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C4 phenyl aporphines with selective *h*5-HT$_{2B}$ receptor affinity

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ABSTRACT

A group of aporphine alkaloids related to (±)-nantenine (**1**) and bearing a C4 phenyl and various C1 or *N*-substituents, was synthesized and evaluated for affinity to *h*5-HT receptors. In general, unlike nantenine, the analogs lack affinity for the *h*5-HT$_{2A}$ receptor and other 5-HT receptors but bind selectively to the *h*5-HT$_{2B}$ receptor. With regards to 5-HT$_{2B}$ affinity, there appears to be a low tolerance for bulky C1 or *N*-substituents when the C4 phenyl moiety is present. Compound **5a** had the highest 5-HT$_{2B}$ affinity of the compounds tested, was found to be an antagonist and is selective vs other CNS receptors.

Aporphine alkaloids display a wide range of pharmacological activities and have been shown to exhibit antimicrobial, antiviral, antimalarial and cytotoxic activities among others.[1–6] Moreover, in the central nervous system (CNS), aporphines have been investigated as acetylcholinesterase inhibitors[7,8] and as ligands for serotonin, adrenergic and dopamine receptors.[9–14]

Research in our group has mainly focused on the synthesis and evaluation of aporphines as ligands for the 5-HT$_{2A}$ receptor.[15–17] The 5-HT$_{2A}$ receptor plays a significant role in various neuropsychiatric disorders such as schizophrenia, anxiety depression and psychostimulant abuse.[18–22] Selective 5-HT$_{2A}$ antagonists are being pursued as novel therapeutics to treat sleep disorders.[23–25]

Our prior structure-activity relationship (SAR) studies on aporphines have focused on modifications on aryl ring A, of the lead molecule (±)-nantenine (**1**, Fig. 1), resulting in the identification of a number of potent 5-HT$_{2A}$ antagonists such as compounds **2** and **3**.[26,15,27] These prior SAR studies indicate that a variety of C1 alkoxy substituents are beneficial for 5-HT$_{2A}$ receptor affinity and selectivity. Small alkoxy groups are tolerated at the C2 position, though the gains in affinity are somewhat moderate compared to that seen for the C1 analogs. C3 halogenated analogs were shown to possess strong affinity for the 5-HT$_{2A}$ receptor.

In an effort to further decipher structural motifs that may be accommodated on the aporphine core for high affinity, antagonism and selectivity for the 5-HT$_{2A}$ receptor, we decided to prepare a series of nantenine analogs bearing a phenyl ring substituent at the C4 position (exemplified by **4**). We expected that the incorporation of a C4 phenyl group would engender improved affinity of the aporphine scaffold for the 5-HT$_{2A}$ receptor, based on structural resemblance to 9-aminomethyl-9,10-dihydroanthracene (AMDA, **5**)—a potent 5-HT$_{2A}$ receptor antagonist.[28,29] Surprisingly, we have found that these novel C4 phenyl analogs lack affinity for the 5-HT$_{2A}$ receptor but have selective affinity for the 5-HT$_{2B}$ receptor.

Herein we describe the synthetic and biological experiments that led to this interesting serendipitous discovery.

Since C1 alkoxy analogs (e.g., **2** and **3**) had displayed improved affinity for the 5-HT$_{2A}$ receptor, it was decided that a C1 alkoxy moiety would be retained in the series of C4 phenyl analogs. Prior SAR studies on nantenine indicated that *N*-substituent groups larger than methyl were not tolerated for 5-HT$_{2A}$ receptor affinity. Nevertheless, we also wanted to determine the extent to which small *N*-alkyl substituents could be tolerated when a C4 phenyl substituent was present on the nantenine template. Synthesis of the requisite C1 alkoxy/C4 phenyl and *N*-substituted/C4 phenyl analogs was achieved via the intermediacy of a key phenolic aporphine (**15**), prepared as outlined in Scheme 1. Thus, commercially available aldehyde **6** was protected as the benzyl ether and the resulting aldehyde condensed with nitromethane to afford nitrostyrene **7**. The Michael acceptor **7** was reacted with phenylmagnesium bromide to furnish compound **8**. Reduction of the nitro group of **8** was accomplished with $SnCl_2$. The primary amine **9** thus formed was coupled to bromoacid **10** to give amide **11**. Bischler–Napieralski reaction on **11** followed by reduction of the intermediate imine gave the secondary amine **12**. Amine **12** was protected as the Boc derivative, **13**. Thereafter, microwave-assisted direct

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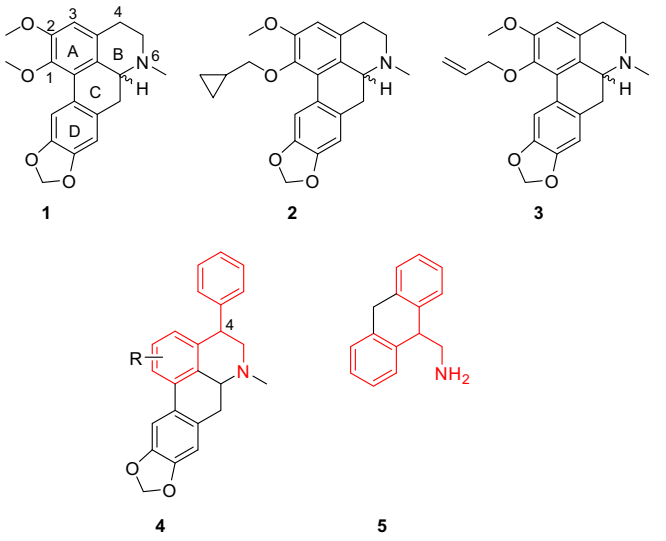


Figure 1. Structures of nantenine [(±)-**1**], C1 analogs (**2** and **3**), C4 phenyl analogs (**4**) and AMDA (**5**).

arylation provided the *O*-benzyl protected aporphine **14**. Removal of the benzyl protecting group of **14** was accomplished via catalytic hydrogenolysis to produce the key precursor **15**. With **15** in hand we proceeded to prepare target C4 phenyl analogs **5a**–**5j**. The synthesis of these analogs from **15** is depicted in Scheme 2. The phenol handle of **15** was used to install a variety of substituent groups via etherification reactions. Subsequently, Boc-deprotection and N-methylation via reductive amination afforded target analogs **5a**–**h**. Phenol analog **5i** was prepared from **15** via Boc-deprotection followed by *N*-methylation. **5j** was prepared from precursor **15** via the intermediacy of *N*-acyl derivative **16**. Compound **16** in turn was synthesized from **15** by sequential *O*-methylation, Boc-deprotection and *N*-amidation with acetic acid. LAH reduction of **16** afforded **5j**. **5k** was accessed from **15** in three steps viz *O*-methylation, Boc-deprotection and *N*-alkylation as shown.

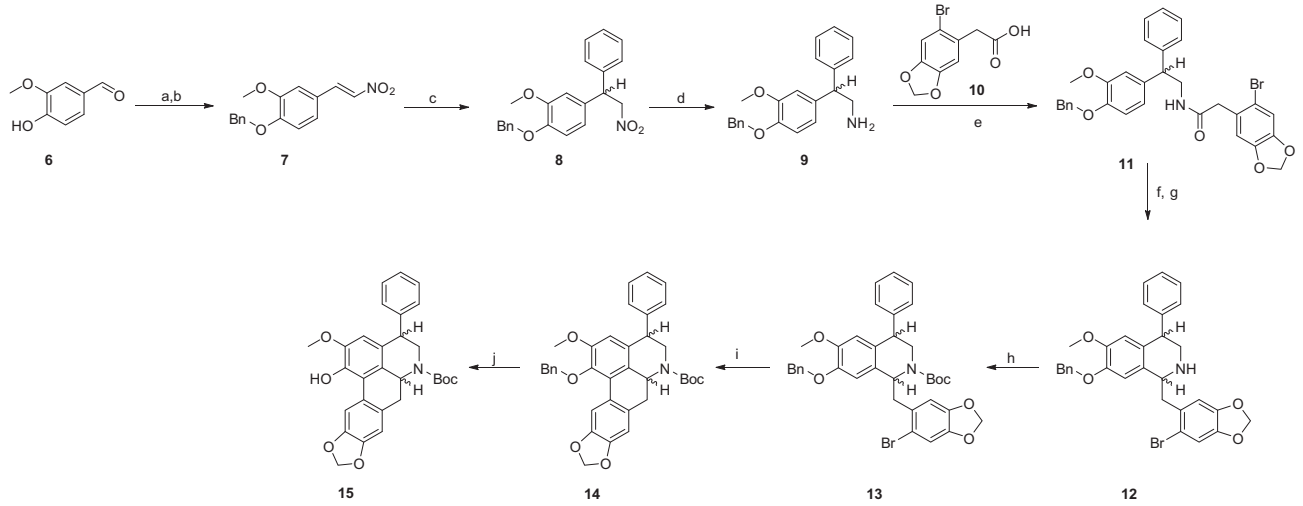
Analogs **5a**–**5k** were evaluated for affinity across various 5-HT receptors at the Psychoactive Drug Screening Program (PDSP). The compounds were tested initially in a primary radioligand binding assay that measures inhibition of serotonin binding, at a compound concentration of 10 μM. Compounds with inhibition values less than 50% at a particular receptor, are deemed inactive at that receptor. Compounds that displayed more than 50% inhibition of serotonin binding in the primary assays, were evaluated for determination of K_i values in secondary assays.

The results of the primary (% inhibition) assay are compiled in Table 1. To our surprise, the compounds demonstrated a remarkable selectivity profile; they were inactive at the 5-HT_{2A} receptor and at most other 5-HT sites. Interestingly, the majority of the compounds were active at the 5-HT_{2B} receptor (save for compound **5h**). Compounds **5c** and **5f** also showed activity at the 5-HT_{1B} receptor.

Data from the follow-up secondary (K_i determination) assay are provided in Table 2. As shown, the compounds display moderate to low affinity (K_i values ranging from 96 to 1429 nM) for the 5-HT_{2B} receptor, with compound **5a** having the highest affinity. Nantenine was found to have poor affinity for the 5-HT_{2B} receptor (K_i = 534 nM).[30] Thus when nantenine is compared to compound **5a** it is apparent that the C4 phenyl substituent positively impacts 5-HT_{2B} affinity and selectivity. When one compares the homologous series **5a**–**5e**, it is evident that an increase in the C1 alkoxy chain length is not good for 5-HT_{2B} affinity; increasing C1 alkoxy chain length coincided with a progressive decrease in 5-HT_{2B} receptor affinity.

The cyclopropylmethyl analog **5f** had similar affinity to the *n*-propyl analog **5c** (K_i values of 307 and 299 nM, respectively) which tends to suggest that some degree of alkyl chain branching is tolerated. The allyl analog **5g** had diminished affinity as compared to its saturated counterpart **5c**, so saturation (at this position in the alkyl chain) is not well tolerated for 5-HT_{2B} affinity. Compound **5i** had lower affinity than most other analogs (except for compound **5k** and compound **5h** which was inactive in the primary assay). This indicates that the C1 phenolic group is not beneficial for 5-HT_{2B} receptor affinity. In comparing *N*-alkyl analogs **5a**, **5j** and **5k**, the trend in affinities again coincides with the size of the alkyl group, that is, the larger the *N*-alkyl substituent the lower is the 5-HT_{2B} receptor affinity. Thus, smaller *N*-alkyl groups are better accommodated for 5-HT_{2B} receptor affinity.

To further characterize the pharmacological activity of the compounds, compound **5a** (which had the highest 5-HT_{2B} receptor



Scheme 1. *Reagents and conditions*: (a) BnBr, K_2CO_3, acetonitrile, reflux, 4 h, 94%; (b) CH_3NO_2, NH_4OAc, CH_3COOH, reflux, 4 h, 82%; (c) phenyl magnesium bromide, THF, 0 °C–rt, 18 h, 32%; (d) $SnCl_2$, EtOH, reflux, 16 h, 65%; (e) CDI, THF, 0 °C–rt, 16 h, 60%; (f) PCl_5, DCM, 0 °C–rt, 16 h; (g) $NaBH_4$.MeOH, 0 °C–rt, 4 h, 88% crude yield over 2 steps; (h) $(BoC)_2O$, DIPEA, DMAP, DCM, rt, 16 h, 85%; (i) $Pd(OAc)_2$, Di-*tert*-butyl(methyl)phosphonium tetrafluoroborate, K_2CO_3, DMSO, 135 °C, microwaves, 200 W, 88%; (j) H_2, Pd/C, THF/MeOH 1:1, rt, 6 h, 90%.