

Supporting Information:

**Design, Synthesis, Radiolabeling, *in Vitro* and *in Vivo* Evaluation of
Bridgehead Iodinated Analogues of *N*-{2-[4-(2-methoxyphenyl)piperazin-
1-yl]ethyl}-*N*-(pyridin-2-yl)cyclohexanecarboxamide (WAY-100635) as
Potential SPECT Ligands for the 5-HT_{1A} Receptor**

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Contents of SI:

Experimental and elemental analysis data of non-key compounds: **2, 4, 5a-d, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19** and **20**.

Chemistry: General procedures. The solvents were dried according to standard procedures. All reactions involving moisture sensitive compounds were performed under an anhydrous atmosphere of dry argon, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from LiAlH₄ freshly prior to use or anhydrous purchased from Sigma-Aldrich. All other commercially available chemicals were used without further purification. Reactions were monitored by using thin-layer chromatography (TLC) on silica-coated plastic sheets (Merck silica gel 60 F₂₅₄) with the indicated eluent. The compounds were visualized by UV light (254 nm), I₂, Ceric Ammonium Molybdate (CAM), Bromocrysol or potassium permanganate staining, followed by charring at 130 °C. Flash chromatography refers to column purification using the indicated eluent and Acros silica gel (0.030-0.075 mm). 3-Hydroxyadamantane-1-carboxylic acid was purchased from Maybridge (Tintagel, UK). Dimethyl 1,4-cubanedicarboxylate and 4-methoxycarbonylcubane-1-carboxylic acid were purchased from Boron Molecular (North Carolina, USA). Diethylsuccinyl succinate was purchased from Sigma-Aldrich (Zwijndrecht, The Netherlands). N-(2-hydroxyphenyl)piperazine was purchased from ABCR GmbH & Co. KG (Karlsruhe, Germany). All other reagents were purchased from Fluka, Sigma-Aldrich or Acros and used without further purification unless stated otherwise. Nuclear magnetic resonance spectra (¹H NMR and ¹³C NMR) were determined in the indicated solvent using a Bruker AC 200 MHz (200.13 MHz and 50.32 MHz, respectively), a Bruker Avance 250 MHz (250.13 and 62.90 MHz, respectively) or a Bruker MSL 400 MHz (400.13 and 100.61 MHz, respectively). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane (¹H, ¹³C) and coupling constants *J* in Hz. Mass spectra were recorded on a Finnigan MAT-90 mass spectrometer. Analytical HPLC was performed on a C18 - 10 μm column (kromasil, 4.6 mm x 250 mm), using MeOH/H₂O/DIPA (65/35/0.02) as eluent and a flow of 1 mL.min⁻¹. Products were detected at λ = 254 nm. All tested compounds have a purity of at least 95% according to NMR and HPLC analysis.

3-Iodoadamantane-1-carboxylic acid (5a).

3-Iodo-adamantane-1-carboxylic acid was synthesized according to literature procedures of Stone and Shechter.^{23,24} In a round bottom flask, provided with stirrer and reflux cooler, 3-hydroxyadamantane-1-carboxylic acid (3 g, 15.3 mmol) was dissolved in a mixture of 85% phosphoric acid (60 mL), P₂O₅ (12.16 g, 85.68 mmol) and KI (3.66 g, 22.06 mmol). The reaction mixture was heated to 120 °C for 3 h and was then allowed to cool to room temperature and poured on ice. The water phase was extracted with ether (3 x 25 mL). The combined organic layers were washed with 25 mL of 10% Na₂S₂O₄ solution and brine (2 x 25 mL), collected and dried over anhydrous Na₂SO₄. Evaporation in vacuo gave 4.44 g (95%) of **5a** as a white solid. ¹H NMR (250.13 MHz, CDCl₃): δ 1.8 (s, 2H, 2 x CH), 1.96-2.04 (m, 6H, 3 x CH₂), 2.54- 2.60 (m, 4H, 2 x CH₂), 2.72 (s, 2H, CH₂). ¹³C NMR (62.90 MHz, CDCl₃): δ 31.81, 34.35, 36.73, 44.45, 45.47, 52.13, 181.61.

This compound was also synthesized by the Hunsdiecker method as used in **5c**, albeit in lower yield (53%).

4-Iodocubanecarboxylic acid (5b).

4-Methoxycarbonylcubanecarboxylic acid was prepared according to a literature procedure of Eaton.²⁵ Starting with dimethyl 1,4-cubanedicarboxylate (2.25 g, 10.2 mmol) in THF (70 mL) and a solution of NaOH in MeOH (10 mmol) gave 2.07 g (98%) of the monoacid as white crystals. ¹H NMR (200.13 MHz, CDCl₃): δ 3.72 (s, 3H, CH₃), 4.27-4.46 (m, 6H, 6 x CH).

Compound **5b** was prepared according to a literature procedure of Harpp.²⁶ To a suspension of the monoacid (1 g, 4.86 mmol) in anhydrous benzene (77 mL) under N₂ atmosphere, iodobenzene diacetate (IBDA, 4.7 g, 14.58 mmol) and I₂ (3.7 g, 14.58 mmol) were added. This reaction mixture was refluxed for 7 h and then cooled to room temperature. Then pentane (40 mL) was

added. The solution was washed with saturated aqueous Na_2SO_3 (2 x 15 mL), water (15 mL) and brine (15 mL). The organic phase was collected, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to near dryness. The red brown solution was then dissolved in THF (25 mL). A solution of NaOH (1.94 g, 4.86 mmol) in MeOH (18 mL) and water (6 mL) was added and this mixture was stirred at room temperature overnight. Solvents were evaporated to near dryness and then the residue was dissolved in water and acidified with concentrated HCl (pH approximate to 1) to give 1.22 g (92%) of **5b**. ^1H NMR (200.13 MHz, CDCl_3): δ 4.23-4.33 (m, 3H, 3 x CH), 4.35-4.45 (m, 3H, 3 x CH).

4-Iodobicyclo[2.2.2]octane-1-carboxylic acid (5c).

Diethyl 2,5-dioxobicyclo[2.2.2]octane-1,4-dicarboxylate (9).

Diethylsuccinyl succinate (**8**) (1 g, 3.90 mmol) was dissolved in 1,2-dimethoxyethane (35 mL). NaH (468 mg, 11.7 mmol, 60% suspension in oil) was carefully added in small portions at 0 °C until the evolution of hydrogen ceased. Then 25% of the solvent was evaporated. The suspension was stirred at room temperature for 30 minutes during which the color changed from grey-yellow to pink. Then 3 mL of 1,2-dibromoethane was added. The mixture was heated until the pink color had disappeared. The hot suspension was filtered and the solid was washed with CH_2Cl_2 (3 x 5 mL). The solvent and the excess of 1,2-dibromoethane were removed from the filtrate in vacuo. Recrystallization of the yellow crude product from n-hexane gave 877 mg (80%) of **9** as a white solid. ^1H NMR (200.13 MHz, CDCl_3): δ 1.28 (t, $J = 7$ Hz, 6H, 2 x CH_3), 1.95-3.28 (m, 8H, 4 x CH_2), 4.25 (q, $J = 7$ Hz, 4H, 2 x CH_2).

Bis-(dimethylene)-mercaptol of diethyl 2,5-dioxobicyclo-[2.2.2]octane-2,4-dicarboxylate (10).

Compound **9** (5 g, 17.7 mmol) was dissolved in CHCl₃ (40 mL) in a 100 mL three-necked flask. 1,2-ethanedithiol (5.90 mL, 70.2 mmol) was added and hydrogen chloride was bubbled through the mixture for 7 h at 0 °C. The reaction mixture was neutralized with 2 N NaOH and then washed with water (3 x 25 mL). The CHCl₃ phase was collected and dried over anhydrous Na₂SO₄. The CHCl₃ was removed in a ventilated hood (STENCH) and the resulting oil was boiled at 100 °C with n-hexane until a powdery white solid formed. This mixture was decanted hot and the solid product was recrystallized from n-hexane to give 6.4 g (84%) of **10** as a white solid. ¹H NMR (200.13 MHz, CDCl₃): δ 1.25 (t, *J* = 7 Hz, 6H, 2 x CH₃), 1.70-2.0 (m, 2H, CH₂), 2.4-2.6 (m, 2H, CH₂), 2.80-3.10 (m, 4H, 2 x CH₂), 3.2-3.4 (m, 8H, 4 x CH₂), 4.10 (q, *J* = 7 Hz, 4H, 2 x CH₂). ¹³C NMR (50.32 MHz, CDCl₃): δ 14.03, 26.27, 39.21, 40.33, 50.74, 52.06, 60.78, 69.93, 172.8.

Diethyl bicyclo[2.2.2]octane-1,4-dicarboxylate (11).

Nickel-aluminum alloy was activated according to a literature procedure.³⁰ Raney Nickel hydrogenation catalyst W-2 is highly pyrophoric and must be kept under a liquid at all times. Compound **10** (1.19 g, 2.70 mmol) was dissolved in absolute ethanol (25 mL) and Raney Nickel (18 g, one teaspoonful equals approximately 3 g) was added. This reaction mixture was refluxed for 4 h. The nickel was filtered over high flow celite. The filtrate was concentrated under reduced pressure to give 631 mg (93%) of **11** as a colorless oil. ¹H NMR (200.13 MHz, CDCl₃): δ 1.10 (t, *J* = 7 Hz, 6H, 2 x CH₃), 1.7 (s, 12H, 6 x CH₂), 3.9 (q, *J* = 7 Hz, 4H, 2 x CH₂). ¹³C NMR (50.32 MHz, CDCl₃): δ 13.84, 27.45, 35.30, 60.28, 177.8.

4-(Ethoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (12).

Diethyl bicyclo[2.2.2]octane-1,4-dicarboxylate **11** (1 g, 3.9 mmol) and KOH (218 mg, 3.9 mmol) were dissolved in 96% ethanol (5.5 mL). This reaction mixture was refluxed overnight. The solvent was evaporated under reduced pressure. Water (10 mL) was added to the residue, and the water layer was extracted with diethyl ether (3 x 15 mL). The alkaline aqueous extract was acidified with 6 N HCl until pH = 3, and 537 mg (62%) of **12** was isolated by filtration as a white solid. The filtrate was further acidified with 6 N HCl until pH = 1, and 21 mg (2.6%) of the diacid was isolated. The ether phase was dried over anhydrous Na₂SO₄, and evaporated in vacuo to give a recovery of 256 mg (26%) of **11**. ¹H NMR (250.13 MHz, CDCl₃): δ 1.26 (t, *J* = 7 Hz, 3H, CH₃), 1.86 (s, 12 H, 6 x CH₂), 4.12 (q, *J* = 7 Hz, 2H, CH₂).

4-Iodobicyclo[2.2.2]octane-1-carboxylic acid (5c).

Compound **12** (640 mg, 2.84 mmol) was dissolved in CH₂Cl₂, HgO (6.15 mg, 2.84 mmol) and I₂ (720 mg, 5.68 mmol) were added. The reaction mixture was heated in a closed vial to 80- 90 °C for 2 h. Next, the mixture was cooled to room temperature and filtered over high flow celite. The filtrate was concentrated under reduced pressure to give the crude product as yellow crystals. Recrystallization from CH₂Cl₂ and hexane gave 719 mg (81.5%) of ethyl 4-iodobicyclo[2.2.2]octane-1-carboxylate as colorless crystals. ¹H NMR (250.13 MHz, CDCl₃): δ 1.23 (t, *J* = 7 Hz, 3H, CH₃), 1.88-2.00 (m, 6H, 3 x CH₂), 2.41-2.54 (m, 6H, 3 x CH₂), 4.09 (q, *J* = 7 Hz, 2H, CH₂). A solution of ethyl 4-iodobicyclo[2.2.2]octane-1-carboxylate (1.285 g, 4.17 mmol) and KOH (235 mg, 4.17 mmol) in 96% ethanol (10 mL) was stirred at room temperature overnight. Solvent was evaporated under reduced pressure. The residue was dissolved in water (5 mL) and extracted with pentane (2 x 15 mL). The water phase was collected and subsequently acidified with 6 N HCl until crystals were formed. Compound **5c** was isolated 1.071 g (92%) as a

white solid. ^1H NMR (250.13 MHz, CDCl_3): δ 1.89- 2.04 (m, 6H, 3 x CH_2), 2.42-2.56 (m, 6H, 2 x CH_2).

4-Iodobicyclo[2.2.1]heptane-1-carboxylic acid (5d).

Cyclopentane-1,3-dicarboxylic acid (14).

In a 2 L round flask, norbornene (**13**) (9.42 g, 100 mmol) was dissolved in a mixture of EtOAc (200 mL) and MeCN (200 mL). While this solution has been cooled in an ice bath, RuCl_3 (0.46 g, 2.2 mmol) was added, followed by a solution of NaIO_4 (87.8 g, 410 mmol) in water (300 mL). This biphasic solution was stirred violently for 2 hours at room temperature. The reaction mixture was filtered over celite and the filtrate was collected. The organic layer was separated and the product was extracted from the organic layer with 0.25 M NaOH in water (3 x 200 mL). The combined basic water layers were acidified to pH = 1 with concentrated HCl and the product was extracted with EtOAc (3 x 150 mL). The EtOAc layers were collected, dried with Na_2SO_4 , filtered and evaporated in vacuo to give compound **14** (9.69 g, 61%) as a white solid. ^1H NMR (250.13 MHz, CDCl_3): δ 1.90-2.27 (m, 6H, 3 x CH_2), 2.84-2.91 (m, 2H, 2 x CH), 9.60 (d, $J = 2$ Hz, 2H, 2 x OH).

Dimethyl cyclopentane-1,3-dicarboxylate (15).

Compound **14** (4.842 g, 30.64 mmol) was dissolved in MeOH (125 mL), and H_2SO_4 (0.25 mL) was added. The reaction mixture was refluxed overnight. The solvent was evaporated and the residue was dissolved in ether (40 mL), washed with saturated Na_2CO_3 (2 x 15 mL) and brine (2 x 25 mL). The organic phase was collected, dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to give 4.984 g (88%) of **15** as colorless oil. ^1H NMR (250.13 MHz, CDCl_3): δ 1.89-2.28 (m, 6H, 3 x CH_2), 2.72-2.76 (m, 2H, 2 x CH), 3.65 (s, 6H, 2 x CH_3).

Dimethyl bicyclo[2.2.1]heptane-1,4-dicarboxylate (16).

DIPA (7.6 mL, 54 mmol) and THF (72 mL) were added to a dry reaction vessel under argon atmosphere. The reaction mixture was cooled to -20 °C and a 1.6 M n-BuLi solution in hexane (31.2 mL, 50 mmol) was added. The reaction mixture was cooled to -40 °C and HMPA (27.9 mL) was added. The mixture was cooled further to -75 °C and **15** (3.72 g, 20 mmol) in THF (24 mL) was added during 15 minutes while maintaining the temperature between -75 °C and -70 °C. The reaction mixture was warmed to -10 °C and stirred for 30 minutes at this temperature. The reaction mixture was cooled again to -75 °C, 1-bromo-2-chloroethane (2.6 mL, 33.3 mmol) was dissolved in THF (40 mL) and added during 30 minutes while maintaining a temperature below -70 °C. The mixture was warmed gradually in 1 hour to room temperature and quenched with 40 mL of saturated aqueous NH₄Cl. The THF was evaporated and water (50 mL) was added. The water layer was extracted with pentane (3 x 50 mL). The combined pentane layers were washed with water (2 x 50 mL), dried with Na₂SO₄, filtered and evaporated in vacuo to give a crude product, which was purified by sublimation to give compound **16** (1.40 g, 33%) as white crystals. ¹H NMR (250.13 MHz, CDCl₃): δ 1.68-1.75 (m, 4H, 2 x CH₂), 1.91 (s, 2H, CH₂), 2.04-2.20 (m, 4H, 2 x CH₂), 3.69 (s, 6H, 2 x CH₃).

4-Iodobicyclo[2.2.1]heptane-1-carboxylic acid (5d).

Compound **16** (1.07 g, 5.051 mmol) was dissolved in THF (35 mL) and a solution of NaOH (202 mg, 5.051 mmol) in MeOH (2 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Solvents were evaporated under reduced pressure without heating. The residue was dissolved in water and extracted with CH₂Cl₂ (3 x 10 mL) and the alkaline aqueous extraction was acidified with 6 N HCl until pH = 3.

4-(methoxycarbonyl)bicyclo[2.2.1]heptane-1-carboxylic acid was obtained as a white solid (1.02 g, 95%). ¹H NMR (250.13 MHz, CDCl₃): δ 1.71 (d, *J* = 6.6, 4H, 2 x CH₂), 1.95 (s, 2H, CH₂), 2.05 (d, *J* = 6.6, 4H, 2 x CH₂), 3.73 (s, 3H). The same method was used as for **5b**, starting with 4-(methoxycarbonyl)bicyclo[2.2.1]heptane-1-carboxylic acid (3.762 g, 19 mmol) in anhydrous benzene (300 mL), iodobenzene diacetate (IBDA, 18.32 g, 56 mmol) and I₂ (14.4 g, 56.9 mmol). Saponification with a solution of methanolic NaOH (7.67 g, 19.2 mmol, 75 mL) in THF (100 mL) gave 2.275 g (45%) of **5d** as a white solid. ¹H NMR (250.13 MHz, CDCl₃): δ 1.65-1.80 (m, 2H, CH₂), 1.98-2.30 (m, 8H, 4 x CH₂), 11.50 (bs, 1H, OH). ¹³C NMR (50.32 MHz, CDCl₃): δ 34.49, 35.06, 43.07, 49.72, 53.35, 175.53.

WAY-100634 (2)

This compound was synthesized according to literature procedures of Pike and Cliffe^{16,21}, with a modification for the synthesis of 2-chloro-N-(pyridin-2-yl)acetamide **A**. See below.

2-Chloro-N-(pyridin-2-yl)acetamide (A).

In flame dried three-neck flask under argon atmosphere, 2-amino pyridine (17.68 g, 187 mmol) was dissolved in 370 mL of THF. This mixture was cooled to 0 °C. Chloroacetylchloride (11.67 g, 103 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in water (50 mL) and extracted with ethyl acetate (2 x 25 mL). The water phase was basified with saturated Na₂CO₃ and then extracted with ethyl acetate (2 x 25 mL). The organic phase was collected, dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure to give 17.62 g (55%) of **A** as pink crystals. ¹H NMR (200.13 MHz, CDCl₃): δ 4.17 (s, 2H, CH₂Cl), 7.09- 7.24 (m, 1H, CH), 7.68-7.75 (m, 1H, CH), 8.16 (d, *J* = 8.4, 1H, CH), 8.30 (dd, 3H, CH).(CAUTION: During the work up of this compound it appears that this mixture cause

sensitization, irritation and rash by inhalation or skin contact. It is strongly recommended to work with gloves and mouth cap in a ventilated hood).

2-(4-(2-Methoxyphenyl)piperazin-1-yl)-N-(pyridin-2-yl)acetamide (B).

Starting with **A** (8.72 g, 50.87 mmol), (9.78 g, 50.87 mmol) of 1-(2-methoxyphenyl)piperazine and (8.16 g, 59 mmol) of potassium carbonate in N,N-dimethylformamide (DMF) (200 mL) gave 12.2 g (74%) of **B**. ^1H NMR (200.13 MHz, CDCl_3): δ 2.78-2.92 (m, 4H, $\text{N}(\text{CH}_2)_2$), 3.13-3.18 (m, 6H, $\text{N}(\text{CH}_2)_3$), 3.84 (s, 3H, CH_3), 6.83-7.06 (m, 5H, 5 x CH), 7.69 (dt, $J = 8.7$ Hz, 1H, CH), 8.22-8.30 (m, 2H, 2 x CH_2), 9.61 (bs, 1H, NH).

N-(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)pyridin-2-amine (2).

Starting with **B** (20.53 g, 62.74 mmol) and (11.15 mL, 125.5 mmol) of borane dimethyl sulphide in 2 M THF gave 17.04 g (87%) of **C**. ^1H NMR (250.13 MHz, CDCl_3): δ 2.57-2.84 (m, 6H, $\text{N}(\text{CH}_2)_3$), 2.98-3.22 (m, 4H, $\text{N}(\text{CH}_2)_2$), 3.30-3.50 (m, 2H, NHCH_2), 3.87 (s, 3H, CH_3), 5.10 (bs, 1H, NH), 6.41 (d, $J = 8.4$ Hz, 1H, CH), 6.48- 6.61 (m, 1H, CH), 6.80-7.07 (m, 4H, 4 x CH), 7.41 (dt, $J = 8.7$ Hz, 1H, CH), 8.09 (d, $J = 5$ Hz, 1H, CH). ^{13}C NMR (50.32 MHz, CDCl_3): δ 38.35, 50.46, 52.96, 55.18, 56.62, 106.93, 110.95, 112.49, 118.04, 120.81, 122.79, 137.19, 141.08, 147.94, 152.07, 158.03.

***O*-desmethyl WAY-100634 (4)**

Compound **4** was synthesized by two different methods. **Method 1:** Compound **2** (3.161 g, 10.1 mmol) was dissolved in anhydrous benzene (316 mL) and anhydrous AlCl_3 (8.072 g, 60.5 mmol) was added. The reaction mixture was refluxed overnight. Next, this reaction mixture was allowed to cool to room temperature and then quenched with water (50 mL) in an ice bath and neutralized

with solid NaHCO₃. This suspension was filtered and washed with CH₂Cl₂ (2 x 15 mL). The organic layers were collected and washed with brine (3 x 25 mL). Again, the organic layers were collected and dried over anhydrous Na₂SO₄, the solvent was evaporated under reduced pressure to give 1.975 g (65%) of **4**. **Method 2:** The same synthetic procedure of **2** was applied, starting with N-(2-hydroxyphenyl)piperazine (0.9 equivalent) to give **4** in a three-step reaction with an overall yield of 64%. The synthetic route is described below:

2-(4-(2-Hydroxyphenyl)piperazin-1-yl)-N-(pyridin-2-yl)acetamide.

2-chloro-N-(pyridin-2-yl)acetamide **A** (500 mg, 2.92 mmol) and potassium carbonate (450 mg, 3.25 mmol) were dissolved in 10 mL of DMF. 1-(2-hydroxyphenyl)piperazine (600 mg, 3.37 mmol) in DMF (5 mL) was dropwise added to the previous reaction mixture and stirred at room temperature for 18 hours. Column chromatography of the crude product (AcOEt: PE:NEt₃; 40: 60: 0.1) gave 746.9 mg (71%) of 2-(4-(2-hydroxyphenyl)piperazin-1-yl)-N-(pyridin-2-yl)acetamide. ¹H NMR (200.13 MHz, CDCl₃): δ 2.6-1.10 (m, 8H, 2 x N(CH₂)₂), 3.20 (s, 2H, N(CH₂)₂), 6.73-7.21 (m, 5H, 5 x CH), 7.65 (dt, *J* = 8.7 Hz, 1H, CH), 8.15-8.32 (m, 2H, 2 x CH₂), 9.56 (bs, 1H, NH).

N-(2-(4-(2-Hydroxyphenyl)piperazin-1-yl)ethyl)pyridin-2-amine (4).

Starting with 2-(4-(2-hydroxyphenyl)piperazin-1-yl)-N-(pyridin-2-yl)acetamide (300 mg, 0.96 mmol) and (1 mL, 1.92 mmol) of borane dimethyl sulphide complex in 2 M THF gave 174.6 mg (61%) of **4** after column chromatography (AcOEt: NEt₃; 99.9: 0.1). ¹H NMR (250.13 MHz, CDCl₃): δ 2.67-2.90 (m, 6H, N(CH₂)₃), 2.93-3.07 (m, 4H, N(CH₂)₂), 3.43-3.55 (m, 2H, NCH₂), 5.61 (bs, 1H, NH), 6.48 (d, *J* = 8.5 Hz, 1H, CH), 6.50- 6.60 (m, 1H, CH), 6.80-7.00 (m, 2H, 2 x CH), 7.10-7.25 (m, 2H, 2 x CH), 7.45 (dt, *J* = 8.7 Hz, 1H, CH), 8.10 (d, *J* = 5, 1H, CH). ¹³C

NMR (62.90 MHz, CDCl₃): δ 52.24, 54.03, 62.07, 113.79, 114.13, 119.84, 120.00, 121.27, 126.38, 138.32, 138.44, 147.78, 150.73, 151.18, 168.77.

Synthesis of precursors:

4-Bromocubanecarboxylic Acid (**18**).

Bromodecarboxylation was performed by a normal Hunsdiecker reaction.^{33,34} In a closed vial, 4-methoxycubane-1-carboxylic acid (326 mg, 1.58 mmol) and HgO (500 mg, 2.31 mmol) were dissolved in CH₂Br₂ (10 mL). Br₂ (450 mg, 2.82 mmol), dissolved in CH₂Br₂ (3 mL), was added dropwise. This reaction mixture was heated at 80-90 °C for 2 h. Next, the reaction mixture was allowed to reach room temperature and filtered over high flow celite. The filtrate was concentrated under reduced pressure at room temperature. The residue was dissolved in water (10 mL) and extracted with pentane (3 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated in vacuo. Purification was performed using column chromatography (EtOAc: Hexane; 20: 80) followed by recrystallization from hexane to give 286 mg (75%) of **17**. ¹H NMR (250.13 MHz, CDCl₃): δ 3.7 (s, 3H, CH₃), 4.12-4.40 (m, 6H, 6 x CH). ¹³C NMR (62.90 MHz, CDCl₃): δ 47.52, 51.54, 54.37, 56.02, 62.92, 171.67. Further, compound **17** (213 g, 0.88 mmol) was dissolved in tetrahydrofuran (10 mL). A solution of NaOH (35.8 mg, 0.90 mmol) in a mixture of MeOH (6 mL) and water (2 mL) was added. This reaction mixture was stirred overnight at room temperature. Solvent was evaporated under reduced pressure. The residue was dissolved in water (5 mL) and subsequently acidified with 6 N HCl until a white solid was formed. Filtration gave 180 mg (90%) of **18**. ¹H NMR (250.13 MHz, CDCl₃): δ 3.90-4.40 (m). ¹³C NMR (62.90 MHz, CDCl₃): δ 47.22, 47.26, 54.07, 54.10, 173.85.

4-Bromo-N-(2-(4-(2-methoxyphenyl)piperazin-1-yl)-N-(pyridine-2-yl)cubyl-1-carboxamide (19).

Under argon atmosphere, a mixture of **18** (258 mg, 1.09 mmol) and thionyl chloride (2 mL) in MeCN (4 mL) was refluxed at 70 °C for 45 minutes. The excess of thionyl chloride was totally evaporated under reduced pressure and co-evaporated with dry MeCN (3 x 1 mL). A mixture of **2** (345 mg, 1.11 mmol) and NEt₃ (142 μL) in MeCN (10 mL) was added. The new reaction mixture was stirred overnight at room temperature. After evaporation the residue was dissolved in water (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The organic phases were combined, dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. Purification by column chromatography (AcOEt containing 1% of NEt₃) gave 463 mg (80%) of **19** as a colorless glass. ¹H NMR (200.13 MHz, CDCl₃): δ 2.4-3.20 (m, 10H, N(CH₂)₃ and N(CH₂)₂), 3.6-4.10 (m, 11H, 6 x CH, CH₃ and NCH₂), 6.5-7.0 (m, 4H, 4 x CH), 7.10-7.20 (m, 2H, 2 x CH), 7.74 (dt, *J* = 7.6 Hz, 1H, CH), 8.51 (d, *J* = 4.9 Hz, 1H, CH). ¹³C NMR (50.32 MHz, CDCl₃): δ 44.80, 48.45, 50.02, 53.06, 53.91, 55.10, 55.69, 59.11, 62.23, 110.90, 117.87, 119.26, 120.68, 121.69, 122.76, 138.13, 140.74, 148.72, 151.90, 154.90, 170.97.

2.2.3. 4-Bromo-N-(2-(4-(2-hydroxyphenyl)piperazin-1-yl)-N-(pyridine-2-yl)cubyl-1-carboxamide (20).

Under argon atmosphere, a mixture of **18** (231 mg, 1 mmol) and thionyl chloride (2 mL) in MeCN (4 mL) was refluxed at 70 °C for 2 hours. The excess of thionyl chloride was totally evaporated under reduced pressure and co-evaporated with dry MeCN (3 x 1 mL). A mixture of **4** (308 mg, 1 mmol) and NEt₃ (142 μL) in MeCN (12 mL) gave the double acylated compound, which was dissolved in a solution of water (1 mL) and NEt₃ (1 mL) in MeCN (5 mL) and heated for 2 hours at 50 °C. The solvent was evaporated and the residue was dissolved in water (1 mL).

The water phase was extracted with CH_2Cl_2 (3 x 1 mL) and the organic phases were combined, dried (Na_2SO_4) and evaporated to dryness to give 101 mg (20%) after column chromatography (AcOEt: NEt_3 ; 99%: 1%) of **20**. ^1H NMR (200.13 MHz, CDCl_3): δ 2.4-2.90 (m, 10H, $\text{N}(\text{CH}_2)_3$ and $\text{N}(\text{CH}_2)_2$), 3.70-4.10 (m, 8H, 6 x CH and NCH_2), 6.69-7.30 (m, 6H, 6 x CH), 7.70 (dt, $J = 7.6$ Hz, 1H, CH), 8.41 (d, $J = 4.9$ Hz, 1H, CH). ^{13}C NMR (50.32 MHz, CDCl_3): δ 44.80, 48.40, 50.02, 53.06, 53.91, 55.39, 58.11, 62.23, 110.90, 116.87, 119.16, 120.65, 121.69, 122.76, 137.12, 140.70, 148.70, 151.85, 154.90, 170.97.