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Original article

Synthesis and preliminary screening of novel indole-3-methanamines as 5-HT$_4$ receptor ligands

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ABSTRACT

Twenty-three indole-3-methanamines were designed, synthesized and evaluated as ligands for the 5-HT$_4$ receptor. Compounds **I-d**, **I-j**, **I-o**, **I-q** and **I-u** showed good affinity at 100 μM and **I-o** was found to be only 5-fold less potent than the agonists serotonin (**1**) and 5-methoxytryptamine (**2**). Substitution on the 3-methanamine nitrogen clearly influenced activity with docking experiments into a homology model of the 5-HT$_4$ receptor showing a range of interactions with these side chain substituents. This modelling work together with the SAR determined in this study has provided promising ideas for future synthetic work.

1. Introduction

Agonists that target 5-HT$_4$ receptors influence the regulation of smooth muscle tone and nerve activity in various parts of the gut as well as the bladder [1–3]. These compounds are used clinically for both gastroesophageal reflux disease [4] and irritable bowel syndrome [5–7]. Notably, cisapride and tegaserod have been restricted for use in humans due to the prevalence of cardiovascular side effects [8–10]. Given these deficits there is a clear need for new compounds with improved receptor selectivity and clinical profiles.

This present study has used a range of methods to influence our design strategy. The use of pharmacophore models developed in our laboratories [11,12] contributed towards our choice of scaffold and side chain substituents. Existing structure–activity information was also used employing an indole-3-methanamine scaffold related to the alkaloid gramine which has shown activity at different 5-HT receptors [13–15]. This series has been limited to the 5-methoxy derivative given the known agonist actions of 5-HT (**1**) and 5-methoxytryptamine (**2**) [Fig. 1]. Primarily the designs seek to determine the effect of shortening the alkylamine side chain and to observe the effect of varying the nature of this side chain. Finally, each compound was modelled into a homology model of the 5-HT$_4$ receptor [16] to gain insight into the interaction with Asp100 and other residues near the alkylamine side chain.

2. Chemistry

The design of various structurally diverse 5-HT$_4$ agonists explored in this study was based on the indole moiety of compound **2** which is known to result in good recognition at 5-HT$_4$ receptors [11]. As the indole moiety (Scheme 1, general structure **I**) is found to be an essential part of the structure of many 5-HT receptor ligands [17], we chose this group as our template for the diverse library of compounds. We varied the side chain to encompass a wide array of groups possessing different electronic, steric, lipophilic and hydrophilic properties. In some cases a second basic centre was also included [11]. A key feature of these compounds was the use of a methylamine side chain. This differs from classic 5-HT ligands which usually possess an ethylamine group.

The general reaction used to prepare each compound (**I-a** to **I-w**) is shown in Scheme 1. Initial nucleophilic attack by the primary amine on the carbonyl carbon of 5-methoxy indole-3-carboxaldehyde (**3**) spontaneously caused the formation of a Schiff's base (**II**). The unstable imine was reduced to the equivalent secondary amine (**I**) with yields ranging from 30 to 90%. While some of these yields were low it was not our aim to optimize the reaction conditions but to generate numerous analogues for screening purposes. The variation in yield may also be attributed to

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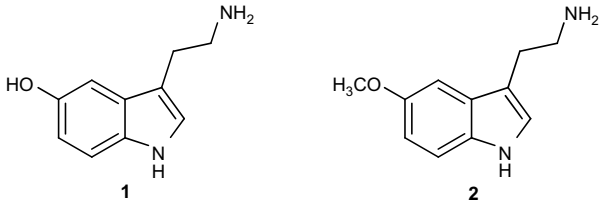
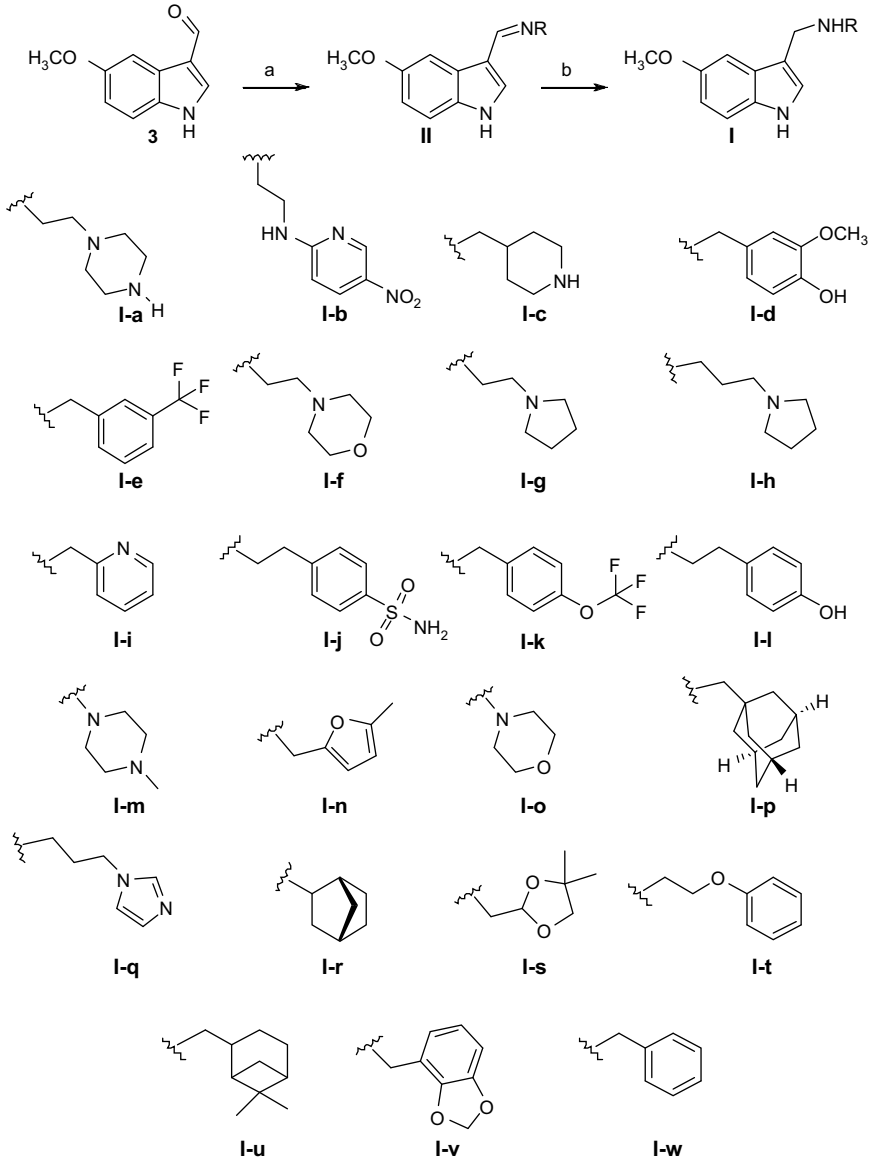


Fig. 1. Structures of serotonin (5-HT, **1**) and 5-methoxytryptamine (5-MeOT, **2**).

the diversity of amino groups used and was influenced by their differing nucleophilic strengths. Each compound was purified by preparative TLC or HPLC. Compounds **I-e** [18] and **I-w** [19] have been described previously.

Using a homology model of the human 5-HT_4 receptor [16] each molecule was docked into the protein using Glide (Schrodinger) [20,21]. Docking used the standard precision (sp) protocol and ionization states of the ligands and protein side chains were carefully checked (e.g. Asp100) [22]. Compounds **1** and **2** bound in a manner similar to that shown previously [16] demonstrating key interactions between Ser197 and the indole oxygen substituent as well as the alkylamine side chain with Asp100 (Fig. 2A). Ten poses were generated for each docking run and within this set a binding mode was found that corresponded to the configuration of the indole moiety of compounds **1** and **2** (Fig. 2B and C). An alternative orientation of the indole ring was also found where the indole nitrogen was placed next to Ser197 (Fig. 2C). A correlation was not found between the docking scores and the percentage displacement data; a result that was not unexpected. It was instructive however, to examine the location and nature of the interactions between the side chains of each ligand and the receptor to stimulate further synthetic ideas.

From the docking studies it was apparent that compounds **I-o**, **I-j** and **I-d** oriented their side chain aromatic/heterocyclic rings above Leu99 making van der Waals contact with the terminal methyl groups of this residue (Fig. 2B). The rings were placed adjacent to and in the same plane as the guanidine group of Arg96 which was located in a position that could form hydrogen bonds with the morpholine, benzenesulphonamide or 3-methoxy-4-hydroxy rings.



Scheme 1. Synthesis of 5-methoxyindole compounds; (a) R-NH_2, in acetonitrile or methanol, reflux 24 h, (b) $NaBH_4$, 0 °C warmed slowly to rt.

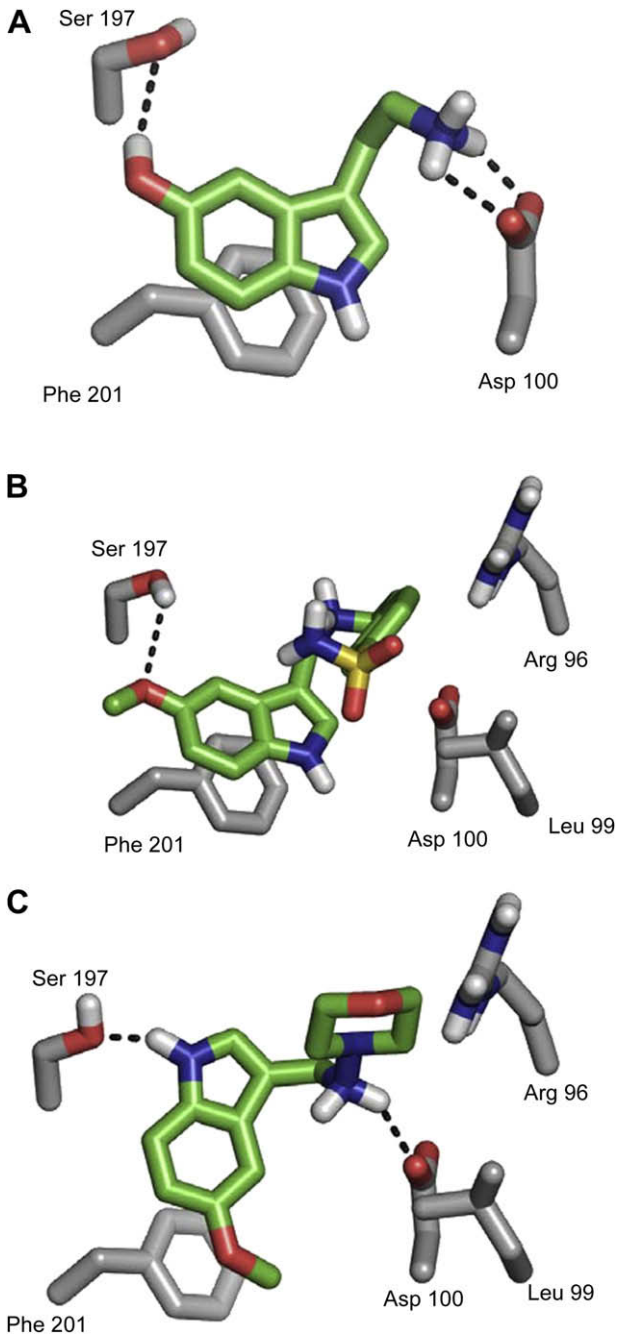


Fig. 2. (A) Compound **1** docked into the homology model of the 5-HT_4 receptor. (B) Compound **I-j** docked into the homology model of the 5-HT_4 receptor. (C) Compound **I-d** docked into the homology model of the 5-HT_4 receptor.

Future studies need to investigate this binding mode which will no doubt involve revising the homology model using the recently described beta-adrenergic receptor structures [23–25]. Particular focus can then be given to the interactions with the side chains of the more active compounds **I-d**, **I-j**, **I-o**, **I-q** and **I-u**. Interestingly, the pyrrolidine side chain of compound **I-h** was found to have a slightly altered configuration in which this group was located close to Ile157. This can be attributed to the longer propyl chain linking the indole and pyrrolidine groups allowing interactions deeper within the binding cavity. The alternative binding mode of the indole group as shown in Fig. 2C illustrates the hydrogen bond between the indole nitrogen and Ser197. Notably, the indole ring is in exactly the same plane as the indole ring of compound **1** (Fig. 2A). In addition, the methanamine nitrogen is able to form an ionic bond with Asp100 as well as placing the morpholine ring adjacent to Arg96 once again. Given the importance of interactions with Asp100 this alternative mode will require further scrutiny and will certainly influence our design strategy.

3. Screening

The compounds were subjected to preliminary radioligand displacement screening using [^{3}H]-GR113808 which is a high affinity and selective 5-HT_4 receptor antagonist [26]. All molecules were screened at 100 μM and 1 μM on the human 5-HT_{4b} (h5-HT_{4b}) receptor splice variant as it is the most commonly expressed 5-HT_4 receptor splice variant [1,2]. Two standard compounds (**1** the endogenous ligand; and **2** a 5-HT_4 preferring full agonist) were screened with the target candidate molecules. The displacements recorded for the standards at 100 μM, **1** and **2** were 99% and 100%, respectively. Compounds **I-d**, **I-j**, **I-l**, **I-m**, **I-o**, **I-q**, **I-r** and **I-u** exhibited high affinity with displacement values not significantly different to the standard compounds (Fig. 3). Only compound **I-o** showed displacement values not significantly different to either **1** or **2** at 1 μM (Fig. 3). Hence a full displacement curve was constructed for compound **I-o** (Fig. 4). The pK_i values obtained were 7.53 ± 0.07, 7.57 ± 0.12 and 6.84 ± 0.20 for **1**, **2** and compound **I-o** respectively. Comparable literature values of pK_i for 5-HT and 5-MeOT at the 5-HT_{4b} receptor are 6.96 ± 0.28 and 6.61 ± 0.30 respectively [27].

4. Discussion

This study has sought to explore a scaffold that has not been extensively used in 5-HT receptor research. Indeed, the choice of the gramine-like backbone was intended to challenge the pharmacophore models established for 5-HT_4 receptors. Shortening the alkylamine side chain of **1** and **2** is contrary to many design strategies that have placed the ionizable nitrogen atom further from the indole/aromatic group. Encouragingly, compounds **I-d**, **I-j**, **I-o**, **I-q** and **I-u** showed good affinity at 100 μM clearly showing that the shorter alkylamine side chain was tolerated within the binding site. Even more encouraging was the finding that **I-o** was only 5-fold less potent than the classic agonists **1** and **2**. Given that this small library of compounds represents the first foray with this scaffold then it certainly needs to be followed up to narrow down the SAR.

An initial attempt to understand the SAR was not entirely clear given that in some cases the biology results between compounds, either at 1 or 100 μM, were very similar. The side chain of compound **I-o** is a simple morpholine ring that is directly attached to the 3-methanamine nitrogen through the morpholine nitrogen atom. Within series **I** only two other compounds (**I-m** and **I-r**) attach a ring directly to the methanamine nitrogen. At 1 μM both **I-m** and **I-r** are inactive which may suggest that the morpholine oxygen of **I-o** has some role to play in binding to the receptor. Given that docking suggests there is a close proximity of this side chain group to Arg96 then it is easy to suggest that there may be a hydrogen bond formed between the morpholine oxygen and the guanidine group. Taking this theme one stage further would suggest that the basic piperazine of **I-m** would not favourably interact with Arg96 and that **I-r** would be unable to make any specific interactions. Another question that arises with **I-o** is the location of the basic centre given that the morpholine ring is directly attached to the scaffold (**I**) (i.e. an N–N bond). Using the ACD/Labs software [28] the pK_a was predicted to be 6.2 and to reside on the 3-methanamine nitrogen itself. As such, the activity seen with **I-o** is not a consequence of moving the basic centre

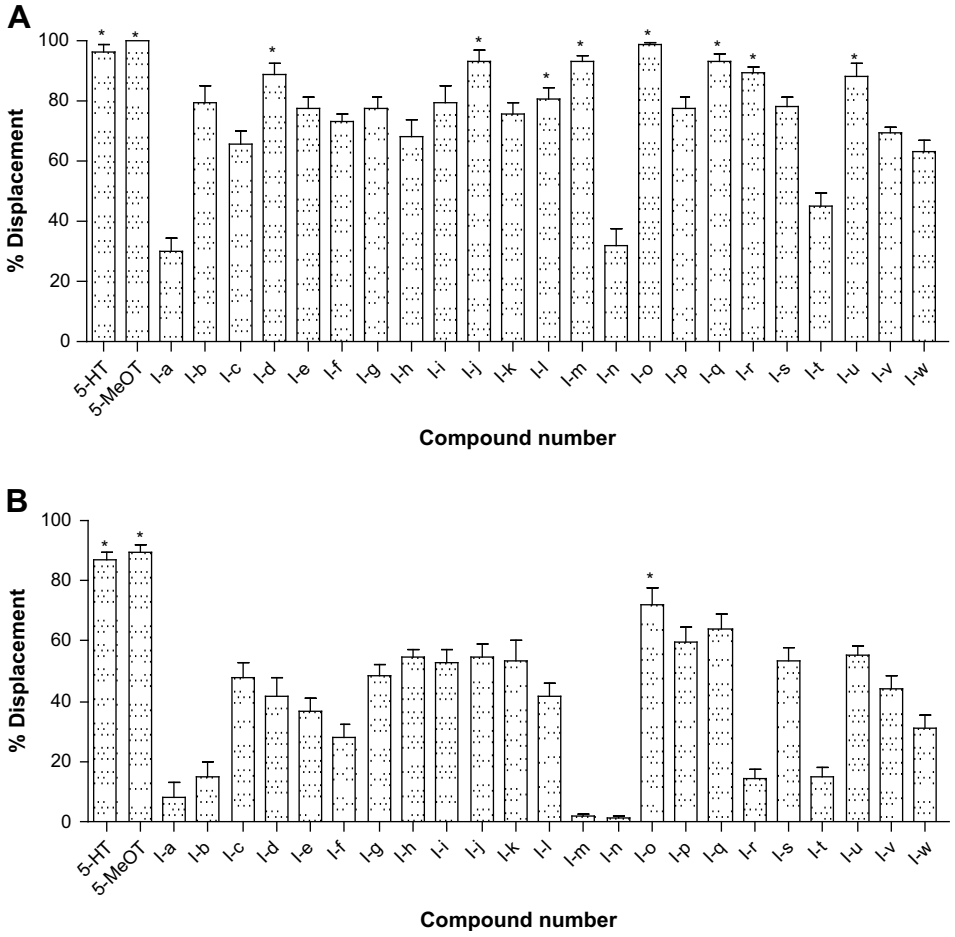


Fig. 3. (A) Percentage displacement of [^{3}H]-GR113808 binding to the h5-HT$_{4b}$ receptor by compounds **I-a** to **I-w** screened at 100 μM, together with the reference compounds **1** and **2**. (B) Percentage displacement of [^{3}H]-GR113808 by each compound at 1 μM. Asterisks indicate compounds with displacement values not significantly different ($P > 0.05$) to 5-MeOT.

where it would have the same registry as either **1** or **2**. The alternative binding mode shown in Fig. 2C does however, allow **I-o** to bind to Asp100 despite the shortening of the side chain. Potentially this binding mode may explain the potency of **I-o** and further work needs to be undertaken to assess the feasibility of this docking orientation. The only other SAR worth discussing is a comparison of compounds to **I-q** which had fair affinity at 1 μM and possessed a 1-propyl-1*H*-imidazole side chain. Other compounds that shared this same three-atom chain to a ring structure were **I-b**, **1-h** and **I-t**. Apart from **I-t** they all have a basic side chain (in addition to the 3-methanamine nitrogen) with predicted pK_a values of 2.4, 10.4 and 7.1 for **I-b**, **I-h** and **I-q**, respectively. Since **I-b** and **I-t** had the lowest activity of these four compounds and that their side chain substituents are essentially neutral at pH 7.4, it may suggest that a second basic group is needed further from the 3-methanamine nitrogen. Indeed our earlier work has shown that a second basic group was well tolerated at 5-HT$_4$ receptors (unpublished observations). This is certainly of interest and further molecules based on the indole-3-methanamine scaffold are planned to explore the optimal location of a second basic centre. While there are other compounds with a second basic centre within the current series there may be additional considerations for activity such as the similar shape that both **1-h** and **I-q** share.

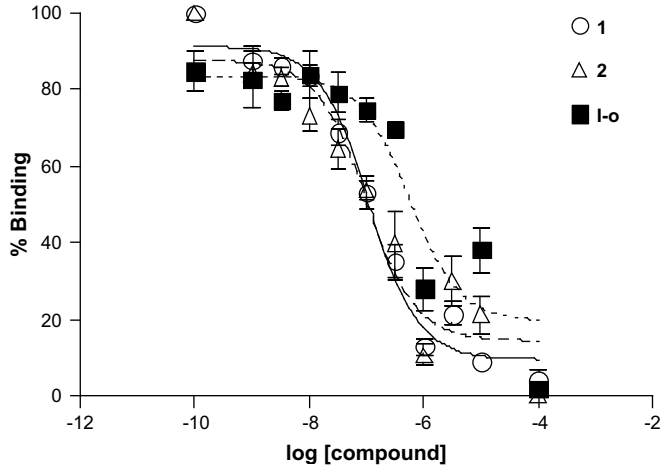


Fig. 4. Displacement curves of [^{3}H]-GR113808 binding to the h5-HT$_{4b}$ receptor by compounds **1** (○), **2** (△) and **I-o** (■).

This study has generated a new scaffold for 5-HT$_4$ receptors which contrasts to previously developed series of compounds. The most potent compound emerging from this set was marginally lower in potency than both **1** and **2** highlighting the utility of this finding. While some SAR's have been cautiously put forward there is a clear need for further experiments to clarify the relative activities of the current set of compounds. In addition, docking experiments will benefit from the development of updated models

of the 5-HT_4 receptors using the recent crystal structures of beta-adrenergic receptors [23–25]. Future chemistry efforts are planned that will explore the SAR around the more active compounds from this study as well as integrating ideas that emerge from the molecular modelling.

5. Experimental

5.1. Binding assay

Membranes were isolated from COS-7 cells 3 days following transient transfection with the 5-HT_{4b} receptor splice variant using Lipofectamine™ 2000 (Invitrogen, Mount Waverley, VIC, Australia). Radioligand binding assays were performed in 96-well plates with a total volume of 300 μl containing 20 μg protein, 0.25 nM [^{3}H]-GR113808 (1-(2-(methylsulphonyl)amino)ethyl-4-piperidinyl)methyl-1-methyl-1*H*-indole-3-carboxylate from GE Healthcare (Little Chalfont, Buckinghamshire, UK) with or without competing unlabelled ligand in phosphate buffered saline (PBS). Incubations were performed at room temperature (20–25 °C) for 60 min and the membranes were harvested onto GF/B UniFilter plates (Perkin–Elmer, Rowville, VIC, Australia) presoaked overnight in 0.5% (v/v) polyethyleneimine (Sigma) using a Filtermate cell harvester (Packard, Meridan, Connecticut, USA), washed three times with PBS and counted using a Top-count Microplate scintillation counter (Packard). For competition (full displacement) assays, the data were fitted by least squares analysis using the one site fit K_i model in GraphPad Prism 5 (GraphPad Software, San Diego, California, USA) and the radioligand value of 0.25 nM and K_d value of 0.087 previously determined for the 5-HT_{4b} receptor splice variant. The mean displacement values of the compounds in the preliminary screening exercise were determined from $n = 3$–6 experiments and the data were analysed by one-way ANOVA followed by the Tukey–Kramer post-hoc test.

5.2. Materials and methods

All synthesized compounds were checked by ESI Mass Spectroscopy and ^{1}H NMR. Nuclear magnetic resonance spectra were recorded at room temperature on a Bruker Avance 300 MHz NMR spectrometer. Chemical shifts are reported relative to tetramethylsilane at 0 ppm. Low Resolution Mass Spectrometry analyses were performed using a Micromass Platform II single quadrupole mass spectrometer equipped with an atmospheric pressure (ESI/APCI) ion source. Sample management was facilitated by an Agilent 1100 series HPLC system and the instrument was controlled using MassLynx software version 3.5. High-Resolution Mass Spectrometry analyses were collected on a Waters Micromass LCT Premier XE Time Of Flight mass spectrometer fitted with either an electrospray (ESI) or Ion Sabre (APCI) ion source and controlled with MassLynx software version 4.1. All compounds were named using Chemdraw Ultra 10.0 and predicted ^{1}H NMR shifts were also used for comparison with experimental data. It was observed that in d_6-DMSO as NMR solvent the indole nitrogen proton was always observed at the same chemical shift, whereas in $CDCl_3$, it was consistently absent.

Anhydrous sodium sulphate was used as the drying agent in organic solutions. Concentration and evaporation of organic solutions were performed using a Buchi rotary evaporator. All reactions requiring reflux were conducted under inert nitrogen atmosphere using oven dried glassware (120 °C). Analytical Thin Layer Chromatography (TLC) was performed using 0.2 mm, aluminium backed Silica Gel 60 F_{254} sheets. Preparative TLC was performed on 2 mm glass backed Silica Gel 60 F_{254} sheets. Isolated compounds were analysed by TLC to ensure that only 1 spot was visible for high purity. All pK_a values were calculated using ACD/Labs pK_a calculator [28].

5.2.1. N-*((5-Methoxy-1*H*-indol-3-yl)methyl)-2-(piperazin-1-yl)ethanamine (**I-a**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 1-(2-aminoethyl)piperazine (77 μL, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL). After 5 h, the mixture was cooled to 0 °C and 3 molar equivalents of $NaBH_4$ were used to complete the reductive amination. The reaction mixture was dried under reduced pressure, and extracted with DCM. The organic fractions were washed with water, and then dried over anhydrous sodium sulphate. The residue obtained was purified by preparative TLC. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)-2-(piperazin-1-yl)ethanamine as a yellow crystalline solid; 4.4 mg, 2.5% yield; ^{1}H NMR (d_6-DMSO) δ 10.75 (1H, s, NH), 7.22 (1H, d, $J = 4.2$ Hz, CH), 7.18 (1H, s, CH), 7.02 (1H, s, CH), 6.74 (1H, dd, $J = 2.4$ Hz, CH), 3.74 (3H, s, OCH_3), 3.64 (2H, m, CH_2), 2.65 (4H, t, CH_2), 2.50 (2H, t, CH_2), 2.39–2.35 (6H, m, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 289.2023 (error 1.7 ppm).

Compounds **5**–**26** were synthesized and purified in a similar way as in compound **4**.

5.2.2. N*1-((5-Methoxy-1*H*-indol-3-yl)methyl)-*N*2-(5-nitropyridin-2-yl)ethane-1,2-diamine (**I-b**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 2(2-aminoethylamino)-5-nitropyridine (107 mg, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded *N*1-((5-methoxy-1*H*-indol-3-yl)methyl)-*N*2-(5-nitropyridin-2-yl)ethane-1,2-diamine as a brown solid; 7.4 mg, 3.7% yield; mp 112 °C; ^{1}H NMR (d_6-DMSO) δ 10.80 (1H, s, NH), 8.60 (1H, s, CH), 8.01 (1H, dd, $J = 2.4$ Hz, CH), 7.65 (1H, s, NH), 7.31 (1H, d, $J = 2.4$ Hz, CH), 7.29 (1H, s, CH), 7.01 (1H, s, CH), 6.80 (1H, dd, $J = 2.4$ Hz, CH), 6.45 (1H, dd, $J = 2.4$ Hz, CH), 3.85 (3H, s, OCH_3), 3.67 (2H, m, CH_2), 3.35 (2H, t, CH_2), 2.53 (2H, t, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 342.1562 (error 1.2 ppm).

5.2.3. *1-(5-Methoxy-1*H*-indol-3-yl)*-N-*(piperidin-4-ylmethyl)methanamine (**I-c**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 4-(aminomethyl)piperidine (70 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 1-(5-methoxy-1*H*-indol-3-yl)-*N*-(piperidin-4-ylmethyl)methanamine as a light-brown coloured solid; 19.1 mg, 11.8% yield; mp 127–128 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.21 (1H, s, CH), 7.15 (1H, d, $J = 2.4$ Hz, CH), 7.09 (1H, s, CH), 6.73 (1H, dd, $J = 2.4$ Hz, CH), 3.80 (3H, s, OCH_3), 3.76 (2H, s, CH_2), 2.91–2.87 (4H, m, CH_2), 2.51 (2H, s, CH_2), 1.66–1.40 (4H, m, CH_2); high-resolution ESIMS, *m*/*z* $(M + H)^+$ 274.1912 (error 2.6 ppm).

5.2.4. *2-Methoxy-4-({[(5-methoxy-1*H*-indol-3-yl)methyl]amino}methyl)phenol (**I-d**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 4-hydroxy-3-methoxy benzylamine (111 mg, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 2-methoxy-4-({[(5-methoxy-1*H*-indol-3-yl)methyl]amino}methyl)phenol as a maroon coloured solid; 1.2 mg, 0.6% yield; ^{1}H NMR (d_6-DMSO) δ 10.25 (1H, s, NH), 9.8 (1H, s, OH), 7.28 (1H, d, $J = 3.0$ Hz, CH), 7.25 (1H, s, CH), 7.11 (1H, s, CH), 6.99 (1H, s, CH), 6.80 (1H, dd, $J = 2.4$ Hz, CH), 6.75 (1H, d, $J = 2.1$ Hz, CH), 6.72 (1H, d, $J = 3.3$ Hz, CH), 3.91 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.76 (2H, s, CH_2), 3.60 (2H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 313.1547 (error 1.6 ppm).

*5.2.5. 1-(5-Methoxy-1*H*-indol-3-yl)*-N*-(3-(trifluoromethyl)benzyl)methanamine (**I-e**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 3-(trifluoromethyl) benzylamine (84 μL, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL) for 5 h. This yielded 1-(5-methoxy-1*H*-indol-3-yl)-*N*-(3-(trifluoromethyl)-benzyl)methanamine as a pink crystalline solid; 6.3 mg, 3% yield; ^{1}H NMR (d_6-DMSO) δ 10.65 (1H, s, NH), 7.76 (1H, s, CH), 7.67 (1H, t, $J = 6.9$ Hz, CH), 7.52 (1H, d, $J = 6.9$ Hz, CH), 7.38 (1H, d, $J = 6.9$ Hz, CH), 7.35 (1H, d, $J = 6.9$ Hz, CH), 7.20 (1H, s, CH), 7.11 (1H, s, CH), 6.76 (1H, dd, $J = 2.4$ Hz, CH), 3.81 (3H, s, OCH_3), 3.78 (2H, s, CH_2), 3.68 (2H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 335.1362 (error 2.7 ppm).

5.2.6. N*-((5-Methoxy-1*H*-indol-3-yl)methyl)-2-morpholinoethanamine (**I-f**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and *N*-(β-aminoethyl) morpholine (77 μL, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL) for 8 h. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)-2-morpholinoethanamine as a brown crystalline solid; 3.7 mg, 2.2% yield; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.27 (1H, d, $J = 3.0$ Hz, CH), 7.19 (1H, s, CH), 7.10 (1H, s, CH), 6.80 (1H, dd, $J = 2.4$ Hz, CH), 3.82 (3H, s, OCH_3), 3.60 (2H, s, CH_2), 3.39 (4H, t, $J = 4.5$ Hz, CH_2, CH_2), 2.57 (2H, t, $J = 6.6$ Hz, CH_2), 2.30–2.20 (2H, m, CH_2, CH_2, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 290.1862 (error 2.4 ppm).

5.2.7. N*-((5-Methoxy-1*H*-indol-3-yl)methyl)-2-(pyrrolidin-1-yl)ethanamine (**I-g**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 2-(2-aminoethyl)pyrrolidine (74 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)-2-(pyrrolidin-1-yl)ethanamine as a brown solid; 7.9 mg, 4.9% yield; mp 115–116 °C; ^{1}H NMR (d_6-DMSO) δ 10.90 (1H, s, NH),7.30 (1H, d, $J = 2.4$ Hz, CH), 7.15 (1H, s, CH), 7.09 (1H, s, CH), 6.89 (1H, dd, $J = 2.7$ Hz, CH), 3.91 (3H, s, OCH_3), 3.62 (2H, s, CH_2), 3.19–3.12 (2H, m, CH_2, CH_2, CH_2), 2.85 (2H, t, $J = 6.0$ Hz, CH_2), 1.35 (2H, m, CH_2, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 274.1911 (error 2.9 ppm).

5.2.8. N*-((5-Methoxy-1*H*-indol-3-yl)methyl)-3-(pyrrolidin-1-yl)propan-1-amine (**I-h**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 1-(3-aminopropyl)pyrrolidine (74 mg, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)-3-(pyrrolidin-1-yl)propan-1-amine as an orange crystalline solid; 25 mg, 15% yield; mp 116–117 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.50 (1H, d, $J = 2.4$ Hz, CH), 7.34 (1H, s, CH), 7.29 (1H, s, CH), 6.84 (1H, dd, $J = 2.4$ Hz, CH), 3.82 (3H, s, OCH_3), 3.53 (2H, m, CH_2), 2.55–2.46 (8H, m, CH_2), 1.91–1.80 (6H, m, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 288.2065 (error 3.8 ppm).

*5.2.9. 1-(5-Methoxy-1*H*-indol-3-yl)*-N*-(pyridin-2-ylmethyl)methanamine (**I-i**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 2-(aminomethyl)pyridine (61 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded a brown solid; 19.1 mg, 12.2% yield; mp 118–119 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 8.51 (1H, d, $J = 4.5$ Hz, CH), 7.77 (1H, t, $J = 7.5$ Hz, CH), 7.47–7.27 (2H, m, CH), 7.26 (1H, s, CH), 7.22 (1H, d, $J = 2.7$ Hz, CH), 7.10 (1H, s, CH), 6.75 (1H, dd, $J = 2.4$ Hz, CH), 3.88 (2H, s, CH_2), 3.76 (3H, s, OCH_3), 3.31 (2H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 268.1444 (error 2.2 ppm).

*5.2.10. 4-(2-{[(5-Methoxy-1*H*-indol-3-yl)methyl]amino}ethyl)benzenesulfonamide (**I-j**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 4(2-aminoethyl) benzenesulphonamide (118 mg, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL) for 3 h. This yielded 4-(2-{[(5-methoxy-1*H*-indol-3-yl)methyl]amino}ethyl)benzenesulfonamide as a brown crystalline solid; 3.2 mg, 1.6% yield; ^{1}H NMR (d_6-DMSO) δ 10.65 (1H, s, NH), 7.75 (2H, d, CH), 7.43 (2H, d, CH), 7.21 (1H, d, $J = 3.3$ Hz, CH), 7.16 (1H, s, CH), 7.02 (1H, s, CH), 6.75 (1H, dd, $J = 4.5$ Hz, CH), 3.71 (3H, s, OCH_3), 3.50 (2H, s, CH_2), 2.83 (2H, t, CH_2), 2.53 (2H, t, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 360.1376 (error 1.7 ppm).

*5.2.11. 1-(5-Methoxy-1*H*-indol-3-yl)*-N*-(4-(trifluoromethoxy)benzyl)methanamine (**I-k**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 4-(trifluoromethoxy)benzylamine (90 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 1-(5-methoxy-1*H*-indol-3-yl)-*N*-(4-(trifluoromethoxy) benzyl)methanamine as a dark green solid; 20.8 mg, 10% yield; mp 94–95 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.55 (1H, d, $J = 8.1$ Hz, CH), 7.41 (1H, s, CH), 7.27 (1H, s, CH), 7.14 (1H, s, CH), 6.97 (1H, dd, $J = 15.9$ Hz, CH), 6.85 (1H, dd, $J = 11.7$ Hz, CH), 3.87 (1H, s, CH_2), 3.77 (1H, s, CH_3), 3.49 (1H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 351.1317 (error 0.85 ppm).

*5.2.12. 4-(2-{[(5-Methoxy-1*H*-indol-3-yl)methyl]amino}ethyl)phenol (**I-l**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and tyramine (81 mg, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 4-(2-{[(5-methoxy-1*H*-indol-3-yl)methyl]amino}ethyl)phenol as a cream-coloured powdery solid; 10 mg, 5.7% yield; mp 220 °C with decomposition; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.23 (1H, d, $J = 2.4$ Hz, CH), 7.21 (1H, s, CH), 7.14 (2H, d, $J = 2.4$ Hz, CH), 7.01 (1H, s, CH), 6.71 (1H, dd, $J = 6.0$ Hz, CH), 6.67 (2H, d, $J = 2.4$ Hz, CH), 3.82 (3H, s, CH_3), 3.74 (2H, s, CH_2), 2.75 (2H, t, CH_2), 2.52 (2H, t, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 297.1594 (error 3.0 ppm).

5.2.13. N*-((5-Methoxy-1*H*-indol-3-yl)methyl)-4-methylpiperazin-1-amine (**I-m**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 1-amino-4-methyl piperazine (71 μL, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL) for 3 h. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)-4-methylpiperazin-1-amine as an orange solid; 17.3 mg, 10.7% yield; ^{1}H NMR (d_6-DMSO) δ 10.45 (1H, s, NH), 7.50 (1H, d, $J = 2.7$ Hz, CH), 7.31, (1H, s, CH), 7.21 (1H, s, CH), 6.82 (1H, dd, $J = 2.7$ Hz, CH), 3.80 (3H, s, OCH_3), 3.37 (2H, s, CH_2), 3.07 (4H, t, $J = 9.3$ Hz, CH_2, CH_2), 2.52 (4H, t, $J = 9.3$ Hz, CH_2, CH_2), 2.24 (3H, s, CH_3); high-resolution ESIMS, *m*/*z* (MH+) 275.1872 (error 0 ppm).

*5.2.14. 1-(5-Methoxy-1*H*-indol-3-yl)*-N*-((5-methylfuran-2-yl)methyl)methanamine (**I-n**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 5-methyl furfurylamine (65 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 1-(5-methoxy-1*H*-indol-3-yl)-*N*-((5-methylfuran-2-yl)methyl)methanamine as a light-brown crystalline solid; 86.3 mg, 52.6% yield; mp 111 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.49 (1H, d, $J = 8.4$ Hz, CH), 7.31 (1H, s, CH), 7.26 (1H, s, CH), 6.85 (1H, dd, $J = 7.5$ Hz, CH), 6.44 (1H, d, $J = 3$ Hz, CH), 5.98 (1H, d, $J = 2.7$ Hz, CH), 3.94 (3H, s, CH_3), 2.95 (2H, s, CH_2), 2.88 (2H, s, CH_2), 2.17 (3H, s, CH_3); high-resolution ESIMS, *m*/*z* (MH+) 271.1447 (error 0 ppm).

5.2.15. N-*((5-Methoxy-1*H*-indol-3-yl)methyl)morpholin-4-amine (**I-o**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 4-aminomorpholine (57 μL, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL) for 3 h. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)morpholin-4-amine as a black oil; 4.3 mg, 2.8% yield; ^{1}H NMR (d_6-DMSO) δ 10.55 (1H, s, NH), 7.46 (1H, d, $J = 2.4$ Hz, CH), 7.30 (1H, s, CH), 7.14 (1H, s, CH), 6.73 (1H, dd, $J = 2.4$ Hz, CH), 3.77 (3H, s, OCH_3), 3.66 (2H, s, CH_2), 3.53 (2H, t, $J = 3.0$ Hz, CH_2), 2.99 (2H, t, $J = 4.8$ Hz, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 262.1556 (error 0 ppm).

*5.2.16. 1-Adamantyl-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine*

5-Methoxyindole-3-carboxaldehyde (100 mg, 0.59 mmol) and 1-adamantylamine (89 mg, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded as a black semi-solid; 32.4 mg, 18% yield; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.26 (1H, d, $J = 2.4$ Hz, CH), 7.19 (1H, s, CH), 7.04 (1H, s, CH), 6.73 (1H, dd, $J = 2.4$ Hz, CH), 3.78 (3H, s, OCH_3), 3.62 (2H, s, CH_2), 2.14–2.07 (9H, m, CH_2, CH_2, CH_2, CH, CH, CH), 1.65 (6H, m, CH_2, CH_2, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 311.2122 (error 0.32 ppm).

*5.2.17. 3-(1*H*-Imidazol-1-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)propan-1-amine (**I-q**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 1-(3-aminopropyl)imidazole (70 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 3-(1*H*-imidazol-1-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)propan-1-amine as a yellow oil; 16.7 mg, 10% yield; ^{1}H NMR (d_6-DMSO) δ 10.65 (1H, s, NH), 8.31 (1H, s, CH), 7.30 (1H, d, $J = 2.1$ Hz, CH), 7.28 (1H, d, $J = 2.7$ Hz, CH), 7.15 (1H, s, CH), 7.05 (1H, s, CH), 6.91 (1H, dd, $J = 2.4$ Hz, CH), 6.86 (1H, d, $J = 2.7$ Hz, CH), 4.08 (2H, t, $J = 6.9$ Hz, CH_2), 3.89 (3H, s, OCH_3), 3.64 (2H, s, CH_2), 2.70 (2H, t, $J = 6.6$ Hz, CH_2), 1.98 (2H, t, $J = 4.2$ Hz, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 285.1707 (error 2.8 ppm).

*5.2.18. (1*R*,2*R*,4*R*)-*N*-((5-Methoxy-1*H*-indol-3-yl)methyl)bicyclo[2.2.1]heptan-2-amine (**I-r**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and Exo-2-aminonorbornane (70 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded (1*R*,2*R*,4*R*)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)bicyclo[2.2.1]-heptan-2-amine as a dark brown solid; 16.6 mg, 10% yield; mp 93–94 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.29 (1H, d, $J = 2.4$ Hz, CH), 7.26 (1H, s, CH), 7.16 (1H, s, CH), 6.78 (1H, dd, $J = 2.4$ Hz, CH), 3.97 (3H, s, OCH_3), 3.78 (2H, s, CH_2), 2.79–2.75 (1H, m, CH), 2.35 (1H, m, CH_2), 2.21 (1H, m, CH_2), 1.57–1.07 (8H, m, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 271.1804 (error 2.2 ppm).

*5.2.19. 1-(4,4-Dimethyl-1,3-dioxolan-2-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine (**I-s**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 2,2-dimethyl-1,3-dioxolane-4-methanamine (76 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded 1-(4,4-dimethyl-1,3-dioxolan-2-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine as an orange semi-solid; 19.9 mg, 12% yield; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.31 (1H, d, $J = 2.4$ Hz, CH), 7.27 (1H, s, CH), 7.19 (1H, s, CH), 6.78 (1H, dd, $J = 2.4$ Hz, CH), 4.27 (1H, t, $J = 6.0$ Hz, CH), 3.79 (3H, s, OCH_3), 3.98 (1H, t, $J = 6.3$ Hz, CH_2), 3.66 (1H, t, $J = 6.0$ Hz, CH_2), 2.83 (1H, m, CH_2), 2.51 (1H, m, CH_2), 1.28 (6H, s, CH_3, CH_3); high-resolution ESIMS, *m*/*z* (MH+) 291.1702 (error 2.4 ppm).

5.2.20. N-*((5-Methoxy-1*H*-indol-3-yl)methyl)-2-phenoxyethanamine (**I-t**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and 2-phenoxyethylamine (77 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) for 3 h. This yielded *N*-((5-methoxy-1*H*-indol-3-yl)methyl)-2-phenoxyethanamine as a light-brown oil; 15 mg, 8.6% yield; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.31 (2H, d, $J = 8.1$ Hz, CH, CH), 7.26 (1H, d, $J = 3.0$ Hz, CH), 7.15 (1H, s, CH), 7.04. (1H, s, CH), 6.91 (1H, s, CH), 6.89 (2H, d, $J = 8.4$ Hz, CH, CH), 6.72 (1H, dd, $J = 2.4$ Hz, CH), 4.11 (2H, t, $J = 5.4$ Hz, CH_2), 3.76 (3H, s, OCH_3), 3.52 (2H, s, CH_2), 3.01 (2H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 297.1599 (error 1.4 ppm).

*5.2.21. 1-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine (**I-u**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and *cis*-myrtanylamine (98 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) overnight. This yielded 1-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine as a white powder; 37 mg, 20% yield; mp 92–93 °C; ^{1}H NMR (d_6-DMSO) δ 10.85 (1H, s, NH), 7.20 (1H, d, $J = 9.0$ Hz, CH), 7.17 (1H, s, CH), 7.10 (1H, s, CH), 6.86 (1H, dd, $J = 2.4$ Hz, CH), 3.98 (3H, s, OCH_3), 3.89 (2H, s, CH_2), 2.91 (2H, m, CH_2), 2.40 (2H, m, CH_2), 2.01–1.82 (9H, m, CH, CH, CH, CH_2, CH_2, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 313.2275 (error 0 ppm).

*5.2.22. 1-(Benzo[*d*][1,3]dioxol-4-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine (**I-v**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and piperonylamine (73 μL, 0.59 mmol) were heated to reflux in anhydrous methanol (20 mL) overnight. This yielded 1-(benzo[*d*][1,3]dioxol-4-yl)-*N*-((5-methoxy-1*H*-indol-3-yl)methyl)methanamine as a cream-coloured powder; 7.8 mg, 4.3% yield; mp 109 °C; ^{1}H NMR (d_6-DMSO) δ 10.75 (1H, s, NH), 7.25 (1H, d, $J = 2.4$ Hz, CH), 7.22 (1H, s, CH), 6.97 (1H, s, CH), 6.82 (1H, dd, $J = 3.0$ Hz, CH), 5.98 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 3.75 (2H, s, CH_2), 3.65 (2H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 311.1391 (error 1.6 ppm).

5.2.23. N-*Benzyl-1-(5-methoxy-1*H*-indol-3-yl)methanamine (**I-w**)*

5-Methoxyindole-3-carboxaldehyde (**3**) (100 mg, 0.59 mmol) and benzylamine (64 μL, 0.59 mmol) were heated to reflux in anhydrous acetonitrile (20 mL) for 3 h. This yielded *N*-benzyl-1-(5-methoxy-1*H*-indol-3-yl)methanamine as a black oil; 24.6 mg, 16% yield; ^{1}H NMR (d_6-DMSO) δ 10.75 (1H, s, NH), 7.43 (2H, m, CH, CH), 7.34 (1H, s, CH), 7.32 (2H, m, CH, CH), 7.24 (1H, d, $J = 2.4$ Hz, CH), 7.14 (1H, s, CH), 7.02 (1H, s, CH), 6.88 (1H, dd, $J = 2.4$ Hz, CH), 3.89 (3H, s, OCH_3), 3.77 (2H, s, CH_2), 3.69 (2H, s, CH_2); high-resolution ESIMS, *m*/*z* (MH+) 267.1490 (error 2.6 ppm).

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