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Synthesis and biological evaluation of bicyclic and tricyclic substituted nortropane derivatives: discovery of a novel selective α_{1D}-adrenergic receptor ligand

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Abstract—A range of 3,6,6-trisubstituted nortropane derivatives based upon 6β-phenyltropane-3β,6α-diol have been synthesised from 6β-hydroxytropinone, including some novel related tricyclic hemi-ketal and tricyclic ketal compounds. Derivatives were assessed for pharmacological affinity and selectivity at α_1-adrenergic receptors, and 6β-phenyl-8-azabicyclo[3.2.1]octan-3-spiro-2′-(1′,3′-dioxolane)-6-ol, a novel lead compound selective for the alpha$_{1D}$-adrenergic receptor, is reported.

1. Introduction

As part of an ongoing programme, we have been pursuing the development of structurally novel and pharmacologically selective alpha$_1$ (α_1)-adrenergic receptor (AR) ligands,[1,2] specifically for the α_{1B}-AR, for therapeutic use in cardiovascular disease,[3] and the α_{1D}-AR, for which there are few selective ligands.[3c,4a] With this purpose in mind, a design model was constructed incorporating a constrained folded conformation of the adrenaline motif, and containing structural features based upon the phenethylamine class of adrenergic receptor ligands. As shown in Figure 1a, this design motif consisted of an aromatic hydrophobic bonding region (A), a hydrogen bond acceptor/hydrogen bond donor region (B), a carbon spacer (C) and a basic amine (to form a H-bond reinforced salt-bridge when protonated) (D). The rationale for the incorporation of a folded conformation of the adrenaline motif was based upon preliminary qualitative pharmacophore work we have undertaken, and the possibility that the flexible side chain of adrenaline has a folded bioactive conformation. Whilst conformationally constrained analogues of adrenaline and noradrenaline have been studied[4b] in the past (for example those in Fig. 1b), we were interested in greater structural variety.

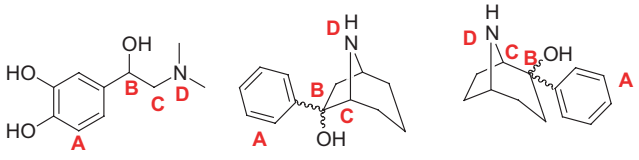

Figure 1a. Presence of the adrenaline motif in bicyclic tropane derivatives, consisting of an aromatic hydrophobic bonding region (A), a hydrogen bond acceptors/hydrogen bond donor region (B), a carbon spacer (C) and a basic amine (to form a H-bond reinforced salt-bridge when protonated) (D).

Our laboratory has an interest in the chemistry and pharmacology of the tropane family of alkaloids.[5–8] In the development of α_1-adrenergic ligands with a constrained folded conformation, and containing an ionisable nitrogen atom, bicyclic derivatives with a tropane framework provide a novel alternative. An important

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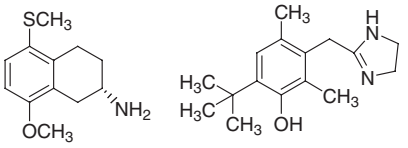


SKF-89748 Oxymetazoline

Figure 1b. SKF-89748 and oxymetazoline: conformationally constrained analogues of adrenaline.

structural feature of tropanes is that of rigidity. Whilst the six-membered ring portion of the molecule may interconvert between chair and boat forms, the fixed conformation of the five-membered pyrrolidine ring provides a rigid framework. This feature renders bicyclic bridged derivatives such as tropanes useful scaffolds when a fixed chemical geometry is desired. This was certainly appealing in the present work with respect to mimicking a fixed conformation of the adrenaline motif. The tropane framework therefore provides a similar geometry to that of a folded conformation of adrenaline (Fig. 1a), with the additional feature of being held in a relatively rigid heterocycle.

Incorporation of the adrenaline motif into bicyclic tropane-based ligands may be achieved by substitution at the 6- and 2-positions of the skeleton (Fig. 1a). Examination of the literature reveals that nortropane based compounds similar to **1** (Fig. 2) have been investigated previously for pharmacological activity: *6β-aryltropan-6-ols* based on **4** were explored some twenty years ago as low potency morphine-like analgesics[9] and later as low potency opiate agonists/antagonists[10] such as **4a**. Further 6-phenyl-8-azabicyclo[3.2.1]octanes and octenes based on **4** have been prepared and they display potential antidepressant, analgesic and unspecified cardiovascular activity.[11] There was no evidence for 2-aryltropan-2-ol derivatives such as **4b** having previously been developed.

Whilst 2-arylhydroxytropane derivatives fit the desired adrenaline motif, their synthetic production would be via a lengthy route from cocaine derivatives. It was therefore decided to undertake the synthesis of the 6-arylhydroxytropane derivatives first and ascertain their pharmacological activity. Target ligands included the novel 3,6,6-trisubstituted nortropane derivatives **1**–**3** (Fig. 2), with incorporation of both phenyl and catechol substituents. The catechol moiety is an important feature in the adrenergic receptor–ligand interaction, and derivative **2** would be a particularly interesting compound for α_1-adrenergic receptor pharmacological investigations.

2. Results and discussion

2.1. Synthesis of 3,6,6-trisubstituted nortropane derivatives

The 3,6,6-trisubstituted nortropanes **1**–**3** may be obtained straightforwardly via a route from commercially available 6*β*-hydroxytropinone (Scheme 1). The synthesis therefore began with the protection of the hindered 6*β*-hydroxyl group of 6*β*-hydroxytropinone as its *tert*-butyldimethylsilyl ether **5** in good yield (Scheme 1). 2,2,2-Trichloroethylchloroformate is a favoured reagent for tropinone *N*-demethylation, producing the trichloroethyl carbamate from tropinone in a high yield (95%).[12] The conditions of carbamate cleavage to furnish the nortropane (zinc/acetic acid) are moderate (62% yield), and sufficiently mild to leave the aryl hydroxyl moiety of the target derivatives intact.[12] Treatment of **5** with 2,2,2-trichloroethylchloroformate[12] afforded **6**, in good yield. In an attempt to reduce the lengthy reaction time, carbamate formation was investigated under novel microwave reaction conditions,[13,14] rapidly furnishing **6** in a reasonable yield.

Two different ketal functionalities were then investigated for protection of the ketone functionality in **6**, the cyclic 1,3-dioxolane and the dimethyl ketal. Initially, **6** was treated with ethanediol and chlorotrimethylsilane[15] to furnish the 1,3-dioxolane derivative **7** in good yield (Scheme 2). The *tert*-butyldimethylsilyl protecting group was removed by treating **7** with tetrabutylammonium fluoride to yield **8** in moderate yield. In order to reduce the reaction time when synthesising **7**, the ketalisation of **6** was again investigated using microwave conditions and this afforded, somewhat surprisingly, compound **8** directly and rapidly, rather than **7**. This is a potential alternative method for desilylation of TBDMS ethers, and for selective ketone protection and alcohol depro-

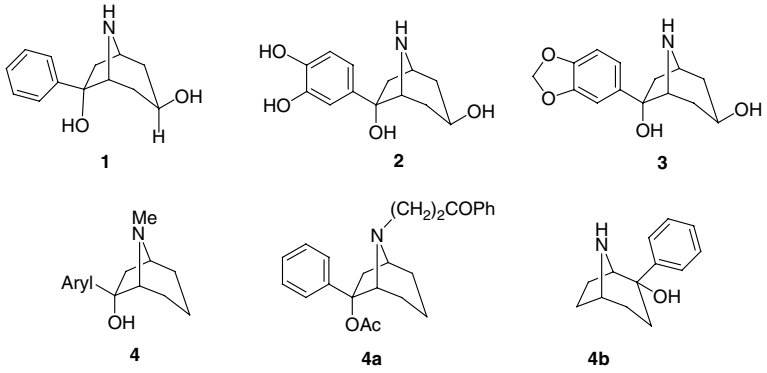
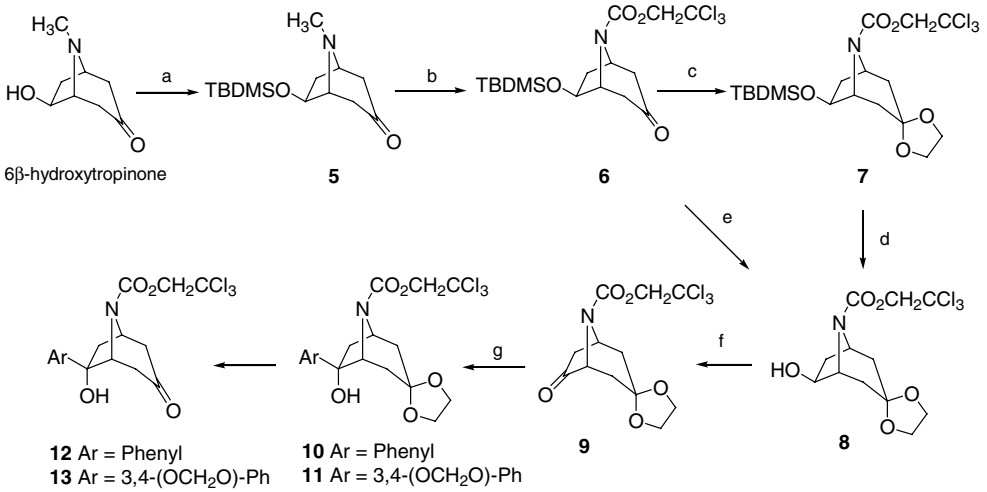
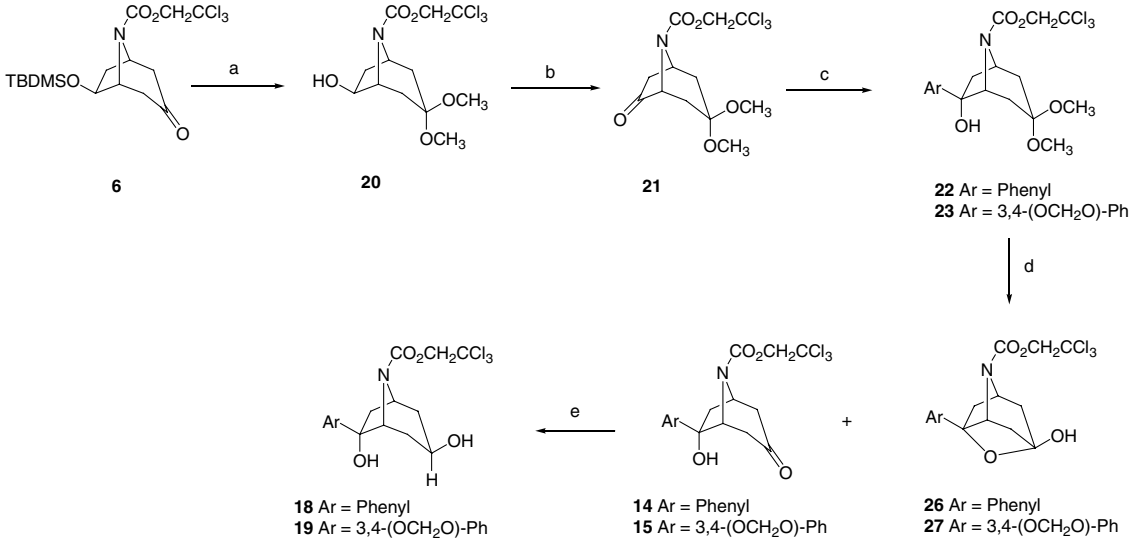


Figure 2. 3,6,6-Trisubstituted tropane target derivatives (**1**–**3**); published 2- and 6-arylhyroxy*nor*tropane derivatives (**4**, **4a**, **4b**).



Scheme 1. Reagents and conditions: (a) 2,6-lutidine, *tert*-butyldimethylsilyltrifluoromethanesulfonate, DCM, O°C-rt, N2, 3 h, 86% yield; (b) 2,2,2-trichloroethylchloroformate, K_2CO_3 (anhydrous), benzene (anhydrous), reflux, N_2, 4 h, 85% yield; (c) ethanediol, chlorotrimethylsilane, DCM, reflux, 48 h, 86% yield; (d) TBAF, THF, 69% yield; (e) ethanediol, acetonitrile, chlorotrimethylsilane, 80 °C, microwave, 25 min, 83% yield; (f) H_3PO_4, DMSO, rt, 3 h, 78% yield; (g) ArMgBr, THF/ether, rt, 3 h, 75–77% yield.



Scheme 2. Reagents and conditions: (a) trimethylorthoformate, *p*-TsOH (cat), MeOH, rt, O/N, 80% yield; (b) H_3PO_4, DMSO, rt, 3 h, 78% yield; (c) ArMgBr, THF or ether, rt, 3 h, 77–78% yield; (d) 1:2 aq TFA–$CHCl_3$, rt, 0.5–4 h, 24–98% yield; (e) $CeCl_3{\cdot}H_2O$/MeOH, $NaBH_4$, rt, 0.5–4 h, 84–100% yield.

tection in these systems. With an efficient route to the cyclic ketal derivative **8** in hand, the secondary hydroxyl group was oxidised via Pfitzner and Moffatt conditions[16] to provide the ketone derivative **9** in good yield. Arylation of **9** with phenylmagnesium bromide and 3,4-methylenedioxyphenylmagnesium bromide afforded the 6-arylhydroxy derivatives **10** and **11** respectively, in good yield.

In order to determine the stereochemistry of the aryl ring at the 6-position, molecular modelling data for **9** (using conformational searching and geometry optimisation at the molecular mechanics level in the SPARTAN® program[17]) was investigated. The lowest energy conformer of **9** was that shown in Figure 3 (left), with the cyclic ketal ring positioned in part below the bicyclic tropane ring. This conformation blocks the concave face of the tropane ring, indicating that the large phenyl Grignard reagent would attack solely from the top face of the tropane skeleton, leading to formation of only the 6*β*-aryl isomers (**10** and **11**). In confirmation of this, NOESY 1D ^{1}H NMR experiments on **10** revealed the hydroxyl proton to have a NOE interaction with the H5, H4 and H2 protons (see Supplementary material), whereas the aromatic *ortho*-protons displayed NOE interactions with only the H5 and H7 protons. This clearly indicated that the phenyl ring functionality was *exo* to the tropane skeleton and the hydroxyl group was *endo*. The same orientation would be expected for **11**.

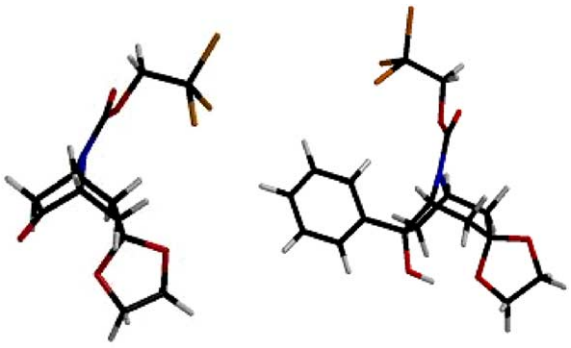


Figure 3. Computer-based (SPARTAN) molecular models of the lowest energy conformations of **9** (left) and **10** (right), indicating the favoured *exo*-aryl functionality in **10**.

With derivatives **10** and **11** synthesised, six target and intermediate compounds, for structure-pharmacological activity relationship assessment were accessible, namely **1**, **3**, **12**, **13**, **16** and **17** (Fig. 4). Direct hydrolysis of the carbamate protecting group in derivatives **10** and **11** would yield derivatives **12** and **13**. Removal of the cyclic ketal from **10** and **11** would provide ligands **14** and **15**, which may be either hydrolysed to afford ligands **16** and **17**, or reduced to afford the β-hydroxylic derivatives **18** and **19**, which in turn could be converted to target derivatives **1** and **3**, and the methylenedioxy functionality could be unmasked to reveal the catechol **2**. A mild, neutral and high-yielding method for the transformation of cyclic ketals to their parent ketones is the use of cerium trichloride heptahydrate and sodium iodide under refluxing conditions.[18] However, extensive treatment of **10** under such conditions failed to yield any of the desired ketone **14**. With few suitably mild and neutral methods for cyclic ketal removal available, an alternative acyclic, dimethyl ketal protecting group was investigated. Compound **6** was therefore treated with trimethylorthoformate and *p*-toluenesulfonic acid,[19] resulting in ketal formation as well as silyl ether cleavage to afford **20** in good yield (Scheme 2). Oxidation of the secondary 6-hydroxyl group of **20** under Pfitzner and Moffatt[16] conditions provided ketone **21** in reasonable yield. The ketone derivative **21** was then treated with phenylmagnesium bromide and 3,4-methylenedioxyphenylmagnesium bromide to afford **22** and **23**, respectively, in good yields. As with the dioxolane derivative **9**, assessment of the lowest energy conformer of the dimethyl ketal derivative **21** suggested that Grignard reagent attack on the ketone would occur preferentially from the *exo*-face (data not shown). Target ligands **1**, **2** and **3** were then potentially accessible from **22** or **23**.

In an attempt to remove the dimethyl ketal protecting group, **22** was treated with 50% aqueous TFA in chloroform,[20] producing a nonseparable mixture of the ketone **14** (minor isomer) and its cyclic hemi-ketal **26** (major isomer) (Scheme 2) as assigned by ^{13}C NMR spectroscopy (a weak signal at δ 203.1 was ascribed to the C3 carbonyl of **16**, and a signal at δ 103.6 to the C3 carbon in the cyclic hemi-ketal **26**). Treatment of the methylenedioxyphenyl derivative **23** with TFA–chloroform produced two separable isomers, ketone derivative **15** (the signal ascribed to the C3 carbonyl appeared in the ^{13}C NMR at δ 204.2) and cyclic hemiketal derivative **27** (on the basis of the signal for the C3 carbon at δ103.6). The ring system embodied in the new cyclic hemi-ketal is that of the tropane alkaloid deoxynorscopoline. The related 7-hydroxylated deoxyscopoline compound, oscine (scopoline), is a direct product of the hydrolysis of scopolamine.[21] The synthesis of both deoxynorscopoline and oscine have been investigated from nonalkaloid sources.[22]

Unreported preliminary qualitative adrenergic ligand pharmacophore work we have undertaken upon 3,6,6-trisubstituted aryl tropane derivatives (such as **1**–**3**) suggested that the stereochemistry of the 3-hydroxyl substitutent may be important; in particular the *β*-stereochemistry may impart greater activity at the alpha$_1$-adrenergic receptors than the α-stereochemistry. We therefore proceeded with the preparation of *β*-

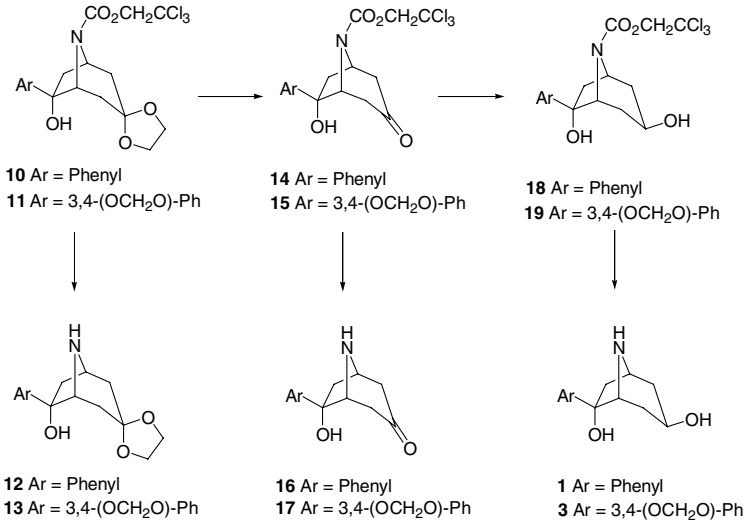


Figure 4. Route to target derivatives from **10** and **11**.

hydroxylic derivatives, via the selective reduction of ketones **14** and **15** (and their hemi-ketal derivatives). Reduction of the ketone/hemi-ketal mixture **14/26** with cerium chloride heptahydrate and sodium borohydride in methanol afforded the β-hydroxy derivative **18**[23–25] (Scheme 2). Compound **15** was also treated with cerium chloride heptahydrate and sodium borohydride in methanol to selectively afford the β-hydroxy derivative **19** (Scheme 2). The axial H3 proton of **19** was represented by two very close but separate peaks: one at δ 3.94 (0.75H integration) and the other at δ 4.07 (0.25H integration), indicative of either carbamate rotamers or slow conformational interchange in this case. The latter was supported by the NOESY 1D NMR, which indicated that the peak at δ 3.94 displayed interactions with H2, H4, $H7_{ax}$ and the tertiary hydroxyl proton, while the H3 peak at δ 4.07 displayed interactions with only $H2_{ax/eq}$ and $H4_{ax/eq}$. This indicated that the tropane was partially existing in the boat conformation, as a result of H-bonding between the 3-hydroxyl and the carbamate carbonyl group (H3 in this conformation would then be equatorially disposed, and would be too far from the 6-hydroxy and $H7_{ax}$ to have a NOE interaction). The equatorial conformation of H3 is reflected in the H2/H4 equatorial–axial coupling constant of 5.4Hz, whilst the equatorial–equatorial coupling constant was too small to be seen.

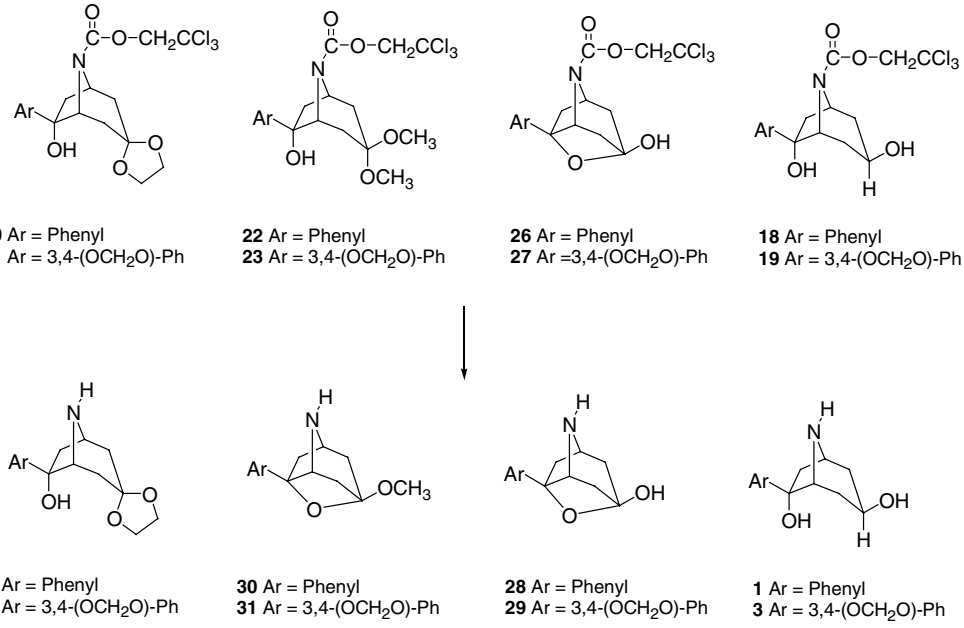
Removal of the carbamate protecting groups of derivatives **10**, **11**, **22**, **23**, **26**, **27**, **18** and **19** utilising zinc in acetic acid[12] afforded the nortropane derivatives **1**, **3**, **12**, **13**, **28**, **29**, **30** and **31**, in moderate to quantitative yields (Scheme 3). Treatment of the dimethyl ketal derivatives **22** and **23** with zinc in acetic acid led not only to removal of the carbamate moiety, but also to the loss of one of the methoxy substituents, resulting in the hemi-ketal derivatives **30** and **31**. Although the unmasking of the methylendioxy functionality was desired to provide the catechol adrenaline mimic, difficulties with the deprotection of the methylenedioxy group hindered the preparation of compound **2** and its derivatives. The synthesis of these catechol derivatives via an alternate method is currently being addressed.

2.2. Evaluation of 3,6,6-trisubstituted derivatives at alpha$_1$-adrenergic receptors

Compounds **1**, **3**, **12**, **13**, **28**, **29**, **30** and **31** (as the hydrochloride salts) were assessed for ligand binding characteristics upon membrane-expressed α_{1A}-, α_{1B}- and α_{1D}-ARs in a series of radioligand binding studies using [^{125}I]-HEAT. Affinity data (IC_{50}, μm) is given in Table 1. Whilst the ligands exhibited poor binding affinity ($IC_{50} > 300\,\mu M$) on both the α_{1A}-AR and α_{1B}-AR, compounds **1**, **12**, **29** and **30** did exhibit some selectivity for the α_{1D}-AR. Of these compounds, **12** exhibited the highest affinity (3.8 μM) and selectivity (> 25-fold) for the α_{1D}-AR, however it displayed only 5.8% of the affinity of the endogenous ligand, adrenaline, for the α_{1D}-AR. Although the affinity of compound **12** for the α_{1D}-AR does not compare to other reported ligands, which display nanomolar affinities,[26,27] it does provide promising selectivity. The bicyclic tropane skeleton is worth pursuing in the search for a new class of α_{1D}-selective adrenergic receptor ligands.

3. Conclusions

Aryl nortropane derivatives **1**, **2** and **3** were designed as conformationally restricted folded mimics of the endogenous adrenergic receptor ligand adrenaline. A range of 3,6,6-trisubstituted tropane derivatives, based upon 6β-phenyltropane-3β,6α-diol (**1**), including some novel related tricyclic hemi-ketal and tricyclic ketal compounds, have been synthesised utilising stereocontrolled



Scheme 3. Reagents and conditions: zinc, acetic acid, 24 h, 40 °C, 30–85% yield.

Table 1. Receptor binding affinity of adrenaline and *nor*tropane ligands

Ligand	α_{1A}-AR				α_{1B}-AR		α_{1D}-AR			
	n	$-\text{Log IC}_{50} \pm \text{SE}$	IC_{50} (μM)[a]	Δ[b]	Relative affinity (%)[c]	$-\text{Log IC}_{50} \pm \text{SE}$	IC_{50} (μM)	$-\text{Log IC}_{50} \pm \text{SE}$	IC_{50} (μM)	Δ[b]	Relative affinity (%)[c]
Adrenaline	6	5.39 ± 0.13	4.1			5.37 ± 0.14	4.2	6.44 ± 0.24	0.37		
12	3	—	> 100			—	§	5.43 ± 0.20	3.8	1.23 ± 0.27	5.83
13	3	—	> 100			—	§	—	> 100		
30	3	—	> 300			—	> 300	4.55 ± 0.34	28.4	1.56 ± 0.92	2.78
31	3	—	> 300			—	> 300	—	> 100		
28	3	3.36 ± 0.15	439	1.78 ± 0.17	1.66	—	> 300	—	> 100		
29	3	—	> 300			—	> 300	4.66 ± 0.20	22.1	1.45 ± 0.77	3.58
1	3	3.88 ± 0.03	131	1.25 ± 0.04	5.58	—	> 100	4.54 ± 0.27	29.1	1.57 ± 0.84	2.71
3	3	—	> 300			—	> 300	—	> 100		

$-\text{Log IC}_{50}/\Delta$ values are expressed as mean±SE.
n represents the number of experiments performed.
§ No binding at concentrations up to 100 μM.
[a] IC_{50}, concentration of ligand resulting in 50% inhibition of ^{125}I-HEAT binding.
[b] Mean log concentration ratio ± SE ($-\log \text{IC}_{50}$ adrenaline minus $-\log \text{IC}_{50}$ ligand).
[c] Relative affinity of ligand as % adrenaline (antilog Δ × 100%).

syntheses. Novel microwave reactions aided in the optimisation of the synthesis. The compound 6*β*-phenyl-8-azabicyclo[3.2.1]octan-3-spiro-2′-(1′, 3′-dioxolane)-6-ol (**12**) exhibited > 25-fold selectivity for the α_{1D}-AR. Given the lack of selective α_{1D}-AR ligands available, compound **12** and the tropane class of compounds provides a new lead for the development of selective α_{1D}-AR ligands.

4. Experimental

4.1. General chemistry methods

Microwave reactions were performed in a Milestone Ethos Sel Microwave Solvent Extractor, employing Easywave software, and using internal reaction temperature control. Sealed Teflon reaction vessels were used, and were washed with concentrated nitric acid between uses. Melting point determinations were carried out on a Griffin melting point apparatus. Low resolution chemical ionisation (isobutane, CI^+) mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer by a direct insertion technique with an electron beam of 70 eV. High-resolution mass spectra (HRMS) (methane, CI^+ and EI^+) were determined on a VG Autospec spectrometer using PFK (perfluorokerosene) as the internal standard. The *m*/*z* values are stated with their peak intensities as a percentage in parentheses. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity 300 MHz or a Varian Mercury 300 MHz spectrometer. Spectra were recorded in deuterated chloroform, unless otherwise specified, and referenced to the residual nondeuterated solvent signal. Chemical shifts (δ) in ppm were measured relative to the internal standard. Analytical thin layer chromatography (TLC) was carried out on Merck Silica gel 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. Chromatography refers to column chromatography, performed under 'flash' conditions on Merck Silica gel 60 (230–400 mesh). Chromatography solvent mixtures were measured by volume, and are reported in parentheses. The R_f values given refer to the determination of a sample on TLC in the same solvent as noted for the chromatography. All compounds were of greater than 95% purity based on ^{1}H NMR and TLC analysis. Organic extracts were dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure (in vacuo) with a Büchi rotary evaporator. Anhydrous solvents were purified and dried according to Perrin and Armarego[28] and distilled immediately before use. Other solvents used were AR grade, and were used as received, with the exception of dichloromethane (DCM) and hexane, which were LR grade and were distilled before use. Starting materials and reagents were purchased from Sigma Aldrich Pty Ltd and were used as received.

4.2. Synthesis

4.2.1. 6β-*O*-*tert*-Butyldimethylsilyl-8-methyl-8-azabicyclo[3.2.1]octan-3-one (5). 6β-Hydroxytropan-3-one (0.554 g, 3.57 mmol) was dissolved in anhydrous DCM

(20 mL) and cooled to 0 °C under nitrogen with stirring. The base 2,6-lutidine (0.833 mL, 7.14 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (1.23 mL, 5.35 mmol) were then added dropwise consecutively via syringe, and stirring was continued for 3 h as the solution was allowed to warm to room temperature. The reaction was quenched by the addition of water (40 mL) and saturated aqueous sodium hydrogen carbonate (10 mL). Extraction with DCM (100 mL), drying and concentration in vacuo yielded a yellow liquid. Chromatography (ethyl acetate; R_f 0.31) provided the ketone **5** ($C_{14}H_{27}NO_2Si$) as a pale yellow oil (0.83 g, 86% yield). ^{1}H NMR (δ): 0.04 (6H, s, $(CH_3)_3Si$); 0.87 (9H, s, $(CH_3)_3$); 2.01–2.06 m (2H, m, H2e, H4e); 2.13 (2H, dd, H2a, H4a, $J_{H2a,2\ e} = J_{H4a,4e} = 15.9$); 2.63 (3H, s, *N*-$CH_3$); 2.57–2.65 (2H, m, H7, H7′); 3.28 (1H, d, H1, $J = 4.8$); 3.55 (1H, ddd, H5, $J_{H5,4e} = 1.5$, $J_{H5,6} = 4.2$,$J_{H5,4a} = 6.0$); 4.08 (1H, dd, H6, $J_{H6,7e} = 3.6$, $J_{H6,5} = 6.9$). ^{13}C NMR (δ): −4.7 ($(CH_3)_2Si$); 18.1 ($(CH_3)_3CSi$); 25.9 ($(CH_3)_3$); 38.2 (N–CH_3); 41.3 (CH_2, C4); 44.4 (CH_2, C2); 46.3 (CH_2, C7); 60.8 (CH, C1); 69.4 (CH, C5); 79.6 (CH, C6); 208.4 (C=O, C3). MS (CI^+): *m*/*z* 270 (M + 1, 100%); 256 (39%); 224 (26%). HRMS (CI^+): Found: 270.1903; Required: 270.1889 for $C_{14}H_{28}NO_2Si$.

4.2.2. 6-*exo*-*O*-*tert*-Butyldimethylsilyl-8-(2,2,2-trichloroethoxycarbonyl)-8-azabicyclo[3.2.1]octan-3-one (6). The base **5** (1.33 g, 4.94 mmol), 2,2,2-trichloroethyl chloroformate (0.748 mL, 5.43 mmol) and anhydrous potassium carbonate (0.683 g, 4.94 mmol) were heated at reflux in anhydrous benzene under nitrogen for 4 days. The benzene was then azeotroped with methanol, and the crude reaction mixture taken up in ethyl acetate (100 mL) and water (100 mL) and separated. The aqueous fraction was extracted with ethyl acetate (3 × 100 mL) and combined organic extracts were washed with sodium chloride (satd) (100 mL), water (100 mL), dried and concentrated in vacuo to yield a brown oil which crystallised upon standing. Chromatography (1:4 ethyl acetate–hexane; R_f 0.46) provided **6** ($C_{16}H_{26}NO_4SiCl_3$) as a white solid (1.80 g, 85% yield). Mp: 68–70 °C. ^{1}H NMR (δ): 0.05 (6H, s, $(CH_3)_2Si$); 0.86 (9H, s, $(CH_3)_3$); 2.04–2.13 (2H, m, H2e, H4e); 2.40 (2H, dd, H2a, H4a, $J_{H2a,2\ e} = J_{H4a,4e} = 16.2$); 2.65–2.74 (2H, m, H7a, H7e); 4.18 (1H, dd, H1, $J_{H1,2a} = 12.6$, $J_{H1,2\ e} = 5.4$); 4.39 (1H, dd, H5, $J_{H5,4e} = 5.7$, $J_{H5,4a} = 6.9$); 4.67–4.77 (2H, m, CH_2); 4.92 (1H, dd, H6, $J = 11.7$, 14.1). ^{13}C NMR (δ): −4.7 ($(CH_3)_2Si$); 18.1 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3$); 41.4 (42.0*) (CH_2, C4); 45.5 (46.0*) (CH_2, C2); 48.5 (48.9*) (CH_2, C7); 53.0 (53.2*) (CH, C1); 62.5 (62.5*) (CH, C5); 74.7 (75.4*) (CH_2CCl_3); 74.8 (75.4*) (CH, C6); 95.8 (CCl_3); 152.0 (NC=O); 206.0 (C=O, C3). MS (CI^+): *m*/*z* 430, 432, 434 (MH^+); 396/398 ($MH^+ - Cl$); 372, 374, 376; 298, 300, 302; 282. HRMS (CI^+): Found: 430.0747; Required: 430.0775 for $C_{16}H_{26}NO_4Si^{35}Cl_3$.

Microwave Method: To **5** (0.83 g, 3.08 mmol) in anhydrous acetonitrile (15 mL) under argon was added 2,2,2-trichloroethyl chloroformate (0.467 mL, 3.39 mmol) and anhydrous potassium carbonate (0.426 g, 3.08 mmol). The reaction mixture was exposed to microwave radiation for 2 min warming to 100 °C, followed by 18 min at 100 °C. The reaction mixture was allowed to cool, then taken up in ethyl acetate (50 mL) and water (50 mL) and separated. The aqueous fraction was extracted with ethyl acetate (3 × 50 mL) and combined organic extracts were washed with sodium chloride (satd) (50 mL), water (50 mL) dried and concentrated in vacuo to yield a brown oil. Chromatography (1:4 ethyl acetate–hexane; R_f 0.46) provided **6** ($C_{16}H_{26}NO_4SiCl_3$) as a white solid (0.796 g, 60% yield). All spectral and melting point data agreed with that previously determined for **6**.

4.2.3. 6β-*O*-*tert*-Butyldimethylsilyl-8-(2,2,2-Trichloroethoxycarbonyl)-8-azabicyclo[3.2.1]-3-spiro-2′-(1′,3′-dioxolane)-octane (7). To a stirred solution of ethanediol (0.27 mL, 4.91 mmol) and anhydrous DCM (15 mL) under nitrogen was added 16 (0.96 g, 2.23 mmol). To this mixture was added chlorotrimethylsilane (1.25 mL, 9.82 mmol) and the mixture was heated at reflux for 72 h. A 5% aqueous solution of sodium hydrogen carbonate (20 mL) was added and the mixture extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with sodium chloride (satd) (100 mL), water (100 mL), dried and concentrated in vacuo to yield a pale yellow oil. Chromatography (1:6 ethyl acetate–hexane; R_f 0.69) provided 17 ($C_{18}H_{30}NO_5SiCl_3$) as a pale yellow oil (0.90 g, 86% yield). ^{1}H NMR (δ): 0.06 (6H, s, $(CH_3)_3Si$); 0.86 (9H, s, $(CH_3)_3$); 1.67–1.90 (2H, m, H2e, H4e); 1.97–2.30 (1H, m, H2a(H4a)); 2.26–2.42 (1H, m, H4a(H2a)); 2.46–2.75 (2H, m, H7a, H7e); 3.83 (1H, t, OCH, $J = 6.3$); 3.91–3.99 (1H, m, OCH); 4.09–4.21 (2H, m, OCH_2); 4.39 (1H, t, H1, $J = 5.7$, 7.2); 4.47–4.59 (1H, m, H5); 4.62–4.74 (2H, m, CH_2); 4.82–4.98 (1H, m, H6). ^{13}C NMR (δ): 4.7 ($(CH_3)_2Si$); 10.1 ($(CH_3)_3CSi$); 25.8 ($(CH_3)_3$); 39.5 (40.1*) (CH_2, C4); 45.5 (46.0*) (CH_2, C2); 48.5 (48.9*) (CH_2, C7); 53.0 (53.5*) (CH, C1); 62.5 (62.6*) (CH, C5); 63.5 (OCH_2); 64.5 (OCH_2); 74.0 (74.7*) (CH, C6); 74.8 (75.4*) (CH_2CCl_3); 95.8 (CCl_3); 106.7 (C3); 151.7 (152.0*) (NC=O). MS (CI^+): *m*/*z* 474, 476, 478 (MH^+); 416, 418, 420; 342, 344, 346; 327; 300; 177. HRMS (CI^+): Found: 474.1037; Required: 474.0952 for $C_{18}H_{31}NO_5Si^{35}Cl_3$.

4.2.4. 8-(2,2,2-Trichloroethoxycarbonyl)-8-azabicyclo-[3.2.1]octan-3-spiro-2′-(1′,3′-dioxolane)-6β-ol (8). To a stirred solution of **7** (0.13 g, 0.274 mmol) in anhydrous THF (5 mL) under nitrogen at 0 °C was added tetrabutylammonium fluoride (1 M in THF). The reaction was stirred at room temperature for 3 h, excess ammonium chloride was added and the mixture stirred for 10 min. The mixture was filtered and the THF was removed in vacuo. The residue was extracted with ethyl acetate (50 mL), washed with water (3 × 50 mL), dried and concentrated in vacuo to yield a yellow oil. Chromatography (1:1 ethyl acetate–hexane; R_f 0.30) provided **8** ($C_{12}H_{16}NO_5Cl_3$) as a colourless oil (0.068 g, 69% yield). ^{1}H NMR (δ): 1.73–2.15 (2H, m, H2e, H4e); 2.32–2.56 (2H, m, H2a, H4a); 2.67–2.76 (2H, m, H7a, H7e); 3.82 (2H, dd, OCH_2, $J = 6.0$, 6.0); 3.96 (2H, dd, OCH_2, $J = 6.3$, 6.3); 4.17–4.26 (1H, m, H1); 4.48 (1H, d, H5, $J_{5,6} = 6.3$); 4.55–4.70 (2H, m, CH_2); 4.88–5.02 (1H, m,

H6). ^{13}C NMR (δ): 38.4 (40.9*) (CH_2, C4); 45.0 (45.5*) (CH_2, C2); 48.3 (48.9*) (CH_2, C7); 52.9 (53.6*) (CH, C1); 62.2 (62.5*) (CH, C5); 63.5 (OCH_2); 64.5 (OCH_2); 73.5 (74.3*) (CH, C6); 74.6 (74.7*) (CH_2CCl_3); 95.8 (CCl_3); 106.5 (C3); 152.2 (NC=O). MS (CI^+): *m/z* 360, 362, 364 (MH^+); 316, 318, 320 ($MH^+ - CH_2CH_2O$); 298, 300, 302 ($MH^+ - H_2O$); 282, 284 ($MH^+ - Cl$). HRMS (CI^+): Found: 360.0153; Required: 360.0173 for $C_{12}H_{17}NO_5Si^{35}Cl_3$.

Microwave method: To a solution of **6** (0.680 g, 1.578 mmol) in anhydrous acetonitrile (10 mL) under an argon stream was added ethanediol (0.194 mL, 3.472 mmol) followed by chlorotrimethylsilane (0.878 mL, 6.944 mmol). The reaction mixture was exposed to microwave radiation: warming to 80 °C for 2 min, followed by heating at 80 °C for 23 min. The reaction mixture was allowed to cool, then diluted with 5% aqueous sodium hydrogen carbonate (20 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic fractions were washed with water (2 × 50 mL), dried (sodium sulfate) and concentrated *in vacuo* to yield a yellow oil. Chromatography (1:1 ethyl acetate–hexane; R_f 0.43) yielded **8** ($C_{12}H_{16}NO_5Cl_3$) as a colourless oil (0.470 g, 83% yield). All spectral data agreed with that previously determined for **8**.

4.2.5. 8-(2,2,2-Trichloroethoxycarbonyl)-8-azabicyclo-[3.2.1]octan-3-spiro-2′-(1′,3′-dioxolane)-6-one (9). The alcohol **8** (0.46 g, 1.28 mmol) was dissolved in a stirred solution of anhydrous dimethylsulfoxide (5 mL) and dicyclohexylcarbodiimide (0.79 g, 3.83 mmol). Phosphoric acid (anhydrous) (0.063 g, 0.64 mmol) in anhydrous dimethylsulfoxide (1 mL) was added dropwise and the mixture stirred at room temperature for 3 h. Ethyl acetate (30 mL) was added, followed by a solution of oxalic acid (0.25 g) in methanol (10 mL) and stirring continued for 30 min. The precipitated dicyclohexylurea was removed by filtration, washed with ethyl acetate (100 mL) and the solution was extracted with aqueous sodium hydrogen carbonate (satd) (50 mL), water (50 mL), dried and concentrated *in vacuo* to yield an off-white semi-solid. Chromatography (1:3 ethyl acetate:hexane; R_f 0.40) provided **9** ($C_{12}H_{14}NO_5Cl_3$) as a white solid (0.324 g, 71% yield). Mp: 87–90 °C. ^{1}H NMR (δ): 1.90 (1H, d, H7e, $J_{7e,7a}$ = 13.5); 2.22–2.42 (2H, m, H2e, H4e); 2.51–2.69 (2H, m, H2a, H4a); 2.89 (1H, m, H7a); 3.88–3.91 (2H, m, OCH_2); 3.92–3.97 (2H, m, OCH_2); 4.60 (1H, d, H1, $J_{1,2e}$ = 2.1); 4.66–4.91 (2H, m, CH_2); 5.03 (1H, br d, H5, $J_{5,6}$ = 6.0). ^{13}C NMR (δ): 38.9 (39.4*) (CH_2, C7); 40.1 (CH_2, C4); 42.3 (42.9*) (CH_2, C2); 51.4 (CH, C1); 59.7 (60.0*) (CH, C5); 64.1 (OCH_2); 64.7 (OCH_2); 74.7 (74.9*) (CH_2CCl_3); 95.8 (CCl_3); 105.9 (C3); 151.8 (NC=O); 202.9 (C=O, C6). MS (CI^+): *m/z* 360, 362, 364 (MH^+); 342, 344, 346 ($MH^+ - H_2O$); 316, 318, 320; 298, 300, 302. HRMS (CI^+): Found: 358.0018; Required: 358.0016 for $C_{12}H_{15}NO_5{}^{35}Cl_3$.

4.2.6. 8-(2,2,2-Trichloroethoxycarbonyl)-6β-phenyl-8-azabicyclo[3.2.1]octan-3-spiro-2′-(1′,3′-dioxolane)-6α-ol (10). The ketone **9** (0.300 g, 0.837 mmol) was dissolved in anhydrous diethyl ether (10 mL) under nitrogen with stirring. Phenylmagnesium bromide (3 M in diethyl ether) (0.558 mL, 1.637 mmol) was added dropwise and stirring continued for 3 h. The reaction mixture was taken up in water (20 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with sodium chloride (satd) (50 mL), water (50 mL), dried and concentrated in vacuo to yield a pale yellow oil. Chromatography (1:2 ethyl acetate–hexane; R_f 0.65) provided **10** ($C_{18}H_{20}NO_5Cl_3$) as a white solid (0.280 g, 77% yield). **10** was recrystallised from ethyl acetate/hexane. Mp: 110–112 °C. ^{1}H NMR (δ): 2.00 (1H, dd, H7a, $J_{7a,7e}$ = 8.4, $J_{7a,5}$ = 7.5); 2.14–2.23 (2H, m, H2e, H4e); 2.36–2.46 (2H, m, H2a, H4a); 2.68–2.80 (1H, m, H7e); 3.97 (2H, dd, OCH_2, J = 6.3, 1.5); 4.02–4.18 (2H, m, OCH_2); 4.29 (1H, br s, OH); 4.55 (1H, dd, H1, $J_{1,2}$ = 10.8, $J_{1,7e}$ = 8.4); 4.70–4.92 (2H, m, CH_2); 5.02 (1H, d, H5, J = 2.7); 7.20–7.35 (3H, m, ArH × 3); 7.52 (2H, t, ArH × 2, J = 7.2). ^{13}C NMR (δ): 36.9 (37.7*) (CH_2, C7); 40.5 (41.4*) (CH_2, C4); 44.9 (45.8*) (CH_2, C2); 52.7 (52.8*) (CH, C1); 62.8 (63.1*) (CH, C5); 63.8 (OCH_2); 64.7 (OCH_2); 74.4 (74.5*) (CH_2CCl_3); 79.8 (80.3*) (C6); 95.5 (95.6*) (CCl_3); 107.0 (C3); 123.9, 124.0, 125.2, 126.7, 128.1 (ArCH × 5); 150.8 (151.1*) (NC=O). MS (CI^+): *m/z* 436, 438, 440 (MH^+, 436, 29%); 418, 420, 422 ($MH^+ - H_2O$, 418, 100%).

4.2.7. 8-(2,2,2-Trichloroethoxycarbonyl)-6β-(3,4-methylenedioxyphenyl)-8-azabicyclo[3.2.1]octan-3-spiro-2′-(1′,3′-dioxolane)-6α-ol (11). To a stirred solution of **9** (0.090 g, 0.251 mmol) in anhydrous diethyl ether (4 mL) under nitrogen was added 3,4-methylenedioxyphenylmagnesium bromide (1M in THF:toluene (50:50)) (0.301 mL, 0.301 mmol) dropwise, and stirring continued for 3 h. The reaction mixture was taken up in water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with sodium chloride (satd) (25 mL), water (25 mL), dried and concentrated in vacuo to yield a pale yellow oil. Chromatography (1:2 ethyl acetate–hexane; R_f 0.45) provided **11** ($C_{19}H_{20}NO_7Cl_3$) as a colourless oil (0.90 g, 75% yield). ^{1}H NMR (δ): 1.94–2.44 (5H, m, H2a, H2e, H4a, H4e, H7a); 2.63–2.76 (1H, m, H7e); 3.96–4.00 (2H, m, OCH_2); 4.05–4.18 (2H, m, OCH_2); 4.23 (1H, dd, OH, J = 3.6, 9.6); 4.53 (1H, dd, H1, J = 11.4, 9.9); 4.70–4.90 (2H, m, CH_2); 4.99 (1H, s, H5); 5.92 (2H, s, OCH_2O); 6.70–6.80 (1H, m, ArH); 6.85–6.98 (1H, m, ArH); 7.05 (1H, dd, ArH, J = 2.1, 8.7). ^{13}C NMR (δ): 36.9 (37.7*) (CH_2, C7); 40.4 (41.4*) (CH_2, C4); 45.0 (45.8*) (CH_2, C2); 52.6 (52.8*) (CH, C1); 53.1 (53.3*) (CH, C5); 63.9 (OCH_2); 64.7 (OCH_2); 74.5 (74.6*) (CH_2CCl_3); 79.8 (80.4*) (C6); 95.5 (95.6*) (CCl_3); 100.8 (OCH_2O); 105.4 (ArCH); 107.0 (C3); 107.6 (ArCH); 117.1 (ArCH); 142.3, 146.1, 147.5 (ipso C × 3); 150.8 (151.2*) (NC=O). HRMS (CI^+): Found: 483.0247; Required: 483.0246 for $C_{19}H_{21}NO_7{}^{35}Cl^{37}Cl_2$.

4.2.8. 8-(2,2,2-Trichloroethoxycarbonyl)-6β-hydroxy-3,3-dimethoxy-8-azabicyclo[3.2.1]-octane (20). A stirred solution of **6** (0.420 g, 0.975 mol) in anhydrous methanol (10 mL) was treated with trimethylorthoformate (0.23 mL, 2.083 mmol) and *p*-toluenesulfonic acid monohydrate (0.004 g, 0.023 mmol) and the resulting solution

was stirred at room temperature for 16 h. The reaction mixture was treated with diethyl ether (10 mL) and potassium carbonate (0.116 g), filtered through a plug of florosil and concentrated to yield **20** ($C_{12}H_{19}NO_5Cl_3$) (0.300 g, 85% yield) as a pale yellow oil after chromatography (ethyl acetate; R_f 0.79). ^{1}H NMR (δ): 1.73-1.77 (1H, m, H7e); 1.84 (2H, dd, H2e, H4e, J = 4.2, 14.4); 1.96-2.00 (1H, m, H2a); 2.12-2.20 (1H, m, H7a); 3.11 (3H, s, OCH_3); 3.15 (3H, s, OCH_3); 4.08–4.18 (1H, m, H1); 4.46 (2H, dd, CH_2, J = 6.3, 7.8); 4.47 (1H, H5, J = 7.2); 4.90 (1H, t, H6, J = 11.7). ^{13}C NMR (δ): 35.8 (36.4*) (CH_2, C2(C4)), 36.5 (37.2*) (CH_2, C4(C2)); 39.5 (40.0*) (CH_2, C7); 47.3 (OCH_3); 48.1 (OCH_3); 53.1 (53.2*) (CH, C1); 62.0 (62.2*) (CH,C5); 73.2 (74.0*) (C6); 74.5 (74.6*) (OCH_2CCl_3); 95.5 (CCl_3); 98.3 (C3); 151.8 (NC=O). MS (CI^+): m/z 362, 364, 366 (MH^+); 330, 332, 334 ($MH^+ - CH_3OH$); 312, 314, 316 ($MH^+ - H_2O$); 296, 298; 278, 280. HRMS (CI^+): Found: 363.0221; Required: 363.0207 for ($C_{12}H_{19}NO_5{}^{35}Cl_2{}^{37}Cl$).

4.2.9. 8-(2,2,2-Trichloroethoxycarbonyl)-3,3-dimethoxy-8-azabicyclo[3.2.1]-octan-6-one (21). Following the method used for **9**, **21** ($C_{12}H_{17}NO_5Cl_3$) (0.490 g, 71% yield) was prepared from **20** (0.700 g, 1.93 moles) as a colourless oil which crystallised to a white solid after chromatography (1:2 ethyl acetate–hexane; R_f 0.74). Mp: 62–63 °C. ^{1}H NMR (δ): 1.75 (1H, dd, H2e, J = 3.9, 13.8); 2.03–2.19 (2H, m, H4e, H7e); 2.42–2.65 (3H, m, H2a, H4a, H7a); 3.04 (3H, s, OCH_3); 3.16 (3H, s, OCH_3); 4.21 (1H, m, H1); 4.72–4.88 (3H, m, H5, CH_2). ^{13}C NMR (δ): 36.2 (36.8*) (CH_2, C4), 36.9 (37.6*) (CH_2, C2); 42.7 (43.1*) (CH_2, C7); 47.4 (OCH_3); 47.7 (OCH_3); 51.4 (51.8*) (CH, C1); 59.3 (60.3*) (CH,C5); 74.7 (OCH_2CCl_3); 95.2 (CCl_3); 98.3 (C3); 151.4 (NC=O); 203.0 (C=O, C6). MS (CI^+): m/z 360, 362, 364 (MH^+); 342, 344, 346 ($MH^+ - H_2O$); 328, 330, 332 ($MH^+ - CH_3OH$); 294, 296. HRMS (CI^+): Found: 359.0103; Required: 359.0094 for ($C_{12}H_{18}NO_5{}^{35}Cl_3$).

4.2.10. 8-(2,2,2-Trichloroethoxycarbonyl)-3,3-dimethoxy-6β-phenyl-8-azabicyclo[3.2.1]-octan-6α-ol (22). Following the method used for **10**, **22** ($C_{18}H_{22}NO_5Cl_3$) (0.293 g, 88% yield) was prepared from **21** (0.273 g, 0.757 moles) as a colourless oil after chromatography (1:4 ethyl acetate–hexane; R_f 0.42),which crystallised to a white solid upon standing. Mp: 100–101 °C. ^{1}H NMR (δ): 1.97 (1H, dd, H7a, J = 3.9, 15.0); 2.02–2.15 (2H, m, H2e, H4e); 2.22–2.31 (1H, m, H2a(H4a)); 2.51–2.61 (1H, m, H4a(H2a)); 2.69–2.80 (1H, m, H7e); 3.23 (3H, s, OCH_3); 3.33 (3H, s, OCH_3); 4.27 (1H, dd, H1 J = 4.2, 5.4); 4.46–4.52 (1H, m, H5); 4.68–4.89 (2H, m, CH_2); 7.19–7.36 (3H, m, ArH × 3); 7.49–7.54 (2H, m, ArH × 2). ^{13}C NMR (δ): 35.3 (35.7*) (CH_2, C4), 36.1 (36.5*) (CH_2, C2); 45.1 (46.0*) (CH_2, C7); 47.8 (OCH_3); 48.1 (OCH_3); 52.3 (52.5*) (CH, C1); 62.5 (62.8*) (CH, C5); 74.4 (74.6*) (OCH_2CCl_3); 79.5 (80.1*) (CH, C6); 95.5 (CCl_3); 99.3 (C3); 124.0, 124.1, 126.7, 128.1, 128.3 (ArC × 5); 147.8 (*ipso C*); 150.8 (151.1*) (NC=O). MS (CI^+): m/z 406, 408, 410 ($MH^+ - CH_3OH$); 372, 374, 376; 354. HRMS (CI^+): Found: 406.0363; Required: 406.0380 for $C_{17}H_{19}NO_4{}^{35}Cl_3$ (loss of CH_3OH).

4.2.11. 8-(2,2,2-Trichloroethoxycarbonyl)-3,3-dimethoxy-6β-(3,4-methylenedioxyphenyl)-8-azabicyclo[3.2.1]-octan-6α-ol (23). Following the method used for **11**, **23** ($C_{19}H_{22}NO_7Cl_3$) (0.199 g, 84% yield) was prepared from **21** (0.177 g, 0.491 moles) as a colourless oil after chromatography (1:4 ethyl acetate–hexane; R_f 0.28). ^{1}H NMR (δ): 1.92–1.99 (1H, m, H7a); 2.02–2.13 (1H, m, H2e); 2.19–2.30 (m, 1H, H4e); 2.49–2.59 (2H, m, H2a, H4a); 2.68 (1H, ddd, H7e, J = 8.4, 14.4, 15.3); 3.22 (3H, s, OCH_3); 3.32 (3H, s, OCH_3); 4.21 (1H, dd, H1, J = 3.3, 12.3); 4.43–4.50 (1H, m, H5); 4.68–4.89 (2H, m, CH_2); 5.28 (1H, s, OH) (exchangeable with D_2O) 5.92 (2H, s, OCH_2O); 6.72 (1H, dd, ArH, J = 1.8. 8.4); 6.93–6.98 (1H, m, ArH); 7.05 (1H, dd, ArH, J = 1.8, 8.4). ^{13}C NMR (δ): 35.2 (35.7*) (CH_2, C4), 36.1 (36.5*) (CH_2, C2); 45.1 (46.0*) (CH_2, C7); 47.5 (47.8*) (OCH_3); 48.1 (OCH_3); 52.2 (52.4*) (CH, C1); 62.8 (63.0*) (CH, C5); 74.5 (74.6*) (OCH_2CCl_3); 79.5 (80.2*) (CH, C6); 95.5 (CCl_3); 99.3 (C3); 100.8 (OCH_2O); 105.4, 107.6 (ArCH × 2); 117.0 (ArCH); 142.1, 146.1, 147.5 (ipso C × 3); 151.1 (NC=O). MS (CI^+): m/z 390, 392, 394; 360, 362, 364; 342, 344, 346; 328, 330, 332; 294, 296. HRMS (EI^+): Found: 449.0157; Required: 449.0200 for $C_{18}H_{18}NO_6{}^{35}Cl_3$ (loss of CH_3OH).

4.2.12. 8-(2,2,2-Trichloroethoxycarbonyl)-6β-phenyl-8-azabicyclo[3.2.1]-3-oxo-octan-6-ol (14) and 4-(2,2,2-trichloroethoxycarbonyl)-6aβ-phenyl-2,5-methano-hexahydro-2*H*-furo[3,2-*b*]pyrrol-6aα,2β-diol (26). A stirred solution of **22** (0.103 g, 0.235 mmol) in a 2:1 mixture of chloroform:trifluoroacetic acid (50% aq) (4 mL) was heated at reflux for 20 h. The cooled solution was poured onto chloroform, separated, and the organic layer washed with water (5 mL), dried and concentrated in vacuo to yield a pale yellow oil. Chromatography (1:4 ethyl acetate:hexane; R_f 0.19) yielded a colourless oil (0.090 g, 98% yield), which proved to be an inseparable mixture of **14** ($C_{16}H_{16}NO_4Cl_3$) and **26** ($C_{16}H_{16}NO_4Cl_3$). ^{1}H NMR (δ): 1.93 (1H, d, H7a, J = 11.4); 2.02–2.19 (5H, m, H2e, H4e, H7e, H2a, H4a); 3.97 (1H, br s, OH); 4.56 (1H, s, H1); 4.72–4.88 (3H, m, CH_2, H5); 7.26–7.43 (5H, m, ArH × 5); ^{13}C NMR (δ): 38.4 (38.5*) (CH_2, C4), 44.6 (44.9*) (CH_2, C2); 45.3 (45.6*) (CH_2, C7); 55.4 (55.8*) (CH, C1); 65.7 (65.7*) (CH, C5); 74.6 (74.9*) (OCH_2CCl_3); 88.4 (89.1*) (C6); 95.5 (95.6*) (CCl_3); 103.6 (103.7*) (C3); 124.7, 124.8, 127.6, 128.3, 128.5 (ArCH × 5); 140.1 (140.2*) (ipso C); 150.6 (151.0*) (NC=O); 203.1 (C=O, C3). MS (CI^+): 392, 394, 396 (MH^+); 374, 376, 378 ($MH^+ - H_2O$); 358, 360, 362; 340, 342, 344; 314, 316, 318; 218; 200.

4.2.13. 8-(2,2,2-Trichloroethoxycarbonyl)-6α-hydroxy-6-β-(3,4-methylenedioxyphenyl)-8-azabicyclo[3.2.1]octan-3-one (15) and 4-(2,2,2-trichloroethoxycarbonyl)-6aβ-(3,4-methylenedioxyphenyl)-2,5-methano-hexahydro-2*H*-furo-[3,2-*b*]pyrrol-6aα,2β-diol (27). A solution of **23** (0.179 g, 0.371 mmol) in a 2:1 mixture of chloroform:trifluoroacetic acid (50% aq) (4 mL) was heated at reflux for 20 h. The cooled solution was poured into chloroform, separated, and the organic layer washed with water

(2 × 5 mL), dried and concentrated in vacuo to yield a pale yellow oil. Chromatography (1:4 ethyl acetate:hexane) isolated 2 products: the ketone derivative **15** and the hemi-ketal derivative **27**. Compound **15** ($C_{17}H_{16}NO_6Cl_3$) was isolated as an off-white solid, which was recrystallised from DCM/diethyl ether (0.039 g, 24% yield); R_f 0.20 (1:4 ethyl acetate–hexane). Mp: 106–108 °C. ^{1}H NMR (δ): 2.19–2.28 (1H, m, H7a); 2.45–2.60 (3H, m, H2e, H4e, H7e); 2.83–2.92 (2H, m, H2a, H4a); 4.72 (1H, dd, H1, J = 4.8, 12.0); 4.94–5.09 (2H, m, CH_2); 5.27 (1H, s, H5); 5.98 (2H, s, OCH_2O); 6.31 (1H, dd, OH, J = 2.4, 5.7) (exchangeable with D_2O); 6.77–6.89 (3H, m, ArH × 3). ^{13}C NMR (δ): 44.4, 45.0, 45.2, 45.8 (CH_2, C4, C2, C7); 57.1 (CH, C1, C5); 74.7 (OCH_2CCl_3); 84.5 (CH, C6); 95.4 (CCl_3); 101.3 (OCH_2O); 105.8, 108.4 (ArCH × 2); 119.8 (123.3*) (ArCH); 125.0 (ispo C); 145.4, 148.2 (ipso C × 2); 150.3 (NC═O); 204.2 (C═O). MS (CI^+): *m/z* 436, 438, 440 (MH^+, 436, 10%); 418, 420, 422 ($MH^+ - H_2O$, 418, 15%); 384, 386, 388 (384, 20%); 314, 316, 318 (314, 20%); 262 (70%); 244 (100%). HRMS (EI^+): Found: 435.0026; Required: 435.0043 for $C_{17}H_{16}NO_6Cl_3$. **27** ($C_{17}H_{16}NO_6Cl_3$) was isolated as a colourless oil (0.100 g, 62% yield); R_f 0.08 (1:4 ethyl acetate–hexane); ^{1}H NMR (δ): 1.89 (1H, br m, H7a); 2.06–2.13 (4H, m, H2e, H4e, H2a, H4a); 2.19–2.31 (1H, m, H7e); 3.75 (1H, d, OH, J = 3.0); 4.50 (1H, s, H1); 4.70–4.76 (2H, m, CH_2CCl_3); 4.87 (1H, dd, H5, J = 6.6, 12.3); 5.95 (2H, s, OCH_2O); 6.78 (1H, dd, ArH, J = 4.5, 8.1); 6.85 (1H, dd, ArH, J = 4.5, 1.5); 6.89 (1H, d, ArH, J = 3.0). ^{13}C NMR (δ): 38.5 (38.8*) (CH_2, C4), 44.6 (45.0*) (CH_2, C2), 45.1 (45.3*) (CH_2, C7); 55.3 (55.7*) (CH, C1); 65.6 (65.7*) (CH, C5); 74.6 (OCH_2CCl_3); 88.4 (89.1*) (CH, C6); 95.5 (CCl_3); 101.1 (OCH_2O); 103.6 (103.7*) (C3); 105.7 (105.8*) (ArCH); 108.0 (ArCH); 118.0 (118.1*) (ArCH); 134.2 (ispo C); 146.5, 148.0 (ipso C × 2); 150.8 (NC═O). MS (CI^+): m/z 436, 438, 440 (MH^+, 436, 60%); 418, 420, 422 ($MH^+ - H_2O$, 418, 100%); 384, 386, 388 (384, 60%). HRMS (EI^+): Found: 435.0049; Required: 435.0043 for $C_{17}H_{16}NO_6Cl_3$.

4.2.14. 8-(2,2,2-Trichloroethylformate)-6β-phenyl-8-azabicyclo[3.2.1]octane-3β,6α-diol (18). To a stirred solution of 0.4 M cerium chloride heptahydrate in methanol (5 mL) under nitrogen was added the mixture of **14** and **26** (0.120 g, 0.306 mmol), followed a few min later by sodium borohydride (0.021 g, 0.547 mmol). Stirring continued for 4 h, after which time 5% aqueous hydrochloric acid was added to the mixture, and then the mixture poured onto DCM (10 mL) and extracted. The organic layer was washed with water (10 mL), dried and concentrated in vacuo to yield a colourless oil which crystallised upon standing to a white solid. Mp: 131–132 °C. Chromatography (1:2 ethyl acetate–hexane) yielded unreacted **14** (0.072 g, 60% recovery) and **18** ($C_{16}H_{18}NO_4Cl_3$) as a colourless oil (R_f 0.43, 1:2 ethyl acetate–hexane, 0.049 g, 100% yield based on recovered **14**). ^{1}H NMR (δ): 1.87 (1H, m, H7a); 2.16–2.38 (3H, m, H2e, H4e, H7e); 2.48 (1H, dd, H2a, $J_{2a,2e}$ = 8.7); 2.68–2.78 (1H, m, H4a); 3.70 (1H, 2 × br s, OH); 4.24–4.27 (2H, m, H1, H3); 4.39–4.47 (1H, m, H5); 4.68–4.89 (2H, m, CH_2CCl_3); 5.55 (1H, br d, OH, J = 12.3); 7.22–7.32 (3H, m, ArH × 3); 7.48–7.54 (2H, m, ArH × 2). ^{13}C NMR (δ): 33.4 (34.1*) (CH_2, C4), 38.0 (38.9*) (CH_2, C2); 45.8 (46.6*) (CH_2, C7); 52.6 (52.9*) (CH, C1); 62.9 (63.1*) (CH, C3); 63.8 (63.9*) (CH, C5); 74.4 (74.5*) (OCH_2CCl_3); 79.7 (80.3*) (C6); 95.5 (CCl_3); 124.0, 126.8, 126.8, 128.2, 128.2 (ArCH × 5); 140.1 (*ipso C*); 151.0 (NC═O). MS (CI^+): *m/z* 394, 396, 398 (MH^+, 394, 60%). HRMS (CI^+): Found: 395.0274; Required: 395.0272 for $C_{16}H_{18}NO_4{}^{35}Cl_2{}^{37}Cl$.

4.2.15. 8-(2,2,2-Trichloroethoxycarbonyl)-6β-(3,4-methylenedioxyphenyl)-8-azabicyclo[3.2.1]octane-3β,6α-diol (19). To a stirred solution of 0.066M cerium chloride heptahydrate in methanol (3 mL) at room temperature was added **15** (0.049 g, 0.112 mmol), followed a few minutes later by sodium borohydride (0.009 g, 0.224 mmol). Stirring continued for 30 min, after which time 5% aqueous hydrochloric acid (2 mL) was added to the mixture, and the mixture was poured onto DCM (10 mL) and extracted. The organic layer was washed with water (10 mL), dried and concentrated in vacuo to yield the crude product as a colourless oil. Chromatography (1:1 ethyl acetate–hexane; R_f = 0.48) yielded **19** ($C_{17}H_{18}NO_6Cl_3$) as a white solid, recrystallised from ethyl acetate (0.048 g, 98% yield). Mp: 131–132 °C. ^{1}H NMR (δ): 1.65–1.85 (3H, m, H7a, H2e, H4e); 1.93–2.39 (3H, m, H2a, H4a, H7e); 3.90 (0.75H, dddd, H3, $J_{3a,2e}$ = 6.3, $J_{3a,2a}$ = 9.6, $J_{3a,4e}$ = 6.3, $J_{3a,4a}$ = 9.6); 4.04 (0.25H, t, H3, $J_{3e,2a}$ = 5.4, $J_{3e,4a}$ = 5.4); 4.69 (1H, dd, H1, J = 6.0, 11.7); 4.80–4.96 (3H, m, OH, CH_2CCl_3); 5.05 (1H, dd, H5, J = 3.3, 6.3); 5.97 (2H, s, OCH_2O); 6.15 (0.75H, dd, OH, J = 2.4, 8.7); 6.41 (0.25H, dd, OH, J = 2.7, 8.7); 6.76–6.96 (3H, m, ArH × 3). ^{13}C NMR (δ): 33.9, 34.1, 34.6, 34.9 (CH_2 × 3, C4, C2, C7); 58.2 (58.3*) (CH, C1); 64.8 (CH, C3); 65.4 (CH, C5); 74.6 (OCH_2CCl_3); 95.6 (CCl_3); 101.3 (101.3*) (OCH_2O); 105.7 (ArCH); 108.4 (108.6*) (ArCH); 119.7 (119.8*), 121.3 (121.5*) (ArCH); 124.6 (C6), 126.0 (126.1*) (*ispo* C); 142.0 (142.1*) (*ispo* C); 147.8 (148.1*) (*ipso C*); 149.9 (NC═O). MS (CI^+): *m/z* 438, 440, 442 (MH^+, 438, 5%); 420, 422, 424 ($MH^+ - H_2O$, 420, 100%); 402, 404, 406 (402, 13%); 386, 388, 390 (386, 25%). HRMS (CI^+): Found: 421.0040; Required: 421.0065 for $C_{17}H_{16}NO_5{}^{35}Cl_2{}^{37}Cl$ (loss of H_2O).

4.2.16. General procedure for the removal of the 2,2,2-trichloroethylformate protecting group to yield secondary amine derivatives. The 2,2,2-trichloroethoxycarbonyl derivative (0.10–1.50 mmol) and zinc dust (10 equiv) were stirred in 90% acetic acid (2–20 mL) at 40 °C for 2 days. The reaction mixture was basified (ammonia, pH 9) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with sodium chloride (satd) (100 mL), water (2 × 100 mL), dried and concentrated in vacuo to give the desired secondary amine derivatives. In this way derivatives 2, 4, 6, 10, 12, 34, 35, 36 and 37 were prepared. Hydrochloride salts of these bases were prepared by dissolving the aryl tropanol derivatives (0.10–1.00 mmol) in diethyl ether (1–2 mL), and treating the solution dropwise with 1 M hydrochloric acid in diethyl ether (0.50–1.00 mL). The precipitate was filtered and dried under high vacuum to yield the desired hydrochloride salt.

4.2.16.1. 6β-Phenyl-8-azabicyclo[3.2.1]octan-3-spiro-2′-(1′,3′-dioxolane)-6-ol (12). Reaction of **10** (0.075 g, 0.17 mmol) yielded **12** ($C_{15}H_{19}NO_3$) after chromatography (ethyl acetate) as a colourless oil (0.025 g, 51% yield). ^{1}H NMR (δ): 1.78 (2H, br s, OH, NH); 1.93 (2H, dd, H2e, H4e, J = 4.2, 15.0); 2.05 (1H, d, H7a, J = 7.2); 2.27 (1H, d, H2a(H4a), J = 14.4); 2.45(1H, d, H4a(H2a), J = 14.4); 2.62 (1H, dd, H7e, J = 7.8, 8.1); 3.38 (1H, s, H1); 3.71 (1H, t, H5 J = 3.9, 7.8); 3.92–3.99 (2H, m, OCH_2); 4.03–4.14 (2H, m, OCH_2); 7.20–7.26 (1H, m, ArH); 7.33 (2H, dd, ArH × 2, J = 7.2, 8.1); 7.67 (2H, dd, ArH × 2, J = 1.2, 8.4). ^{13}C NMR (δ): 39.5 (CH_2, C7); 43.4 (CH_2, C4); 44.9 (CH_2, C2); 53.5 (CH × 2, C1, C5); 63.6 (OCH_2); 64.4 (OCH_2); 82.2 (C6); 107.5 (C3); 124.7, 126.4, 127.9 (ArCH × 5); 148.9 (*ipso*-C). MS (CI^+): *m/z* 262 (MH^+); 244 ($MH^+ - H_2O$); 184.

4.2.16.2. 6β-(3,4-Methylenedioxy)-8-azabicyclo[3.2.1]-octan-3-spiro-2′-(1′,3′-dioxolane)-6-ol (13). Reaction of **11** (0.09 g, 0.19 mmol) yielded **13** ($C_{16}H_{19}NO_5$) after chromatography (ethyl acetate) as a white solid (0.021 g, 37% yield). Mp: 218–220 °C. ^{1}H NMR (δ): 1.74 (2H, br s, OH, NH); 1.91 (2H, dd, H2e, H4e, J = 4.2, 14.7); 2.03 (1H, d, H7a, J = 6.6); 2.24 (1H, d, H2a(H4a), J = 14.4); 2.41 (1H, d, H4a(H2a), J = 14.4); 2.55 (1H, dd, H7e, J = 8.1, 14.1); 3.38 (1H, d, H1, J = 4.2); 3.69 (1H, dd, H5, J = 4.2, 8.1); 3.94–3.99 (2H, m, OCH_2); 4.02–4.16 (2H, m, OCH_2); 5.92 (2H, s, OCH_2O) 6.75 (1H, d, ArH5, J = 8.1); 7.10 (1H, dd, ArH6, J = 1.8, 8.1); 7.27 (1H, d, ArH2, J = 2.1). ^{13}C NMR (δ): 37.4 (CH_2, C7); 40.8 (CH_2, C4); 44.2 (CH_2, C2); 56.2 (CH × 2, C1, C5); 61.3 (OCH_2); 67.3 (OCH_2); 66.5 (C6); 101.2 (OCH_2O); 105.7, 106.2 (ArCH × 2); 107.6 (C3); 118.1 (ArCH); 135.8, 147.0, 147.9 (*ipso-C* × 3). MS (CI^+): *m/z* 306 (MH^+); 288 ($MH^+ - H_2O$); 244, 184. HRMS (CI^+): Found: 305.1254; Required: 305.1263 for $C_{16}H_{18}NO_5$.

4.2.16.3. 2-Methoxy-6aβ-phenyl-2,5-methano-hexahydro-2*H*-furo[3,2-*b*]pyrrol-6α-ol (30). Reaction of **22** (0.05 g, 0.114 mmol) yielded **30** ($C_{14}H_{17}NO_2$) after chromatography (ethyl acetate) as a pale yellow oil (0.022 g, 85% yield). ^{1}H NMR (δ): 1.78 (1H, d, H7a, J = 10.5); 1.92–2.04 (3H, m, H2e, H4e, H7e); 2.23–2.29 (2H, m, H2a, H4a); 2.50 (1H, br s, *N*H); 3.49 (3H, s, OCH_3); 3.79 (1H, d, H1, J = 5.1); 3.88 (1H, d, H5, J = 2.7); 7.24–7.46 (5H, m, ArH × 5). ^{13}C NMR (δ): 38.1 (CH_2, C4), 41.4 (CH_2, C2); 48.5 (CH_2, C7); 49.7 (OCH_3); 56.4 (CH, C1); 67.3 (CH, C5); 88.7 (C6); 106.2 (C3); 124.6, 126.9, 128.1, 128.3 (ArC × 5); 142.0 (*ipso C*). MS (CI^+): *m/z* 232 (MH^+, 100%); 200 (MH^+ – MeOH, 40%). HRMS (CI^+): Found: 231.1266; Required: 231.1260 for $C_{14}H_{17}NO_2$.

4.2.16.4. 2-Methoxy-6aβ-(3,4-methylenedioxyphenyl)-2,5-methano-hexahydro-2*H*-furo[3,2-*b*]pyrrol-6α-ol (31). Reaction of **23** (0.058 g, 0.120 mmol) yielded **31** ($C_{15}H_{17}NO_4$) as a pale yellow oil (0.025 g, 78% yield). ^{1}H NMR (δ): 1.91–2.01 (3H, m, H2e, H4e, H7a); 2.11–2.28 (3H, m, H2a, H4a, H7e); 2.62 (1H, br s, *N*H); 3.48 (3H, s, OCH_3); 3.74 (1H, br d, H1, J = 3.6); 3.87 (1H, br s, H5); 5.95 (2H, s, OCH_2O); 6.77–6.80 (1H, m, ArH); 6.88–6.95 (2H, m, ArH × 2). ^{13}C NMR (δ): 37.9 (CH × 2, C4), 41.4 (CH × 2, C2); 48.0 (CH × 2, C7); 49.7 (OCH × 3); 56.2 (CH, C1); 67.1 (CH, C5); 88.6 (C6); 100.9 (OCH_2O); 105.8, 106.2 (ArCH × 2); 107.9 (C3); 117.8 (ArCH); 136.0, 146.4, 147.5 (*ipso C* × 3). MS (CI^+): *m/z* 276 (MH^+, 70%); 244 (MH^+ – MeOH, 65%); 154 (55%). HRMS (CI^+): Found: 276.1240; Required: 276.136 for $C_{15}H_{18}NO_4$.

4.2.16.5. 6aβ-Phenyl-2,5-methano-hexahydro-2*H*-furo-[3,2-*b*]pyrrol-6aα,2β-diol (28). Reaction of **26** (0.090 g, 0.229 mmol) yielded hemi-ketal **28** ($C_{13}H_{15}NO_2$) after chromatography (10:2 ethyl acetate–methanol; R_f 0.12) as a colourless oil (0.015 g, 30% yield). ^{1}H NMR (δ): 1.88 (1H, d, H7a, J = 12.3); 1.89–2.20 (4H, m, H2e, H4e, H2a, H4a); 2.24 (1H, d, J = 11.7, H7e); 2.99 (2H, br s, *N* H, OH); 3.81 (1H, s, H1); 3.89 (1H, s, H5); 7.23–7.44 (5H, m, ArH × 5). ^{13}C NMR (δ): 39.5 (CH_2, C4), 46.1 (CH_2, C2); 47.7 (CH_2, C7); 56.1 (CH, C1); 67.3 (CH, C5); 89.3 (C6); 103.5 (C3); 124.8, 126.8, 127.1, 127.9, 128.2 (ArCH × 5); 141.6 (*ipso C*). MS (CI^+): *m/z* 218 (MH^+); 200 ($MH^+ - H_2O$). HRMS (CI^+): Found: 218.1175; Required: 218.1181 for $C_{13}H_{16}NO_2$.

4.2.16.6. 6aβ-(3,4-Methylenedioxyphenyl)-2,5-methano-hexahydro-2*H*-furo[3,2-*b*]pyrrol-6aα,2β-diol (29). Reaction of **27** (0.040 g, 0.092 mmol) yielded **29** ($C_{14}H_{15}NO_4$) after chromatography (10:2 ethyl acetate–methanol; R_f 0.13) as a colourless oil (0.014 g, 58% yield). ^{1}H NMR (δ):1.84 (1H, dd, H7a, $J_{7a,7e}$ = 12.0,$J_{7a,1}$ = 3.3); 1.95–2.03 (4H, m, H2e, H4e, H2a, H4a); 2.18 (1H, d, $J_{7a,7e}$ = 11.7, H7e); 3.07 (2H, br s, *N*H, OH); 3.75 (1H, s, H1); 3.86 (1H, s, H5); 5.93 (2H, s, OCH_2O); 6.76 (1H, d, J = 8.1, ArH); 6.66 (1H, d, J = 1.5, ArH); 6.90 (1H, dd, J = 8.1, 1.5 ArH). ^{13}C NMR (δ): 39.3 (CH_2, C4), 46.1 (CH_2, C2); 47.3 (CH_2, C7); 55.9 (CH, C1); 67.1 (CH, C5); 89.3 (C6); 101.0 (OCH_2O); 103.5 (C3); 106.0 (ArCH); 107.9 (ArCH); 118.1 (ArCH); 135.7.0, 146.7, 147.8 (*ipso C* × 3). MS (CI^+): *m/z* 262 (MH^+, 40%); 244 ($MH^+ - H_2O$, 80%). HRMS (CI^+): Found: 261.1002; Required: 261.1001 for $C_{14}H_{15}NO_4$.

4.2.16.7. 6β-Phenyl-8-azabicyclo[3.2.1]octane-3α,6β-diol (1). Reaction of **18** (0.059 g, 0.149 mmol) yielded **1** ($C_{13}H_{17}NO_2$) after chromatography (10:2 ethyl acetate–methanol, R_f 0.18) as a colourless oil, which was crystallised from DCM (0.012 g, 36% yield). ^{1}H NMR (δ): 1.89 (1H, dd, H7a, J = 11.1, 14.7); 2.03 (1H, 2 × dd, H4e, J = 4.5, 4.8); 2.13 (1H, 2 × dd, H2e, J = 4.5, 4.8); 2.36 (2H, dd, H2a, H4a, J = 14.4, 15.6); 2.64 (1H, dd, H7e, J = 7.5, 14.4); 3.29 (1H, s, OH); 3.53–3.56 (4H, m, H1, H5, NH, OH); 4.17 (1H, dd, H3a, J = 5.1, 10.2); 7.25 (1H, d, ArH, J = 7.2); 7.34 (2H, dd, ArH × 2, J = 7.2, 7.8); 7.60 (2H, dd, ArH × 2, J = 7.2, 1.2). ^{13}C NMR (δ): 33.5 (CH_2, C4), 40.6 (CH_2, C2); 45.5 (CH_2, C7); 53.0 (CH, C1); 63.7 (CH, C3); 64.1 (CH, C5); 82.8 (C6); 124.7, 126.7, 128.3 (ArCH × 5); 148.7 (*ipso C*). MS (CI^+): *m/z* 220 (MH^+, 40%); 202 ($MH^+ - H_2O$, 100%). HRMS (CI^+): Found: 220.1335; Required: 220.1338 for $C_{13}H_{18}NO_2$.

4.2.16.8. 6β-(3,4-Methlenedioxyphenyl)-8-azabicyclo-[3.2.1]octane-3α,6β-diol (3). Reaction of **19** (0.048 g, 0.109 mmol) yielded **3** ($C_{14}H_{17}NO_2$) after chromatography (10:2 ethyl acetate–methanol; R_f 0.12) as a colourless oil which was crystallised from diethyl ether (0.015 g, 52% yield). ^{1}H NMR (δ): 1.90 (1H, dd, H7a, J = 15.0, 16.5); 2.01–2.20 (2H, m, H2e, H4e); 2.35 (2H, dd, H2a, H4a, J = 14.4, 22.2); 2.60 (1H, dd, H7e, J = 7.8, 14.4); 3.23 (1H, s, OH); 3.56 (1H, dd, H1, J = 3.9, 7.8); 3.77 (3H, br s, H5, NH, OH); 4.18 (1H, dd, H3a, J = 4.5, 9.9); 5.94 (2H, s, OCH_2O); 6.75 (1H, d, ArH, J = 8.4); 7.00 (1H, dd, ArH, J = 1.8, 8.1); 7.19 (1H, dd, ArH, J = 1.8, 8.1). ^{13}C NMR (δ): 35.2 (CH_2, C4), 40.4 (CH_2, C2); 45.4 (CH_2, C7); 52.8 (CH, C1); 63.7 (CH, C3); 64.1 (CH, C5); 82.5 (C6); 100.9 (OCH_2O); 106.3 (ArCH); 107.5 (ArCH); 117.5 (ArCH); 142.8 (*ipso C*); 146.3 (*ipso C*); 147.8 (*ipso C*). MS (CI^+): *m/z* 246 ($MH^+ - H_2O$, 10%).

4.3. Pharmacological assessment of ligands

The ligand binding characteristics of membrane expressed receptors (α_{1A}, α_{1B} and α_{1D}) (COS-1) were determined in a series of radioligand binding studies using [^{125}I]-HEAT, an alpha-1-specific antagonist as the radioligand, as previously described.[4b,29] For competition studies, 200 pM of [^{125}I]-HEAT was used with increasing amounts of nonradioligand competing ligand. The membrane concentration used in these studies was selected to allow binding of less than 10% of the total radioligand added. After incubation for 1 h, the reactions were stopped by addition of HEM-buffer (20 mM HEPES pH 7.5, 1.4 mM EGTA and 12.5 mM $MgCl_2$) and the membranes collected on Whatman GF/C glass filters using a Brandel Cell Harvester. The filters were washed three times with HEM to remove unbound radiolabel and then counted for bound activity using a Packard Auto-gamma5000 counter. Binding data were analysed using the iterative, nonlinear, curve-fitting program, Prism. Binding affinity was measured in terms of IC_{50}, which represents the concentration of unlabelled ligand which inhibits 50% of the radioligand binding.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2004.07.063.

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