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Aminimides as Potential CNS-Acting Agents. III. Design, Synthesis, and Receptor Binding of Aminimide Analogues of Dopamine, Serotonin, Morphine, and Nicotine

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A series of aminimide derivatives of centrally acting agents, namely dopamine, serotonin, morphine and nicotine, were designed on the basis of the physicochemical properties of the aminimide functional group and synthesized to investigate their central nervous system (CNS) receptor affinity. The target compounds were readily prepared from an appropriate tertiary amine by *N*-acylation of a hydrazinium salt intermediate using acetic anhydride or acetyl chloride. The aminimides were tested for in vitro affinity at the dopaminergic D_4, serotonergic 5-HT_{2A}, opiate (μ, κ, and non-selective) and nicotinic acetylcholine receptors and were found to possess mixed affinities for the aforementioned receptor systems.

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Introduction

As an extension of our interest in the aminimide functional group and its incorporation into potential antipsychotic agents,[1,2] we embarked on the synthesis and preliminary pharmacological evaluation of aminimide analogues of other centrally acting agents (Fig. 1, shown as in their physiologically relevant ions) to investigate the biochemical influence of this functionality. The biogenic amines dopamine (**1**) and serotonin (**2**), and the narcotic alkaloid morphine (**3**) were chosen as these compounds exert their effects on the central nervous system (CNS) by action at G-protein coupled receptors (GPCRs), namely the dopaminergic, serotonergic, and μ-opiate (OP3) receptors, respectively. Nicotine (**4**) was also investigated as a representative of compounds that act at ligand-gated ion channels, specifically the nicotinic acetylcholine receptor. These four parent amines were also chosen on the basis that they varied significantly in their ability to cross the blood–brain barrier (BBB). Dopamine and serotonin do not cross the BBB themselves but their zwitterionic amino acid precursors, L-dihydroxyphenylalanine (L-DOPA) and L-tryptophan, respectively, demonstrate facile BBB penetration.[3,4] Morphine and nicotine do cross the BBB with nicotine more readily than morphine.[5] The incorporation of an aminimide functional group into these compounds may provide balanced hydrophilic and hydrophobic character for effective passage across the BBB. Furthermore, the reported enzymatic and proteolytic stability of this functional group[6,7] could render these analogues superior to agents such as L-DOPA for the delivery of a dopaminergic agent to the CNS. Thus, the dual nature of organic and aqueous solubility of simple aminimides and the electrically neutral and zwitterionic nature of these compounds make them attractive targets as novel CNS-acting agents. Here we report the design, chemical synthesis and preliminary receptor binding affinity of such aminimide-containing CNS active compounds.

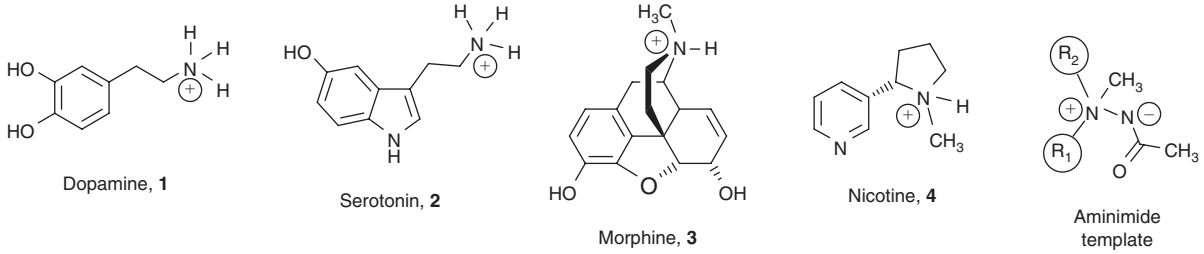

Fig. 1. The chemical structures of dopamine (**1**), serotonin (**2**), morphine (**3**), nicotine (**4**) and the aminimide template at physiological pH.

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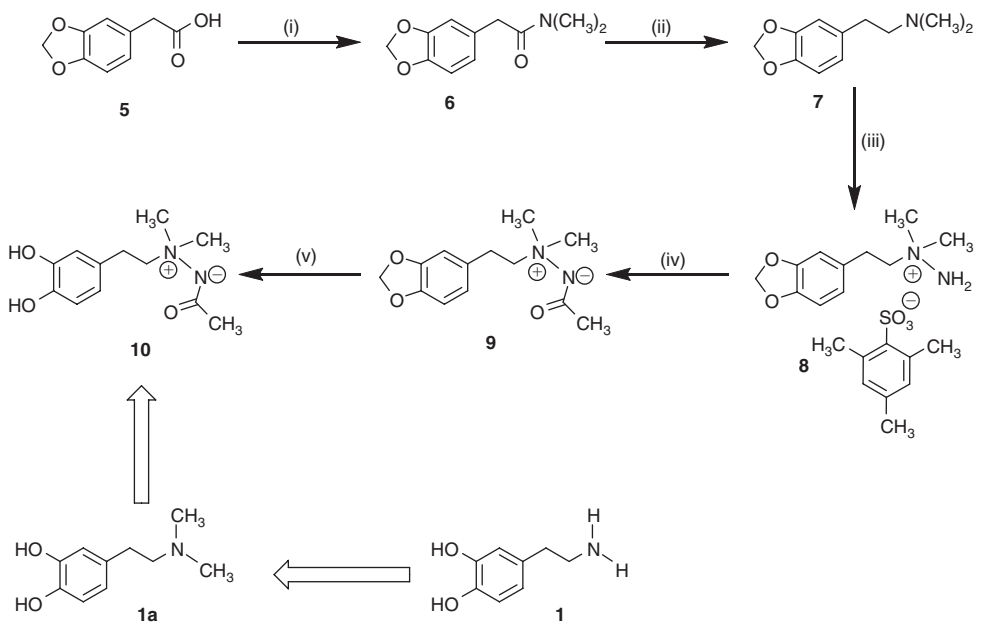


Scheme 1. Reagents and conditions: (i) $(CH_3)_2NH{\cdot}HCl$, TBTU, NEt_3, RT; (ii) BH_3-THF, THF, reflux; (iii) *O*-mesitylenesulfonylhydroxylamine ($MesSO_3NH_2$), CH_2Cl_2, 0°C; (iv) a. Ac_2O, 120°C; b. Amberlite IRA-400(OH), MeOH; (v) BBr_3, CH_2Cl_2, RT.

Chemistry

The synthesis of acetyl aminimides from hydrazinium salts has been described previously[8] using acetic anhydride or acetyl chloride as the acylating species. Both of these methods were examined for the synthesis of the desired acetyl aminimides of the designated CNS-active agents. The tertiary amines morphine (**3**) and nicotine (**4**) could be used directly for the generation of the corresponding hydrazinium salts (**16**) and (**19**) respectively. In the case of the primary amines, dopamine and serotonin, the corresponding *O*-alkylidene or alkyl *N*,*N*-dimethyl derivatives (**7**) and (**11**), respectively, were utilized as the tertiary amines required for aminimide synthesis.

Dopamine

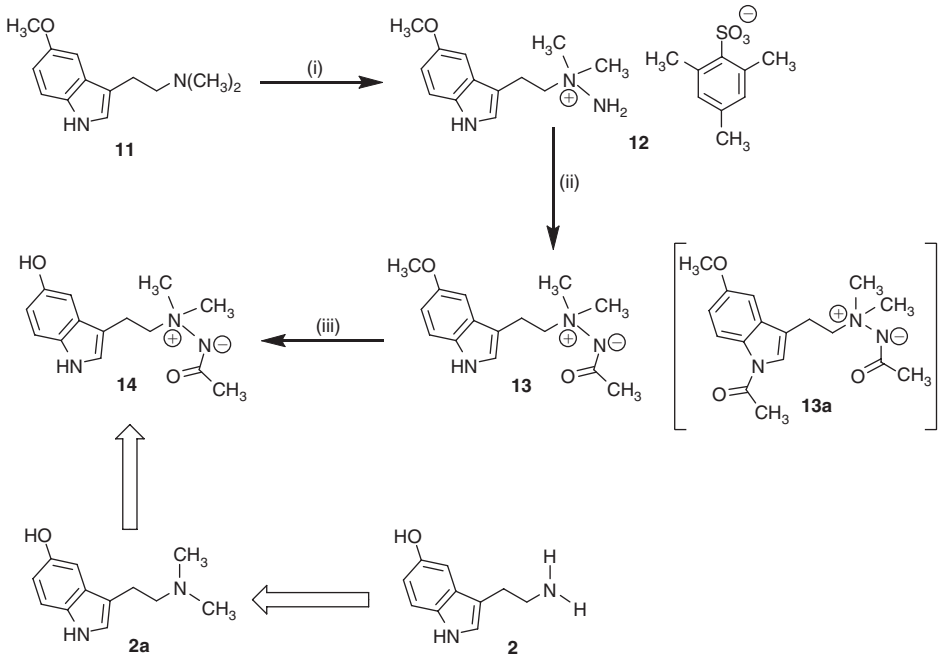
The *N*,*N*-dimethyl analogue of dopamine, **1a**, was selected as the parent tertiary amine for the synthesis of the dopamine aminimide (**10**; Scheme 1). The *O*-protected tertiary amine (**7**) was envisaged as an appropriate substitute for **1a** because it was considered that problems might be encountered with the free hydroxy groups during aminimide synthesis. Compound **7** was synthesized from commercially available 3,4-methylenedioxyphenylacetic acid (**5**) in two steps. The activated hydroxybenzotriazolyl ester of **5** was prepared from 3,4-methylenedioxyphenylacetic acid (**5**) and 1-(bis(dimethylamino)methylene)-1*H*-benzo[*d*][1,2,3]triazol-1-ium 3-oxide tetrafluoroborate (TBTU) in *N*,*N*-dimethylformamide. Subsequent treatment with dimethylamine hydrochloride in the presence of triethylamine gave, after flash chromatography and distillation, the amide (**6**) in 69% yield. Treatment of the amide (**6**) with borane–tetrahydrofuran complex gave the tertiary amine (**7**) in 83% distilled yield. The boiling points of compounds **6** and **7** were in good agreement with those reported in the literature.[9]

N-Amination of **7** by *O*-mesitylenesulfonylhydroxylamine[10] gave the hydrazinium salt **8** as cream-coloured needles in 84% yield. A downfield shift observed for the ^1H and ^{13}C NMR resonances of both the *N*,*N*-dimethyl group and adjacent methylene group (H1) and an ion (M^+, 209) observed in the positive ion electrospray mass spectrum indicated that *N*-amination had occurred successfully. The 2,4,6-trimethylbenzenesulfonate anion was also observed in the ^1H and ^{13}C NMR, spectrum confirming the formation of **8**. *N*-acylation of **8** using acetic anhydride smoothly afforded the aminimide (**9**) in 92% yield. Subsequent de-etherification on treatment with boron tribromide gave the target dopamine aminimide analogue (**10**) in 42% overall yield from **5**.

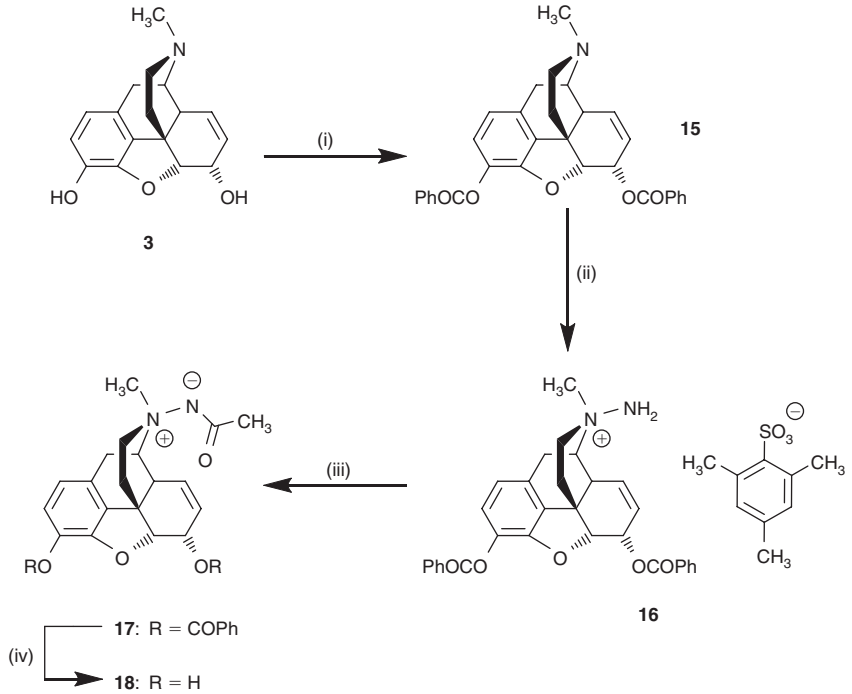
Serotonin

N,*N*-dimethyl-5-hydroxytryptamine (bufotenin, **2a**) was selected as the parent amine for the synthesis of an acetyl aminimide analogue of 5-hydroxytryptamine (serotonin, **14**; Scheme 2). As in the dopamine scenario, the *O*-protected tertiary amine (**11**) was envisaged as an appropriate substitute for **2a** owing to possible side-reactions in the aminimide synthesis arising from an unprotected hydroxy group. By reason of the commercial availability of *N*,*N*-dimethyl-5-methoxytryptamine (**11**), we decided to utilize this material as the aminimide precursor and complete the desired synthesis of **14** by *O*-demethylation. *N*-Amination of **11** proceeded smoothly to give the hydrazinium salt (**12**) in 98% yield. Unfortunately, attempts to *N*-acylate **12** using acetic anhydride proved problematic in this case, because not only did *N*-acylation occur at the hydrazinium nitrogen (**13**), but also at the indole nitrogen to afford **13a** (Scheme 2). Di-acetylation was indicated by the presence of two singlet resonances (δ 1.90 and 2.57 ppm) in the ^1H NMR spectrum of **13a** (see Accessory Publication). Further analysis revealed the doublet resonances assigned to H7 and H2 had shifted downfield from δ 7.29 and 7.04 ppm for the desired aminimide (**13**) to δ 8.29 and 7.27 ppm (s), respectively, for **13a**. The absence of the characteristic indole N–H proton resonance observed for **13** (H1, δ 9.46 ppm) was also supportive of the formation of **13a**.

N-acylation of **12** to afford **13** using acetyl chloride (Scheme 2) proved more successful with only a small amount of the doubly acetylated product detected by TLC and in the mass



Scheme 2. Reagents and conditions: (i) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, 0°C; (ii) CH_3COCl, NaH, DMF, −15°C–RT; (iii) BBr_3, CH_2Cl_2, RT.



Scheme 3. Reagents and conditions: (i) PhCOCl, pyridine, 0–50°C; (ii) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, 0°C; (iii) a. Ac_2O, 120°C; b. Amberlite IRA-400(OH), MeOH; (iv) 1% aq. NaOH, MeOH.

spectrum of the crude reaction mixture. The compound was isolated in 56% recrystallized yield as pale orange plates. Treatment of **13** with boron tribromide under standard aromatic demethylation conditions[11] proceeded smoothly to give the indolol, **14**, in 42% yield.

Morphine

The chemical synthesis of the target morphine aminimide is depicted in Scheme 3. Morphine (**3**) was protected as the dibenzoate ester (**15**) to avoid possible side reactions during the *N*-amination step. Amination of **15** proceeded smoothly at the tertiary nitrogen on treatment with *O*-mesitylenesulfonylhydroxylamine[10] to afford the dibenzoate-protected hydrazinium salt (**16**) in 75% yield. The method described by Tamura et al.[8] utilising acetic anhydride as the acylating species was preferred, as the acid chloride gave a complex mixture of products. Examination of the positive ion electrospray mass spectrum of the reaction mixture resulting from treatment

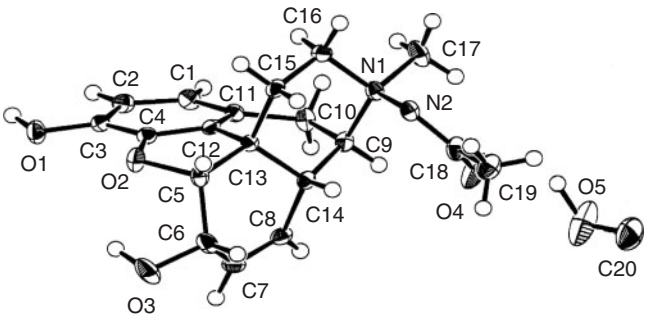


Fig. 2. An *ORTEP* view of **18**. Displacement ellipsoids are drawn at the 50% probability level.

of **16** with acetyl chloride indicated that not only had the formation of the acetyl aminimide occurred, but also debenzoylation and *O*-acetylation to varying degrees of both the aminimide and the hydrazinium salt. Deamination to the tertiary amine was also detected. This is in contrast to the treatment of **16** with acetic anhydride, which proceeded smoothly to afford the dibenzoyl-protected morphine aminimide (**17**) in 69% yield. Removal of the benzoyl groups by treatment with aqueous sodium hydroxide (1%) in methanol gave the target morphine aminimide (**18**), which afforded colourless needles from methanol in 78% yield suitable for X-ray analysis.

All dibenzoate morphine analogues were characterized by the presence of two ester carbonyl stretching frequencies between 1735 and 1710 cm^{-1} in their infrared spectra. The two morphine aminimides, **17** and **18**, showed the characteristic aminimide infrared absorption bands (1587, 1563 cm^{-1}) due to the major contribution of the $^{-}$OC=N resonance form observed for aminimides.[12] Structural assignments of **15**–**18** were achieved by one- and two-dimensional NMR techniques and comparisons of the ^{1}H and ^{13}C NMR spectra with those of morphine and its *O*-acetyl derivatives in the literature (see Accessory Publication).[13] Several key features such as the proton resonances associated with the benzoate groups of **15**–**17**, the ^{+}N-methyl proton resonances (δ 3.6–3.9 ppm) for **16**–**17**, and the acetimide methyl proton resonances (δ 1.8–1.9 ppm) for **17** and **18** were used for confirmation of structure. Also observed were downfield shifts for the proton resonances in the vicinity of the nitrogen, namely H9, H10, H15, H16 and H17, due to the effect of the ionized nitrogen for analogues **16**–**18**. The crystal structure of **18** was also determined by X-ray crystallography and an *ORTEP* view of the molecule together with the atomic numbering is shown in Fig. 2. The atomic coordinates, anisotropic displacement parameters, bond lengths, bond angles and torsion angles of the derivative **18** are listed as Accessory Publication.

The morphine moiety of **18** adopts a similar 'T-shaped' conformation to that observed for the parent compound, morphine (**3**).[14] The 'T-shaped' conformation ideally comprises two mean planes that intersect in a near-normal fashion. Each mean plane is defined by the rings of the morphine molecule such that the first plane comprises rings A, B, and C, and the second rings D and E. As was observed for morphine (**3**),[14] the piperidine ring of **18** adopts a chair conformation with the methyl group assuming an equatorial orientation and the acetimide group axial (Fig. 3). Charge delocalisation is observed on the carbonyl oxygen (O4) of the aminimide group for **18**. The N(1)–N(2) (1.482(2) Å) bond is similar to a single bond in length and the N(2)–C(18) (1.324(3) Å) and C(18)–O(4) (1.250(3) Å) bonds are

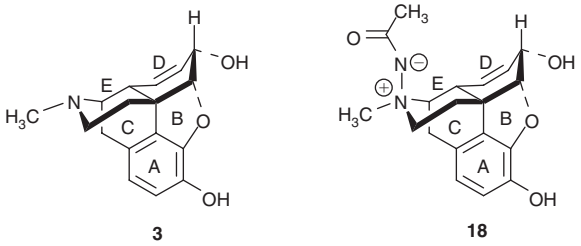


Fig. 3. The absolute structures of **3** and **18**.

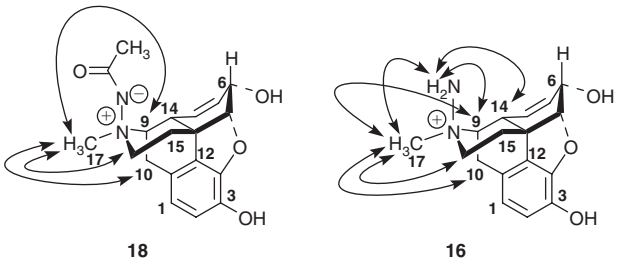


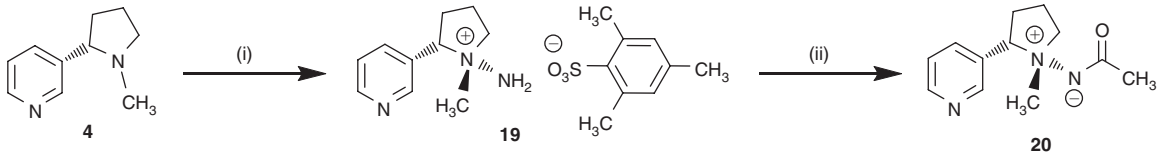
Fig. 4. NOEs observed for **18** and **16** for the determination of stereochemistry about the quaternized nitrogen.

both slightly longer than expected for double bonds, thus indicating that there is significant charge delocalisation present about the acyl aminimide moiety. This delocalization is also supported by the characteristic aminimide infrared resonance ($^{-}$OC=N) at 1563 cm^{-1}.

The stereochemistry about the quaternary nitrogen is assigned as the *R* configuration. This is supported by the crystal structure of **18** and the correlations observed in the nuclear Overhauser effect correlation spectroscopy (NOESY) spectrum for both the aminimide, **18**, and the hydrazinium salt, **16** (Fig. 4). Nuclear Overhauser effects (NOEs) were observed for **18** from the ^{+}N-methyl resonance, H17 (δ 3.45 ppm) to H9 (δ 4.95 ppm) and the respective axial and equatorial proton resonances of H10 (δ 2.77, 3.26 ppm) and H16 (δ 2.90, 3.85 ppm). This indicates that the ^{+}N-methyl group is equatorial. Similarly, NOEs were observed for **16** from the ^{+}N-methyl resonance, H17 (δ 3.95 ppm) to the equatorial resonance of H10 (δ 3.38 ppm), the axial H16 resonance (δ 3.17 ppm), and H9 (δ 4.78 ppm). NOEs were also observed from the hydrazinium amino resonance (δ 6.64 ppm) to H17 (δ 3.95 ppm), H14 (δ 4.20 ppm), H9 (δ 4.78 ppm), and H5 (δ 5.33 ppm). This evidence indicates an equatorial methyl group and an axial hydrazinium amino or acetimide group about the positively charged nitrogen, confirming the *R* stereochemistry for **16**–**18**, which was also observed in the solid state (Fig. 2).

Nicotine

Scheme 4 illustrates the chemical synthesis of the target nicotine aminimide. (*S*)-(−)-Nicotine (**4**) was mono-*N*-aminated at the more basic nitrogen by the procedure described by Tamura et al.[8] to give the hydrazinium salt **19** in 58% yield. The cation of **19** appeared at *m*/*z* 178 in the positive ion electrospray mass spectrum indicating that mono-*N*-amination had occurred. Confirmation that reaction had occurred only at the tertiary aliphatic amine nitrogen was obtained on examination of the ^{1}H and ^{13}C NMR spectra of **19**, which revealed a methyl group attached to a positively charged nitrogen (δ_H 3.14 ppm, δ_C 51.9 ppm). The methylene and methine carbons (C5 and C2) resonated at δ 67.8 and 76.6 ppm, respectively, in the ^{13}C NMR spectrum, which



Scheme 4. Reagents and conditions: (i) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, 0°C; (ii) a. Ac_2O, 120°C; b. Amberlite IRA-400(OH), MeOH.

is consistent with these carbons being attached to a positively charged nitrogen. All other data collected in the experimental section were consistent with those reported in the literature.[8]

As (*S*)-(−)-nicotine is a chiral molecule, *N*-amination could potentially produce two diastereomers. Only one diastereomer, **19**, was visible by ^1H and ^{13}C NMR spectroscopy and by TLC. Examination of a ^1H-^1H NOESY spectrum (Accessory Publication) indicated that the stereochemistry about the quaternary nitrogen is *S*. NOEs were observed for **19** from the methine proton resonance, H2 (δ 4.93 ppm) to the ^+N-methyl resonance (δ 3.14 ppm), thus indicating that the ^+N-methyl group is *syn* to H2. NOEs were also observed from H2 (δ 4.93 ppm) to H3a (δ 2.37 ppm), and H5a (δ 3.81 ppm), indicating that these two protons are also *syn* to H2. Furthermore, NOEs were observed from the hydrazinium amino proton resonance (δ 5.55 ppm) to the ^+N-methyl resonance (δ 3.14 ppm), H5b (δ 3.88 ppm), and H3b (δ 2.64 ppm), thus indicating that the amino group, H5b and H3b are all *anti* to H2. Subsequent acetylation of the hydrazinium salt (**19**) with acetic anhydride at 120°C, followed by treatment with Amberlite IRA-400(OH) ion-exchange resin gave, after repeated chromatography, the desired nicotine acetyl aminimide (**20**) in 37% yield.

Receptor Binding Studies

Biological Results

Binding data were obtained from MDS Panlabs (Taiwan). Each compound was tested at a concentration of 10^{-6} M at the receptors indicated and compared with the affinity of the amine from which the aminimide was obtained. In the case of the dopamine and serotonin analogues, affinities were also compared with that of the endogenous neurotransmitters dopamine and serotonin, respectively.

The affinities of aminimide analogues of dopamine, **9** and **10**, for the dopamine $D_{4.4}$ receptor in human recombinant CHO cells using [^{3}H]spiperone as the competing radioligand were −3 and −5% inhibition at 10^{-6} M (Table 1). These values were well below that of the reference compound dopamine, which displayed a 55% inhibition of radioligand.

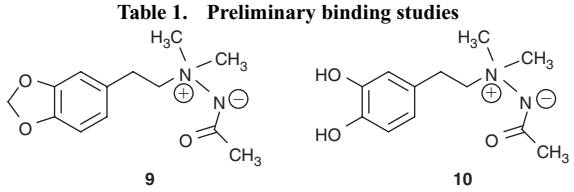
Both the 5-methoxy (**13**) and the 5-hydroxy (**14**) aminimide analogues of serotonin were tested at a concentration of 10^{-6} M for their binding affinities for the 5-HT_{2A} receptor in rat cerebral cortex (Table 2). Serotonin (**2**) and *N*,*N*-dimethyl-5-methoxytryptamine (**11**) were also evaluated at this receptor for comparative purposes. A significant reduction in binding affinity for the 5-HT_{2A} receptor was evident on replacement of the tertiary amine group (**11**, 60% I) with an aminimide group (**13**, 16% I). A comparable affinity for the 5-HT_{2A} receptor was observed on the removal of the 5-methoxy group of **13** to afford the 5-hydroxy analogue (**14**, 26% I); however, these values were significantly below that of the reference compound serotonin (77% I).

Both morphine (**3**) and the morphine aminimide (**18**) were evaluated at the human recombinant μ and κ opiate receptors along with the rat brain opiate (non-selective) receptor (Table 3). As was observed for the aminimides of the biogenic amines dopamine and serotonin, there was a pronounced decrease in binding affinity on introduction of the aminimide functional group.

Both nicotine (**4**) and the nicotine aminimide (**20**) were evaluated at the central nicotinic acetylcholine receptor (Table 4). The introduction of the aminimide group into nicotine to give **20** only produced a modest reduction in receptor affinity compared with nicotine. This result was quite pleasing when evaluated against the relative drop in affinity associated with the dopamine, serotonin, and morphine aminimides compared with their respective parent compounds.

The nicotinic acetylcholine receptor is a ligand-gated ion channel, not a GPCR like the dopamine, 5-HT, and opiate receptors used in the present study. Consequently, the binding interactions are somewhat different when comparing the two

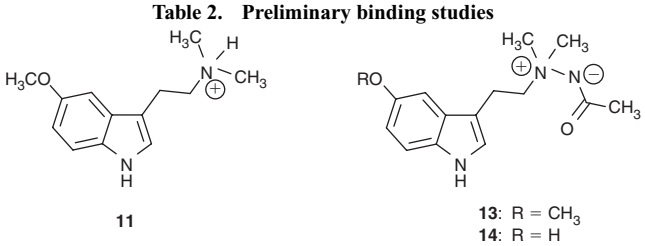
Table 1. Preliminary binding studies



Compound	Binding affinity percentage inhibition (% I) at 10^{-6} M $D_{4,4}$[^{3}H]spiperone[A]
Dopamine, **1**	55
9	−5
10	−3

[A]Determined in duplicate by MDS PANLABS (Taiwan).

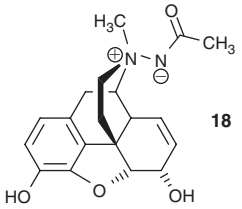
Table 2. Preliminary binding studies



Compound	Binding affinity percentage inhibition (% I) at 10^{-6} M 5-HT_{2A}[^{3}H]ketanserin[A]
Serotonin	77
11	60
13	16
14	26

[A]Determined in duplicate by MDS PANLABS (Taiwan).

Table 3. Preliminary binding studies

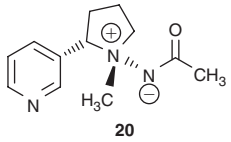


18

Compound	Binding affinity percentage inhibition (% I) at 10^{-6} M		
	μ Opiate[^{3}H] diprenorphine[A]	κ Opiate[^{3}H] diprenorphine[A]	Opiate, non-selective [^{3}H]naloxone
Morphine, **3**	99	72	94
18	17	−10	14

[A]Determined in duplicate by MDS PANLABS (Taiwan).

Table 4. Preliminary binding studies



20

Compound	Binding affinity percentage inhibition (% I) at 10^{-6} M
	Central nicotinic acetylcholine *α4β2* (rat)[^{3}H]cytisine[A]
Nicotine, **4**	92
20	71

[A]Determined in duplicate by MDS PANLABS (Taiwan).

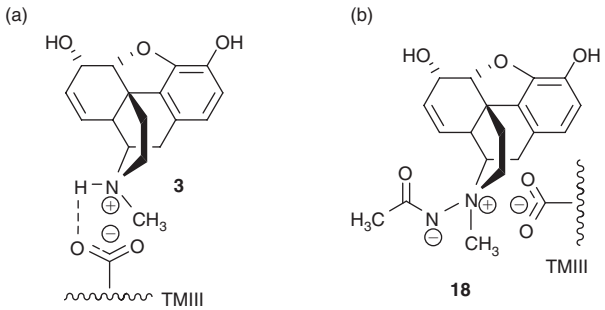


Fig. 5. Salt bridge formation at TMIII between the aspartate residue and (a) morphine (**3**) and (b) morphine aminimide (**18**).

classes of receptor. The positively charged amine of the drug and ligand is thought to interact electrostatically with an ionized aspartic acid residue on the receptor in the GPCRs, for example, Asp-311 on transmembrane unit III (TMIII) for the dopamine receptor.[15] This binding interaction can occur between the conserved aspartate residue on TMIII of the dopamine, serotonin, and opiate receptors and can be stabilized in the case of the tertiary amine compounds such as morphine for the μ-receptor (Fig. 5). Although there is a quaternized nitrogen that could participate in an electrostatic interaction on receptor binding, there is no available hydrogen bonding group for stabilization. There is also a possibility of electrostatic repulsion from the opposing negative charges of the aspartate and the aminimide nitrogen.

A three-dimensional structure determined by electron microscopy has described the structure of the nicotinic acetylcholine receptor in both the open and closed state.[16] These structures and affinity labelling studies indicate that acetylcholine interacts predominantly with the α-subunit of the receptor.[17] A model of the binding site[18] has described interactions between the ionized amine of the ligand, in this case acetylcholine, and the negatively charged region of the binding site. Traditional ion pair-type interactions between the ionized amine and aspartic acid and serine residues, and cation–π interactions of the ionized amine with aromatic residues (tyrosine and tryptophan) have been described. This cation–π interaction is thought to stabilize the positive charge of the trimethylammonium group of acetylcholine, forming an anionic solvation shell.[19] This cation–π interaction could stabilize the positive charge of the aminimide group, which may not be available in the models of the GPCRs.

Conclusion

A marked reduction in affinity was observed for the dopamine, morphine, and serotonin aminimide analogues that were evaluated for their affinity at GPCRs. Conversely, the same marked reduction in affinity was not observed for the nicotine aminimide analogue and an explanation relating to the different binding interactions proposed for the nicotinic acetylcholine receptor is given. Clearly, more detailed information relating to the affinity of these compounds at the targeted receptors is required to support the explanations for the reduced affinity of these compounds. Further studies are needed that investigate aminimide analogues of other CNS-acting agents that exert their action at a larger selection of G-protein coupled as well as other types of receptors within the CNS. Also the introduction, at an alternative site not thought to be involved in receptor binding, of the aminimide group to several CNS-acting agents could be investigated in an effort to balance the lipophilic and hydrophilic characteristics of these molecules. Other functional groups could also be investigated in an effort to increase the binding affinity and improve aqueous solubility of several CNS-acting agents.

Experimental

General

Melting points were determined using a Reichert Micromelting point apparatus and are uncorrected. Microanalyses were carried out by Chemical and Micro Analytical Services Pty Ltd, Melbourne, Australia or the Chemistry Department, University of Queensland. Infrared spectra were recorded using a Hitachi 270–30 infrared spectrometer as potassium bromide (KBr) discs for solids, as thin films of liquids (neat) between sodium chloride plates and as chloroform ($CHCl_3$) solutions of gums. UV-Visible spectra were recorded as ethanolic solutions using a Pharmacia Biotech Ultraspec 2000 UV-VIS spectrometer utilizing *Swift II* software. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300.13 MHz and 75.47 MHz, respectively. Chemical shifts are reported in δ units relative to internal tetramethylsilane for ^{1}H NMR spectra and the deuterated solvent resonance for ^{13}C spectra. NOESY, homonuclear (^{1}H/^{1}H) correlation spectroscopy (DQFCOSY and gradient correlation spectroscopy (COSY)) and inverse heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HMQC and gradient HMBC) were obtained using the standard Bruker pulse sequences for structural assignment of some NMR spectra. Mass spectra were recorded on a JEOL JMS-DX300

or a Micromass Platform II mass spectrometer in positive ion electrospray mode. High resolution mass spectra (HRMS) were recorded using a Bruker Bio Apex II FTICR mass spectrometer. Silica gel (Merck Kieselgel 60 silica gel 230–400 mesh) was used for column chromatography. TLC was performed on silica gel plates (Merck, ART 5554 60 F_{254}). Preparative TLC was performed on glass plates (Merck ART 5717). Solvents were purified by literature methods.[20,21] Hexane refers to the hydrocarbon fraction boiling between 60°C and 80°C.

2-(1,3-Benzodioxol-5-yl)-N,N-*dimethylacetamide* ***6***

A solution of 2-(1,3-benzodioxol-5-yl)acetic acid (**5**) (1.00 g, 5.55 mmol), dimethylamine hydrochloride (498 mg, 6.11 mmol) and TBTU (2.16 g, 6.73 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred at room temperature under an atmosphere of nitrogen for 1 h. Triethylamine (3.1 mL, 2.23 g, 22.0 mmol) was then added and the reaction mixture allowed to stir at room temperature for a further 14 h. The solvent was removed under vacuum to afford a brown gum, which was partitioned between sodium hydroxide (2 M, 50 mL) and ethyl acetate (80 mL) and the aqueous phase extracted with ethyl acetate (2 × 100 mL). The combined organic phases were washed with water (150 mL), dried over anhydrous sodium sulfate, then evaporated under vacuum. The resulting brown oil was purified by flash chromatography (7:3 ethyl acetate/hexane) to afford **6**, after concentrating the appropriate fraction, as a pale yellow oil. Vacuum distillation afforded the title compound **6** (796 mg, 69%) as a colourless oil, bp 164–166°C/270 Pa (lit.[9] 145°C/40 Pa). ν_{max} (KBr)/cm^{-1} 2902, 1632, 1500. λ_{max}/nm (ε/M^{-1} cm^{-1}) 238 (4070), 289 (3720). δ_H ($CDCl_3$) 2.97 (3H, s, CH_3N), 3.01 (3H, s, CH_3N), 3.63 (2H, s, H2), 5.94 (2H, s, H2′), 6.69 (1H, dd, *J* 8, 2, H6′), 6.75 (1H, d, *J* 8, H7′), 6.78 (1H, d, *J* 2, H4′). δ_C ($CDCl_3$) 35.8 (CH_3N), 37.8 (CH_3N), 40.7 (C2), 101.1 (C2′), 108.4 (C4′), 109.4 (C7′), 121.9 (C6′), 128.9 (C5′), 146.5 (C7a′), 148.0 (C3a′), 171.2 (C1). *m*/*z* (+ESI, 30 V) 208 (100%, MH^+).

2-(1,3-Benzodioxol-5-yl)-N,N-*dimethylethanamine* ***7***

To a solution of **6** (586 mg, 2.83 mmol) in dry, oxygen-free tetrahydrofuran (40 mL), at 0°C, was added dropwise a solution of borane in tetrahydrofuran (1.0 M, 4.7 mL, 4.7 mmol). Once the addition was complete, the reaction mixture was heated at reflux for 1 h and then allowed to cool. Aqueous hydrochloric acid (5 M, 10 mL) was added and the reaction mixture left to stir for a further 20 min. The solvent was removed under vacuum, water (30 mL) added and the resulting mixture adjusted to pH 12 by the addition of solid potassium hydroxide pellets. Following extraction with ethyl acetate (3 × 50 mL), the organic fractions were dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by flash chromatography (100:8:1, dichloromethane/ethanol/ammonia) to afford **7**, after concentrating the appropriate fraction, as a pale yellow oil. Vacuum distillation afforded the title compound **7** (449 mg, 83%) as a colourless oil, bp 123–125°C/65 Pa (lit.[9] 95°C/15 Pa). ν_{max} (KBr)/cm^{-1} 2950–2782, 1608. δ_H ($CDCl_3$) 2.29 (6H, s, $(CH_3)_2N$), 2.47–2.52 (2H, m, H2), 2.68–2.73 (2H, m, H1), 5.92 (2H, s, H2′), 6.65 (1H, dd, *J* 8, 1.5, H6′), 6.71 (1H, d, *J* 1.5, H4′), 6.73 (1H, d, *J* 8, H7′). δ_C ($CDCl_3$) 33.9 (C2), 45.3 (CH_3N), 61.6 (C1), 100.7 (C2′), 108.1 (C4′), 109.0 (C7′), 121.3 (C6′), 134.2 (C5′), 145.7 (C7a′), 147.5 (C3a′). *m*/*z* (+ESI, 30 V) 194 (100%, MH^+).

1-[2-(1,3-Benzodioxol-5-yl)ethyl]-1,1-dimethylhydrazinium 2,4,6-Trimethylbenzenesulfonate ***8***

A solution of *O*-mesitylenesulfonylhydroxylamine[10] (501 mg, 2.33 mmol) in dichloromethane (5 mL) was added, with ice cooling, to a solution of **7** (375 mg, 1.94 mmol) in dichloromethane (8 mL) and the mixture left to stir for 20 min. Hexane was then added to precipitate the crude product (668 mg, 84%), which recrystallized from ethyl acetate/methanol to give **8** (598 mg, 76%) as cream needles, mp 179–180°C (Found: C 58.8, H 7.0, N 6.8. $C_{20}H_{28}N_2O_5S$ requires C 58.8, H 6.9, N 6.9%). ν_{max} (KBr)/cm^{-1} 3292, 1635, 1608. λ_{max}/nm (ε/M^{-1} cm^{-1}) 223 (12600), 284 (4370) nm. δ_H ([D_4]methanol) 2.30 (3H, s, $ArCH_3$), 2.70 (6H, s, 2 × $ArCH_3$), 3.17 (2H, m, H2), 3.40 (6H, s, $(CH_3)_2N^+$), 3.70 (2H, m, H1), 6.00 (2H, s, H2′), 6.83–6.88 (3H, m, H4′, H6′, H7′), 6.94 (2H, s, ArH). δ_C ([D_4]methanol) 21.0 ($ArCH_3$), 23.0 (2 × $ArCH_3$), 30.1 (C2), 56.7 ($(CH_3)_2N^+$), 71.1 (C1), 102.6 (C2′), 109.7 (C4′), 110.4 (C7′), 123.4 (C6′), 130.6 (C5′), 131.9 (C3″, C5″), 138.4 (C2″, C6″), 140.3 (C4″), 141.1 (C1″), 148.4 (C7a′), 149.7 (C3a′). *m*/*z* (+ESI, 30 V) 209 (M^+, 100%).

1-Acetyl-2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2,2-dimethylhydrazin-2-ium-1-ide ***9***

A solution of **8** (253 mg, 0.62 mmol) in acetic anhydride (20 mL) was heated at 120°C for 5 h. The reaction mixture was concentrated under vacuum to afford a brown syrup, which was dissolved in methanol and treated with Amberlite IRA-400(OH) ion-exchange resin. The resin was removed by filtration and the filtrate concentrated under vacuum. The resulting orange gum was purified by flash chromatography (100:8:1, dichloromethane/ethanol/ammonia) to afford a colourless oil (142 mg, 92%), which solidified on cooling. Recrystallization from ether/hexane gave the *title compound* **9** (104 mg, 67%) as colourless plates, mp 32°C (Found: C 57.9, H 7.7, N 10.3, MH^+ 251.1387. $C_{13}H_{18}N_2O_3{\cdot}H_2O$ requires C 58.2, H 7.5, N 10.4%, MH^+ 251.1390). ν_{max} (KBr)/cm^{-1} 2974, 1578. λ_{max}/nm (ε/M^{-1} cm^{-1}) 237 (3240), 288 (3020). δ_H ($CDCl_3$) 1.86 (3H, s, CH_3CO), 2.96 (2H, m, H2′), 3.32 (6H, s, $(CH_3)_2N^+$), 3.87 (2H, m, H1′), 5.92 (2H, s, H2″), 6.67 (1H, br d, *J* 8, H6″), 6.71 (1H, br s, H4″), 6.74 (1H, d, *J* 8, H7″). δ_C ($CDCl_3$) 23.1 (CH_3CO), 29.7 (C2′), 56.7 ($(CH_3)_2N^+$), 66.1 (C1′), 100.9 (C2″), 108.3 (C4″), 109.1 (C7″), 121.7 (C6″), 130.2 (C5″), 146.4 (C7a″), 147.8 (C3a″), 173.9 (CO). *m*/*z* (+ESI, 30 V) 251 (40%, MH^+), 149 (100).

1-Acetyl-2-(3,4-dihydroxyphenethyl)-2,2-dimethylhydrazin-2-ium-1-ide ***10***

A solution of **9** (200 mg, 0.80 mmol) in anhydrous dichloromethane (10 mL) was treated with a solution of boron tribromide in dichloromethane (1.0 M, 4.0 mL, 4.0 mmol) at room temperature and the reaction mixture left to stir overnight. Methanol (10 mL) was added and the reaction mixture was stirred for a further 20 min. The methanol was removed under vacuum and the brown residue resuspended in methanol (10 mL) and reconcentrated to afford the *title compound* **10** (180 mg, 94%) as a pale brown gum (Found: MH^+ 239.1385. $C_{12}H_{18}N_2O_3$ requires MH^+ 239.1390). ν_{max} (KBr)/cm^{-1} 3292, 3154, 1599, 1554. λ_{max}/nm (ε/M^{-1} cm^{-1}) 224 (5370), 284 (2750). δ_H ([D_4]methanol) 2.06 (3H, s, CH_3CO), 2.94 (2H, m, H2′), 3.68 (6H, s, $(CH_3)_2N^+$), 4.16 (2H, m, H1′), 6.68 (1H, d, *J* 8, H6″), 6.76 (1H, d, *J* 2, H3″), 6.68 (1H, dd, *J* 8, 2, H5″). δ_C (D_2O) 20.6 (CH_3CO), 27.8 (C2′), 54.8 (CH_3N^+), 66.4 (C1′), 115.8 (C6″),

116.0 (C3″), 127.3 (C4″), 120.8 (C5″), 142.5 (C1″), 143.6 (C2″), 169.6 (CO). *m/z* (+ESI, 30 V) 239 (100, MH^+), 103 (90).

*1-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]-1,1-dimethylhydrazinium 2,4,6-Trimethylbenzenesulfonate* ***12***

A solution of *O*-mesitylenesulfonylhydroxylamine[10] (592 mg, 2.8 mmol) in dichloromethane (5 mL) was added over 5 min, with ice cooling, to a solution of *N,N*-dimethyl-5-methoxytryptamine (**11**) (500 mg, 2.3 mmol) in dichloromethane (8 mL). The reaction mixture was left to stir for a further 10 min after which hexane was added to precipitate the crude product (976 mg, 98%). Recrystallization from ethyl acetate/methanol gave the *title compound* **12** (814 mg, 82%) as cream-coloured needles, mp 161–162°C (Found: C 61.0, H 7.2, N 9.6. $C_{22}H_{31}N_3O_4S$ requires C 61.0, H 7.2, N 9.7%). ν_{max} (KBr)/cm^{-1} 3272, 1650, 1623, 1602. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 222 (41700), 276 (34700), 298 (22400), 310 (13200). δ_H ([D_4]methanol) 2.24 (3H, s, $ArCH_3$), 2.65 (6H, s, $2 \times ArCH_3$), 3.31 (2H, m, H2′), 3.40 (6H, s, CH_3N^+), 3.72 (2H, m, H1′), 3.86 (3H, s, CH_3O), 6.83 (1H, dd, *J* 9, 2.5, H6″), 6.88 (2H, s, H3‴, H5‴), 7.10 (1H, d, *J* 2.5, H4″), 7.18 (1H, br s, H2″), 7.29 (1H, d, *J* 9, H7″). δ_C ([D_4]methanol) 20.4 (C2′), 21.0 (CH_3Ar), 23.5 ($2 \times CH_3Ar$), 56.5 ($(CH_3)_2N^+$, CH_3O), 70.4 (C1′), 101.3 (C4″), 109.2 (C3″), 113.1 (C6″), 113.4 (C7″), 125.1 (C2″), 128.6 (C3a″), 131.9 (C3‴, C5‴), 133.5 (C7a″), 138.4 (C2‴, C6‴), 140.3 (C4‴), 141.1 (C1‴), 155.5 (C5″). *m/z* (+ESI, 30 V) 234 (M^+, 100%), 174 (80).

*1-Acetyl-2-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-2,2-dimethylhydrazin-2-ium-1-ide* ***13***

Sodium hydride (74 mg, 1.85 mmol, 60% dispersion in oil) was washed with anhydrous hexane, dried under a stream of dry nitrogen and cooled to −15°C (dry ice–benzyl alcohol). A solution of **12** (200 mg, 0.46 mmol) and acetyl chloride (50 μL, 0.70 mmol) in anhydrous *N,N*-dimethylformamide (8 mL, −15°C) was then added dropwise with stirring over 5 min, the mixture maintained at −15°C for a further 6 h, then allowed to warm to room temperature overnight. The solvent was removed under vacuum to afford a brown residue, which was resuspended in ethyl acetate, and a white solid removed by filtration. The filtrate was evaporated under vacuum and the resulting residue purified by flash chromatography (50:5:2, dichloromethane/ethanol/ammonia) to give a pale yellow solid (83 mg, 65%). The crude product was recrystallized from dichloromethane/hexane to afford the *title compound* **13** (71 mg, 56%) as pale orange plates, mp 182–184°C (Found: MH^+ 276.1701. $C_{15}H_{21}N_3O_2{\cdot}H_2O$ requires MH^+ 276.1706). ν_{max} (KBr)/cm^{-1} 3488, 1626, 1572. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 222 (22900), 277 (6030), 298 (4680), 309 (3470). δ_H ($CDCl_3$) 1.90 (3H, s, CH_3CO), 3.21 (2H, m, H2′), 3.54 (6H, s, $(CH_3)_2N^+$), 3.86 (3H, s, CH_3O), 4.10 (2H, m, H1′), 6.87 (1H, dd, *J* 9, 2.5, H6″), 7.04 (1H, d, *J* 2, H2″), 7.08 (1H, d, *J* 2.5, H4″), 7.29 (1H, d, *J* 9, H7″), 9.46 (1H, br s, H1″). δ_C ($CDCl_3$) 20.0 (C2′), 56.2 ($(CH_3)_2N^+$, CH_3O), 65.3 (C1′), 100.7 (C4″), 109.8 (C3″), 112.2 (C7″), 112.4 (C6″), 123.5 (C2″), 127.6 (C3a″), 132.0 (C7a″), 154.2 (C5″), 174.2 (CO). *m/z* (+ESI, 30 V) 276 (20%, MH^+), 173 (100).

*1-Acetyl-2-(2-(5-hydroxy-1*H*-indol-3-yl)ethyl)-2,2-dimethylhydrazin-2-ium-1-ide* ***14***

A solution of boron tribromide in dichloromethane (1 M, 1.5 mL, 1.5 mmol) was added to a stirred solution of **13** (81 mg, 0.29 mmol) in anhydrous dichloromethane (10 mL) at room temperature. After stirring overnight, methanol (10 mL) was added, the reaction mixture stirred for a further 30 min and then evaporated to dryness. The residue was redissolved in methanol (10 mL) and the methanol removed under vacuum. The resulting brown residue was purified by flash chromatography (50:8:1, dichloromethane/ethanol/ammonia) to afford the *title compound* **14** (33 mg, 42%) as a brown gum (Found: MH^+ 262.1549. $C_{14}H_{19}N_3O_2$ requires MH^+ 262.1550). ν_{max} (KBr)/cm^{-1} 3600–3200, 1629, 1605, 1572. λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 223 (23400), 278 (5890), 298 (4680), 310 (3390). δ_H ([D_4]methanol) 1.83 (3H, s, CH_3CO), 3.03 (2H, m, H2′), 3.30 (6H, s, $(CH_3)_2N^+$), 3.93 (2H, m, H1′), 6.63 (1H, dd, *J* 9, 2, H6″), 6.94 (1H, d, *J* 2, H4″), 7.01 (1H, br s, H2″), 7.12 (1H, d, *J* 9, H7″). δ_C ([D_4]methanol) 20.9 (C2′), 54.6 ($(CH_3)_2N^+$), 66.2 (C1′), 103.5 (C4″), 110.0 (C3″), 112.9 (C7″), 113.0 (C6″), 124.9 (C2″), 129.2 (C3a″), 133.2 (C7a″), 151.6 (C5″), 175.3 (CO). *m/z* (+ESI, 30 V) 262 (20%, MH^+), 173 (100).

(5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-dibenzoate (Dibenzoylmorphine) ***15***

Benzoyl chloride (620 μL, 742 mg, 5.3 mmol) was added, at 0°C, to a stirred solution of morphine (**3**) (300 mg, 1.1 mmol) in anhydrous pyridine (20 mL). The solution was heated to 50°C for 2.5 h, cooled and the pyridine removed under vacuum. The resulting brown oily residue was purified using flash chromatography (200:8:1, dichloromethane/ethanol/ammonia) to afford a colourless solid (487 mg, 93%), which recrystallized from chloroform to give the *title compound* **15** as white needles (391 mg, 75%), mp 197–198°C. ν_{max} (KBr)/cm^{-1} 1730, 1713 (lit.[22] 1732, 1715 cm^{-1}). λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$) 231 (33100), 276 (4680), 282 (4570). δ_H ($CDCl_3$) 2.00 (1H, br dd, *J* 12.5, 1.5, $H15_{eq}$), 2.17 (1H, ddd, *J* 13, 12.5, 5, $H15_{ax}$), 2.42 (1H, dd, *J* 19, 5.5, $H10_{ax}$), 2.47 (1H, app. td, 12.5, 3.5, $H16_{ax}$), 2.52 (3H, s, H17), 2.72 (1H, br dd, *J* 12.5, 3.5, $H16_{eq}$), 2.84 (1H, app. p, *J* 2.5, H14), 3.14 (1H, d, *J* 19, $H10_{eq}$), 3.50 (1H, dd, *J* 5.5, 3.5, H9), 5.27 (1H, d, *J* 7, H5), 5.42–5.47 (1H, m, H6), 5.54 (1H, app. dt, *J* 10, 2.5, H8), 5.82 (1H, br app. dt, *J* 10, 2, H7), 6.68 (1H, d, *J* 8, H1), 6.95 (1H, d, *J* 8, H2), 7.25 (2H, app. t, *J* 7.5, H3″, H5″), 7.35 (2H, app. t, *J* 8, H3′, H5′), 7.45 (1H, td, *J* 7.5, 1.5, H4″), 7.54 (1H, td, *J* 8, 1.5, H4′), 7.93 (2H, dd, *J* 8, 1.5, H2′, H6′), 8.01 (2H, dd, *J* 7.5, 1.5, H2″, H6″). δ_C ($CDCl_3$) 21.0 (C10), 35.3 (C15), 40.8 (C14), 43.0 (C13), 43.2 (C17), 46.8 (C16), 59.3 (C9), 68.3 (C6), 89.0 (C5), 119.6 (C1), 122.3 (C2), 128.3 (C3′, C5′), 128.5 (C3″, C5″), 128.9 (C7), 129.4 (C4), 129.7 (C8), 130.0 (C2″, C6″), 130.2 (C2′, C6′), 131.8 (C12), 132.5 (C11, C1′, C1″), 133.0 (C4″), 133.3 (C4′), 149.8 (C3), 164.4 (CO′), 166.1 (CO″). *m/z* (+ESI, 30 V) 494 (100%, MH^+).

*(5α,6α)-7,8-Didehydro-4,5-epoxy-17(*R*)-aminomethylmorphinan-3,6-dibenzoyl 2,4,6-Trimethylbenzenesulfonate* ***16***

To an ice-cooled solution of **15** (350 mg, 0.71 mmol) in dichloromethane (5 mL) was added dropwise a solution of *O*-mesitylenesulfonylhydroxylamine[10] (183 mg, 0.85 mmol) in dichloromethane (5 mL). Once the addition was complete, the reaction mixture was allowed to stir for a further 10 min and the solvent removed under vacuum to afford an oily residue, which was redissolved in ethanol. Diethyl ether was then added to precipitate the product as a white powder (482 mg, 96%), which was recrystallized from chloroform to give the *title compound* **16** (397 mg, 79%) as colourless rhomboids, mp 166–168°C

(Found: C 66.2, H 5.6, N 3.8, M^+ 509.2071. $C_{40}H_{40}N_2O_8S{\cdot}H_2O$ requires C 66.1, H 5.8, N 3.9%, M^+ 509.2071). ν_{max} (KBr)/cm^{-1} 3286, 3154, 1737, 1712, 1623, 1602. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (38000), 278 (4790), 282 (4570). δ_H ($CDCl_3$) 1.91 (1H, br d, *J* 12, $H15_{eq}$), 2.24 (3H, s, $ArCH_3$), 2.70 (6H, s, 2 × $ArCH_3$), 2.77 (1H, app. td, *J* 13, 4, $H15_{ax}$), 2.94 (1H, dd, *J* 20.5, 6, $H10_{ax}$), 3.17 (1H, app. td, *J* 12.5, 2.5, $H16_{ax}$), 3.38 (1H, d, *J* 20.5, $H10_{eq}$), 3.95 (3H, s, H17), 3.96 (1H, br d, *J* 18, $H16_{eq}$), 4.20 (1H, br s, H14), 4.78 (1H, br s, H9), 5.33 (1H, d, *J* 7, H5), 5.36 (1H, d, *J* 10, H8), 5.42 (1H, dd, *J* 7, 2.5, H6), 5.86 (1H, br app. dt, *J* 10, 3, H7), 6.64 (2H, s, NH_2), 6.70 (1H, d, *J* 8.5, H1), 6.87 (2H, s, H3‴, H5‴), 7.00 (1H, d, *J* 8.5, H2), 7.28 (2H, app. t, *J* 7, H3″, H5″), 7.31 (2H, app. t, *J* 7.5, H3′, H5′), 7.46 (1H, t, *J* 7, H4″), 7.53 (1H, t, *J* 7.5, H4′), 7.80 (2H, d, *J* 7.5, H2′, H6′), 7.98 (2H, d, *J* 7.0, H2″, H6″). δ_C NMR ($CDCl_3$) 21.0 (Ar*C*H_3), 23.4 (2 × Ar*C*H_3), 25.1 (C10), 29.8 (C15), 32.9 (C14), 41.0 (C13), 57.5 (C17), 58.4 (C16), 67.1 (C6), 71.5 (C9), 87.7 (C5), 120.1 (C1), 124.0 (C2), 126.3 (C8), 127.2 (C4), 128.4, 128.5 (C3′, C3″, C5′, C5″), 129.0 (C12), 129.7, 129.8 (C1′, C1″), 130.0 (C2″, C6″), 130.3 (C7, C2′, C6′), 131.1 (C3‴, C5‴), 133.1 (C4″), 133.4 (C11), 133.6 (C4′), 137.0 (C2‴, C6‴), 139.1 (C4‴), 140.1 (C1‴), 149.6 (C3), 164.1 (CO′), 165.8 (CO″). *m*/*z* (+ESI, 30 V) 509 (100%, M^+), 85 (90).

*(5α,6α)-7,8-Didehydro-4,5-epoxy-17(*R*)-acetimidemethylmorphinan-3,6-dibenzoate* ***17***

A solution of **16** (253 mg, 0.36 mmol) in acetic anhydride (20 mL) was heated at 120°C for 6 h. The reaction mixture was concentrated under vacuum to give a brown syrup, which was redissolved in methanol and treated with Amberlite IRA-400(OH) ion-exchange resin. The resin was filtered off and the methanol removed under vacuum to give a colourless gum, which was purified by flash chromatography (100:8:1, dichloromethane/ethanol/ammonia) to afford a colourless oil (159 mg, 80%), which solidified on standing. Recrystallization from diethyl ether gave the *title compound* **17** (137 mg, 69%) as colourless prisms, mp 188–191°C (Found: C 72.1, H 5.6, N 4.9. $C_{33}H_{30}N_2O_6$ requires C 72.0, H 5.5, N 5.1%). ν_{max} (KBr)/cm^{-1} 1731, 1716, 1630, 1587. λ_{max}/nm (ε/M^{-1} cm^{-1}) 231 (34700), 2.77 (4900), 282 (4790). δ_H ($CDCl_3$) 1.91 (1H, br d, *J* 11.5, $H15_{eq}$), 1.92 (3H, s, $COCH_3$), 2.76 (1H, app. td, *J* 13, 4, $H15_{ax}$), 2.90 (1H, dd, *J* 20.5, 6.5, $H10_{ax}$), 2.92 (1H, app. td, *J* 12, 3, $H16_{ax}$), 3.21 (1H, d, *J* 20.5, $H10_{eq}$), 3.57 (3H, s, H17), 3.80 (1H, br d, *J* 12, $H16_{eq}$), 3.91 (1H, app. p, *J* 2.5, H14), 5.29 (1H, br d, *J* 7, H5), 5.45–5.49 (3H, m, H6, H8, H9), 5.80 (1H, br app. dt, *J* 9.5, 3, H7), 6.66 (1H, d, *J* 8, H1), 6.94 (1H, d, *J* 8, H2), 7.21 (2H, app. t, *J* 7.5, H3′, H5′), 7.26 (2H, app. t, *J* 8, H3″, H5″), 7.40 (1H, t, *J* 7.5, H4′), 7.47 (1H, t, *J* 8, H4″), 7.76 (2H, d, *J* 8, H2″, H6″), 7.92 (2H, d, *J* 7.5, H2′, H6′). δ_C ($CDCl_3$) 23.9 (*C*H_3CO), 25.2 (C10), 30.8 (C15), 33.8 (C14), 41.2 (C13), 51.3 (C17), 58.3 (C16), 67.4 (C9), 67.5 (C6), 88.1 (C5), 119.8 (C1), 123.6 (C2), 127.7 (C8), 128.2 (C4), 128.4, 128.6 (C3′, C3″, C5′, C5″), 129.1 (C12), 129.6 (C1′, C1″), 129.8 (C7), 129.9 (C2″, C6″), 130.2 (C2′, C6′), 133.1 (C4″), 133.3 (C11), 133.5 (C4′), 149.8 (C3), 164.2 (CO′), 165.9 (CO″), 174.1 (NCO). *m*/*z* (+ESI, 30 V) 551 (100%, MH^+).

*(5α,6α)-7,8-Didehydro-4,5-epoxy-17(*R*)-acetimidemethylmorphinan-3,6-diol* ***18***

An aqueous solution of sodium hydroxide (1% w/v, 5 mL) was added dropwise over 5 min to a stirred solution of **17** (190 mg, 0.35 mmol) in methanol (5 mL). The reaction mixture was allowed to stir for a further 30 min at room temperature after which time TLC showed complete consumption of starting material. Removal of the solvent under vacuum and purification of the brown solid by flash chromatography (50:8:1, dichloromethane/ethanol/ammonia) afforded **18** (106 mg, 90%) as a colourless powder. Recrystallization from methanol gave the *title compound* **18** (93 mg, 78%) as colourless needles, mp 272–275°C (dec.) (Found: C 66.4, H 6.5, N 8.1. $C_{19}H_{22}N_2O_4$ requires C 66.7, H 6.5, N 8.2%). ν_{max} (KBr)/cm^{-1} 3550, 3406, 1641, 1563. λ_{max}/nm (ε/M^{-1} cm^{-1}) 245 (3890), 288 (1820). δ_H ([D_6]DMSO) 1.61 (1H, br d, *J* 11, $H15_{eq}$), 1.61 (3H, s, $COCH_3$), 2.48 (1H, app. td, *J* 13, 4, $H15_{ax}$), 2.77 (1H, dd, *J* 20.5, 7, $H10_{ax}$), 2.90 (1H, app. td, *J* 13, 3.5, $H16_{ax}$), 3.26 (1H, d, *J* 20.5, $H10_{eq}$), 3.45 (3H, s, H17), 3.60 (1H, app. p, *J* 2.5, H14), 3.85 (1H, br d, *J* 11.5, $H16_{eq}$), 4.10 (1H, br s, *J* 5.5, 3, H6), 4.78 (1H, br d, *J* 6, H5), 4.94–4.96 (1H, m, H9), 5.21 (1H, app. dt, *J* 10, 2.5, H8), 5.57 (1H, br d, *J* 9.5, H7), 6.50 (1H, d, *J* 8, H1), 6.52 (1H, d, *J* 8, H2). δ_C ([D_6]DMSO) 23.8 (*C*H_3CO), 23.8 (C10), 30.7 (C15), 33.5 (C14), 41.3 (C13), 50.1 (C17), 55.5 (C16), 66.0 (C9), 67.1 (C6), 90.5 (C5), 118.9 (C1), 117.0 (C2), 122.2 (C11), 126.5 (C8), 129.8 (C12), 135.1 (C7), 139.0 (C3), 146.0 (C4), 170.9 (CO). *m*/*z* (+ESI, 30 V) 343 (100%, MH^+).

(1S,2S)-1-Amino-1-methyl-2-(pyridin-3-yl)pyrrolidinium 2,4,6-Trimethylbenzenesulfonate ***19***

A solution of *O*-mesitylenesulfonylhydroxylamine[10] (1.88 g, 8.7 mmol) in dichloromethane (10 mL) was added over 10 min, with ice cooling, to a stirred solution of (*S*)-(−)-nicotine (**4**) (1.18 g, 7.3 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to stir for a further 10 min and the solvent removed under vacuum to afford a yellow oil, which was redissolved in ethanol. Diethyl ether was added to precipitate the crude product as a white powder (1.59 g, 58%), which was recrystallized from acetone to give the *title compound* **19** (1.36 g, 49%) as fine colourless needles, mp 183–185°C (lit.[8] 184–185°C). ν_{max} (KBr)/cm^{-1} 3256, 3142. δ_H ([D_6]DMSO) 2.13 (6H, s, 2 × $ArCH_3$), 2.16–2.23 (2H, m, H4), 2.32–2.42 (1H, m, H3a), 2.49 (3H, s, $ArCH_3$), 2.57–2.70 (1H, m, H3b), 3.14 (3H, s, CH_3N^+), 3.77–3.91 (2H, m, H5), 4.93 (1H, dd, *J* 11.5, 8, H2), 5.55 (2H, s, NH_2), 6.70 (2H, s, ArH), 7.55 (1H, dd, *J* 8, 5, H5′), 8.03 (1H, br d, *J* 8, H4′), 8.72 (1H, d, *J* 5, H6′), 8.75 (1H, d, *J* 2, H2′). δ_C ([D_6]DMSO) 19.0 (C4), 20.3 (2 × $ArCH_3$), 22.7 ($ArCH_3$), 26.1 (C3), 51.9 (CH_3N^+), 67.8 (C5), 76.6 (C2), 123.8 (C5′), 125.3 (C3′), 129.9 (C3″, C5″), 135.9 (C1″), 136.5 (C2″, C6″), 138.9 (C4′), 142.5 (C4″), 151.4 (C2′), 152.1 (C6′). *m*/*z* (+ESI, 30 V) 178 (60%, M^+).

Acetyl((1S,2S)-1-methyl-2-(pyridin-3-yl)pyrrolidinium-1-yl)amide ***20***

A solution of **19** (503 mg, 1.33 mmol) in acetic anhydride (30 mL) was heated at 120°C for 4 h. The solvent was removed under vacuum to afford a brown syrup, which was taken up in methanol and treated with Amberlite IRA-400(OH) ion-exchange resin. The resin was filtered off and the filtrate concentrated to afford a brown gum, which was purified by flash chromatography on neutral alumina (85:15, chloroform/methanol) to give the crude aminimide. Further purification using flash chromatography on neutral alumina (95/5, chloroform/methanol) afforded the *title compound* **20** (108 mg, 37%) as a yellow gum which rapidly discoloured in air (Found: MH^+ 220.1440. $C_{12}H_{17}N_3O$ requires MH^+ 220.1444). ν_{max} (KBr)/cm^{-1} 1572. λ_{max}/nm (ε/M^{-1} cm^{-1}) 255 (12000), 260

(2630), 266 (2880), 295 (2340). δ_H ($CDCl_3$) 1.67 (3H, s, CH_3CO), 1.87–2.02 (1H, m, H4a), 2.09–2.15 (1H, m, H4b), 2.19–2.28 (1H, m, H3a), 2.52–2.66 (1H, m, H3b), 3.09–3.24 (1H, m, H5a), 3.23 (3H, s, CH_3N^+), 4.07 (1H, dd, *J* 11, 7, H2), 5.13 (1H, ddd, *J* 11.5, 9, 3, H5b), 7.28 (1H, dd, *J* 8, 5, H5′), 8.12 (1H, app dt, *J* 8, 2, H4′), 8.56 (1H, dd, *J* 5, 2, H6′), 8.64 (1H, br d, *J* 2, H2′). δ_C ($CDCl_3$) 20.0 (C4), 23.9 (CH_3CO), 29.0 (C3), 48.2 (CH_3N^+), 62.3 (C5), 79.2 (C2), 123.1 (C5′), 128.2 (C3′), 139.9 (C4′), 151.1 (C6′), 152.2 (C2′), 174.1 (CO). *m/z* (+ESI, 30 V) 220 (100%, MH^+), 132 (20). Compound **20** was converted to the pale yellow dihydrochloride salt for microanalysis and testing by treatment with ethereal hydrogen chloride followed by evaporation to dryness (Found: C 46.5, H 6.7, N 13.5%. $C_{12}H_{17}N_3O{\cdot}2HCl{\cdot}H_2O$ requires C 46.5, H 6.8, N 13.6%).

Receptor Binding Assays

Receptor affinities were determined by MDS Panlabs, Taiwan, by the ability of the tested compounds to displace selective radioligands. All assayed compounds were dissolved in DMSO to a stock concentration of 10×10^{-3} M, then diluted with assay buffer to a final concentration of 10^{-6} M. The assays were carried out using the following: (i) for dopamine $D_{4.4}$; human recombinant (mammalian CHO-K_1 cells), [^{3}H]spiperone (0.3×10^{-9} M) as radioligand, and haloperidol (10×10^{-6} M) as reference compound for non-specific binding; (ii) for serotonin 5-HT_{2A}; rat brain, [^{3}H]ketanserin (0.5×10^{-9} M) as radioligand and ketanserin (10^{-6} M) as reference compound for non-specific binding; for μ opiate; human recombinant (mammalian CHO-K_1 cells), [^{3}H]diprenorphine (0.6×10^{-9} M) as radioligand and naloxone (10×10^{-6} M) as reference compound for non-specific binding; for κ opiate; human recombinant (mammalian CHO-K_1 cells), [^{3}H]diprenorphine (0.6×10^{-9} M) as radioligand and naloxone (10×10^{-6} M) as reference compound for non-specific binding; for opiate, non-selective; rat brain, [^{3}H]naloxone (10^{-9} M) as radioligand and naloxone (10^{-6} M) as reference compound for non-specific binding; for central nicotinic acetylcholine *α4β2*; rat brain, [^{3}H]cytosine (2×10^{-9} M) as radioligand and (*S*)-(−)-nicotine (10×10^{-6} M) as reference compound for non-specific binding. The binding results are expressed as the percentage inhibition (% I) of specific binding at a concentration of 10^{-6} M for the tested compound and represent the mean of duplicate tubes with a maximum standard error in the mean of ±5.

Accessory Publication

The Accessory Publication showing ^{1}H NMR spectra for **13** and **13a**, crystal data, bond angles, and bond lengths for **18** is available from the authors, or, until June 2013, the *Australian Journal of Chemistry*.

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