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SYNTHESIS OF 7,7′-LINKED-BIS-INDOLES VIA 7-TRYPTAMINES

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Dedicated to Prof. Dr. Lutz F. Tietze on the occasion of his 75th birthday

Abstract – The synthesis of 7-tryptamines was accomplished via the reduction of 7-nitrovinylindoles which were developed by the condensation of indole-7-carbaldehydes with nitromethane and ammonium acetate. 7-Tryptamines were subsequently used for the construction of 2,3-disubstituted and 3-substituted 7,7′-linked-bis-indoles.

INTRODUCTION

Tryptamine **1** and its derivatives are a class of organic compounds built around an indole nucleus with an ethanamine substituent at the C3 position (**Figure 1**). Many members of this family display various biological properties. For example, the neurotransmitter serotonin (5-hydroxytryptamine) **2** is active in the central nervous system and regulates mood, appetite, sleep and self-control,[1] and melatonin (*N*-acetyl-5-methoxytryptamine) **3** is responsible for the control of circadian rhythm and blood pressure regulation.[2] It has recently been reported that tryptamine derivatives may also function as bacterial efflux

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pumps and inhibitors of CDK4, an anticancer drug.[3,4]

In addition to the biological importance of tryptamine and its derivatives, the ethanamine substituent offers a great number of possibilities for functionalisation and derivatisation, allowing a large number of analogues to be synthesised. Importantly, it is also possible to functionalise the benzenoid ring, allowing the addition of primary amines at the C7 position and subsequent formation of 7,7′-tryptamine based bis-indole systems.

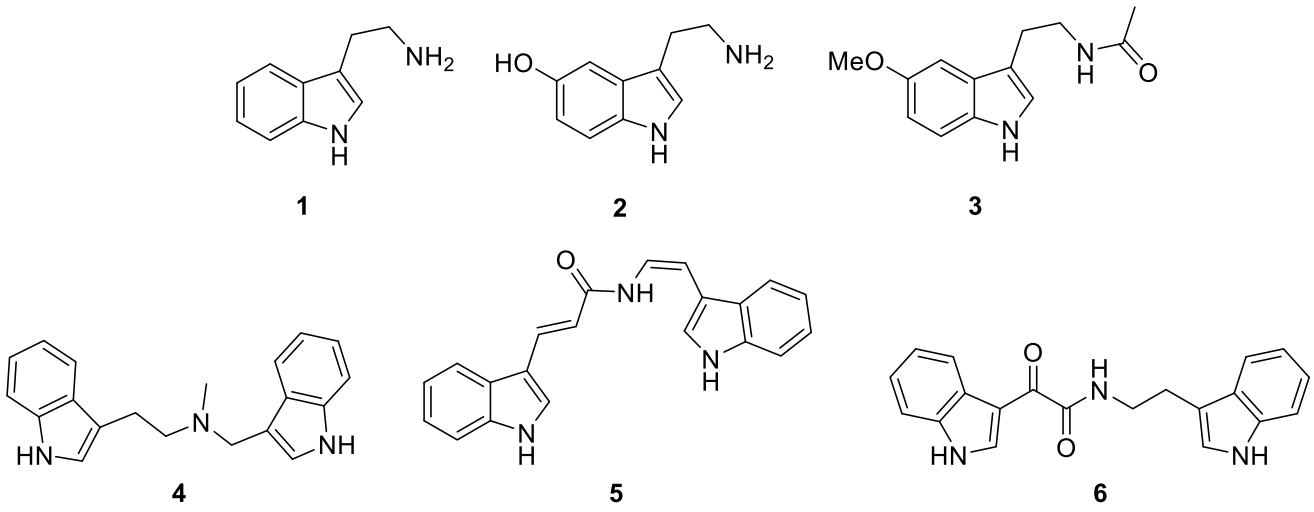


Figure 1. Examples of naturally occurring and biologically active tryptamines

Tryptamine based bis-indoles have been isolated from natural sources and demonstrate potential as biologically active compounds and useful synthetic targets. For example, bis-indole **4**, isolated from the roots of *Antirhea lucida*, has been synthesized from tryptamine derivatives through acid catalysed nucleophilic substitution of 1-hydroxytryptamine,[5] while chondriamide C **5** was isolated from red alga *Chondria atropurpurea* and possesses anthelmintic activity.[6]

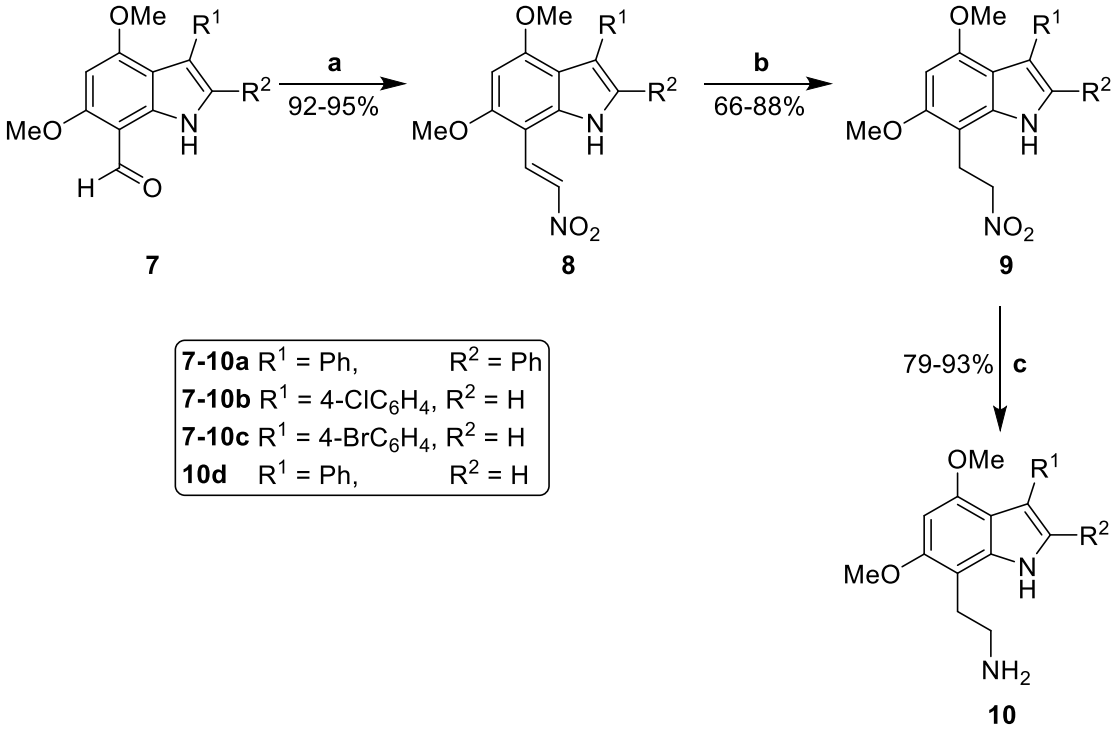
Recently, other analogues of marine natural products containing a tryptamine nucleus have been synthesized and screened for biological activity. For instance, 8,9-dihydrocoscinamide **6**, with a structure derived from tryptamine and indole oxalyl chloride, was found to display inhibition against promastigote and amastigote protozoa.[7]

Given the important biological activities of tryptamine derivatives and their related bis-indoles, we were interested in the development of novel 4,6-dimethoxyindole-7-tryptamine analogues and related bis-indoles. In 1969, lithium aluminium hydride reduction of 4,6-dimethoxy-7-nitrovinylindole was reported to give 4,6-dimethoxy-7-tryptamine as a dark gum that gave a gummy hydrochloride and eventually a crystalline picrate.[8]

RESULTS AND DISCUSSION

SYNTHESIS OF 7-TRYPTAMINE ANALOGUES

The general development of 4,6-dimethoxy-7-tryptamines was successfully achieved over a convenient three-step process as demonstrated in **Scheme 1**. The first step involved the reaction of readily available 7-carbaldehydes **7a-c** with excess ammonium acetate in nitromethane for 3 hours to give the target 7-nitrovinylindoles **8a-c** in 92-95% yields. The reduction of these nitrovinylindoles to the corresponding amines was then examined. Accordingly, 7-nitrovinylindole **8a** was treated with lithium aluminium hydride in tetrahydrofuran, however, the reaction was found to produce many side products and the desired tryptamine **10a** could not be isolated.



Scheme 1. Reagents and conditions: (a) $MeNO_2$, ammonium acetate, reflux, 3 h; (b) $NaBH_4$, absolute EtOH and THF, rt; (c) $NH_2NH_2 \cdot H_2O$, Pd/C, absolute EtOH, 4 h.

As an alternative strategy, a two stage reduction of the 7-nitrovinylindoles **8a-c** was undertaken in an attempt to avoid the formation of a complex mixture. In the first step, indoles **8a-c** were reduced with sodium borohydride in a mixture of tetrahydrofuran and ethanol (1:1) to produce the 7-nitroethylindoles **9a-c** in yields of 66-88%. The reaction was found to similarly produce a number of unwanted side products, however, they were minimised upon cooling the reaction mixture in an ice bath. The appearance of two triplet signals at 3.44 ppm and 4.65 ppm, and the disappearance of the nitrovinyl doublets at 8.14

ppm and 8.67 ppm in the ^{1}H NMR of compound **9b** provided evidence for the reduction occurring at the double bond.

In order to reduce the nitro group to the primary amine, the 7-nitroethylindoles **9a-c** were heated with hydrazine hydrate and 10% Pd/C in ethanol for 4 hours to give in each case a single product in 79-93% yield (**Scheme 1**).

The ^{1}H NMR spectrum of the compound **10a** showed the upfield shift of the methylene triplets to 3.04 ppm and 3.11 ppm respectively. The ^{13}C NMR spectrum also indicated the methylene carbon attached to C7 of the indole nucleus at 27.5 ppm and the methylene carbon adjacent to the amino group at 41.9 ppm. Interestingly, the ^{1}H NMR spectra of the anticipated compounds **10b** and **10c** did not demonstrate the two characteristic aromatic doublets expected for the para-substituted rings. Instead, the aryl protons appeared as multiplets between 7.15-7.55 ppm and integrated for 5H, indicating that the halogen atoms had been lost during the reduction to give amine **10d**. This dehalogenation was further confirmed by high resolution mass spectrometry, as well as through the presence of three aryl CH resonances at 125.8, 127.9 and 129.9 ppm in the ^{13}C NMR spectrum, as opposed to the two aryl CH resonances expected. This result is not entirely surprising as the Pd/C-catalysed dehalogenation of aromatic halides is well documented in the literature.[9-12] Moreover; the reducing reagent hydrazine hydrate is also known to cause dehalogenation.[13]

The 7-tryptamines **10a** and **10d** were found to be air stable, and it was not necessary to convert them to the hydrochloride or hydrobromide salt in order to increase their stability. Purification, however, was hindered by their high polarity such that they remained on the baseline of thin layer chromatography plates even with the use of highly polar solvent systems such as methanol or ethanol. Because of this, purification was instead achieved by washing the crude product with diethyl ether.

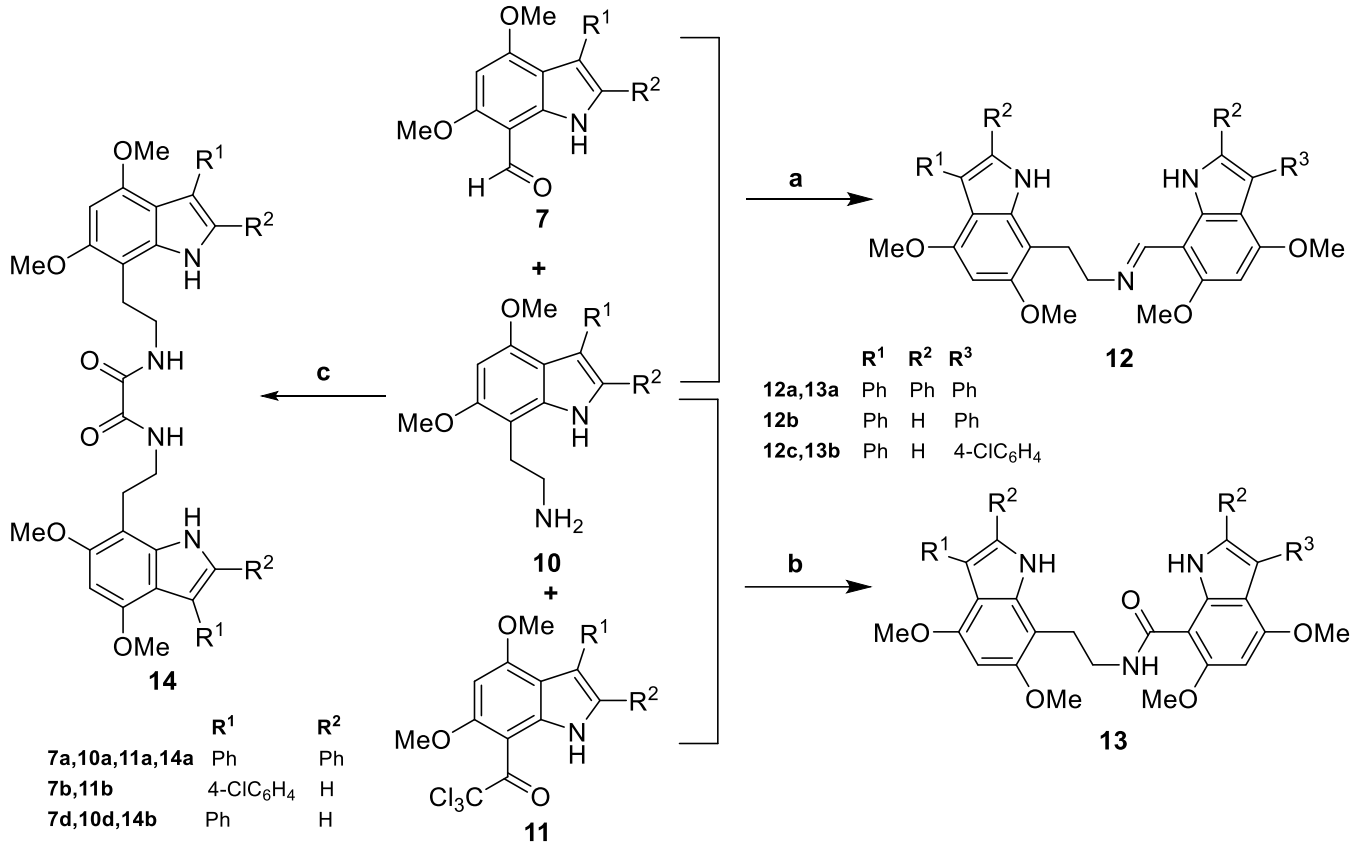
SYNTHESIS OF 7-TRYPTAMINE-BASED BIS-INDOLES

The primary amine functionality of the developed 7-tryptamines was used as a functional handle in the synthesis of a range of unsymmetrical and symmetrical bis-indoles.

Unsymmetrical 7,7′-imine linked bis-indoles were prepared from indoles **10a** and **10d** upon reflux with 7-formylindoles **7a**, **7b** and **7d** in ethanol. Bis-indoles **12a-c** precipitated out of solution and were collected by filtration to give yields of 43-69% (**Scheme 2**).

The structure of bis-indole **12a** was confirmed by high resolution mass spectrometry, which showed the molecular ion at 712.3159 $(M+H)^{+}$. The ^{1}H NMR spectrum showed the imine proton signal at 8.30 ppm and four methoxy protons at 3.72, 3.76, 3.88 and 3.91 ppm. However, compound **12a** was found to be highly insoluble and this inhibited the collection of a satisfactory ^{13}C NMR spectrum.

Unsymmetrical 7,7′-amide linked bis-indoles were then synthesised at room temperature *via* the reaction of 7-tryptamines **10a** and **10d** with 7-trichloroacetylindoles **11a** and **11b** in acetonitrile in the presence of triethylamine. The target amide linked bis-indoles **13a** and **13b** were isolated in 59% and 79% yield respectively (**Scheme 2**).



Scheme 2. Reagents and conditions: (a) absolute EtOH, reflux; (b) Et_3N, MeCN, rt; (c) oxalyl chloride, Et_3N, DCM, rt.

The new amide functionality was clearly evident in the ^1H and ^{13}C NMR spectra of compound **13a**, with the amide NH proton present as a triplet at 8.38 ppm and the carbonyl group appearing at 167.3 ppm. The ^1H NMR spectrum also showed the indole NH protons as singlets at 11.13 ppm and 11.30 ppm and the ethylene protons as a quartet at 2.48 ppm (J = 5.4 Hz) and triplet at 3.18 ppm (J = 13.5 Hz).

Symmetrically linked 7-bisoxalamides **14a** and **14b** were prepared in moderate yields by reacting 7-tryptamines **10a** and **10d** with oxalyl chloride in dichloromethane at room temperature.

Evidence for the formation of compound **14b** was provided by the ^1H NMR spectra, which showed the appearance of a triplet at 8.53 ppm corresponding to the amide NH proton while the indole NH was a doublet at 11.02 ppm. The ^{13}C NMR spectrum showed the presence of the carbonyl carbon at 160.2 ppm,

and the IR spectrum further supported the structure by showing the distinctive carbonyl absorption at 1650 cm^{-1}.

In all cases, the synthesised bis-indoles were found to be very stable under standard laboratory conditions but showed poor solubility in the majority of organic solvents.

BIOLOGICAL EVALUATION OF 7-TRYPTAMINE INDOLE ANALOGUES

The 7-tryptamines were tested for their effect on the cell viability and proliferation of the SH-SY5Y human neuroblastoma cell line. **Table 1** details the potency of the tested compounds, giving the pIC_{50} values of each. **10a** was the most potent of the compounds, displaying both cytotoxic and cytostatic behaviour towards neuroblastoma cells. **10b** and **10d** also displayed cytotoxic and cytostatic behaviour, but with less potency. The pIC_{50} values for proliferation were unable to be calculated for **10b** and **10d** because of a large overlap between cytotoxic and cytostatic concentrations, however **Table 2** demonstrates that at concentrations which did not impair viability, these 2 compounds still displayed cytostatic effects.

Table 1. Potency to inhibit viability and proliferation of SH-SY5Y neuroblastoma cells

Compound	Viability pIC_{50}	Proliferation pIC_{50}
10a	4.86 ± 0.06	5.25 ± 0.03
10b	4.45 ± 0.08	N/A
10d	4.58 ± 0.08	N/A

N/A indicates pIC_{50} values could not be calculated due to cell death at 100 μM. Values are mean ± S.D.

Table 2. Viable cells and level of proliferation as a percentage of vehicle for **10b** and **10d**

Compound	Percentage viability			Percentage proliferation		
	1 μM	10 μM	100 μM	1 μM	10 μM	100 μM
10b	101.7 ± 1.0	101.8 ± 2.3	0.2 ± 0.1**	99.3 ± 11.8	74.3 ± 5.2*	N/A
10d	100.1 ± 3.5	97.4 ± 1.8	0.3 ± 0.2**	91.5 ± 6.5	55.7 ± 17.3**	N/A

Threshold for statistical significance: * $p<0.01$; ** $p<0.001$ when compounds compared to vehicle.

CONCLUSION

A general synthesis of 7-tryptamines has been developed by a sequence of reactions involving the conversion of indole-7-carbaldehydes to 7-nitrovinylindoles, followed by sequential reduction of the alkene and the nitro groups. The 7-tryptamines were used to form amide and imine bonds in the construction of a variety of 7,7′-linked-bis-indoles. Preliminary biological assays also indicate that the

7-tryptamines have a moderate impact on the viability and proliferation of the SH-SY5Y neuroblastoma cancer cell line.

EXPERIMENTAL

GENERAL

All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyses EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on Bruker DPX300 (300 MHz) and Bruker DPX600 (600 MHz) spectrometers. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI). Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Pressure column chromatography was carried out using Merck 230-400 mesh ASTM silica gel. Vacuum column chromatography was carried out using Merck 60H silica gel. Gravity column chromatography was carried out using Merck 70-230 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 $60GF^{254}$.

4,6-Dimethoxy-2,3-diphenyl-7-(2-nitroethenyl)-1*H*-indole **(8a)**

A mixture of 7-carbaldehyde **7a** (1.98 g, 5.53 mmol) and ammonium acetate (3.8 g, 49.29 mmol) in $MeNO_2$ (25 mL) was heated at reflux for 3 h and evaporated to dryness in *vacuo*. The residue was quenched with water and the solid obtained was filtered, dried and washed with EtOH to give the *title compound* **8a** (2.1 g, 95%) as a red solid, mp 215-217 ºC. Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00%. Found: C, 71.89; H, 5.02; N, 7.03. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (3H, s, OMe), 4.03 (3H, s, OMe), 6.46 (1H, s, H5), 7.22-7.28 (10H, m, aryl H), 8.14, 8.86 (2H, 2d, *J* 12.6 Hz, CH), 11.83 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 56.9 (OMe), 89.2 (C5), 132.4, 135.1 (ethenyl CH) 126.5, 127.6, 127.7, 128.4, 129.2, 131.5 (aryl CH), 96.9, 112.7, 114.8, 132.3, 134.1, 135.8, 138.2, 159.5, 160.4 (aryl C); ν_{max} (KBr): 3342, 1601, 1460, 1280, 1247, 1140, 989, 696 cm^{-1}; λ_{max} (MeOH): 204 nm (ε 37,600 $cm^{-1}M^{-1}$), 241 (26,800), 314 (15,300); HRMS (+ESI): $[M+H]^+$, found 401.1492. $C_{24}H_{20}N_2O_4$ requires 401.1501.

3-(4-Chlorophenyl)-4,6-dimethoxy-7-(2-nitrovinyl)-1*H*-indole **(8b)**

A mixture of 7-carbaldehyde **7b** (0.73 g, 2.31 mmol) and ammonium acetate (1.114 g, 14.45 mmol) in $MeNO_2$ (18 mL) was heated at reflux for 3 h and evaporated to dryness in *vacuo*. The residue was quenched with water and the solid obtained was filtered, dried and washed with EtOH to give the *title*

compound **8b** (0.77 g, 93%) as a red solid, mp 228-230 ºC. Anal. Calcd for $C_{18}H_{15}ClN_2O_4$ requires C, 60.26; H, 4.21; N, 7.81%. Found: C, 60.41; H, 4.26; N, 7.71. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 3.93 (3H, s, OMe), 4.06 (3H, s, OMe), 6.54 (1H, s, H5), 7.35 (1H, s, H2), 7.40, 7.55 (4H, *J* 8.40 Hz, 2d, aryl H), 8.14, 8.66 (2H, 2d, *J* 13.2 Hz, CH), 11.89 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 56.0, 57.0 (OMe), 89.1 (C5), 123.8 (C2), 131.7, 134.6 (ethenyl CH), 127.9, 131.1 (aryl CH), 96.9, 110.2, 117.1, 130.7, 134.7, 138.4, 159.5, 160.3 (aryl C); ν_{max} (KBr): 3439, 3293, 1614, 1578, 1292, 1274, 1254, 1181, 1103, 979 cm^{-1}; λ_{max} (MeOH): 202 nm (ε 33,350 cm^{-1}M^{-1}), 228 (30,650), 283 (14,400); HRMS (+ESI): $[M+H]^+$, found 359.0793. $C_{18}H_{15}ClN_2O_4$ requires 359.0799.

3-(4-Bromophenyl)-4,6-dimethoxy-7-(2-nitroethenyl)-1*H*-indole **(8c)**

A mixture of 7-carbaldehyde **7c** (3.73 g, 10.38 mmol) and ammonium acetate (4.78 g, 62 mmol) in $MeNO_2$ (25 mL) was heated at reflux for 3 h and evaporated to dryness in *vacuo*. The residue was quenched with water and the solid obtained was filtered, dried and washed with EtOH to give the *title compound* **8c** (3.84 g, 92%) as a red solid. mp 226-228 ºC. Anal. Calcd for $C_{18}H_{15}BrN_2O_4$: C, 53.62; H, 3.75; N, 6.95%. Found: C, 53.67; H, 3.67; N, 6.94. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 3.94 (3H, s, OMe), 4.07 (3H, s, OMe), 6.55 (1H, s, H5), 7.36 (2H, d, *J* 1.9 Hz, H2), 7.48, 7.54 (4H, 2d, *J* 8.6 Hz, aryl H), 8.14, 8.67 (2H, 2d, *J* 13.2 Hz, CH), 11.90 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 56.0, 57.0 (OMe), 89.1 (C5), 123.8 (C2), 131.7, 134.6 (ethenyl CH), 130.8, 131.5 (aryl CH), 96.9, 110.2, 117.1, 119.2, 135.1, 138.4, 159.5, 160.3 (aryl C); ν_{max} (KBr): 3279, 1618, 1577, 1461, 1209, 1111, 795 cm^{-1}; λ_{max} (MeOH): 202 nm (ε 40,900 cm^{-1}M^{-1}), 228 (40,150), 284 (19,200); HRMS (+ESI): $[M+H]^+$, found 403.0284. $C_{18}H_{15}BrN_2O_4$ requires 403.0293.

4,6-Dimethoxy-2,3-diphenyl-7-(2-nitroethyl)-indole **(9a)**

Sodium borohydride (1.00 g, 26.31 mmol) was added in portions to a stirred suspension of 7-nitroethenylindole **8a** (1.85 g, 4.62 mmol) in a mixture of EtOH/THF (45 mL) (2:1) at room temperature with cooling using an ice bath. Stirring was continued with cooling for 1 h. The mixture was poured into ice water and acidified to pH 3 with dilute hydrochloric acid (2 M). The resulting precipitate was filtered, dried and recrystallised from DCM/*n*-hexane to yield the *title compound* **9a** (1.23 g, 66%) as a yellow solid, mp 196-198 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53 (2H, t, *J* 13.9 Hz, CH_2), 3.72 (3H, s, OMe), 3.94 (3H, s, OMe), 4.72 (2H, t, *J* 13.2 Hz, CH_2), 6.32 (1H, s, H5), 7.25-7.43 (10H, m, aryl H), 8.40 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3 (CH_2), 55.6, 56.5 (OMe), 74.8 (CH_2-NO_2), 89.0 (C5), 126.0, 127.2, 127.3, 128.0, 128.5, 131.4 (aryl CH), 98.2, 113.5, 115.2, 132.8, 133.0, 135.8, 137.1, 154.5, 154.5 (aryl C); ν_{max} (KBr): 3443, 2359, 2341, 1600, 1548, 1220, 1126, 697 cm^{-1}; λ_{max} (MeOH): 206 nm (ε

46,750 $cm^{-1}M^{-1}$), 246 (27,600), 323 (15,800); HRMS (+ESI): $[M+Na]^+$, found 425.1460. $C_{24}H_{22}N_2O_4$ requires 425.1472.

3-(4-Chlorophenyl)-4,6-dimethoxy-7-(2-nitroethyl)-indole **(9b)**

Sodium borohydride (1.00 g, 26.31 mmol) was added in portions to a stirred suspension of 7-nitroethenylindole **8b** (0.7 g, 1.95 mmol) in a mixture of EtOH/THF (30 mL) (2:1) at room temperature with cooling using an ice bath. Stirring was continued with cooling for 1 h. The mixture was poured into ice water and acidified to pH 3 with dilute hydrochloric acid (2 M). The resulting precipitate was filtered, dried and recrystallised from DCM/*n*-hexane to yield the *title compound* **9b** (0.62 g, 88%) as a yellow solid, mp 176-178 ºC; Anal. Calcd for $C_{18}H_{17}ClN_2O_4$: 59.92; H, 4.75; N, 7.76%. Found: C, 60.00; H, 4.72; N, 7.86. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.41 (2H, t, *J* 15.1 Hz, CH_2), 3.77 (3H, s, OMe), 3.83 (3H, s, OMe), 4.64 (2H, t, *J* 14.4 Hz, CH_2), 6.42 (1H, s, H5), 7.28 (1H, d, *J* 2.7 Hz, H2), 7.34, 7.52 (4H, 2d, *J* 8.4 Hz, aryl H), 11.25 (1H, d, *J* 1.6 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.0 (CH_2), 55.5, 57.1 (OMe), 74.6 (CH_2-NO_2), 89.4 (C5), 123.3 (C2), 127.8, 130.9 (aryl CH), 99.0, 110.1, 116.2, 135.5, 138.2, 153.4, 154.2 (aryl C); ν_{max} (KBr): 3386, 2938, 2840, 1622, 1597, 1541, 1328, 1121, 1099, 835 cm^{-1}; λ_{max} (MeOH): 228 nm (ε 32,950 $cm^{-1}M^{-1}$), 282 (15,450); HRMS (+ESI): $[M+H]^+$, found 361.0948. $C_{18}H_{17}ClN_2O_4$ requires 361.0955.

3-(4-Bromophenyl)-4,6-dimethoxy-7-(2-nitroethyl)-indole **(9c)**

Sodium borohydride (2.00 g, 52.62 mmol) was added in portions to a stirred suspension of 7-nitroethenylindole **8c** (2.8 g, 6.96 mmol) in EtOH/THF (75 mL) (2:1) at room temperature with cooling using an ice bath. Stirring was continued with cooling for 1 h. The mixture was poured into ice water and acidified to pH 3 with dilute hydrochloric acid (2 M). The resulting precipitate was filtered, dried and recrystallised from DCM/*n*-hexane to yield the *title compound* **9c** (2.02 g, 72%) as a yellow solid, mp 184-186ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44 (2H, t, *J* 13.6 Hz, CH_2), 4.65 (2H, t, *J* 13.6 Hz, CH_2), 3.81 (3H, s, OMe), 3.91 (3H, s, OMe), 6.32 (1H, s, H5), 7.03 (1H, d, *J* 2.5 Hz, H2), 7.42-7.49 (4H, m, aryl H), 8.37 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (CH_2), 55.2, 56.3 (OMe), 74.6 (CH_2-NO_2), 88.5 (C5), 121.5 (C2), 130.5, 131.0 (aryl CH), 98.3, 110.3, 118.0, 119.7, 134.8, 137.9, 153.9, 154.4 (aryl C); ν_{max}. (KBr): 3392, 2937, 2839, 1621, 1593, 1541, 1328, 1120, 1007, 798 cm^{-1}; λ_{max} (MeOH): 203 nm (ε 50,400 $cm^{-1}M^{-1}$), 221 (46,350), 283 (18,800); HRMS (+ESI): $[M+Na]^+$, found 427.0263. $C_{18}H_{17}N_2O_4$ requires 427.0264.

2-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-ethanamine **(10a)**

To a refluxing solution of 7-nitroethylindole **9a** (1.00 g, 2.48 mmol) in absolute EtOH/THF (60 mL) (3.1), 10% Pd/C (0.32 g) was added under argon followed by the dropwise addition of hydrazine monohydrate (5 mL) over 15 min. The reaction mixture was heated under reflux for another 4 h, then filtered through Celite and the solvent was removed under reduced pressure. The residue was quenched with water and the resulting precipitate was filtered, dried and washed with Et_2O to yield the *title compound* **10a** (0.73 g, 79%) as a grey solid, mp 170-172 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.04 (2H, t, *J* 9.9 Hz, CH_2), 3.11 (2H, t, *J* 10.0 Hz, CH_2), 3.69 (3H, s, OMe), 3.88 (3H, s, OMe), 6.31 (1H, s, H5), 7.17-7.44 (10H, m, aryl H), 10.98 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.5, 41.9 (CH_2), 55.5, 57.6 (OMe), 90.2 (C5), 125.7, 126.6, 127.2, 127.9, 128.2 (aryl CH), 104.5, 113.6, 114.5, 132.9, 133.4, 136.4, 137.9, 153.3, 153.2 (aryl C); ν_{max} (KBr): 3341, 3193, 2936, 1601, 1454, 1292, 1104, 701 cm^{-1}; λ_{max} (MeOH): 246 nm (ε 29,350 cm^{-1}M^{-1}), 323 (16,550). HRMS (+ESI): $[M+H]^+$, found 373.1917. $C_{24}H_{24}N_2O_2$ requires 373.1916.
The related acetamide was formed by reaction of 7-tryptamine **10a** with acetic anhydride in 57% yield as a yellow solid, mp 223-225 ºC; ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.96 (2H, t, *J* 14.5 Hz, CH_2), 3.17-3.24 (2H, m, CH_2), 3.60 (3H, s, OMe), 3.82 (3H, s, OMe), 6.35 (1H, s, H5), 7.19-7.30 (10H, m, aryl H),7.96 (1H, t, *J* 10.4 Hz, NH), 11.00 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 23.0 (Me), 24.4, 39.2 (CH_2), 55.5, 57.2 (OMe), 90.0 (C5), 126.1, 127.1, 127.6, 128.5, 128.7, 131.5 (aryl CH), 102.7, 112.9, 114.2, 133.01, 133.2, 136.7, 137.5, 153.1, 153.8 (aryl C), 170.1 (C=O); ν_{max} (KBr): 3436, 3187, 1655, 1600, 1454, 1271, 1214, 1163, 1125, 765, 700 cm^{-1}; λ_{max} (MeOH): 205 nm (ε 71,250 cm^{-1}M^{-1}), 247 (42,400), 325 (24,450); HRMS (+ESI): $[M+H]^+$, found 415.2009. $C_{26}H_{26}N_2O_3$ requires 415.2021.

2-(4,6-Dimethoxy-3-phenyl-1*H*-indol-7-yl)-ethanamine **(10d)**

To a refluxing solution of 7-nitroethylindole **9b** (1.59 g, 4.4 mmol) in absolute EtOH/THF (60 mL) (3:1), 10% Pd/C (0.4 g) was added under argon followed by the dropwise addition of hydrazine monohydrate (6 mL) over 15 min. The reaction mixture was heated under reflux for another 4 h then filtered through Celite and the solvent was removed under reduced pressure. The residue was quenched with water and the resulting precipitate was filtered, dried and washed with Et_2O to yield the *title compound* **10d** (1.10 g, 93%) as a grey solid, mp 135-137 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90, 2.94 (4H, 2d, *J* 4.5 Hz, CH_2), 3.71 (3H, s, OMe), 3.79 (3H, s, OMe), 6.26 (1H, s, H5), 6.98 (1H, s, H2), 7.15-7.55 (5H, m, aryl H), 10.23 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 42.3 (CH_2), 55.9, 56.0 (OMe), 90.5 (C5), 122.1 (C2), 125.8, 127.9, 129.9 (aryl CH), 104.9, 111.4, 119.0, 136.9, 139.4, 153.6, 154.1 (aryl C); ν_{max} (KBr): 2933, 2359, 1600, 1519, 1462, 1331, 1215, 1127 cm^{-1}; λ_{max} (MeOH): 229 nm (ε 44,550 cm^{-1}M^{-1}), 281 (16,800). HRMS (+ESI): $[M+H]^+$, found 297.1596. $C_{18}H_{20}N_2O_2$ requires 297.1603.

(*E*)-2-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-*N*-((4,6-dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-

methylene)-ethanamine **(12a)**

A mixture of 7-carbaldehyde **7a** (0.19 g, 0.53 mmol) and 7-tryptamine **10a** (0.20 g, 0.53 mmol) was heated under reflux in absolute EtOH (25 mL) for 24 h. The precipitate was filtered, washed with water and dried. The crude product was purified by flash chromatography using DCM/EtOAc (90:10) as eluent to yield the *title compound* **12a** (0.16 g, 43%) as a pale yellow solid, mp 131-133 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22 (2H, t, *J* 12.3 Hz, CH_2), 3.71 (3H, s, OMe), 3.75 (3H, s, OMe), 3.87 (3H, s, OMe), 3.91 (3H, s, OMe), 4.00 (2H, t, *J* 11.7 Hz, CH_2), 6.16 (1H, s, H5), 6.35 (1H, s, H5′), 6.75-7.32 (20H, m, aryl H), 8.30 (1H, s, CH), 8.86 (1H, bs, NH); ν_{max} (KBr): 3427, 2931, 2835, 1624, 1597, 1462, 1361, 1244, 1123, 696 cm^{-1}; λ_{max} (CH_2Cl_2): 229 nm (ε 81,100 cm^{-1}M^{-1}), 251 (78,450), 328 (46,750); HRMS (+ESI): $[M+H]^+$, found 712.3159. $C_{47}H_{41}N_3O_4$ requires 712.3175. The sample was not soluble enough for ^{13}C NMR measurement.

(*E*)-2-(4,6-Dimethoxy-3-phenyl-1*H*-indol-7-yl)-*N*-((4,6-dimethoxy-3-phenyl-1*H*-indol-7-yl)-methylene)-ethanamine **(12b)**

A mixture of 7-carbaldehyde **7d** (0.21 g, 0.75 mmol) and 7-tryptamine **10d** (0.23 g, 0.75 mmol) was heated under reflux in absolute EtOH (30 mL) for 8 h. The precipitate was filtered, washed with water and dried. The crude product was purified by flash chromatography using DCM/EtOAc (90:10) as eluent to yield the *title compound* **28** (0.29 g, 69%) as a yellow solid, mp 229-231 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (2H, t, *J* 13.9 Hz, CH_2), 3.77 (3H, s, OMe), 3.85 (6H, s, OMe), 3.87 (3H, s, OMe), 3.91 (3H, s, OMe), 6.42 (1H, s, H5), 6.45 (1H, s, H5′), 7.17-7.56 (12H, m, H2, H2′, aryl H), 8.76 (1H, s, CH), 11.17 (1H, d, *J* 2.2 Hz, NH), 11.26 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.9 (CH_2), 55.5, 55.7, 57.1, 57.2 (OMe), 61.1 (CH_2), 88.5 (C5), 89.8 (C5′), 122.9 (C2), 125.4 (C2′), 125.8, 127.9, 128.0, 129.3, 129.4 (aryl CH), 101.3, 103.7, 109.9, 110.3, 117.4, 117.5, 136.3, 136.9, 137.0, 138.8, 152.8, 153.7, 157.2, 157.7 (aryl C), 156.8 (C=N); ν_{max} (KBr): 3425, 3314, 2927, 2834, 1625, 1596, 1517, 1462, 1358, 1328, 1209, 1148, 1085, 1025, 701 cm^{-1}; λ_{max} (THF): 311 nm (ε 28,750 cm^{-1}M^{-1}); HRMS (+ESI): $[M+H]^+$, found 560.2538. $C_{35}H_{33}N_3O_4$ requires 560.2549.

(*E*)-*N*-((3-(4-Chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl)-methylene)-2-(4,6-dimethoxy-3-phenyl-1*H*-indol-7-yl)-ethanamine **(12c)**

A mixture of 7-carbaldehyde **7b** (0.22 g, 0.71 mmol) and 7-tryptamine **10d** (0.23 g, 0.71 mmol) was refluxed in absolute EtOH (30 mL) for 24 h. The precipitate was filtered, washed with water and dried. The crude product was purified by flash chromatography using DCM/EtOAc (90:10) as eluent to yield the *title compound* **12c** (0.25 g, 65%) as a yellow solid, mp 284-286 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.18 (2H, t, *J* 13.7 Hz, CH_2), 3.75 (3H, s, OMe), 3.84 (6H, s, OMe), 3.88 (3H, s, OMe), 6.41 (1H, s, H5),

6.42 (1H, s, H5′), 7.16 (2H, t, *J* 6.8 Hz, H2, H2′), 7.21-7.52 (9H, m, aryl H), 8.72 (1H, s, CH), 11.14 (1H, bs, NH), 11.27 (1H, bs, NH); ν_{max} (KBr): 3336, 1593, 1463, 1344, 1210, 1173, 1148, 1089 cm^{-1}; λ_{max} (THF): 228 nm (ε 69,600 $cm^{-1}M^{-1}$), 286 (28,450); HRMS (+ESI): $[M+H]^+$, $C_{35}H_{32}ClN_3O_4$ requires 594.2160, found 594.2153. The sample was not soluble enough for ^{13}C NMR measurement.

N-(2-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-ethyl)-4,6-dimethoxy-2,3-diphenyl-1*H*-indole-7-carboxamide **(13a)**

To a suspension of 7-tryptamine **10a** (0.15 g, 0.4 mmol) and 7-trichloroacetylindole **11a** (0.19 g, 0.4 mmol) in MeCN (20 mL), triethylamine (3 drops) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water and the resulting precipitate was filtered, washed with water, dried and recrystallised from MeOH to afford the *title compound* **13a** (0.26 g, 80%) as a pale green solid, mp 283-285 ºC; Anal. Calcd for $C_{47}H_{41}N_3O_5$: C, 77.56; H, 5.68; N, 5.82%: Found: C, 77.27; H, 5.72; N, 5.82. ^1H NMR (300 MHz, DMSO-d_6): δ 2.48 (2H, q, *J* 5.4 Hz, CH_2), 3.18 (2H, t, *J* 13.5 Hz, CH_2), 3.62 (3H, s, OMe), 3.70 (3H, s, OMe), 3.82 (3H, s, OMe), 3.84 (3H, s, OMe), 6.38 (1H, s, H5), 6.40 (1H, s, H5′), 7.10-7.27 (20H, m, aryl H), 8.38 (1H, t, *J* 10.3 Hz, NH), 11.1 (1H, bs, NH), 11.30 (1H, bs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.2, 39.2 (CH_2), 55.6, 55.8, 57.0, 57.3 (OMe), 88.8 (C5), 90.0 (C5′), 126.1, 126.5, 127.1, 127.6, 127.8, 127.9, 128.4, 128.7, 129.0, 131.5, 131.5 (aryl CH), 97.1, 102.4, 112.9, 113.0, 113.7, 114.1, 132.4, 132.5, 133.1, 133.3, 135.9, 136.7, 137.7, 138.1, 153.3, 153.9, 156.9, 157.4 (aryl C), 167.3 (C=O); ν_{max} (KBr): 3407, 2927, 1618, 1502, 1264, 1213, 1116, 697 cm^{-1}. λ_{max} (CH_2Cl_2): 228 nm (ε 75,000 $cm^{-1}M^{-1}$), 250 86,750), 335 (54,100); HRMS (+ESI): $[M+H]^+$, found 728.3115. $C_{47}H_{41}N_3O_5$requires 728.3124.

3-(4-Chlorophenyl)-*N*-(2-(4,6-dimethoxy-3-phenyl-1*H*-indol-7-yl)-ethyl)-4,6-dimethoxy-1*H*-indole-7-carboxamide **(13b)**

To a suspension of 7-tryptamine **10d** (0.20 g, 0.6 mmol) and 7-trichloroacetylindole **11b** (0.26 g, 0.6 mmol) in MeCN (20 mL), triethylamine (3 drops) was added and the mixture was stirred at room temperature for 4 h, then poured into ice-water and the resulting precipitate was filtered, washed with water and recrystallised from MeOH to give the *title compound* **13b** (0.22 g, 60%) as a cream solid, mp 196-198 ºC; Anal. Calcd for $C_{35}H_{32}ClN_3O_5$ 0.25 CH_3OH: C, 68.50; H, 5.38; N, 6.80%: Found: 68.31; H, 5.30; N, 6.94. ^1H NMR (300 MHz, $CDCl_3$): δ 3.21 (2H, t, *J* 15.3 Hz, CH_2), 3.66 (2H, q, *J* 21.7 Hz, CH_2), 3.84 (3H, s, OMe), 3.88 (3H, s, OMe), 3.92 (3H, s, OMe), 3.95 (3H, s, OMe), 6.25 (1H, s, H5), 6.36 (1H, s, H5′), 7.19 (1H, d, *J* 2.0 Hz, H2), 7.24 (1H, d, *J* 2.4 Hz, H2′), 7.25-7.68 (9H, m, aryl H), 8.52 (1H, t, *J* 11.8 Hz, NH), 10.43 (1H, bs, NH), 11.29 (1H, bs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 39.6 (CH_2), 55.1, 55.4, 56.7, 57.5 (OMe), 87.4 (C5), 89.5 (C5′), 122.0 (C2), 122.2 (C2′), 125.3, 127.5, 127.6, 129.4,

130.7 (aryl CH), 97.5, 102.7, 110.7, 110.9, 116.7, 118.3, 131.5, 134.3, 136.4, 138.9, 139.3, 153.2, 153.3, 156.8, 157.3 (aryl C), 168.6 (C=O); ν_{max} (KBr): 3397, 2927, 2834, 1619, 1593, 1540, 1330, 1264, 1209, 1106 cm^{-1}; λ_{max} (THF): 232 nm (ε 74,900 $cm^{-1}M^{-1}$), 286 (31,800); HRMS (+ESI): $[M+Na]^+$, found 634.1896. $C_{35}H_{32}{}^{37}ClN_3O_5$ requires 634.1899.

*N*1,*N*2-Bis-(2-(4,6-dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-ethyl)-oxalamide **(14a)**

Oxalyl chloride (0.05 mL, 0.48 mmol) in dry DCM (5 mL) was added dropwise to a solution of 7-tryptamine **10a** (0.30 g, 0.81 mmol) in dry DCM (10 mL) containing triethylamine (0.11 mL, 0.81 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue was quenched with water. The resulting precipitate was filtered, dried and recrystallised from EtOH to yield the *title compound* **14b** (0.15 g, 46%) as a pale yellow solid, mp 278-280 ºC; Anal. Calcd for $C_{50}H_{46}N_4O_6$ 0.16 CH_2Cl_2 requires C, 74.15; H, 5.75; N, 6.90%. Found: C, 73.93; H, 5.82; N, 7.18. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.04 (4H, s, CH_2), 3.61 (6H, s, OMe), 3.81 (6H, s, OMe), 6.36 (2H, s, H5), 7.22-7-26 (20H, m, aryl H), 8.50 (2H, s, NH), 10.86 (2H, bs, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.9, 39.6 (CH_2), 55.5, 57.1 (OMe), 89.8 (C5), 126.1, 127.2, 127.5, 128.5, 129.0, 131.5 (aryl CH), 102.0, 112.8, 114.1, 133.1, 133.3, 136.6, 137.4, 153.2, 153.9 (aryl C), 160.1 (C=O); ν_{max} (KBr): 3353, 1646, 1598, 1518, 1326, 1217, 1128, 698 cm^{-1}; λ_{max} (THF): 214 nm (ε 112,150 $cm^{-1}M^{-1}$), 248 (73,200), 329 (41,000); HRMS (+ESI): $[M+H]^+$, found 799.3487. $C_{50}H_{46}N_4O_6$ requires 799.3496.

*N*1,*N*2-Bis-(2-(4,6-dimethoxy-3-phenyl-1*H*-indol-7-yl)-ethyl)-oxalamide **(14b)**

Oxalyl chloride (0.06 mL, 0.69 mmol) in dry DCM (6 mL) was added dropwise to a solution of 7-tryptamine **10d** (0.36 g, 1.22 mmol) in dry DCM (10 mL) containing triethylamine (0.15 mL, 1.09 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was quenched with water. The resulting precipitate was filtered, dried and recrystallised from MeOH to yield the *title compound* **14b** (0.2 g, 51%) as a pale yellow solid, mp 284-286 ºC; Anal. Calcd for $C_{38}H_{38}N_4O_6$ 0.05 CH_2Cl_2: C, 70.20; H, 5.90; N, 8.61%. Found: C, 70.07; H, 5.99; N, 8.72. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.01 (4H, t, *J* 13.9 Hz, CH_2), 3.78 (6H, s, OMe), 3.85 (6H, s, OMe), 6.42 (2H, s, H5), 7.16-7.57 (12H, m, H2, aryl H), 8.53 (1H, t, *J* 11.3 Hz, NH), 11.02 (2H, d, *J* 1.7 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.1, 39.7 (CH_2), 55.6, 57.2 (OMe), 89.7 (C5), 122.9 (C2), 125.5, 127.9, 129.4 (aryl CH), 102.3, 110.4, 117.7, 136.8, 138.5, 153.1, 153.7 (aryl C), 160.2 (C=O); ν_{max} (KBr): 3350, 1650, 1600, 1520, 1323, 1204, 1054 cm^{-1}; λ_{max} (CH_2Cl_2): 230 nm (ε 66,700 $cm^{-1}M^{-1}$), 286 (28,200); HRMS (+ESI): $[M+H]^+$, found 647.2855. $C_{38}H_{38}N_4O_6$ requires 647.2870.

BIOLOGICAL METHODS

SH-SY5Y cells were cultured in 10% Dulbecco's modified Eagle's medium/F-12 (DMEM/F-12; Invitrogen) with 1% penicillin-streptomycin (Life Technologies). For assessment of viability, cells were plated at $5x10^4$ cells per well in 96-well plates and were cultured for 24 h before addition of compounds for 24 h. Viability was then assessed using CellTiter-Blue (Promega) as per the manufacturer's protocol. For assessment of proliferation, cells were plated at $2x10^4$ cells per well in 96-well plates and were cultured for 24 h before addition of compounds for 24 h. Effects on proliferation were then assessed using a 5–bromo–2'–deoxyuridine (BrdU) enzyme–linked immunosorbent assay (ELISA) according to the manufacturer's protocol (Roche Molecular Diagnostics). Experiments were conducted on three independent occasions, and results expressed as mean ± standard deviation.

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