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N-Arylsulfonyl-2-vinyltryptamines as new 5-HT$_6$ serotonin receptor Ligands

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Abstract
Several new 2-vinyl-N_b,N_b-dimethyltryptamines were prepared using Fischer indole synthesis followed by simple functional group transformations and evaluated on 5-HT$_4$, 5-HT$_5$, 5-HT$_6$ and 5-HT$_7$ serotonin receptors. It was found that 2-vinyl substitution conferred a potent and selective 5-HT$_6$ binding activity to these molecules which could be enhanced by N_a-arylsulfonyl substituents.

Keywords: *2-vinyl-N_b,N_b-dimethyltryptamines, N_a-arylsulfonyl-tryptamines, 5-HT$_6$ receptor inhibitors, radioligand binding tests*

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) receptor family represents seven main classes (5-HT$_1$ to 5-HT$_7$) and within these classes fourteen different subtypes have been reported [1]. Among these, human 5-HT$_6$ receptors were recently identified as members of the G-protein superfamily, positively coupled to an adenyl cyclase second messenger system, and mainly localised in the central nervous system [2,3]. The observed high binding affinity of some therapeutically important antipsychotic and antidepressant agents at 5-HT$_6$ receptors suggested their implication in the treatment of schizophrenia, anxiety, depression and related disorders [4]. Recent studies pointed out that 5-HT$_6$ receptors might be involved in behavioural and memory dysfunctions [2,5].

After the discovery of the first bisaryl sulfonamide type 5-HT$_6$ selective antagonists [6–8], Glennon has recently reported several 2-substituted tryptamines as selective 5-HT$_6$ ligands [9]. Both 2-ethyl- and 2-phenyl-5-methoxy-*N*,*N*-dimethyltryptamines **1** and **2** were found to be highly potent ligands, displaying agonist and antagonist effect, respectively (Figure 1).

As part of our research programme concerning the preparation and synthetic application of 2-vinylindoles [10], we were interested to know whether functionalized 2-vinyltryptamines **3** could act as 5-HT$_6$ receptor ligands. The vinyl moiety could be considered to possess similar steric and electronic character to that of ethyl and phenyl groups, respectively.

Here we describe the preparation and biological activity of new 2-vinyltryptamines showing promising 5-HT$_6$ binding activities.

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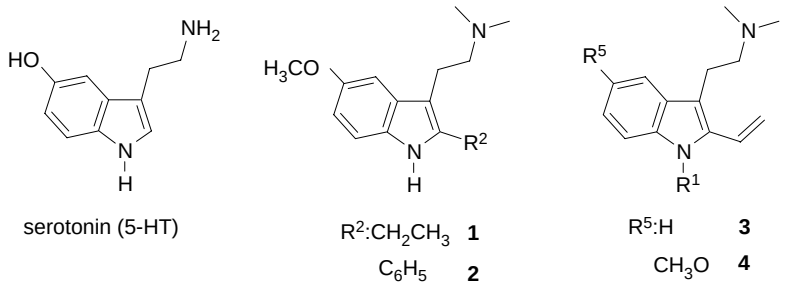


Figure 1. Structure of serotonin and some 2-substituted tryptamines.

Materials and methods

Chemistry

General. Melting points, determined on a Reichert hot plate apparatus, are uncorrected. IR spectra were recorded on a Bomem FTIR apparatus with Cosmic interferometer. UV spectra (in MeOH) were recorded on a Unicam 8700 spectrometer. ^{1}H- and ^{13}C- NMR spectra, using TMS as internal standard, were measured on a Bruker AC 300 apparatus at 300 and 75 MHz, respectively. MS spectra were obtained on a VG Autospec (Fisons) spectrometer.

Synthesis

2-METHYL-2,3,4,5-TETRAHYDRO-1H-PYRIDO[4,3-b]INDOLE (7). Prepared according to the described method [11]. Yield: 95%.

8-METHOXY-2-METHYL-2,3,4,5-TETRAHYDRO-1H-PYRIDO[4,3-b]INDOLE (8). To an ice-cooled solution of 4-methoxyphenylhydrazine hydrochloride (6.0 g, 34.38 mmol) in methanol saturated with HCl gas (100 mL) was added dropwise 1-methyl-4-piperidone (4.69 g, 41.46 mmol) and the reaction mixture was stirred at room temperature for 30 min. After evaporation of the solvent under reduced pressure, the residue was dissolved in water (40 mL), alkalinized under cooling with a 10% aqueous solution of NaOH to pH = 12–13, and extracted with dichloromethane (4 × 40 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, and evaporated to dryness to afford **8** (7.0 g, 94%) as an amorphous solid. IR (KBr), cm^{-1}: 3388 (NH), 2905, 1630 (C=C); ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.55 (s, 3H, NCH_3), 2.65–2.77 (m, 4H, CH_2-CH_2NCH_3), 3.65 (s, 2H, CH_2-NCH_3), 3.82 (s, 3H, OCH_3), 6.70 (dd, J = 7.8, 2.1, 1H, H-7), 6.83 (d, J = 2.1, 1H, H-9), 7.01 (d, J = 7.8, 1H, H-6), 8.70 (s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.5 (CH_2-CH_2NCH_3), 45.6 (NCH_3), 51.7 (CH_2-CH_2NCH_3), 52.3 (CH_2NCH_3), 55.8 (OCH_3), 99.8 (C-9), 107.8 (C-9b), 110.5 (C-6), 111.3 (C-7), 126.2 (C-9a), 131.3 (C-4a), 132.7 (C-5a), 153.7 (C-8); MS (m/z, %) 216 (M^+, 25), 173 (100), 158 (55), 130 (9).

2,2-DIMETHYL-2,3,4,5-TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-2-IUM IODIDE (9). Prepared according to the described method [11]. Yield: 95%.

2,2-DIMETHYL-8-METHOXY-2,3,4,5-TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-2-IUM IODIDE (10). A solution of **8** (7.0 g, 32.4 mmol) in methanol (70 mL) was stirred with methyl iodide (14.1 g, 6.2 mL, 97.2 mmol) at 35°C for 3 h. After evaporation of the solvent the residue was crystallized from diethyl ether to obtain white crystals (9.6 g, 83%) **10**, m.p. 210°C (diethyl ether). IR (KBr), cm^{-1}: 3240 (NH), 1625 (C=C); ^{1}H NMR ($CDCl_3$ + CD_3OD), δ, ppm; J, Hz: 3.22 (t, J = 7.5, 2H, CH_2-CH_2N^+), 3.35 (s, 6H, $N(CH_3)_2$), 3.74 (t, J = 7.5, 2H, CH_2-CH_2N^+), 3.81 (s, 3H, OCH_3), 4.78 (s, 2H, CH_2N^+), 6.81 (dd, J = 8.1, 2, 1H, H-8), 6.91 (d, J = 2, 1H, H-6), 7.31 (d, J = 8.1, 1H, H-9), 10.5 (s, 1H, NH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6), δ, ppm: 19.2 (CH_2-CH_2N^+), 50.9 ($^+N(CH_3)_2$), 55.3 (OCH_3), 59.8 (CH_2-CH_2N^+), 60.8 (-CH_2N^+), 99.2 (C-9), 99.4 (C-9b), 110.3 (C-6), 111.7 (C-7), 124.6 (C-9a), 127.5 (C-4a), 131.4 (C-5a), 153.6 (C-8).

[2-(2-DIMETHYLAMINOETHYL)-1H-INDOL-3-YL]ACETONITRILE (11). Prepared according to the described method [11]. Yield: 81%.

[2-(2-DIMETHYLAMINOETHYL)-5-METHOXY-1H-INDOL-3-YL]ACETONITRILE (12). A solution of iodide **10** (9.0 g, 25.1 mmol) in ethanol (100 mL) was heated under reflux with a solution of potassium cyanide (8.9 g, 137 mmol) in water (30 mL) for 5 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in water (30 mL), alkalinized (pH = 13) under cooling with a 10% aqueous solution of NaOH, and the mixture was extracted with dichloromethane (4 × 40 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated to afford **12** (6.0 g, 93%), as white crystals, m.p. 101°C (dichloromethane). IR (KBr), cm^{-1}: 3318 (NH), 2925, 2241 (CN), 1630 C=C); ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.35 (s, 6H, $N(CH_3)_2$), 2.65 (t, J = 7.4, 2H, CH_2-CH_2-NCH_3), 2.77 (t, J = 7.4, 2H,

CH_2-C*H*$_2$-NCH_3), 3.71 (s, 2H, CH_2-CN), 3.85 (s, 3H, OCH_3), 6.82 (dd, J = 8.1, 1.8, 1H, H-6), 7.02 (d, J = 1.8, 1H, H-4), 7.25 (d, J = 8.1, 1H, H-7), 10.2 (s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 12.7 (-*C*H$_2$-$N(CH_3)_2$), 22.3 (*C*H$_2$-CH_2-$N(CH_3)_2$), 44.9 ($N(CH_3)_2$), 55.8 (OCH_3), 58.0 (CH_2-*C*H$_2$-$N(CH_3)_2$), 98.2 (C-3), 99.3 (C-4), 111.3 (C-7), 111.7 (C-6), 118.2 (CN), 127.2, 129.9, 137.7, 154.1; MS (m/z, %) 257 (M^+, 25), 212 (100), 197 (57), 186 (18), 173 (16), 169 (41).

*[2-(3-CYANOMETHYL-1H-INDOL-2-YL) ETHYL]TRIMETHYLAMMONIUM IODIDE (**13**)*. Prepared according to the described method [11]. Yield: 95%.

*[2-(3-CYANOMETHYL-5-METHOXY-1H-INDOL-2-YL)ETHYL]TRIMETHYLAMMONIUM IODIDE (**14**)*. A solution of **12** (6.00 g, 23.3 mmol) in dichloromethane (190 mL) and ethyl acetate (60 mL) was heated under reflux with methyl iodide (6.62 g, 46.6 mmol) for 4 h. After evaporation of the solvent the residue was crystallized from diethyl ether to give quaternary ammonium iodide **14** (9.1 g, 98%), as white crystals, m.p. 210°C (diethyl ether). IR (KBr), cm^{-1}: 3358 (NH), 3220, 2942, 2244 (CN), 1625 (C=C); ^{1}H NMR (DMSO-d_6), δ, ppm; J, Hz: 3.21 (s, 9H, $N^+(CH_3)_3$), 3.32 (t, J = 7.2, 2H, C*H*$_2$-CH_2-$N^+(CH_3)_3$), 3.62 (t, J = 7.2, 2H, CH_2-C*H*$_2$-$N^+(CH_3)_3$), 3.81 (s, 3H, OCH_3), 4.15 (s, 2H, CH_2-CN), 6.81 (dd, J = 8, 1.8, 1H, H-6), 7.12 (d, J = 1.8, 1H, H-4), 7.28 (d, J = 8, 1H, H-7), 11.2 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 12.4 (CH_2CN), 19.6 (*C*H$_2$-CH_2-$N^+(CH_3)_3$), 52.6 (-$N^+(CH_3)_3$), 55.6 (OCH_3), 64.1 (CH_2-*C*H$_2$-$N^+(CH_3)_3$), 100.1 (C-4), 101.1 (C-3), 111.7 (C-7), 112.0 (C-6), 119.5 (CN), 127.4 (C-3a), 130.5 (C-2), 131.9 (C-7a), 153.7 (C-5).

*(2-VINYL-1H-INDOL-3-YL)ACETONITRILE (**5a**)*. Prepared according to the described method [11]. Yield: 88%.

*(5-METHOXY-2-VINYL-1H-INDOL-3-YL)ACETONITRILE (**6a**)*. A solution of salt **14** (9.00 g, 22.5 mmol) in methanol (120 mL) and water (80 mL) was stirred with a 30% aqueous solution of NaOH (30 mL) at room temperature for 4 h. After evaporation of methanol under reduced pressure the residue was heated at 80°C for 20 min and then extracted with dichloromethane (4 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, evaporated to dryness and purified by flash chromatography (eluent: CH_2Cl_2:MeOH 9:1) to afford **6a** (4.2 g, 88%), as pale yellowish crystals, m.p. 127°C (methanol). IR (KBr), cm^{-1}: 3340 (NH), 3220, 2935, 2220 (CN), 1622 (C=C); ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 3.71 (s, 2H, CH_2CN), 3.82 (s, 3H, OCH_3), 5.32 (d, J = 11.1, 1H, CH_2 =), 5.51 (d, J = 18.2, 1H, CH_2 =), 6.70 (dd, J = 18.2, 11.1, 1H, CH_2 = C*H*), 6.85 (dd, J = 8.1, 2.1, 1H, H-6), 7.02 (d, J = 2.1, 1H, H-4), 7.15 (d, J = 8.1, 1H, H-7), 8.41 (s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm 12.7 (*C*H$_2$-CN), 55.8 (OCH_3), 100.2 (C-4), 102.2 (C-3), 111.8 (C-7), 113.6 (CH = *C*H$_2$), 113.7 (C-6), 117.7 (CN), 124.3 (*C*H = CH_2), 127.7 (C-3a), 131.1 (C-2), 134.1 (C-7a), 154.6 (C-5). MS (m/z, %) 212 (M^+, 100), 197 (48), 185 (11), 169 (26).

*(1-METHYL-2-VINYL-1H-INDOL-3-YL)ACETONITRILE (**5b**)*. To a stirred solution of 2-vinylindole **5a** (300 mg, 1.64 mmol) in dichloromethane (20 mL) were added a solution of sodium hydroxide (35%, 1.32 mL, 16 mmol) tetrabutylammonium hydrogen sulfate (56 mg, 0.16 mmol) and iodomethane (0.25 mL, 570 mg, 4.01 mmol). Stirring was continued at room temperature until the disapperance of the starting material. The reaction mixture was extracted with dichloromethane (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, evaporated and the residue was purified by chromatography (eluent: CH_2Cl_2/cyclohexane 6:4) affording **5b** (293 mg, 91%), which was crystallized in diethyl ether, m.p. 91–92°C (diethyl ether).UV (MeOH), λ_{max}, nm: 210, 228, 301; IR (KBr), cm^{-1}: 2938, 2238 (CN), 1626 (C=C), 1470; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 3.66 (s, 3H, NC*H*$_3$), 3.82 (s, 2H, CH_2N), 5.60 (d, J = 17.7, 1H, CH = C*H*$_2$), 5.68 (d, J = 11.6, 1H, CH = C*H*$_2$), 6.72 (dd, J = 17.7, 11.6, 1H, C*H* = CH_2), 7.11–7.30 (m, 3H, H-5, H-6, H-7), 7.62 (d, J = 7.8, 1H, H-4); ^{13}C NMR ($CDCl_3$), δ, ppm: 13.8 (*C*H$_2$-CN), 30.4 (NCH_3), 101.1 (C-3), 109.4 (C-7), 118.1 (CN), 118.2 (C-4), 120.1 (C-5), 121.5 (CH = *C*H$_2$), 122.7 (C-6), 125.1 (*C*H = CH_2), 126.5 (C-3a), 136.0 (C-2), 136.8 (C-7a); MS (m/z, %) 196 (M^+, 100), 181 (18), 169 (39), 156 (9), 154 (17), 144 (10), 140 (6), 127 (14). Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27%; Found: C, 79.44; H, 6.19; N, 14.20%.

*(1-METHOXYMETHYL-2-VINYL-1H-INDOL-3-YL)ACETONITRILE (**5c**)*. To a stirred solution of 2-vinylindole **5a** (690 mg, 3.79 mmol) in dichloromethane (40 mL) were added at 0°C a solution of sodium hydroxide (35%, 2.15 mL, 26 mmol) tetrabutylammonium hydrogensulfate (126 mg, 0.37 mmol) and methoxymethyl chloride (0.48 mL, 6.31 mmol). After 2 h stirring at room temperature the reaction mixture was diluted with water (15 mL) and, extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, evaporated and the residue was purified by chromatography (eluent: cyclohexane/ethyl acetate 1:1 → 6:4) affording **5c** (830 mg, 97%), as a viscous yellowish oil. UV (EtOH), λ_{max}, nm: 209, 224, 297; IR (film), cm^{-1}: 2940, 2907, 2254 (CN), 1628 (C=C), 1464; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 3.24 (s, 3H, CH_2OC*H*$_3$), 3.82 (s, 2H, CH_2N), 5.38 (s, 2H,

CH_2OCH_3), 5.68 (d, J = 12.1, 1H, CH = CH_2), 5.70 (d, J = 17.3, 1H, CH = CH_2), 6.80 (dd, J = 17.3, 12.1, 1H, CH = CH_2), 7.20 (dt, J = 8.2, 1.1, 1H, H-5), 7.28 (dt, J = 8.2, 1.1, 1H, H-6), 7.42 (d, J = 8.2, 1H, H-7), 7.63 (d, J = 8.2, 1H, H-4); ^{13}C NMR ($CDCl_3$), δ, ppm: 13.6 (CH_2-CN), 55.8 ($CH_2O\underline{C}H_3$), 74.2 (CH_2OCH_3), 102.9 (C-3), 109.6 (C-7), 117.8 (CN), 118.3 (C-4), 120.8 (C-5), 122.1 (CH = CH_2), 123.3 (C-6), 124.6 (CH = CH_2), 126.7 (C-3a), 136.0 (C-2), 136.9 (C-7a); MS (m/z, %) 226 (M^+, 100), 183 (6), 169 (18), 160 (62). Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38%; Found: C, 74.11; H, 5.99; N, 12.71%.

*2-(2-VINYL-1H-INDOL-3-YL)ETHYLAMINE (**15a**)*. Prepared according to the described method [11]. Yield: 82%.

*2-(5-METHOXY-2-VINYL-1H-INDOL-3-YL) ETHYLAMINE (**16a**)*. To a solution of nitrile **6a** (0.60 g, 2.83 mmol) in diethyl ether (100 mL) and tetrahydrofuran (30 mL), lithium aluminium hydride (0.4 g, 10.54 mmol) was added in small portions and the reaction mixture was stirred at room temperature for 30 min. The excess of the reagent was decomposed at 0°C by careful addition of a saturated aqueous Na_2SO_4 solution; the precipitate was filtered, washed with dichloromethane (4 × 10 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), filtered and evaporated to dryness to afford **16** (0.61 g, 99%), as an amorphous solid which was crystallized in diethyl ether, m.p. 106–108°C (diethyl ether); UV (MeOH), λ_{max}, nm: 209, 221, 308; IR (KBr), cm^{-1}: 3428 (NH), 2936, 1632 (C=C), 1582, 1485; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 1.45 (sl, 2H, NH_2), 2.93 (m, 4H, CH_2CH_2N), 3.85 (s, 3H, OCH_3), 5.22 (d, J = 11.3, 1H, CH = CH_2), 5.62 (d, J = 17.7, 1H, CH = CH_2), 6.80 (m, 2H, CH = CH_2, H-6), 6.97 (s, 1H, H-4), 7.20 (d, J = 8.7, 1H, H-7), 9.65 (sl, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 27.9 (CH_2-CH_2-NH_2), 42.6 (CH_2-CH_2-NH_2), 55.5 (OCH_3), 100.3 (C-4), 111.2 (CH = CH_2), 111.3 (C-6), 112.4 (C-7), 112.4 (C-3), 125.4 (CH = CH_2), 128.6 (C-3a), 131.5 (C-2), 134.0 (C-7a), 153.3 (C-5); MS (m/z, %) 216 (M^+, 32), 186 (100), 171 (12), 154 (11), 143 (26). Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.45; N, 12.95%; Found: C, 72.31; H, 7.47; N, 13.18%.

*DIMETHYL-[2-(2-VINYL-1H-INDOL-3-YL) ETHYL]AMINE (**3a**)*. A solution of 2-vinylindole **5a** (2.00 g, 10.98 mmol) in tetrahydrofuran (30 mL) and diethyl ether (20 mL) was stirred with lithium aluminium hydride (2.00 g, 52.70 mmol) at room temperature for 30 min. The excess of the reagent was decomposed at 0°C by careful addition of a saturated aqueous Na_2SO_4 solution; the precipitate was filtered, washed with dichloromethane (3 × 20 mL) and methanol (3 × 2 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL), the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. To the obtained crude tryptamine, dissolved in methanol (100 mL), acetic acid (2.5 mL) and sodium cyanoborohydride (1.37 g, 21.80 mmol) were added. After 10 min stirring 37% formaldehyde (2.42 mL) in methanol (15 mL) was added dropwise at 0°C and stirring was continued for 1.5 h. After evaporation of the solvent the residue was partitioned between dichloromethane (60 mL) and 10% K_2CO_3 (60 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL), the combined organic layers were dried (Na_2SO_4), filtered, evaporated and the residue was purified by chromatography (eluent: CH_2Cl_2/MeOH 100:4 → 100:6/with five drops of NH_4OH). Dimethyl-2-vinyltryptamine **3a** was obtained (1.92 g, 82%) as a yellowish amorphous solid. UV (MeOH), λ_{max}, nm: 208, 228, 303, 313; IR (film), cm^{-1}: 3428 (NH), 3275–3055, 2944, 1634 (C=C), 1460; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.33 (s, 6H, $N(CH_3)_2$), 2.54 (m, 2H, CH_2N), 2.98 (m, 2H, CH_2CH_2N), 5.26 (d, J = 11.3, 1H, CH = CH_2), 5.46 (d, J = 17.7, 1H, CH = CH_2), 6.80 (dd, J = 17.7, 11.3, 1H, CH = CH_2), 7.09 (dt, J = 8.0, 1.0, 1H, H-5), 7.17 (dt, J = 8.0, 1.0, 1H, H-6), 7.26 (d, J = 8.0, 1H, H-7), 7.55 (d, J = 8.0, 1H, H-4), 8.32 (sl, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 22.4 (CH_2-CH_2-$N(CH_3)_2$), 45.2 ($N(CH_3)_2$), 60.4 (CH_2-CH_2-$N(CH_3)_2$), 110.7 (C-7), 111.3 (CH = CH_2), 113.5 (C-3), 118.8 (C-4), 119.4 (C-5), 122.9 (C-6), 125.3 (CH = CH_2), 128.5 (C-3a), 132.4 (C-2), 136.2 (C-7a); MS (m/z, %) 214 (M^+, 100), 183 (14), 168 (58), 159 (97), 143 (19), 128 (74). Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07%; Found: C, 78.21; H, 8.89; N, 12.81%.

*DIMETHYL-[2-(1-METHYL-2-VINYL-1H-INDOL-3-YL)ETHYL]AMINE (**3b**)*. A solution of **5b** (276 mg, 1.41 mmol) in a mixture of tetrahydrofuran (4 mL) and diethyl ether (3 mL) was stirred with lithium aluminium hydride (267 mg, 7.02 mmol), at room temperature for 1.5 h. The excess of the reagent was decomposed at 0°C by careful addition of a saturated aqueous Na_2SO_4 solution, the precipitate was filtered, washed with dichloromethane (3 × 10 mL) and methanol (3 × 1 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL), the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. To the obtained crude product, dissolved in methanol (15 mL), acetic acid (0.22 mL) and sodium cyanoborohydride (132 mg, 2.10 mmol) were added. After 20 min stirring at 0°C, 37% formaldehyde (0.31 mL) in methanol (5 mL) was added dropwise and stirring was continued for 1.5 h. After evaporation of the solvent, the residue was partitioned between dichloromethane (20 mL) and 10% K_2CO_3 (20 mL).

The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, evaporated and the residue was purified by chromatography (eluent: CH_2Cl_2/MeOH 100:1- > 100:5/with five drops of NH_4OH). Dimethyl-2-vinyltryptamine **3b** was obtained (92 mg, 29%), as a yellowish amorphous solid. UV (MeOH), λ_{max}, nm: 209, 228, 301; IR (film), cm^{-1}: 2940, 1626, 1470; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.68 (s, 6H, $N(CH_3)_2$), 2.68 (m, 2H, CH_2N), 3.05 (m, 2H, CH_2CH_2N), 3.72 (s, 3H, NCH_3), 5.50 (dd, J = 11.7, 1.2, 1H, CH = CH_2), 5.59 (dd, J = 17.8, 1.2, 1H, CH = CH_2), 6.79 (dd, J = 17.8, 11.7, 1H, $CH = CH_2$), 7.10 (dd, J = 7.9, 1.3, 1H, H-5), 7.24 (m, 2H, H-6, H-7), 7.69 (d, J = 7.9, 1H, H-4); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.2 (CH_2-CH_2-$N(CH_3)_2$), 30.6 (NCH_3), 45.3 ($N(CH_3)_2$), 60.2 (CH_2-CH_2-$N(CH_3)_2$), 109.1 (C-7), 111.7 (C-3), 117.9 ($CH = CH_2$), 118.7 (C-4), 119.1 (C-5), 122.1 (C-6), 125.9 ($CH = CH_2$), 127.5 (C-3a), 134.4 (C-2), 138.8 (C-7a); MS (m/z, %) 228 (M^+, 76), 197 (5), 184 (13), 170 (100), 154 (33), 128 (23), 115 (16). Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27%; Found: C, 79.18; H, 9.05; N, 11.91%.

*[2-(1-METHOXYMETHYL-2-VINYL-1H-INDOL-3-YL)ETHYL]DIMETHYLAMINE (**3c**)*. To a stirred suspension of sodium hydride (60%, 84 mg, 2.10 mmol) in tetrahydrofuran (1.5 mL) was added dropwise a dimethylsulfoxide (1.5 mL) solution of 2-vinyldimethyltryptamine **3a** (150 mg, 0.70 mmol). After 30 min stirring at 0°C under nitrogen, methoxymethyl chloride (MOMCl) (64 μL, 0.84 mmol) was added and stirring was continued at room temperature for a further 30 min. After evaporation of the solvent the residue was partitioned between dichloromethane (10 mL) and a 10% aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, evaporated and the crude product was purified by chromatography (eluent: CH_2Cl_2/MeOH 100:5/five drops of NH_4OH) to give **3c** (56 mg, 30%), as an amorphous solid. UV (MeOH), λ_{max}, nm: 212, 227, 300; IR (film), cm^{-1}: 3289 (NH), 2945, 1615 (C=C), 1464, 1346; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.63 (s, 6H, $N(CH_3)_2$), 2.89 (m, 2H, CH_2N), 3.23 (m, 2H, CH_2CH_2N), 3.31 (s, 3H, OCH_3), 5.44 (s, 2H, CH_2OCH_3), 5.60 (dd, J = 11.8, 1.3, 1H, CH = CH_2), 5.73 (dd, J = 17.8, 1.3, 1H, CH = CH_2), 6.85 (dd, J = 17.8, 11.8, 1H, $CH = CH_2$), 7.17 (dt, J = 7.8, 1.1, 1H, H-5), 7.25 (dt, J = 7.8, 1.1, 1H, H-6), 7.43 (d, J = 7.8, 1H, H-7), 7.63 (d, J = 7.8, 1H, H-4); ^{13}C NMR ($CDCl_3$), δ, ppm: 21.4 (CH_2-CH_2-$N(CH_3)_2$), 43.8 ($N(CH_3)_2$), 55.7 (CH_2-OCH_3), 58.5 (CH_2-$N(CH_3)_2$), 74.3 (CH_2-OCH_3), 109.5 (C-7), 111.0 (C-3), 118.6 (C-4), 119.6 ($CH = CH_2$), 120.4 (C-5), 123.0 (C-6), 125.1 ($CH = CH_2$), 127.6 (C-3a), 134.9 (C-2), 137.5 (C-7a); MS (m/z, %) 259 (M + 1, 100), 214 (13), 184 (4), 170 (3); Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84%; Found: C, 74.11; H, 8.35; N, 11.18%.

*3-(2-DIMETHYLAMINOETHYL)-2-VINYL-1H-INDOLE-1-CARBOXYLIC ACID TERT-BUTYL ESTER (**3d**)*. A solution of **3a** (200 mg, 0.93 mmol) in acetonitrile (12 mL) was stirred with di-*tert*-butyl dicarbonate (480 mg, 2.20 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (10 mg, 0.08 mmol) at room temperature for 4 h. After evaporation of the solvent, the residue was partitioned between dichloromethane (20 mL) and a 10% aqueous solution of $NaHCO_3$ (20 mL) and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, the solvent was evaporated and the residue was purified by chromatography (eluent: CH_2Cl_2/MeOH 100:3) affording **3d** (198 mg, 68%), as an amorphous solid. UV (MeOH), λ_{max}, nm: 212, 227, 300; IR (film), cm^{-1}: 3342 (NH), 2972, 2945, 2774, 1730 (CO), 1458; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 1.66 (s, 9H, $C(CH_3)_3$), 2.36 (s, 6H, $N(CH_3)_2$), 2.57 (m, 2H, CH_2N), 2.98 (m, 2H, CH_2CH_2N), 5.39–5.42 (dd, J = 11.5, 1.8, 1H, CH = CH_2), 5.42–5.51 (dd, J = 17.7, 1.8, 1H, CH = CH_2), 6.95 (dd, J = 17.7, 11.5, 1H, $CH = CH_2$), 7.26 (m, 2H, H-5, H-6), 7.54 (dd, J = 7.2, 1.1, 1H, H-4), 8.08 (dd, J = 7.2, 1.1, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.0 (CH_2-CH_2-$N(CH_3)_2$), 28.1 ($CO_2C(CH_3)_3$), 45.2 ($N(CH_3)_2$), 59.7 (CH_2-CH_2-$N(CH_3)_2$), 83.7 ($CO_2C(CH_3)_3$), 115.5 (C-7), 116.9 ($CH = CH_2$), 117.7 (C-3), 118.6 (C-4), 122.8 (C-5), 124.3 (C-6), 129.0 ($CH = CH_2$), 130.0 (C-3a), 134.8 (C-2), 135.3 (C-7a), 150.4 ($NCO_2C(CH_3)_3$); MS (m/z, %) 314 (M^+, 13), 272 (12), 239 (10), 214 (30), 183 (9), 168 (46), 154 (100). Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.57; H, 8.33; N, 8.91%; Found: C, 72.81; H, 8.05; N, 9.18%.

*[2-(5-METHOXY-2-VINYL-1H-INDOL-3-YL)ETHYL]DIMETHYLAMINE (**4a**)*. To a solution of **16a** (0.60 g, 2.78 mmol) in methanol (50 mL), acetic acid (0.41 mL) and sodium cyanoborohydride (0.3 g, 4.78 mmol) were added and after 10 min stirring 37% formaldehyde (0.58 mL) in methanol (10 mL) was added dropwise at 0°C and stirring was continued for 1.5 h. After evaporation of the solvent, the residue was partitioned between dichloromethane (20 mL) and a 10% aqueous solution of K_2CO_3 (20 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, evaporated and the residue was purified by chromatography (eluent: CH_2Cl_2/MeOH 50:1 → 10:1) to give **4a** (0.42 g, 59%), as an amorphous solid. UV (MeOH), λ_{max}, nm: 209, 219,

307; IR (film), cm^{-1}: 3328 (NH), 2945, 1632 (C=C), 1487, 1466, 1437; ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.36 (s, 6H, $N(CH_3)_2$), 2.52 (m, 2H, CH_2CH_2N), 2.95 (m, 2H, CH_2N), 3.86 (s, 3H, OCH_3), 5.24 (d, J = 11.3, 1H, CH = CH_2), 5.47 (d, J = 17.7, 1H, CH = CH_2), 6.76–6.87 (m, 2H, $CH = CH_2$, H-6), 7.00 (s, 1H, H-4), 7.19 (d, J = 8.7, 1H, H-7), 8.19 (s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 22.6 (CH_2-CH_2-$N(CH_3)_2$), 45.4 ($N(CH_3)_2$), 55.9 (OCH_3), 60.4 (CH_2-$N(CH_3)_2$), 100.8 (C-4), 111.0 (CH = CH_2), 111.4 (C-6), 112.9 (C-7), 113.5 (C-2), 125.4 ($CH = CH_2$), 128.9 (C-3), 131.4 (C-3a), 133.2 (C-7a), 153.9 (C-5); MS (m/z, %) 244 (M^+, 82), 230 (20), 215 (62), 199 (35), 186 (100), 173 (36), 158 (30), 154 (39). Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47%; Found: C, 73.44; H, 8.01; N, 11.58%.

General method for the synthesis of arylsulfonyl tryptamines 3e-i and 4e. To a stirred suspension of sodium hydride (60%, 2.0–3.0 mmol) in tetrahydrofuran (1.5 mL) was added *via* a syringe a dimethylsulfoxide (1 mL) solution of 2-vinyldimethyltryptamines **3a** or **4a** (1.0 mmol). After 30 min stirring at 0°C under nitrogen a solution of arylsulfonylchloride (1.6–4.3 mmol) in tetrahydrofuran (1.5–2 mL) was added and stirring was continued at room temperature until the disappearance of the starting material. After evaporation of the solvent the residue was partitioned between dichloromethane (10 mL) and 10% aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, evaporated and the crude product was purified by chromatography (eluent: CH_2Cl_2/MeOH 100:2 → 100:10) to give protected dimethyl-2-vinyltryptamines **3e-i, 4e**.

*[2-(1-BENZENESULFONYL-2-VINYL-1H-INDOL-3YL)ETHYL]DIMETHYL AMINE (**3e**)*. Yield: 61%. Amorphous solid. UV (MeOH), λ_{max}, nm: 208, 222, 269, 275, 287; IR (film), cm^{-1}: 3406 (NH), 2693, 2778, 1620 (C=C), 1149, 1371; ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.30 (s, 6H, $N(CH_3)_2$), 2.45 (m, 2H, CH_2N), 2.91 (m, 2H, CH_2CH_2N), 5.45 (dd, J = 17.7, 1.7, 1H, CH = CH_2), 5.60 (dd, J = 11.4, 1.7, 1H, CH = CH_2), 7.11 (dd, J = 17.7, 11.4, 1H, $CH = CH_2$), 7.21–7.37 (m, 4H, H-5, H-6, H-$PhSO_2$), 7.47 (m, 2H, H-4, H-$PhSO_2$), 7.72 (d, J = 7.5, 2H, H-$PhSO_2$), 8.20 (d, J = 8.3, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.2 (CH_2-CH_2-$N(CH_3)_2$), 45.1 ($N(CH_3)_2$), 59.3 (CH_2-CH_2-$N(CH_3)_2$), 115.1 (C-7), 119.2 (C-4), 119.6 (CH = CH_2), 120.9 (C-3), 123.7 (C-5), 125.1 (C-6), 126.5 ($CH_{benzene}$), 127.4 ($CH = CH_2$), 128.7 ($CH_{benzene}$), 130.8 (C-3a), 133.4 ($CH_{benzene}$),135.1 (C-2), 136.2 ($C_{benzene}$-SO_2), 138.0 (C-7a); MS (m/z, %) 354 (M^+, 11), 296 (5), 213 (39), 199 (8), 168 (30), 154 (100); HREIMS: calcd. 354.14021, found 354.14262.

*{2-[1-(TOSYL-4-SULFONYL)-2-VINYL-1H-INDOL-3-YL]ETHYL}DIMETHYL AMINE (**3f**)*. Yield: 51%. Amorphous solid. UV (MeOH), λ_{max}, nm: 204, 223, 270, 277, 285; IR (film), cm^{-1}: 3312 (NH), 2945, 2776, 1622 (C=C), 1452, 1371; ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.31 (s, 3H, CH_3), 2.43 (s, 6H, $N(CH_3)_2$), 2.60 (m, 2H, CH_2N), 3.00 (m, 2H, CH_2CH_2N), 5.45 (dd, J = 17.7, 1.6, 1H, CH = CH_2), 5.62 (dd, J = 11.4, 1.6, 1H, CH = CH_2), 7.08–7.18 (m, 3H, $CH = CH_2$, H-$ArSO_2$), 7.22–7.36 (m, 2H, H-5, H-6), 7.50 (d, J = 8.2, 1H, H-4), 7.61 (d, J = 8.3, 2H, H-$ArSO_2$), 8.20 (d, J = 8.2, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 21.4 ($C_{benzene}$-CH_3), 23.1 (CH_2-CH_2-$N(CH_3)_2$), 45.1 ($N(CH_3)_2$), 59.2 (CH_2-CH_2-$N(CH_3)_2$), 115.1 (C-7), 119.1 C-4), 119.5 (CH = CH_2), 120.5 (C-3), 123.6 (C-5), 125.0 (C-6), 127.6 ($CH = CH_2$), 129.4 ($CH_{benzene}$), 130.7 (C-3a), 135.0 ($CH_{benzene}$), 135.1 (C-2), 135.2 (C-7a), 136.1 ($C_{benzene}$-SO_2), 144.5 ($C_{benzene}$-CH_3); MS (m/z, %) 368 (M^+, 26), 213 (100), 155 (22). Anal. Calcd. for $C_{21}H_{24}N_2O_2S$: C, 68.44; H, 6.56; N, 7.60%; Found: C, 68.81; H, 6.45; N, 7.37%.

*{2-[1-(4-CHLOROBENZENESULFONYL)-2-VINYL-1H-INDOL-3-YL]ETHYL}DIMETHYLAMINE (**3g**)*. Yield: 46%. Amorphous solid. UV (MeOH), λ_{max}, nm: 205, 228, 272, 277, 286; IR (film), cm^{-1}: 3324 (NH), 2942, 2776, 1620 (C=C), 1452, 1375; ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.29 (s, 6H, $N(CH_3)_2$), 2.43 (m, 2H, CH_2N), 2.90 (m, 2H, CH_2CH_2N), 5.47 (dd, J = 17.7, 1.7, 1H, CH = CH_2), 5.62 (dd, J = 11.4, 1.7, 1H, CH = CH_2), 7.10 (dd, J = 17.7, 11.4, 1H, $CH = CH_2$), 7.30 (m, 4H, H-5, H-6, H-$ArSO_2$), 7.47 (dd, J = 7.7, 1.1, 1H, H-4), 7.65 (dd, J = 6.8, 1.9, 2H, H-$ArSO_2$), 8.16 (d, J = 7.7, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.2 (CH_2-CH_2-$N(CH_3)_2$), 45.2 ($N(CH_3)_2$), 59.2 (CH_2-CH_2-$N(CH_3)_2$), 115.1 (C-7), 119.3 (C-4), 119.8 (CH = CH_2), 121.3 (C-3), 124.0 (C-5), 125.3 (C-6), 127.5 ($CH = CH_2$), 128.0 ($CH_{benzene}$), 129.1 ($CH_{benzene}$), 130.9 (C-3a), 135.0 (C-2), 136.1 (C-7a), 136.3 ($C_{benzene}$-SO_2), 140.1 ($C_{benzene}$-Cl),; MS (m/z, %) 388 (M^+, 25), 390 (9), 213 (100), 168 (70), 154 (81). Anal. Calcd. for $C_{20}H_{21}N_2ClO_2S$: C, 61.76; H, 5.44; N, 7.20%; Found: C, 61.91; H, 5.59; N, 7.41%.

*{2-[1-(2,4,6-TRIISOPROPYLBENZENESULFONYL)-2-VINYL-1H-INDOL-3-YL]ETHYL}DIMETHYLAMINE (**3h**)*. Yield: 25%. Amorphous solid. UV (MeOH) λ_{max}, nm: 209, 237, 283; IR (film), cm^{-1}: 2961, 2866, 2774, 1458, 1373, 1346;

^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 1.01 (d, 12H, $CH(CH_3)_2$-*o*SO_2), 1.23 (d, 6H, $CH(CH_3)_2$-*p*SO_2), 2.34 (s, 6H, $N(CH_3)_2$), 2.52 (m, 2H, CH_2N), 2.90 (m, 3H, $CH(CH_3)_2$-*p*SO_2, CH_2CH_2N), 4.07 (m, 2H, $CH(CH_3)_2$-*o*SO_2), 5.52 (dd, J = 12.0, 1.1, 1H, CH = CH_2), 5.58 (dd, J = 16.9, 1.1, 1H, CH = CH_2), 6.54 (dd, J = 16.9, 12.0, 1H, $CH = CH_2$), 7.10 (s, 2H, H-ArSO_2), 7.27 (m, 2H, H-5, H-6), 7.52 (d, J = 7.6, 1H, H-4), 7.98 (d, J = 7.6, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 22.9 (CH_2-CH_2-$N(CH_3)_2$), 23.5 ($CH(CH_3)_2$), 24.2 ($CH(CH_3)_2$), 29.1 ($CH(CH_3)_2$), 34.1 ($CH(CH_3)_2$), 45.2 ($N(CH_3)_2$), 59.6 (CH_2-CH_2-$N(CH_3)_2$), 114.1 (C-7), 117.4 (C-3), 119.1 (C-4), 119.8 (CH = CH_2), 122.4 (C-5), 123.7 ($CH_{benzene}$), 124.6 (C-6), 126.0 ($CH = CH_2$), 129.1 (C-3a), 133.6 ($C_{benzene}$-SO_2), 134.8 (C-2), 136.2 (C-7a), 150.9 ($C_{benzene}$), 154.2 ($C_{benzene}$); MS (m/z, %) 481 (M + 1), 467 (3), 436 (5), 398 (4), 348 (1), 259 (8). Anal. Calcd. for $C_{29}H_{40}N_2O_2S$: C, 72.45; H, 8.39; N, 5.83%; Found: C, 72.59; H, 8.71; N, 6.10%.

{2-[1-(NAPHTHYL-2-SULFONYL)-2-VINYL-1H-INDOL-3-YL]ETHYL}DIMETHYLAMINE ***(3i)***. Yield: 53%. Amorphous solid. UV (MeOH), λ_{max}, nm: 207, 228, 278, 329; IR (film), cm^{-1}: 2934, 1668, 1622, 1593, 1452, 1373; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.29 (s, 6H, $N(CH_3)_2$), 2.43 (m, 2H, CH_2N), 2.98 (m, 2H, CH_2CH_2N), 5.48 (dd, J = 17.7, 1.7, 1H, CH = CH_2), 5.65 (dd, J = 11.4, 1.7, 1H, CH = CH_2), 7.12–7.36 (m, 3H, $CH = CH_2$, H-5, H-6), 7.43 (d, J = 8.2, 1H, H-4), 7.50–7.64 (m, 3H, H-Ar), 7.72–7.80 (m, 2H, H-Ar), 7.87 (d, J = 7.8, 1H, H-Ar), 8.28 (d, J = 8.2, 1H, H-7), 8.36 (s, 1H, H-Ar); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.0 (CH_2-CH_2-$N(CH_3)_2$), 45.0 ($N(CH_3)_2$), 59.1 (CH_2-CH_2-$N(CH_3)_2$), 115.8 (C-7), 119.2 (C-4), 119.7 ($CH = CH_2$), 120.6 (C-3), 121.3 ($CH_{naphthalene}$), 123.7 (C-5), 125.1 (C-6), 127.5 ($CH = CH_2$), 127.6 ($CH_{naphthalene}$), 127.7 ($CH_{naphthalene}$), 128.3 ($C_{naphthalene}$), 129.1 ($CH_{naphthalene}$), 129.2 ($CH_{naphthalene}$), 129.3 ($CH_{naphthalene}$), 130.7 (C-3a), 131.6 ($CH_{naphthalene}$), 131.8 ($C_{naphthalene}$), 135.0 ($C_{naphthalene}$), 135.1 (C-2), 136.2 (C-7a); MS (m/z, %) 404 (M^+, 40), 359 (6), 346 (21), 280 (7), 213 (13), 154 (26), 127 (100), 115 (18). Anal. Calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.25; H, 5.98; N, 6.93%; Found: C, 71.07; H, 6.17; N, 7.01%.

2-(1-BENZENSULFONYL-5-METHOXY-2-VINYL-1H-INDOL-3-YL)ETHYL]DIMETHYLAMINE ***(4e)***. Yield: 33%. Amorphous solid. UV (MeOH), λ_{max}, nm: 207, 218, 272, 312, 354; IR (film), cm^{-1}: 3428, 2955, 1616, 1478; ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.22 (s, 6H, $N(CH_3)_2$), 2.45 (m, 2H, CH_2N), 2.89 (m, 2H, CH_2CH_2N), 3.84 (s, 3H, OCH_3), 5.45 (dd, J = 17.7, 1.3, 1H, CH = CH_2), 5.60 (dd, J = 11.4, 1.3, 1H, CH = CH_2), 6.91 (m, 2H, H-4, H-6), 7.10 (dd, J = 17.7, 11.4, 1H, $CH = CH_2$), 7.35 (dd, J = 8.0, 1.0, 2H, H-PhSO_2), 7.47 (dd, J = 8.0, 1.0, 1H, H-PhSO_2), 7.68 (d, J = 8.0, 2H, H-PhSO_2), 8.10 (d, J = 8.7, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 23.1 (CH_2-CH_2-$N(CH_3)_2$), 45.0 ($N(CH_3)_2$), 55.5 (OCH_3), 58.9 (CH_2-CH_2-$N(CH_3)_2$), 101.9 (C-4), 113.5 (C-6), 116.1 (C-7), 119.4 ($CH = CH_2$), 120.8 (C-3), 126.5 ($CH_{benzene}$), 127.6 ($CH = CH_2$), 128.7 ($CH_{benzene}$), 130.7 (C-7a), 131.9 (C-3a), 133.4 ($CH_{benzene}$), 135.9 (C-2), 137.7 ($C_{benzene}$-SO_2), 156.7 (C-5); MS (m/z, %) 384 (M^+, 14), 243 (49), 199 (28), 185 (100), 170 (81); Anal. Calcd. for $C_{21}H_{24}N_2O_3S$: C, 65.59; H, 6.29; N, 7.29%; Found: C, 65.41; H, 6.01; N, 7.05%.

Pharmacology

Evaluation on 5-HT$_4$ receptors. Briefly, male guinea pigs (220–224 g, Iffa Credo, France) were subjected to euthanasia and decapitated. Brains were rapidly removed at 4°C and striatal regions carefully dissected and pooled. The tissues were then suspended in 10 volumes of HEPES buffer (50 mM, pH 7.4) at 4°C. After homogenization at 4°C (Ultra-Turrax, maximal speed, 15 s), and ultracentrifugation (23000 × g, 60 min, 4°C), the pellet was resuspended in HEPES buffer (50 mM, pH 7.4) at 4°C in order to obtain a tissue concentration of about 15 mg protein/ml. The protein concentrations were determined by the method of Lowry et al. [12] using bovine serum albumin as the standard. For radioligand binding studies, membrane preparations were incubated in duplicate (HEPES buffer: 50 mM, pH 7.4) at 37°C for 30 min with 0.6 nM [^{3}H]-GR 113808 (Amersham, France) and fixed concentrations of compounds under study. Incubation was terminated by rapid filtration through 0.5% polyethylenimine-presoaked Whatman GF/B filters using a Brandel cell harvester [13]. Filters were subsequently washed three times with 4 ml of HEPES buffer (50 mM, pH 7.4) at 4°C. Non-specific binding of [^{3}H]-GR 113808 was defined in the presence of 10 μM 5-HT. Results were expressed as the percentage of inhibition of the [^{3}H]-GR 113808 binding (at 10^{-6} and 10^{-8} M of compounds under study, concentrations chosen to initially screen for intermediate and high affinity compounds).

Evaluation on 5-HT$_5$ receptors. In brief, 3 μg of proteins (CHO-K1 cells transiently expressing the human 5-HT$_5$ receptors, RB-HS5AM, Perkin Elmer Life Sciences) were incubated at 37°C for 60 min in duplicate in the absence or the presence of 10^{-6} or 10^{-8} M of each drug and 2 nM [^{3}H]-LSD in 50 mM Tris-HCl buffer (pH 7.4) supplemented with 10 mM $MgCl_2$ and 0.5 mM EDTA according to Rees et al [14]. At the end of the incubation, homogenates were

filtered through Whatman 934-AH filters presoaked with 0.5% polyethylenimine and washed 5 times with ice-cold 50 mM Tris-HCl buffer. Non-specific binding was evaluated in parallel in the presence of 500 μM serotonin. Radioactivity associated with proteins was then quantified in the presence of a scintillation cocktail and expressed as the percentage of inhibition for each concentration of drugs under study.

Evaluation on 5-HT$_6$ receptors. The compounds were evaluated in terms of their ability to compete with the binding of [^{3}H]-LSD on membranes of *sf9* cells transiently expressing the human 5-HT$_6$ receptor (CRM-044, Perkin-Elmer Life Science) according to Monsma et al. [15] In brief, 4 μg of proteins were incubated at 27°C for 90 min in duplicate in the absence or the presence of 10^{-6} or 10^{-8} M of each compound and 2 nM [^{3}H]-LSD in 50 mM Tris-HCl buffer (pH 7.4) supplemented with 10 mM $MgSO_4$ and 0.5 mM EDTA. At the end of the incubation, the homogenates were filtered through Whatman GF/A filters and washed five times with ice-cold 50 mM Tris-HCl buffer. Non-specific binding was evaluated, in parallel, in the presence of 10^{-5} M clozapine. Radioactivity associated with proteins was then quantified and expressed as the percentage of inhibition for each concentration of the compound under study.

Evaluation on 5-HT$_7$ receptors. All synthesized compounds were evaluated in terms of their ability to compete with the binding of [^{3}H]-LSD on membranes of *sf9* cells transiently expressing the human 5-HT$_7$ receptor (CRM 047, Perkin-Elmer Life Science) according to Shen et al. [16]. In brief, proteins were incubated at 27°C for 60 min in duplicate in the absence or the presence of 10^{-6} or 10^{-8} M of each drug and 2 nM [^{3}H]-LSD in 50 mM Tris-HCl buffer (pH 7.4) supplemented with 10 mM $MgSO_4$ and 0.5 mM EDTA. At the end of the incubation, homogenates were filtered through Whatman GF/A filters presoaked with 0.5% polyethylenimine and washed 5 times with ice-cold 50 mM Tris-HCl buffer. Non-specific binding was evaluated in parallel in the presence of 250 μM clozapine. Radioactivity associated with proteins was then quantified in the presence of a scintillation cocktail and expressed as the percentage of inhibition for each concentration of drugs under study.

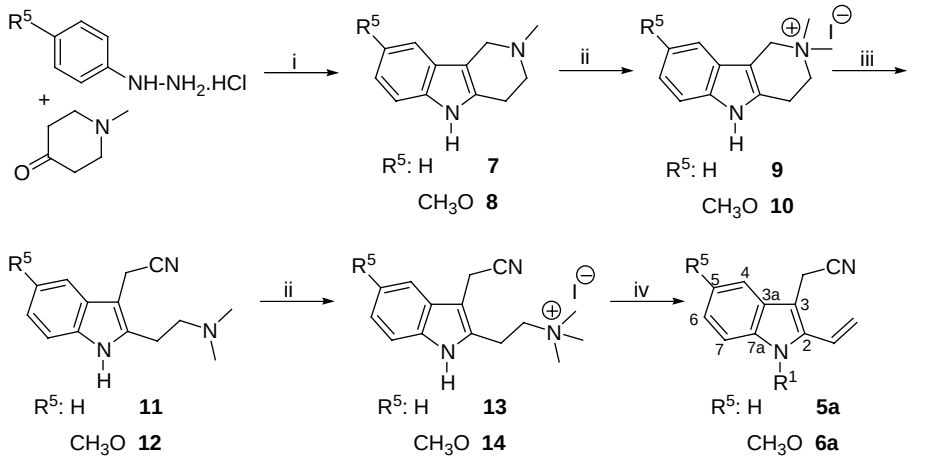
Results and discussion

Chemistry

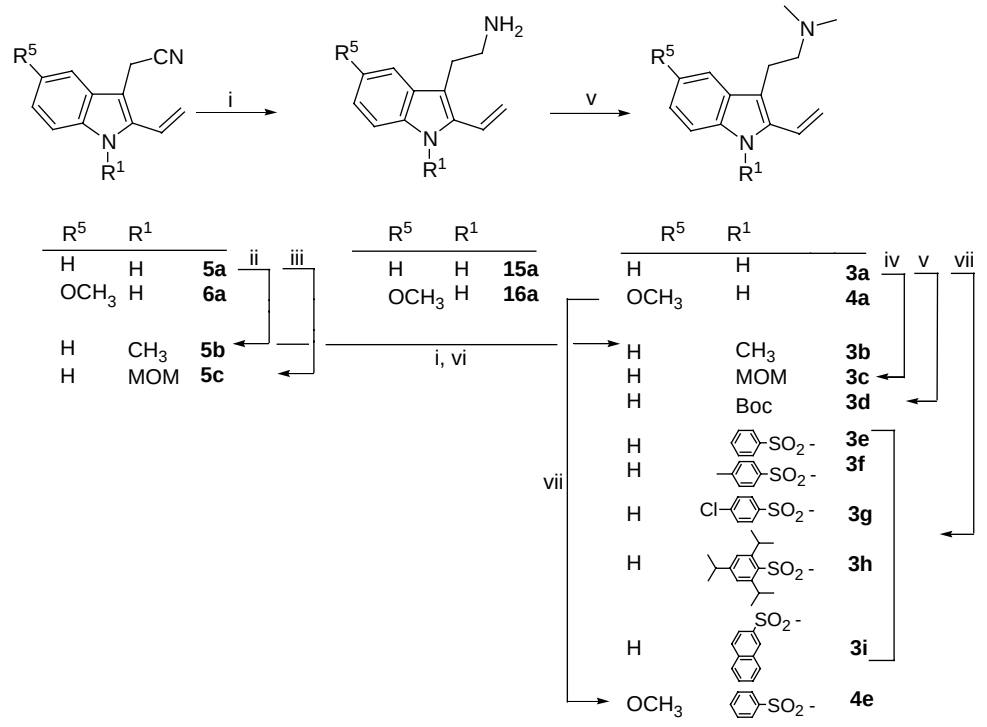
The key intermediate 2-vinylindole **5a** was prepared by a two step quaternization, Hofmann elimination procedure from **11**. This dimethylaminoethyl indole derivative was obtained by cyanide cleavage of cyclic gramine derivative **7** [11]. Apart from some minor modifications, its 5-methoxy counterpart **6a** was synthesized following the same way starting from the corresponding tetrahydro-γ-carboline **8** (Scheme 1).

Lithium aluminium hydride mediated reduction of nitriles **5a**, **6a** afforded the corresponding 2-vinyltryptamines **15a**, **16a** which were smoothly dimethylated to **3a**, **4a** according to the well-known method [17] (Scheme 2).

To avoid the N_b-quaternization for the introduction of electron-donating substituents on the indole nitrogen, alkylation prior to nitrile reduction was preferred. By this way, N_a-methyl-N_b,N_b-dimethyl-2-vinyltryptamine **3b** was prepared in a 29% yield, but as reduction and dimethylation of **5c** could not be carried out in a satisfactory yield, the MOM derivative **3c** was prepared starting from **3a** by treatment with methoxymethyl chloride (MOMCl) in the presence of sodium hydride, in a 30% yield.



Scheme 1. Synthesis of 2-vinylindoles **5a** and **6a**. Reagents: i: HCl-CH_3OH; ii: CH_3I; iii: KCN, EtOH-H_2O reflux; iv: NaOHaq.



Scheme 2. Synthesis of 2-vinyltryptamines. Reagents: i: $LiAlH_4$; ii: CH_3I, CH_2Cl_2-NaOHaq; iii: MOMCl, CH_2Cl_2-NaOHaq; iv: NaH, MOMCl; v: Boc_2O, DMAP; vi: HCOHaq, $NaBH_3CN$, AcOH; vii: NaH, $ArSO_2Cl$.

As for the electron-withdrawing substituents, *t*-butoxycarbonyl (Boc) and different arylsulfonyl groups were chosen. N_a-Arylsulfonyl-N_b,N_b-dimethyl-2-vinyltryptamines **3e-i**, **4e** were prepared by treating N_b,N_b-dimethyl-2-vinyltryptamine **3a** or **4a** with the appropriate arylsulfonyl chloride, using sodium hydride as a base in a mixture of anhydrous tetrahydrofuran and dimethylsulfoxide.

Pharmacology

All the synthesized compounds were evaluated on 5-HT$_4$, 5-HT$_5$, 5-HT$_6$ and 5-HT$_7$ receptors (Table I). Compounds **3a** and **4a** exhibited a moderate affinity for the 5-HT$_6$ receptor (77 and 79% of inhibition at 10^{-6} M, respectively) showing that replacing the 2-ethyl or 2-phenyl group of the tryptamine by a vinyl retained affinity for this receptor. However, introduction of a 5-methoxy group (**4a**) had only a slight influence on binding. The presence of electron donating groups on the indole nitrogen induced significantly diminished affinity towards all types of investigated 5-HT receptors (**3b**, **3c** *vs.* **3a**).

According to the findings of Glennon [18] and Russel [19], N_a substitution of tryptamine with a benzenesulfonyl group enhanced the 5-HT$_6$ receptor binding activity (ie. **3e**). The substitution pattern of the phenyl group had little effect on affinity (ie. **3f-i**)

Table I. Inhibition values (%) of various 2-vinyltryptamines on 5-HT$_6$, 5-HT$_4$, 5-HT$_5$ and 5-HT$_7$ receptors

N°	R^1	5-HT$_6$		5-HT$_4$		5-HT$_5$		5-HT$_7$	
		10^{-6} M	10^{-8} M	10^{-6} M	10^{-8} M	10^{-6} M	10^{-8} M	10^{-6} M	10^{-8} M
3a	H	77	1	7	0	27	10	55	2
4a	H	79	12	0	0	20	0	54	0
3b	CH_3	25	0	22	17	0	0	17	0
3c	MOM	0	4	11	9	0	0	5	0
3d	Boc	53	26	44	0	35	0	24	0
3e	SO_2Ph	97	45	22	1	29	25	18	0
3f	$SO_2C_6H_4p$-CH_3	90	39	nd	nd	45	14	22	16
3g	$SO_2C_6H_4p$-Cl	97	27	16	5	2	0	18	0
3h	$SO_2C_6H_2$(*i*-Pr)$_3$	90	39	nd	nd	45	14	22	16
3i	SO_2(2-naphtyl)	97	48	15	13	0	0	40	0
4e	SO_2Ph	95	32	16	0	0	0	4	0
17		90	24	14	0	0	0	4	0

nd: not determined.

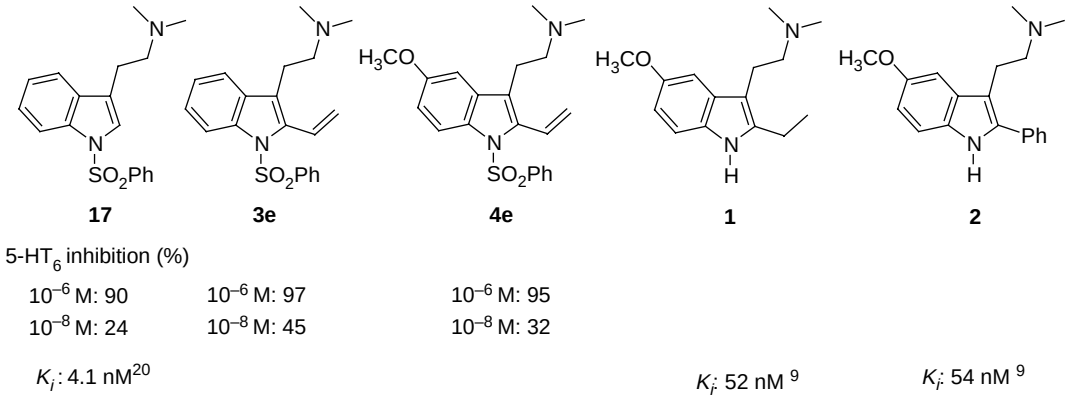


Figure 2. Comparison of 5-HT_6 binding data.

and introduction of a methoxy group in position 5 had no influence (ie. **4e**), except for receptor selectivity. Compound **4e** was found to have a more selective 5-HT_6 inhibitory activity compared to its non-methoxylated counterpart (**3e**). Generally, N_a-arylsulfonyl derivatives, especially **3 g** and **3i** displayed a good selectivity towards other tested receptors (ie. 5-HT_4, 5-HT_5 and 5-HT_7).

In order to compare our pharmacological data (inhibition %) with that of the literature (K_i), N_a-benzenesulfonyl-N_b,N_b-dimethyltryptamine **17** was prepared and submitted to affinity studies. This compound proved to be a potent and selective ligand of 5-HT_6 receptor in accord with its high affinity ($K_i = 4.1$ nM) reported by Glennon et al. [20]. Comparison of biological data of these different methods led to the conclusion that N_a-arylsulfonyl-N_b,N_b-dimethyltryptamines (**3e-3i, 4a**) were at least as potent as **17** and displayed about ten-fold higher affinity than 2-ethyl (**1**) or 2-phenyl (**2**) analogues (Figure 2).

These results showed that it was possible to replace an alkyl or aryl group in position 2 by a vinyl group without modification of the 5-HT_6 receptor affinity. The pharmacological profile of these compounds will be further evaluated.

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