SUPPORTING INFORMATION

Discovery of 1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): A Novel Multimodal Compound for the Treatment of Major Depressive Disorders

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Pharmacology

Chemistry

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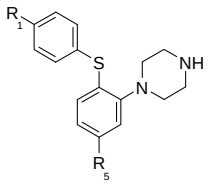
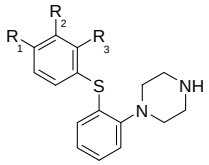
Table 1: pK_i/pIC_{50} values



			pK_i- and pIC_{50}-values ± SEM		
Compounds	R_1	R_5	h5-HT_{3A} (pK_i)	h5-HT_{1A} (pK_i)	rSERT (pIC_{50})
4a	H	CH_3	6,55±0,02	5,97 ±0,03	6,83±0,10
4b	OCH_3	CH_3	6,98±0,15	5,39±0,44	8,10±0,10
4c	Cl	CH_3	6,30±0,07	5,61±0, 05	8,02±0,12
4d	F	CH_3	6,36±0,03	5,95±0,06	7,17±0,05
4e	CH_3	CH_3	6,60±0,03	5,56±0,04	7,70±0,18
4f	H	H	7,20±0,18	7,53±0,03	6,41±0,05
4g	OCH_3	H	7,45±0,09	6,90±0,03	8,10±0,07
4h	Cl	H	7,44±0,10	7,16±0,04	7,87±0,08
4i	F	H	7,20±0,077	7,41±0,04	7,17±0,03
4j	CH_3	H	7,30±0,19	7,36±0,03	7,74±0,06
4k	CF_3	H	6,34±0,08	5,60±0,04	6,96±0,10
4l	$C(CH_3)_3$	H	6,35±0,08	5,60±0,02	5,68±0,04

Table 2: pK_i/pIC_{50} values



				pK_i- and pIC_{50}-values ± SEM		
Compounds	R_1	R_2	R_3	h5-HT_{3A}(pK_i)	h5-HT_{1A} (pK_i)	rSERT (pIC_{50})
5a	H	OCH_3	H	7,21±0,09	6,84±0,03	7,26±0,0 6
5b	H	CH_3	H	7,19±0,67	7,00±0,04	7,27±0,10
5c	H	H	OCH_3	7,29±0,01	7,23±0,05	6,49±0,04
5d	H	H	CH_3	7,49±0,06	7,86±0,06	7,29±0,08
5e	OCH_3	OCH_3	H	7,07±0,10	6,80±0,05	7,82±0,03
5f	Cl	Cl	H	6,95±0,03	7,17±0,03	8,35±0,06
5g	CH_3	CH_3	H	7,48±0,03	7,38±0,06	8,23±0,11
5h	H	OCH_3	OCH_3	7,10±0,06	7,17±0,04	7,44±0,07
5i	H	Cl	Cl	7,17±0,07	7,13±0,03	7,77±0,06
5j	H	CH_3	CH_3	7,53±0,04	7,51±0,03	8,35±0,14
5k	OCH_3	H	OCH_3	7,50±0,10	6,48±0,04	8,12±0,07
5l	Cl	H	Cl	7,58±0,05	7,11±0,03	8,34±0,06
5m	CH_3	H	CH_3	7,63±0,07	6,74±0,02[a]	8,58±0,15
5n	OCH_3	H	Cl	7,91±0,11	7,03±0,04	8,05±0,32
5o	CH_3	H	OCH_3	7,77±0,08	6,68±0,05	7,95±0,09
5p	CH_3	H	Cl	8,13±0,24	7,11±0,06	8,01±0,04

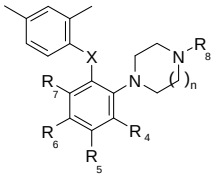
[a] pK_i±SD

Table 3: pIC_{50} values

Compounds	pIC_{50}-values ± SEM		
	rSERT	rDAT	rNAT
4h	7,87±0,08	7,44±0,19[a] / 7,35 [b]	6,65±0,12[a] / 6,72[b]
4j	7,74±0,06	6,96±0,53[a]	6,34±0,20[a]
5g	8,23±0,11	6,92[b]	6,05[b]
5i	7,77±0,06	7,68[b]	6,92 [b]
5j	8,35±0,14	6,77 [b]	7,05 [b]
5l	8,34±0,06	6,60 [b]	6,92[b]
5m	8,58±0,15	6,05±0,07[a]	6,86±0,19[a]
5p	8,01±0,04	6,49[b]	6,49[b]

[a]pIC_{50} ± SD. [b]Data were generated at Cerep. IC_{50} values were determined from the mean values of two individual determinations of seven different concentrations covering four decades.

Table 4: pK_i/pIC_{50} values



								pK_i- and pIC_{50}-values ± SEM		
Compounds	R_4	R_5	R_6	R_7	R_8	n	X	h5-HT_{3A} (pK_i)	h5-HT_{1A} (pK_i)	r5-SERT (pIC_{50})
6a	CH_3	H	H	H	H	1	S	6,79±0,03	6,37±0,04	7,36±0,09
6b	H	CH_3	H	H	H	1	S	6,83±0,02	5,56±0,05	7,60±0,11
6c	H	H	CH_3	H	H	1	S	7,35±0,01	5,86±0,03	6,74±0,10
6d	H	H	H	CH_3	H	1	S	6,18±0,06	6,26±0,03	6,44±0,14
6e	H	H	H	H	CH_3	1	S	6,87±0,06	6,91±0,05	6,17±0,01
6f	H	H	H	H	H	2	S	7,57±0,05	6,51±0,04	6,88±0,07
6g	H	H	H	H	H	1	O	6,57±0,11	7,19±0,05	6,67±0,09

Detailed descriptions of in vitro assays

In general for binding affinity assays, data points were expressed as percent of the specific binding and the IC_{50} values were determined by nonlinear regression analysis using a sigmoidal variable slope curve fitting. The dissociation constant (K_i) was calculated from the Cheng-Prusoff equation ($K_i = IC_{50}/(1 + (L/K_d))$), where the concentration of free radioligand L is approximated to the concentration of added radioligand in the assay and K_d equals the affinity of the radioligand to the receptor. In general IC_{50} values are based on 6-8 different concentrations covering 4-6 decades.

h5-HT_{3A} Binding Affinity Assay. [^{3}H]Granisetron (Perkin Elmer) binding to human 5-HT_{3A} was assayed in a final incubation volume of 200 µL, consisting of 0.5 µg of membrane preparation isolated from a HEK-293 cell line stably expressing the human 5-HT_{3A} receptor and [^{3}H]granisetron (1.0 nM), and the displacing agent in an appropriate range of concentrations. Nonspecific binding was measured in the presence of 10 µM bemesetron. Incubation was initiated by the addition of the membrane

preparation. After 30 minutes of incubation, the incubation was stopped, by harvesting the cell membranes on a GF/C filter pretreated with 0.1% PEI for 30 minutes and washing filters with buffer (Tris-HCl, pH 8.00). The filters were dried and 35 μL of scintillation liquid was added. After 2 h, the filters were measured in a scintillation counter. Compounds were tested at least 3 times over a 6 log concentration range. IC_{50} values were determined by non-linear regression analysis using Hill equation curve fitting. K_i values were determined using the Cheng-Prusoff equation.

Assessment of Efficacy at the the h5-HT_{3A} and r5-HT_{3A} Receptor Using Electrophysiological Testing in Oocytes. Compound **5m** was dissolved in DMSO to give a stock solution of 1 mM or 10 mM. Further dilution was performed in phosphate buffer saline (PBS). Stock solutions of test compounds were prepared freshly each day of testing. The test solutions were adjusted to a pH of 7.4. Total RNA was isolated from rat brain with RNAeasy mini kit (Qiagen, Hilden, Germany). cDNA was prepared by oligo-dT primed reverse transcription using the TaqMan kit (Applied Biosystems, Foster City, USA). The genes were amplified by polymerase chain reaction (PCR) with Pfu polymerase (Stratagene, Heidelberg, Germany), and the resulting products were extracted from agarose gel with Freeze'n Squeeze DNA (Biorad, Hercules, USA) and cloned into pGEMHE. After validation by sequencing, the pGEMHE DNAs were linearized with Nhe1 and the linearized DNA molecules were transcribed *in vitro* to cRNA using the mMessage mMachine kit from Ambion (Austin, Texas). The quality of the RNA was evaluated by electrophoresis. Oocytes were surgically removed from mature female *Xenopus laevis* anaesthetized in 0.4% MS-222 for 10-15 min. The oocytes were then digested at room temperature for 2-3 h with 0.5 mg/mL collagenase (type IA Sigma-Aldrich) in OR2 buffer (82.5 mM NaCl, 2.0 mM KCl, 1.0 mM $MgCl_2$ and 5.0 mM HEPES, pH 7.6). Oocytes devoid of the follicle layer were selected and incubated for 24 h in modified Barth's saline buffer [88 mM NaCl, 1 mM KCl, 15 mM HEPES, 2.4 mM $NaHCO_3$, 0.41 mM $CaCl_2$, 0.82 mM $MgSO_4$, 0.3 mM $Ca(NO_3)_2$] supplemented with 2 mM sodium pyruvate, 0.1 U/L penicillin and 0.1 μg/L streptomycin. Stage IV oocytes were identified and injected with 12-48 nL of nuclease-free water containing 14-50 pg of cRNA coding for rat 5-HT_{3A} or human 5-HT_{3A} receptors and incubated at 18°C until they were used for

electrophysiological recordings. The oocytes were used for electrophysiological recordings 2-7 days after injection. Oocytes were placed in a 1 mL bath and perfused with Ringer buffer (115 mM NaCl, 2.5 mM KCl, 10 mM HEPES, 1.8 mM $CaCl_2$, 0.1 mM $MgCl_2$, pH 7.5). Cells were impaled with agar plugged 0.5-1 MΩ electrodes containing 3 M KCl and voltage clamped at −90 mV using a GeneClamp 500B amplifier. The oocytes were continuously perfused with Ringer buffer in which the drugs were dissolved. 5-HT agonist-solutions were applied for 10-30 s. The potencies of 5-HT_3 receptor antagonists were determined by measuring concentration-dependent inhibition against 10 μM 5-HT stimulation. The experiments were performed at room temperature.

h5-HT_{1A} Binding Affinity Assay. The binding assay was performed as a scintillation proximity assay (SPA)-based competition-binding assay in a 50 mM Tris pH 7.4 buffer containing 120 mM NaCl, 5 mM KCl, 4 mM $MgCl_2$, 1.5 mM $CaCl_2$ and 1 mM EDTA. The test compound was mixed with 0.15 nM [^{3}H]5-carboxamidotryptamine (CT) (PerkinElmer) before the addition of 0.5 μg of a homogenized membrane preparation isolated from a CHO cell line stably expressing the human $5HT_{1A}$ receptor and 0.25 mg WGA SPA beads (Amersham) in a total volume of 60 μL. The assay plates were under agitation incubated for 60 minutes at room temperature before the plates were centrifuged and counted in a top counter. Total and non-specific binding were defined using assay buffer and 10 μM 5-HT, respectively. Data was expressed in percent of the specific binding of [^{3}H]CT and the IC_{50} values were determined by non-linear regression analysis using sigmoidal variable slope curve fitting. The K_i values were calculated from the Cheng-Prusoff equation using a K_d value of 0.28 nM determined from saturation binding assays. Affinity for h5-HT_{1A} receptors was also evaluated by MDS Pharm Service (MDS catalog number 271110). Binding was measured by displacement of 1.5 nM [^{3}H]-8-hydroxy-2-(di-n-propylamino) tetraline ([^{3}H]8-OH-DPAT) using cloned receptors in CHO cell membranes. The binding reaction was performed for 60 minutes at 37 °C.

h5-HT_{1B} Binding Affinity Assay. The binding assay was performed as a SPA-based competition-binding assay in a 50 mM Tris pH 7.4 buffer containing 120 mM NaCl, 5 mM KCl, 4 mM $MgCl_2$, 1,5

mM $CaCl_2$ and 1 mM EDTA. Test compound was mixed with 0.45 nM [^{3}H]CT (PerkinElmer) before addition of 2 µg of a homogenized membrane preparation isolated from a HELA cell-line stably expressing the human 5-HT_{1B} receptor and 0,25 mg WGA SPA beads (Amersham) in a total volume of 60 µl. The assay plates were under agitation incubated for 60 minutes at room temperature before the plates were centrifugated and counted in a topcounter. Non-specific and total binding were defined using assay buffer and 10 µM 5-HT, respectively. Data was expressed in percent of the specific binding of [^{3}H]CT and the IC_{50} values were determined by non-linear regression analysis using sigmoidal variable slope curve fitting. The K_i values were calculated from the Cheng Prusoff equation using a K_d value of 0.9 nM determined from saturation binding assays.

r5-HT_{1A} Binding Affinity Assay. The binding of 8-hydroxy-DPAT (8-OH-DPAT) to the rat 5-HT_{1A} receptor was performed at MDS pharmaservices according to a protocol previously described.[1] Brain cortices were obtained from male rats and a membrane fraction was prepared by standard techniques.[1] The binding buffer consisted of 50 mM Tris-HCl, pH 7.4, 10 mM $MgSO_4$, 0.5 mM EDTA and 0.1% ascorbic acid. 1.25 mg rat brain of membrane preparation was incubated with 0.25 nM [^{3}H]8-OH-DPAT for 60 minutes at 25 °C. Non-specific binding was estimated in the presence of 10 µM cold Metergoline. Membranes were filtered over Whatman GF-C filters and washed 3 times and the filters were counted to determine [^{3}H]8-OH-DPAT specifically bound. Compounds were screened at eight concentrations in duplicate: 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 µM final concentration.

Assessment of Efficacy at the h5-HT_{1A} and h5-HT_{1B} Receptors Using GTPγS Binding.

h5-HT_{1A} Functional [^{35}S]GTPγS Binding Assay. The functional intrinsic activity (IA) was assessed by MDS Pharma (MDS catalog number 355150) in [^{35}S]-guanosine 5'-[γ-thio] triphosphate ([^{35}S]GTPγS) binding using cloned h5-HT_{1A} receptors in CHO cells. The binding was performed for 30 minutes at 30 °C. Compound stimulated [^{35}S]GTPγS binding values, which were expressed as the percentage of the maximal binding effect stimulated by 5-HT, were obtained by MDS Pharmaservices, and subsequently analyzed at Lundbeck by sigmoidal dose response curve-fittings using GraphPad

Prism 4 to generate EC_{50} and intrinsic activity (IA) results. The sigmoidal dose response equation was used, Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope)), where X is the logarithm of concentration and Y is the response. With Bottom fixed to 0, curve fittings for 2 of the 3 individual experiments as well as for the average data were statistically better by F-test when Hillslope was allowed to be free, than when Hillslope was fixed to 1.

h5-HT_{1B} Functional [^{35}S]GTPγS Binding Assay. The functional intrinsic activity (IA) was determined using a SPA-based [^{35}S]-GTPγS binding assay using membranes isolated from a HELA cell-line stably expressing human 5-HT_{1B} receptors. 10 µg of the homogenised membrane preparation, 1 mg WGA SPA beads, 3 µM GDP, 0.1 nM [^{35}S]-GTPγS (Perkin Elmer) and test compound were incubated in a 50 mM Tris pH 7.7 buffer containing 10 mM $MgCl_2$, 2 mM $CaCl_2$, 100 mM NaCl and 0,2 mM EGTA in a total volume of 200 µl at 25 °C for 90 minutes under agitation. The plates were subsequently centrifugated and counted in a topcounter. All data points were normalized using buffer and 10 µM 5-HT, and analyzed by sigmoidal dose response curve-fittings using GraphPad Prism 4 to determine the EC_{50} and intrinsic activity (IA). For **5m**, the data indicated two potential sites in the assay and in order to determine the IA relevant to the 5-HT_{1B} receptor, data points from concentrations 100-fold higher than the 5-HT_{1B} receptor affinity was left out in the curve fitting.

Inhibition of [^{3}H]5-HT Uptake from Rat Synaptosomes. Forebrain from male rats (125-225 g) was weighed and homogenized with a cooled glass/teflon homogenizer in about 10 mL 0.40 M sucrose buffer containing 1 mM nialamid. The suspension was centrifuged for 10 min at 1000 x g at 4°C. The resulting supernatant was centrifuged for 20 min. at 40000 x g at 4 °C. The pellet was resuspended in 180 x volume KRP-buffer and kept on ice until use. Aliquots consisted of 10 µL compound, 10 µL 10 nM [^{3}H]5-HT and 180 µL membrane (0.5 mg/well), resulting in a total volume of 200 µL. Non-specific binding/uptake was determined in the presence of 10 µM citalopram and the total uptake was determined in the presence of buffer. The plate was incubated for 15 minutes at 37 °C. After incubation, bound ligand was separated from unbound by filtration through Unifilter GF/C, presoaked in 0.1% PEI

for 30 min, using a Tomtec Cell Harvester program. Filters were washed once with 1 mL ice-cold buffer, dried at 50 °C and 35 µL scintillation liquid was added. Bound radioactivity was counted in a Wallac OY 1450 MicroBeta counter.

Affinity Binding Assay for hSERT. The affinities for cloned hSERT were determined using membranes prepared from Peakr293 cells in which the transporter was transiently expressed. [^{3}H]escitalopram (79 ci/mmol) was used at final concentrations of 1-2 nM. Binding experiments were performed for 90 minutes at room temperature. After filtration, bound radioligands were measured by scintillation counting.

Inhibition of [^{3}H]NE Uptake from Rat Synaptosomes. Cortex (occipital-, temporal- and parietal cortex) from male rats (125-225 g) was weighed out and homogenized with a cooled glass/teflon homogenizer in about 5 mL 0.40 M sucrose buffer. The suspension was centrifuged for 10 min at 1000 x g at 4 °C. The resulting supernatant was centrifuged for 20 min. at 40000 x at 4 °C. The pellet was resuspended in 140 x volume KRP-buffer and kept on ice until use. Aliquots of 10 µL compound and 140 µL membrane (1.0 mg/well) were preincubated for 10 min at 37 °C, after which 50 µL 10 nM [^{3}H]NA was added, resulting in a total volume of 200 µL. Non-specific uptake was determined in the presence of 10 µM talsupram (final conc 10 µM) and the total uptake was determined in the presence of buffer. The plate was incubated for 15 min at 37 °C. After incubation, bound ligand was separated from unbound by filtration through Unifilter GF/C, presoaked in 0.1% PEI for 30 minutes, using a Tomtec Cell Harvester program (Uptake) 96-well plate. Filters were washed once with 1 mL ice-cold buffer, dried at 50 °C and 35 µL scintillation liquid was added. Bound radioactivity was counted in a Wallac OY 1450 MicroBeta counter.

Inhibition of [^{3}H]DA Uptake from Rat Synaptosomes. Cortex (occipital-, temporal- and parietal cortex) from male rats (125-225 g) was weighed and homogenized with a cooled glass/teflon homogenizer in about 5 mL 0.40 M sucrose buffer. The suspension was centrifuged for 10 min at 1000 x g at 4 °C. The resulting supernatant was centrifuged for 20 min. at 40000 x g at 4 °C. The pellet was

resuspended in 140 x volume KRP-buffer and kept on ice until use. Aliquots consisted of 10 µL compound and 140 µL membrane (0.25 mg/well), were preincubated for 5 min at 20 °C, and then 50 µL 12.5 nM [^{3}H]DA were added, resulting in a total volume of 200 µL. Non-specific uptake was determined in the presence of 100 µM bentropine and the total uptake was determined in the presence of buffer. The plate was incubated for 5 minutes at 20°C. After incubation, bound ligand was separated from unbound by filtration through Unifilter GF/C, presoaked in 0.1% PEI for 30 min, using a Tomtec CellHarvester program (Uptake) 96-well plate. Filters were washed once with 1 mL ice-cold buffer, dried at 50 °C, and 35 µL scintillation liquid was added. Bound radioactivity was counted in a Wallac OY 1450 MicroBeta.

Broad screening of 5m. The affinities for 75 targets (enzymes, GPCRs and ionchannels) in standard binding assays were assessed at Cerep by standard methods at 1000 nM in an in vitro pharmacology: High throughput profile (2002). Full inhibition curves and subsequent K_i calculations were made for relevant target. Assay descriptions follow below.

Serotonin h5-HT$_{2C}$ Binding Affinity Assay. CHO cells expressing the human 5-HT$_{2C\ (vsv)}$ receptor were cultured and then harvested in 50 mM TRIS buffer pH 7.7 + 125 mM NaCl and frozen at -80 °C. The membranes are stored at -80 °C up to 24 months. The K_d value of [^{3}H]mesulergine was determined to 1.0 nM. Before the experiment, membranes are thawed and homogenized in icecold 50 mM TRIS 7.7, using an Ultra-Turrax homogenizer. Cell suspension is diluted to at final concentration of 7.5 µg/670 µL. Total binding was determined using buffer. Nonspecific binding was determined using 5-HT (10 µM). Aliquots consisting of 10 µL test compound/total/nonspecific, 10 µL [^{3}H]Mesulergine (Final concentration 1.0 nM) and 180 µL membrane suspension were incubated at 37 °C for 30 minutes. After 30 minutes incubation, the incubation was stopped, by harvesting the cell membranes on a GF/B filter pretreated with 0.1% PEI for 30 minutes. The filters were dried and added 35 µL of scintillation liquid. After 2 hours, the filters are measured in a scintillation counter.

Serotonin h5HT$_{5A}$ Binding Affinity Assay. The affinity for h5-HT$_{5A}$ receptors was measured by displacement of 1 nM [^{3}H]LSD binding at cloned receptors in HEK-293 cell membranes. Incubation was done at 37 °C for 30 min. Nonspecific binding was determined in the presence of 100 μM 5-HT (Cerep, 2002). K_i values represent the mean of 2 independent values.

Serotonin h5HT$_6$ Binding Affinity Assay. The affinity for h5-HT$_6$ receptors was measured by displacement of 1 nM [^{3}H]LSD binding at cloned receptors in HEK-293 cell membranes. Incubation was done at 37 °C for 60 min. Nonspecific binding was determined in the presence of 100 μM 5-HT. (Cerep, 2002). K_i values represent the mean of 2 independent values.

Serotonin h5HT$_7$ Binding Affinity Assay. The affinity for human 5-HT$_7$ receptor was determined by displacement of [^{3}H]LSD (~ 4 nM), using recombinant human 5-HT$_7$ receptors expressed in CHO cells. Incubation was done at 22 °C for 120 min. Nonspecific binding was determined in the presence of 10 μM 5-HT. (Cerep, 2002). K_i values represent the mean of 4 independent values.

Adrenergic hβ$_1$ Binding Affinity Assay. The affinity for hβ$_1$ receptors was measured by displacement of 0.15 nM [^{3}H](-)CGP12177 binding at cloned receptors expressed in sf9 cell membranes. Incubation was done at 22 °C for 60 min. Nonspecific binding was determined in the presence of 50 μM alprenolol. (Cerep, 2002). K_i values represent the mean of 2 independent values.

Adrenergic hβ$_2$ Binding Affinity Assay. The affinity for hβ$_2$ receptors was measured by displacement of 0.15 nM [^{3}H](-)CGP12177 binding at cloned receptors expressed in sf9 cell membranes. Incubation was done at 22 °C for 60 min. Nonspecific binding was determined in the presence of 50 μM alprenolol. (Cerep, 2002). K_i values represent the mean of 2 independent values.

Histamine H_2 Binding Affinity Assay.

The affinity for hH_2 receptors was measured by displacement of 0.10 nM [^{125}I]APT binding at membranes made from guinea-pig striatum. Incubation was done at 22 °C for 150 min. Nonspecific binding was determined in the presence of 100 μM tiotidine. (Cerep, 2002). K_i values represent the mean of 2 independent values.

Detailed descriptions of in vivo assays

Animals. Rats (300-350 g; Harlan, Horst, The Netherlands) were used for the experiments. The animals were housed in a 12 h light/dark cycle with conditions maintained at standard indoor temperature (21 ± 2° C) and humidity (55 ± 5%) and had access to food and water *ad libitum*. Experiments were conducted in accordance with the declarations of Helsinki and were approved by the Institutional Animal Care and Use Committee.

Drug administration. For acute administration **5m** was dissolved in 10% hydroxypropyl-beta-cyclodextrin and administered subcutaneously in a volume of 1 ml/kg. For 3-day treatment with **5m** minipumps were used to deliver the solutions.

Minipumps. Under isoflurane anesthesia osmotic minipumps were implanted in a subcutaneous pocket created on the right side parallel to the spine of the animal. The osmotic minipump (2ML2, Alzet, USA) was then inserted into the subcutaneous pocket and the skin was closed. During the 3 days of treatment the animals were daily handled and the position of the osmotic minipump was massaged preventing skin necrosis and stimulating reliable distribution of the drug.

Surgery. Rats were anesthetized using isoflurane. Bupivacain/epinephrine was used for local anesthesia. Flunixin (1 ml/kg) was used, pre/peri operative as analgesia. The animals were placed in a stereotaxic frame and I-shaped probes (Hospal AN 69 membrane, 4 mm exposed surface; BrainLink) were inserted into the ventral hippocampus or medial prefrontal cortex (mPFC). Coordinates for ventral

hippocampus: posterior (AP) = -5.3 mm to bregma, lateral (L) = + 4.8 mm to midline and ventral (V) = - 8.0 mm to dura and for mPFC: posterior (AP) = + 3.4 mm to bregma, lateral (L) = + 0.8 mm to midline and ventral (V) = - 5.0 mm realtive to dura.

Experiment. Experiments were performed 24-48 hours after surgery. On the day of the experiment, the probes of the animals were connected microperfusion pump and were perfused with artificial CSF (147 mM NaCl, 3.0 mM KCl, 1.2 mM $CaCl_2$, and 1.2 mM $MgCl_2$) at a flow rate of 1.5 µl/min. Microdialysis samples were collected at 20 or 30 min intervals into mini-vials containing 30 µl of 0.02 M formic acid and stored at -80 ºC pending analysis. After the experiment the rats were sacrificed and the brains were removed. The brains were incubated for 3 days in a 4% (w/v) solution of paraformaldehyde. The position of each probe was histologically verified by making coronal sections of the brain.

Serotonin analysis. Aliquots (20 µl) were injected onto the HPLC column (Hypersil column, 100 x 2.0 mm, Phenomenex, USA). Chromatographic separation was performed using a mobile phase consisting of a sodium acetate (4.1 g/l) with methanol (4.5 % v/v), Titriplex (500 mg/l), heptanesulfonic acid (50 mg/l), and tetraethylammonium (30 µl/l) and adjusted with glacial acetic acid to pH = 4.74 (isocratic). Mobile phase was run through the system at a flow rate of 0.4 ml/min by an HPLC pump (Shimadzu, model LC-10AD vp). Serotonin was detected electrochemically at +500 mV.

Microdialysis data analysis. Four consecutive pre-treatment samples were taken as baseline and their mean concentration was set to 100 %. Drug effects were expressed as percentages of basal level (mean ± SE) within the same subject. Treatment effects were compared to baseline and vehicle using two-way ANOVA for repeated measurements followed by Student Newman Keuls post-hoc test. Dose and time were the main effects. Differences between basal outputs of 5-HT (fmol/30 min sample) after treatment with **5m** or vehicle for 3 days were compared with One-way ANOVA followed by Student Newman Keuls post-hoc test. The level of statistical significance was set at $p < 0.05$.

SERT occupancy. After the microdialysis experiments rats were sacrificed the brains were removed and frozen using methylbutane at – 20 ºC and stored at -80 ºC until cutting. Sections of 20 µm

containing the striatum were cut and air-dried before the binding experiment. For SERT occupancy 0.5 nM [^{3}H]DASB was used as radioligand. The control for non-specific binding was 1 μM escitalopram. The binding buffer consisted of 50 mM Tris, 150 mM NaCl and 5 mM KCl, pH 7.4, and the incubation time was 90 min. Slides were washed in the respective buffers at 4 ºC three times for 5 min, then briefly dipped in distilled water and air dried. The slides were analysed in a Biospace beta-imager 2000 for at least 6 h.

Chemistry

Experimental for intermediates

General Procedure 1 for the Formation of Diaryl Sulfides.[2] Potassium *tert*-butoxide (1.1 equiv) and a solution of an aryl bromide/iodide (1.0 equiv; if this was a solid) were added to Pd_2dba_3 (2.5 mol%) and DPEphos (10 mol%) Subsequently, toluene (the amount required to make a ca. 10% w/w solution of the aryl bromide/iodide), the aryl bromide/iodide (1.0 equiv; if this was a liquid), and the thiophenol (1.0 equiv) were added. The flask was immersed in an oil bath preheated to 100 °C. The mixture was stirred at this temperature until the reaction was complete (typically <2h for aryl iodides and overnight for aryl bromides). The crude mixture was loaded onto a silica gel column and eluted with heptane/ethyl acetate to give the products in >95% purity as determined by ^{1}H NMR.

General Procedure 2 for the Formation of Boc-Protected Aryl Piperazines from Aryl Bromides.[3] Aryl bromide (1.0 equiv; if this was a solid), Boc-piperazine (1.2 equiv), and sodium *tert*-butoxide (1.4 equiv) were added to Pd_2dba_3 (2.5 mol%) and racemic BINAP (7.5 mol%). Subsequently, toluene (the amount required to make a ca. 10% w/w solution of the aryl bromide) and the aryl bromide (1.0 equiv; if this was a liquid) were added. The flask was immersed in an oil bath preheated to 100 °C. The mixture was stirred at this temperature overnight. The crude mixture was loaded onto a silica gel column and eluted with heptane/ethyl acetate to give the products in >95% purity as determined by ^{1}H NMR.

General Procedure 3 for the Cleavage of Boc-Groups. The substrate was dissolved in methanol (the amount required to make a solution of approximately 20% w/w of the substrate). An HCl solution (2M) in Et_2O (approximately 3 equivalents) was added to the mixture, and the resulting mixture was stirred at room temperature overnight. If required, the mixture was cooled in an ice/water bath and diluted with Et_2O to precipitate the product as the hydrochloride salt. No attempts were made to isolated additional product from the filtrate.

General Procedure 4 for the Formation of Boc-Protected Aryl Piperazines from Aryl Iodides.[4] Pd_2dba_3 (2.5%) and xantphos (10%) were added to a flask containing a stirring bar, followed by the aryl iodide (1.0 equiv; if this was a solid), Boc-piperazine (1.2 equiv), and sodium *tert*-butoxide (1.4 equiv). Toluene (the amount required to make a ca. 10% w/w solution of the aryl iodide) and the aryl iodide (1.0 equiv; if this was a liquid) were added. The flask was immersed in an oil bath preheated to 100 °C. The mixture was stirred at this temperature for 2-5h. The crude mixture was loaded onto a silica gel column and eluted with heptane/ethyl acetate to give the products in >95% purity as determined by ^{1}H NMR.

4-(2-Bromo-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (7a).[4] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 8.0, 7.4, 1.5, 1H), 7.27 (dd, *J* = 7.9, 1.5, 1H), 7.02 (dd, *J* = 8.0, 1H), 6.93 (ddd, *J* = 7.9, 7.4, 1H), 3.61 (t, *J* = 4.7, 4H), 2.98 (t, *J* = 4.6, 4H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 150.6, 134.0, 128.5, 124.8, 121.2, 120.2, 79.9, 51.8 (2C), 44.5 (broad s, 2C), 28.6 (3C). HRMS calcd for $C_{15}H_{22}BrN_2O_2$+H: 341.0859, found 341.0855.

4-(2-Bromo-4-methyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (7c). Prepared according to general procedure 4 starting from Boc-piperazine and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 1H), 6.99 (d, *J* = 7.4, 1H), 6.90 – 6.86 (m, 1H), 3.63 (2, 4H), 2.97 (s, 4H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30, 148.31, 135.04, 134.64, 129.28, 121.08, 120.28, 80.13, 52.20, 28.86, 20.75. HRMS calcd for $C_{16}H_{24}BrN_2O_2$+H: 355.1022, found 355.1028.

4-(2-Bromo-3-methyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (7d). Prepared according to general procedure 4 starting from Boc-piperazine and 2-bromo-1-iodo-3-methyl-benzene (this material was prepared from 2-bromo-3-methyl-aniline according to a general procedure[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8, 1H), 7.21 (d, *J* = 7.6, 1H), 6.92 (dd, *J* = 7.6, 7.8, 1H), 2.52 (s, 3H)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.08 (d, *J* = 8.1, 1H), 6.93 (d, *J* = 8.1, 1H), 3.61 (s, 4H), 2.95 (s, 4H), 2.29 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30, 148.31, 135.04,

134.64, 129.28, 121.08, 120.28, 80.13, 52.21 (4C), 28.86 (3C), 20.75. HRMS calcd for $C_{16}H_{24}BrN_2O_2$+H: 355.1022, found 355.1017.

2-Bromo-4-methyl-1-phenylsulfanyl-benzene (8a). Prepared according to general procedure 1 starting from thiophenol and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.41 – 7.29 (m, 5H), 6.99 (d, *J* = 18.7, 2H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.86, 134.69, 134.42, 134.13, 132.34 (2C), 131.87, 129.82 (2C), 129.27, 128.06, 125.05, 21.04. HRMS calcd for $C_{13}H_{11}BrS$: 277.9759, found 277.9754.

2-Bromo-1-(4-methoxy-phenylsulfanyl)-4-methyl-benzene (8b). Prepared according to general procedure 1 starting from 4-methoxy-thiophenol and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.38 (s, 1H), 6.97 – 6.92 (m, 3H), 6.69 (d, *J* = 8.1, 1H), 3.86 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.68, 137.25, 137.09, 136.63 (2C), 133.73, 129.03, 128.73, 123.46, 121.93, 115.66 (2C), 55.79, 20.89. HRMS calcd for $C_{14}H_{13}BrOS$: 307.9865, found 307.9861.

2-Bromo-1-(4-chloro-phenylsulfanyl)-4-methyl-benzene (8c). Prepared according to general procedure 1 starting from 4-chloro-thiophenol and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.31 (d, *J* = 8.5, 2H), 7.27 (d, *J* = 8.7, 2H), 7.05 (q, *J* = 8.1, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.53, 134.34, 133.98, 133.65, 133.50, 133.06 (2C), 132.50, 129.95 (2C), 129.41, 125.72, 21.08. HRMS calcd for $C_{13}H_{10}BrClS$: 311.9370, found 311.9357.

2-Bromo-1-(4-fluoro-phenylsulfanyl)-4-methyl-benzene (8d). Prepared according to general procedure 1 starting from 4-fluoro-thiophenol and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 3H), 7.08 (t, *J* = 8.6, 2H), 7.00 (d, *J* = 8.0, 1H), 6.89 (d, *J* = 8.0, 1H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.14 (d, *J* = 248.6), 138.58, 135.33 (d, *J* = 8.2, 2C), 135.08, 134.10, 130.76, 129.3 (shoulder), 129.3, 124.04, 117.09 (d, *J* = 22.0, 2C), 21.00. HRMS calcd for $C_{13}H_{10}BrFS$: 295.9665, found 295.9665.

2-Bromo-4-methyl-1-p-tolylsulfanyl-benzene (8e). Prepared according to general procedure 1 starting from 4-methyl-thiophenol and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.34 (d, *J* = 8.1, 2H), 7.19 (d, *J* = 8.0, 2H), 6.97 (d, *J* = 8.0, 1H), 6.87 (d, *J* = 8.1, 1H), 2.38 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.73, 138.03, 135.72, 133.91, 133.60 (2C), 130.73 (2C), 130.38, 130.28, 129.13, 123.59, 21.62, 20.96. HRMS calcd for $C_{14}H_{13}BrS$: 291.9916. Found 291.9912.

1-Bromo-2-(2-methyl-phenyl)sulfanyl-benzene (9c). Prepared according to general procedure 1 starting from 2-methoxy-thiophenol and 1-bromo-2-iodo-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9, 1H), 7.42 – 7.35 (m, 1H), 7.32 (dd, *J* = 7.5, 1.2, 1H), 7.15 (t, *J* = 7.6, 1H), 7.04 (dt, *J* = 16.8, 5.2, 1H), 7.00 – 6.94 (m, 2H), 6.90 (dd, *J* = 7.9, 1.2, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.32, 138.00, 135.13, 133.36, 130.69, 130.04, 128.08, 127.51, 123.71, 121.90, 121.11, 111.79, 56.37. HRMS calcd for $C_{13}H_{11}BrOS$: 293.9708, found 293.9702.

1-Bromo-2-(2-methoxy-phenyl)sulfanyl-benzene (9d). Prepared according to general procedure 1 starting from 2-methyl-thiophenol (o-thiocresol) and 1-bromo-2-iodo-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.9, 1.2, 1H), 7.47 (d, *J* = 7.5, 1H), 7.35 (d, *J* = 4.0, 2H), 7.27 – 7.21 (m, 1H), 7.14 – 7.08 (m, 1H), 7.01 (td, *J* = 7.7, 1.5, 1H), 6.67 (dd, *J* = 7.9, 1.5, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.44, 140.61, 135.87, 133.35, 131.75, 131.41, 129.80, 129.63, 128.45, 128.16, 127.56, 126.97, 20.99. HRMS calcd for $C_{13}H_{11}BrS$: 277.9759, found 277.9760.

4-(2-Bromo-phenylsulfanyl)-1,2-dimethoxy-benzene (9e). Prepared according to general procedure 1 starting from 3,4-dimethoxy-thiophenol and 1-bromo-2-iodo-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9, 1H), 7.16 (dd, *J* = 8.3, 1.9, 1H), 7.11 (dd, *J* = 11.1, 4.1, 1H), 7.06 (d, *J* = 1.8, 1H), 7.01 – 6.90 (m, 2H), 6.72 (dd, *J* = 8.0, 1.2, 1H), 3.93 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.64, 150.18, 141.18, 133.12, 129.01, 128.09, 127.78, 126.63, 122.59, 121.05, 118.30, 112.43, 56.47, 56.38. HRMS calcd for $C_{14}H_{13}BrO_2S$: 323.9814, found 323.9808.

1-(2-Bromo-phenylsulfanyl)-2,3-dimethoxy-benzene (9h). Prepared according to general procedure 1 starting from 2,3-dimethoxy-1-iodobenzene and 2-bromo-thiophenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.0, 1H), 7.23 – 7.18 (m, 1H), 7.24-7.06 (m, 2H), 7.02 (t, *J* = 8.0, 1H), 6.92 (dd, *J* = 8.2, 1.1, 1H), 6.76 (dd, *J* = 7.9, 1.3, 1H), 3.91 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.76, 148.80, 137.30, 133.54, 133.07, 132.02, 128.78, 128.27, 125.23, 125.08, 124.84, 112.77, 61.18, 56.37. HRMS calcd for $C_{14}H_{13}BrO_2S$: 323.9814, found 323.9824.

1-(2-Bromo-phenylsulfanyl)-2,3-dimethyl-benzene (9j). Prepared according to general procedure 1 starting from 2,3-dimethyl-1-iodobenzene and 2-bromo-thiophenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 1H), 7.37 (d, *J* = 7.6, 1H), 7.25 (d, *J* = 7.5, 1H), 7.12 (m, 2H), 6.99 (td, *J* = 7.7, 1.4, 1H), 6.63 (dd, *J* = 7.9, 1.3, 1H), 2.37 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.06, 139.75, 138.75, 133.99, 133.26, 131.60, 129.46, 128.20, 128.11, 126.98, 126.71, 121.94, 21.42, 17.46. HRMS calcd for $C_{14}H_{13}BrS$: 291.9916, found 291.9909.

1-(2-Bromo-phenylsulfanyl)-2,4-dimethoxy-benzene (9k). Prepared according to general procedure 1 starting from 2,4-dimethoxy-1-iodobenzene and 2-bromo-thiophenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.9, 1.1, 1H), 7.45 (d, *J* = 8.1, 1H), 7.11 – 7.06 (m, 1H), 6.95 (td, *J* = 7.7, 1.5, 1H), 6.63 (dd, *J* = 8.0, 1.4, 1H), 6.59 – 6.55 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.15, 161.66, 140.20, 138.72, 133.01, 127.82, 127.20, 126.23, 121.03, 110.54, 106.10, 99.87, 56.39, 55.94. HRMS calcd for $C_{14}H_{13}BrO2S$: 323.9814, found 323.9808.

1-(2-Bromo-phenylsulfanyl)-2-chloro-4-methoxy-benzene (9n). Prepared according to general procedure 1 starting from 2-chloro-4-methoxy-1-bromobenzene and 2-bromo-thiophenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.9, 1.0, 1H), 7.51 – 7.46 (m, 1H), 7.18 – 7.08 (m, 2H), 7.05 – 6.98 (m, 1H), 6.87 (dd, *J* = 8.6, 2.7, 1H), 6.70 (dd, *J* = 7.9, 1.3, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.60, 140.46, 138.81, 138.13, 133.35, 128.22, 128.15, 127.14, 122.09, 121.95, 116.47, 114.52, 56.12. HRMS calcd for $C_{13}H_{10}BrClOS$: 327.9319, found 327.9314.

1-(2-Bromo-phenylsulfanyl)-2-methoxy-4-methyl-benzene (9o). Prepared according to general procedure 1 starting from 2-methoxy-4-methyl-1-iodobenzene (prepared from 5-methyl-2-nitro-anisole by catalytic hydrogenation and subsequent diazotization according to a general literature procedure.[4] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1, 1H), 6.67 (s, 1H), 6.59 – 6.52 (m, 1H), 3.88 (s, 3H), 2.34 (s, 3H)) and 2-bromo-thiophenol. 1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.9, 1.2, 1H), 7.33 – 7.26 (m, 1H), 7.11 (td, *J* = 7.9, 1.3, 1H), 6.99 (td, *J* = 7.7, 1.5, 1H), 6.86-6.80 (m, 2H), 6.78 (s, 1H), 3.82 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.79, 141.97, 139.13, 136.33, 133.15, 128.57, 127.92, 126.78, 122.71, 122.32, 116.72, 112.90, 56.32, 22.21. HRMS calcd for $C_{14}H_{13}BrOS$: 307.9865, found 307.9861.

1-(2-Bromo-phenylsulfanyl)-2-chloro-4-methyl-benzene (9p). Prepared according to general procedure 1 starting from 2-chloro-4-methyl-1-iodobenzene and 2-bromo-thiophenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 1H), 7.35 (s, 1H), 7.27 (t, *J* = 4.8, 1H), 7.22 – 7.16 (m, 1H), 7.11 – 7.04 (m, 2H), 6.91 (dd, *J* = 7.9, 1.4, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.81, 137.46, 137.39, 135.01, 133.59, 131.36, 130.41, 129.07, 129.03, 128.30, 128.04, 124.01, 21.36. HRMS calcd for $C_{13}H_{10}BrClS$: 311.9370, found 311.9375.

1-(2-Bromo-3-methyl-phenylsulfanyl)-2,4-dimethyl-benzene (10a). Prepared according to general procedure 1 starting from 2,4-dimethyl-thiophenol and 2-bromo-1-iodo-3-methyl-benzene (prepared by diazotization of 2-bromo-3-methyl aniline according to a general literature procedure.[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.8, 1H), 7.19 (broad s, 1H), 7.08 (t, *J* = 8.3, 1H), 7.01-6.96 (m, 2H), 6.45 – 6.31 (m, 1H), 2.46 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.15, 140.70, 140.54, 139.59, 137.01, 132.55, 128.65, 128.49, 127.82, 127.66, 124.95, 123.90, 24.31, 21.89, 21.18. HRMS calcd for $C_{15}H_{15}BrS$: 306.0078, found 306.0085.

1-(2-Bromo-4-methyl-phenylsulfanyl)-2,4-dimethyl-benzene (10b). Prepared according to general procedure 1 starting from 2,4-dimethyl-thiophenol and 2-bromo-1-iodo-4-methyl-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.38 (d, *J* = 7.8, 1H), 7.20 (s, 1H), 7.07 (t, *J* = 9.4, 1H), 6.95 (d, *J* =

8.0, 1H), 6.63 (d, *J* = 8.1, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.12, 139.78, 137.19, 135.84, 135.77, 133.87, 132.29, 129.16, 128.70, 128.48, 128.36, 122.35, 21.67, 20.99. HRMS calcd for $C_{15}H_{15}BrS$: 306.0078, found 306.0077.

1-(2-Bromo-phenylsulfanyl)-2,4-dimethyl-benzene (10c). Prepared according to general procedure 1 starting from 2,4-dimethyl-thiophenol and 1-bromo-2-iodo-benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.9, 1.1, 1H), 7.41 (d, *J* = 7.8, 1H), 7.21 – 7.15 (m, 1H), 7.11 – 7.06 (m, 2H), 6.97 (td, *J* = 7.7, 1.4, 1H), 6.59 (dd, *J* = 7.9, 1.4, 1H), 2.39 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.39, 139.93, 139.50, 136.21, 132.80, 131.94, 128.02, 127.66, 127.34, 127.11, 126.09, 121.17, 21.22, 20.51. HRMS calcd for $C_{14}H_{13}BrS$: 291.9916, found 291.9911.

4-(5-Methyl-2-phenylsulfanyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (11a). Prepared according to general procedure 2 starting from **8a** and Boc-piperazine in a yield of 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.0, 2H), 7.32 (t, *J* = 7.4, 2H), 7.29-7.25 (m, 1H), 6.92 (d, *J* = 7.9, 1H), 6.86 (s, 1H), 6.80 (d, *J* = 7.9, 1H), 3.50 (s, 4H), 2.98 (s, 4H), 2.32 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.88, 150.75, 137.47, 134.95, 131.90 (2C), 130.73, 129.12 (2C), 128.82, 127.14, 125.14, 121.06, 79.64, 51.65 (4C), 28.46 (3C), 21.16. HRMS calcd for $C_{22}H_{28}N_2O_2S$+H: 385.1944, found 385.1957.

4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (11b). Prepared according to general procedure 2 starting from **8b** and Boc-piperazine in a yield of 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7, 2H), 6.98 – 6.88 (m, 2H), 6.84 (s, 1H), 6.74 (d, *J* = 7.2, 1H), 6.63 (d, *J* = 8.0, 1H), 3.85 (s, 3H), 3.59 (s, 4H), 3.00 (s, 4H), 2.28 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.34, 155.33, 149.32, 136.61 (2C), 136.22, 132.35, 127.73, 125.64, 121.13, 119.21, 115.45 (2C), 80.06, 55.77, 52.09 (4C), 28.88 (3C), 21.40. HRMS calcd for $C_{23}H_{30}N_2O_3S$+H: 415.2050, found 415.2066.

4-[2-(4-Chloro-phenylsulfanyl)-5-methyl-phenyl]-piperazine-1-carboxylic acid tert-butyl ester (11c). Prepared according to general procedure 2 starting from **8c** and Boc-piperazine in a yield of 82%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 4H), 6.95 (d, *J* = 7.9, 1H), 6.87 (s, 1H), 6.82 (d, *J* = 8.0, 1H), 3.49 (s, 4H), 2.97 (s, 4H), 2.33 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.24, 151.47, 138.49, 134.32, 133.37 (2C), 133.05, 131.61, 129.63 (2C), 128.34, 125.66, 121.66, 80.10, 52.09 (4C), 28.86 (3C), 21.60. HRMS calcd for $C_{22}H_{27}ClN_2O_2S$: 419.1555, found 419.1562.

4-[2-(4-Fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (11d). Prepared according to general procedure 2 starting from **8d** and Boc-piperazine in a yield of 57%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.08 – 7.02 (m, 2H), 6.86 (s, 1H), 6.78 (d, *J* = 7.5, 2H), 3.54 (s, 4H), 2.98 (s, 4H), 2.31 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.91 (d, *J* = 247.7), 155.28, 150.41, 137.51, 135.26 (d, *J* = 8.1, 2C), 130.21, 129.72, 125.71, 121.50, 116.80 (d, *J* = 21.8, 2C), 80.11, 52.10 (4C), 28.86 (3C), 21.50. HRMS calcd for $C_{22}H_{27}FN_2O_2S$: 403.1850, found 403.1853.

4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (11e). Prepared according to general procedure 2 starting from **8e** and Boc-piperazine in a yield of 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0, 2H), 7.17 (d, *J* = 8.0, 2H), 6.85 (s, 1H), 6.80 – 6.74 (m, 2H), 3.56 (s, 4H), 2.99 (s, 4H), 2.36 (s, 3H), 2.30 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.31, 150.25, 138.15, 136.97, 133.68 (2C), 130.80, 130.74, 130.48 (2C), 129.44, 125.57, 121.25, 80.04, 52.07 (4C), 28.87 (3C), 21.59, 21.48. HRMS calcd for $C_{23}H_{30}N_2O_2S$: 399.2101, found 399.2102.

4-(2-Phenylsulfanyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (11f). Prepared according to general procedure 1 starting from **7a** and thiophenol in a yield of 81%. ^{1}H NMR (500 MHz, $CDCl_3$; major rotamer) δ 7.45 (d, *J* = 6.8, 2H), 7.37 (dd, *J* = 12.8, 5.4, 2H), 7.20 – 7.13 (m, 1H), 7.07 – 7.02 (m, 1H), 6.98 – 6.93 (m, 2H), 6.90 (d, *J* = 7.9, 1H), 3.56 (s, 4H), 3.00 (s, 4H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$; major rotamer) δ 153.00, 148.06, 131.44 (2C), 127.44 (2C), 127.20, 125.96, 124.82, 122.79, 122.62, 119.12, 118.21, 77.79, 49.74 (4C), 26.57 (3C). HRMS calcd for $C_{22}H_{28}N_2O_2S$: 371.1788, found 371.1798.

4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (11g). Prepared according to general procedure 1 starting from **7a** and 4-methoxy-thiophenol in a yield of 24%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.7, 2H), 7.09 (dd, *J* = 10.9, 4.1, 1H), 7.03 (d, *J* = 7.0, 1H), 6.98 – 6.89 (m, 3H), 6.70 – 6.65 (m, 1H), 3.86 (s, 3H), 3.63 (s, 4H), 3.01 (s, 4H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.64, 155.33, 148.97, 137.34 (2C), 136.64, 126.90, 125.94, 124.99, 123.01, 120.21, 115.59 (2C), 80.09, 55.78, 52.06 (4C), 32.29, 28.88 (3C). HRMS calcd for $C_{23}H_{31}N_2O_3S$: 401.1893, found 401.1910.

4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (11h). Prepared according to general procedure 1 starting from **7a** and 4-chloro-thiophenol in a yield of 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 4H), 7.22 – 7.16 (m, 1H), 7.05 (dd, *J* = 9.3, 8.4, 1H), 7.00 – 6.95 (m, 1H), 6.92 (dd, *J* = 7.9, 1.4, 1H), 3.54 (s, 4H), 2.99 (s, 4H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.74, 150.12, 134.07 (2C), 133.73, 132.83, 132.44, 129.37 (2C), 129.33, 127.08, 124.52, 120.20, 79.63, 51.55 (4C), 28.34 (3C). HRMS calcd for $C_{22}H_{27}ClN_2O_2S$: 405.1398, found 405.1407.

4-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (11i). Prepared according to general procedure 1 starting from **7a** and 4-fluoro-thiophenol in a yield of 51%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.18 – 7.12 (m, 1H), 7.10 (m, 2H), 7.07 – 7.03 (m, 1H), 6.98 – 6.93 (m, 1H), 6.78 (dd, *J* = 7.9, 1.1, 1H), 3.59 (s, 4H), 3.00 (s, 4H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.87 (d, *J* = 248.6), 154.88, 149.38, 136.13 (d, *J* = 8.2, 2C), 134.51, 128.27, 127.86, 126.44, 124.66, 120.15, 116.62 (d, *J* = 21.8, 2C), 79.72, 51.67 (4C), 28.46 (3C). HRMS calcd for $C_{22}H_{27}FN_2O_2S$: 389.1694, found 389.1710.

4-[2-(3-Methoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12a). Prepared starting from **7a** and 3-methoxy-thiophenol according to general procedure 1 in a yield of 34%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.20 – 7.14 (m, 1H), 7.06-7.01 (m, 2H), 6.97 (m, 2H), 6.88 (dd, *J* = 8.1, 2.2, 1H), 3.80 (s, 3H), 3.61 – 3.51 (m, 4H), 3.00 (s, 4H), 1.50 (s, 9H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 155.30, 144.38, 135.31, 133.83, 131.94, 130.48, 129.75, 127.24, 125.83, 124.94, 120.51, 118.52, 114.28, 80.09, 55.74 (4C), 52.07, 28.87 (3C). HRMS calcd for $C_{22}H_{28}N_2O_3S$+H: 401.1893, found 401.1888.

4-[2-(2-Methoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12c). Prepared starting from **9c** and Boc-piperazine according to general procedure 2 in a yield of 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.17 – 7.12 (m, 1H), 7.04 (dd, *J* = 7.9, 1.0, 1H), 6.99 – 6.91 (m, 3H), 6.82 (dd, *J* = 7.9, 1.3, 1H), 3.85 (s, 3H), 3.61 – 3.55 (m, 4H), 3.15-3.05 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.55, 155.32, 150.58, 135.35, 133.19, 130.10, 129.22, 126.85, 124.76, 121.78, 121.70, 120.35, 111.55, 80.03, 56.33 (2C), 52.01 (2C), 28.88 (3C). HRMS calcd for $C_{22}H_{28}N_2O_3S$+H: 401.1893, found 401.1901.

4-[2-(2-Methyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12d). Prepared starting from **9d** and Boc-piperazine according to general procedure 2 in a yield of 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7, 1H), 7.35 – 7.28 (m, 2H), 7.24 – 7.18 (m, 1H), 7.13 (td, *J* = 7.8, 1.4, 1H), 7.08 – 7.02 (m, 1H), 6.94 – 6.88 (m, 1H), 6.63 (dd, *J* = 7.9, 1.3, 1H), 3.62 – 3.57 (m, 4H), 3.10-3.01 (m, 4H), 2.39 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.33, 149.94, 142.28, 135.63, 134.11, 132.41, 131.13, 129.17, 127.80, 127.31, 126.46, 125.01, 120.45, 80.09, 52.03 (4C), 28.88 (3C), 22.1. HRMS calcd for $C_{22}H_{28}N_2O_2S$+H: 385.1944, found 385.1942.

4-[2-(3,4-Dimethoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12e). Prepared starting from **9e** and Boc-piperazine according to general procedure 2 in a yield of 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 8.2, 2.0, 1H), 7.12 – 7.07 (m, 1H), 7.06-7.02 (m, 2H), 6.95 – 6.91 (m, 2H), 6.69 (dd, *J* = 7.9, 1.1, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.63 (s, 4H), 3.02 (s, 4H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.32, 150.24, 149.99, 148.82, 136.62, 128.98, 126.69, 125.95, 125.08, 123.07, 120.24, 118.47, 112.30, 80.13, 56.42, 56.36, 52.08 (4C), 28.88 (3C). HRMS calcd for $C_{23}H_{30}N_2O_4S$+H: 431.1999, found 431.2001.

4-[2-(3,4-Dichloro-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12f). Prepared starting from **7a** and 3,4-dichloro-thiophenol according to general procedure 1 in a yield of 74%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 2.0, 1H), 7.40 (d, *J* = 8.4, 1H), 7.27 – 7.23 (m, 1H), 7.19 (dd, *J* = 8.3, 2.0, 1H), 7.11 – 7.00 (m, 3H), 3.51 (s, 4H), 2.95 (s, 4H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.32, 149.52, 133.60, 131.54, 129.91, 129.63, 129.40, 129.37, 129.33, 126.66, 123.25, 123.18, 119.11, 78.29, 50.21 (4C), 26.95 (3C). HRMS calcd for $C_{21}H_{24}Cl_2N_2O_2S$+H: 439.1008, found 439.1026.

4-[2-(2,3-Dimethoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12h). Prepared starting from **9h** and Boc-piperazine according to general procedure 2 in a yield of 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.17 (m, 1H), 7.06 – 6.95 (m, 4H), 6.88 (d, *J* = 7.2, 1H), 6.78 (dd, *J* = 7.9, 1.2, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.59 – 3.48 (m, 4H), 3.09 – 2.95 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30, 153.63, 151.57, 149.05, 132.30, 131.35, 129.56, 127.67, 125.15, 124.75, 120.48, 119.41, 112.32, 80.02, 61.07, 56.37, 52.05 (4C), 28.86 (3C). HRMS calcd for $C_{23}H_{30}N_2O_4S$+H: 431.1999, found 431.2005.

4-[2-(2,3-Dimethyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12j). Prepared starting from **9j** and Boc-piperazine according to general procedure 2 in a yield of 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.6, 1H), 7.21 (d, *J* = 7.4, 1H), 7.15-7.02 (m, 1.6, 2H), 7.05 (d, *J* = 7.0, 1H), 6.93 – 6.87 (m, 1H), 6.58 (dd, *J* = 7.9, 1.2, 1H), 3.66 – 3.57 (m, 4H), 3.03 (s, 4H), 2.35 (s, 3H), 2.35 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.35, 149.57, 141.06, 138.40, 134.85, 133.90, 132.18, 131.06, 127.44, 126.75, 126.13, 124.99, 120.34, 80.09, 52.05 (4C), 28.88 (3C), 21.43, 17.51. HRMS calcd for $C_{23}H_{30}N_2O_2S$+H: 399.2101, found 399.2106.

4-[2-(2,4-Dimethoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12k). Prepared starting from **9k** and Boc-piperazine according to general procedure 2 in a yield of 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2, 1H), 7.11 – 7.04 (m, 1H), 7.02 (dd, *J* = 7.8, 1.2, 1H), 6.92 – 6.85 (m, 1H), 6.60 – 6.51 (m, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.63 (s, 4H), 3.04 (s, 4H), 1.51 (s, 9H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 162.33, 161.36, 154.96, 148.72, 138.36, 135.24, 125.92, 125.19, 124.41, 119.67, 110.66, 105.50, 99.34, 79.63, 55.97, 55.50, 51.60 (4C), 28.48 (3C). HRMS calcd for $C_{23}H_{30}N_2O_4S$+H: 431.1999, found 431.1996.

4-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12m). Prepared starting from **7a** and 2,4-dimethyl-thiophenol according to general procedure 1 in a yield of79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8, 1H), 7.17 (s, 1H), 7.11 – 7.01 (m, 3H), 6.92 – 6.85 (m, 1H), 6.54 (dd, *J* = 7.9, 1.1, 1H), 3.63 (s, 4H), 3.03 (s, 4H), 2.36 (s, 3H), 2.35 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.35, 149.41, 148.79, 142.77, 139.65, 136.53, 135.05, 132.10, 128.22, 126.69, 125.91, 124.99, 120.28, 80.07, 52.02 (4C), 28.88 (3C), 21.60, 21.00. HRMS calcd for $C_{23}H_{30}N_2O_2S$+H: 399.2101, found 399.2092.

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12n). Prepared starting from **9n** and Boc-piperazine according to general procedure 2 in a yield of 87%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.3, 1H), 7.16 – 7.09 (m, 2H), 7.05 (d, *J* = 7.9, 1H), 6.94 (t, *J* = 7.6, 1H), 6.85 (dd, *J* = 8.6, 2.7, 1H), 6.62 (t, *J* = 8.5, 1H), 3.86 (s, 3H), 3.61 (s, 4H), 3.02 (s, 4H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.19, 155.32, 149.58, 140.37, 137.98, 134.22, 127.27, 126.55, 125.08, 122.72, 120.52, 116.25, 114.35, 80.08, 56.08 (4C), 52.03, 28.88 (3C). HRMS calcd for $C_{22}H_{27}ClN_2O_3S$+H: 435.1511, found 435.1516.

4-[2-(4-Methyl-2-methoxy-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12o). Prepared starting from **9o** and Boc-piperazine according to general procedure 2 in a yield of 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2, 1H), 7.09 (tt, *J* = 9.5, 4.7, 1H), 7.05 – 6.99 (m, 1H), 6.90 (dt, *J* = 12.3, 2.6, 1H), 6.83-6.79 (m, 2H), 6.69 (dd, *J* = 7.9, 1.3, 1H), 3.81 (s, 3H), 3.60 (s, 4H), 3.04 (s, 4H), 2.41 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.60, 154.94, 149.41, 140.88, 136.13, 134.09, 127.29, 125.71, 124.35, 122.15, 119.76, 116.89, 112.30, 79.61, 55.88, 51.60 (4C), 28.47 (3C), 21.75. HRMS calcd for $C_{23}H_{30}N_2O_3S$+H: 415.2050, found 415.2062.

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (12p). Prepared starting from **9p** and Boc-piperazine according to general procedure 2 in a yield of 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.28-7.23 (m, 1H), 7.21 – 7.16 (m, 1H), 7.09 – 7.02 (m, 2H), 7.00 – 6.94 (m, 1H), 6.81 (dd, *J* = 7.8, 1.3, 1H), 3.57 – 3.52 (m, 4H), 3.05 – 2.95 (m, 4H), 2.37 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.30, 150.66, 140.18, 137.56, 135.07, 132.59, 131.14, 129.67, 129.44, 128.76, 127.44, 125.00, 120.70, 80.08, 51.97 (4C), 28.87 (3C), 21.33. HRMS calcd for $C_{22}H_{27}N_2O_2SCl$+H: 419.1555, found 419.1553.

4-[2-(2,4-Dimethyl-phenylsulfanyl)-6-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (13a). Prepared starting from **10a** and Boc-piperazine according to general procedure 2 in a yield of 23%. ^{1}H NMR (500 MHz, $CDCl_3$; for major rotamer) δ 7.37 (d, *J* = 7.7, 1H), 7.16 (s, 1H), 7.03 (t, *J* = 11.1, 1H), 6.89-6.84 (m, 2H), 6.33 (t, *J* = 4.7, 1H), 3.23 (broad s, 4H), 3.11 (broad s, 4H), 2.38 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$; for major rotamer) δ 155.48, 145.52, 142.70, 140.80, 139.47, 137.35, 136.66, 132.08, 129.44, 128.39, 128.16, 126.64, 123.92, 79.94, 49.77 (4C), 28.92 (3C), 21.60, 20.90, 19.93. HRMS calcd for $C_{24}H_{32}N_2O_2S$+H: 413.2264, found 413.2270.

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (13b). Prepared starting from **10b** and Boc-piperazine according to general procedure 2 in a yield of 35%. ^{1}H NMR (500 MHz, $CDCl_3$; for major rotamer) δ 7.36-7.30 (m, 2H), 7.17-7.13 (m, 2H), 7.06-7.00 (m, 2H), 3.61 (broad s, 4H), 3.02 (broad s, 4H), 2.37 (broad s, 6H), 2.29 (s, 3H), 1.52 (s, 9H). ^{13}C NMR not reported due to rotamers. HRMS calcd for $C_{24}H_{32}N_2O_2S$+H: 413.2264, found 413.2259.

4-[2-(2,4-Dimethyl-phenylsulfanyl)-4-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (13c). Prepared starting from **7c** and 2,4-dimethyl-thiophenol according to general procedure 1 in a yield of 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.03 (d, *J* = 7.7, 2H), 6.97-6.87 (m, 2H), 3.60 (s, 4H), 2.98 (s, 4H), 2.37 (s, 3H), 2.34 (s, 3H), 2.10 (s, 3H), 1.51 (s, 9H). ^{13}C NMR not reported due to rotamers. HRMS calcd for $C_{24}H_{32}N_2O_2S$+H: 413.2264, found 413.2278.

4-[2-(2,4-Dimethyl-phenylsulfanyl)-3-methyl-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (13d). Prepared starting from **7d** and 2,4-dimethyl-thiophenol according to general procedure 1 in a yield of 61%. ^{1}H NMR (500 MHz, $CDCl_3$; for major rotamer) δ 7.33-7.25 (m, 1H), 7.07-70.2 (m, 2H), 6.97-6.92 (m, 1H), 6.74 (d, *J* = 10.4, 1H), 6.45 – 6.36 (m, 1H), 3.39 (broad s, 4H), 2.92 (broad s, 4H), 2.39 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 1.47 (s, 9H). ^{13}C NMR not reported due to rotamers. HRMS calcd for $C_{24}H_{32}N_2O_2S$+H: 413.2264, found 413.2272.

2,4-dimethyl-1-(2-nitro-phenoxy)-benzene (14). Sodium *tert*-butoxide (11.5 g) was added to a 500 mL round-bottom flask followed by NMP (100 mL), 2,4-dimethylphenol (12.2 g), and 2-fluoronitrobenzene (14.1 g). The mixture was stirred at 100 °C for 1h. The crude reaction was cooled to room temperature and diluted with ethyl acetate (250 mL), brine (250 mL), and water (250 mL). The organic layer was washed five times with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a thick brown oil that solidified on standing. The solid was dissolved in hot ethyl acetate and allowed to cool to precipitate 2,4-dimethyl-1-(2-nitro-phenoxy)-benzene (**14**) (21.5 g, 88%) as an off-white/beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.1, 1.6, 1H), 7.43 (ddd, *J* = 8.9, 7.5, 1.7, 1H), 7.13-7.06 (m, 2H), 7.03 (d, *J* = 8.2, 1H), 6.87 (d, *J* = 8.2, 1H), 6.80 (dd, *J* = 8.4, 1.0, 1H), 2.35 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.04, 150.94, 140.54, 135.44, 134.41, 132.83, 130.26, 128.36, 126.17, 122.15, 120.51, 118.20, 21.19, 16.32. HRMS calcd for $C_{14}H_{13}NO_3$: 291.9916, found 291.9911.

2-(2,4-dimethyl-phenoxy)-phenylamine (15). Compound **14** (21.5g) was dissolved in a mixture of ethanol (250 mL) and methylene chloride (100 mL). Platinum oxide (0.55 g, catalyst) was added. The mixture was treated with hydrogen gas (2 bar) on a Parr shaker overnight. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford 2-(2,4-dimethyl-phenoxy)-phenylamine (**15**) as a thick yellow/brown oil (18.5 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.99 – 6.89 (m, 2H), 6.83 (dd, *J* = 7.8, 1.3, 1H), 6.75 (d, *J* = 8.2, 1H), 6.71 – 6.57 (m, 2H), 3.87 (broad s, 2H), 2.32 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.82, 145.12, 137.93, 133.29, 132.40, 129.12, 127.91, 123.84, 119.03, 118.43, 117.75, 116.47, 21.06, 16.44. HRMS calcd for $C_{14}H_{15}NO$+H: 214.1232, found 214.1240.

Experimental for final compounds

1-(5-Methyl-2-phenylsulfanyl-phenyl)-piperazine Hydrochloride (**4a**). Prepared according to general procedure 3 from intermediate **11a** in a yield of 81%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.56 (s, 2H), 7.37 (t, J = 7.3, 2H), 7.34 – 7.25 (m, 2H), 7.25 – 7.07 (m, 1H), 6.99 (s, 1H), 6.86 (s, 2H), 3.06 (broad s, 8H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.18, 138.10, 134.51, 131.59 (2C), 131.12, 129.85 (2C), 129.43, 127.79, 125.93, 121.61, 48.43 (2C), 43.45 (2C), 21.06. HRMS calcd for $C_{17}H_{20}N_2S$+H: 285.1420, found 285.1422. LC/MS (method 1): RT = 0.97 min, UV-purity 98%, ELS-purity 100%.

1-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperazine Hydrochloride (4b). Prepared according to general procedure 3 from intermediate **11b** in a yield of 68%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (s, 2H), 7.37 (d, J = 8.7, 2H), 7.01 (d, J = 8.7, 2H), 6.94 (s, 1H), 6.80 (d, J = 8.0, 1H), 6.54 (d, J = 8.0, 1H), 3.79 (s, 3H), 3.17 (broad s, 8H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.11, 148.25, 136.22, 136.22 (2C), 131.18, 127.54, 125.95, 122.65, 121.20, 115.80 (2C), 55.67, 48.46 (2C), 43.56 (2C), 20.90. HRMS calcd for $C_{17}H_{22}N_2OS$+H: 315.1526, found 315.1537. LC/MS (method 1): RT= 0.97 min, UV-purity 99%, ELS-purity 100%.

1-[2-(4-Chloro-phenylsulfanyl)-5-methyl-phenyl]-piperazine Hydrochloride (4c). Prepared according to general procedure 3 from intermediate **11c** in a yield of 76%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 2H), 7.42 (d, J = 8.5, 2H), 7.28 (s, 2H), 7.01 (s, 1H), 6.96 (d, J = 7.9, 1H), 6.90 (d, J = 8.0, 1H), 3.04 (broad s, 8H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.23, 138.42, 133.72, 131.99 (2C), 131.67, 131.62, 129.25 (2C), 126.11, 125.59, 121.36, 48.00 (2C), 43.01 (2C), 20.63. HRMS calcd for $C_{17}H_{19}ClN_2S$+H: 319.1030, found 319.1038. LC/MS (method 1): RT = 1.09 min, UV-purity 96%, ELS-purity 100%.

1-[2-(4-Fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperazine Hydrochloride (4d). Prepared according to general procedure 3 from intermediate **11d** in a yield of 48%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (s, 2H), 7.39 (dd, J = 8.5, 5.4, 2H), 7.25 (t, J = 8.8, 2H), 6.99 (s, 1H), 6.86 (d, J = 7.9, 1H),

6.77 (d, *J* = 7.9, 1H), 3.24 – 2.95 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.21 (d, *J* = 245.5), 149.59, 137.74, 134.79 (d, *J* = 8.3, 2C), 130.00, 129.48, 128.68, 126.05, 121.60, 117.05 (d, *J* = 22.0, 2C), 48.48 (2C), 43.51 (2C), 21.01. HRMS calcd for $C_{17}H_{19}FN_2S$+H: 303.1326, found 303.1335. LC/MS (method 1): RT = 1.00 min, UV-purity 100%, ELS-purity 100%.

1-(5-Methyl-2-p-tolylsulfanyl-phenyl)-piperazine Hydrochloride (4e). Prepared according to general procedure 3 from intermediate **11e** in a yield of >95%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (s, 2H), 7.28-7.20 (m, 4H), 6.96 (s, 1H), 6.83 (d, *J* = 8.0, 1H), 6.70 (d, *J* = 8.0, 1H), 3.11 (broad s, 8H), 2.31 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.28, 138.01, 137.16, 133.02 (2C), 130.66 (2C), 129.95, 129.42, 129.35, 125.92, 121.38, 48.45 (2C), 43.50 (2C), 21.08, 20.98. HRMS calcd for C18H22N2S+H : 299.1576, found 299.1582. LC/MS (method 1): RT = 1.06 min, UV-purity 100%, ELS-purity 100%.

1-(2-Phenylsulfanyl-phenyl)-piperazine Hydrochloride (4f). Prepared according to general procedure 3 from intermediate **11f** in a yield of 20%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (s, 2H), 7.51 – 7.24 (m, 5H), 7.24 (s, 2H), 7.03 (t, *J* = 7.1, 1H), 6.82 (d, *J* = 7.8, 1H), 3.25-3.18 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.27, 133.20 (2C), 133.08, 132.79, 130.11 (2C), 129.25, 128.60, 127.65, 125.42, 120.89, 48.48 (2C), 43.56 (2C).. HRMS calcd for $C_{16}H_{18}N_2S$+H: 271.1263, found 271.1262. LC/MS (method 1): RT = 0.85 min, UV-purity 98%, ELS-purity 100%. Anal. ($C_{16}H_{18}N_2S$-HBr) C, H, N for a batch of the hydrobromide salt.

1-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (4g). Prepared according to general procedure 3 from intermediate **11g** in a yield of 79%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 2H), 7.86 (d, *J* = 8.7, 2H), 7.60 – 7.51 (m, 2H), 7.48 (d, *J* = 8.7, 2H), 7.43 – 7.34 (m, 1H), 6.98 (d, *J* = 7.9, 1H), 4.23 (s, 3H), 3.60 (broad s, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.37, 148.69, 138.01 (2C), 136.45, 127.40, 127.23, 126.37, 122.57, 121.45, 116.89 (2C), 56.62, 49.44 (2C), 44.60 (2C). HRMS calcd for $C_{17}H_{21}N_2OS$+H: 301.1369, found 301.1373. LC/MS (method 1): RT = 0.87 min, UV-purity 100%, ELS-purity 100%.

1-[2-(4-Chloro-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (4h). Prepared according to general procedure 3 from intermediate **11h** in a yield of 31%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (s, 2H), 7.48 (d, J = 6.4, 2H), 7.42 – 7.34 (m, 2H), 7.27 (t, J = 7.2, 1H), 7.20 (d, J = 7.7, 1H), 7.06 (d, J = 7.0, 1H), 6.92 (d, J = 7.7, 1H), 3.22-3.08 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.73, 134.19 (2C), 133.10, 132.69, 131.70, 130.14, 130.01 (2C), 128.27, 125.58, 121.10, 48.54 (2C), 43.62 (2C). HRMS calcd for $C_{16}H_{17}ClN_2S$+H: 305.0874, found 305.0876. LC/MS (method 1): RT = 0.98 min, UV-purity 97%, ELS-purity 100%. Anal. ($C_{16}H_{17}ClN_2S$-HCl) C, H, N.

1-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (4i). Prepared according to general procedure 3 from intermediate **11i** in a yield of >95%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (s, 2H), 7.50 (dd, J = 8.6, 5.4, 2H), 7.31 (t, J = 8.8, 2H), 7.20 (dt, J = 14.6, 6.8, 2H), 7.07 – 7.00 (m, 1H), 6.73 (d, J = 7.8, 1H), 3.18 (broad s, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.97 (d, J = 245.7 Hz), 149.09, 136.61 (d, J = 8.6 Hz, 2C), 133.83, 128.61, 128.52, 127.68, 125.87, 121.19, 117.62 (d, J=22.2 Hz, 2C), 48.83 (2C), 43.91 (2C). HRMS calcd for $C_{16}H_{17}FN_2S$+H: 289.1169, found 289.1166. LC/MS (method 1): RT = 0.88 min, UV-purity 99%, ELS-purity 100%.

1-(2-p-Tolylsulfanyl-phenyl)-piperazine Hydrochloride (4j). Prepared according to general procedure 3 from impure 4-[2-(4-methyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**11j**) in a yield of 60%. **11j** was prepared from **7a** and 4-methyl-thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 2H), 7.35 (d, J = 8.0, 2H), 7.28 (d, J = 8.0, 2H), 7.22 – 7.13 (m, 2H), 7.05 – 6.96 (m, 1H), 6.69 (d, J = 7.6, 1H), 3.18 (broad s, 8H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.51, 138.82, 134.33 (2C), 134.13, 130.91 (2C), 128.69, 127.86, 126.94, 125.44, 120.69, 48.53 (2C), 43.67 (2C), 21.14. HRMS calcd for $C_{17}H_{20}N_2S$+H: 285.1420, found 285.1422. LC/MS (method 1): RT = 0.96 min, UV-purity 98%, ELS-purity 100%. Anal. ($C_{17}H_{20}N_2S$-HBr) C, H, N for a batch of the hydrobromide salt.

1-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (4k). Prepared according to general procedure 3 from impure 4-[2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**11k**) in a yield of 62% in 2 steps. **11k** was prepared from

7a and 4-(trifluoromethyl)thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 2H), 7.69 (d, *J* = 8.3, 2H), 7.45 – 7.35 (m, 3H), 7.27-7.20 (m, 2H), 7.14 (dd, *J* = 11.0, 4.0, 1H), 3.19 (s, 4H), 3.01 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.89, 141.72, 133.82, 130.28 (2C), 128.67, 127.62 (q, *J* = 32.1 Hz), 126.72 (q, *J* = 3.3Hz, 2C), 125.89, 124.85 (q, *J* = 271.7 Hz), 121.79, 48.83 (2C), 43.80 (2C). HRMS calcd for $C_{17}H_{17}F_3N_2S$+H: 339.1137, found 339.1127. LC/MS (method 1): RT = 1.05 min, UV-purity 100%, ELS-purity 100%.

1-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (4l). Prepared according to general procedure 3 from impure 4-[2-(4-*tert*-butyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**11l**) in a yield of 56% over 2 steps. **11l** was prepared from **7a** and 4-*tert*-butyl-thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 2H), 7.47 (d, *J* = 8.4, 2H), 7.37 (d, *J* = 8.3, 2H), 7.23 – 7.13 (m, 2H), 7.05 – 7.00 (m, 1H), 6.75 (d, *J* = 7.8, 1H), 3.17 (broad s, 8H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.03, 149.14, 134.08 (2C), 129.49, 128.69, 127.54, 127.48 (2C), 125.85, 121.17, 116.81, 48.94 (2C), 44.04 (2C), 35.22, 31.77 (3C). HRMS calcd for $C_{20}H_{26}N_2S$+H: 327.1889, found 327.1887. LC/MS (method 1): RT = 1.19 min, UV-purity 97%, ELS-purity 100%.

1-[2-(3-Methoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5a). Prepared according to general procedure 3 from intermediate **12a** in a yield of 54%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (s, 2H), 7.37-7.31 (m, 1H), 7.26-7.12 (m, 2H), 7.04 (t, *J* = 7.5, 1H), 6.98 – 6.92 (m, 3H), 6.88 (d, *J* = 7.8, 1H), 3.74 (s, 3H), 3.25 – 3.06 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.05, 147.13, 132.14, 130.23, 128.72, 127.27, 125.50, 123.17, 122.82, 118.60, 115.81, 112.07, 53.38, 46.24 (2C), 41.29 (2C). HRMS calcd for $C_{18}H_{22}N_2O$+H: 283.1805, found 283.1818. LC/MS (method 1): RT = 0.91 min, UV-purity 96%, ELS-purity 100%.

1-[2-(3-Methyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5b). Prepared according to general procedure 3 from impure 4-[2-(3-methyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**12b**) in a yield of 57% over 2 steps. **12b** was prepared from **7a** and 3-methyl-thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (s, 2H), 7.32 (t, *J* = 7.6, 1H),

7.24 (s, 1H), 7.22 – 7.11 (m, 4H), 7.02 (t, *J* = 7.0, 1H), 6.80 (d, *J* = 6.9, 1H), 3.25-3.17 (m, 8H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.10, 139.58, 133.86, 133.13, 132.63, 130.52, 129.95, 129.43, 128.96, 127.43, 125.40, 120.80, 48.45 (2C), 43.53 (2C), 21.17. HRMS calcd for $C_{17}H_{20}N_2S$+H: 285.1420, found 285.1416. LC/MS (method 1): RT = 0.95 min, UV-purity 100%, ELS-purity 100%.

1-[2-(2-Methoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5c). Prepared according to general procedure 3 from intermediate **12c** in a yield of 81%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (s, 2H), 7.41 (t, *J* = 7.6, 1H), 7.30 – 7.07 (m, 4H), 7.04 – 6.96 (m, 2H), 6.70 (d, *J* = 7.7, 1H), 3.77 (s, 3H), 3.25-3.08 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.12, 149.24, 134.79, 132.23, 130.66, 128.70, 127.20, 125.21, 121.70, 120.62, 120.32, 112.30, 56.21, 48.37 (2C), 43.57 (2C). HRMS calcd for $C_{17}H_{20}N_2OS$+H: 301.1369, found 301.1368. LC/MS (method 1): RT = 0.86 min, UV-purity 100%, ELS-purity 100%.

1-[2-(2-Methyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5d). Prepared according to general procedure 3 from intermediate **12d** in a yield of 71%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 2H), 7.48 – 7.11 (m, 6H), 7.02 – 6.94 (m, 1H), 6.53 (d, *J* = 7.6, 1H), 3.27 – 3.11 (m, 8H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.68, 141.51, 135.14, 132.77, 131.31, 131.27, 129.58, 127.68, 127.25, 126.96, 125.52, 120.84, 48.52 (2C), 43.84 (2C), 20.50. HRMS calculated for $C_{17}H_{20}N_2S$+H: 285.1420, found 285.1426. LC/MS (method 1): RT = 0.96 min, UV-purity 99%, ELS-purity 100%. Anal. ($C_{17}H_{20}N_2$-HBr) C, H, N.

1-[2-(3,4-Dimethoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5e). Prepared according to general procedure 3 from intermediate **12e** in a yield of 72%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (s, 2H), 7.19 – 6.93 (m, 6H), 6.60 (d, *J* = 7.9, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.18 (broad s, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.19, 149.86, 147.65, 135.59, 128.52, 126.40, 126.24, 125.47, 121.65, 120.48, 118.35, 113.15, 56.05, 55.95, 48.49 (2C), 43.63 (2C). HRMS calcd for $C_{18}H_{22}N_2O_2S$+H: 331.1475, found 331.1481. LC/MS (method 1): RT = 0.81 min, UV-purity 100%, ELS-purity 100%.

1-[2-(3,4-Dichloro-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5f). Prepared according to general procedure 3 from intermediate **12f** in a yield of 26%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 2H), 7.65 (d, J = 8.4, 1H), 7.58 (d, J = 2.0, 1H), 7.34 (dd, J = 10.8, 4.3, 1H), 7.28 (dd, J = 8.4, 2.0, 1H), 7.23 (d, J = 7.9, 1H), 7.16 – 7.03 (m, 2H), 3.30-3.25 (m, 4H), 3.09 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.44, 135.56, 132.54, 132.27, 131.79, 131.59, 131.51, 130.55, 130.09, 129.16, 125.72, 121.33, 48.59 (2C), 43.62 (2C). HRMS calcd for $C_{16}H_{16}Cl_2N_2S$+H: 339.0484, found 339.0492. LC/MS (method 1): RT = 1.09 min, UV-purity 100%, ELS-purity 100%.

1-[2-(3,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5g). Prepared according to general procedure 3 from impure 4-[2-(3,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**12g**) in a yield of 70% over 2 steps. **12g** was prepared from **7a** and 3,4-dimethyl-thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (s, 2H), 7.30 – 7.10 (m, 5H), 7.05 – 6.94 (m, 1H), 6.66 (d, J = 7.8, 1H), 3.18 (broad s, 8H), 2.25 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.57, 143.74, 143.01, 140.66, 139.74, 137.36, 136.54, 133.80, 132.80, 131.96, 130.65, 125.84, 53.75 (2C), 48.87 (2C), 24.85, 24.75. HRMS calcd for $C_{18}H_{22}N_2S$+H: 299.1576, found 299.1586. LC/MS (method 1): RT = 1.03 min, UV-purity 97%, ELS-purity 100%.

1-[2-(2,3-Dimethoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5h). Prepared according to general procedure 3 from intermediate **12h** in a yield of 83%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.31 (s, 2H), 7.30 – 7.19 (m, 1H), 7.16 (d, J = 7.2, 1H), 7.10 – 6.97 (m, 3H), 6.86 (dd, J = 7.8, 1.1, 1H), 6.76 – 6.67 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.26-3.08 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.66, 150.36, 148.64, 131.72, 130.92, 128.28, 128.11, 125.58, 125.49, 124.93, 121.06, 113.63, 60.76, 56.55, 48.77 (2C), 43.94 (2C). HRMS calcd for $C_{18}H_{22}N_2O_2S$+H: 331.1475, found 331.1481. LC/MS (method 1): RT = 0.85 min, UV-purity 100%, ELS-purity 100%.

1-[2-(2,3-Dichloro-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5i). Prepared according to general procedure 3 from impure 4-[2-(2,3-dichloro-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**12i**) in a yield of 6%. **12i** was prepared from **7a** and 2,3-dichloro-thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 2H), 7.59 (dd, J = 8.0, 1.1,

1H), 7.40 (dd, *J* = 10.9, 4.3, 1H), 7.34 – 7.24 (m, 2H), 7.19 – 7.07 (m, 2H), 7.03 – 6.97 (m, 1H), 3.22 – 3.13 (m, 4H), 3.04 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.34, 135.99, 131.80, 130.41, 129.20, 129.01, 128.38, 128.12, 127.25, 124.81, 120.70, 112.10, 47.62 (2C), 42.72 (2C). HRMS calcd for $C_{16}H_{16}Cl_2N_2S$+H: 339.0484, found 339.0486. LC/MS (method 1): RT = 1.03 min, UV-purity 99%, ELS-purity 100%.

1-[2-(2,3-Dimethyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5j). Prepared according to general procedure 3 from intermediate **12j** in a yield of 48%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (s, 2H), 7.29-7.25 (m, 2H), 7.15 (t, *J* = 6.4, 3H), 6.97 (dt, *J* = 8.3, 4.3, 1H), 6.48 (d, *J* = 7.8, 1H), 3.25-3.17 (m, 8H), 2.31 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.42, 140.37, 138.43, 133.54, 133.31, 131.23, 131.10, 127.03, 126.97, 126.63, 125.46, 120.72, 48.48 (2C), 43.61 (2C), 20.92, 17.16. HRMS calcd for $C_{18}H_{22}N_2S$+H: 299.1576, found 299.1582. LC/MS (method 1): RT = 1.05 min, UV-purity 98%, ELS-purity 100%.

1-[2-(2,4-Dimethoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (**5k**). Prepared according to general procedure 3 from intermediate **12k** in a yield of 52%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 2H), 7.36 (d, *J* = 8.4, 1H), 7.14 – 7.03 (m, 2H), 6.98 – 6.89 (m, 1H), 6.71 (d, *J* = 2.3, 1H), 6.62 (dd, *J* = 8.5, 2.4, 1H), 6.44 (d, *J* = 8.1, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.21 (broad s, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.64, 161.41, 147.76, 138.35, 134.73, 125.84, 125.84, 125.18, 120.24, 109.21, 106.76, 99.82, 56.31, 55.86, 48.33 (2C), 43.62 (2C). HRMS calcd for $C_{18}H_{22}N_2O_2S$+H: 331.1475, found 331.1484. LC/MS (method 1): RT = 0.89 min, UV-purity 100%, ELS-purity 100%.

1-[2-(2,4-Dichloro-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5l). Prepared according to general procedure 3 from impure 4-[2-(2,4-dichloro-phenylsulfanyl)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (**12l**) in a yield of 6%. **12l** was prepared from **7a** and 2,4-dichloro-thiophenol according general procedure 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 2H), 8.33 (s, 1H), 8.00 – 7.85 (m, 2H), 7.79 (d, *J* = 7.9, 1H), 7.74 – 7.63 (m, 2H), 7.53 (d, *J* = 7.8, 1H), 3.72 (s, 4H), 3.62 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.69, 135.51, 133.93, 133.22, 132.68, 131.55, 129.90, 129.39, 128.95,

128.69, 125.79, 121.56, 48.52 (2C), 43.66 (2C). HRMS calcd for $C_{16}H_{16}Cl_2N_2S$+H: 339.0484, found 339.0492. LC/MS (method 1): RT = 1.07 min, UV-purity 96%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5m). Prepared according to general procedure 3 from intermediate **12m** in a yield of 78%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 2H), 7.33 (d, J = 7.7, 1H), 7.24 (s, 1H), 7.17 – 7.07 (m, 3H), 6.96 (dd, J = 7.6, 6.0, 1H), 6.41 (d, J = 7.8, 1H), 3.21 (broad s, 8H), 2.31 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.22, 142.04, 139.68, 136.11, 133.74, 132.14, 128.46, 127.19, 126.40, 126.13, 125.46, 120.64, 48.47 (2C), 43.67 (2C), 21.10, 20.47. HRMS calcd for $C_{18}H_{22}N_2S$+H: 299.1576, found 299.1584. LC/MS (method 1): RT = 1.02 min, UV-purity 97%, ELS-purity 100%. Anal. ($C_{18}H_{22}N_2S$-HCl) C, H, N.

1-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5n). Prepared according to general procedure 3 from intermediate **12n** in a yield of 22%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 2H), 7.51 (d, J = 8.6, 1H), 7.29 (d, J = 2.3, 1H), 7.18 (d, J = 3.9, 2H), 7.10 – 6.98 (m, 2H), 6.49 (d, J = 7.8, 1H), 3.84 (s, 3H), 3.20 (broad s, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.33, 148.18, 139.44, 138.31, 133.30, 126.85, 126.48, 125.65, 120.89, 120.84, 116.32, 115.20, 56.26, 48.52 (2C), 43.72 (2C). HRMS calcd for $C_{17}H_{20}ClN_2OS$+H: 336.1065, found 366.1071. LC/MS (method 1): RT = 0.96 min, UV-purity 99%, ELS-purity 100%.

1-[2-(2-Methoxy-4-methyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5o). Prepared according to general procedure 3 from intermediate **12o** in a yield of 75%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 2H), 7.21 (t, J = 11.7, 1H), 7.15 – 7.06 (m, 2H), 7.02 – 6.90 (m, 2H), 6.81 (d, J = 7.7, 1H), 6.55 (d, J = 7.7, 1H), 3.73 (s, 3H), 3.29 – 3.08 (m, 8H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.57, 148.47, 141.44, 136.00, 133.48, 127.19, 126.44, 125.16, 122.44, 120.38, 115.88, 113.26, 56.13, 48.31 (2C), 43.54 (2C), 21.64. HRMS calcd for $C_{18}H_{22}N_2OS$+H: 315.1526, found 315.1537. LC/MS (method 1): RT = 0.96 min, UV-purity 97%, ELS-purity 100%.

1-[2-(2-Chloro-4-methyl-phenylsulfanyl)-phenyl]-piperazine Hydrochloride (5p). Prepared according to general procedure 3 from intermediate **12p** in a yield of 44%. ^{1}H NMR (500 MHz, DMSO-

d_6) δ 9.47 (s, 2H), 7.48 (s, 1H), 7.35-7.25 (m, 4H), 7.04 (t, *J* = 7.5, 1H), 6.68 (d, *J* = 7.8, 1H), 3.24 – 3.07 (m, 8H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.33, 140.95, 136.48, 135.19, 131.47, 131.04, 129.49, 128.72, 128.27, 127.85, 125.60, 121.07, 48.44 (2C), 43.58 (2C), 20.74. HRMS calcd for $C_{17}H_{19}ClN_2S$+H: 319.1030, found 319.1032. LC/MS (method 1): RT = 1.04 min, UV-purity 98%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-6-methyl-phenyl]-piperazine Hydrochloride (6a). Prepared according to general procedure 3 from intermediate **13a** in a yield of 26%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 2H), 7.34 (d, *J* = 7.7, 1H), 7.16 (s, 1H), 7.04 (d, *J* = 7.4, 1H), 6.93 – 6.83 (m, 2H), 6.30 (d, *J* = 6.9, 1H), 3.48 (broad s, 8H), 2.37 (broad s, 6H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.11, 142.77, 140.73, 139.87, 137.30, 136.74, 132.21, 128.48, 128.39, 128.30, 127.37, 123.70, 47.03 (2C), 45.10 (2C), 21.61, 20.90, 19.83. HRMS calcd for $C_{19}H_{25}N_2S$+H: 313.1733, found 313.1735. LC/MS (method 3): RT = 0.71 min, UV-purity 97%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperazine Hydrochloride (6b). Prepared according to general procedure 3 from intermediate **13b** in a yield of 38%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 2H), 7.31 – 7.21 (m, 1H), 7.15 (s, 1H), 7.01 (d, *J* = 7.4, 1H), 6.92 (s, 1H), 6.78 (d, *J* = 7.9, 1H), 6.54 (d, *J* = 7.9, 1H), 3.40 (broad s, 8H), 2.36 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.19, 141.82, 139.31, 136.69, 135.32, 132.11, 130.77, 128.50, 128.17, 127.92, 126.72, 121.76, 49.05 (2C), 44.50 (2C), 21.54, 21.34, 20.94. HRMS calcd for $C_{19}H_{25}N_2S$+H: 313.1733, found 313.1745. LC/MS (method 2): RT = 1.34 min, UV-purity 100%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-4-methyl-phenyl]-piperazine Hydrochloride (6c). Prepared according to general procedure 3 from intermediate **13c** in a yield of 37%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (broad s, 2H), 7.34 (d, *J* = 7.8, 1H), 7.21-7.13 (m, 2H), 7.05 (d, *J* = 7.2, 1H), 6.87 (d, *J* = 8.4, 1H), 6.31 (d, *J* = 6.6, 1H), 3.57-3.31 (m, 8H), 2.42-2.34 (m, 6H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.09, 142.76, 140.71, 139.87, 137.30, 136.72, 136.72, 132.22, 128.50, 128.31, 127.39, 123.74, 47.08 (2C), 45.00 (2C), 21.61, 20.90, 19.83. HRMS calcd for $C_{19}H_{25}N_2S$+H: 313.1733, found 313.1725. LC/MS (method 3): RT = 0.71 min, UV-purity 94%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-3-methyl-phenyl]-piperazine (6d). Prepared according to general procedure 3 from intermediate **13d** in a yield of 5%. The crude hydrochloride was not sufficiently pure, and a small pure sample was obtained after preparative HPLC-purification. Only LC/MS data and HRMS were obtained for this compound: HRMS calcd for $C_{19}H_{25}N_2S$+H: 313.1733, found 313.1739. LC/MS (method 3): RT = 0.71 min, UV-purity 93%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-4-methyl-piperazine Hydrochloride (6e). Prepared according to general procedure 2 from intermediate **10c** and methyl-piperazine in a yield of 15%. The free base was dissolved in methanol and treated with 2M HCl in Et_2O to precipitate the hydrochloride salt. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.6, 1H), 7.17 (s, 1H), 7.12 – 7.01 (m, 3H), 6.90 – 6.82 (m, 1H), 6.51 (d, *J* = 8.3, 1H), 3.13 (s, 4H), 2.66 (s, 4H), 2.39 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.58, 142.90, 139.60, 136.67, 135.01, 132.06, 128.40, 128.18, 126.48, 125.82, 124.72, 120.25, 55.93 (2C), 51.98 (2C), 46.56, 21.59, 21.00. HRMS calcd for $C_{19}H_{24}N_2S$+H: 313.1733, found 313.1734. LC/MS (method 1): RT = 1.09 min, UV-purity 100%, ELS-purity 100%.

1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-[1,4]diazepane Hydrochloride (6f). Prepared according to general procedure 3 from impure 4-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (**13f**) in a yield of 18% over 2 steps. **13f** was obtained from **10c** and [1,4]diazepane-1-carboxylic acid *tert*-butyl ester according to general procedure 2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 2H), 7.32-7.27 (m, 1H), 7.24-7.17 (m, 2H), 7-12-7.03 (m, 2H), 6.93 (t, *J* = 7.4, 1H), 6.41 (d, *J* = 7.7, 1H), 3.40 – 3.11 (m, 8H), 2.32 (s, 3H), 2.23 (s, 3H), 2.14-2.04 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.63, 141.76, 139.45, 135.83, 134.18, 132.12, 128.40, 127.74, 126.43, 126.31, 125.27, 122.83, 53.80, 51.36, 47.04, 44.15, 25.69, 21.09, 20.42. HRMS calcd for $C_{19}H_{25}N_2S$+H: 313.1733, found 313.1736. LC/MS (method 1): RT = 1.10 min, UV-purity 100%, ELS-purity 98%.

1-[2-(2,4-Dimethyl-phenoxy)-phenyl]-piperazine Hydrochloride (6g). Compound **15** (2.13 g) and *bis*-(2-bromoethyl)amine hydrobromide[6] (3.89 g) were suspended in chlorobenzene (50 mL). The mixture was boiled under reflux for 4h. The solvent was evaporated off, and the residual oil was partitioned between water (100 mL) and ethyl acetate (50 mL). The aqueous layer was basified and

extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford an oil. This material was purified by column flash chromatography (eluent: EtOAc/MeOH 9:1 → EtOAc/MeOH/Et_3N 9:1:1) to afford the crude title compound. This material was partitioned between water/brine and methylene chloride. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the free base. This material was dissolved in ethyl acetate and treated with 2M HCl in Et_2O to precipitate the title compound (0.83 g, 26%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 2H), 7.13 – 7.08 (m, 2H), 7.06 (t, *J* = 7.4, 1H), 7.00-6.92 (m, 2H), 6.69-6.60 (m, 2H), 3.31 (s, 4H), 3.08 (s, 4H), 2.24 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.17, 147.60, 139.38, 130.82, 130.23, 126.23, 126.01, 122.14, 122.01, 118.10, 116.47, 116.07, 45.41 (2C), 41.24 (2C), 18.66, 14.25. HRMS calcd for $C_{18}H_{22}N_2O$+H: 283.1805, found 283.1818. LC/MS (method 1): RT = 0.98 min, UV-purity 100%, ELS-purity 98%.

Compound overview including combustion analysis and high-resolution MS data

The characterization data for all compounds is summarized on the next three pages.

	Formula	High-resolution MS Calcd	Found	HPLC >95% pure	CHN calcd C	H	N	CHN found C	H	N	NMR ^{1}H	^{13}C
4a	$C_{17}H_{20}N_2S$+H	285.1420	285.1422	✓							✓	✓
4b	$C_{18}H_{22}N_2OS$+H	315.1526	315.1537	✓							✓	✓
4c	$C_{17}H_{19}ClN_2S$+H	319.1030	319.1038	✓							✓	✓
4d	$C_{17}H_{19}FN_2S$+H	303.1326	303.1335	✓							✓	✓
4e	$C_{18}H_{22}N_2S$+H	299.1576	299.1582	✓							✓	✓
4f	$C_{16}H_{18}N_2S$-HBr			✓	54.70	5.45	7.97	54.69	5.53	7.87		
	$C_{16}H_{18}N_2S$+H	271.1263	271.1262								✓	✓
4g	$C_{17}H_{21}N_2OS$+H	301.1369	301.1373	✓							✓	✓
4h	$C_{16}H_{17}ClN_2S$-HCl			✓	56.31	5.32	8.21	56.26	5.42	8.04	✓	✓
	$C_{16}H_{17}ClN_2S$+H	305.0874	305.0876								✓	✓
4i	$C_{16}H_{17}FN_2S$+H	289.1169	289.1166	✓							✓	✓
4j	$C_{17}H_{20}N_2S$-HBr			✓	55.89	5.75	7.67	55.71	5.94	7.55		
	$C_{17}H_{20}N_2S$+H	285.1420	285.1422	✓							✓	✓
4k	$C_{17}H_{17}F_3N_2S$+H	339.1137	339.1127	✓							✓	✓
4l	$C_{20}H_{26}N_2S$+H	327.1889	327.1887	✓							✓	✓
5a	$C_{18}H_{22}N_2O$+H	283.1805	283.1818	✓							✓	✓
5b	$C_{17}H_{20}N_2S$+H	285.1420	285.1416	✓							✓	✓
5c	$C_{17}H_{20}N_2OS$+H	301.1369	301.1368	✓							✓	✓
5d	$C_{17}H_{20}N_2$-HBr			✓	55.89	5.79	7.67	56.10	5.96	7.67		
	$C_{17}H_{20}N_2S$+H	285.1420	285.1426	✓							✓	✓
5e	$C_{18}H_{22}N_2O_2S$+H	331.1475	331.1481	✓							✓	✓
5f	$C_{16}H_{16}Cl_2N_2S$+H	339.0484	339.0492	✓							✓	✓
5g	$C_{18}H_{22}N_2S$+H	299.1576	299.1586	✓							✓	✓
5h	$C_{18}H_{22}N_2O_2S$+H	331.1475	331.1481	✓							✓	✓
5i	$C_{16}H_{16}Cl_2N_2S$+H	339.0484	339.0486	✓							✓	✓
5j	$C_{18}H_{22}N_2S$+H	299.1576	299.1582	✓							✓	✓
5k	$C_{18}H_{22}N_2O_2S$+H	331.1475	331.1484	✓							✓	✓
5l	$C_{16}H_{16}Cl_2N_2S$+H	339.0484	339.0492	✓							✓	✓
5m	$C_{18}H_{22}N_2S$-HCl	299.1576	299.1584	✓	63.70	6.89	8.27	63.51	6.96	8.16	✓	✓
5n	$C_{17}H_{20}ClN_2OS$+H	336.1065	366.1071	✓							✓	✓
5o	$C_{18}H_{22}N_2OS$+H	315.1526	315.1537	✓							✓	✓
5p	$C_{17}H_{19}ClN_2S$+H	319.1030	319.1032	✓							✓	✓

	Formula	High-resolution MS Calcd	Found	HPLC >95% pure	CHN calcd C	H	N	CHN found C	H	N	NMR ^{1}H	^{13}C
6a	$C_{19}H_{25}N_2S$+H	313.1733	313.1735	✓							✓	✓
6b	$C_{19}H_{25}N_2S$+H	313.1733	313.1745	✓							✓	✓
6c	$C_{19}H_{25}N_2S$+H	313.1733	313.1725	94% pure							✓	✓
6d	$C_{19}H_{25}N_2S$+H	313.1733	313.1739	93% pure							✓	✓
6e	$C_{19}H_{25}N_2S$+H	313.1733	313.1734	✓							✓	✓
6f	$C_{19}H_{25}N_2S$+H	313.1733	313.1736	✓							✓	✓
6g	$C_{18}H_{22}N_2O$+H	283.1805	283.1818	✓							✓	✓
7a	$C_{15}H_{22}BrN_2O_2$	341.0859	341.0855								✓	✓
7c	$C_{16}H_{24}BrN_2O_2$	355.1022	355.1028								✓	✓
7d	$C_{16}H_{24}BrN_2O_2$	355.1022	355.1017								✓	✓
8a	$C_{13}H_{11}BrS$	277.9759	277.9754								✓	✓
8b	$C_{14}H_{13}BrO$	307.9865	307.9861								✓	✓
8c	$C_{13}H_{10}BrClS$	311.9370	311.9357								✓	✓
8d	$C_{13}H_{10}BrF$	295.9665	295.9665								✓	✓
8e	$C_{14}H_{13}BrS$	291.9916	291.9912								✓	✓
9c	$C_{13}H_{11}BrOS$	293.9708	293.9702								✓	✓
9d	$C_{13}H_{11}BrS$	277.9759	277.9760								✓	✓
9e	$C_{14}H_{13}BrO_2S$	323.9814	323.9808								✓	✓
9h	$C_{14}H_{13}BrO_2S$	323.9814	323.9824								✓	✓
9j	$C_{14}H_{13}BrS$	291.9916	291.9909								✓	✓
9k	$C_{14}H_{13}BrO_2S$	323.9814	323.9808								✓	✓
9n	$C_{13}H_{10}BrClOS$	327.9319	327.9314								✓	✓
9o	$C_{14}H_{13}BrOS$	307.9865	307.9861								✓	✓
9p	$C_{13}H_{10}BrClS$	311.9370	311.9375								✓	✓
10a	$C_{15}H_{15}BrS$	306.0078	306.0085								✓	✓
10b	$C_{15}H_{15}BrS$	306.0078	306.0077								✓	✓
10c	$C_{14}H_{13}BrS$	291.9916	291.9911								✓	✓
11a	$C_{22}H_{28}N_2O_2S$+H	385.1944	385.1957								✓	✓
11b	$C_{23}H_{30}N_2O_3S$+H	415.2050	415.2066								✓	✓
11c	$C_{22}H_{27}ClN_2O_2S$	419.1555	419.1562								✓	✓
11d	$C_{22}H_{27}FN_2O_2S$	403.1850	403.1853								✓	✓
11e	$C_{23}H_{30}N_2O_2S$	399.2101	399.2102								✓	✓
11f	$C_{22}H_{28}N_2O_2S$	371.1788	371.1798								✓	✓

	Formula	High-resolution MS Calcd	Found	HPLC >95% pure	CHN calcd C	H	N	CHN found C	H	N	NMR ^{1}H	^{13}C
11g	$C_{23}H_{31}N_2O_3S$	401.1893	401.1910								✓	✓
11h	$C_{22}H_{27}ClN_2O_2S$	405.1398	405.1407								✓	✓
11i	$C_{22}H_{27}FN_2O_2S$	389.1694	389.1710								✓	✓
12a	$C_{22}H_{28}N_2O_3S$+H	401.1893	401.1888								✓	✓
12c	$C_{22}H_{28}N_2O_3S$+H	401.1893	401.1901								✓	✓
12d	$C_{22}H_{28}N_2O_2S$+H	385.1944	385.1942								✓	✓
12e	$C_{23}H_{30}N_2O_4S$+H	431.1999	431.2001								✓	✓
12f	$C_{21}H_{24}Cl_2N_2O_2S$+H	439.1008	439.1026								✓	✓
12h	$C_{21}H_{24}Cl_2N_2O_2S$+H	431.1999	431.2005								✓	✓
12j	$C_{23}H_{30}N_2O_2S$+H	399.2101	399.2106								✓	✓
12k	$C_{23}H_{30}N_2O_4S$+H	431.1999	431.1996								✓	✓
12m	$C_{23}H_{30}N_2O_2S$+H	399.2101	399.2092								✓	✓
12n	$C_{22}H_{27}ClN_2O_3S$+H	435.1511	435.1516								✓	✓
12o	$C_{23}H_{30}N_2O_3S$+H	415.2050	415.2062								✓	✓
12p	$C_{22}H_{27}N_2O_2SCl$+H	419.1555	419.1553								✓	✓
13a	$C_{24}H_{32}N_2O_2S$+H	413.2264	413.2270								✓	✓
13b	$C_{24}H_{32}N_2O_2S$+H	413.2264	413.2259								✓	
13c	$C_{24}H_{32}N_2O_2S$+H	413.2264	413.2278								✓	
13d	$C_{24}H_{32}N_2O_2S$+H	413.2264	413.2272								✓	
14	$C_{14}H_{13}NO_3$	291.9916	291.9911								✓	✓
15	$C_{14}H_{15}NO$+H	214.1232	214.1240								✓	✓

References

1. Hall, M. D.; el, M. S.; Emerit, M. B.; Pichat, L.; Hamon, M.; Gozlan, H. [3H]8-hydroxy-2-(di-n-propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of the rat brain. *J Neurochem* **1985,** *44*, 1685-1696.

2. Schopfer, U.; Schlapbach, A. A general palladium-catalysed synthesis of aromatic and heteroaromatic thioethers. *Tetrahedron* **2001,** *57*, 3069-3073.

3. Wolfe, J. P.; Buchwald, S. L. Scope and limitations of the Pd/BINAP-catalyzed amination of aryl bromides. *J. Org. Chem.* **2000,** *65*, 1144-1157.

4. Larsen, S. B.; Bang-Andersen, B.; Johansen, T. N.; Jørgensen, M. Palladium-catalyzed monoamination of dihalogenated benzenes. *Tetrahedron* **2008,** *64*, 2938-2950.

5. Tunney, S. E.; Stille, J. K. Palladium-catalyzed coupling of aryl halides with (trimethylstannyl)diphenylphosphine and (trimethylsilyl)diphenylphosphine. *J. Org. Chem.* **1987,** *52*, 748-753.

6. Pettit, G. R.; Chamberland, M. R.; Blonda, D. S.; Vickers, M. A. Antineoplastic agents: XI. N-bis(2-bromoethyl)amines. *Can. J. Chem.* **1964,** *42*, 1699-1706.