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Synthesis and binding studies of 2-*O*- and 11-*O*-substituted *N*-alkylnoraporphines

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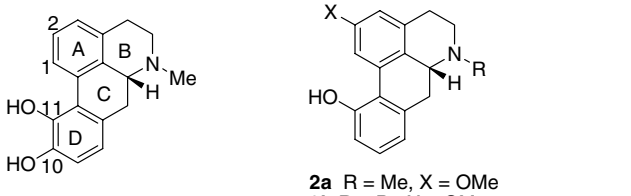
ABSTRACT

We synthesized several novel 2-*O*- or 11-*O*-substituted *N*-alkylnoraporphines and assessed their affinities at dopamine D_1 and D_2, and serotonin 5-HT_{1A} receptors in rat forebrain tissue. Tested compounds displayed moderate to high affinities to D_2 receptors but low affinities to D_1 and $5HT_{1A}$ receptors. The findings accord with previous evidence of a lipophilic cavity on the surface of the D_2 receptor to accommodate *N*-alkyl moieties of aporphines. The most D_2-potent (K_i = 97 nM) and selective novel agent (>100-fold vs. D_1 and 5-HT_{1A} sites) was *R*(−)-2-(2-hydroxyethoxy)-11-hydroxy-*N*-*n*-propylnoraporphine (compound **11**).

The centrally active, dopaminergic, catecholaporphine *R*(−)-apomorphine-HCl (APO) is approved for the treatment of Parkinson's disease and erectile dysfunction, but its poor oral bioavailability owing to susceptibility to oxidation and *O*-methylation of the 10,11-catechol moiety limits its clinical utility (Fig. 1).[1] Many aporphine analogues have been synthesized and evaluated for potency and selectivity of their interactions at central dopamine (DA) D_2 receptors in an effort to increase oral activity and extend duration of action.[2] Several 11-monohydroxy-aporphines have shown similar neuropharmacological properties to 10,11-catecholaporphines, including high potency and selectivity for DA D_2 receptors (Fig. 1).[3] Moreover, 11-hydroxyaporphines, and especially their esters, have more prolonged behavioral arousal-inducing activity with far superior oral bioavailability.[4] Structure-activity relationships of 2-substituted aporphines suggest their potential to increase selectivity and affinity at DA D_2 receptors. A number of 2-substituted aporphines have been synthesized in several laboratories including ours.[5] Such aporphines can be 2-substituted with aryl,[5a,b] *O*-alkyl,[5c] methylthio,[5d] or halogen.[5e–h] substituents. The neuropharmacological characteristics of these analogues point to the existence of a lipophilic cleft or region on the surface of DA D_2 receptor proteins, corresponding to 2-substituents of aporphines, the lipophilicity of which seems more important than their spatial parameters.

We recently reported the synthesis and evaluation of *N*-alkyl-2-methoxy-11-hydroxynoraporphines, with additional evidence that *N*-alkyl substituents have a major effect on D_2 affinity and D_2/D_1 selectivity of 2-methoxy-11-monohydroxy-substituted aporphines. D_1 receptor affinity is preferred with *N*-methyl, and D_2 is preferred with an *N*-*n*-propyl substituent (Fig. 1).[6] To further develop insights into the structure-activity relationships of 2- and 11-substituted aporphines, we now report on the design and synthesis of six novel aporphines, with their potencies at DA D_2 and D_1 receptors as well as serotonin 5-HT_{1A} receptors in mammalian forebrain tissue.



1 *R*-(-)-APO

2a R = Me, X = OMe
2b R = Pr, X = OMe
2c R-(-)-11-OH-NPa(R = Pr, X = H)

Figure 1. Structures of potent aporphine analogues.

We synthesized 2-methoxyaporphine and 2-methoxy-*N*-propylnoraporphine starting from thebaine (Scheme 1) as starting materials. Then 2-methoxy-11-hydroxyaporphines were prepared according to a published procedure[6] in 7 steps, followed by removal of the 11-hydroxy group to yield the compounds **4a** and **4b** (Scheme 1). We also synthesized 2-hydroxy-11-alkyloxyaporphines **8a–c** from thebaine or oripavine (Scheme 2). 3-*O*-Triflation of oripavine[7] followed by acid-catalyzed rearrangement and 2-demethylation led to the 2,11-dihydroxy-10-*O*-trifluoromethylsulfonyl aporphine **6**. Alkylation of the 2,11-dihydroxy-10-*O*-tri-

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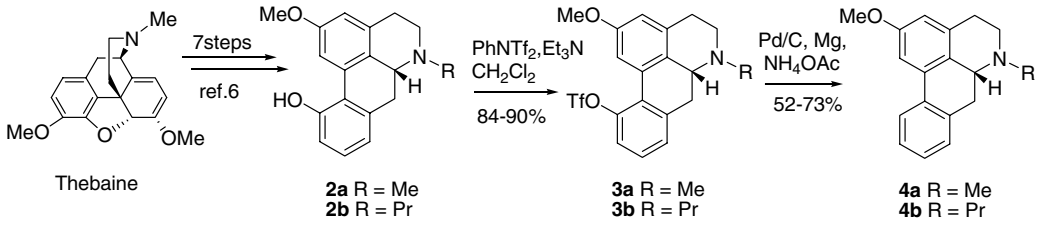
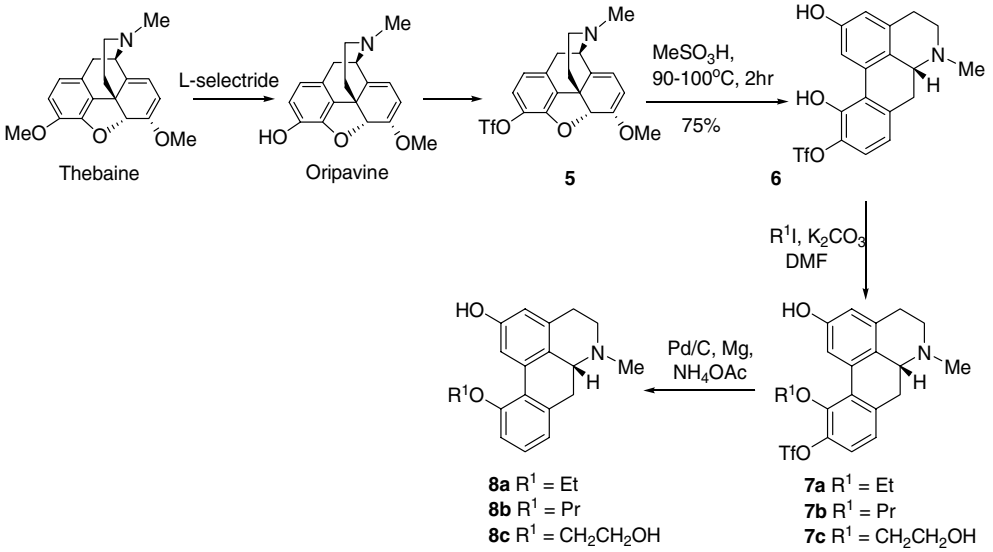


Scheme 1. Synthesis of compounds **4a** and **4b**.



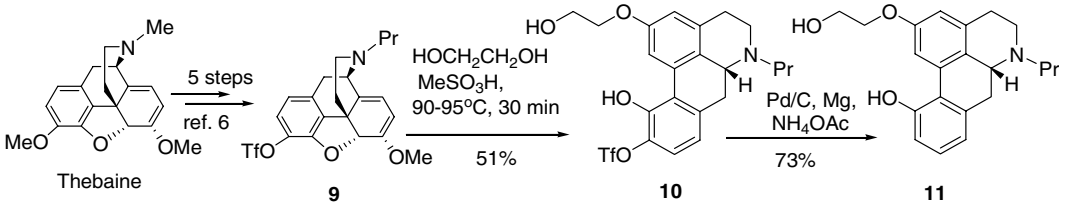
Scheme 2. Synthesis of compounds **8a**, **8b** and **8c**.

fluoromethylsulfonyl aporphine **6** with alkyl iodide in *N,N*-dimethylformamide gave only the 11-alkylated products **7a–c**. Further Pd/C-catalyzed reduction of **7a–c** with Mg metal in MeOH at room temperature provided compounds **8a–c**. 2-*O*-(2-hydroxyethyl)-11-hydroxy-*N*-*n*-propylnoraporphine **11** was synthesized from thebaine (Scheme 3). The triflate **9** was prepared following our published procedure.[6] Acid-catalyzed rearrangement of **9** in the presence of glycol[5c] followed by Pd/C-catalyzed reduction gave compound **11**. Spectral (^{1}H NMR and ^{13}C NMR) data and combustion analysis for the target compounds were consistent with their proposed structures.[8]

The receptor affinities of the six novel compounds **4a**, **4b**, **8a–c**, **11** at D_2 and D_1 DA receptors and the serotonin 5-HT_{1A} receptor were assessed using competitive radioreceptor binding assays with membrane-containing homogenates of rat corpus striatum tissue, following procedures reported in detail previously.[4] The results are summarized in Table 1.

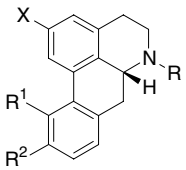
The findings indicate that removal of the 11-hydroxy group from the 2-methoxy-11-hydroxy-*N*-alkylaporphines decreased affinity at DA receptors, and afforded low affinity for the serotonin 5-HT_{1A} receptor. Blocking the 11-hydroxy group with an alkyl, but adding a hydroxy substituent on the 2-position also decreased the affinities at DA and 5-HT receptors. These findings support the proposal that 11-hydroxy substitution in aporphines (homologous to critical position-3 of DA) is required for dopaminergic activity as reflected in affinity at DA, and is also required for affinity at some 5-HT receptors. Compared with the potent compound *R*-(−)-2-methoxy-11-hydroxy-*N*-*n*-propylnoraporphine, introduction of a hydrophilic group such as a hydroxyethoxy at the 2-position reduced affinity at D_2 receptors by half, while increasing the D_2-over D_1 selectivity by >3-fold. These observations support previous findings indicating that a lipophilic cavity is present on the surface of the D_2 receptor at a location that accommodates 2-substituents of aporphines.[5]

The neuropharmacological profiles of the newly synthesized 2-substituted and 11-substituted aporphines, together with the previously reported characteristics of 2-substituted-11-monohydroxyaporphines support the following tentative conclusions: (1) The presence of a single hydroxy group in 11-position is both necessary and sufficient to confer affinity and activity at DA D_2 recep-



Scheme 3. Synthesis of compound **11**.

Table 1
Affinities (K_i) for rat brain D_1, D_2, and $5HT_{1A}$ receptors



Compound	R	R^1	R^2	X	K_i[a] (nM)			D_2/D_1
					D_1	D_2	$5HT_{1A}$	
1[b]	Me	OH	OH	H	1010 ± 105	1.9 ± 0.5	—	532
2a[b]	Me	OH	H	OMe	46.0 ± 2.8	235 ± 32	—	0.19
2b[b]	Pr	OH	H	OMe	1690 ± 130	44.0 ± 8.3	—	38.4
2c[c]	Pr	OH	H	H	699 ± 118	28.5 ± 12.8	—	24.5
4a	Me	H	H	OMe	1300 ± 250	731 ± 155	2660 ± 400	1.8
4b	Pr	H	H	OMe	>10,000	230 ± 35	1600 ± 280	>43
8a	Me	OEt	H	OH	3680 ± 760	641 ± 110	432 ± 99	5.7
8b	Me	OPr	H	OH	1810 ± 380	230 ± 40	—	7.8
8c	Me	OCH_2CH_2OH	H	OH	>10,000	3340 ± 690	289 ± 39	3.0
11	Pr	OH	H	OCH_2CH_2OH	>10,000	97 ± 18	—	>103

[a] Radioligands: D_1: [^{3}H]SCH23390; D_2: [^{3}H]nemonapride; $5HT_{1A}$: [^{3}H]8-OH-DPAT.
[b] Data from Ref. 6.
[c] Data from Ref. 4.

tors; (2) for the 2-position of aporphines, several factors contribute to dopaminergic activity, including lipophilicity, steric effects, and hydrogen-bonding of the 2-substituent. However, the lipophilicity of the substituent appears to be more important than the other factors; (3) D_2 potency and activity are optimal with an *N*-*n*-propyl substituent, whereas D_1 potency is preferred with *N*-methyl substituent but also greatly affected by the character of 2- and 11-substituents. Further conformation of these conclusions must await the preparation of additional aporphine analogues substituted in the 2, 11, and 6N-positions.

Acknowledgments

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8. *Compound* **4a**: *mp (HCl* salt) 248–250 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.5 Hz, 1H), 7.34–7.23 (m, 3H), 7.12 (d, J = 2.6 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 3.84 (s, 3H), 3.25–3.03 (m, 4H), 2.75–2.50 (m, 3H), 2.55 (s, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 158.4, 135.6, 134.9, 134.6, 134.1, 128.4, 127.6, 127.2, 126.3, 123.7, 112.3, 108.1, 61.6, 55.2, 53.4, 43.8, 34.4, 29.3; Anal. calcd for $C_{18}H_{19}NO{\cdot}HCl{\cdot}0.2H_2O$: C, 70.91; H, 6.69; N, 4.59. Found: C, 70.67; H, 6.64; N, 4.52. *Compound* **4b**: mp (HCl salt): 234–236 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 1H), 7.34–7.23 (m, 3H), 7.10 (d, J = 2.6 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 3.83 (s, 3H), 3.43 (dd, J = 13.8 and 3.9 Hz, 1H), 3.22–3.06 (m, 3H), 2.92 (m, 1H), 2.74–2.41 (m, 4H), 1.67–1.56 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H);^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 158.3, 135.8, 135.2, 134.9, 134.3, 128.4, 127.6, 127.2, 127.0, 123.7, 112.3, 108.1, 58.9, 56.1, 55.2, 49.3, 34.3, 29.4, 19.2, 12.1; Anal. calcd for $C_{20}H_{23}NO{\cdot}HCl{\cdot}1.4H_2O$: C, 67.75; H, 7.56; N, 3.95. Found: C, 67.88; H, 7.23; N, 3.59. *Compound* **8a**: *mp (HCl* salt) 248–250 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.63 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 7.8 and 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.81(d, J = 7.8 Hz, 1H), 6.32 (d, J = 2.4 Hz, 1H), 4.03 (m, 1H), 3.93 (m, 1H), 3.12–2.90 (m, 4H), 2.64–2.45 (m, 3H), 2.53 (s, 3H), 1.35 (t, J = 6.9 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 155.9, 154.5, 137.8, 133.1, 132.6, 127.8, 125.8, 122.9, 120.6, 114.5, 113.8, 111.6, 64.1, 61.8, 53.0, 43.6, 35.2, 28.7, 14.7. Anal. calcd for $C_{19}H_{21}NO_2{\cdot}HCl{\cdot}0.2H_2O$: C, 67.97; H, 6.68; N, 4.17. Found: C, 67.91; H, 6.76; N, 4.00. *Compound* **8b**: *mp (HCl* salt) 186–188 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.64 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.1 and 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.82(d, J = 8.1 Hz, 1H), 6.32 (d, J = 2.1 Hz, 1H), 3.93 (m, 1H), 3.81 (m, 1H), 3.13–2.90 (m, 4H), 2.64–2.46 (m, 3H), 2.53 (s, 3H), 1.81–1.74 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 156.14, 154.4, 137.8, 133.1, 132.7, 127.8, 125.8, 122.9, 120.6, 114.6, 113.7, 111.5, 70.2, 61.8, 53.0, 43.6, 35.2, 28.7,22.5, 10.6. Anal. calcd for $C_{20}H_{23}NO_2{\cdot}HCl{\cdot}0.6H_2O$: C, 67.35; H, 7.07; N, 3.92. Found: C, 67.13; H, 6.97; N, 3.86. *Compound* **8c**: *mp (HCl* salt) 189–191 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.75 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 7.8 and 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 4.10 (m, 1H), 3.84 (m, 3H), 3.09–2.87 (m, 4H), 2.60–2.40 (m, 3H), 2.47 (s, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 155.7, 154.3, 137.7, 133.2, 132.4, 127.9, 125.7, 122.6, 121.0, 114.3, 114.0, 111.1, 69.9, 61.7, 60.8, 52.9, 43.4, 35.0, 28.7. Anal. calcd for $C_{19}H_{21}NO_3{\cdot}HCl{\cdot}H_2O$: C, 62.38; H, 6.61; N, 3.83. Found: C, 62.36; H, 6.57; N, 3.65. *Compound* **11**: *mp* (HCl salt) 178–180 °C (Dec); ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.60 (d, J = 2.6 Hz, 1H), 7.08 (t, J = 8.2 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 4.06 (t, J = 4.3 Hz, 2H), 3.94 (t, J = 4.3 Hz, 2H), 3.36 (m, 1H), 3.20–3.06 (m, 3H), 2.89 (m, 1H), 2.73–2.46 (m, 4H), 1.63–1.55 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 156.8, 153.3, 138.1, 134.1, 132.9, 120.9 120.2, 115.7, 112.5, 112.3, 69.1, 61.2, 59.0, 55.9, 48.8, 34.8, 28.8, 18.8, 11.9. Anal. calcd for $C_{21}H_{25}NO_3{\cdot}HCl{\cdot}1.5H_2O$: C, 62.26; H, 7.15; N, 3.46. Found: C, 62.26; H, 6.76; N, 3.48.