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LETTER

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Synthesis and Evaluation of Fluorinated Aporphines: Potential Positron Emission Tomography Ligands for D_2 Receptors

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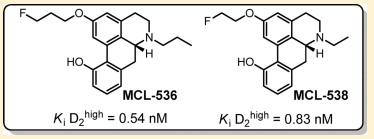
Supporting Information

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.[1,2] Early diagnosis of these disorders is desirable, as early treatment would allow for a better outcome for the patient, by either 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)[3] and single photon emission computed tomography (SPECT)[4,5] are invaluable tools for the investigation of human neurochemistry and neuropharmacology in vivo.[6] 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.[3] However, these radioligands do not elucidate the postsynaptic dopamine functions in neurological disorders. To gain more insight into dopamine D_2 receptor function, several different D_2 receptor radioligands have been developed to date. These include radioligands for striatal D_2 binding, [^{11}C]methylspiperone and [^{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).[7]

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 the 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.[8] It has been hypothesized that in schizophrenia and other DA-dependent neurological disorders, more D_2 receptors exist in the D_2^{high} state[9−12] and that D_2^{high} is the primary and common target for the antiparkinson action of dopamine agonists.[13,14] 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.[15,16] 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.[17] 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.[18,19] 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,[20]

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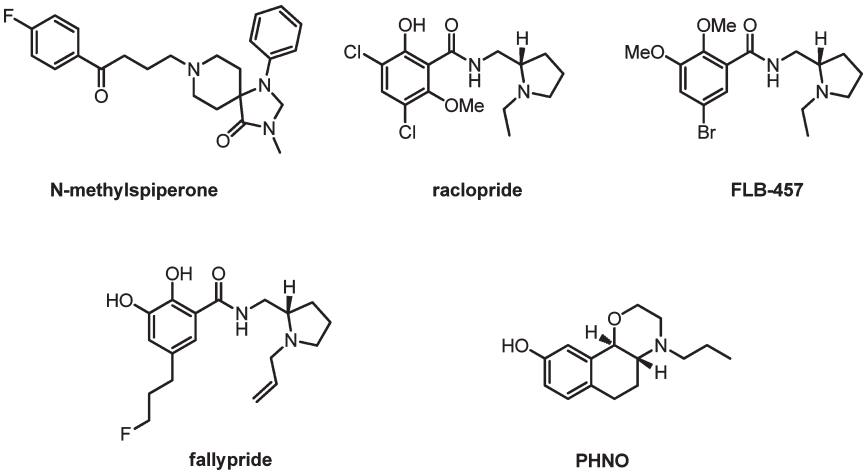
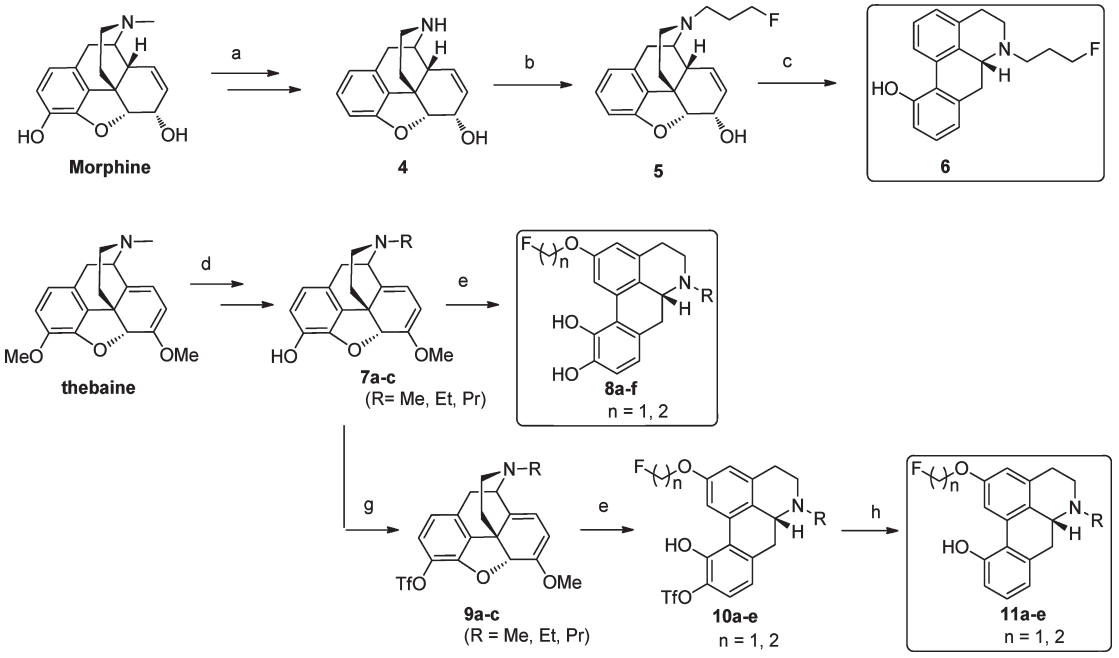


Figure 1. High affinity D_2 ligands used in PET imaging.

Scheme 1. Synthesis of Aporphine Analogues 6, 8a−f, and 11a−e[a]



[a] Reagents and conditions: (a) Ref 34. (b) 1-Bromo-3-fluoropropane, $NaHCO_3$, EtOH/reflux. (c) $MeSO_3H$, 95 °C. (d) Ref 35. (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.

N-*n*-3-[^{18}F]fluoropropylnorapomorphine,[21,22] *N*-*n*-2-[^{18}F]fluoroethylnorapomorphine,[22] *N*-[^{11}C]-propylnor-apomorphine (NPA),[23] 2-[^{11}C]methoxy-NPA,[24,25] and 2-chloro-*N*-[^{11}C-propyl]norapomorphine.[26]

A need for even more potent dopamine ligands, with higher selectivity and oral availability, has led to the development of many novel aporphines.[27] Furthermore, substituents in the 2-position of aporphines have been demonstrated to modulate the dopaminergic receptor potency and D_2/D_1 selectivity.[28−33] In this report, several novel 2-fluoroalkoxy aporphines were synthesized and tested for dopamine receptor affinities and selectivities.

The synthesis of the 12 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 four steps.[34] *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 noroipavines **7b,c** were prepared in four steps using our previously reported procedure.[35] Acid-catalyzed rearrangement of oripavine **7a** or noroipavines **7b,c** with methanesulfonic acid at 90−95 °C[36] in the presence of 2-fluoroethanol or 3-fluoropropanol yielded the corresponding fluorinated compounds **8a−f**. *N*-*n*-Alkyl-3-*O*-[(trifluoromethyl)sulfonyl]noroipavines **9b,c** were prepared in five steps from thebaine according the published procedure.[37] 3-*O*-[(Trifluoromethyl)sulfonyl] oripavine **9a** was obtained in one step from oripavine.[37] Acid-catalyzed rearrangement of **9a−c** with methanesulfonic acid at 90−100 °C

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in the presence of either fluoroethanol or fluoropropanol yielded **10a**−**e**. Pd/C-catalyzed reduction of the latter with Mg metal in MeOH at room temperature in the presence of NH_4OAc[37] 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**.[38]

The receptor affinities of the 12 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 detail[14] (see the 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 detail[39] (see the 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]-(+)-PHNO[17−19] and [^{18}F]fallypride,[8] 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 analogue **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.[41] 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 analogues (**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.[41] Unfortunately, the 2-fluoropropanoxy analogue **8a** exhibited a loss of D_2^{high} affinity as compared to NPA (**2a**), 2-MeO-NPA (**2b**),[40] and 2-F-NPA (**2c**) (27 vs 5.1 to 2.7 nM range). However, in comparison, we found that by removing one carbon from the 2-substituent, 2-fluoroethoxy analogue (**8b**) restored D_2^{high} affinity (3.7 nM) without compromising the remaining DA receptor binding affinity profile.

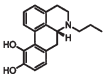
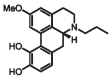
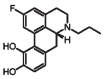
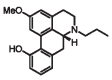
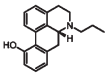
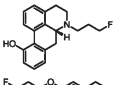
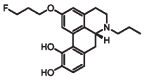
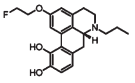
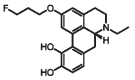
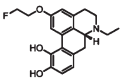
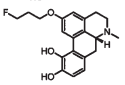
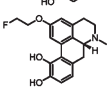
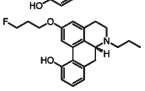
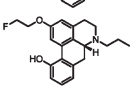
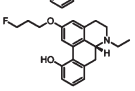
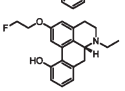
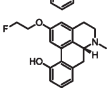
We next focused our attention on *N*-ethyl analogues, with the expectation that we may be able to improve D_2^{high} binding affinities. In comparison to the *N*-propyl catechol-aporphine analogue **8a**, the *N*-ethyl-2-fluoropropanoxy catechol-aporphine **8c** afforded about a 4-fold increase in D_2^{high} affinity, while simultaneously showing higher selectivity against D_3. The 2-fluoroethoxy analogue (**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 analogue **8f** afforded further improvement in D_2^{high} binding over the *N*-propyl and *N*-ethyl analogues **8b** and **8d**, again with no appreciable affinity to D_3.

Finally, we investigated the series of 11-monohydroxy aporphines 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 as compared to the 10,11-dihydroxy analogues (see **3a**, **3b**, and **6** as compared to **1** and **2a**−**c**, 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. Because 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 analogue, **11e**. We expected to obtain a more stable analogue, hopefully without significantly sacrificing D_2^{high} binding. We were pleased to find that the binding profile of analogue **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 analogue 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 analogue **11d** was found to have binding affinity on the order of 1 nM and exhibiting an improved binding affinity than its 10,11-dihydroxy analogue **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} as compared to its 10,11-dihydroxy analogue **8c**. Unexpectedly, the last analogue, *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 analogue **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 radiolabeling and in vivo PET studies.

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 analogues. 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 active[42] as 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}

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
	**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
	**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
	**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
	**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 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 13. [c] Calculated using the chemical properties feature in CambridgeSoft ChemDraw Ultra, version 12.0. [d] Data from ref 13. [e] Data from ref 14. [f] For preparation, see ref 40. [g] See ref 25; HEK293T cell homogenate used with [^{3}H]methylspiperone. [h] The following compounds were also found to have D_3^{high} affinity: **2c** (K_i = 3.8 ± 2 nM), **3a** (K_i = 130 ± 100 nM), **3b** (K_i = 1.2 ± 1 nM), **8a** (K_i = 1.1 ± 2 nM), **8b** (K_i = 1.9 ± 1.5 nM), **8c** (K_i = 230 ± 140 nM), 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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binding site. Unlike the series of catechol-aporphines, no clear structure−activity relationships between the substituents and the 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.

■ ASSOCIATED CONTENT

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

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