Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 4128–4130
Bioorganic & Medicinal Chemistry Letters

R-(−)-*N*-alkyl-11-hydroxy-10-hydroxymethyl- and 10-methyl-aporphines as 5-HT$_{1A}$ receptor ligands

Yu-Gui Si,[a] Matthew P. Gardner,[b] Frank I. Tarazi,[b] Ross J. Baldessarini[b] and John L. Neumeyer[a,*]

[a]*Alcohol Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA*
[b]*Mailman Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA*

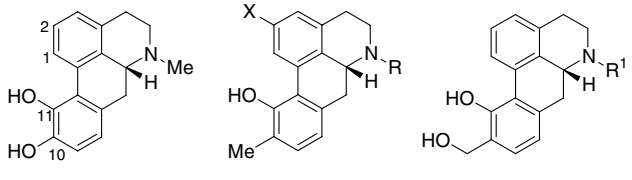
Received 12 April 2007; revised 16 May 2007; accepted 17 May 2007
Available online 23 May 2007

Abstract—Several *N*-substituted-11-hydroxy-10-hydroxymethyl- and 11-hydroxy-10-methylaporphines were synthesized and their binding affinities at dopamine D_1 and D_2 receptors and serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors in rat forebrain tissue were evaluated. Tested compounds displayed moderate to high affinity to 5-HT$_{1A}$ receptors but low affinity to D_1 and D_2 receptors. The most potent novel 5-HT$_{1A}$ agent was *R*-(−)-*N*-methyl-10-hydroxymethyl-11-hydroxyaporphine.

R-Apomorphine, first synthesized in 1869, is an agonist on central dopamine (DA) D_1 and D_2 receptors.[1] Small changes in the structure of apomorphine can lead to major changes in pharmacological profiles.[2] For example, elimination of the 10-hydroxy group of apomorphine produced a dopamine DA D_1 receptor antagonist.[3] Cannon reported that replacement of the C10-hydroxy moiety with a methyl group resulted in potent binding affinity at the serotonin (5-hydroxytryptamine) 5-HT$_{1A}$ receptor but low affinity at DA receptors.[4] A previously prepared series of 10-substituted-11-oxygenated *R*-(−)-aporphines also lacked DA receptor affinity but showed potent and selective affinity toward the 5-HT$_{1A}$ receptor.[5] Hedberg proposed that the selective serotonin receptor affinity of these aporphines appears to be due to a C10-methyl group, and a binding-site model suggested the presence of a 'methyl pocket' in the 5-HT$_{1A}$ receptor binding site.[5c] In contrast, the C10-methyl group of these aporphines was not accommodated by a binding-site model for DA receptors.[5]

To develop additional insight into the importance of C10 as well as *N*-substituents in aporphines for 5-HT and DA receptor affinity, we synthesized several *N*-alkyl-11-hydroxy-10-hydroxymethyl- and 11-hydroxy-10-methylaporphines and evaluated their affinity at DA (D_1 and D_2) and 5-HT (5-HT$_{1A}$ and 5-HT$_{2A}$) receptors (Fig. 1) .

R-(−)-10-methyl-11-hydroxyaporphine **2** was synthesized starting from morphine by a procedure reported by Hedberg.[5b] Triflation of the 3-hydroxy moiety of morphine followed by a palladium-catalyzed coupling reaction led to **8**. Acid-catalyzed rearrangement of **8** yielded the desired aporphine **2** (Scheme 1). Scheme 2 shows the synthesis of 2-methoxy-10-methyl-11-hydroxy-aporphines **3** and **4**. Thebaine **9** and *N*-*n*-propylnorthebaine **10** were *O*-demethylated to **11** and **12**, respectively, using the procedure reported by Coop,[6] and then *O*-triflated to produce compounds **13** and **14**. A palladium-catalyzed coupling reaction of **13** and **14** with Sn(Me)$_4$ gave **15** and **16**, followed by their acid-catalyzed rearrangement produced target compounds **3** and **4**.[5a] The synthesis of 11-hydroxy-10-hydroxymethyla-

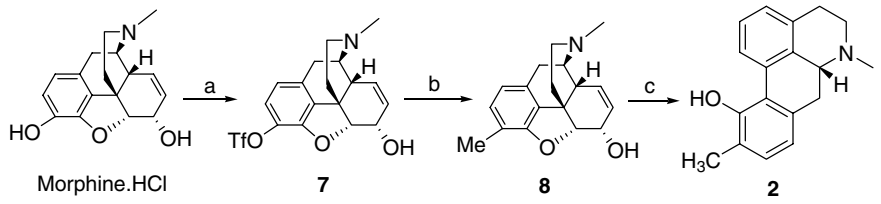


1 (*R*)-Apomorphine
2 X = H, R = Me
3 X = OMe, R = Me
4 X = OMe, R = *n*-Pr
5 R^1 = Me
6 R^1 = *n*-Pr

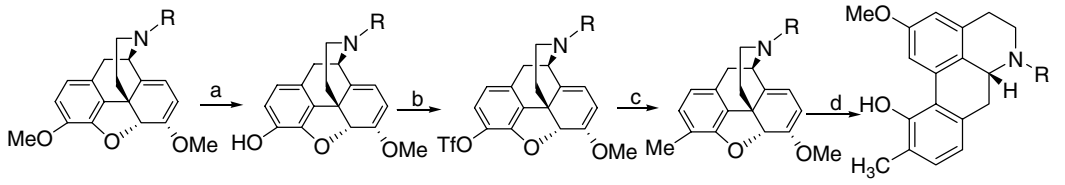
Figure 1. Structures of aporphine analogs.

Keywords: Aporphines, Binding affinities; 5-HT$_{1A}$ receptor ligands.
* Corresponding author. E-mail: jneumeyer@mclean.harvard.edu

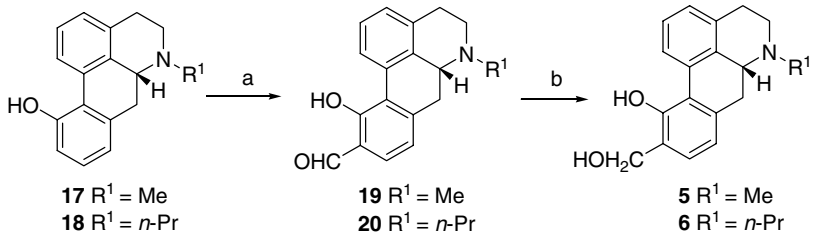
0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.05.057



Scheme 1. Reagents: (a) $PhNTf_2$, Et_3N, CH_2Cl_2, 90%; (b) Me_4Sn, $(Ph_3P)PdCl_2$, PPh_3, LiCl, DMF, 75%; (c) $MeSO_3H$, 65%.



Scheme 2. Reagents: (a) L-selectride, THF, 23–28%; (b) $PhNTf_2$, Et_3N, CH_2Cl_2, 90–93%; (c) Me_4Sn, $(Ph_3P)_2PdCl_2$, PPh_3, LiCl, DMF, 41–50%; (d) $MeSO_3H$, 45–50%.



Scheme 3. Reagents: (a) MeMgBr, HMPA, $(HCHO)_n$, benzene, 85–91%; (b) $NaBH_4$, MeOH, 90–92%.

porphines **5** and **6** is shown in Scheme 3. We synthesized the *R*-(−)-enantiomer of 11-hydroxyaporphines **17** and **18** using a previously reported procedure.[7] *Ortho*-formylation of the 11-hydroxy aporphines **17** and **18** employed a modification of Cannon's procedure[4b] and afforded the desired products **19** (85%) and **20** (91%) in high yields, followed by reduction of **19** and **20** with $NaBH_4$ to produce the target compounds **5** and **6**. Spectral (^1H NMR and ^{13}C NMR) data and combustion analysis for the target compounds were consistent with their proposed structures.[8]

The affinities of compounds **2**–**6** for DA (D_1 and D_2) and 5-HT (5-HT_{1A} and 5-HT_{2A}) receptors were assessed using competitive binding assays with membrane homogenates of whole rat brain tissue (5-HT_{1A} and 5-HT_{2A}) or rat striatal tissue (D_1 and D_2). The following tritiated radioligands were used: [^{3}H]SCH23390 (D_1), [^{3}H]nemonapride (D_2), [^{3}H]8-OH-DPAT (5-HT_{1A}), and [^{3}H]ketanserin (5-HT_{2A}).[9] The results are summarized in Table 1.

The *N*-substituted 11-hydroxy-10-hydroxylmethyl aporphine **5** and 11-hydroxy-2-methoxy-10-methyl congener **3** displayed selective and potent affinity for the serotonin 5-HT_{1A} receptor but low affinity at DA receptors D_1 and D_2 (Table 1). These findings support the proposal that *ortho*-dihydroxy substitution in the aporphine D ring enhances affinity to DA receptors, whereas analogous methyl or hydroxymethyl substitution enhances interactions with the 5-HT_{1A} receptor. Of note, the 10-hydroxymethyl-substituted compound **5** displayed 100-fold higher 5-HT_{1A} receptor affinity (K_i = 2.4 nM) than the 10-methyl substituted compound **2** (K_i = 216 nM), suggesting that a 10-methyl group is not required for affinity to the 5-HT_{1A} receptor. The 2-methoxy group in compound **3** seems to increase the affinity to 5-HT_{1A} receptors (K_i = 21.5 nM) 10-fold higher than compound **2** (K_i = 216 nM). That the 10-hydroxymethyl compounds **5** and **6** were inactive at DA receptors supports the impression that a 10-hydroxymethyl group is not required for high DA-receptor activity and that the interaction of 10-hydroxymethylaporphines with DA receptors does not involve hydrogen bonding. We also evaluated compounds **3** and **5** for affinity to 5-HT_{2A} receptors and found 108-fold and 57-fold lower potency than at 5-HT_{1A} receptors, respectively (for compound **5**: K_i = 137 vs 2.4 nM; for **3**: K_i = 271 vs 2.5 nM). It is worthy to note that the *N*-propyl substitution is preferred over *N*-methyl substitution in the interaction with DA receptors.[10] In contrast *N*-methyl substitution (K_i = 2.4 for compound **5** at 5-HT_{1A}; K_i = 21.5 for compound **3** at 5-HT_{1A}) is preferred in the interaction with 5-HT receptor than the *N*-*n*-propyl substitution (K_i = 375 for compound **6** at 5-HT_{1A}; K_i = 480 for compound **4** at 5-HT_{1A}).

Table 1. Affinities (K_i) for rat brain D_1, D_2, 5-HT_{1A}, and 5-HT_{2A} receptors

Compound	K_i (nM)			
	[^{3}H]SCH23390 (D_1)	[^{3}H]nemonapride (D_2)	[^{3}H]8-OH-DPAT (5-HT_{1A})	[^{3}H]Ketanserin (5-HT_{2A})
1	214 ± 18[a]	13 ± 2[a]	296 ± 15[b]	—
2	9650 ± 1250	11500 ± 1900	216 ± 40	—
3	1780 ± 320	3760 ± 760	21.5 ± 2.7	271 ± 19
4	2790 ± 640	1350 ± 250	480 ± 62	—
5	1390 ± 160	7000 ± 850	2.4 ± 0.4	137 ± 12
6	1980 ± 380	6060 ± 1110	375 ± 84	—

[a] From Ref. 7.
[b] From Ref. 5c.

In addition, both 10-methyl and 10-hydroxymethyl substituted 11-hydroxyaporphines displayed high affinity toward serotonin 5-HT_{1A} receptors but very low affinity at DA (D_1 and D_2) receptors. Finally, the *N*-methyl-substituted 11-hydroxy-10-methyl- and 10-hydroxymethyl-aporphines were more potent than the *N*-*n*-propyl analogs at 5-HT_{1A} receptors.

Acknowledgments

This work was supported by the Branfman Family Foundation (to J. L. N. and R. J. B.), HD-052752 (to FIT), by the Bruce J. Anderson Foundation, and the McLean Private Donors Neuropsychopharmacology Research Fund (R. J. B.). Morphine and thebaine were generously supplied by Mallinkrodt Inc.

References and notes

1. Baldessarini, R. J.; Kula, N. S.; Zong, R.; Neumeyer, J. L. *Eur. J. Pharmacol.* **1994**, *254*, 199.
2. Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171.
3. Schaus, J. M.; Titus, R. D.; Foreman, M. M.; Mason, N. R.; Truex, L. L. *J. Med. Chem.* **1990**, *33*, 600.
4. (a) Cannon, J. G.; Mohan, P.; Bojarski, J.; Long, J. P.; Bhatnagar, R. K.; Leonard, P. A.; Flynn, J. R.; Chatterjee, T. K. *J. Med. Chem.* **1988**, *31*, 313; (b) Cannon, J. G.; Moe, S. T.; Long, J. P. *Chirality* **1991**, *3*, 19.
5. (a) Hedberg, M. H.; Johansson, A. M.; Hacksell, U. *J. Chem. Soc., Chem. Commun.* **1992**, 845; (b) Hedberg, M. H.; Johansson, A. M.; Nordvall, G.; Yliniemela¨, A.; Li, H.-B.; Martin, A. R.; Hjorth, S.; Unelius, L.; Sundell, S.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 647; (c) Hedberg, M. H.; Jansen, J. M.; Nordvall, G.; Hjorth, S.; Unelius, L.; Johansson, A. M. *J. Med. Chem.* **1996**, *39*, 3491.
6. Coop, A.; Lewis, J. W.; Rice, K. C. *J. Org. Chem.* **1996**, *61*, 6774.
7. Csutoras, C.; Zhang, A.; Zhang, K.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem.* **2004**, *12*, 3553.
8. Compound **2**: mp (free base) 270–271 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 7.25 (dd, J = 7.5 and 7.5 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 3.23–3.14 (m, 1H), 3.08–3.00 (m, 3H), 2.75 (dd, J = 3.3 and 16.5 Hz, 1H), 2.55–2.45 (m, 2H), 2.52 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 135.6, 135.4, 133.8, 131.5, 129.6, 127.6, 126.5, 123.6, 123.5, 120.9, 119.9, 62.39, 52.9, 44.0, 34.9, 29.1, 16.1; Anal. Calcd for $C_{18}H_{19}NO$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.34; H, 6.65; N, 4.60. Compound **3**: mp (HCl salt) 183–185 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.50 (d, J = 2.7 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 3.82 (s, 3H), 3.24–3.00 (m, 4H), 2.72 (dd, J = 3.0 and 16.2 Hz, 1H), 2.56–2.47 (m, 2H), 2.52 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 158.1, 150.8, 135.9, 135.0, 132.6, 129.7, 123.4, 120.1, 111.9, 110.3, 109.8, 62.1, 55.2, 53.0, 44.0, 35.3, 29.5, 16.1; Anal. Calcd for $C_{19}H_{22}ClNO_2{\cdot}H_2O$ (salt): C, 65.23; H, 6.91; N, 4.00. Found: C, 64.88; H, 6.56; N, 3.85. Compound **4**: mp (HCl salt) 159–160 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.48 (d, J = 2.1 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H), 3.82 (s, 3H), 3.31–2.39 (m, 9H), 2.30 (s, 3H), 1.67–1.54 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 158.1, 150.8, 136.0, 135.4, 132.8, 129.7, 123.4, 120.7, 120.0, 111.9, 110.2, 59.5, 56.4, 55.2, 48.9, 35.2, 29.6, 19.5, 16.1, 12.1; Compound **5**: mp (HCl salt) >250 °C; (free base) 203–205 °C; ^{1}H NMR (base, 300 MHz, DMSO-d_6) δ 8.97 (br, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 5.74 (br, 1H), 4.66 (s, 2H), 3.15–2.90 (m, 4H), 2.7 (m, 1H), 2.44 (s, 3H), 2.42–2.25 (m, 2H); ^{13}C NMR (base, 75 MHz, DMSO-d_6) δ 152.2, 136.3, 134.7, 132.5, 131.5, 127.4, 126.8, 126.3, 125.7, 125.6, 121.5, 119.4, 61.9, 60.9, 52.4, 43.8, 34.5, 28.8; Anal. Calcd for $C_{18}H_{19}NO_2{\cdot}HCl{\cdot}H_2O$ (salt): C, 64.38; H, 6.50; N, 4.17. Found: C, 63.83; H, 6.01; N, 4.09. Compound **6**:(free base) 160–161 °C; ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 8.16 (d, J = 7.8 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 4.85 (ab, J = 12.9 and 36.0 Hz, 2H), 3.35–2.46 (m, 9H), 1.60 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 153.8, 138.4, 133.1, 131.8, 127.7, 126.6, 126.3, 126.1, 124.5, 122.3, 119.6, 119.2, 65.0, 59.7, 56.5, 49.1, 35.0, 29.2, 19.5, 12.3; Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.03; H, 7.52; N, 4.50.
9. Kula, N. S.; Baldessarini, R. J.; Kebabian, J. W.; Bakthavachalam, V.; Xu, L. *Eur. J. Pharmacol.* **1997**, *331*, 333.
10. Menon, M. K.; Clark, W. G.; Neumeyer, J. L. *Eur. J. Pharm.* **1978**, *52*, 1.