 nM) and **11e** (K_i = 340±44 nM); and no affinity to D_1^{high}, except for the following: **1** (K_i = 4.6±1.2 nM), **2a** (K_i = 1±0.2 nM), and **2b** (K_i = 8.1±0.7nM); data for **1** and **2a** obtained from ref. 9a.

[c] Calculated using the chemical properties feature in CambridgeSoft ChemDraw Ultra, version 12.0.

[d] Data from ref. 9a.

[e] Data from ref. 9b.

[f] For preparation see ref. 22.

[g] See ref. 13e; HEK293T cell homogenate used with [3H]methylspiperone.

[h] The following compounds were also found to have D_3^{high} affinity: **2c** (K_i=3.8±2nM), **3a** (K_i=130±100nM) **3b** (K_i=1.2±1nM); **8a** (K_i = 1.1±2nM); **8b** (K_i = 1.9±1.5nM); **8c** (K_i = 230±140nM); and **8d** (K_i = 250±19 nM).

[i] Source and radioligands: D_3 rat clone [^{3}H] domperidone; data provided by PDSP

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