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 serotoninergic 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 serotoninergic 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 tetrahydrosquoline 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 D1 and D2 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-HT1A 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-HT2A and 5-HT7 receptors. Selective 5-HT2A ligands have promising applications in the treatment of drug abuse and insomnia. Mixed dopamine/5-HT2A ligands have potential for the alleviation of symptoms of depression and schizophrenia [12,13]. Ligands at the 5-HT7 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 α1-adrenergic receptor and thus have potential therapeutic role in the treatment of Alzheimer's disease and hypertension respectively [18-21].

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-HT1A receptor. Some of this previous work has been nicely summarized in previously published reviews [1,3].

Aporphine as 5-HT1A 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 serotoninergic agonistic activity with a high degree of selectivity for the 5-HT1A receptor. Further studies revealed that the S isomer of 3 (S - 3) was an antagonist at the 5-HT1A 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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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\textsubscript{\text{\text{1a}}} activity [24]. This clearly indicated a significant role of the C-10 methyl group towards the enhanced 5-HT\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{1a}} receptor [26]. High affinity for the 5-HT\textsubscript{\text{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\textsubscript{\text{1a}} receptor. The absence of a similar lipophilic pocket around the C-10 methyl group in the D\textsubscript{2} receptor explained the high selectivity of 3 for the 5-HT\textsubscript{\text{1a}} receptor over the D\textsubscript{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{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\textsubscript{\text{1a}} affinity as indicated by compounds 27 and 28, an increase in affinity and selectivity for the 5-HT\textsubscript{\text{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\textsubscript{\text{2A}} Ligands**

Majority of the work of aporphine alkaloids as ligands at the 5-HT\textsubscript{\text{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 (5-HT\textsubscript{P}) induced head-twitch response by blocking 5-HT\textsubscript{\text{2A}} receptors in mice [34]. Later the same group reported SAR studies showing nantenine as an antagonist at the 5-HT\textsubscript{\text{2A}} and α\textsubscript{1A} 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\textsubscript{\text{2A}} and α\textsubscript{1A} receptors [37] (Figure 7).

Research in our group has focused on the synthesis and evaluation of nantenine analogues as 5-HT\textsubscript{\text{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\textsubscript{1A} receptor (K\textsubscript{i}=2 nM) compared to other α\textsubscript{1} subtypes. At the 5-HT\textsubscript{\text{2A}} receptor, nantenine was found to have moderate affinity (K\textsubscript{i}=850 nM) [38]. In order to improve the potency and selectivity of nantenine analogues for the 5-HT\textsubscript{\text{2A}} receptor,
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 $\alpha_{1A}$ receptor was completely abolished, thus suggesting that the C1 position could play a vital role in fine tuning 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.

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

| Compound | R$_1$ | R$_2$ | R$_3$ | R$_4$ | $K_i$ (nM) | Ref. |
|----------|-------|-------|-------|-------|-----------|------|
| 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      | -    | - [25]      |
| S-5      | H     | Me    | H     | Me    | 6.80      | -    | - [25]      |
| 6        | H     | OH    | Me    | Me    | -         | -    | - [26]      |
| 7        | H     | Me    | OH    | Me    | -         | -    | - [26]      |
| 8        | OH    | CH$_2$OH | 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$_2$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$_2$CCH | H | H     | Pr    | 55        | -    | - [30]      |
| 18       | O-Allyl | H   | H     | Me    | 12        | -    | - [30]      |
| 19       | OCH$_2$CCH | H | H     | Me    | 14        | -    | - [30]      |
| 20       | NHCOEt | H     | H     | Pr    | 94        | 54.6 | 44.3 [31]  |
| 21       | NHCOBu | H     | H     | Pr    | 96        | 70.2 | 871 [31]   |
| 22       | NH$_2$ | H     | H     | Pr    | 276      | 57.1 | 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]   |

$^{a}$ID$_{50}$ values (µM)
$^b$% inhibition values

Figure 6: Structure of compounds 24, 25 and 28.

Figure 7: Structure of (±)-nantenine.
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\(_{1A}\) receptor.

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 groupings 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\(_{1A}\) receptor. Compound 46 that has a p - bromobenzyl unit attached at the C1 position was the most potnet 5-HT\(_{1A}\) ligand identified in this series. In fact compound 46 is the most potent 5-HT\(_{1A}\) aporphinoid antagonist known till date (Table 2).

Molecular modeling studies were used to identify key interactions of the 5-HT\(_{1A}\) 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 propoxy 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\(_{1A}\) 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 \(\alpha_1\) 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\(_{1A}\) receptor. A substitution at the C2 position is not absolutely required for affinity at the 5-HT\(_{1A}\) 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\(_{1A}\) receptor, but affinity at the \(\alpha_1\) receptor was retained. This suggested that the N-Methyl group is important for affinity at the 5-HT\(_{1A}\) 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\(_{1A}\) receptor. The requirement of this salt bridge interaction was proven by evaluating the isochroman compounds 39 and 60 which were found to be completely inactive at the 5-HT\(_{1A}\) receptor [43].
It is also worth mentioning that both the R and S enantiomers of nantenine displayed antagonist effects at the 5-HT$_{1A}$ receptor. This trend is in contrast to the effect of aporphine enantiomers at other receptor system including 5-HT$_{2A}$ and dopamine D$_1$ and D$_2$, where enantiomers display opposing pharmacological effects as previously described. Furthermore in an _in vitro_ 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$_{1A}$ affinity. Compounds 62-64 showed doubling of 5-HT$_{1A}$ 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$_{1A}$ 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$_{1A}$ 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$_{1A}$ receptor [45]. These compounds were initially designed to increase the 5-HT$_{1A}$ receptor affinity of nantenine; however, to our surprise displayed no appreciable affinity for the 5-HT$_{1A}$ receptor. This clearly indicated that a phenyl group at the C4 position of nantenine is detrimental for its 5-HT$_{1A}$ receptor affinity. This in turn might be due to the inability of the 5-HT$_{1A}$ 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$_{1A}$ receptor (K$_i$=96 nM). When nantenine (5-HT$_{1A}$ K$_i$=534 nM) is compared to compound 67 it is apparent that the C4 phenyl substituent positively impacts 5-HT$_{1A}$ 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$_{1A}$ receptor affinity. Thus with increasing C1 alkyl chain length, the 5-HT$_{1A}$ 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 N6 alkyl substituent in compounds 67, 76 and 77. Thus the larger the N-alkyl group the lower is the 5-HT$_{1A}$ receptor affinity. Both the trends suggest that the binding pocket occupied by the C1 alkyl and N6 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 alkyl 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$_{1A}$ receptor affinity as indicated by 75 (K$_i$=715 nM) (Table 5).

Compound 67 has excellent selectivity for the 5-HT$_{1A}$ receptor as it did not display any affinity across a broad range of other CNS receptors (α$_{1A}$, α$_{1D}$, β$_1$, β$_2$, β$_3$, BZP rat brain site, CB$_1$, D$_1$, D$_2$, D$_3$, D$_4$).

| Compound | R$_1$ | R$_2$ | R$_3$ | 5-HT$_{1A}$, K$_i$ (nM) | α$_{1A}$, Ref. |
|----------|-------|-------|-------|----------------------|---------------|
| 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    | Br    | Me    | 154                   | 1917          | [40] |
| 53       | Allyl | H     | Me    | 47                    | 744           | [40] |
| 54       | Me    | Me    | N-Et  | > 10000               | 26            | [40] |
| 55       | Me    | Me    | N-Pr  | > 10000               | 38            | [40] |
| 56       | Me    | Me    | N-Bu  | > 10000               | 210           | [40] |
| 57       | Me    | Me    | 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 N6 nantenine analogues.
D₂, DAT, DOR, GABAₐ, H₁, H₂, H₃, KOR, M₁, M₂, M₃, MOR, NET, NMDA, SERT, sigma-1, sigma-2). 67 showed affinities for the following receptors other than 5-HT₂B: 5-HT₆ (627 nM), α₂a (719 nM), α₂B (3220 nM), α₂C (433 nM), M₁ (>10,000 nM) and PBR (2897 nM). In the 5-HT₂B functional activity testing, 67 displayed antagonistic activity (IC₅₀ = 1 µM). It is also of relevance that no 5-HT₂B 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-HT₂B receptor and hence serves a valuable starting point for the design of potent 5-HT₂B antagonists.

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

| Compound | R₁ | X | Kₑ (nM) | αₑ (nM) |
|----------|----|---|---------|---------|
| 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 5: Binding affinity data of C-4 phenyl nantenine analogues

| Compound | R₁ | R₂ | 5-HT₂B-Kₑ (nM) |
|----------|----|----|----------------|
| 67       | Me | Me | 96             |
| 68       | Et | Me | 209            |
| 69       | n-Pr| Me | 307            |
| 70       | n-butyl| Me | 601            |
| 71       | hexyl| Me | 663            |
| 72       | Cyclopropyl| Me | 299           |
| 73       | allyl| Me | 416            |
| 74       | p-bromobenzyl| Me | ND            |
| 75       | H | Me | 715            |
| 76       | Me | Et | 419            |
| 77       | Me | Cyclopropyl| Me | 1429   |
| (±)-29   | OMe| Me | 850            |

**Aporphines as 5-HT₇ Ligands**

As mentioned previously, compound 14 was identified by Hedberg and co-workers as a potent 5-HT₁₅ ligand. An expanded screening of 14 revealed it to have a decent affinity at the 5-HT₁₅ 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-HT₁₅ receptor as well as 5-HT₂B and D₂ receptors. These substitutions however resulted in increased selectivity for the 5-HT₁₅ receptor.
Compound | \( R_1 \) | \( R_2 \) | \( K_i \) (nM)
---|---|---|---
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)
---|---|---|---
88 | 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 21
82 | - | - | 88 80 527

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

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

In a more recent study, our group reported the evaluation of a series of C9 alkyalted aporphine derivatives [48]. The design of these compounds was based on the structure of compound 88, which was previously reported to have 5-HT1A and 5-HT7 receptor affinity [49]. Most of these compounds displayed moderate to good affinity for the 5-HT7 receptor with a moderate selectivity over the 5-HT1A receptor. Overall it was found that a C9 phenolic OH group is not absolutely required for 5-HT7 receptor affinity, and that small alkoxy groups are well tolerated at this position (Table 8).

Conclusions

Aporphine alkaloids have been studied in much detail over the past two decades mainly at the dopaminergic and 5-HT7 receptor systems. Much of the recent work has focused on the evaluation of aporphine alkaloids as ligands at the 5-HT7 and 5-HT1A receptor system. This review concentrated on the SAR of aporphine alkaloids at the 5-HT1A, 5-HT7, 5-HT1B, and 5-HT2 receptors. At the 5-HT7 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-HT7 receptor. Several rigidified aporphine alkaloids displayed enhanced affinity at the 5-HT7 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-HT7, and C1 for 5-HT7). 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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