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(±)-Nantenine analogs as antagonists at human 5-HT$_{2A}$ receptors: C1 and flexible congeners

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ABSTRACT

C1 and flexible analogs of (±)-nantenine were synthesized and evaluated for antagonist activity at human 5-HT$_{2A}$ receptors in a calcium mobilization assay. This work has resulted in the identification of the most potent 5-HT$_{2A}$ antagonist known based on an aporphine. Our results also suggest that the C1 position may be a key site for increasing 5-HT$_{2A}$ antagonist activity in this compound series. In addition, the structural rigidity of the aporphine core appears to be required for nantenine to function as a 5-HT$_{2A}$ antagonist.

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The monoamine neurotransmitter, serotonin (5-hydroxytryptamine, 5-HT, **1**) is known to play a significant role in the central nervous system (CNS) modulation of appetite, mood, body temperature and sleep in humans.[1] There are 14 serotonin receptors presently known, of which all except one (5-HT$_3$) are G-protein coupled receptors.[2] Ligands for the 5-HT$_{2A}$ receptor are constantly being developed as chemical tools to study the functional role of this receptor in hallucinations, depression, anxiety and psychosis.[3–7] The role of 5-HT$_{2A}$ receptor blockade in the neuropharmacological processes of addiction is also of growing interest.[8–13]

Aporphines are a diverse group of tetracyclic alkaloids found in several plant species and have been found to show a range of interesting biological activities such as antiplasmoidal, anthelminthic and antitumour activities.[14–18] As a result of their biological activities, new and facile synthetic methodologies to prepare these compounds are always being explored.[19,20]

Others have reported the 5-HT$_{2A}$ antagonist properties of the aporphine alkaloid nantenine (**2**).[21,22] This pharmacodynamic property seems to be relevant to it's in vivo activity as an antagonist of the designer drug MDMA (methylenedioxymethamphetamine, 'Ecstasy').[23] Although aporphines have been evaluated as 5-HT$_{1A}$, α-adrenergic, and dopaminergic D1 and D2 ligands, very little SAR work has been performed on aporphines as 5-HT$_{2A}$ antagonists.[21,24–28] Part of our program is geared towards understanding the importance of selective receptor blockade as well as multi-potent antagonism involving 5-HT$_{2A}$ receptors in the antagonism of MDMA-induced effects. Aporphines may be a valuable structural template for such a study, given the apparent promiscuity of these compounds across various CNS targets including 5-HT subtypes. As such, we have embarked on a study to evaluate the 5-HT$_{2A}$ antagonist activity of aporphines using **2** as a lead molecule. In this Letter, we report results on the synthesis and evaluation of C1 and less rigid nantenine analogs (Fig. 1).

Preparation of C1 analogs commenced with readily available[29] 4-benzyloxy-3-methoxy phenethylamine (**3**) which was condensed with bromoacid (**4**) under standard peptide coupling conditions (Scheme 1). The amide (**5**) thus produced was cyclized under Bischler–Napieralski[30] conditions to afford imine **6**, which was

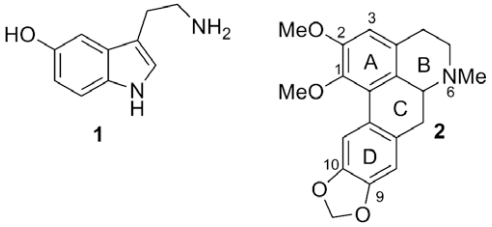

Figure 1. Structures of serotonin (**1**) and nantenine (**2**).

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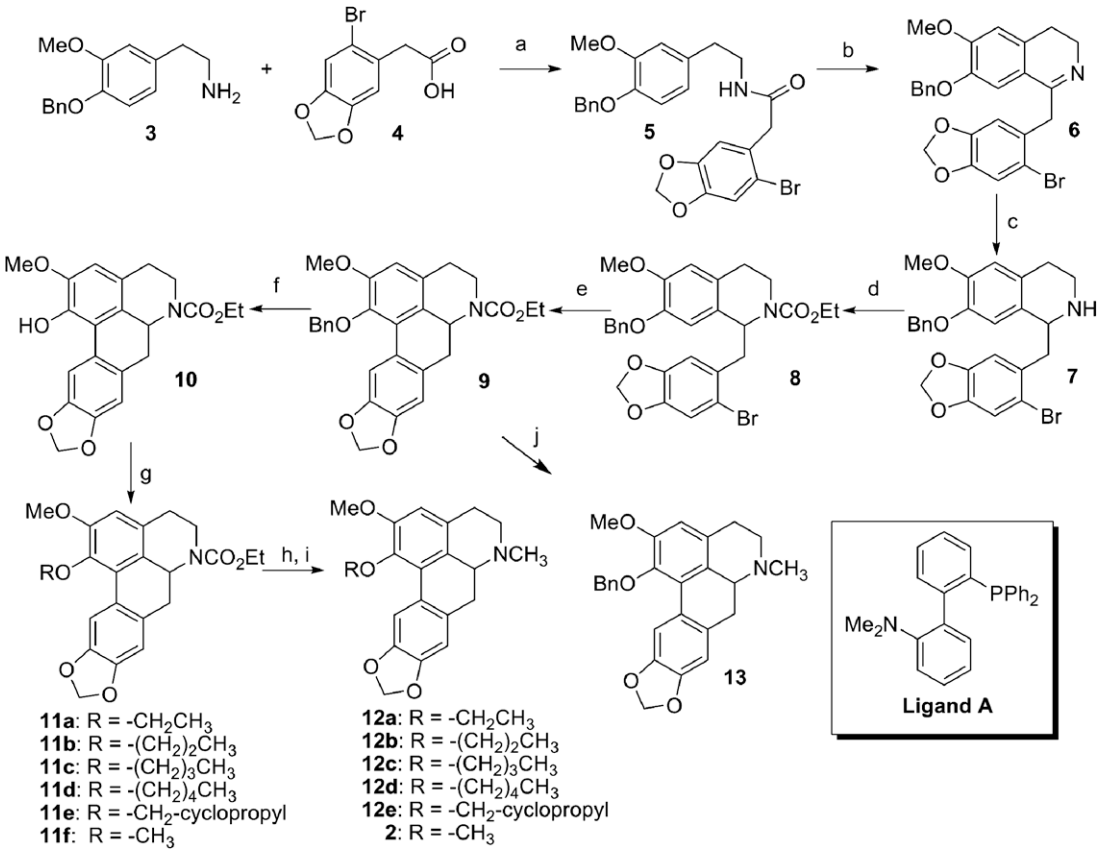


Scheme 1. Reagents and conditions: (a) CDI, THF, rt, 20 h, 90%; (b) PCl_5, DCM, 0 °C–rt, 96%; (c) $NaBH_4$, MeOH, 0 °C, 4 h, 99%; (d) ethyl chloroformate, K_2CO_3, DCM, rt, 12 h, 76%; (e) $Pd(OAc)_2$, ligand A, K_2CO_3, $(CH_3)_3CCOOH$, DMA, 130 °C, 17 h, 76%; (f) H_2/Pd–C, MeOH–THF, rt, 38 h, 75%; (g) alkyl bromide, K_2CO_3, acetone, reflux 12 h; (h) $LiAlH_4$, THF, 0 °C, 5 h, 91%; (i) aq HCHO, $NaBH(OAc)_3$, DCM, rt, 24 h, 96%; (j) $LiAlH_4$, Et_2O, 0 °C, 5 h, 91%.

immediately reduced to give **7** without purification (due to apparent instability of the imine).

Following protection of amine **7** as the ethyl carbamate, we were now in a position to attempt the direct biaryl cyclization[31] of **8** to give the aporphine core—a key step in this synthetic route. Following similar methodology to that previously described[31] with some optimization of reaction conditions, we obtained **9** in 76% yield. Hydrogenolysis of the C1 benzyl group gave key intermediate **10** which served as a precursor for the C1 alkyl intermediates **11a**–**11f**.

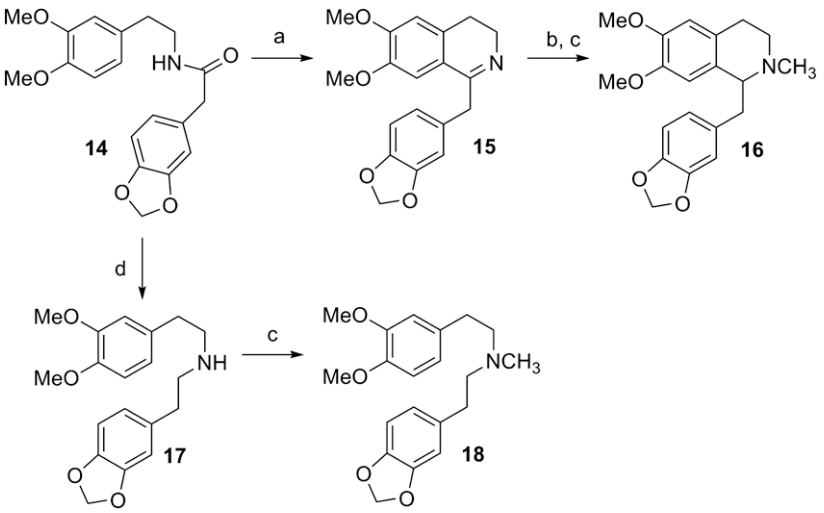
Our plan at this juncture was to reduce the carbamate functionalities of **11a**–**11f** with LAH to provide the C1 target analogs **12a**–**12e** and nantenine (**2**).

However, when LAH reduction was attempted, cleavage of the carbamate group occurred, giving the corresponding secondary amines as major products. This result was surprising and is in need of further investigation. Nevertheless, subsequent reductive amination of the derived secondary amines with formaldehyde afforded the target analogs **12a**–**12e** and **2**. The C1 benzyl derivative **13** was accessed via LAH reduction of **9**.

To begin to evaluate the role of molecular rigidity on the 5-HT_{2A} activity of nantenine, we prepared the benzyltetrahydroisoquinoline **16** and tertiary amine **18** (Scheme 2). Thus, following similar procedures as in Scheme 1, the readily available amide **14** was cyclized under Bischler–Napieralski conditions. Subsequently, the imine prepared was reduced and then subjected to reductive amination conditions providing the *seco*-ring C derivative **16**. Borane reduction of amide **14** followed by N-alkylation gave compound **18**. All compounds were characterized with routine spectroscopic techniques including ^1H NMR, ^{13}C NMR and HRMS.

Compounds **2**, **12a**–**12e**, **13**, **16** and **18** were evaluated for functional activity at human 5-HT_{2A} receptors using a calcium mobilization assay.[32] Results are presented in Table 1. The less rigid analogs, that is, compounds **16** and **18** had significantly reduced antagonist activities as compared to nantenine, suggesting that the structural rigidity of the aporphine nucleus is required for 5-HT_{2A} activity. Increasing the C1 alkyl chain length by one carbon (compound **12a**) had little effect on 5-HT_{2A} antagonist activity. However, incremental additions of 2, 3 and 4 carbons gave a progressive increase in 5-HT_{2A} antagonist activity (**12b**, **12c**, **12d**). Replacement of the C1 methyl group of nantenine with a methylenecyclopropyl moiety (compound **12e**) resulted in a 12-fold enhancement in activity as compared to nantenine. Interestingly, the C1 benzyl analog was found to be a negative allosteric modulator (IC_{50} = 4600 nM). In keeping with attributes of successful CNS agents,[33] the Clog *P* values of the C1 analogs represent reasonable starting points for simultaneous optimization of pharmacodynamic properties and blood-brain barrier penetrability in this compound series.

In conclusion, our biological results indicate that increasing the length of the C1 alkyl chain beyond two carbon atoms, results in an increase in 5-HT_{2A} antagonist activity in this series of aporphines. The C1 site may thus be a key position for further structural modifications to increase 5-HT_{2A} antagonist activity. Compound **12e**[34] was the most active compound identified and showed a 12-fold increase in activity as compared to nantenine. This compound is the most potent 5-HT_{2A} antagonist known with an aporphine skeleton. Our work has also identified a low activity negative allosteric modulator, **13**. We are continuing to explore the SAR of other nantenine-derived aporphines at human 5-HT_{2A} receptors and will report our findings in due course.



Scheme 2. Reagents and conditions: (a) PCl_5, DCM, 0 °C–rt; (b) $NaBH_4$, MeOH, rt; (c) aq HCHO, $NaBH(OAc)_3$, DCM, rt, 62% over three steps; (d) $BF_3{\cdot}OEt_2$, $BH_3{\cdot}THF$, THF, 88%.

Table 1
Apparent affinity of nantenine analogs at human 5-HT_{2A} receptors and Clog*P* values[32]

Compd	R	K_e[a] (nM)	CLog*P*[b]
2	CH_3	850 (±5.8)	3.60
12a	$-CH_2CH_3$	890 (±430)	4.13
12b	$-(CH_2)_2CH_3$	297 (±130)	4.66
12c	$-(CH_2)_3CH_3$	274 (±80)	5.19
12d	$-(CH_2)_4CH_3$	171 (±50)	5.72
12e	$-CH_2$–cyclopropyl	68 (±8)	4.58
13	$-CH_2Ph$	4600[c]	5.37
16	—	>10,000	3.82
18	—	5180[d]	3.69
Ketanserin	—	32[c,d]	—

[a] K_e (apparent affinity) values are means of at least two experiments carried out in duplicate; standard deviation is given in parentheses.
[b] Determined with ChemBioDraw Ultra 11.0.
[c] IC_{50} determined in the presence of 5-HT EC_{80}.
[d] Experiment run once.

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References and notes

1. Nichols, D. E.; Nichols, C. D. *Chem. Rev.* **2008**, *108*, 1614.
2. Costall, B.; Naylor, R. J. *Curr. Drug Targets* **2004**, *3*, 27.
3. Schmidt, C. J.; Sorensen, S. M.; Kehne, J. H.; Carr, A. A.; Palfreyman, M. G. *Life Sci.* **1995**, *56*, 2209.
4. Olivier, B.; Mos, J.; van Oorschot, R.; Hen, R. *Pharmacopsychiatry* **1995**, *28*, 80.
5. Pae, C. U.; Serretti, A.; Patkar, A. A.; Masand, P. S. *CNS Drugs* **2008**, *22*, 367.
6. Moller, H. J. *Expert Opin. Pharmacother.* **2005**, *6*, 803.
7. Graeff, F. G.; Guimaraes, F. S.; De Andrade, T. G.; Deakin, J. F. *Pharmacol., Biochem. Behav.* **1996**, *54*, 129.
8. Auclair, A.; Drouin, C.; Cotecchia, S.; Glowinski, J.; Tassin, J. P. *Eur. J. Neurosci.* **2004**, *20*, 3073.
9. Herin, D. V.; Liu, S.; Ullrich, T.; Rice, K. C.; Cunningham, K. A. *Psychopharmacology* **2005**, *178*, 505.
10. Szucs, R. P.; Frankel, P. S.; McMahon, L. R.; Cunningham, K. A. *Behav. Neurosci.* **2005**, *119*, 1173.
11. Zaniewska, M.; McCreary, A. C.; Przegalinski, E.; Filip, M. *Eur. J. Pharmacol.* **2007**, *571*, 156.
12. Lanteri, C.; Salomon, L.; Torrens, Y.; Glowinski, J.; Tassin, J. P. *Neuropsychopharmacology* **2008**, *33*, 1724.
13. Levin, E. D.; Slade, S.; Johnson, M.; Petro, A.; Horton, K.; Williams, P.; Rezvani, A. H.; Rose, J. E. *Eur. J. Pharmacol.* **2008**, *600*, 93.
14. Rasoanaivo, P.; Ratsimamanga-Urverg, S.; Rafatro, H.; Ramanitrahasimbola, D.; Palazzino, G.; Galeffi, C.; Nicoletti, M. *Planta Med.* **1998**, *64*, 58.
15. Ayers, S.; Zink, D. L.; Mohn, K.; Powell, J. S.; Brown, C. M.; Murphy, T.; Brand, R.; Pretorius, S.; Stevenson, D.; Thompson, D.; Singh, S. B. *Planta Med.* **2007**, *73*, 296.
16. Abdalla, S.; al-Khalil, S.; Afifi, F. *Gen. Pharmacol.* **1991**, *22*, 253.
17. Stevigny, C.; Bailly, C.; Quetin-Leclercq, J. *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 173.
18. Huang, R. L.; Chen, C. C.; Huang, Y. L.; Ou, J. C.; Hu, C. P.; Chen, C. F.; Chang, C. *Planta Med.* **1998**, *64*, 212.
19. Hamamoto, H.; Shiozaki, Y.; Nambu, H.; Hata, K.; Tohma, H.; Kita, Y. *Chem. Eur. J.* **2004**, *10*, 4977.
20. Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307.
21. Indra, B.; Matsunaga, K.; Hoshino, O.; Suzuki, M.; Ogasawara, H.; Ishiguro, M.; Ohizumi, Y. *Can. J. Physiol. Pharmacol.* **2002**, *80*, 198.
22. Tsuchida, H.; Ohizumi, Y. *Eur. J. Pharmacol.* **2003**, *477*, 53.
23. Fantegrossi, W. E.; Kiessel, C. L.; Leach, P. T.; Van Martin, C.; Karabenick, R. L.; Chen, X.; Ohizumi, Y.; Ullrich, T.; Rice, K. C.; Woods, J. H. *Psychopharmacology* **2004**, *173*, 270.
24. Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171.
25. Si, Y. G.; Gardner, M. P.; Tarazi, F. I.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4128.
26. Cannon, J. G.; Flaherty, P. T.; Ozkutlu, U.; Long, J. P. *J. Med. Chem.* **1995**, *38*, 1841.
27. Ivorra, M. D.; Valiente, M.; Martinez, S.; Madrero, Y.; Noguera, M. A.; Cassels, B. K.; Sobarzo, E. M.; D'Ocon, P. *Planta Med.* **2005**, *71*, 897.
28. Westkaemper, R. B.; Yousif, M.; Teitler, M.; Glennon, R. A. *Med. Chem. Res.* **1992**, *2*, 482.
29. Batra, S.; Sabnis, Y. A.; Rosenthal, P. J.; Avery, M. A. *Bioorg. Med. Chem.* **2003**, *11*, 2293.
30. Wang, Y. C.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675.
31. Lafrance, M.; Blaquiere, N.; Fagnou, K. *Chem. Commun.* **2004**, 2874.
32. *Calcium mobilization human 5-HT_{2A} receptor functional assays.* Stably expressed human 5-HT_{2A} receptor in CHO-K1 cells (ATCC), were used for the calcium mobilization functional assay. The calcium 4 dye assays (Molecular Devices, Sunnyvale, CA) were run according to manufacturer's specifications. Briefly, wells of black clear-bottom 96-well tissue culture-treated plates were seeded with 20,000 cells the afternoon before assay. On the day of assay, the cells were incubated with the calcium indicator dye for 1 h @ 37 °C. The test compounds were preincubated with the cells during the last 15 min of the dye incubation. The plate was then placed into a FlexStation pre-warmed to 37 °C. Basal or unstimulated fluorescence intensity was recorded for 13 s followed by the addition of 5-HT (antagonist and K_e assays). Fluorescence intensity was recorded for an additional 47 s. The effect of test compound was determined by subtracting the minimum from the maximum fluorescence recorded for each well during the 47 s recording period. Thus, each well served as its own control. All samples were run in duplicate.
33. Pajouhesh, H.; Lenz, G. R. *NeuroRx* **2005**, *2*, 541.
34. *Compound 12e*. ^1H NMR ($CDCl_3$, 500 MHz): δ 0.12 (m, 2H), 0.48 (m, 2H), 1.15 (m, 1H), 2.50–2.54 (obscured, 2H), 2.53 (s, 3H), 2.67 (dd, J = 3.2, 16.3 Hz, 1H), 2.97 (m, 2H), 3.03 (dd, J = 5.7, 11.4 Hz, 1H), 3.13 (m, 1H), 3.40 (dd, J = 7.6, 10.0 Hz, 1H), 3.71 (dd, J = 7.0, 10.0 Hz, 1H), 3.86 (s, 3H), 5.96 (d, J = 1.1 Hz, 1H), 5.98 (d, J = 1.1 Hz, 1H), 6.57 (s, 1H), 6.74 (s, 1H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 3.1, 3.4, 11.0, 29.1, 35.1, 44.0, 53.2, 55.8, 62.5, 77.8, 100.8, 108.2, 109.5, 110.4, 125.9, 127.1, 127.5, 128.5, 130.6, 143.3, 146.2, 146.3, 152.1; HRESIMS Calcd for $C_{23}H_{25}NO_4$: 379.1784. Found: 379.1783.