SUPPORTING INFORMATION

New Hits as Antagonists of GPR103 Identified by HTS

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General Description.

^{1}H NMR spectra were recorded on a Bruker Avance II or III spectrometer at 25°C at a proton frequency of 300, 400, 500 or 600 MHz, frequency stated in each experiment, and ^{13}C NMR at 101 or 126 MHz. The chemical shifts (δ) are reported in ppm and referenced indirectly to TMS via the solvent signals (^{1}H: $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm, CD_3OD at 3.31 ppm; ^{13}C: $CDCl_3$ at 77.16 ppm, DMSO-d_6 at 39.52 ppm). UHPLC-MS experiments and high-resolution molecular mass (HRMS) determination were performed using a Waters Acquity UHPLC system combined with a SQD Mass Spectrometer. The UHPLC system was equipped with both a BEH C18 column (1.7 µm, 2.1×50 mm) in combination with a 46 mM $(NH_4)_2CO_3/NH_3$ buffer at pH 10 and a HSS C18 column (1.8 µm, 2.1×50 mm) in combination with 10 mM formic acid and 1 mM ammonium formate buffer at pH 3. The flow rate was 1 mL/min. The Mass Spectrometer used ESI+/- as ion source. All microwave-assisted synthesis was carried out in an Initiator synthesizer single mode cavity instrument producing controlled irradiation at 2450 MHz (Biotage AB, Uppsala, Sweden). Preparative HPLC was performed on a Waters Fraction Lynx combined with ZQ MS detector, under basic conditions equipped with a Waters Xbridge C18 ODB (5 µm, 19×150 mm) column at a flow rate of 30 mL/min, using a 5 – 95% gradient with MeCN/0.2% NH_3 at pH 10. Under acidic conditions, run on the same system, a Waters Sunfire C18 ODB (5 µm, 19×150 mm) column at a flow rate of 30 mL/min and a 5 – 95% gradient with MeCN/0.1 M HCO_2H at pH 3 was used. Additionally preparative HPLC was performed using a Gilson preparative HPLC combined with UV/VIS detector 155, under acidic conditions equipped with a Kromasil C8 (10 µm, 20×250 mm) column at a flow rate of 19 mL/min or a Kromasil C8 (10 µm, 50×250 mm) column at a flow rate of 100 mL/min, using a H_2O/MeCN/HCO_2H 95/5/0.2 gradient. Under basic conditions, run on the same system, an XBridge C18 (10 µm, 19×250 mm) column at a flow rate of 19 mL/min or XBridge C18 (10 µm, 50×250 mm) column at a flow rate of 100 mL/min and a H_2O/MeCN/NH_3 95/5/0.2 gradient was used. Flash chromatography was performed using a Biotage high-performance flash chromatography system (SP1 or SP4) using KP-Sil (normal phase) columns with a particle size of 40 – 65 micron (average 50 micron). Thin-layer chromatography was performed with silica gel 60 F_{254} glass plates 5×10 cm (Merck). All products were >95% pure according to LC-MS unless otherwise stated. All reactants and reagents were commercially available and used without further purification unless otherwise stated.

Experimental Procedures.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-thiophene-2-carboximidamide (1).** To a solution of 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (100 mg, 0.42 mmol) in *i*-propanol (10 mL) was added methyl thiophene-2-carboximidothioate (**35**) (113 mg, 0.72 mmol). The resulting mixture was stirred for 4 h at 85°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:5) to afford the titled compound (8 mg, 2%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 – 7.76 (m, 1H), 7.54 – 7.62 (m, 1H), 7.09 (dd, *J* = 3.8, 5.0 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.66 – 6.80 (m, 2H), 6.33 (brs, 2H), 3.77 (s, 3H), 3.67 (s, 2H), 2.97 – 3.11 (m, 1H), 1.85 – 2.01 (m, 2H), 1.58 – 1.73 (m, 2H), 1.33 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.29, 149.50, 142.11, 141.96, 129.06, 127.40, 127.32, 126.55, 123.78, 120.87, 111.76, 55.63, 42.88, 33.20, 29.71, 24.44. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2OS_2$ 347.1252; Found 347.1250.

2-[(Cyclopentylsulfanyl)methyl]-1-methoxy-4-nitrobenzene (5). To a 250-mL round-bottom flask was added cyclopentanethiol (5.43 g, 53.1 mmol) and K_2CO_3 (11.3 g, 81.8 mmol) in DMF (30 mL). A solution of 2-(bromomethyl)-1-methoxy-4-nitrobenzene (**25**) (10.0 g, 40.6 mmol) in DMF (20 mL) was added dropwise under stirring and the resulting mixture was stirred for 15 h at rt. The reaction mixture was extracted with DCM (3×90 mL) and the combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:50) to afford the titled compound (9.5 g, 87%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 2.8 Hz, 1H), 8.15 (dd, *J* = 2.8, 9.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.96 (s, 3H), 3.77 (s, 2H), 2.97 – 3.11 (m, 1H), 1.90 – 2.08 (m, 2H), 1.66 – 1.82 (m, 2H), 1.44 – 1.64 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.30, 141.27, 128.98, 125.70, 124.70, 110.28, 56.41, 43.90, 33.79, 30.42, 25.06.

3-[(Cyclopentylsulfanyl)methyl]-4-methoxyaniline (6). Iron dust (2.70 g, 48.4 mmol) was added to a solution of 2-[(cyclopentylsulfanyl)methyl]-1-methoxy-4-nitrobenzene (**5**) (1.00 g, 3.74 mmol) in HOAc (20 mL). The reaction mixture was stirred under N_2(g) and heated slowly to 60°C. When the reaction mixture reached 30°C, additional HOAc (10 mL) was added. After 6 h and 20 min at 60°C, the reaction mixture was filtered through a pad of celite and rinsed with EtOAc. The filtrate was washed with NaOH (1 M, 180 mL), H_2O

(180 mL) and brine (180 mL). The organic layer was dried through a phase separator, filtered and concentrated. The crude was dissolved in EtOAc (100 mL) and washed with 8% $NaHCO_3$ (2×50 mL) followed by H_2O (50 mL). The organic layer was concentrated *in vacuo* to afford the titled compound (0.750 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 2.7 Hz, 1H), 6.41 (dd, *J* = 2.8, 8.6 Hz, 1H), 4.59 (s, 2H), 3.65 (s, 3H), 3.57 (s, 2H), 2.94 – 3.07 (m, 1H), 1.86 – 1.98 (m, 2H), 1.59 – 1.72 (m, 2H), 1.47 – 1.59 (m, 2H), 1.35 – 1.46 (m, 2H).

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-thiophene-3-carboximidamide (7a).** To a solution of 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (42 mg, 0.18 mmol) in 1,2-dichloroethane (0.5 mL) was added thiophene-3-carbonitrile (0.016 mL, 0.18 mmol) and $AlCl_3$ (24 mg, 0.18 mmol). The reaction mixture was heated at 115°C overnight. The mixture was allowed to cool to rt over 10 min and thereafter quenched with H_2O (0.5 mL). The aqueous layer was extracted with DCM (2×2 mL) and the combined organic layers were concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the titled compound (2.0 mg, 2.8%). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2OS_2$ 347.1252; Found 347.1266.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-benzenecarboximidamide (7b).** To a microwave vial equipped with stirrer was added 3-(cyclopentylsulfanylmethyl)-4-methoxyaniline (**6**) (310 mg, 1.31 mmol) in toluene (10 mL) under N_2(g) and the resulting mixture was cooled with an ice bath. $AlMe_3$ (2 M in toluene, 0.78 mL, 1.6 mmol) was added dropwise via a syringe. The reaction mixture was allowed to reach rt and stirred for 30 min. Benzonitrile (162 mg, 1.57 mmol) dissolved in toluene (5.0 mL) was added dropwise via a syringe. The microwave vial was flushed with N_2(g) and the reaction mixture was heated at 95°C by microwave irradiation for 2 h. The reaction mixture was cooled to 0°C and $NaHCO_3$ (sat, 50 mL) was added slowly. The mixture was extracted with DCM (50 mL) and the organic layer was dried through a phase separator. The residue was purified by automated flash chromatography using *n*-heptane/EtOAc as mobile phase to provide the titled compound (213 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.3 Hz, 2H), 7.35 – 7.50 (m, 3H), 6.89 – 6.96 (m, 1H), 6.78 – 6.88 (m, 2H), 4.43 – 5.49 (brs, 2H), 3.83 (s, 3H), 3.74 (s, 2H), 3.00 – 3.13 (m, 1H), 1.88 – 2.03 (m, 2H), 1.63 – 1.79 (m, 2H), 1.44 – 1.6 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.47, 153.37, 142.23, 136.00, 130.51, 128.55, 128.52, 126.84, 123.64, 120.88, 111.91, 55.94, 43.57, 33.76, 30.65, 25.04. HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}N_2OS$ 341.1688; Found 341.1704.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-4-methylthiophene-2-carboximidamide (7c).** A stirred solution of 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (42 mg, 0.18 mmol), 4-methylthiophene-2-carbonitrile (22 mg, 0.18 mmol) and $AlCl_3$ (23.6 mg, 0.18 mmol) in 1,2-dichloroethane (0.5 mL) was heated at 115°C overnight. The mixture was allowed to cool to rt over 10 min and thereafter quenched with H_2O (500 µL). The aqueous phase was extracted with DCM (×3), the combined organic layers were dried through a phase separator and concentrated *in vacuo.* The residue was purified by preparative HPLC to provide the titled compound (11 mg, 17%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.61 (s, 1H), 7.30 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.78 – 6.91 (m, 2H), 3.78 (s, 3H), 3.68 (s, 2H), 3.00 – 3.10 (m, 1H), 2.23 (s, 3H), 1.85 – 2.01 (m, 2H), 1.59 – 1.73 (m, 2H), 1.47 – 1.58 (m, 2H), 1.37 – 1.46 (m, 2H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2OS_2$ 361.1408; Found 361.1416.

4-Bromo-*N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}thiophene-2-carboximidamide (7d). A stirred solution of 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (42 mg, 0.18 mmol), 4-bromothiophene-2-carbonitrile (33 mg, 0.18 mmol) and $AlCl_3$ (24 mg, 0.18 mmol) in 1,2-dichloroethane (0.5 mL) was heated at 115°C overnight. The mixture was allowed to cool to rt over 10 min and thereafter quenched with H_2O (0.5 mL). The aqueous phase was extracted with DCM (×3), the combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the titled compound (7 mg, 9%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.73 – 7.78 (m, 2H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.72 – 6.80 (m, 2H), 6.40 – 6.68 (brs, 2H), 3.77 (s, 3H), 3.67 (s, 2H), 3.00 – 3.08 (m, 1H), 1.86 – 1.98 (m, 2H), 1.59 – 1.70 (m, 2H), 1.47 – 1.57 (m, 2H), 1.37 – 1.46 (m, 2H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}BrN_2OS_2$ 425.0357; Found 425.0388.

5-Bromo-*N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}thiophene-2-carboximidamide (7e). 3-[(Cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (42 mg, 0.18 mmol) in THF (1 mL) was cooled under N_2(g) to -78°C and ethylmagnesium bromide (0.37 mL, 0.37 mmol) in THF was added dropwise over 4 min. The reaction mixture was stirred for 10 min at 0°C and thereafter 5-bromothiophene-2-carbonitrile (0.020 mL, 0.18 mmol) in THF (0.5 mL) was added slowly over 2 min. The reaction mixture was stirred at rt overnight. Additional ethylmagnesium bromide (0.18 mL, 0.18 mmol) was added and the mixture was stirred an extra night at rt. The reaction mixture was quenched by the addition of H_2O (1.5 mL) at 0°C. EtOAc (2 mL) was added and the aqueous phase was extracted with EtOAc (3×4 mL). The combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by automated flash chromatography using EtOAc/heptane as mobile phase to afford the titled compound (19 mg, 25%) as an orange oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, *J* = 4.0 Hz, 1H), 7.21 (d, *J* = 3.9 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.64 – 6.79 (m, 2H), 6.45 (s, 2H), 3.77 (s, 3H), 3.67 (s, 2H), 2.97 – 3.09 (m, 1H), 1.85 – 2.00 (m, 2H), 1.58 – 1.72 (m, 2H), 1.35 – 1.57 (m, 4H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}BrN_2OS_2$ 425.0357; Found 425.0376.

4-Chloro-*N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}benzenecarboximidamide (7f). To a solution of 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (66 mg, 0.28 mmol) in toluene (1.3 mL) under N_2(g) and cooled with an ice bath was added $AlMe_3$ (2 M in toluene, 0.14 mL, 0.28 mmol) dropwise via a syringe (reaction turned green). The reaction mixture was allowed to reach rt and stirred for 1 h. 4-Chlorobenzonitrile (32 mg, 0.23 mmol) dissolved in toluene (2.5 mL) was added dropwise via a syringe and the reaction mixture was heated at 95°C for 4.5 h and thereafter at rt overnight. The reaction mixture was cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a

phase separator and concentrated *in vacuo* to give an orange oil. The residue was purified by preparative HPLC to provide the titled compound (57 mg, 66%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.86 – 8.05 (m, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.70 – 6.86 (m, 2H), 3.77 (s, 3H), 3.66 (s, 2H), 2.96 – 3.10 (m, 1H), 1.84 – 1.99 (m, 2H), 1.59 – 1.70 (m, 2H), 1.47 – 1.55 (m, 2H), 1.36 – 1.45 (m, 2H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}ClN_2OS$ 375.1298; Found 375.1313.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-2-phenylethanimidamide (7g).** A microwave vial was loaded with 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (66 mg, 0.28 mmol) dissolved in toluene (1.3 mL) under N_2(g) and cooled with an ice bath. $AlMe_3$ (2 M in toluene, 0.14 mL, 0.28 mmol) was added dropwise via a syringe and the reaction mixture was allowed to reach rt and stirred for 1 h. 2-Phenylacetonitrile (27 mg, 0.23 mmol) dissolved in toluene (2.5 mL) was added dropwise via a syringe and the reaction mixture was heated at 95°C overnight. The mixture was cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a phase separator and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the titled compound (57 mg, 69%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.28 – 7.46 (m, 4H), 7.20 – 7.27 (m, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 1H), 6.39 – 6.52 (m, 1H), 3.73 (s, 2H), 3.42 – 3.66 (m, 5H), 2.97 – 3.05 (m, 1H), 1.83 – 1.96 (m, 2H), 1.56 – 1.71 (m, 2H), 1.45 – 1.56 (m, 2H), 1.35 – 1.45 (m, 2H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{21}H_{27}N_2OS$ 355.1844; Found 355.1862.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-propanimidamide (7h).** A microwave vial was loaded with 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (66 mg, 0.28 mmol) dissolved in toluene (1.3 mL) under N_2(g) and cooled with an ice bath. $AlMe_3$ (2 M in toluene, 0.14 mL, 0.28 mmol) was added dropwise via a syringe and the reaction mixture was allowed to reach rt and stirred for 1 h. Propionitrile (13 mg, 0.23 mmol) dissolved in toluene (2.5 mL) was added dropwise via a syringe and the reaction mixture was heated at 95°C overnight. The reaction mixture was cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a phase separator and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the titled compound (37 mg, 55%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.87 (m, 1H), 6.66 – 6.73 (m, 1H), 6.55 (dd, *J* = 2.9, 8.5 Hz, 1H), 3.82 – 3.86 (m, 3H), 3.72 – 3.76 (m, 2H), 2.96 – 3.18 (m, 1H), 2.39 (q, *J* = 7.7 Hz, 2H), 1.91 – 2.06 (m, 2H), 1.66 – 1.81 (m, 2H), 1.45 – 1.60 (m, 4H), 1.21 – 1.29 (m, 3H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{16}H_{25}N_2OS$ 293.1688; Found 293.1685.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-1,3-thiazole-2-carboximidamide (7i).** A solution of 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (300 mg, 1.26 mmol) in toluene (10 mL) in a 25-mL round-bottom flask was purged with N_2(g). $AlMe_3$ (5.0 mL, 10 mmol) was added and the reaction mixture was stirred for 3.5 h at 25°C. Finally 1,3-thiazole-2-carbonitrile (167 mg, 1.5 mmol) was added and the reaction mixture was stirred for 17 h at 80°C and thereafter quenched with H_2O/ice (5 mL). The aqueous phase was extracted with EtOAc (3×25 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:3) to provide the titled compound (194 mg, 44%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J* = 3.2 Hz, 1H), 7.87 (d, *J* = 3.2 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.83 (dd, *J* = 2.6, 8.5 Hz, 1H), 6.49 (brs, 2H), 3.78 (s, 3H), 3.68 (s, 2H), 2.98 – 3.1 (m, 1H), 1.85 – 2.00 (m, 2H), 1.58 – 1.73 (m, 2H), 1.33 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.07, 152.76, 148.16, 143.06, 141.08, 127.52, 124.06, 123.74, 120.88, 111.73, 55.65, 42.94, 33.20, 29.65, 24.43. HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3OS_2$ 348.1204; Found 348.1213.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-pyridine-4-carboximidamide (7j).** A microwave vial was loaded with 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (66 mg, 0.28 mmol) dissolved in toluene (1.3 mL) under N_2(g) and cooled with an ice bath. $AlMe_3$ (2 M in toluene, 0.14 mL, 0.28 mmol) was added dropwise via a syringe, the mixture was allowed to reach rt and stirred for 1 h. Isonicotinonitrile (24 mg, 0.23 mmol) dissolved in toluene (2.5 mL) was added dropwise via a syringe to the reaction mixture which was heated at 95°C for 4.5 h. The reaction mixture was cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The phases were separated and the aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a phase separator and concentrated to give an orange semisolid. The residue was purified by preparative HPLC to provide the titled compound (58 mg, 73%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (t, *J* = 5.8 Hz, 2H), 7.88 (d, *J* = 5.5 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.71 – 6.82 (m, 2H), 6.47 (brs, 2H), 3.77 (s, 3H), 3.68 (s, 2H), 3.00 – 3.09 (m, 1H), 1.88 – 1.97 (m, 2H), 1.6 – 1.69 (m, 2H), 1.47 – 1.54 (m, 2H), 1.39 – 1.45 (m, 2H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{19}H_{24}N_3OS$ 342.1640; Found 342.1658.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-pyridine-3-carboximidamide (7k).** 3-[(Cyclopentylsulfanyl)-methyl]-4-methoxyaniline (**6**) (66 mg, 0.28 mmol) dissolved in toluene (1.3 mL) was added to a microwave vial under N_2(g) and cooled with an ice bath. $AlMe_3$ (2 M in toluene, 0.14 mL, 0.28 mmol) was added dropwise via a syringe and the reaction mixture was allowed to reach rt and stirred for 30 min. Nicotinonitrile (24 mg, 0.23 mmol) dissolved in toluene (2.5 mL) was added dropwise via a syringe and the reaction mixture was heated at ca 95°C for 2 h. The reaction mixture was allowed to reach rt and cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a phase separator and concentrated *in vacuo* to give an orange semisolid. The residue was purified by preparative HPLC to provide the titled compound (56 mg, 71%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.65 (d, *J* = 4.1 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 4.9, 7.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.72 – 6.86 (m, 2H), 6.45 (s, 2H), 3.78 (s, 3H), 3.68 (s, 2H), 3.01 – 3.09 (m, 1H), 1.84 – 1.99 (m, 2H), 1.58 – 1.70 (m, 2H), 1.47 – 1.55 (m, 2H), 1.38 – 1.45 (m, 2H).

HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{24}N_3OS$ 342.1640; Found 342.1642.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-thiophene-2-carboxamide (8).** To a solution of thiophene-2-carboxylic acid (1.2 g, 9.4 mmol) in DMF (20 mL) was added EDC (2.12 g, 11.0 mmol), HOBt (1.5 g, 11 mmol) and TEA (1.72 g, 17.0 mmol). The mixture was stirred for 30 min at rt, and thereafter 3-[(cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (2.0 g, 8.5 mmol) was added. The resulting mixture was stirred for 3 h at rt. The mixture was diluted with EtOAc (30 mL) and the organic layer was washed with $NaHCO_3$ (3×20 mL) followed by brine (3×20 mL). The organic layer was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:15) to provide the titled compound (1.7 g, 57%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.99 (dd, *J* = 1.0, 3.8 Hz, 1H), 7.83 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.54 – 7.63 (m, 2H), 7.21 (dd, *J* = 3.8, 5.0 Hz, 1H), 6.93 – 7.01 (m, 1H), 3.79 (s, 3H), 3.69 (s, 2H), 2.97 – 3.12 (m, 1H), 1.85 – 2.02 (m, 2H), 1.58 – 1.73 (m, 2H), 1.35 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.52, 153.24, 140.25, 131.50, 131.39, 128.71, 128.00, 126.85, 122.67, 120.33, 111.03, 55.67, 42.96, 33.18, 29.62, 24.46. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{22}NO_2S_2$ 346.0936; Found 346.0939.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-*N*'-methylthiophene-2-carboximidamide (9a).** To a solution of *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-thiophene-2-carboxamide (**8**) (1.00 g, 2.88 mmol) in toluene (15 mL) was added Lawesson reagent (2.33 g, 5.76 mmol). The resulting mixture was stirred for 4 h at 80°C. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:50) to afford *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-thiophene-2-carbothioamide (700 mg, 65%) as a yellow solid. m/z (ES^+) $[M + H]^+$= 364.

To a solution of *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}thiophene-2-carbothioamide (500 mg, 1.38 mmol) in MeOH (10 mL) was added methylamine (30%, 1.4 g, 45 mmol). The resulting mixture was stirred for 4 h at 50°C. The reaction mixture was concentrated *in vacuo* and the crude was purified by preparative HPLC to afford the titled compound (225 mg, 45%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (dd, *J* = 0.8, 5.0 Hz, 1H), 7.06 (s, 1H), 6.86 – 7.00 (m, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 6.41 (s, 1H), 3.71 (s, 3H), 3.51 (s, 2H), 2.80 (s, 3H), 2.61 – 2.72 (m, 1H), 1.72 – 1.86 (m, 2H), 1.54 – 1.67 (m, 2H), 1.40 – 1.52 (m, 2H), 1.26 – 1.38 (m, 2H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2OS_2$ 361.1408; Found 361.1424.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-*N*,*N*'-dimethylthiophene-2-carboximidamide (9b).** To a solution of *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}thiophene-2-carboxamide (**8**) (1.9 g, 5.5 mmol) in THF (20 mL) was added NaH (262 mg, 11 mmol). The mixture was stirred for 30 min at 0°C and thereafter methyl iodide (3.88 g, 27 mmol) was added. The resulting mixture was stirred for 2 h at 0°C. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/hexane (1:10) to afford *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-*N*-methylthiophene-2-carboxamide (1.8 g, 91%) as a grey solid. m/z (ES^+) $[M + H]^+$= 362.

Lawesson reagent (3.36 g, 8.31 mmol) was added to a solution of *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-*N*-methylthiophene-2-carboxamide (1.5 g, 4.2 mmol) in toluene (20 mL). The resulting mixture was stirred for 4 h at 80°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/hexane (1:50) to afford *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-*N*-methylthiophene-2-carbothioamide (600 mg, 38%) a light yellow solid.

Methylamine (30%) was added to a solution of *N*-{3-[(cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-*N*-methylthiophene-2-carbothioamide (200 mg, 0.53 mmol) in MeOH (10 mL). The resulting mixture was stirred for 6 h at 50°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to afford the titled compound (13 mg, 7%, purity >91%) as a yellow oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.50 – 7.60 (m, 1H), 7.05 – 7.11 (m, 1H), 6.88 – 7.00 (m, 3H), 6.75 – 6.85 (m, 1H), 3.70 (s, 3H), 3.52 (s, 2H), 3.18 (s, 3H), 2.99 (s, 3H), 2.65 – 2.80 (m, 1H), 1.78 – 1.88 (m, 2H), 1.45 – 1.75 (m, 4H), 1.28 – 1.40 (m, 2H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}N_2OS_2$ 375.1565; Found 375.1579.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-pyridin-2-amine (10).** 3-[(Cyclopentylsulfanyl)methyl]-4-methoxyaniline (**6**) (50 mg, 0.2 mmol), DMA (1.5 mL), 2-fluoropyridine (0.50 mL, 6 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol) were added to a 2 mL microwave vial which was flushed with N_2(g) and capped. The reaction mixture was heated at 200°C by microwave irradiation for 7 h. The mixture was concentrated *in vacuo* and the crude was re-dissolved in DCM (20 mL), washed with H_2O (10 mL) and dried through a phase separator. The residue was purified by automated flash chromatography using *n*-heptane/EtOAc followed by EtOAc/MeOH as eluent to provide the titled compound (1 mg, 2%, purity >94%). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2OS$ 315.1531; Found 315.1543.

***N*-{3-[(Cyclopentylsulfinyl)methyl]-4-methoxyphenyl}-benzenecarboximidamide (11a).** A solution of *N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-benzenecarboximidamide (**7b**) (50 mg, 0.15 mmol) in DCM (dry, 5 mL) was stirred at rt for 5 min and then 3-chlorobenzoperoxoic acid (32 mg, 0.19 mmol) was added. The resulting mixture was stirred at rt overnight. DCM (20 mL) was added and the organic layer was washed with $NaHCO_3$ (sat, 15 mL), dried through a phase separator and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the titled compound (24 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.95 (m, 2H), 7.44 – 7.48 (m, 3H), 6.95 – 7.02 (m, 1H), 6.85 – 6.94 (m, 2H), 3.73 – 4.06 (m, 5H), 2.86 – 3.09 (m, 1H), 2.11 – 2.24 (m, 1H), 1.80 – 1.95 (m, 2H), 1.55 – 1.79 (m, 5H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}N_2O_2S$ 357.1637; Found 357.1666.

***N*-{3-[(Cyclopentylsulfonyl)methyl]-4-methoxyphenyl}-benzenecarboximidamide (11b).** *N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-benzene-carboximidamide (**7b**) (50 mg, 0.15 mmol) dissolved in DCM (dry, 5 mL) was stirred at rt for 5 min before 3-chlorobenzoperoxoic acid

(33 mg, 0.19 mmol) was added. The reaction mixture was stirred overnight. DCM (20 mL) was added and the organic layer was washed with $NaHCO_3$ (sat, 15 mL), dried through a phase separator and concentrated *in vacuo*. The residue was purified by preparative HPLC to provide the titled compound (15 mg, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (brs, 2H), 7.37 – 7.51 (m, 3H), 7.11 (brs, 1H), 7.02 (dd, *J* = 2.2, 8.6 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.29 (s, 2H), 3.85 (s, 3H), 3.21 – 3.40 (m, 1H), 2.02 – 2.14 (m, 2H), 1.86 – 1.98 (m, 2H), 1.72 – 1.84 (m, 2H), 1.53 – 1.66 (m, 2H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}N_2O_3S$ 373.1586; Found 373.1606.

(5-Chloro-2-methoxybenzyl)(cyclopentyl)sulfane (13). To a 100 mL round-bottom flask with stirrer was added 4-chloro-2-(chloromethyl)-1-methoxybenzene (**12**) (1.0 g, 5.2 mmol), DMF (dry, 15 mL), cyclopentanethiol (0.64 g, 6.3 mmol) and K_2CO_3 (1.45 g, 10 mmol). The flask was flushed with N_2(g), capped and the resulting mixture was stirred for 90 min at rt. The reaction mixture was diluted with EtOAc and quenched by the addition of H_2O (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by automated flash chromatography using *n*-heptane/EtOAc as mobile phase to afford the titled compound (1.27 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 2.6 Hz, 1H), 7.16 (dd, *J* = 2.6, 8.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 2H), 2.98 – 3.11 (m, 1H), 1.89 – 2.06 (m, 2H), 1.66 – 1.83 (m, 2H), 1.45 – 1.64 (m, 4H).

3-[(Cyclopentylsulfanyl)methyl]-4-methoxybenzonitrile (14). DMA (1 mL) was added to a microwave vial loaded with (5-chloro-2-methoxybenzyl)(cyclopentyl)sulfane (**13**) (100 mg, 0.39 mmol), tris(dibenzylideneacetone)-dipalladium(0) (71 mg, 0.08 mmol), 2-(dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (149 mg, 0.31 mmol), zinc (5.0 mg, 0.08 mmol) and $Zn(CN)_2$ (27 mg, 0.23 mmol). The vial was sealed, evacuated and backflushed with nitrogen a couple of times. The resulting dark brown mixture was heated under microwave irradiation at 150°C for 2 h. The reaction mixture was diluted with EtOAc, filtered through a pad of celite and concentrated *in vacuo*. The crude was re-dissolved in EtOAc and the organic layer was washed with brine (3×2 mL) and dried through a phase separator. The residue was purified by automated flash chromatography using EtOAc/*n*-heptane as mobile phase to afford the titled compound (56 mg, 58%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 2.1, 8.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 2H), 2.94 – 3.08 (m, 1H), 1.88 – 2.07 (m, 2H), 1.67 – 1.83 (m, 2H), 1.43 – 1.65 (m, 4H).

3-[(Cyclopentylsulfanyl)methyl]-4-methoxy-*N*-phenylbenzenecarboximidamide (15). A microwave vial loaded with aniline (0.029 mL, 0.32 mmol) dissolved in toluene (1 mL) under N_2(g) was cooled with an ice bath. $AlMe_3$ (2 M in toluene, 0.16 mL, 0.32 mmol) was added dropwise via a syringe, the mixture was allowed to reach rt and stirred for 20 min. 3-[(Cyclopentylsulfanyl)methyl]-4-methoxybenzonitrile (**14**) (56 mg, 0.23 mmol) dissolved in toluene (2 mL) was added dropwise via a syringe to the reaction mixture which was heated at 95°C overnight. The reaction mixture was allowed to reach rt and cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added and the mixture was diluted with DCM (13 mL). The phases were separated and the aqueous phase was extracted with DCM (3×10 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL), dried by passing through a phase separator and concentrated *in vacuo*. The crude was purified by automated flash chromatography using MeOH (1% TEA) in DCM as mobile phase to afford the titled compound (50 mg, 65%) as a yellow oil. The oil solidified to give an off-white to light yellow solid when MeOH was added and removed by evaporation. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 – 8.01 (m, 2H), 7.22 – 7.41 (m, 2H), 6.95 – 7.12 (m, 2H), 6.79 – 6.94 (m, 2H), 6.30 (brs, 2H), 3.85 (s, 3H), 3.73 (s, 2H), 2.97 – 3.13 (m, 1H), 1.85 – 2.03 (m, 2H), 1.59 – 1.76 (m, 2H), 1.36 – 1.58 (m, 4H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}N_2OS$ 341.1688; Found 341.1716.

3-[(Cyclopentylsulfanyl)methyl]aniline (17a). A suspension of cyclopentanethiol (640 mg, 6.26 mmol), K_2CO_3 (1.38 g, 9.98 mmol) and 1-(bromomethyl)-3-nitrobenzene (**16**) (1.08 g, 5.00 mmol) in DMF (15 mL) was stirred for 4.5 h at rt. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (3×50 mL), dried through a phase separator and concentrated *in vacuo* to give 1-[(cyclopentylsulfanyl)methyl]-3-nitrobenzene (1.1 g, 93%) as a yellow solid which was used directly in the next step.

To a 50-mL round-bottom flask was added a solution of 1-[(cyclopentylsulfanyl)methyl]-3-nitrobenzene (500 mg, 2.1 mmol) in HOAc (15 mL). Iron dust (1.20 g, 21.5 mmol) was added portionwise and the mixture was stirred for 3.5 h at 60°C. The solid was filtered off and the filter cake was washed with EtOAc (3×15 mL). The filtrate was concentrated *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed with $NaHCO_3$ (4×30 mL) and brine, dried and concentrated *in vacuo* to afford the titled compound (400 mg) as a brown oil which was used in the next step without further purification.

3-[(Cyclopentylsulfanyl)methyl]-4-methylaniline (17b). 2-(Bromomethyl)-1-methyl-4-nitrobenzene (**20**) (2.4 g, 10 mmol) dissolved in MeOH (10 mL) was added dropwise with stirring under 2 min to a solution of cyclopentanethiol (1.17 g, 11.5 mmol) and NaOH (460 mg, 11.5 mmol) in MeOH (20 mL). The resulting reaction mixture was stirred for 2 h at 0°C. The solvent was concentrated *in vacuo* and the crude was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with petroleum ether:EtOAc (10:1) to afford 2-[(cyclopentylsulfanyl)methyl]-1-methyl-4-nitrobenzene (1.40 g, 53%) as a yellow oil.

Iron dust (0.33 g, 5.9 mmol) and NH_4Cl (330 mg, 6.2 mmol) was added to a solution of 2-[(cyclopentylsulfanyl)methyl]-1-methyl-4-nitrobenzene (500 mg, 1.99 mmol) in MeOH/THF/H_2O (3:3:1; 10 mL). The resulting mixture was stirred for 1 h at 60°C. The solvent was concentrated *in vacuo* and the residue was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound (350 mg, 79%) as a yellow oil which was used directly in the next step.

3-[(Cyclopentylsulfanyl)methyl]-4-fluoroaniline (17c). To a solution of *tert*-butyl *N*-[4-fluoro-3-(hydroxymethyl)-phenyl]carbamate (**22a**) (1.10 g, 45.6 mmol) in DCM (20 mL) at 0°C was added PPh_3 (2.39 g, 9.12 mmol) and NBS (1.61 g, 9.11 mmol) and the resulting mixture was stirred for 3 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:25) to afford *tert*-butyl *N*-[3-(bromomethyl)-4-fluorophenyl]-carbamate (0.70 g, 55%) as a colorless solid.

To a 50-mL round-bottom flask was added cyclopentanethiol (281 mg, 2.75 mmol) and K_2CO_3 (585 mg, 4.23 mmol) in DMF (10 mL). The mixture was stirred for 30 min at rt and then *tert*-butyl *N*-[3-(bromomethyl)-4-fluorophenyl]carbamate (640 mg, 2.12 mmol) in DMF (5 mL) was added dropwise under stirring. The resulting mixture was stirred for 15 h at rt and thereafter extracted with DCM (3×30 mL). The combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:50) to afford *tert*-butyl *N*-{3-[(cyclopentylsulfanyl)methyl]-4-fluorophenyl}carbamate (600 mg, 88%) as a colorless solid.

To a 25-mL round-bottom flask was added a solution of *tert*-butyl *N*-{3-[(cyclopentylsulfanyl)methyl]-4-fluorophenyl}carbamate (550 mg, 1.69 mmol) in HCl (12 M, 5 mL). The reaction mixture was stirred for 3 h at rt. The pH value of the solution was adjusted to 7 with $NaHCO_3$ (sat) and then extracted with EtOAc (3×10 mL). The combined organic layers were dried through a phase separator and concentrated *in vacuo* to afford the titled compound (350 mg, 80%) as a colorless solid. m/z (ES^+) $[M + H + MeCN]^+ = 267$.

4-Chloro-3-[(cyclopentylsulfanyl)methyl]aniline (17d). PPh_3 (2.45 g, 9.34 mmol) and NBS (1.64 g, 9.21 mmol) were added to a solution of *tert*-butyl *N*-[4-chloro-3-(hydroxymethyl)phenyl]carbamate (**22b**) (1.20 g, 4.66 mmol) in DCM (20 mL) and the resulting mixture was stirred for 3 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:25) to afford *tert*-butyl *N*-[3-(bromomethyl)-4-chlorophenyl]carbamate (0.46 g, 31%) as a colorless solid.

To a 250-mL round-bottom flask was added cyclopentanethiol (192 mg, 1.9 mmol) and K_2CO_3 (399 mg, 2.9 mmol) in DMF (10 mL). A solution of *tert*-butyl *N*-[3-(bromomethyl)-4-chlorophenyl]carbamate (460 mg, 1.4 mmol) in DMF (5 mL) was added dropwise under stirring. The resulting mixture was stirred for 15 h at rt and then extracted with DCM (3×90 mL). The combined organic layers were concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:40) to afford *tert*-butyl *N*-[4-chloro-3-[(cyclopentylsulfanyl)methyl]phenyl]carbamate (350 mg, 71%) as a colorless solid.

To a 25-mL round-bottom flask was added a solution of *tert*-butyl *N*-[4-chloro-3-[(cyclopentylsulfanyl)methyl]-phenyl]carbamate (250 mg, 0.73 mmol) in HCl (12 M, 3 mL). The resulting mixture was stirred for 3 h at rt and then the pH value of the solution was adjusted to 7 with $NaHCO_3$ (sat). The reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried through a phase separator and concentrated *in vacuo* to afford the titled compound (150 mg, 84%) as a colorless solid. m/z (ES^+) $[M + H + MeCN]^+ = 283$.

3-[(Cyclopentylsulfanyl)methyl]-4-(trifluoromethoxy)-aniline (17e). To a solution of (5-nitro-2-(trifluoromethoxy)-phenyl)methanol (**24**) (665 mg, 2.80 mmol) in DCM (11.6 mL) was added TEA (0.47 mL, 3.4 mmol) and methanesulfonyl chloride (0.26 mL, 3.4 mmol). The reaction mixture was stirred at rt for 1 h. The mixture was quenched with $NaHCO_3$ (sat) and extracted with DCM. The organic layers were washed with brine, dried through a phase separator and concentrated *in vacuo* to give the crude product (as a mixture of 2-(chloromethyl)-4-nitro-1-(trifluoromethoxy)-benzene and [5-nitro-2-(trifluoromethoxy)phenyl]methyl methanesulfonate (880 mg) as an orange oil. The products were used in the next step without further purification.

To a mixture of 2-(chloromethyl)-4-nitro-1-(trifluoromethoxy)benzene and [5-nitro-2-(trifluoromethoxy)phenyl]-methyl methanesulfonate (880 mg) and Cs_2CO_3 (1.36 g, 4.2 mmol) in DMF (12 mL) was added cyclopentanethiol (0.33 mL, 3.07 mmol). The reaction mixture was stirred for 2 h and 20 min at rt under N_2(g). The reaction was quenched by the addition of H_2O (25 mL) and the aqueous layer was extracted with EtOAc (4×50 mL). The combined organic layers were dried through a phase separator, concentrated *in vacuo* and co-concentrated with *p*-xylol a couple of times to reduce the amount of DMF. The residue was purified by automated flash chromatography using EtOAc/heptane as mobile phase to afford 2-[(cyclopentylsulfanyl)methyl]-4-nitro-1-(trifluoro-methoxy)benzene (734 mg, 82% over two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.8 Hz, 1H), 8.16 (dd, *J* = 2.8, 9.1 Hz, 1H), 7.36 – 7.42 (m, 1H), 3.83 (s, 2H), 2.94 – 3.09 (m, 1H), 1.90 – 2.06 (m, 2H), 1.66 – 1.82 (m, 2H), 1.45 – 1.64 (m, 4H).

To a solution of 2-[(cyclopentylsulfanyl)methyl]-4-nitro-1-(trifluoromethoxy)benzene (730 mg, 2.3 mmol) in HOAc (20 mL) was added iron dust (1.27 g, 22.7 mmol). The reaction mixture was stirred for 1.5 h at 60°C under N_2(g). The mixture was filtered through a pad of celite and rinsed with EtOAc (100 mL). The filtrate was concentrated *in vacuo* and the crude was re-dissolved in EtOAc (200 mL). The organic layer was washed with $NaHCO_3$ (1 M, 200 mL + 100 mL), H_2O (150 mL) and brine (150 mL). The organic layer was dried through a phase separator and concentrated *in vacuo*. The residue was purified by automated flash chromatography using EtOAc/heptane as mobile phase to afford the titled compound (488 mg, 74%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 1.4, 8.7 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.58 (dd, *J* = 2.9, 8.7 Hz, 1H), 4.18 (brs, 2H), 3.70 (s, 2H), 2.94 – 3.12 (m, 1H), 1.87 – 2.06 (m, 2H), 1.65 – 1.83 (m, 2H), 1.43 – 1.63 (m, 4H).

2-(Bromomethyl)-1-methyl-4-nitrobenzene (20). A solution of 2-methyl-5-nitrobenzoic acid (**19**) (10.0 g, 55.2 mmol) in THF (50 mL) was purged with N_2(g) and maintained under an inert atmosphere. A solution of borane (1.53 g, 111 mmol) in THF (110 mL) was added dropwise with stirring over 5 min at 0°C. The resulting mixture was stirred for 2 h at 30°C. The solvent was concentrated *in vacuo* and the residue was partitioned between EtOAc and $NaHCO_3$ (sat). The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford (2-methyl-5-nitro-

phenyl)methanol as a colorless solid, which was directly used in the next step.

To a 100-mL round-bottom flask purged with N_2(g) and maintained under an inert atmosphere was added a solution of (2-methyl-5-nitrophenyl)methanol (2.00 g, 12.0 mmol) in DCM (20 mL). A solution of PBr_3 (4.86 g, 18.0 mmol) in DCM (10 mL) was added dropwise with stirring over 5 min at 0°C. The resulting mixture was stirred for 2 h at 0°C. The reaction mixture was concentrated *in vacuo* and the crude was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2×50 mL) and the combined organic layers were washed with $NaHCO_3$, dried and concentrated *in vacuo* to afford the titled compound (2.4 g, 86%) as an off-white solid.

***tert*-Butyl *N*-[4-fluoro-3-(hydroxymethyl)phenyl]-carbamate (22a).** To a solution of 2-fluoro-5-nitrobenzaldehyde (**21a**) (5.1 g, 30 mmol) in THF/MeOH (55 mL) was added $NaBH_4$ (2.2 g, 59 mmol) in portions at 0°C. The resulting mixture was stirred for 1 h at 0°C. The crude product was precipitated by the addition of H_2O (5 mL). The solid was filtered to afford (2-fluoro-5-nitrophenyl)methanol (4.0 g, 79%) as a yellow solid.

To a solution of (2-fluoro-5-nitrophenyl)methanol (5.0 g, 23 mmol) in HOAc (40 mL) was added iron dust (13.1 g, 234 mmol). The resulting mixture was stirred for 3 h at 70°C. The pH value of the solution was adjusted to 7 with $NaHCO_3$ (sat). The reaction mixture was extracted with EtOAc (3×90 mL) and the combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:10) to afford (5-amino-2-fluorophenyl)-methanol (1.1 g, 22%) as a dark oil.

Boc_2O (4.64 g, 21.3 mmol) was added to a solution of (5-amino-2-fluorophenyl)methanol (1.1 g, 7.1 mmol) in DMF (20 mL) and the resulting mixture was stirred for 3 h at 60°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:25) to afford the titled compound (2.0 g, 90%) as a colorless solid.

***tert*-Butyl *N*-[4-chloro-3-(hydroxymethyl)phenyl]-carbamate (22b).** To a solution of 2-chloro-5-nitrobenzaldehyde (**21b**) (5.58 g, 40 mmol) in THF/MeOH (10:1) (55 mL) was added $NaBH_4$ (2.22 g, 59 mmol) in portions at 0°C. The resulting mixture was stirred for 1 h at 0°C. The crude product was precipitated by the addition of H_2O (5 mL). The solid was filtered to afford (2-chloro-5-nitrophenyl)methanol (3.76 g, 68%) as a yellow solid. The product was used in the next step without further purification.

To a solution of (2-chloro-5-nitrophenyl)methanol (3.76 g, 20.0 mmol) in HOAc (50 mL) was added iron dust (11.2 g, 200 mmol). The resulting mixture was stirred for 3 h at 70°C. The solid was filtered off and the pH value of the filtrate was adjusted to 7 with $NaHCO_3$ (sat). The filtrate was extracted with EtOAc (3×90 mL) and the combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:10) to afford (5-amino-2-chlorophenyl)-methanol (1.5 g, 47%) as a dark oil. m/z (ES^+) $[M + H]^+$ = 158.

To a solution of (5-amino-2-chlorophenyl)methanol (1.0 g, 6.4 mmol) in DMF (20 mL) was added Boc_2O (3.45 g, 15.8 mmol). The resulting mixture was stirred for 3 h at 60°C. The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:20) to afford the titled compound (1.2 g, 75%) as a colorless solid.

[5-Nitro-2-(trifluoromethoxy)phenyl]methanol (24). To a mixture of nitric acid (0.80 mL, 19 mmol) and sulfuric acid (4.0 mL, 75 mmol) cooled in an ice bath was added 2-(trifluoromethoxy)benzaldehyde (**23**) (0.75 mL, 5.3 mmol) dropwise over 2 min. The reaction mixture was stirred at 0°C for 1 h and thereafter poured into ice. The suspension was stirred for 30 min and the crude product was precipitated. The solid was filtered, rinsed with H_2O (2×5 mL) and dried *in vacuo* to afford 5-nitro-2-(trifluoromethoxy)benzaldehyde (0.97 g, 79%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.81 (d, *J* = 2.9 Hz, 1H), 8.53 (dd, *J* = 2.9, 9.1 Hz, 1H), 7.47 – 7.67 (m, 1H).

5-Nitro-2-(trifluoromethoxy)benzaldehyde (685 mg, 2.9 mmol) was suspended in MeOH (12 mL) and $NaBH_4$ (132 mg, 3.5 mmol) was added. The mixture started to effervesce (due to gas evolution). The effervescence ceased after 2 min to give a clear orange solution and the reaction mixture was stirred 1.5 h at rt. The residue was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (2×12 mL). The organic extracts were combined, dried through a phase separator and evaporated to afford the titled compound (666 mg, 96%) as an orange oil that solidifies over time. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, *J* = 2.9 Hz, 1H), 8.27 (dd, *J* = 2.9, 9.0 Hz, 1H), 7.43 – 7.67 (m, 1H), 4.75 (s, 2H).

***N*-{3-[(Cyclopentylsulfanyl)methyl]phenyl}thiophene-2-carboximidamide (18a).** To a 50-mL round-bottom flask was added a solution of 3-[(cyclopentylsulfanyl)methyl]aniline (**17a**) (280 mg, 1.35 mmol) and methyl thiophene-2-carboximidothioate (**35**) (275 mg, 1.75 mmol) in *i*-propanol (12 mL). The resulting mixture was stirred for 3.5 h at 85°C. The solvent was concentrated *in vacuo*, the crude was dissolved in acetone (20 mL) and the precipitation was filtered off. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with petroleum ether/EtOAc (6:1) to afford the titled compound (89 mg, 21%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.79 (m, 1H), 7.56 – 7.65 (m, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.10 (dd, *J* = 3.8, 4.8 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.77 – 6.84 (m, 1H), 6.67 – 6.76 (m, 1H), 6.38 (brs, 2H), 3.71 (s, 2H), 2.90 – 3.07 (m, 1H), 1.80 – 2.00 (m, 2H), 1.58 – 1.75 (m, 2H), 1.35 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.48, 141.76, 139.74, 129.27, 129.03, 127.36, 126.78, 122.49, 122.35, 120.16, 104.49, 42.59, 35.39, 33.07, 24.39. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}N_2S_2$ 317.1146; Found 317.1158.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methylphenyl}-thiophene-2-carboximidamide (18b).** A solution of 3-[(cyclopentylsulfanyl)methyl]-4-methylaniline (**17b**) (350 mg, 1.6 mmol) in *i*-propanol (10 mL) was purged with N_2(g) and maintained under inert atmosphere. Methyl thiophene-2-carboximidothioate (**35**) (248 mg, 1.6 mmol) was added and the resulting mixture was stirred for 12 h at 80°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to afford the titled compound (50 mg, 10%) as a colorless solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.93 (dd, *J* = 0.9, 3.6 Hz, 1H), 7.74 – 7.86 (m, 1H), 7.22 – 7.37 (m, 2H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.85 (dd, *J* = 2.1, 7.9 Hz, 1H), 6.52 (brs, 2H), 3.90 (s, 2H), 3.17 – 3.33 (m, 1H), 2.50 (s, 3H), 2.03 – 2.23 (m, 2H), 1.79 – 1.95 (m, 2H), 1.56 – 1.79 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.54, 147.15, 141.85, 137.01, 131.01, 129.53, 129.16, 127.34, 126.67, 123.11, 120.26, 42.91, 33.70, 33.18, 24.43, 18.17. HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2S_2$ 331.1302; Found 331.1319.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-fluorophenyl}-thiophene-2-carboximidamide (18c).** To a 25-mL round-bottom flask was added a solution of 3-[(cyclopentylsulfanyl)methyl]-4-fluoroaniline (**17c**) (350 mg, 1.6 mmol) in *i*-propanol (10 mL). Methyl thiophene-2-carboximidothioate (**35**) (295 mg, 1.9 mmol) was added and the resulting mixture was stirred for 4 h at 85°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:8) to afford the titled compound (202 mg, 40%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, *J* = 1.0, 3.7 Hz, 1H), 7.62 (dd, *J* = 1.0, 5.1 Hz, 1H), 7.03 – 7.16 (m, 2H), 6.83 (dd, *J* = 2.3, 6.9 Hz, 1H), 6.69 – 6.78 (m, 1H), 6.46 (brs, 2H), 3.72 (s, 2H), 2.97 – 3.15 (m, 1H), 1.83 – 2.03 (m, 2H), 1.59 – 1.74 (m, 2H), 1.35 – 1.58 (m, 4H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}FN_2S_2$ 335.1052; Found 335.1058.

***N*-{4-Chloro-3-[(cyclopentylsulfanyl)methyl]phenyl}-thiophene-2-carboximidamide (18d).** To a solution of 4-chloro-3-[(cyclopentylsulfanyl)methyl]aniline (**17d**) (150 mg, 0.63 mmol) in *i*-propanol (10 mL) was added methyl thiophene-2-carboximidothioate (**35**) (170 mg, 1.1 mmol). The resulting mixture was stirred for 4 h at 85°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:5) to afford the titled compound (42 mg, 19%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 3.1 Hz, 1H), 7.62 (dd, *J* = 1.0, 5.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 3.8, 5.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 2.3, 8.4 Hz, 1H), 6.54 (brs, 2H), 3.78 (s, 2H), 2.97 – 3.17 (m, 1H), 1.86 – 2.06 (m, 2H), 1.59 – 1.74 (m, 2H), 1.35 – 1.58 (m, 4H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}ClN_2S_2$ 351.0756; Found 351.077.

***N*-{3-[(Cyclopentylsulfanyl)methyl]-4-(trifluoromethoxy)phenyl}thiophene-2-carboximidamide (18e).** A microwave vial was loaded with 3-(cyclopentylsulfanylmethyl)-4-(trifluoromethoxy)aniline (**17e**) (120 mg, 0.41 mmol) in toluene (2.3 mL) under N_2(g) and cooled in an ice bath. $AlMe_3$ (2 M in toluene, 0.41 mL, 0.82 mmol) was added dropwise via a syringe and the reaction mixture was allowed to reach rt and stirred for 45 min. Thiophene-2-carbonitrile (90 mg, 0.82 mmol) dissolved in toluene (3.1 mL) was added dropwise via a syringe and the clear yellow mixture was heated at 95°C for 4 h. The reaction mixture was cooled to 0°C and $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The aqueous phase was extracted with DCM (2×10 mL) and the combined organic layers were dried by passing through a phase separator. The residue was purified by preparative HPLC to afford the titled compound (78 mg, 47%) as an orange oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.76 (d, *J* = 2.7 Hz, 1H), 7.60 – 7.67 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.07 – 7.15 (m, 1H), 6.93 – 6.97 (m, 1H), 6.83 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.59 (brs, 2H), 3.74 (s, 2H), 3.00 – 3.31 (m, 1H), 1.85 – 2.01 (m, 2H), 1.6 – 1.73 (m, 2H), 1.47 – 1.58 (m, 2H), 1.35 – 1.47 (m, 2H). HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}F_3N_2OS_2$ 401.0969; Found 401.0986.

2-(Bromomethyl)-1-methoxy-4-nitrobenzene (25). To a solution of 1-methoxy-4-nitrobenzene (**4**) (22.0 g, 144 mmol) in HOAc (16 mL) and sulfuric acid (42 mL) was added paraformaldehyde (4.36 g, 145 mmol) and NaBr (16.0 g, 158 mmol). The resulting mixture was stirred for 3 h at 85°C. The pH value of the solution was adjusted to 7 with $NaHCO_3$ (sat). The reaction mixture was extracted with EtOAc (3×90 mL) and the combined organic layers were dried through a phase separator and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluted with EtOAc/petroleum ether (1:50) to afford the titled compound (15 g, 42%) as a yellow solid.

2-(Cyclopentoxymethyl)-1-methoxy-4-nitrobenzene (26). To a solution of 2-(bromomethyl)-1-methoxy-4-nitrobenzene (**25**) (2.0 g, 8.1 mmol) in THF (70 mL) was added cyclopentanol (3.5 g, 41 mmol) and *t*-BuOK (2.3 g, 21 mmol) at 0°C. The resulting mixture was stirred for 3 h at 50°C. The reaction mixture was diluted with EtOAc (300 mL) and washed with H_2O (3×30 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude was purified by flash chromatography on silica gel eluted with petroleum ether/EtOAc (50:1) to afford the titled compound (1.37 g, 67%) as a colorless solid.

***N*-{3-[(Cyclopentoxy)methyl]-4-methoxyphenyl}-thiophene-2-carboximidamide (27)** To a solution of 2-(cyclopentoxymethyl)-1-methoxy-4-nitrobenzene (**26**) (500 mg, 1.99 mmol) in HOAc (30 mL) at rt was added iron dust (1.11 g, 19.8 mmol). The resulting mixture was stirred for 5 h at 70°C. The solid was filtered off, the filtrate was diluted with DCM (500 mL) and washed with H_2O (100 mL). The organic layer was dried through a phase separator and concentrated *in vacuo*. The crude was purified by preparative TLC eluted with petroleum ether/EtOAc (1:1) to afford 3-(cyclopentoxymethyl)-4-methoxy-aniline (300 mg, 68%) as a yellow oil. m/z (ES$^+$) $[M + H]^+$= 222.

To a solution of 3-(cyclopentoxymethyl)-4-methoxyaniline (300 mg, 1.36 mmol) in *i*-propanol (10 mL) was added methyl thiophene-2-carboximidothioate (**35**) (426 mg, 2.71 mmol). The resulting mixture was heated to reflux for 3 h. The solvent was concentrated *in vacuo* and the residue was purified by preparative-TLC eluted with petroleum ether:EtOAc (1:1) to afford the titled compound (73 mg, 16%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (dd, *J* = 1.1, 3.7 Hz, 1H), 7.58 (dd, *J* = 1.1, 5.1 Hz, 1H), 7.08 (dd, *J* = 3.7, 5.1 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.72 (dd, *J* = 2.2, 8.4 Hz, 1H), 6.29 (brs, 2H), 4.38 (s, 2H), 3.91 – 4.05 (m, 1H), 3.75 (s, 3H), 1.55 – 1.78 (m, 6H), 1.39 – 1.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.74, 149.72, 142.25, 141.97, 129.02, 127.54, 127.30, 126.51, 121.79, 120.77, 111.25, 80.29, 64.65, 55.47, 31.86, 23.24. HRMS (ESI$^+$) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_2S$ 331.1480; Found 331.1486.

3-(2-Cyclopentylethyl)-4-methoxyaniline (28). To a solution of 2-(bromomethyl)-1-methoxy-4-nitrobenzene (**25**) (5.0 g, 20 mmol) in DMF (15 mL) was added PPh_3 (5.1 g, 19 mmol) and the resulting mixture was stirred for 2 h at 100°C. The reaction mixture was allowed to reach rt and the

product was precipitated by the addition of DCM. The solid was collected by filtration and dried *in vacuo* to afford [(2-methoxy-5-nitrophenyl)methyl]-triphenylphosphonium bromide (6.2 g, 63%) as a yellow solid. The product was used directly in the next step.

To a 50-mL 3-necked round-bottom flask was added a solution of [(2-methoxy-5-nitrophenyl)methyl]triphenylphosphonium bromide (1.00 g, 1.97 mmol) in THF (10 mL). The reaction mixture was cooled to 0°C, *t*-BuOK (193 mg, 1.72 mmol) was added and the mixture was stirred for 20 min. Cyclopentanecarbaldehyde (161 mg, 1.64 mmol) was added and the resulting mixture was stirred for 2 h at 0°C in an ice/salt bath. The reaction mixture was quenched by the addition of H_2O (0.5 mL) and the resulting mixture was concentrated *in vacuo*. The residue was purified by preparative-TLC to afford 2-[(*E*)-2-cyclopentylethenyl]-1-methoxy-4-nitrobenzene (237 mg, 58%) as a yellow oil.

To a 50-mL round-bottom flask was added a solution of 2-[(*E*)-2-cyclopentylethenyl]-1-methoxy-4-nitrobenzene (237 mg, 0.96 mmol) in MeOH (8 mL). Palladium on charcoal (46 mg) was added and the resulting mixture was stirred under H_2(g) for 2 h at 25°C. The reaction mixture was filtered and concentrated *in vacuo* to afford the titled compound (190 mg, 90%) as a yellow oil. m/z (ES^+) $[M + H]^+$ = 220.

***N*-[3-(2-Cyclopentylethyl)-4-methoxyphenyl]benzenecarboximidamide (29).** A solution of 3-(2-cyclopentylethyl)-4-methoxyaniline (**28**) (190 mg, 0.87 mmol) and methyl benzenecarboximidothioate (196 mg, 1.30 mmol) in *i*-propanol (10 mL) was stirred for 2 h at 88°C. The resulting mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to afford the titled compound (102 mg, 36%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, *J* = 7.0 Hz, 2H), 7.35 – 7.53 (m, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.57 – 6.75 (m, 2H), 6.17 (brs, 2H), 3.75 (s, 3H), 2.51 – 2.58 (m, 2H), 1.68 – 1.86 (m, 3H), 1.37 – 1.65 (m, 6H), 1.02 – 1.20 (m, 2H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{27}N_2O$ 323.2123; Found 323.2142.

1-Methoxy-4-nitro-2-[(phenylsulfanyl)methyl]benzene (30). To a mixture of 2-(bromomethyl)-1-methoxy-4-nitrobenzene (**25**) (900 mg, 3.66 mmol) and K_2CO_3 (758 mg, 5.49 mmol) dissolved in DMF (17 mL) was added benzenethiol (0.39 mL, 3.89 mmol). The reaction mixture was stirred at rt over the weekend under N_2(g). The mixture was quenched with H_2O (36 mL) and extracted with EtOAc (4×40 mL). The combined organic layers were concentrated *in vacuo* and the crude was co-evaporated with *p*-xylol a couple of times to reduce the amount of DMF to afford the titled compound (1.01 g, 100%) as a yellow oil. The product was used without further purification ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (dd, *J* = 2.9, 9.1 Hz, 1H), 8.08 (d, *J* = 2.9 Hz, 1H), 7.26 – 7.38 (m, 4H), 7.17 – 7.26 (m, 2H), 4.24 (s, 2H), 3.93 (s, 3H).

***N*-{4-Methoxy-3-[(phenylsulfanyl)methyl]phenyl}benzenecarboximidamide (31).** To a solution of 1-methoxy-4-nitro-2-[(phenylsulfanyl)methyl]benzene (**30**) (1.01 g, 3.67 mmol) in HOAc (30 mL) was added iron dust (2.05 g, 36.7 mmol). The reaction mixture was stirred for 1.5 h at 60°C under N_2(g). The resulting mixture was filtered through a pad of celite and rinsed with EtOAc (80 mL). The mixture was diluted with EtOAc (200 mL) and washed with NaOH (1 M, 180 mL), H_2O (180 mL) and brine (180 mL). The organic layer was dried through a phase separator and concentrated *in vacuo*. The residue was purified by automated flash chromatography using EtOAc/heptane as mobile phase to afford 4-methoxy-3-[(phenylsulfanyl)methyl]aniline (0.716 g, 80%) as an orange oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 – 7.34 (m, 4H), 7.13 – 7.2 (m, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 6.44 (dd, *J* = 2.8, 8.6 Hz, 1H), 4.62 (s, 2H), 4.05 (s, 2H), 3.66 (s, 3H).

$AlMe_3$ (2 M in toluene, 0.14 mL, 0.27 mmol) was added dropwise via a syringe to a solution of 4-methoxy-3-[(phenylsulfanyl)methyl]aniline (66 mg, 0.27 mmol) in toluene (1.3 mL) under N_2(g) and cooled with an ice bath. The reaction mixture was allowed to reach rt and stirred for 40 min. Benzonitrile (0.023 mL, 0.22 mmol) dissolved in toluene (2.5 mL) was added dropwise via a syringe and the reaction mixture was heated at 95°C for 4 h 15 min. The heating was turned off and the reaction mixture was stirred at rt overnight. The reaction mixture was cooled to 0°C, $NaHCO_3$ (sat, 4 mL) was added slowly and the mixture was diluted with DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a phase separator and concentrated *in vacuo* to afford an orange oil. The crude was dissolved in DCM (2 mL) and the residue was purified by automated flash chromatography using MeOH (1% TEA) in DCM as mobile phase to provide the titled compound (50 mg, 65%) as a yellow oil. The oil solidified by adding MeOH and the solvent was concentrated *in vacuo*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.39 – 7.52 (m, 3H), 7.26 – 7.38 (m, 4H), 7.13 – 7.21 (m, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.69 – 6.82 (m, 2H), 6.18 (brs, 2H), 4.15 (s, 2H), 3.78 (s, 3H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2OS$ 349.1375; Found 349.1397.

***N*-[(2-Methoxy-5-nitrophenyl)methyl]cyclopentanecarboxamide (33).** To a stirred suspension of cyclopentanecarboxylic acid (0.064 mL, 0.59 mmol) and (2-methoxy-5-nitrophenyl)-methanamine hydrochloride (**32**) (130 mg, 0.59 mmol) in DMF (1 mL) and DCM (1.8 mL) was added at 0 – 5°C *N*,*N*'-diisopropylethylamine (0.414 mL, 2.38 mmol) and *o*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyl-uronium tetrafluoroborate (229 mg, 0.71 mmol). The resulting suspension was stirred for 30 min at 0°C and thereafter allowed to reach rt and stirred for additional 30 min. The reaction mixture was quenched with Na_2CO_3 (1 M, 12 mL). DCM (6 mL) was added and the organic layer was dried through a phase separator and concentrated *in vacuo*. The residue was purified by automated flash chromatography using EtOAc/heptane as mobile phase to afford the titled compound (136 mg, 82%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 2.8, 9.0 Hz, 1H), 8.14 (d, *J* = 2.8 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 4.48 (d, *J* = 6.1 Hz, 2H), 3.97 (s, 3H), 2.51 – 2.66 (m, 1H), 1.68 – 1.98 (m, 6H), 1.47 – 1.67 (m, 2H). m/z (ES^+) $[M+H^+]$ 279.

***N*-(5-{[Imino(phenyl)methyl]amino}-2-methoxybenzyl)-cyclopentanecarboxamide (34).** Iron dust (273 mg, 4.89 mmol) was added to a solution of *N*-(2-methoxy-5-nitrobenzyl)-cyclopentanecarboxamide (**33**) (136 mg, 0.49 mmol) in HOAc (4 mL) and the reaction mixture was stirred overnight at 60°C under N_2(g). The mixture was filtered through a pad of celite and rinsed with EtOAc (40 mL). The filtrate was concentrated *in vacuo* and the residue was redissolved in EtOAc (20 mL). The organic layer was washed with NaOH (1 M, 15 mL), H_2O (15 mL) and brine (15 mL), dried through a phase separator and concentrated *in vacuo*.

The residue was purified by automated flash chromatography using MeOH (1% TEA) in DCM as mobile phase to afford *N*-[(5-amino-2-methoxyphenyl)methyl]cyclopentane-carboxamide (103 mg, 85%) as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 – 6.75 (m, 2H), 6.64 (dd, *J* = 2.8, 8.6 Hz, 1H), 4.36 (d, *J* = 5.9 Hz, 2H), 3.78 (s, 3H), 2.42 – 2.57 (m, 1H), 1.64 – 1.91 (m, 6H), 1.47 – 1.62 (m, 2H). m/z (ES^+) $[M+H^+]$ 249.

$AlMe_3$ (2 M in toluene, 0.20 mL, 0.40 mmol) was added dropwise via a syringe to a solution of *N*-[(5-amino-2-methoxy-phenyl)methyl]-cyclopentanecarboxamide (100 mg, 0.40 mmol) in toluene (1.8 mL) under N_2(g) and cooled to 0°C in an ice bath. The reaction mixture was allowed to reach rt and stirred for 30 min. Benzonitrile (0.034 mL, 0.34 mmol) dissolved in toluene (3.6 mL) was added dropwise via a syringe and the reaction mixture was heated at 95°C overnight. The mixture was cooled to 0°C, $NaHCO_3$ (sat, 5 mL) was added slowly and the mixture was diluted with DCM (15 mL). The phases were separated and the aqueous phase was extracted with DCM (2×10 mL). The combined organic layers were dried by passing through a phase separator and concentrated *in vacuo* to afford an orange oil. The residue was purified by preparative HPLC to provide the titled compound (4 mg, 4%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.05 (t, *J* = 5.7 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.52 (m, 3H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.66 – 6.81 (m, 2H), 6.02 – 5.49 (brs, 2H), 4.22 (d, *J* = 5.7 Hz, 2H), 3.78 (s, 3H), 2.58 – 2.66 (m, 1H), 1.69 – 1.79 (m, 2H), 1.56 – 1.68 (m, 4H), 1.42 – 1.54 (m, 2H). HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}N_3O_2$ 352.2025; Found 352.2032.

Methyl thiophene-2-carboximidothioate (35). To a 250-mL round-bottom flask was added a solution of thiophene (9.0 g, 107 mmol) and KSCN (12.0 g, 123 mmol) in MsOH (100 mL). The resulting mixture was stirred for 5 h at rt. The reaction mixture was diluted with ice/H_2O (200 mL) and the pH value of the solution was adjusted to 7 – 8 with $NaHCO_3$ (sat) The resulting solution was extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford thiophene-2-carbothioamide (8.0 g) as a yellow solid which was used in the next step without further purification.

A solution of thiophene-2-carbothioamide (2.85 g, 19.9 mmol) in acetone (100 mL) was cooled to 0°C in a H_2O/ice bath and methyl iodide (24.2 g, 171 mmol) was added dropwise. The resulting mixture was stirred for 8 h at rt. The solid was collected by filtration and washed with acetone (2×25 mL) to afford the titled compound (2.8 g, 89%) as a yellow solid.

Functional assay (Inositol-1-phosphate). Cryopreserved, human QRFP (peptide P518/GPR103) Receptor Cell Line (Perkin Elmer) was thawed in stimulation buffer and preincubated with compound at 37ºC in a humidified incubator with 5% CO_2.The cells were treated with *h*QRFP43 (Phoenix Pharmaceuticals) at EC_{80} in stimulation buffer and incubated at 37ºC. After 50 min, reagents from the IP-1 Tb HTRF® kit (CisBio Bioassays, France) were added and the resulting signal ratio (665 nm/620 nm) was measured in Pherastar (BMG, Germany). Reported values are the mean of n ≥ 2 determinations, with confidence interval ratio (CIR) 2.0. Compounds were considered active in ten point CR if a proper IC_{50} curve could be fitted. Compounds was given an active flag if they displayed a percent effect >30% at 41.1 µM.

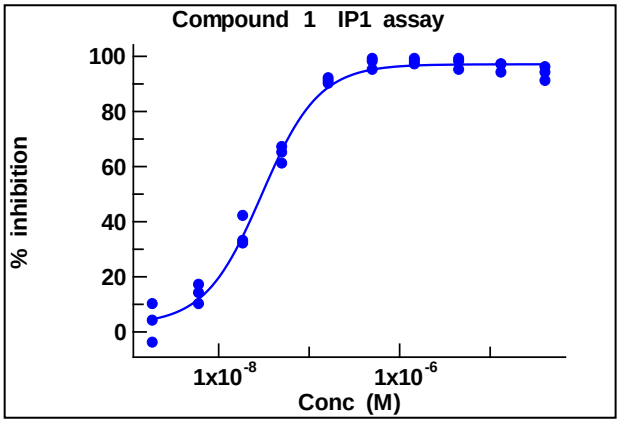

Figure S1. Concentration response curve from the *in vitro* IP-1 assay GPR103 displayed for compound **1**.

Functional assay (Dynamic mass redistribution). Cryopreserved, human QRFP (peptide P518/GPR103) Receptor Cell Line (Perkin Elmer) was seeded in plates (Corning #5042) two days before the assay. The cells were serum-starved at least 18 h before the assay was performed. On the day of the assay, the cells were washed with buffer (HEPES, 20 mM, pH 7.4, HBSS, 0.01% BSA) with 0.5% DMSO and temperature stabilized in the instrument for 1 h. Test compounds and *h*QRFP43 were added to the cells using a CybiWell (CyBio, Germany) and the change in dynamic mass redistribution with agonist *h*QRFP43 present was measured in the EPIC instrument (Corning) for 30 min.

Radioligand binding assay. Membranes from HEK cells overexpressing the human GPR103 receptor were incubated in 96 well microplates with compound and 0.25 nM radioligand [^{125}I]-*h*QRFP43 (NEX408, Perkin Elmer) in binding buffer (50 mM Tris, pH 7.4, 1 mM EDTA, and 0.1% BSA) at 30ºC. After 90 min incubation, the reaction was filtered through filter plates (Whatman GF/C, 7700 – 4301) with wash buffer (50 mM Tris, pH 7.4, 2 mM EDTA, 10 mM $MgCl_2$, 0.04% Tween) *in vacuo*; the plates were dried, treated with scintillation liquid and counted in Trilux Microbeta (Wallac). Reported values are the mean of n ≥ 2 determinations, with confidence interval ratio (CIR) 1.7. Compounds were considered active in the single concentration RLB assay if they had a percent effect >3×SD of the baseline.

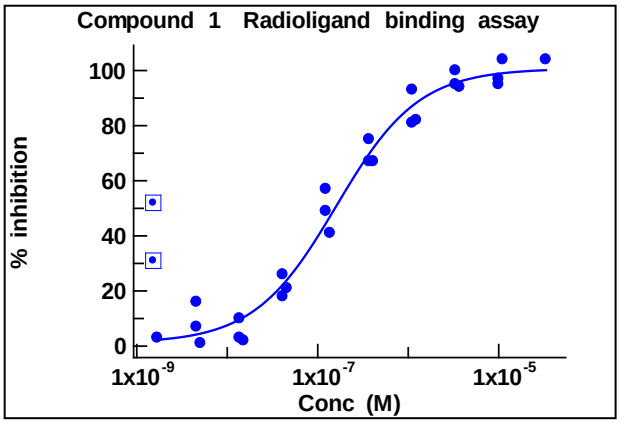

Figure S2. Concentration response curve from the *in vitro* radio ligand binding assay of GPR103 displayed for compound **1**.

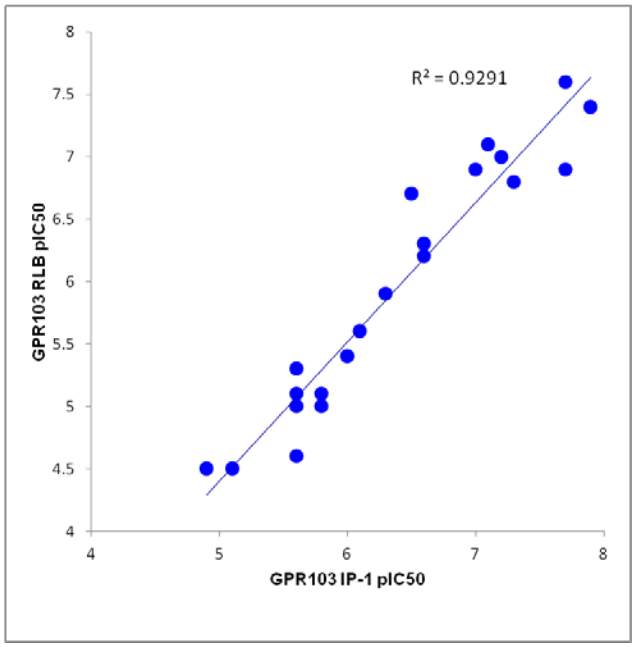

Figure S3. Correlation between functional data IP-1 pIC_{50} and radioligand binding (RLB) pIC_{50} for GPR103 for all compounds presented in Table 1 and Table 2.

$LogD_{7.4}$ Octanol/H_2O partitioning using the shake-flask method. Partitioning of compounds between 1-octanol and 0.1 M phosphate buffer, pH 7.4, at 20°C were determined using a modified version of the shake-flask method described by Leo.[23] Compounds were dissolved, in a 96-well plate, in 400 µL octanol, and 400 µL of buffer was added to each well. The plate was vigorously stirred for 5 min and thereafter put on an Edmund Bühler shaker (Edmund Bühler GmbH, Hechingen, Germany) for 18 h at 20°C. Aliquots of 5 µL octanol was transferred and diluted with 495 µL MeCN/H_2O (1/1) and, to avoid contamination of the buffer, the rest of the octanol was removed before 150 µL of buffer samples were transferred. Octanol and buffer samples were diluted with MeCN/H_2O (1/1) in four steps of 10 times to yield octanol samples diluted 100 to 1000000 times and buffer samples diluted 1 to 10000 times. LC/MS/MS was used for analysis, and logD was calculated from the integrated peak areas of the samples in the linear MS response range.

pK_a measurements potentiometric method.[24] Measurements of the acid dissociation constant (pK_a) of ionizing groups were performed using a Sirius GLpKa (Sirius Analytical) instrument equipped with a Dip Probe Absorption Spectroscopy (DPAS). The Sirius GLpKa instrument was directly connected to a dedicated PC, supporting software for assay setup and subsequent data analysis. Assays were set up and analyzed using the RefinementPro software. The software also allowed determination of multiple pK_a's using complex curve fitting analysis. Solutions for the experiment; ionic strength adjusted (0.10 M KCl) distilled H_2O, nominally 0.50 M HCl, nominally 0.50 M KOH and 80% v/v MeOH:H_2O were kept in polytetrafluoroethylene (PTFE) containers and housed in the instrument. Titration solutions were constantly purged with oxygen free nitrogen. The titration of compounds (*e.g.* 20 µL of a 10 mM DMSO solution) were thereafter typically executed from a minimum pH (1.80 for operational minimum of electrode) to a maximum pH (12.20 for operational maximum of electrode), with assay direction low to high pH (recommended for bases) or high to low pH (recommended for acids) at pH step between points, *i.e.* ΔpH between 0.05 - 0.20 units recommended. At the end of the run, the titration data was uploaded to the PC and analyzed using the RefinementPro software. The pK_a's of the compounds were extracted by using curve fitting procedures fitting the observed data to a theoretical curve.

pK_a measurements through pressure-assisted capillary electrophoresis and mass spectrometry. pK_a values were obtained by the high throughput method developed by Wan and co-workers.[25] The method utilizes pressure-assisted capillary electrophoresis (HPCE^{3D}, Agilent Technologies) coupled online with an ion trap mass spectrometer (1100 series LC/MSD trap).

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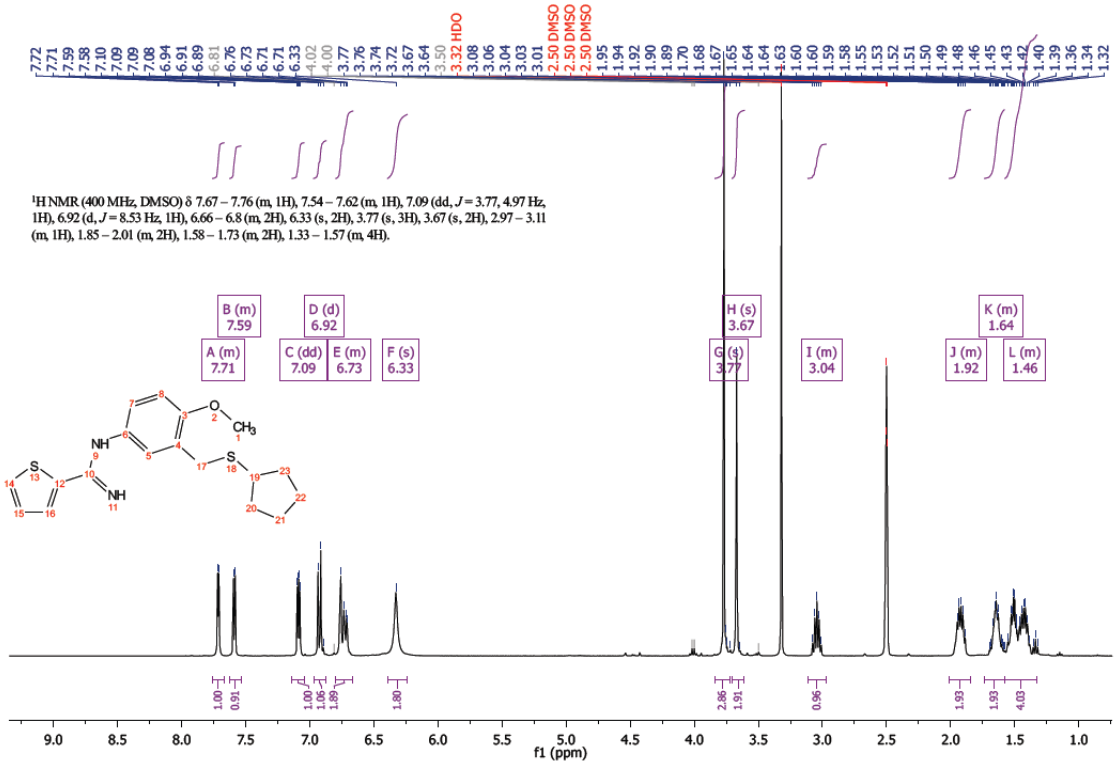
(23) Leo, A.; Hansch, C.; Elkins, D. Partition coefficients and their uses. *Chem. Rev.* **1971**, *71*, 525-616.

(24) Tam, K. Y.; Takács-Novák, K. Multi-wavelength spectrophotometric determination of acid dissociation constants: a validation study. *Anal. Chim. Acta.* **2001**, *434*, 157-167.

(25) Wan, H.; Holmén, A. G.; Wang, Y.; Lindberg, W.; Englund, M.; Någård, M. B.; Thompson, R. A. High-throughput screening of pKa values of pharmaceuticals by pressure-assisted capillary electrophoresis and mass spectrometry. *Rapid Communications in Mass Spectrometry.* **2003**, *17*, 2639-2648.

^{1}H and ^{13}C NMR Spectra for compound *N*-{3-[(Cyclopentylsulfanyl)methyl]-4-methoxyphenyl}-thiophene-2-carboximidamide (1)



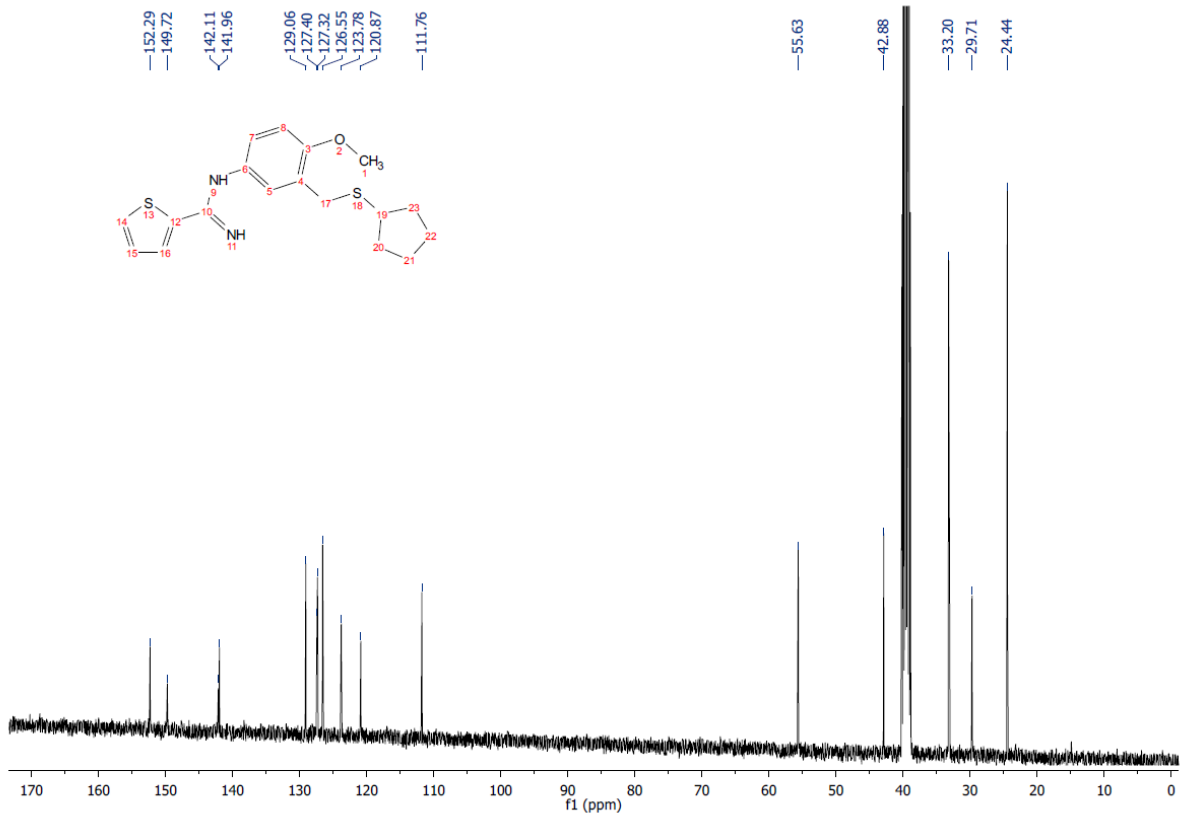
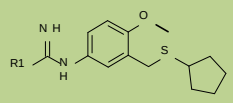
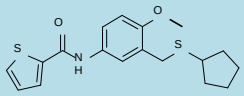
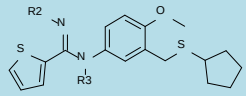
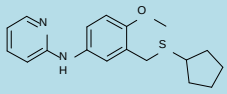
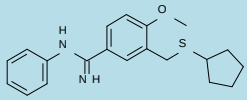
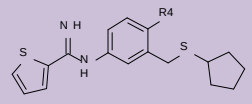
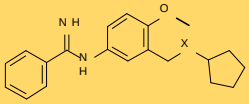
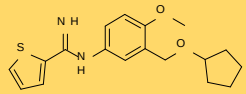
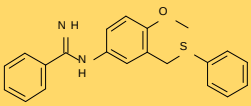
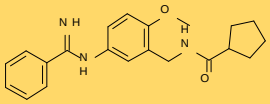


Table 2. Functional Activity and Radioligand Binding for Analogues of Compound 1 and Their Measured $logD_{7.4}$

Compound		R1	R2/R3	R4	X	pIC_{50} IP-1[a]	pIC_{50} RLB[a]	$logD_{7.4}$	LLE[b]
	**1**	Thiophene-2-yl				7.3±0.2 (4)	6.8±0.2 (3)	3.3±0.1 (3)	4.0
	7a	Thiophene-3-yl				7.0±0.04 (3)	6.9±0.04 (2)	2.5±0.1 (2)	4.5
	7b	Phenyl				7.7±0.2 (3)	7.6±0.1 (2)	2.5±0.3 (4)	5.2
	7c	4-Methyl-thiophene-2-yl				7.2±0.02 (3)	7.0±0 (2)	3.7±0.1 (2)	3.5
	7d	4-Bromo-thiophene-2-yl				6.8±0.1 (3)		4.7±0.6 (2)	2.1
	7e	5-Bromo-thiophene-2-yl				7.7±0.2 (2)	6.9±0.2 (3)	>5 (2)	<2.7
	7f	4-Chlorophenyl				7.9 (1)	7.4±0.2 (3)	3.7±0 (2)	4.2
	7g	Benzyl				5.2±0.1 (2)		2.3±0.1 (2)	2.9
	7h	Ethyl				<4.4 (2)		1.2±0.2 (2)	<3.2
	7i	Thiazole-2yl				5.6±0.04 (2)	4.6±0.1 (2)	4.0±0.4 (3)	1.6
	7j	Pyridine-4-yl				5.8±0.01 (2)		2.9±0 (2)	2.9
	7k	Pyridine-3-yl				6.6±0.2 (3)	6.3±0.1 (2)	2.6±0.1 (2)	4.0
	**8**					5.1±0.03 (2)	<4.5 (2)	>4.2 (2)	<0.9
	**9a**		Me/H			6.6±0.01 (2)	6.2±0.04 (2)	3.1±0.2 (5)	3.5
	9b		Me/Me			<4.4 (1)		1.9±0.2 (3)	<2.5
	**10**					4.9±.0.03 (3)	<4.5 (2)	4.6±0.9 (2)	0.3
	**15**					6.0±0.3 (3)	5.4±0.1 (2)	2.8±0.1 (2)	3.2
	**18a**			H		6.1±0.03 (2)	5.6±0.1 (3)	3.8±0.2 (4)	2.3
	18b			Me		5.8±0.1 (2)	5.0±0.03 (2)	>3.8 (4)	<2.0
	18c			F		6.3±0.1 (2)	5.9±0.1 (2)	>3.9 (2)	<2.4
	18d			Cl		6.0±0.01 (2)	5.4±0.2 (2)	3.9±0.6 (2)	2.1
	18e			OCF_3		5.7±0.1 (2)		>4.8 (2)	<0.9
	**11a**				SO	<4.4 (2)		0.8±0.1 (2)	<3.6
	11b				SO_2	4.5±0.01 (2)		0.7±0.2 (2)	3.8
	29				CH_2	6.5±0.1 (2)	6.7±0.1 (2)	3.8±0.1 (3)	2.7
	**27**					5.6±0.1 (2)	5.0±0.2 (2)	2.7±0 (2)	2.9
	**31**					5.8±0.2 (2)	5.1±0.1 (2)	2.6±0.1 (2)	3.2
	**34**					5.6±0.1 (2)	5.1±0.1 (2)	1.1±0.1 (2)	4.5

[a] pIC_{50} is reported as mean±SD, n=2–4 from ten point CR with the number of experiments in parentheses

[b] LLE was calculated as LLE = $pIC_{50} - logD_{7.4}$