Development of Fluorescent Ligands for the Human 5-HT_{1A} Receptor

Dulce Alonso,[a,#] Henar Vázquez-Villa,[a,#] Ana M. Gamo,[a] María F. Martínez-Esperón,[c] Mariola Tortosa,[c] Alma Viso,[c] Roberto Fernández de la Pradilla,[c] Elena Junquera,[b] Emilio Aicart,[b] Mar Martín-Fontecha,[a] Bellinda Benhamú,[a] María L. López-Rodríguez,[a,] and Silvia Ortega-Gutiérrez[a,*]*

[a]Dpto. de Química Orgánica I and [b]Dpto. de Química Física I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, E-28040 Madrid, Spain, [c]Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, Juan de la Cierva 3, E-28006 Madrid, Spain

Supporting Information

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1. Chemistry

Melting points (uncorrected) were determined on a Stuart Scientific electrothermal apparatus. Infrared (IR) spectra were measured on a Bruker Tensor 27 instrument equipped with a Specac ATR accessory of 5200-650 cm^{-1} transmission range; frequencies (ν) are expressed in cm^{-1}. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or Bruker Avance 300-AM (^{1}H, 300 MHz; ^{13}C, 75 MHz) at the UCM's NMR facilities or a on a Varian INOVA-500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or Varian INOVA-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) at the CSIC's NMR facilities. Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane; coupling constants (*J*) are in hertz (Hz). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), app (apparent). 2D NMR experiments (HMQC and HMBC) of representative compounds were carried out to assign protons and carbons of the new structures. High resolution mass spectrometry (HRMS) was carried out on a FTMS Bruker APEX Q IV (UCM) or Agilent QTOF 6520 (CSIC) spectrometers in electrospray ionization (ESI) mode. High Pressure Liquid Chromatography-Mass Spectrometry (HPLC-MS) analysis was performed using an Agilent 1200LC-MSD VL. LC separation was achieved with an Eclipse XDB-C18 column (5 μm, 4.6 mm x 15 mm) together with a guard column (5 μm, 4.6 mm x 12.5 mm). The gradient mobile phases consisted of A (95:5 water:acetonitrile) and B (5:95 water:acetonitrile) with 0.1% ammonium hydroxide and 0.1 % formic acid as the solvent modifiers. MS analysis was performed with an ESI source. The capillary voltage was set to 3.0 kV and the fragmentor voltage was set at 70 eV. The drying gas temperature was 350 ºC, the drying gas flow was 10 L/min and the nebulizer pressure was 20 psi. Elemental analyses (C, H, N, S) were obtained on a LECO CHNS-932 apparatus at the UCM's or CSIC's analysis services and were within 0.4% of the theoretical values, confirming a purity of at least 96% for all tested compounds. Analytical thin-layer chromatography (TLC) was run on Merck silica gel plates (Kieselgel 60 F-254) with detection by UV light (254 nm), ninhydrin solution, or 10% phosphomolybdic acid solution in ethanol. Flash chromatography was performed on glass column using silica gel type 60 (Merck, particle 230-400 mesh). Unless stated otherwise, starting materials, reagents

and solvents were purchased as high-grade commercial products from Sigma-Aldrich, Lancaster, Acros, Scharlab or Panreac, and were used without further purification. In general, solvents were obtained via elution through a Pure Solv™ column drying system from Innovative Technology, Inc. THF was distilled from sodium benzophenone ketyl and used immediately. Dichloromethane was distilled from calcium hydride.

The following compounds were synthesized according to described procedures: 2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (**1**),[1] 2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (**2**),[2] 2-(4-bromobutyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (**26**),[1] *N*,*N*-dimethyl-*N*-[5-(piperazin-1-ylsulfonyl)-1-naphthyl]amine (**27**),[3] and their spectroscopic data are in agreement with those previously reported. Collected data for compounds **3**-**12** refer to free bases, and then hydrochloride salts were prepared prior to elemental analyses and biological assays. Spectroscopic data of all described compounds were consistent with the proposed structures. Satisfactory HPLC chromatograms were also obtained for the final compounds **1**-**12**.

General Procedure for the Synthesis of Bromoalkyl Derivatives 13-17. To a solution of diisopropylamine (2 equiv) in anhydrous THF (1.3 mL/mmol), *n*-Butyllithium (2.5 M in hexane, 2 equiv) was added dropwise under an argon atmosphere at 0 ºC. The reaction mixture was stirred at this temperature for 30 min, before a solution of 1 equiv of arylpiperazine **1** or **2** in anhydrous THF (2.5 mL/mmol) was added dropwise. After stirring for 30 min at 0 ºC, the corresponding dibromoalkane (4 equiv) was added in one portion and the reaction mixture was stirred at 0 ºC for 1 h, allowed to reach room temperature and stirred for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl, the crude was basified with a 20% aqueous solution of K_2CO_3 and extracted with EtOAc. The

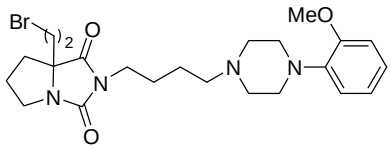
[1] López-Rodríguez, M. L.; Rosado, M. L.; Benhamú, B.; Morcillo, M. J.; Sanz, A. M.; Orensanz, L.; Beneitez, M. E.; Fuentes, J. A.; Manzanares, J. Synthesis and Structure-Activity Relationship of a New Model of Arylpiperazines. 1. 2-[[4-(*o*-Methoxyphenyl)piperazin-1-yl]methyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine: A Selective 5-HT_{1A} Receptor Agonist. *J. Med. Chem.* **1996**, *39*, 4439-4450.

[2] López-Rodríguez, M. L.; Morcillo, M. J.; Fernández, E.; Benhamú, B.; Tejada, I.; Ayala, D.; Viso, A.; Campillo, M.; Pardo, L.; Delgado, M.; Manzanares, J.; Fuentes, J. A. Synthesis and Structure-Activity Relationship of a New Model of Arylpiperazines. 8. Computational Simulation of Ligand-Receptor Interaction of 5-HT_{1A}R Agonists with Selectivity over α_1-Adrenoceptors. *J. Med. Chem.* **2005**, *48*, 2548-2558.

[3] Sashuk, V.; Schoeps, D.; Plenio H. Fluorophore tagged cross-coupling catalysts. *Chem. Commun.* **2009**, 770-772.

organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography using the appropriate eluent, to afford pure **13-17**.

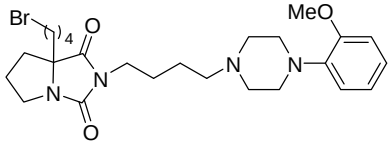
7a-(2-Bromoethyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (13)



Obtained from **1** (1.03 mmol) and 1,2-dibromoethane (4.12 mmol) in 46% yield.

Chromatography: CH_2Cl_2/EtOH, 95:5. IR ($CHCl_3$) ν 1768, 1706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.68 (m, 4H, $2CH_2$), 1.76-1.95 (m, 2H, CH_{2cyc}), 2.01-2.20 (m, 3H, CH_2, $1/2CH_{2cyc}$), 2.38-2.43 (m, 2H, CH_2N_{pip}), 2.45-2.56 (m, 1H, $1/2CH_{2cyc}$), 2.61 (m, 4H, $2CH_{2pip}$), 3.07 (m, 4H, $2CH_{2pip}Ar$), 3.15-3.25 (m, 2H, CH_2Br), 3.29-3.37 (m, 1H, $1/2CH_{2cyc}$), 3.43-3.50 (m, 2H, $CH_2N(CO)_2$), 3.73-3.79 (m, 1H, $1/2CH_{2cyc}$), 3.84 (s, 3H, CH_3), 6.82-7.00 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 33.2 (CH_2), 37.7 (CH_2), 39.0 (CH_2), 45.0 (CH_2), 50.5 ($2CH_2$), 53.3 ($2CH_2$), 55.2 (CH_3), 57.9 (CH_2), 71.8 (C), 111.0 (CH), 118.1 (CH), 120.9 (CH), 122.7 (CH), 141.3 (C), 152.2 (C), 163.3 (CO), 175.0 (CO). MS (ESI) 493.3 ($M(^{79}Br)+H)^+$, 495.3 ($M(^{81}Br)+H)^+$.

7a-(4-Bromobutyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (14)

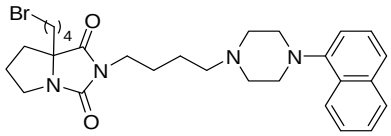


Obtained from **1** (0.26 mmol) and 1,4-dibromobutane (1.04 mmol) in 89% yield.

Chromatography: CH_2Cl_2/MeOH, 98:2. IR ($CHCl_3$) ν 1769, 1707. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-1.38 (m, 1H, $1/2CH_{2cyc}$), 1.49-1.71 (m, 6H, $3CH_2$), 1.81-1.93 (m, 5H, $2CH_2$, $1/2CH_{2cyc}$), 1.95-2.08 (m, 2H, CH_{2cyc}), 2.43 (t, J = 7.2, 2H, CH_2N_{pip}), 2.63 (m, 4H, $2CH_{2pip}$), 3.09 (m, 4H, $2CH_{2pip}Ar$), 3.18 (ddd, J = 11.8, 7.9, 6.2, 1H, $1/2CH_{2cyc}$), 3.36 (t, J = 6.7, 2H, CH_2Br), 3.47-3.53 (m, 2H, $CH_2N(CO)_2$), 3.79 (ddd, J = 11.8, 8.1, 6.4, 1H, $1/2CH_{2cyc}$), 3.85 (s, 3H, CH_3), 6.83-7.01 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$)

δ 22.6 (CH_2), 23.8 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 32.2 (CH_2), 33.0 (CH_2), 33.2 (CH_2), 34.0 (CH_2), 38.8 (CH_2), 44.8 (CH_2), 50.5 ($2CH_2$), 53.3 ($2CH_2$), 55.2 (CH_3), 57.9 (CH_2), 72.1 (C), 111.0 (CH), 118.1 (CH), 120.8 (CH), 122.8 (CH), 141.2 (C), 152.1 (C), 160.5 (CO), 176.0 (CO). MS (ESI) 520.6 $(M(^{79}Br))^+$, 522.6 $(M(^{81}Br))^+$.

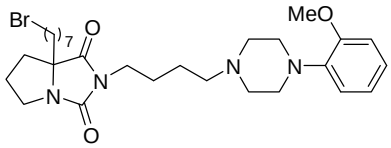
7a-(4-Bromobutyl)-2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (15)



Obtained from **2** (0.47 mmol) and 1,4-dibromobutane (1.88 mmol) in 62% yield.

Chromatography: CH_2Cl_2/EtOH, 9:1. IR ($CHCl_3$) ν 1769, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30-1.61 (m, 7H, $3CH_2$, $1/2CH_{2cyc}$), 1.64-1.81 (m, 5H, $2CH_2$, $1/2CH_{2cyc}$), 1.85-1.99 (m, 2H, CH_{2cyc}), 2.36 (t, *J* = 7.3, 2H, CH_2N_{pip}), 2.59 (m, 4H, $2CH_{2pip}$), 3.00 (m, 4H, $2CH_{2pip}Ar$), 3.05 (ddd, *J* = 11.8, 8.0, 6.6, 1H, $1/2CH_{2cyc}$), 3.23 (t, *J* = 6.7, 2H, CH_2Br), 3.30-3.45 (m, 2H, $CH_2N(CO)_2$), 3.65 (ddd, *J* = 11.8, 8.0, 6.6, 1H, $1/2CH_{2cyc}$), 6.95 (d, *J* = 7.3, 1H, Ar), 7.25 (app t, *J* = 7.8, 1H, Ar), 7.27-7.36 (m, 2H, Ar), 7.39 (d, *J* = 8.1, 1H, Ar), 7.64-7.68 (m, 1H, Ar), 8.03-8.06 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (CH_2), 24.0 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 32.4 (CH_2), 33.0 (CH_2), 33.1 (CH_2), 34.2 (CH_2), 38.9 (CH_2), 45.0 (CH_2), 53.0 ($2CH_2$), 53.7 ($2CH_2$), 58.1 (CH_2), 72.2 (C), 114.7 (CH), 123.4 (CH), 123.6 (CH), 125.3 (CH), 125.8 (CH), 125.9 (CH), 128.4 (CH), 128.9 (C), 134.8 (C), 149.7 (C), 160.7 (CO), 176.2 (CO). MS (ESI) 541.2 $(M(^{79}Br)+H)^+$, 543.2 $(M(^{81}Br)+H)^+$.

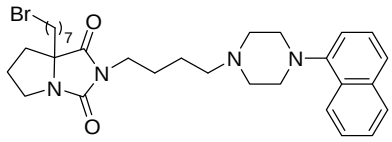
7a-(7-Bromoheptyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (16)



Obtained from **1** (0.26 mmol) and 1,7-dibromoheptane (1.04 mmol) in 78% yield.

Chromatography: CH_2Cl_2/MeOH, 95:5. IR ($CHCl_3$) ν 1769, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.45 (m, 8H, 4CH_2), 1.48-1.69 (m, 5H, 2CH_2, 1/2CH_{2cyc}), 1.77-1.87 (m, 5H, 2CH_2, 1/2CH_{2cyc}), 1.98-2.07 (m, 2H, CH_{2cyc}), 2.43 (t, *J* = 7.3, 2H, CH_2N_{pip}), 2.63 (m, 4H, 2CH_{2pip}), 3.08 (m, 4H, 2CH_{2pip}Ar), 3.17 (ddd, *J* = 11.7, 7.9, 6.1, 1H, 1/2CH_{2cyc}), 3.37 (t, *J* = 6.8, 2H, CH_2Br), 3.45-3.51 (m, 2H, $CH_2N(CO)_2$), 3.77 (ddd, *J* = 11.7, 8.1, 6.5, 1H, 1/2CH_{2cyc}), 3.85 (s, 3H, CH_3), 6.83-6.99 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.1 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 28.1 (CH_2), 28.6 (CH_2), 29.3 (CH_2), 32.8 (CH_2), 33.2 (CH_2), 33.9 (CH_2), 35.1 (CH_2), 38.9 (CH_2), 45.0 (CH_2), 50.7 (2CH_2), 53.5 (2CH_2), 55.5 (CH_3), 58.2 (CH_2), 72.5 (C), 111.4 (CH), 118.3 (CH), 121.1 (CH), 123.0 (CH), 141.5 (C), 152.4 (C), 160.8 (CO), 176.5 (CO). MS (ESI) 562.6 (M(^{79}Br))$^+$, 564.6 (M(^{81}Br))$^+$.

7a-(7-Bromoheptyl)-2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (17)

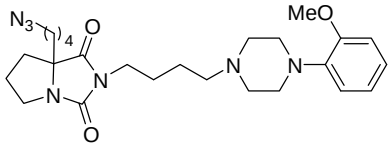


Obtained from **2** (0.58 mmol) and 1,7-dibromoheptane (2.32 mmol) in 56% yield.

Chromatography: CH_2Cl_2/EtOH, 9:1. IR ($CHCl_3$) ν 1769, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12-1.42 (m, 8H, 4CH_2), 1.52-1.72 (m, 5H, 2CH_2, 1/2CH_{2cyc}), 1.82-1.95 (m, 5H, 2CH_2, 1/2CH_{2cyc}), 2.00-2.10 (m, 2H, CH_{2cyc}), 2.50 (t, *J* = 6.8, 2H, CH_2N_{pip}), 2.73 (m, 4H, 2CH_{2pip}), 3.15 (m, 4H, 2CH_{2pip}Ar), 3.19 (ddd, *J* = 11.8, 7.9, 5.9, 1H, 1/2CH_{2cyc}), 3.38 (t, *J* = 6.8, 2H, CH_2Br), 3.44-3.59 (m, 2H, $CH_2N(CO)_2$), 3.78 (ddd, *J* = 11.8, 8.1, 6.7, 1H, 1/2CH_{2cyc}), 7.09 (d, *J* = 7.4, 1H, Ar), 7.40 (app t, *J* = 7.8, 1H, Ar), 7.43-7.50 (m, 2H, Ar), 7.54 (d, *J* = 8.2, 1H, Ar), 7.79-7.83 (m, 1H, Ar), 8.17-8.20 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 28.1 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 32.8 (CH_2), 33.2 (CH_2), 34.0 (CH_2), 35.2 (CH_2), 38.9 (CH_2), 45.0 (CH_2), 53.1 (2CH_2), 53.9 (2CH_2), 58.2 (CH_2), 72.5 (C), 114.8 (CH), 123.6 (CH), 123.7 (CH), 125.4 (CH), 125.9 (CH), 126.0 (CH), 128.5 (CH), 129.0 (C), 134.9 (C), 150.2 (C), 160.8 (CO), 176.6 (CO). MS (ESI) 582.5 (M(^{79}Br))$^+$, 584.5 (M(^{81}Br))$^+$.

General Procedure for the Synthesis of Alkyl Azides 18-21. To a solution of 1 equiv of the corresponding bromo alkyl derivatives **14-17** in DMF (1.6 mL/mmol), a solution of sodium azide (2.2 equiv) in water (0.3 mL/mmol) was added dropwise under an argon atmosphere at room temperature. The reaction mixture was stirred at 50 ºC for 24 h and then poured into ice-cold water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated at reduced pressure to obtain alkyl azides **18-21**, which were used for the next step without further purification.

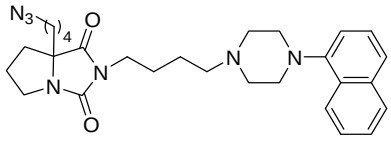
7a-(4-Azidobutyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (18)



Obtained from **14** (0.22 mmol) and sodium azide (0.48 mmol) in 90% yield.

IR ($CHCl_3$) ν 2096, 1769, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.30 (m, 1H, 1/2CH_{2cyc}), 1.40-1.70 (m, 8H, 4CH_2), 1.83-1.93 (m, 3H, CH_2, 1/2CH_{2cyc}), 1.95-2.08 (m, 2H, CH_{2cyc}), 2.43 (t, *J* = 7.3, 2H, CH_2N_{pip}), 2.63 (m, 4H, 2CH_{2pip}), 3.09 (m, 4H, 2CH_{2pip}Ar), 3.18 (ddd, *J* = 11.7, 7.9, 6.2, 1H, 1/2CH_{2cyc}), 3.25 (t, *J* = 6.7, 2H, CH_2N_3), 3.46-3.52 (m, 2H, $CH_2N(CO)_2$), 3.78 (ddd, *J* = 11.7, 8.2, 6.5, 1H, 1/2CH_{2cyc}), 3.85 (s, 3H, CH_3), 6.83-7.00 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_2), 24.1 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 28.8 (CH_2), 33.2 (CH_2), 34.7 (CH_2), 39.0 (CH_2), 45.1 (CH_2), 50.7 (2CH_2), 51.3 (CH_2), 53.5 (2CH_2), 55.5 (CH_3), 58.2 (CH_2), 72.3 (C), 111.4 (CH), 118.4 (CH), 121.1 (CH), 123.0 (CH), 141.5 (C), 152.4 (C), 160.8 (CO), 176.3 (CO). MS (ESI) 483.7 $(M)^+$, 484.7 $(M+H)^+$.

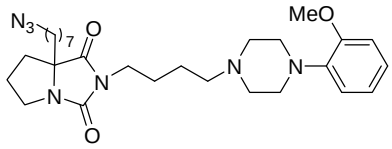
7a-(4-Azidobutyl)-2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (19)



Obtained from **15** (0.43 mmol) and sodium azide (0.95 mmol) in 92% yield.

IR ($CHCl_3$) ν 2096, 1769, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14-1.72 (m, 9H, $4CH_2$, $1/2CH_{2cyc}$), 1.84-2.10 (m, 5H, CH_2, $3/2CH_{2cyc}$), 2.49 (t, *J* = 7.3, 2H, CH_2N_{pip}), 2.70 (m, 4H, $2CH_{2pip}$), 3.14 (m, 4H, $2CH_{2pip}Ar$), 3.20 (ddd, *J* = 11.7, 8.0, 6.7, 1H, $1/2CH_{2cyc}$), 3.26 (td, *J* = 6.7, 1.7, 2H, CH_2N_3), 3.46-3.56 (m, 2H, $CH_2N(CO)_2$), 3.79 (ddd, *J* = 11.7, 8.0, 6.7, 1H, $1/2CH_{2cyc}$), 7.08 (dd, *J* = 7.3, 0.8, 1H, Ar), 7.39 (app t, *J* = 7.8, 1H, Ar), 7.42-7.49 (m, 2H, Ar), 7.54 (d, *J* = 8.2, 1H, Ar), 7.79-7.83 (m, 1H, Ar), 8.16-8.20 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_2), 24.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 28.8 (CH_2), 33.2 (CH_2), 34.7 (CH_2), 39.0 (CH_2), 45.1 (CH_2), 51.3 (CH_2), 53.1 ($2CH_2$), 53.9 ($2CH_2$), 58.2 (CH_2), 72.3 (C), 114.8 (CH), 123.5 (CH), 123.7 (CH), 125.4 (CH), 125.9 (CH), 126.0 (CH), 128.5 (CH), 129.0 (C), 134.9 (C), 149.8 (C), 160.8 (CO), 176.3 (CO). MS (ESI) 503.7 $(M)^+$, 504.7 $(M+H)^+$.

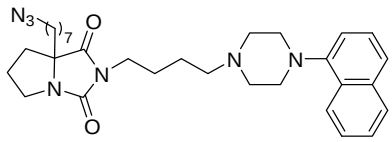
7a-(7-Azidoheptyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (20)



Obtained from **16** (0.19 mmol) and sodium azide (0.42 mmol) in 89% yield.

IR ($CHCl_3$) ν 2095, 1769, 1709. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24-1.38 (m, 8H, $4CH_2$), 1.48-1.68 (m, 7H, $3CH_2$, $1/2CH_{2cyc}$), 1.81-1.91 (m, 3H, CH_2, $1/2CH_{2cyc}$), 1.99-2.11 (m, 2H, CH_{2cyc}), 2.42 (t, *J* = 7.2, 2H, CH_2N_{pip}), 2.63 (m, 4H, $2CH_{2pip}$), 3.08 (m, 4H, $2CH_{2pip}Ar$), 3.17 (ddd, *J* = 11.7, 7.9, 5.9, 1H, $1/2CH_{2cyc}$), 3.23 (t, *J* = 6.8, 2H, CH_2N_3), 3.43-3.53 (m, 2H, $CH_2N(CO)_2$), 3.76 (ddd, *J* = 11.7, 8.1, 6.7, 1H, $1/2CH_{2cyc}$), 3.85 (s, 3H, CH_3), 6.83-7.01 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.1 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.7 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 33.2 (CH_2), 35.1 (CH_2), 38.9 (CH_2), 44.9 (CH_2), 50.7 ($2CH_2$), 51.5 (CH_2), 53.5 ($2CH_2$), 55.4 (CH_3), 58.2 (CH_2), 72.5 (C), 111.2 (CH), 118.3 (CH), 121.1 (CH), 123.0 (CH), 141.4 (C), 152.4 (C), 160.8 (CO), 176.5 (CO). MS (ESI) 525.8 $(M)^+$, 526.8 $(M+H)^+$.

7a-(7-Azidoheptyl)-2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (21)

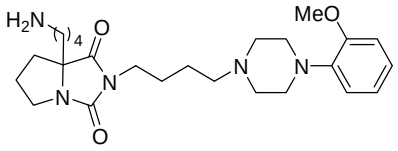


Obtained from **17** (0.31 mmol) and sodium azide (0.68 mmol) in 87% yield.

IR ($CHCl_3$) ν 2095, 1770, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11-1.35 (m, 9H, $4CH_2$, $1/2CH_{2cyc}$), 1.51-1.72 (m, 6H, $3CH_2$), 1.82-1.92 (m, 3H, CH_2, $1/2CH_{2cyc}$), 1.99-2.12 (m, 2H, CH_{2cyc}), 2.49 (t, *J* = 7.2, 2H, CH_2N_{pip}), 2.72 (m, 4H, $2CH_{2pip}$), 3.14-3.24 (m, 7H, $2CH_{2pip}$Ar, $1/2CH_{2cyc}$, CH_2N_3), 3.45-3.56 (m, 2H, $CH_2N(CO)_2$), 3.77 (ddd, *J* = 11.8, 8.1, 6.7, 1H, $1/2CH_{2cyc}$), 7.08 (d, *J* = 6.9, 1H, Ar), 7.39 (t, *J* = 7.8, 1H, Ar), 7.42-7.50 (m, 2H, Ar), 7.53 (d, *J* = 8.2, 1H, Ar), 7.78-7.83 (m, 1H, Ar), 8.16-8.20 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.1 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.7 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 38.9 (CH_2), 44.9 (CH_2), 51.5 (CH_2), 53.1 ($2CH_2$), 53.8 ($2CH_2$), 58.2 (CH_2), 72.5 (C), 114.7 (CH), 123.5 (CH), 123.7 (CH), 125.4 (CH), 125.9 (CH), 126.0 (CH), 128.5 (CH), 129.0 (C), 134.8 (C), 149.8 (C), 160.8 (CO), 176.5 (CO). MS (ESI) 545.7 $(M)^+$, 546.7 $(M+H)^+$.

General Procedure for the Synthesis of Primary Amines 22-25. To a solution of 1 equiv of the corresponding alkyl azide **18-21** and water (0.4 mL/mmol) in THF (10 mL/mmol), triphenylphosphine (2 equiv) was added under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The residue was dissolved in EtOAc and the solution was extracted with a 1 M aqueous solution of HCl. The aqueous layer was basified with a 20% aqueous solution of K_2CO_3 and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford amines **22-25**, which were used for the next step without further purification.

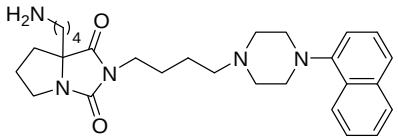
7a-(4-Aminobutyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (22)



Obtained from **18** (0.19 mmol) and triphenylphosphine (0.38 mmol) in 86% yield.

IR ($CHCl_3$) ν 2929, 1769, 1706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.70 (m, 7H, $3CH_2$, $1/2CH_{2cyc}$), 1.79-2.15 (m, 7H, $2CH_2$, $3/2CH_{2cyc}$), 2.47 (t, J = 7.4, 2H, CH_2N_{pip}), 2.67 (m, 4H, $2CH_{2pip}$), 2.73 (t, J = 6.9, 2H, $C\underline{H}_2NH_2$), 3.09 (m, 4H, $2CH_{2pip}Ar$), 3.19 (ddd, J = 11.8, 8.0, 5.8, 1H, $1/2CH_{2cyc}$), 3.41-3.50 (m, 2H, $CH_2N(CO)_2$), 3.77 (ddd, J = 11.8, 8.1, 6.7, 1H, $1/2CH_{2cyc}$), 3.85 (s, 3H, CH_3), 6.83-7.02 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (CH_2), 24.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 32.6 (CH_2), 33.4 (CH_2), 35.0 (CH_2), 39.2 (CH_2), 41.6 (CH_2), 45.2 (CH_2), 50.8 ($2CH_2$), 53.7 ($2CH_2$), 55.6 (CH_3), 58.6 (CH_2), 72.6 (C), 111.4 (CH), 118.5 (CH), 121.3 (CH), 123.2 (CH), 141.6 (C), 152.5 (C), 161.0 (CO), 176.7 (CO).

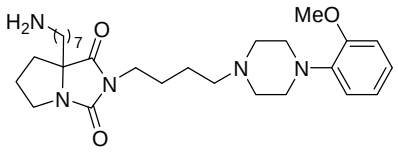
7a-(4-Aminobutyl)-2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (23)



Obtained from **19** (0.17 mmol) and triphenylphosphine (0.35 mmol) in 92% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.74 (m, 7H, $3CH_2$, $1/2CH_{2cyc}$), 1.79-2.34 (m, 7H, $2CH_2$, $3/2CH_{2cyc}$), 2.48 (t, J = 7.3, 2H, CH_2N_{pip}), 2.65-2.72 (m, 6H, $2CH_{2pip}$, $C\underline{H}_2NH_2$), 3.13 (m, 4H, $2CH_{2pip}Ar$), 3.18 (ddd, J = 11.7, 7.9, 5.9, 1H, $1/2CH_{2cyc}$), 3.45-3.56 (m, 2H, $CH_2N(CO)_2$), 3.77 (ddd, J = 11.7, 8.0, 6.7, 1H, $1/2CH_{2cyc}$), 7.01 (dd, J = 7.4, 0.8, 1H, Ar), 7.38 (app t, J = 7.8, 1H, Ar), 7.42-7.49 (m, 2H, Ar), 7.53 (d, J = 8.2, 1H, Ar), 7.78-7.82 (m, 1H, Ar), 8.16-8.20 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (CH_2), 24.3 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 33.4 (CH_2), 33.6 (CH_2), 35.2 (CH_2), 39.2 (CH_2), 42.1 (CH_2), 45.2 (CH_2), 53.3 ($2CH_2$), 54.0 ($2CH_2$), 58.4 (CH_2), 72.7 (C), 114.9 (CH), 123.7 (CH), 123.9 (CH), 125.6 (CH), 126.1 (CH), 126.2 (CH), 128.7 (CH), 129.2 (C), 135.0 (C), 150.0 (C), 160.8 (CO), 175.8 (CO).

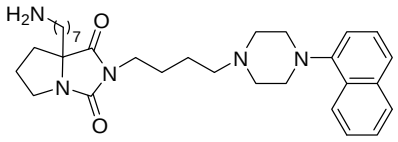
7a-(7-Aminoheptyl)-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (24)



Obtained from **20** (0.15 mmol) and triphenylphosphine (0.30 mmol) in 87% yield.

IR ($CHCl_3$) ν 2925, 1769, 1706. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.70 (m, 15H, $7CH_2$, $1/2CH_{2cyc}$), 1.81-1.92 (m, 3H, CH_2, $1/2CH_{2cyc}$), 1.97-2.11 (m, 2H, CH_{2cyc}), 2.42 (t, *J* = 7.4, 2H, CH_2N_{pip}), 2.54-2.70 (m, 6H, $2CH_{2pip}$, $C\underline{H}_2NH_2$), 3.09 (m, 4H, $2CH_{2pip}Ar$), 3.18 (ddd, *J* = 11.7, 8.0, 5.1, 1H, $1/2CH_{2cyc}$), 3.40-3.56 (m, 2H, $CH_2N(CO)_2$), 3.76 (ddd, *J* = 11.7, 8.2, 6.5, 1H, $1/2CH_{2cyc}$), 3.85 (s, 3H, CH_3), 6.83-7.03 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (CH_2), 24.3 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 27.1 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 33.3 (CH_2), 33.9 (CH_2), 35.3 (CH_2), 39.1 (CH_2), 42.4 (CH_2), 45.1 (CH_2), 50.9 ($2CH_2$), 53.7 ($2CH_2$), 55.6 (CH_3), 58.4 (CH_2), 72.7 (C), 111.4 (CH), 118.5 (CH), 121.3 (CH), 123.2 (CH), 141.7 (C), 152.6 (C), 161.0 (CO), 176.8 (CO).

7a-(7-Aminoheptyl)-2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (25)

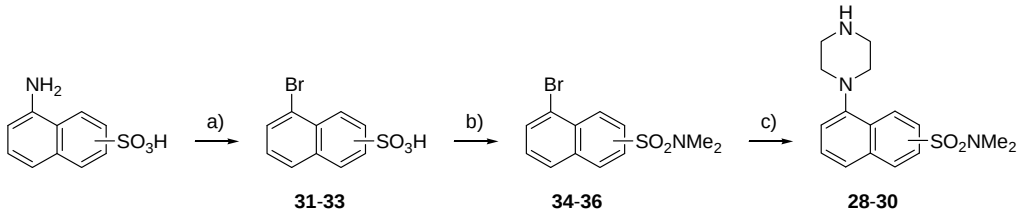


Obtained from **21** (0.12 mmol) and triphenylphosphine (0.24 mmol) in 84% yield.

IR ($CHCl_3$) ν 3053, 1769, 1708. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.69 (m, 15H, $7CH_2$, $1/2CH_{2cyc}$), 1.82-1.92 (m, 3H, CH_2, $1/2CH_{2cyc}$), 2.00-2.09 (m, 2H, CH_{2cyc}), 2.49 (t, *J* = 7.2, 2H, CH_2N_{pip}), 2.64 (t, *J* = 6.9, 2H, $C\underline{H}_2NH_2$), 2.72 (m, 4H, $2CH_{2pip}$), 3.13 (m, 4H, $2CH_{2pip}Ar$), 3.19 (ddd, *J* = 11.7, 7.9, 5.9, 1H, $1/2CH_{2cyc}$), 3.46-3.56 (m, 2H, $CH_2N(CO)_2$), 3.77 (ddd, *J* = 11.7, 8.0, 6.7, 1H, $1/2CH_{2cyc}$), 7.08 (d, *J* = 6.9, 1H, Ar), 7.39 (app t, *J* = 7.8, 1H, Ar), 7.42-7.50 (m, 2H, Ar), 7.53 (d, *J* = 8.2, 1H, Ar), 7.79-7.83 (m, 1H, Ar), 8.17-8.20 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2 (CH_2), 24.3 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 27.1 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 34.1 (CH_2), 35.4 (CH_2), 39.1 (CH_2), 42.5 (CH_2), 45.1 (CH_2), 53.3 ($2CH_2$), 54.0 ($2CH_2$), 58.4 (CH_2), 72.8 (C), 114.9 (CH), 123.7 (CH), 123.9 (CH), 125.6 (CH), 126.1 (CH), 126.2 (CH), 128.7 (CH), 129.2 (C), 135.0 (C), 150.0 (C), 160.8 (CO), 175.8 (CO).

Synthesis of Arylpiperazines 28-30

These compounds were synthesized starting from commercially available 5-aminonaphthalene-1- or 2-sulfonic acid or 8-aminonaphthalene-2-sulfonic acid following the synthetic route shown below.

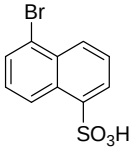


31-33 **34-36** **28-30**

Reagents and conditions: a) i) 0.55 M NaOH, 33% HBr in acetic acid, 7 M $NaNO_2$, -5 ºC, 30 min; ii) urea, CuBr, 33% HBr in acetic acid, 80 ºC, 30 min. b) i) $SOCl_2$, DMF, 85 ºC, 5 h; ii) $(CH_3)_2NH$, CH_2Cl_2/THF, 0 ºC to rt, 12 h. c) Piperazine, (±)-BINAP, $Pd(OAc)_2$, *t*-BuONa, toluene, 75 ºC, 20 h.

General Procedure for the Synthesis of Bromonaphthalenesulfonic Acids 31-33. Corresponding aminonaphthalenesulfonic acid (1 equiv) was added to a solution of NaOH (0.55 M in H_2O, 0.96 equiv). Next, a solution of HBr (33% in acetic acid, 0.45 mL/mmol of sulfonic acid) was added at room temperature. The mixture was cooled to −5 ºC and a solution of $NaNO_2$ (7 M in H_2O, 1.09 equiv) was added dropwise, keeping the temperature below 2 ºC. Once the addition was complete, the reaction mixture was stirred for 30 min at −5 ºC and then urea (0.13 equiv) was added in one portion. The resulting solution was slowly added to a freshly prepared and heated (80 ºC) solution of CuBr (1 equiv) in HBr (33% in acetic acid, 0.87 mL/mmol of CuBr). The mixture was stirred at 80 ºC for 30 min, cooled to room temperature and then saturated with NaCl. The precipitate was filtered, recrystallized in H_2O and dried under vacuum.

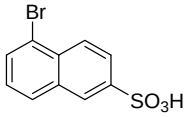
5-Bromonaphthalene-1-sulfonic acid (31)



Obtained from 5-aminonaphthalene-1-sulfonic acid (22.4 mmol) in 54% yield.

IR (KBr) ν 3573, 3453, 1494, 1227, 1199. ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (dd, *J* = 8.6, 7.5, 1H, Ar), 8.42 (dd, *J* = 8.5, 7.2, 1H, Ar), 8.69 (dd, *J* = 7.4, 1.0, 1H, Ar), 8.87 (dd, *J* = 7.2, 1.2, 1H, Ar), 8.97 (d, *J* = 8.5, 1H, Ar), 9.73 (d, *J* = 8.7, 1H, Ar). ^{13}C NMR (75 MHz, CD_3OD) δ 123.6 (C), 126.9 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 131.1 (CH), 131.5 (CH), 131.9 (C), 133.7 (C), 142.7 (C). MS (ESI) 287.0 ($M(^{79}Br)+H)^+$, 289.0 ($M(^{81}Br)+H)^+$.

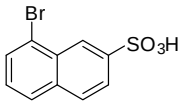
5-Bromonaphthalene-2-sulfonic acid (32)



Obtained from 5-aminonaphthalene-2-sulfonic acid (11.2 mmol) in 58% yield.

IR (KBr) ν 3436, 1635, 1590, 1559, 1492, 1335, 1197. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.37 (br s, 1H, SO_3H), 7.44 (dd, *J* = 8.1, 7.5, 1H, Ar), 7.85 (dd, *J* = 7.8, 1.7, 1H, Ar), 7.88 (dd, *J* = 5.8, 1.0, 1H, Ar), 8.05 (d, *J* = 7.3, 1H, Ar), 8.08 (d, *J* = 8.5, 1H, Ar), 8.20 (d, *J* = 1.7, 1H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.1 (C), 125.0 (CH), 126.1 (CH), 126.2 (CH), 127.3 (CH), 129.1 (CH), 130.7 (CH), 131.1 (C), 133.9 (C), 146.7 (C). MS (ESI) 309.0 ($M(^{79}Br)+Na)^+$, 311.0 ($M(^{81}Br)+Na)^+$.

8-Bromonaphthalene-2-sulfonic acid (33)



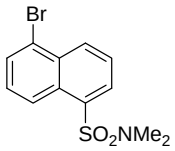
Obtained from 8-aminonaphthalene-2-sulfonic acid (13.4 mmol) in 54% yield.

IR (KBr) ν 3430, 1661, 1558, 1356, 1185. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.40 (br s, 1H, SO_3H), 7.44 (dd, *J* = 8.2, 7.5, 1H, Ar), 7.78 (dd, *J* = 8.5, 1.6, 1H, Ar), 7.89 (dd, *J* = 7.5, 1.0, 1H, Ar), 7.95 (d, *J* = 8.5, 1H, Ar), 7.97 (d, *J* = 8.2, 1H, Ar), 8.40 (br s, 1H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6) δ 122.6 (C), 123.0 (CH), 125.2 (CH), 127.4 (CH), 128.2 (CH), 128.6 (CH), 130.7 (CH, C), 134.3 (C), 147.4 (C). MS (ESI) 309.0 ($M(^{79}Br)+Na)^+$, 311.0 ($M(^{81}Br)+Na)^+$.

General Procedure for the Synthesis of Bromo-*N*,*N*-dimethylnaphthalenesulfonamides 34-36. A solution of bromonaphthalenesulfonic acid **31-33** (1 equiv) and $SOCl_2$ (40 equiv) in anhydrous DMF (3

mL/mmol of sulfonic acid) was heated at 85 ºC for 5 h under an argon atmosphere. The excess of $SOCl_2$ was azeotropically removed with toluene under vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (3 mL/mmol sulfonyl chloride) and cooled to 0 ºC under an argon atmosphere. A 2.0 M solution of dimethylamine in THF (20 equiv) was added dropwise and the mixture was stirred for 12 h at room temperature. Et_2O was added and the organic layer was washed with a 10% aqueous solution of HCl and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography using the appropriate eluent to afford pure bromo-*N*,*N*-dimethylnaphthalenesulfonamides **34-36**.

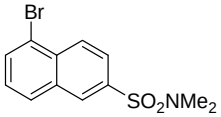
5-Bromo-*N*,*N*-dimethylnaphthalene-1-sulfonamide (34)



Obtained from 5-bromonaphthalene-1-sulfonic acid **31** (1 mmol) and dimethylamine (20 mmol) in 61% yield.

Chromatography: Hexane/EtOAc, 90:10 to 80:20. IR (KBr) ν 2918, 1559, 1495, 1456, 1337, 1160. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (s, 6H, $N(CH_3)_2$), 7.45 (dd, *J* = 8.7, 7.6, 1H, Ar), 7.63 (dd, *J* = 8.6, 7.5, 1H, Ar), 7.86 (d, *J* = 7.5, 1H, Ar), 8.22 (d, *J* = 7.4, 1H, Ar), 8.52 (d, *J* = 8.6, 1H, Ar), 8.77 (d, *J* = 8.7, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.4 ($2CH_3$), 123.6 (C), 125.2 (CH), 125.5 (CH), 128.2 (CH), 130.4 (C), 131.0 (CH), 131.2 (CH), 132.8 (C), 133.4 (CH, C). MS (ESI) 314.0 $(M(^{79}Br)+H)^+$, 316.0 $(M(^{81}Br)+H)^+$.

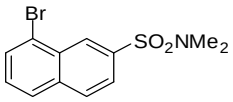
5-Bromo-*N*,*N*-dimethylnaphthalene-2-sulfonamide (35)



Obtained from 5-bromonaphthalene-2-sulfonic acid **32** (1.74 mmol) and dimethylamine (34.8 mmol) in 54% yield.

Chromatography: Hexane/EtOAc, 90:10 to 80:20. IR (KBr) ν 2920, 1667, 1585, 1558, 1490, 1353, 1158. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, 6H, $N(CH_3)_2$), 7.48 (t, *J* = 7.9, 1H, Ar), 7.88 (dd, *J* = 8.9, 1.9, 1H, Ar), 7.96 (dd, *J* = 7.6, 1.1, 1H, Ar), 7.97 (d, *J* = 8.2, 1H, Ar), 8.35 (d, *J* = 1.8, 1H, Ar), 8.41 (d, *J* = 8.9, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.4 ($2CH_3$), 123.3 (C), 124.8 (CH), 128.4 (CH), 129.1 (CH), 129.6 (2CH), 133.1 (CH), 133.9 (2C), 134.3 (C). MS (ESI) 314.0 $(M(^{79}Br)+H)^+$, 316.0 $(M(^{81}Br)+H)^+$.

8-Bromo-*N*,*N*-dimethylnaphthalene-2-sulfonamide (36)

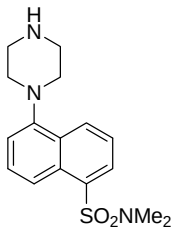


Obtained from 8-bromonaphthalene-2-sulfonic acid **33** (1.74 mmol) and dimethylamine (34.8 mmol) in 53% yield.

Chromatography: Hexane/EtOAc, 90:10 to 80:20. IR (KBr) ν 2918, 1585, 1453, 1330, 1158. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 6H, $N(CH_3)_2$), 7.45 (dd, *J* = 8.3, 7.5, 1H, Ar), 7.85 (dd, *J* = 8.6, 1.8, 1H, Ar), 7.91 (m, 2H, Ar), 8.00 (d, *J* = 8.6, 1H, Ar), 8.71 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.0 ($2CH_3$), 123.9 (C), 124.1 (CH), 127.8 (CH), 128.1 (CH), 129.0 (CH), 129.7 (CH), 131.3 (C), 131.5 (CH), 134.5 (C), 136.0 (C). MS (ESI) 314.0 $(M(^{79}Br)+H)^+$, 316.0 $(M(^{81}Br)+H)^+$.

General Procedure for the Synthesis of Arylpiperazines 28-30. To a solution of bromonaphthalenesulfonamide **34-36** (1 equiv) in toluene (10 mL/mmol) under an argon atmosphere, were successively added piperazine (4 equiv), (±)-BINAP (0.1 equiv), $Pd(OAc)_2$ (0.1 equiv) and *t*-BuONa (1.4 equiv). The reaction mixture was heated at 75 ºC for 20 h, cooled to room temperature, filtered through celite, and finally concentrated under reduced pressure. The residue was purified by column chromatography using the appropriate eluent to afford pure arylpiperazines **28-30**.

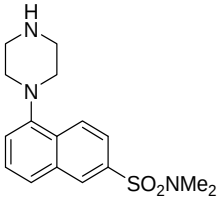
***N*,*N*-Dimethyl-5-(piperazin-1-yl)naphthalene-1-sulfonamide (28)**



Obtained from 5-bromo-*N*,*N*-dimethylnaphthalene-1-sulfonamide **34** (0.51 mmol) and piperazine (2.04 mmol) in 43% yield.

Chromatography: CH_2Cl_2/MeOH, 100:0 to 80:20. IR (film) ν 2945, 2817, 1588, 1572, 1456, 1330, 1156. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (br s, 1H, NH), 2.82 (s, 6H, $N(CH_3)_2$), 3.00-3.17 (m, 4H, $2CH_{2pip}$), 3.17-3.20 (m, 4H, $2CH_{2pip}$), 7.21 (d, *J* = 7.5, 1H, Ar), 7.51-7.59 (m, 2H, Ar), 8.19 (dd, *J* = 7.3, 1.2, 1H, Ar), 8.46 (d, *J* = 8.7, 1H, Ar), 8.55 (d, *J* = 8.4, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.4 ($2CH_3$), 46.0 ($2CH_2$), 53.8 ($2CH_2$), 116.3 (CH), 121.0 (CH), 123.6 (CH), 128.1 (CH), 129.6 (CH), 130.2 (C), 130.5 (CH, C), 133.2 (C), 150.3 (C). MS (ESI) 320.2 $(M+H)^+$.

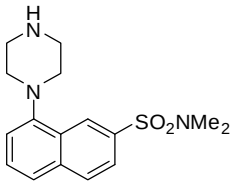
***N*,*N*-Dimethyl-5-(piperazin-1-yl)naphthalene-2-sulfonamide (29)**



Obtained from 5-bromo-*N*,*N*-dimethylnaphthalene-2-sulfonamide **35** (0.48 mmol) and piperazine (1.92 mmol) in 77% yield.

Chromatography: CH_2Cl_2/MeOH, 100:0 to 80:20. IR (film) ν 2958, 2838, 1576, 1456, 1335, 1157. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (br s, 1H, NH), 2.75 (s, 6H, $N(CH_3)_2$), 3.06-3.15 (m, 4H, $2CH_{2pip}$), 3.15-3.24 (m, 4H, $2CH_{2pip}$), 7.25 (d, *J* = 7.7, 1H, Ar), 7.54 (dd, *J* = 8.1, 7.6, 1H, Ar), 7.68 (d, *J* = 8.2, 1H, Ar), 7.76 (dd, *J* = 8.9, 1.8, 1H, Ar), 8.31 (d, *J* = 1.5, 1H, Ar), 8.35 (d, *J* = 8.9, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9 ($2CH_3$), 45.5 ($2CH_2$), 52.9 ($2CH_2$), 117.8 (CH), 122.6 (CH), 124.8 (2CH), 127.6 (CH), 129.3 (CH), 130.4 (C), 132.7 (C), 133.5 (C), 149.6 (C). MS (ESI) 320.1 $(M+H)^+$.

***N*,*N*-Dimethyl-8-(piperazin-1-yl)naphthalene-2-sulfonamide (30)**

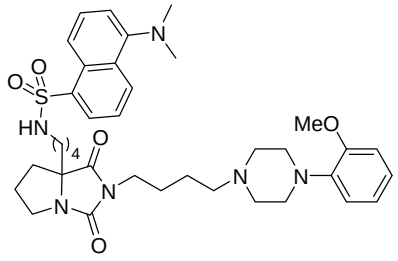


Obtained from 8-bromo-*N*,*N*-dimethylnaphthalene-2-sulfonamide **36** (0.32 mmol) and piperazine (1.28 mmol) in 72% yield.

Chromatography: CH_2Cl_2/MeOH, 100:0 to 80:20. IR (film) ν 2956, 2826, 1617, 1574, 1446, 1338, 1157. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (br s, 1H, NH), 2.75 (s, 6H, $N(CH_3)_2$), 3.11-3.18 (m, 8H, $4CH_{2pip}$), 7.19 (dd, *J* = 6.8, 1.4, 1H, Ar), 7.53-7.61 (m, 2H, Ar), 7.75 (dd, *J* = 8.6, 1.7, 1H, Ar), 7.94 (d, *J* = 8.6, 1H, Ar), 8.68 (br s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9 ($2CH_3$), 45.0 ($2CH_2$), 52.7 ($2CH_2$), 116.6 (CH), 123.1 (CH), 123.5 (CH), 124.7 (CH), 127.7 (C), 128.9 (CH), 129.6 (CH), 132.3 (C), 136.2 (C), 150.5 (C). MS (ESI) 320.1 $(M+H)^+$.

General Procedure for the Synthesis of Final Compounds 3-6. Triethylamine (3 equiv) was added to a solution of the corresponding amine **22-25** (1 equiv) in anhydrous CH_2Cl_2 (10 mL/mmol) at room temperature under an argon atmosphere. A solution of dansyl chloride (1.5 equiv) in 1 mL of anhydrous CH_2Cl_2 was then added and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with a 10% aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography using the appropriate eluent, to afford pure **3-6**.

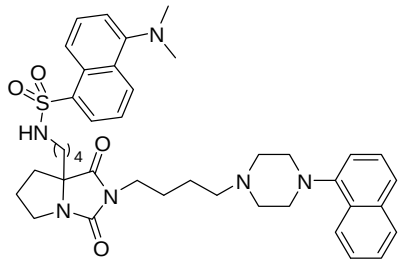
5-(Dimethylamino)-*N*-{4-[2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-7a(5*H*)-yl]butyl}naphthalene-1-sulfonamide (3).



Obtained from **22** (0.30 mmol) and dansyl chloride (0.45 mmol) in 80% yield.

Chromatography: CH_2Cl_2/EtOH, 98:2. IR ($CHCl_3$) ν 3271, 1768, 1705. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-2.02 (m, 14H, 5CH_2, 2CH_{2cyc}), 2.40 (t, *J* = 7.4, 2H, CH_2N_{pip}), 2.62 (m, 4H, 2CH_{2pip}), 2.80-3.00 (m, 8H, $N(CH_3)_2$, C$\underline{H}_2$NH), 3.03-3.15 (m, 5H, 2CH_{2pip}Ar, 1/2CH_{2cyc}), 3.36-3.53 (m, 2H, $CH_2N(CO)_2$), 3.64-3.76 (m, 1H, 1/2CH_{2cyc}), 3.84 (s, 3H, CH_3O), 5.20 (br t, *J* = 5.9, 1H, NH), 6.81-7.01 (m, 4H, Ar), 7.18 (d, *J* = 7.5, 1H, Ar), 7.50 (dd, *J* = 8.4, 7.4, 1H, Ar), 7.54 (dd, *J* = 8.4, 7.8, 1H, Ar), 8.21 (dd, *J* = 7.3, 1.1, 1H, Ar), 8.27 (d, *J* = 8.7, 1H, Ar), 8.53 (d, *J* = 8.5, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_2), 24.3 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 29.7 (CH_2), 33.2 (CH_2), 34.6 (CH_2), 39.1 (CH_2), 43.2 (CH_2), 45.1 (CH_2), 45.7 (2CH_3), 50.8 (2CH_2), 53.7 (2CH_2), 55.7 (CH_3), 58.4 (CH_2), 72.5 (C), 111.5 (CH), 115.6 (CH), 118.6 (CH), 119.0 (CH), 121.3 (CH), 123.2 (CH), 123.5 (CH), 128.7 (CH), 129.8 (CH), 129.9 (C), 130.2 (C), 130.7 (CH), 135.4 (C), 141.7 (C), 152.3 (C), 152.6 (C), 160.8 (CO), 176.5 (CO). HRMS (ESI) calcd for $C_{37}H_{51}N_6O_5S$ ($[M+H]^+$): 691.3636; found: 691.3623. Anal. ($C_{37}H_{50}N_6O_5S\cdot3HCl\cdot3H_2O$) C, H, N, S.

5-(Dimethylamino)-*N*-{4-[2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-7a(5*H*)-yl]butyl}naphthalene-1-sulfonamide (4)

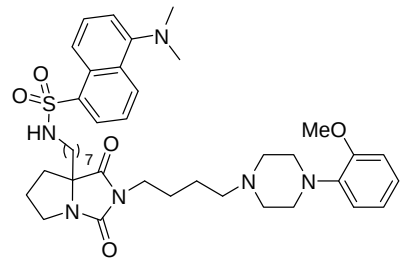


Obtained from **23** (0.11 mmol) and dansyl chloride (0.16 mmol) in 55% yield.

Chromatography: CH_2Cl_2/EtOH, 95:5. IR ($CHCl_3$) ν 3285, 1767, 1703. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.80 (m, 12H, 5CH_2, CH_{2cyc}), 1.94-2.04 (m, 2H, CH_{2cyc}), 2.49 (t, *J* = 7.1, 2H, CH_2N_{pip}), 2.73 (m, 4H, 2CH_{2pip}), 2.81-2.97 (m, 8H, $N(CH_3)_2$, C$\underline{H}_2$NH), 3.03-3.13 (m, 5H, 2CH_{2pip}Ar, 1/2CH_{2cyc}), 3.43-3.53 (m, 2H, $CH_2N(CO)_2$), 3.67-3.77 (m, 1H, 1/2CH_{2cyc}), 5.27 (br s, 1H, NH), 7.01 (d, *J* = 6.7, 1H, Ar), 7.17 (d, *J* = 7.5, 1H, Ar), 7.38 (app t, *J* = 7.8, 1H, Ar), 7.32-7.59 (m, 5H, Ar), 7.78-7.84 (m, 1H, Ar), 8.13-8.20 (m, 1H, Ar), 8.22 (dd, *J* = 7.3, 1.2, 1H, Ar), 8.28 (d, *J* = 8.7, 1H, Ar), 8.52 (d, *J* = 8.5, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (CH_2), 24.3 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 29.7 (CH_2), 33.2 (CH_2), 34.6 (CH_2), 39.1 (CH_2), 43.2 (CH_2), 45.1 (CH_2), 45.7 (2CH_3), 53.0 (2CH_2), 54.0 (2CH_2), 58.4 (CH_2), 72.5 (C), 115.0

(CH), 115.5 (CH), 119.0 (CH), 123.5 (CH), 123.8 (CH), 123.9 (CH), 125.6 (CH), 126.1 (CH), 126.2 (CH), 128.7 (2CH), 129.1 (C), 129.8 (CH), 129.9 (C), 130.2 (C), 130.7 (CH), 135.0 (C), 135.3 (C), 149.8 (C), 152.2 (C), 160.8 (CO), 176.5 (CO). HRMS (ESI) calcd for $C_{40}H_{51}N_6O_4S$ ($[M+H]^+$): 711.3687; found: 711.3666. Anal. ($C_{40}H_{50}N_6O_4S{\cdot}3HCl{\cdot}2H_2O$) C, H, N, S.

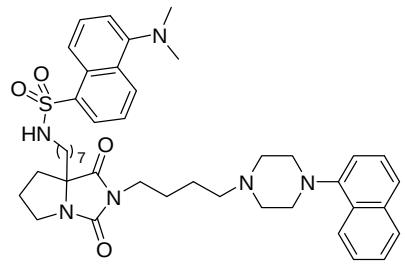
5-(Dimethylamino)-*N*-{7-[2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-7a(5*H*)-yl]heptyl}naphthalene-1-sulfonamide (5)



Obtained from **24** (0.08 mmol) and dansyl chloride (0.12 mmol) in 82% yield.

Chromatography: CH_2Cl_2/EtOH, 98:2. IR ($CHCl_3$) ν 3284, 1767, 1705. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.35 (m, 8H, $4CH_2$), 1.48-1.70 (m, 6H, $3CH_2$), 1.75-1.91 (m, 4H, CH_2, CH_{2cyc}), 1.98-2.12 (m, 2H, CH_{2cyc}), 2.40 (m, 2H, CH_2N_{pip}), 2.66 (m, 4H, $2CH_{2pip}$), 2.80-2.95 (m, 8H, $N(CH_3)_2$, $C\underline{H}_2NH$), 3.00-3.25 (m, 5H, $2CH_{2pip}Ar$, $1/2CH_{2cyc}$), 3.40-3.59 (m, 2H, $CH_2N(CO)_2$), 3.71-3.83 (m, 1H, $1/2CH_{2cyc}$), 3.86 (s, 3H, CH_3O), 4.71 (br s, 1H, NH), 6.83-7.05 (m, 4H, Ar), 7.19 (d, J = 7.6, 1H, Ar), 7.53 (dd, J = 8.3, 7.5, 1H, Ar), 7.57 (app t, J = 8.1, 1H, Ar), 8.24 (dd, J = 7.3, 0.9, 1H, Ar), 8.29 (d, J = 8.6, 1H, Ar), 8.55 (d, J = 8.5, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (CH_2), 24.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 35.2 (CH_2), 39.1 (CH_2), 43.5 (CH_2), 45.1 (CH_2), 45.8 ($2CH_3$), 50.9 ($2CH_2$), 53.7 ($2CH_2$), 55.7 (CH_3), 58.4 (CH_2), 72.7 (C), 111.5 (CH), 115.5 (CH), 118.5 (CH), 119.0 (CH), 121.3 (CH), 123.3 (CH), 123.5 (CH), 128.7 (CH), 130.0 (CH, C), 130.2 (C), 130.7 (CH), 135.1 (C), 141.6 (C), 152.3 (C), 152.6 (C), 161.0 (CO), 176.7 (CO). HRMS (ESI) calcd for $C_{40}H_{57}N_6O_5S$ ($[M+H]^+$): 733.4107; found: 733.4080. Anal. ($C_{40}H_{56}N_6O_5S{\cdot}3HCl{\cdot}2H_2O$) C, H, N, S.

5-(Dimethylamino)-*N*-{7-[2-{4-[4-(1-naphthyl)piperazin-1-yl]butyl}-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-7a(5*H*)-yl]heptyl}naphthalene-1-sulfonamide (6)

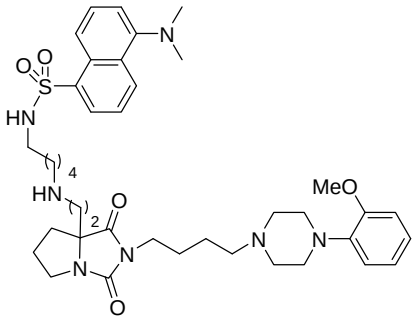


Obtained from **25** (0.14 mmol) and dansyl chloride (0.21 mmol) in 70% yield.

Chromatography: CH_2Cl_2/EtOH, 95:5. IR ($CHCl_3$) ν 3291, 1766, 1703. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.32 (m, 8H, $4CH_2$), 1.47-1.68 (m, 6H, $3CH_2$), 1.78-1.87 (m, 4H, CH_2, CH_{2cyc}), 1.95-2.14 (m, 2H, CH_{2cyc}), 2.48 (t, *J* = 7.3, 2H, CH_2N_{pip}), 2.71 (m, 4H, $2CH_{2pip}$), 2.84 (q, *J* = 6.6, 2H, $C\underline{H}_2NH$), 2.88 (s, 6H, $N(CH_3)_2$), 3.13 (m, 4H, $2CH_{2pip}Ar$), 3.17 (ddd, *J* = 11.6, 7.8, 5.9, 1H, $1/2CH_{2cyc}$), 3.43-3.56 (m, 2H, $CH_2N(CO)_2$), 3.77 (ddd, *J* = 11.6, 8.0, 6.6, 1H, $1/2CH_{2cyc}$), 4.65 (br t, *J* = 6.1, 1H, NH), 7.07 (d, *J* = 7.3, 1H, Ar), 7.18 (d, *J* = 7.3, 1H, Ar), 7.39 (app t, *J* = 7.8, 1H, Ar), 7.41-7.58 (m, 5H, Ar), 7.77-7.85 (m, 1H, Ar), 8.14-8.20 (m, 1H, Ar), 8.23 (dd, *J* = 7.3, 1.2, 1H, Ar), 8.28 (d, *J* = 8.7, 1H, Ar), 8.53 (d, *J* = 8.5, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0 (CH_2), 24.3 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 29.0 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 35.2 (CH_2), 39.1 (CH_2), 43.5 (CH_2), 45.1 (CH_2), 45.7 ($2CH_3$), 53.3 ($2CH_2$), 54.0 ($2CH_2$), 58.4 (CH_2), 72.7 (C), 114.9 (CH), 115.5 (CH), 119.0 (CH), 123.5 (CH), 123.7 (CH), 123.9 (CH), 125.6 (CH), 126.1 (CH), 126.2 (CH), 128.6 (CH), 128.7 (CH), 129.2 (C), 130.0 (CH, C), 130.2 (C), 130.7 (CH), 135.0 (C), 135.1 (C), 150.0 (C), 152.3 (C), 161.0 (CO), 176.8 (CO). HRMS (ESI) calcd for $C_{43}H_{57}N_6O_4S$ ($[M+H]^+$) 753.4156, found: 753.4130. Anal. ($C_{43}H_{56}N_6O_4S{\cdot}3HCl{\cdot}H_2O$) C, H, N, S.

General Procedure for the Synthesis of Final Compounds 7-8. To a solution of the corresponding bromoalkyl derivative **13** or **14** (1 equiv), NaI (2 equiv) and triethylamine (2 equiv) in anhydrous DMF (30 mL/mmol), 2 equiv of dansyl cadaverine were added under an argon atmosphere at room temperature. The reaction was stirred at 50 ºC for 16 h and then concentrated under reduced pressure. The residue was purified by column chromatography using the appropriate eluent, to afford pure **7** or **8**, respectively.

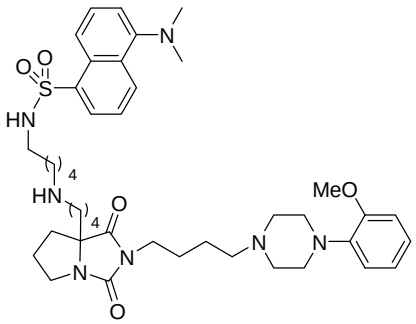
5-(Dimethylamino)-*N*-[5-({2-[2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-7a(5*H*)-yl]ethyl}amino)pentyl]naphthalene-1-sulfonamide (7)



Obtained from **13** (0.09 mmol) and dansyl cadaverine (0.18 mmol) in 40% yield.

Chromatography: CH_2Cl_2/MeOH, 95:5. IR ($CHCl_3$) ν 3428, 1769, 1705. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42-1.48 (m, 4H, $2CH_2$), 1.71-1.97 (m, 6H, $2CH_2$, CH_{2cyc}), 2.05-2.13 (m, 2H, CH_{2cyc}), 2.53-2.59 (m, 2H, CH_2), 2.86-2.89 (m, 10H, $N(CH_3)_2$, CH_2, CH_2N_{pip}), 2.94-3.12 (m, 6H, $3C\underline{H}_2NH$), 3.28-3.40 (m, 5H, $2CH_{2pip}$, $1/2CH_{2cyc}$), 3.46 (m, 4H, $2CH_{2pip}Ar$), 3.58-3.61 (m, 2H, $CH_2N(CO)_2$), 3.69-3.76 (m, 1H, $1/2CH_{2cyc}$), 3.84 (s, 3H, CH_3O), 5.77 (br s, 1H, NH), 6.85-6.90 (m, 3H, Ar), 7.03-7.07 (m, 1H, SO_2NH), 7.16-7.18 (m, 2H, Ar), 7.49-7.59 (m, 2H, Ar), 8.21 (dd, J = 7.3, 1.2, 1H, Ar), 8.35 (d, J = 8.6, 1H, Ar), 8.51 (d, J = 8.5, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6 (CH_2), 23.4 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 28.5 (CH_2), 30.9 ($2CH_2$), 31.9 (CH_2), 38.0 (CH_2), 42.6 (CH_2), 43.8 (CH_2), 45.1 (CH_2), 45.4 ($2CH_3$), 47.6 ($2CH_2$), 53.0 ($2CH_2$), 55.5 (CH_3), 57.3 (CH_2), 70.3 (C), 111.3 (CH), 115.3 (CH), 118.8 (CH), 119.0 (CH), 121.2 (CH), 123.2 (CH), 124.4 (CH), 128.5 (CH), 129.0 (C), 129.5 (CH), 129.8 (C), 130.3 (CH), 134.5 (C), 138.9 (C), 151.9 (C), 152.0 (C), 159.6 (CO), 175.7 (CO). MS (ESI) 748.8 $(M+H)^+$. Anal. ($C_{40}H_{57}N_7O_5S \cdot 7/2HCl \cdot 15/2H_2O$) C, H, N, S.

5-(Dimethylamino)-*N*-[5-({4-[2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-7a(5*H*)-yl]butyl}amino)pentyl]naphthalene-1-sulfonamide (8)



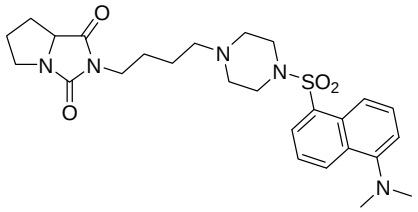
Obtained from **14** (0.12 mmol) and dansyl cadaverine (0.24 mmol) in 80% yield.

Chromatography: CH_2Cl_2/MeOH, 95:5. IR ($CHCl_3$) ν 3435, 1766, 1704. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.75 (m, 10H, $5CH_2$), 1.79-2.11 (m, 10H, $3CH_2$, $2CH_{2cyc}$), 2.86 (m, 8H, $N(CH_3)_2$, CH_2N_{pip}), 2.96-3.05 (m, 6H, $3C\underline{H}_2NH$), 3.13-3.27 (m, 5H, $2CH_{2pip}$, $1/2CH_{2cyc}$), 3.36 (m, 4H, $2CH_{2pip}Ar$), 3.46-3.58 (m, 2H, $CH_2N(CO)_2$), 3.68-3.75 (m, 1H, $1/2CH_{2cyc}$), 3.83 (s, 3H, CH_3O), 6.06 (br s, 1H, NH), 6.83-6.89 (m, 4H, Ar), 6.99-7.03 (m, 1H, SO_2NH), 7.16 (d, J = 7.6, 1H, Ar), 7.48-7.57 (m, 2H, Ar), 8.19 (dd, J = 7.3, 1.8, 1H, Ar), 8.36 (d, J = 8.7, 1H, Ar), 8.50 (d, J = 8.5, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4 (CH_2), 22.0 (CH_2), 23.5 (CH_2), 25.2 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 28.5 (CH_2), 33.0 (CH_2), 34.2 (CH_2), 38.2 (CH_2), 44.9 (CH_2), 45.2 ($2CH_2$, $2CH_3$), 45.4 (CH_2), 48.0 ($2CH_2$), 48.1 (CH_2), 52.8 ($2CH_2$), 55.4 (CH_3), 57.2 (CH_2), 72.2 (C), 111.2 (CH), 115.3 (CH), 118.6 (CH), 119.1 (CH), 121.0 (CH), 123.2 (CH), 123.9 (CH), 128.5 (CH), 129.3 (CH), 129.4 (C), 129.7 (C), 130.3 (CH), 134.6 (C), 139.5 (C), 151.8 (C), 152.0 (C), 160.4 (CO), 176.2 (CO). MS (ESI) 777.5 $(M+H)^+$. Anal. ($C_{42}H_{61}N_7O_5S\cdot4HCl\cdot5H_2O$) C, H, N, S.

General Procedure for the Synthesis of Final Compounds 9-12. Alkyl bromide **26**[1] (1 equiv) and corresponding arylpiperazine **27**[3]**-30** (1 or 1.7 equiv) were suspended in CH_3CN (5 mL/mmol), followed by addition of triethylamine (1 equiv). The mixture was heated at 60 ºC for 24 h, then cooled to room temperature and concentrated under reduced pressure. H_2O and CH_2Cl_2 were added to the residue and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The

residue was purified by column chromatography using the appropriate eluent to afford pure *N*-alkylated arylpiperazines **9-12**.

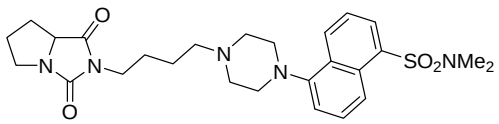
2-[4-(4-{5-(Dimethylamino)-1-naphthylsulfonyl}piperazin-1-yl)butyl]tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (9)



Obtained from alkyl bromide **26** (0.09 mmol) and arylpiperazine **27** (0.16 mmol) in 99% yield.

Chromatography: EtOAc. IR (film) ν 1770, 1709, 1587, 1574, 1444, 1330, 1163, 1144. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35-1.66 (m, 5H, $2CH_2$, $1/2CH_{2cyc}$), 1.98-2.06 (m, 2H, CH_{2cyc}), 2.20 (m, 1H, $1/2CH_{2cyc}$), 2.29 (t, *J* = 7.1, 2H, CH_2N_{pip}), 2.43 (m, 4H, $2CH_{2pip}$), 2.86 (s, 6H, $N(CH_3)_2$), 3.17-3.21 (m, 5H, $2CH_{2pip}$, $1/2CH_{2cyc}$), 3.40 (m, 2H, $CH_2N(CO)_2$), 3.62 (m, 1H, $1/2CH_{2cyc}$), 4.01 (m, 1H, CH_{cyc}), 7.16 (d, *J* = 7.4, 1H, Ar), 7.49-7.53 (m, 2H, Ar), 8.16 (dd, *J* = 7.3, 1.0, 1H, Ar), 8.43 (d, *J* = 8.7, 1H, Ar), 8.54 (d, *J* = 8.5, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 27.4 (CH_2), 38.5 (CH_2), 45.4 ($2CH_2$, $2CH_3$), 45.6 (CH_2), 52.3 ($2CH_2$), 57.4 (CH_2), 63.2 (CH), 115.1 (CH), 119.8 (CH), 123.1 (CH), 127.9 (CH), 130.0 (C), 130.5 (2CH, C), 132.4 (C), 151.6 (C), 160.7 (CO), 173.8 (CO). MS (ESI) 514.1 $(M+H)^+$. Anal. ($C_{26}H_{35}N_5O_4S{\cdot}2HCl{\cdot}H_2O$) C, H, N, S.

5-{4-[4-(1,3-Dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-2(3*H*)-yl)butyl]piperazin-1-yl}-*N*,*N*-dimethylnaphthalene-1-sulfonamide (10)

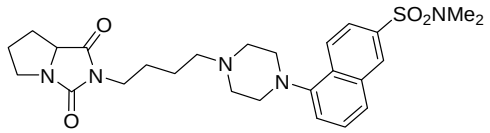


Obtained from alkyl bromide **26** (0.11 mmol) and arylpiperazine **28** (0.19 mmol) in 82% yield.

Chromatography: CH_2Cl_2/MeOH 100:0 to 95:5. IR (film) ν 1771, 1711, 1588, 1572, 1445, 1335, 1155. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-1.77 (m, 5H, $2CH_2$, $1/2CH_{2cyc}$), 2.02-2.16 (m, 2H, CH_{2cyc}), 2.26 (m, 1H, $1/2CH_{2cyc}$), 2.53 (t, *J* = 7.6, 2H, CH_2N_{pip}), 2.75-2.86 (m, 10H, $2CH_{2pip}$, $N(CH_3)_2$), 3.08-3.17 (m, 4H,

2CH_{2pip}Ar), 3.25 (m, 1H, 1/2CH_{2cyc}), 3.52 (t, *J* = 7.0, 2H, $CH_2N(CO)_2$), 3.68 (dt, *J* = 11.2, 7.6, 1H, 1/2CH_{2cyc}), 4.08 (dd, *J* = 8.9, 7.6, 1H, CH_{cyc}), 7.21 (d, *J* = 7.5, 1H, Ar), 7.50-7.58 (m, 2H, Ar), 8.18 (dd, *J* = 7.4, 1.1, 1H, Ar), 8.45 (d, *J* = 8.7, 1H, Ar), 8.52 (d, *J* = 8.5, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 (CH_2), 26.0 (CH_2), 27.0 (CH_2), 27.5 (CH_2), 37.5 (2CH_3), 38.7 (CH_2), 45.5 (CH_2), 53.0 (2CH_2), 53.5 (2CH_2), 57.9 (CH_2), 63.3 (CH), 116.1 (CH), 120.6 (CH), 123.4 (CH), 128.1 (CH), 129.8 (CH), 130.1 (C), 130.4 (CH, C), 133.1 (C), 150.2 (C), 160.8 (CO), 174.0 (CO). HRMS (ESI) calcd. for $C_{26}H_{36}N_5O_4S$ ($[M+H]^+$): 514.2488; found: 514.2487. Anal. ($C_{26}H_{35}N_5O_4S{\cdot}HCl{\cdot}H_2O$) C, H, N, S.

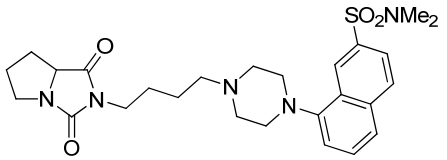
5-{4-[4-(1,3-Dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-2(3*H*)-yl)butyl]piperazin-1-yl}-*N*,*N*-dimethylnaphthalene-2-sulfonamide (11)



Obtained from alkyl bromide **26** (0.19 mmol) and arylpiperazine **29** (0.19 mmol) in 53% yield.

Chromatography: CH_2Cl_2/MeOH, 100:0 to 95:5. IR (film) ν 1770, 1711, 1576, 1444, 1338, 1158. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.76 (m, 5H, 2CH_2, 1/2CH_{2cyc}), 2.02-2.14 (m, 2H, CH_{2cyc}), 2.26 (m, 1H, 1/2CH_{2cyc}), 2.52 (t, *J* = 7.0, 2H, CH_2N_{pip}), 2.69-2.80 (m, 10H, 2CH_{2pip}, $(NCH_3)_2$), 3.12-3.19 (m, 4H, 2CH_{2pip}Ar), 3.25 (ddd, *J* = 11.3, 7.8, 5.0, 1H, 1/2CH_{2cyc}), 3.52 (t, *J* = 6.9, 2H, $CH_2N(CO)_2$), 3.68 (dt, *J* = 11.2, 7.6, 1H, 1/2CH_{2cyc}), 4.08 (dd, *J* = 9.0, 7.6, 1H, CH_{cyc}), 7.25 (d, *J* = 7.4, 1H, Ar), 7.53 (t, *J* = 7.6, 1H, Ar), 7.67 (d, *J* = 8.1, 1H, Ar), 7.75 (dd, *J* = 8.8, 2.0, 1H, Ar), 8.31 (d, *J* = 1.2, 1H, Ar), 8.32 (d, *J* = 8.6, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 27.4 (CH_2), 37.9 (2CH_3), 38.6 (CH_2), 45.4 (CH_2), 52.6 (2CH_2), 53.3 (2CH_2), 57.8 (CH_2), 63.2 (CH), 117.5 (CH), 122.4 (CH), 124.4 (CH), 124.9 (CH), 127.6 (CH), 129.3 (CH), 130.4 (C), 132.4 (C), 133.5 (C), 149.6 (C), 160.7 (CO), 173.9 (CO). HRMS (ESI) calcd for $C_{26}H_{36}N_5O_4S$ ($[M+H]^+$): 514.2488; found: 514.2487. Anal. ($C_{26}H_{35}N_5O_4S{\cdot}2HCl{\cdot}2H_2O$) C, H, N, S.

8-{4-[4-(1,3-Dioxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-2(3*H*)-yl)butyl]piperazin-1-yl}-*N*,*N*-dimethylnaphthalene-2-sulfonamide (12)

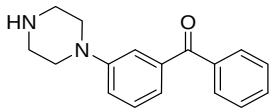


Obtained from alkyl bromide **26** (0.33 mmol) and arylpiperazine **30** (0.33 mmol) in 58% yield.

Chromatography: CH_2Cl_2/MeOH, 100:0 to 95:5. IR (film) ν 1770, 1711, 1574, 1444, 1342, 1158. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-1.76 (m, 5H, $2CH_2$, $1/2CH_{2cyc}$), 2.03-2.14 (m, 2H, CH_{2cyc}), 2.26 (m, 1H, $1/2CH_{2cyc}$), 2.57 (t, *J* = 6.6, 2H, CH_2N_{pip}), 2.75 (s, 6H, $N(CH_3)_2$), 2.82 (m, 4H, $2CH_{2pip}$,), 3.13-3.29 (m, 5H, $2CH_{2pip}Ar$, $1/2CH_{2cyc}$), 3.52 (t, *J* = 6.7, 2H, $CH_2N(CO)_2$), 3.68 (dt, *J* = 11.2, 7.7, 1H, $1/2CH_{2cyc}$), 4.09 (dd, *J* = 8.9, 7.6, 1H, CH_{cyc}), 7.00 (d, *J* = 7.0, 1H, Ar), 7.53-7.62 (m, 2H, Ar), 7.75 (dd, *J* = 8.6, 1.7, 1H, Ar), 7.94 (d, *J* = 8.6, 1H, Ar), 8.65 (br s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 27.5 (CH_2), 38.0 ($2CH_3$), 38.5 (CH_2), 45.4 (CH_2), 52.5 ($2CH_2$), 53.1 ($2CH_2$), 57.6 (CH_2), 63.3 (CH), 116.3 (CH), 123.0 (CH), 123.1 (CH), 124.9 (CH), 127.7 (C), 128.9 (CH), 129.5 (CH), 131.9 (C), 136.1 (C), 150.5 (C), 160.7 (CO), 173.9 (CO). HRMS (ESI) calcd for $C_{26}H_{36}N_5O_4S$ ($[M+H]^+$): 514.2488; found: 514.2480. Anal. ($C_{26}H_{35}N_5O_4S{\cdot}2HCl{\cdot}2H_2O$) C, H, N, S.

Synthesis of 2-{4-[4-(3-Benzoylphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione

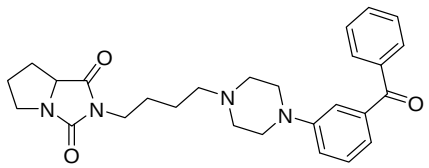
Phenyl[(3-piperazin-1-yl)phenyl]methanone



To a solution of 3-bromo-benzophenone (1 equiv, 0.50 mmol) in toluene (5 mL) under an argon atmosphere, were successively added piperazine (4 equiv, 2.0 mmol), (±)-BINAP (0.1 equiv, 0.05 mmol), $Pd(OAc)_2$ (0.1 equiv, 0.05 mmol) and *t*-BuONa (1.4 equiv, 0.7 mmol). The reaction mixture was heated at 75 ºC for 20 h, cooled to room temperature, filtered through celite, and finally concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 100:0 to 80:20) to afford phenyl[(3-piperazin-1-yl)phenyl]methanone in 98% yield.

IR (film) ν 3058, 1655, 1595, 1447. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06-3.09 (m, 4H, $2CH_{2pip}$), 3.22-3.25 (m, 4H, $2CH_{2pip}$), 3.66 (br s, 1H, NH), 7.14 (ddd, *J* = 8.2, 2.6, 0.9, 1H, Ar), 7.21 (dt, *J* = 7.5, 1.2, 1H, Ar), 7.35 (t, *J* = 7.9, 1H, Ar), 7.37 (m, 1H, Ar), 7.45-7.51 (m, 2H, Ar), 7.59 (m, 1H, Ar), 7.79-7.83 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.4 ($2CH_2$), 49.4 ($2CH_2$), 116.7 (CH), 119.9 (CH), 121.7 (CH), 128.1 (2CH), 128.7 (CH), 129.9 (2CH), 132.2 (CH), 137.6 (C), 138.2 (C), 151.3 (C), 196.9 (CO). MS (ESI) 267.1 $(M+H)^+$.

2-{4-[4-(3-Benzoylphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione



Phenyl[(3-piperazin-1-yl)phenyl]methanone (1 equiv, 1.13 mmol) and alkyl bromide **26** (1 equiv, 1.13 mmol) were suspended in CH_3CN (6 mL), followed by addition of triethylamine (1 equiv, 1.13 mmol). The mixture was heated at 60 ºC for 24 h, then cooled to room temperature and concentrated under reduced pressure. H_2O and CH_2Cl_2 were added to the residue and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 100:0 to 95:5) to afford 2-{4-[4-(3-benzoylphenyl)piperazin-1-yl]butyl}tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione in 57% yield.

IR (film) ν 1771, 1713, 1658, 1595, 1575, 1445, 1349, 1133. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48-1.75 (m, 5H, $2CH_2$, $1/2CH_{2cyc}$), 1.99-2.12 (m, 2H, CH_{2cyc}), 2.25 (m, 1H, $1/2CH_{2cyc}$), 2.41 (t, *J* = 7.4, 2H, CH_2N_{pip}), 2.59 (m, 4H, $2CH_{2pip}$), 3.24 (m, 5H, $2CH_{2pip}Ar$, $1/2CH_{2cyc}$), 3.50 (t, *J* = 7.0, 2H, $CH_2N(CO)_2$), 3.68 (dt, *J* = 11.2, 7.7, 1H, $1/2CH_{2cyc}$), 4.07 (dd, *J* = 9.0, 7.5, 1H, CH_{cyc}), 7.13 (ddd, *J* = 8.2, 2.6, 1.0, 1H, Ar), 7.19 (dt, *J* = 7.5, 1.4, 1H, Ar), 7.34 (t, *J* = 7.8, 1H, Ar), 7.36 (m, 1H, Ar), 7.44-7.50 (m, 2H, Ar), 7.59 (m, 1H, Ar), 7.79-7.83 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 27.5 (CH_2), 38.7 (CH_2), 45.4 (CH_2), 48.7 ($2CH_2$), 53.0 ($2CH_2$), 57.8 (CH_2), 63.2 (CH), 116.6 (CH), 119.7

(CH), 121.4 (CH), 128.1 (2CH), 128.7 (CH), 130.0 (2CH), 132.2 (CH), 137.7 (C), 138.3 (C), 151.1 (C), 160.7 (CO), 173.9 (CO), 197.0 (CO). HRMS (ESI) calcd for $C_{27}H_{33}N_4O_3$ ($[M+H]^+$): 514.2488; found: 514.2480. Anal. ($C_{27}H_{32}N_4O_3 \cdot HCl \cdot 5/2H_2O$) C, H, N.

2. Elemental Analysis Data

compd	molecular formula	calculated				found			
		C	H	N	S	C	H	N	S
3	$C_{37}H_{50}N_6O_5S \cdot 3HCl \cdot 3H_2O$	52.02	6.96	9.84	3.75	51.98	6.61	9.51	3.54
4	$C_{40}H_{50}N_6O_4S \cdot 3HCl \cdot 2H_2O$	56.10	6.71	9.81	3.74	56.22	6.77	9.55	3.60
5	$C_{40}H_{56}N_6O_5S \cdot 3HCl \cdot 2H_2O$	54.69	7.23	9.57	3.65	54.30	7.20	9.18	3.30
6	$C_{43}H_{56}N_6O_4S \cdot 3HCl \cdot H_2O$	58.66	6.98	9.55	3.64	58.52	7.05	9.17	3.51
7	$C_{40}H_{57}N_7O_5S \cdot 7/2HCl \cdot 15/2H_2O$	47.53	7.53	9.70	3.17	47.32	7.40	10.01	3.11
8	$C_{42}H_{61}N_7O_5S \cdot 4HCl \cdot 5H_2O$	49.85	7.47	9.69	3.17	49.48	7.09	10.05	2.90
9	$C_{26}H_{35}N_5O_4S \cdot 2HCl \cdot H_2O$	51.65	6.50	11.58	5.30	51.68	6.72	11.76	5.02
10	$C_{26}H_{35}N_5O_4S \cdot HCl \cdot H_2O$	54.97	6.74	12.33	5.64	55.22	6.39	12.11	5.51
11	$C_{26}H_{35}N_5O_4S \cdot 2HCl \cdot 2H_2O$	50.16	6.64	11.25	5.15	50.44	6.29	11.10	5.26
12	$C_{26}H_{35}N_5O_4S \cdot 2HCl \cdot 2H_2O$	50.16	6.64	11.25	5.15	50.55	6.27	10.90	4.94

3. Binding Assays

Membranes from HEK-293-EBNA (5-HT_{1A}) and HEK-293 (5-HT_6 and 5-HT_7) cells expressing the indicated human serotonin receptors were purchased from Perkin-Elmer and conserved at -80 ºC in packaging buffer for subsequent use. Competitive inhibition assays were performed according to standard procedures detailed below.

5-HT_{1A} receptor. Cell membranes (6.4 mg/mL) were homogenized in 7 volumes of assay buffer (50 mM Tris-HCl, 0.5 mM $MgSO_4$, pH 7.4 at 25 ºC). Fractions of 20 µL of the membranes suspension were incubated at 37 ºC for 120 min with 2 nM [^{3}H]-8-hydroxy-DPAT (170.2 Ci/mmol, Perkin-Elmer), in the presence or absence of the competing drug (ranging from 10^{-5} to 10^{-10} M), in a final volume of 200 µL of

assay buffer. Nonspecific binding was determined by radioligand binding in the presence of a saturating concentration of 10 μM serotonin, and represented less than 10% of total binding.

5-HT$_6$ receptor. Cell membranes (6.0 mg/mL) were homogenized in 7 volumes of assay buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 0.5 mM EDTA, pH 7.4 at 25 ºC). Fractions of 20 μL of the membranes suspension were incubated at 37 ºC for 60 min with 2.5 nM [^{3}H]LSD (79.2 Ci/mmol, Perkin-Elmer), in the presence or absence of the competing drug (ranging from 10^{-5} to 10^{-10} M), in a final volume of 200 μL of assay buffer. Nonspecific binding was determined by radioligand binding in the presence of a saturating concentration of 100 μM serotonin, and represented less than 10% of total binding.

5-HT$_7$ receptor. Cell membranes (6.8 mg/mL) were homogenized in 200 volumes of assay buffer (50 mM Tris-HCl, 10 mM $MgSO_4$, 0.5 mM EDTA, pH 7.4 at 25 ºC). Fractions of 500 μL of the membranes suspension were incubated at 27 ºC for 120 min with 3 nM [^{3}H]LSD (79.2 Ci/mmol, Perkin-Elmer), in the presence or absence of the competing drug (ranging from 10^{-5} to 10^{-10} M), in a final volume of 540 μL of assay buffer. Nonspecific binding was determined by radioligand binding in the presence of a saturating concentration of 25 μM clozapine, and represented less than 15% of total binding.

For all binding assays, competing drug, nonspecific, total, and radioligand bindings were defined in triplicate. Incubation was terminated by rapid vacuum filtration through Wallac Filtermat A filters, presoaked in polyethylenimine (0.5% for 5-HT$_{1A}$ and 5-HT$_6$ receptors and 0.3% for the 5-HT$_7$ receptor), using a FilterMate Unifilter 96-Harvester. The filters were then washed 9 times with 500 μL of ice-cold 50 mM Tris-HCl buffer (pH 7.4 at 25 ºC) and dried. The radioactivity bound to the filters was measured by scintillation spectrometry, using a Microbeta TopCount instrument. The data were analyzed by an iterative curve-fitting procedure using GraphPad Prism program. K_i values were calculated from the Cheng-Prusoff equation[4] and are the mean of two to four experiments performed in triplicate.

5-HT$_{2A}$, 5-HT$_{4e}$, and 5-HT$_{5a}$ receptors. Compound **4** was screened at a concentration of 1 μM for affinity at 5-HT$_{2A}$, 5-HT$_{4e}$, and 5-HT$_{5a}$ Rs at CEREP (http://www.cerep.fr/Cerep/Users/index.asp; Le Bois l'Eveque, 86600 Celle L'Evescault, France).

[4] Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.

4. Fluorescence Spectroscopy

Absorption spectra of compounds **3-12** were determined in 10 μM solutions of the corresponding compound in binding assay buffer (50 mM Tris-HCl, 0.5 mM $MgSO_4$, pH 7.4) at 25 ºC, on a Shimadzu UV-2550 UV-Vis spectrophotometer in 1 cm path length quartz cells. Spectra were recorded between 250 and 700 nm (0.5 nm increments and 0.1 s integration time) and they were corrected for background absorbance by subtracting a blank scan of the buffer solution.

Emission spectra of compounds **3-12** were determined for the same solutions on a PerkinElmer LS50B luminescence spectrometer in 1 cm path length quartz cells. The spectra were recorded between 340 and 690 nm (0.5 nm increments and 0.1 s integration time) with excitation set at the appropriate excitation wavelength. Slit widths were set to 2.5 nm for excitation and 2.5, 5 or 10 nm for emission, depending on the observed emission intensity. All the spectra were corrected for background fluorescence by subtracting a blank scan of the buffer solution.

Fluorescent quantum yields (Φ_f) were calculated with respect to quinine sulfate (Aldrich) in 0.1 M H_2SO_4 as a standard (Φ_f = 0.54).[5] Solutions of both the sample and the reference were prepared by dilution of stock solutions whose absorbance was below 0.1 at the same excitation wavelength (350 nm). Fluorescence measurements were taken for each solution with the same instrument parameters, and the fluorescence spectra were corrected for instrumental response before integration. The integrated corrected emission intensities were plotted against the absorbance and data were least-squared fitted to a straight line. The slopes of these lines are proportional to the quantum yield of the different samples. Absolute values are calculated using standard samples of known Φ_f, according to the following equation:[5]

$$\Phi_{f,x} = \Phi_{f,s} \frac{F_x}{A_x} \frac{A_s}{F_s} \left(\frac{\eta_x}{\eta_s} \right)^2 = \Phi_{f,s} \frac{slope_x}{slope_s} \left(\frac{\eta_x}{\eta_s} \right)^2$$

[5] Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*, 2nd ed.; Kluwer Academic/Plenum Press: New York, 1999.

where A is the absorbance at the excitation wavelength, F is the area under the corrected emission curve, η is the refractive index of the solvent, and the slopes refer to the integrated corrected emission vs absorbance plots for the sample (X) and the standard (S). The correction for the refractive index $(\eta_x / \eta_s)^2$ was found[6] to be very close to one (0.9997), as expected for diluted aqueous solutions. Therefore, it was considered to be of no significance.

5. Cell Visualization

For fluorescence microscopy, stock solutions of the compounds were prepared in DMSO and then diluted to the final concentration with PBS buffer so that DMSO content was < 1%. Chinese Hamster Ovary (CHO) cells stably transfected with the human 5-HT_{1A} receptor, kindly donated by Prof. Probal Banerjee (The College of Staten Island CUNY, New York, USA), were grown in D-MEM/F-12 media (Invitrogen) supplemented with 10% fetal bovine serum (FBS; Gibco), 1% Penicillin-Streptomycin solution (Gibco) and 200 μg/mL geneticin (Gibco) in a humidified atmosphere with 5% CO_2 at 37 °C. For labeling studies, cells were treated with 0.125% trypsin (Invitrogen) and plated onto gelatin-coated glass coverslips in 24-well tissue culture dishes at a density of 8,000 cells/well and cultured under the same conditions than above for additional 48 h. For cell labeling, culture media was aspirated off, cells were washed with PBS and incubated in the presence or absence of the compound(s) in PBS buffer for 10 minutes at ~20 °C. Afterwards, buffer was removed, cells were washed with PBS, fixed with 2% paraformaldehyde, washed again and mounted on glass slides with Immu-mount (Thermo Scientific). Preparations were observed with a SP2 Leica confocal microscope with the 63X, 1.4 NA, oil immersion objective (excitation at 405 nm and emission window at 461-568 nm).

[6] *Handbook of Organic Photochemistry*, Scaiano, J. C. Ed.; CRC Press: Boca Raton, Florida, 1989.