Medicinal chemistry

Kapadia and Harding, Med chem (Los Angeles) 2016, 6:4
DOI: 10.4172/2161-0444.1000353

Review Article Open Access

Aporphine Alkaloids as Ligands for Serotonin Receptors

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Abstract

The aporphine alkaloids are known to have affinities as the dopaminergic, adrenergic and serotonergic receptor system. Hence the aporphine template can be considered as a privileged scaffold for the design of selective mono-potent as well as multi-potent Central Nervous System (CNS) ligands. This review attempts to summarize the recent Structure Activity Relationship (SAR) studies of aporphine alkaloids specifically at the serotonin receptor system. Based on the obtained SAR information it can be concluded that aporphines have great potential to be developed as potent serotonergic ligands.

Keywords: Aporphine; Central nervous system; Ligands; Alkaloids

Introduction

Aporphine alkaloids are natural and synthetic alkaloids that possess a tetracyclic framework. Chemically they incorporate a tetrahydroisoquinoline substructure and belong to the isoquinoline class of alkaloids. More than 500 members of this class of alkaloids have been isolated. Aporphine alkaloids are widely distributed in *Annonaceae*, *Lauraceae*, *Monimiaceae*, *Menispermaceae*, *Hernandiaceae* and other plant families [1] (Figure 1).

Both naturally occurring and synthetic aporphine alkaloids possess diverse range of pharmacological actions. Figure 1 shows the basic aporphine skeleton [2].

Pharmacological Effects of Aporphine Alkaloids

Aporphine alkaloids exhibit a plethora of effects within the Central Nervous System (CNS). There are a number of aporphine alkaloids reported as ligands at dopamine and serotonin receptors [1,3]. Ligands at the D_1 and D_2 dopamine receptor subtypes have a potential role in the treatment of Parkinson's disease, schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD), depression, and drug abuse [4-6]. In fact, (*R*) - Apomorphine (**2**) which is considered to be a prototype of aporphine alkaloids by many, has been approved for the treatment of advanced stages of Parkinson's disorder [7]. Ligands at the 5-HT_{1A} serotonin receptor subtype have been useful in the treatment of anxiety, schizophrenia and depression [8-11] (Figure 2).

Aporphines are also ligands at the 5-HT_{2A} and 5-HT_7 receptors. Selective 5-HT_{2A} ligands have promising applications in the treatment of drug abuse and insomnia. Mixed dopamine/5-HT_{2A} ligands have potential for the alleviation of symptoms of depression and schizophrenia [12,13]. Ligands at the 5-HT_7 receptor have shown promising results for the treatment of sleep disorders, migraine and depression [14-16]. Moreover aporphines possessing affinity at the dopamine and serotonin receptors have potential use as PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) radiotracers for brain imaging studies [17]. Aporphines are also reported as inhibitors of the enzyme Acetylcholinesterase and as antagonists of the α_1-adrenergic receptor and thus have potential therapeutic role in the treatment of Alzheimer's disease and hypertension respectively [18-21].

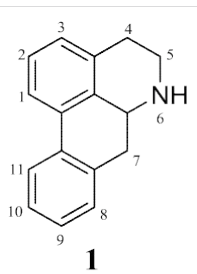

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Figure 1: Basic aporphine skeleton.

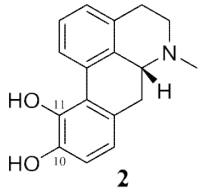

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Figure 2: (*R*) – Apomorphine.

Thus the aporphine scaffold can be considered a privileged scaffold for the design of CNS ligands. A majority of the work in the early 1990s has focused on the design of aporphine alkaloids as ligands for the dopamine receptor system. In terms of the serotonin receptors, aporphines have mostly been studied as ligands at the 5-HT_{1A} receptor. Some of this previous work has been nicely summarized in previously published reviews [1,3].

Aporphine as 5-HT_{1A} Ligands

The first aporphine alkaloid reported as a selective serotonin ligand was reported by Canon and co- workers in 1988 [22]. The (*R*) - (-) - 10-Methyl-11-hydroxyaporphine (*R* - **3**) (Figure 3) was originally designed as a dopamine receptor ligand. Surprisingly *R* - *3* displayed serotonergic agonistic activity with a high degree of selectivity for the 5-HT_{1A} receptor. Further studies revealed that the *S* isomer of **3** (*S* - **3**) was an antagonist at the 5-HT_{1A} receptor [23]. This trend of enantiomers having opposing pharmacological effects was found to be consistent with other aporphine enantiomers displaying opposing effects at the dopaminergic receptors (Figure 3).

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Received March 26, 2016; **Accepted** April 12, 2016; **Published** April 18, 2016

Citation: Kapadia N, Harding W (2016) Aporphine Alkaloids as Ligands for Serotonin Receptors. Med chem (Los Angeles) 6: 241-249 doi:10.4172/2161-0444.1000353

In order to probe the role of the C-10 methyl group compound **4** that lacked a C-10 methyl group was evaluated for dopaminergic and serotonergic activity. Both the enantiomers of compound **4** were found to possess dopaminergic activity but lacked any appreciable serotonin 5-HT_{1A} activity [24]. This clearly indicated a significant role of the C-10 methyl group towards the enhanced 5-HT_{1A} affinity of **3** (Figure 4).

It was further shown that both the C-10 methyl and C-11 hydroxyl group in compound **3** are required for affinity at the 5-HT_{1A} receptor. This was evident from the observed lower affinity of the mono methylated compound **5** [25]. Furthermore, the high affinity at the 5-HT_{1A} receptor of compound **3** is unique and specific to an 11-hydroxy, 10-methyl substitution pattern. Having this substitution at other positions (such as in compounds **6** and **7**) resulted in complete loss of affinity at the 5-HT_{1A} receptor [26]. High affinity for the 5-HT_{1A} receptor was also observed in the case of compound **8**, which possesses a similar *ortho* hydroxyl/hydroxyl methyl substitution [27] (Figure 5).

Based on molecular docking studies, the C-11 hydroxyl group makes a hydrogen bond interaction with Ser198 and Ser193 residues of the 5-HT_{1A} and D_2 receptors respectively. The main difference however is the interaction of the C-10 methyl group wherein it interacts with a lipophilic pocket in the 5-HT_{1A} receptor, which is not available in the case of the D_2 receptor. The absence of a similar lipophilic pocket around the C-10 methyl group in the D_2 receptor explained the high selectivity of 3 for the 5-HT_{1A} receptor over the D_2 receptor [28].

The existence of this lipophilic pocket was further tested by Hedberg and co-workers by the evaluation of a series of C-10 substituted aporphine compounds [29]. Substitution of bulky groups at the C-10 position (compound **9**, **10**, **11** and **12**) resulted in dramatic loss of affinity for the 5-HT_{1A} receptor whereas small alkyl group substituents (compound **13**) were well tolerated, thus confirming the existence of the lipophilic "methyl" pocket, which is able to accommodate only small groups.

In contrast to the previously observed strict requirement of a C-11 hydroxyl/C-10 methyl substitution, a series of mono C-11 substituted aporphine compounds (**14**, **15** and **16**) were found to have good affinity as well as selectivity for the 5-HT_{1A} receptors [29]. Based on molecular modeling studies substituents at the C-11 position interacted in a manner that was different from the previously seen hydrogen bond interaction of the C-11 hydroxyl group with the 5-HT_{1A} receptor. In the case of C-11 substituents, significant interactions were seen with a pocket lined by Ser168, Met172, Thr196. Ser199, Thr200, Phe362, Ala365 and Leu366. This indicated that the proposed methyl pocket was much larger, and suitable C-11 substituents could interact with it. This hypothesis of a larger lipophilic pocket was further confirmed by Zhang et al. by the synthesis and evaluation of compounds **17**, **18** and **19** that lacked a C-11 hydroxyl group yet displayed high affinity at the 5-HT_{1A} receptor [30].

Other reported SAR studies include the evaluation of C10 substituted long chain carbamate (**20** and **21**) or amide (**22** and **23**) aporphines [31]. These compounds displayed only moderate affinity at the 5-HT_{1A} receptor as shown in Table 1. Similarly limited studies have been done at other positions of the aporphine scaffold with regards to the 5-HT_{1A} affinity. Zhang and co-workers reported the evaluation of C-2 substituted aporphine compounds (**24**, **25** and **26**) which did not show any appreciable affinity at the 5-HT_{1A} receptor, although the number of compounds studies are too less to make a general conclusion [32] (Figure 6).

Although an *N*-methyl group is not absolutely required for 5-HT_{1A} affinity as indicated by compounds **27** and **28**, an increase in affinity and selectivity for the 5-HT_{1A} receptor was observed when the size of the substituent was decreased to a methyl or a hydrogen group (Table 1).

Aporphines as 5-HT_{2A} Ligands

Majority of the work of aporphine alkaloids as ligands at the 5-HT_{2A} receptor has mainly focused on the natural alkaloid nantenine. Nantenine (**29**) was isolated from the fruit of *Nandina domestica* Thunberg [33]. Indra and co-workers in 2002 showed that nantenine inhibited 5-hydroxy-L-tryptophan (*l*-5-HTP) induced head-twitch response by blocking 5-HT_{2A} receptors in mice [34]. Later the same group reported SAR studies showing nantenine as an antagonist at the 5-HT_{2A} and α_1 receptors [35,36]. Studies done by Fantegrossi revealed the ability of nantenine to block and reverse MDMA induced physiological effects such as hyperthermia, locomotor stimulation and head-twitch responses in mice. These anti-MDMA effects of nantenine were attributed to its antagonism at the 5-HT_{2A} and α_1 receptors [37] (Figure 7).

Research in our group has focused on the synthesis and evaluation of nantenine analogues as 5- HT_{2A} antagonists. The first accomplished step in this direction was to synthesize racemic nantenine and screen it across available CNS receptors via the Psychoactive Drug Screening Program (PDSP) of the NIH. Results from this screening showed that nantenine is highly selective for the α_{1A} receptor (K_i=2 nM) compared to other α_{1A} subtypes. At the 5-HT_{2A} receptor, nantenine was found to have moderate affinity (K_i=850 nM) [38]. In order to improve the potency and selectivity of nantenine analogues for the 5-HT_{2A} receptor,

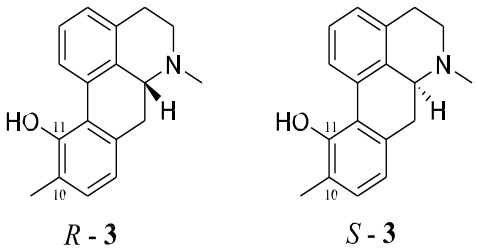


Figure 3: Structure of *R* and *S* enantiomers of compound **3**.

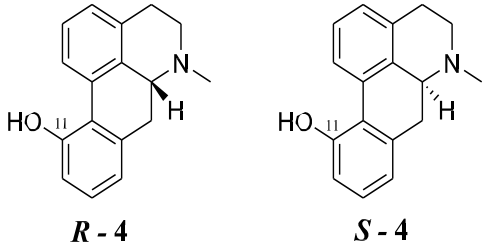


Figure 4: Structure of *R* and *S* enantiomers of compound **4**.

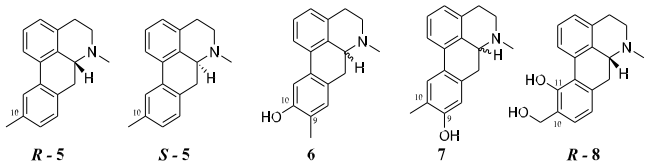
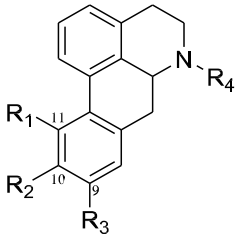


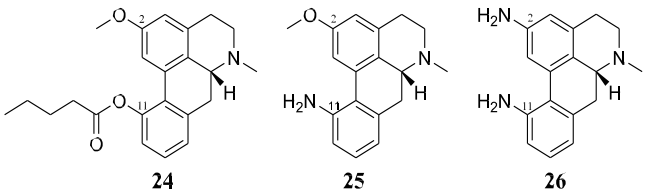
Figure 5: Structure of *R* and *S* enantiomers of compounds **5**, positional isomers **6** and **7** and compound **8**.



Compound	R_1	R_2	R_3	R_4	K_i (nM)			Ref.
					5-HT_{1A}	D_1	D_2	
***R*-3**	OH	Me	H	Me	0.45	382	1070	[22,29]
***S*-3**	OH	Me	H	Me	39	-	-	[23]
***R*-4**	OH	H	H	Me	296	236	41.90	[24,29]
***S*-4**	OH	H	H	Me	-	-	-	[24]
***R*-5**	H	Me	H	Me	1.20[a]	-	-	[25]
***S*-5**	H	Me	H	Me	6.80[a]	-	-	[25]
6	H	OH	Me	Me	-	-	-	[26]
7	H	Me	OH	Me	-	-	-	[26]
8	OH	CH2OH	H	Me	2.4	1390	7000	[27]
9	OH	Ph	H	Me	1090	9400	>1000	[29]
10	OMe	2-furyl	H	Me	995	14000	582	[29]
11	OH	COMe	H	Me	1720	4620	2760	[29]
12	OMe	$CH=CH_2$	H	Me	108	1440	1750	[29]
13	OH	Et	H	H	9.20	782	2050	[29]
14	Ph	H	H	Me	1.80	3630	233	[29]
15	2-OMe-Ph	H	H	Me	26.90	>3000	1330	[29]
16	2-OH-Ph	H	H	Me	28.50	3750	1570	[29]
17	OCH_2CCH	H	H	Pr	55	-	-	[30]
18	O-Allyl	H	H	Me	12	-	-	[30]
19	OCH2CCH	H	H	Me	14	-	-	[30]
20	NHCOOEt	H	H	Pr	94	54.6[b]	44.3[b]	[31]
21	NHCOO^{t}Bu	H	H	Pr	96	70.2[b]	871	[31]
22	NH_2	H	H	Pr	276	57.1[b]	352	[31]
23	NHCOPr	H	H	Pr	380	16.1	13.5	[31]
27	OH	Me	H	H	3.20	23800	>10000	[29]
28	OH	Me	H	Pr	12.30	>2000	249	[29]

[a] $_b$ID50 values (μM)
% inhibition values

Table 1: Affinity values of aporphine derivatives at the 5-HT_{1A} receptor.



24 **25** **26**

Figure 6: Structure of compounds **24**, **25** and **26**.

a systematic SAR study was initiated. A brief discussion of our previous findings is described.

At the C1 position several linear and branched alkyl substitutions were evaluated [39,40]. Table 2 shows the binding affinity (K_e) values for a series of C1 substituted nantenine analogues. Progressive increase in the alkyl chain length at this position, resulted in increased affinity at the 5-HT_{2A} receptor. More importantly the affinity of these compounds at the α_{1A} receptor was completely abolished, thus suggesting that the C1 position could play a vital role in fine tuning

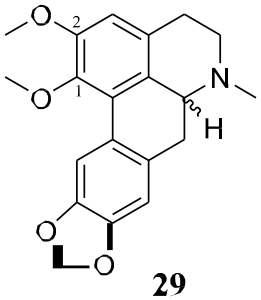


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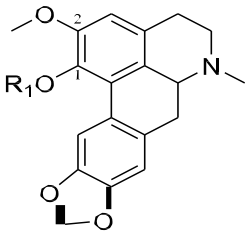
Figure 7: Structure of (±)-nantenine.

the selectivity of nantenine. As seen in Table 2, the C1 ethyl analogue (**30**, K_e=890 nM) was found equipotent to nantenine. Substitution with propyl (**31**, K_e=297 nM) and butyl (**32**, K_e=274 nM) groups resulted in three times increase in potency. The *n*-hexyloxy analogue (**34**, K_e=71 nM) which was the most potent compound identified in this series, was 11 times more potent than nantenine at the 5-HT_{2A} receptor.



Compound	R_1	K_e (nM)[a]		Ref.
		5-HT_{2A}	α_{1A}	
(±)- 29	Me	850	36	[39]
30	Et	890	-	[39]
31	*n*-Pr	297	-	[39]
32	*n*-Bu	274	-	[39]
33	*n*-Pen	171	-	[39]
34	*n*-hex	71	>10000	[40]
35	CyclopropylMe	68	>10000	[40]
36	CyclobutylMe	ND	>10000	[40]
37	CyclopentylMe	ND	>10000	[40]
38	CyclohexylMe	1722	>10000	[40]
39	Isobut	367	>10000	[40]
40	Isopen	ND	>10000	[40]
41	2-EthylBu	806	>10000	[40]
42	allyl	70	>10000	[40]
43	CH_2CN	>10000	711	[41]
44	$CH_2CH=CHCH_3$ (*E*)	723	1980	[41]
45	$CH_2CH=C(CH_3)_2$ (*E*)	2074	>10000	[41]
46	$CH_2C_6H_4$-*p*-Br	9.2	>10000	[41]

[a]ND=Not determined

Table 2: Binding affinity data of C-1 nantenine analogues.

Compound 35 which can be considered as branched analogue of the *n*-butyl analogue also displayed significant improved affinity (**35**, K_e=68 nM). However an increase in the size of the ring (from 3 membered up to 6 membered) resulted in either compounds having weak agonist activity (**36** and **37**) or compounds having complete loss of affinity (**38**). Alternatively compound **39** which is an open chain analogue of the cyclopropyl analogue methyl analogue resulted in a 5 fold drop in affinity. Similarly homologation of **39** to compounds **40** and **41** produced compounds having reduced affinity for the 5-HT_{2A} affinity.

Incorporation of an allyl group at the C1 position resulted in comparable activity to the cyclopropylmethyl analogue. This can be attributed to the electronic similarity between the allyl and the cyclopropylmethyl group. (**42**, K_e=70 nM). In a more recent study, we explored several other allylic groups at the C1 position [41]. Overall from this study it was concluded that branched allylic substituents (compounds **44** and **45**) as well as other allylic isosteric replacements (compound **43**) were not tolerated for affinity at the 5-HT_{2A} receptor. Compound **46** that has a *p* - bromobenzyl unit attached at the C1 position was the most potent 5-HT_{2A} ligand identified in this series. In fact compound **46** is the most potent 5-HT_{2A} aporphinoid antagonist known till date (Table 2).

Molecular modeling studies were used to identify key interactions of the 5-HT_{2A} receptor with the nantenine analogues [42]. Accordingly the protonated nitrogen atom and the oxygen atom in the methylenedioxy ring are involved in a hydrogen bond interaction with the Asp155 and Ser242 residues respectively. In addition, the alkyl side chain of the C1 alkyl analogues is buried in a hydrophobic pocket comprising of Phe234, Gly238, Leu228 and Ile341 side chains. This interaction seems to be critical for the observed enhanced affinity of the C1 alkyl analogues. Alternatively the moderate affinity of nantenine can be explained by the lack of this hydrophobic interaction.

At the C2 position the effect of small alkyl group substitution was studied [40]. Replacement with ethoxy (**47**, K_e=378 nM) and propyloxy groups (**48**, K_e=485 nM) resulted in a moderate (2 and 1.7 times respectively) increase in potency. However replacements with larger alkoxy groups were detrimental for 5-HT_{2A} receptor affinity (**49**, K_e=943 nM; and **33**, K_e>10,000 nM). These substitutions also led to a decrease in affinity at the α_{1A} receptor and a similar trend (decreased affinity with increase size of the alkyl substitution) was observed. Compound **52** (K_e=154 nM) with a benzyloxy group at the C2 position was the most potent compound in this series. Overall a C2 group larger than propyl is not well tolerated for affinity at the 5-HT_{2A} receptor. A substitution at the C2 position is not absolutely required for affinity at the 5-HT_{2A} receptor as exemplified by compound **53** [43].

Replacement of the *N*-methyl group with other groups (compound **54** - **58**) resulted in complete loss of affinity for the 5-HT_{2A} receptor, but affinity at the α_{1A} receptor was retained. This suggested that the *N*-Methyl group is important for affinity at the 5-HT_{2A} receptor. This trend is in contrast to the effect of similar *N*-substituted aporphine alkaloids at the 5-HT_{1A} and dopamine D_1 and D_2 receptors. Molecular docking studies indicate that the protonated nitrogen atom is involved in a hydrogen bond interaction with an Asp155 residue of the 5-HT_{2A} receptor. The requirement of this salt bridge interaction was proven by evaluating the isochroman compounds **59** and **60** which were found to be completely inactive at the 5-HT_{2A} receptor [43].

It is also worth mentioning that both the *R* and *S* enantiomers of nantenine displayed antagonist effects at the 5-HT_{2A} receptor. This trend is in contrast to the effect of aporphine enantiomers at other receptor system including 5-HT_{1A} and dopamine D_1 and D_2, where enantiomers display opposing pharmacological effects as previously described. Furthermore in an *in vivo* rat assay, both the *R* and *S* enantiomers of nantenine completely blocked the effects of MDMA at a dose of 0.3 mg/kg. This observation was found in concurrence by previous observations made by Indra et al. (Table 3).

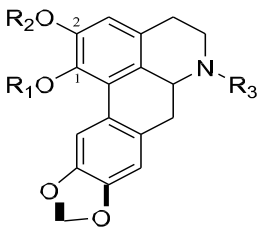
Substitutions at the C3 position included the evaluation of a series of C3 halogenated compounds **62**-**66** [44]. In general halogenation is very well tolerated at the C3 position and all the halogenated nantenine analogues displayed enhanced 5-HT_{2A} affinity. Compounds **62**-**64** showed doubling of 5-HT_{2A} antagonist potency (compared to their non-halogenated counterpart (**61**) irrespective of the halogen group present. Methylation of the C2 OH group resulted in further enhancement in the 5- HT_{2A} potency as seen by the C3 chloro (**65**) and C3 bromo (**66**) compounds respectively. This trend in enhancement of affinity following C3 halogenation has been reported in other aporphine compounds at the dopamine D_1 and D_2 receptors as well as for the α_1 adrenergic receptor subtypes (i.e., α_{1A}, α_{1B}, and α_{1D} receptors) (**32**).

Modeling studies show the C3 halogenated compounds to have a completely different binding pose than the non-halogenated aporphines. In the case of the halogenated aporphines, the C3 halogen atom is oriented towards F339 and F340 residues, and it is this interaction that might be responsible for the higher affinity observed in this series of compounds. This lipophilic space can be further explored by suitable C3 hydrophobic substituents (Table 4).

Aporphines as 5-HT_{2B} Ligands

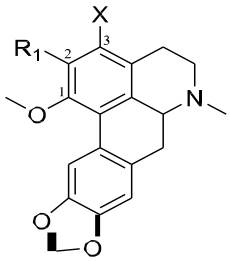
Recently we reported a fortuitous discovery wherein a series of aporphine alkaloids having a C4 phenyl group were found to have affinity for the 5-HT_{2B} receptor [45]. These compounds were initially designed to increase the 5-HT_{2A} receptor affinity of nantenine; however to our surprise displayed no appreciable affinity for the 5-HT_{2A} receptor. This clearly indicated that a phenyl group at the C4 position of nantenine is detrimental for its 5-HT_{2A} receptor affinity. This in turn might be due to the inability of the 5-HT_{2A} binding cavity to accommodate the C4 phenyl group or due to a steric clash between a receptor side chain and the C4 phenyl group. Amongst this series, compound **67** had the highest affinity for the 5-HT_{2B} receptor (K_i=96 nM). When nantenine (5-HT_{2B}, K_i=534 nM) is compared to compound **67** it is apparent that the C4 phenyl substituent positively impacts 5-HT_{2B} affinity and selectivity. Binding affinity of other analogues indicated a clear trend between the length of alkyl group at the C1 position and 5-HT_{2B} receptor affinity. Thus with increasing C1 alkyl chain length, the 5-HT_{2B} receptor affinity was found to decrease as evident from compound **67** to **71**. A similar trend was also observed with respect to the size of the *N*6 alkyl substituent in compounds **67**, **76** and **77**. Thus the larger the *N*-alkyl group the lower is the 5-HT_{2B} receptor affinity. Both the trends suggest that the binding pocket occupied by the C1 alkyl and *N*6 alkyl groups are small and do not accommodate larger substituents. The C1 cyclopropylmethyl analogue (**72**, K_i=299 nM) has similar affinity compared to the propyl analogue (**69**, K_i=307 nM), which indicates that some degree of branching is tolerated. The allyl analogue (**73**, K_i=416 nM) had reduced affinity compared to its saturated analogue (**69**, K_i=307 nM) suggesting that saturation in this part of the alkyl chain is not tolerated. A phenolic OH group is not well tolerated for 5-HT_{2B} receptor affinity as indicated by **75** (K_i=715 nM) (Table 5).

Compound **67** has excellent selectivity for the 5-HT_{2B} receptor as it did not display any affinity across a broad range of other CNS receptors (α_{1A}, α_{1B}, α_{1D}, β_1, β_2, β_3, BZP rat brain site, CB_2, D_1, D_2, D_3, D_4,



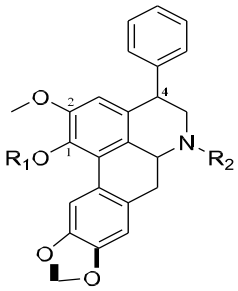
Compound	R_1	R_2	R_3	K_e (nM)		Ref.
				5-HT_{2A}	α_{1A}	
47	Me	Et	Me	378	52	[40]
48	Me	*n*-Pr	Me	389	133	[40]
49	Me	*n*-Bu	Me	943	234	[40]
50	Me	*n*-Pen	Me	> 10000	449	[40]
51	Me	CyclopropylMe	Me	484	195	[40]
52	Me	Bn	Me	154	1917	[40]
53	Allyl	H	Me	47	744	[40]
54	Me	Me	*N*-Et	> 10000	26	[40]
55	Me	Me	*N*-n-Pr	> 10000	38	[40]
56	Me	Me	*N*-n-Bu	> 10000	210	[40]
57	Me	Me	*N*-n-Pen	> 10000	720	[40]
58	Me	Me	*N*-CyclopropylMe	> 10000	319	[40]
59	Me	Me	O	> 3000	> 3000	[43]
60	Allyl	Me	O	> 3000	> 3000	[43]
(***R***)-**29**	Me	Me	*N*-Me	946	70	[43]
(***S***)-**29**	Me	Me	*N*-Me	657	196	[43]
(±)- 29	Me	Me	*N*-Me	850	36	[39]

Table 3: Binding affinity data of C-2 and *N*6 nantenine analogues.



Compound	R_1	X	K_e (nM)	
			5-HT_{2A}	α_{1A}
61	OH	H	282	255
62	OH	Cl	130	1279
63	OH	Br	126	68
64	OH	I	133	60
65	OMe	Cl	63	1273
66	OMe	Br	48	>10000
(±)- 29	OMe	H	850	36

Table 4: Binding affinity data of C-3 nantenine analogues.



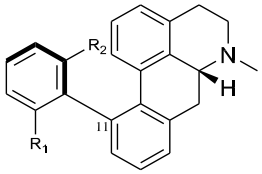
Compound	R_1	R_2	5-HT_{2A}-K_e (nM)
67	Me	Me	96
68	Et	Me	209
69	*n*-Pr	Me	307
70	*n*-butyl	Me	601
71	hexyl	Me	663
72	CyclopropylMe	Me	299
73	allyl	Me	416
74	*p*-bromobenzyl	Me	ND
75	H	Me	715
76	Me	Et	419
77	Me	CyclopropylMe	1429
(±)- 29	OMe	Me	850

Table 5: Binding affinity data of C-4 phenyl nantenine analogues

D_5, DAT, DOR, $GABA_A$, H_1, H_2, H_3, H_4, KOR, M_2, M_3, M_4, M_5, MOR, NET, NMDA, SERT, sigma-1, sigma-2). **67** showed affinities for the following receptors other than 5-HT_{2B}: 5- HT_6 (627 nM), α_{2a} (719 nM), α_{2B} (3220 nM), α_{2C} (433 nM) M1 (>10,000 nM) and PBR (2897 nM). In the 5-HT_{2B} functional activity testing, **67** displayed antagonistic activity (IC_{50}=1 μM). It is also of relevance that no 5-HT_{2B} agonist activity was found. To the best of our knowledge compound **67** is the first reported aporphine alkaloid to have selective affinity for the 5-HT_{2B} receptor and hence serves a valuable starting point for the design of potent 5-HT_{2B} antagonist.

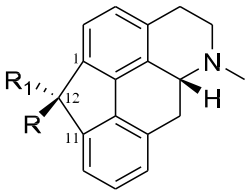
Aporphines as 5-HT_7 Ligands

As mentioned previously, compound **14** was identified by Hedberg and co-workers as a potent 5- HT_{1A} ligand. An expanded screening of **14** revealed it to have a decent affinity at the 5-HT_7 receptor and accordingly a systematic structure activity relationship study was initiated [46]. Incorporation of symmetrically di-*ortho*-substituted C-11phenyl rings resulted in compounds (compound **78** and **79**) with pronounced decrease in affinity at the 5-HT_7 receptor as well as 5-HT_{1A} and D_2 receptors. These substitutions however resulted in increased selectivity for the 5-HT_7 receptor



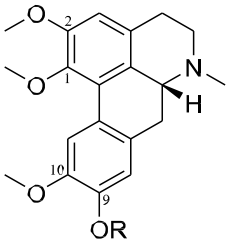
Compound	R_1	R_2	K_i (nM)		
			5-HT_7	5-HT_{1A}	D_2
78	OH	OH	13	554	2030
79	OTf	OTf	708	>10000	2260
80	Me	CN	20.80	778	2470
81	CN	Me	3.79	142	498
14	H	H	9.78	1.80	233

Table 6: Binding affinity data of C-11 phenyl aporphine analogues.



Compound	R_1	R_2	K_i (nM)		
			5-HT_7	5-HT_{1A}	D_2
83	H	H	6.90	40.70	83.20
84	OH	H	13.50	31	23.80
85	H	OH	103	1210	215
86	OH	Me	27.70	315	182
87	Me	OH	4.30	61.50	26
82	-	-	88	80	527

Table 7: Binding affinity data of 1, 11 rigidified aporphine analogues



Compound	R	K_i (nM)		
		5-HT_7	5-HT_{1A}	5-HT_{2A}
88	H	20	314	-
89	Me	43	171	966
90	Et	69	506	818
91	*n*-butyl	15	153	268
92	CyclopropylMe	22	224	582
93	Allyl	20	361	383
94	*p*-bromobenzyl	54	102	418

Table 8: Binding affinity data of C9 alkoxy aporphine analogues.

over 5-HT_{1A} receptor. A similar trend in selectivity was observed when unsymmetrical di-*ortho*-substituted C-11 phenyl rings were incorporated. Compound **80** in particular was the most potent compound identified in this series. Interestingly compound **81** (an atropisomer of compound **80**) was 5 fold less potent than **80** (Figure 8).

Similarly SAR studies on the rigidified 1, 11 methyleneaporphine scaffold produced compounds having a diverse and interesting range of affinities at the 5-HT_7 receptor [47]. When compared to compound **82**, the rigidified methylene derivative **83** displayed 12 fold higher affinity at the 5-HT_7 receptor. This clearly indicated that the added strain of the rigidified methylene group was beneficial in increasing the 5-HT_7 receptor affinity. Introduction of substituents on the methylene carbon produced interesting pharmacological effects. For example,

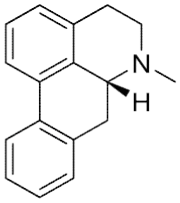


Figure 8: Structure of **82**.

compound **84** (6a*R*, 12*R* - OH group above the plane) displayed higher affinity than compound **85** (6a*R*, 12*S* - OH group below the plane). Adding a methyl group of C-12 resulted in an opposite trend. Thus compound **87** (6a*R*, 12*S* – OH group below the plane) displayed more affinity than compound **86** (6a*R*, 12*R* – OH group above the plane) (Tables 6 and 7).

In a more recent study, our group reported the evaluation of a series of C9 alkylated aporphine derivatives [48]. The design of these compounds was based on the structure of compound **88**, which was previously reported to have 5-HT_{1A} and 5-HT_7 receptor affinity [49]. Most of these compounds displayed moderate to good affinity for the 5-HT_7 receptor with a moderate selectivity over the 5- HT_{1A} receptor. Overall it was found that a C9 phenolic OH group is not absolutely required for 5- HT_7 receptor affinity, and that small alkoxy groups are well tolerated at this position (Table 8).

Conclusions

Aporphine alkaloids have been studies in much detail over the past two decades mainly at the dopaminergic and 5-HT_{1A} receptor systems. Much of the recent work has focused on the evaluation of aporphine alkaloids as ligands at the 5-HT_{2A} and 5-HT_7 receptor system. This review concentrated on the SAR of aporphine alkaloids at the 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_7 receptor subtypes. At the 5-HT_{1A} receptor, various alkyl substitutions are tolerated at the C-10 and C-11 position, where a lipophilic pocket seems to interact with this substituents. Long chain alkyl substitutions at the C1 position were beneficial for affinity at the 5-HT_{2A} receptor. Several rigidified aporphine alkaloids displayed enhanced affinity at the 5-HT_7 receptor. Although several analogues of aporphine alkaloids have been prepared and evaluated at these receptors, in general most of the SAR study has been limited to specific positions for particular receptor subtypes (for example C10 and C11 for 5-HT_{1A} and 5-HT_7, C1 and C2 for 5-HT_{2A}). Considering the fact that small modifications on the aporphine scaffold produces diverse range of pharmacological actions, the unexplored chemical space around the aporphine template needs to be systematically evaluated. Furthermore, a truly selective aporphine alkaloid for either of these targets still needs to be discovered. Such a discovery will help medicinal chemist understand the often complex CNS receptor signaling process involved in the progression of several neuropsychiatric disorders and hence design better drugs targeting such disorders.

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