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Arene- and quinoline-sulfonamides as novel 5-HT$_7$ receptor ligands

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ABSTRACT

Novel arene- and quinolinesulfonamides were synthesized using different solutions and a solid-support methodology, and were evaluated for their affinity for 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$, and 5-HT$_7$ receptors. Compound **54** (*N*-Ethyl-N-[4-(1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-2-yl)butyl]-8-quinolinesulfonamide) was identified as potent 5-HT$_7$ antagonist (K_i = 13 nM, K_B = 140 nM) with good selectivity over 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$ receptors. In the FST in mice, it reduced immobility in a manner similar to the selective 5-HT$_7$ antagonist SB-269970.

1. Introduction

Of the 14 serotonin receptors (5-HTR), a recently identified 5-HT$_7$ subtype has focused considerable attention. Since its cloning in 1993 by several independent laboratories a number of information has been gathered. A physiological role of 5-HT$_7$ receptor in CNS has been established in the control of circadian rhythms, thermoregulation, learning and memory and neuroendocrine regulation; suggested functions in the periphery are related to the control of smooth muscles cells.[1] These data followed by identification of pharmacological tools allowed to outline therapeutical potential of 5-HT$_7$ receptor in depression, anxiety, epilepsy, pain, migraine, and cognition.[2,3] The obtained data were further supported by the discovery that several psychotropic drugs displayed a relatively high affinity and antagonistic activity at 5-HT$_7$R.[4] Moreover, it was suggested that this mechanism may, at least in part, account for their therapeutic antidepressant properties observed in the clinic.[5–7]

Among several classes of 5-HT$_7$R ligands a pre-eminent position is held by aromatic sulfonamides and sulfones connected to aryl- or alkyl-amine fragments via an aliphatic spacer of different length (Fig. 1).[8–11]

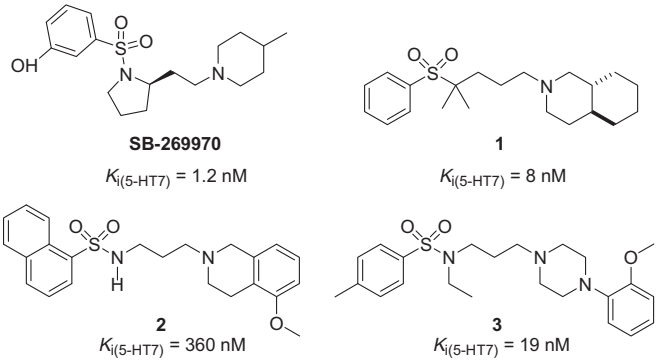

Figure 1. Representatives of the sulfone/sulfonamide class of 5-HT$_7$ receptor ligands.

Herein, we report on the design and synthesis of a new series of arene- and their bioisosteric quinoline-sulfonamides as 5-HT$_7$ receptor ligands, followed by their pharmacological evaluation in an animal model of depression.

2. Chemistry

As a first step we designed and synthesized a series of THIQ derivatives of N-unsubstituted (**11**–**17**) and *N*-(ω-aminoalkyl)substituted (**18**–**21**) arenesulfonamides. The synthesis of both

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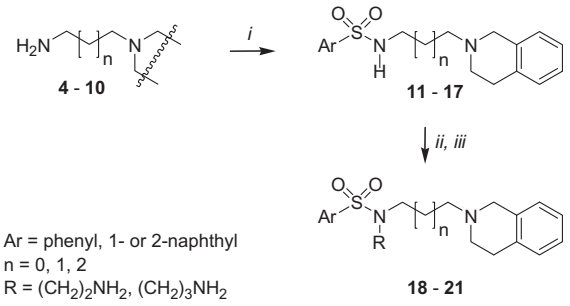


Scheme 1. The synthesis of *N*-substituted sulfonamide derivatives: Reagents and conditions: (i) $ArSO_2Cl$, H_2O/OH^-, 60 °C; (ii) *N*-(2-bromoethyl)- or *N*-(3-chloropropyl)phthalimide, toluene, $NaOH/K_2CO_3$, TBAB, reflux; (iii) N_2H_4, EtOH, H^+.

those series started with coupling of a primary amine with arenesulfonyl chloride (Scheme 1).

Introduction of an *N*-(ω-aminoalkyl) fragment to the sulfonamide nitrogen atom was achieved by alkylation with an appropriate phthalimide derivative and subsequent deprotection with hydrazine to yield compounds **18**–**21**.

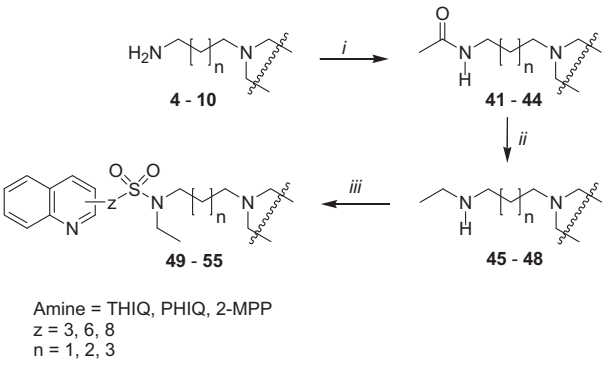
For the synthesis of a next series of compounds (**28**–**40**) we employed the previously elaborated method using a BAL linker, and TBDPSi-protected aminoalcohols as synthons for diversification of the polymethylene linker length.[12] Quinolinesulfonyl chlorides were synthesized according to the previously reported method.[13] Solid-phase work-flow started by attaching the TBDPSi-protected 3-aminopropan-1-ol and 4-aminobutan-1-ol to resin **22** (Scheme 2). Subsequent sulfonylation of the resin bound product **23**, followed by silyl protection removal with TBAF and mesylation, yielded the key intermediate **26** for the introduction of secondary amines on the resin. Then, it was readily converted into the amine-bound product **27**. Final sulfonamides **28**–**40** were cleaved from the resin under acidic treatment.

The synthetic procedures for the last series of N-alkylated quinoline-sulfonamides proceeded according to Scheme 3. The acetylation of primary amines and the reduction of acetamide derivatives yielded their respective secondary amines which were further sulfonylated with quinolinesulfonyl chloride to give the final products **49**–**55**.

3. Pharmacology

3.1. In vitro biological evaluation

Radioligand binding assays were employed for determination of the affinity and selectivity profile of the synthesized compounds



Scheme 3. The synthesis of N-substituted quinolinesulfonamide derivatives: Reagents and conditions: (i) Ac_2O, $NaHCO_3$, RT, 6 h; (ii) $LiAlH_4$, anh. THF, reflux, 12 h, 94%; (iii) quinolinesulfonyl chloride, Et_3N, DCM, 5 h.

for native 5-HT_{1A}, 5-HT_{2A} and adrenergic α_1 receptors as well as for cloned human 5-HT_6 and 5-HT_7 receptors. This was accomplished by displacement of [^{3}H]-8-OH-DPAT from rat hippocampus for 5-HT_{1A}R, and [^{3}H]-ketanserin and [^{3}H]-prazosin from rat cortex for 5-HT_{2A}R and α_1R, respectively.[14,15] Displacement of [^{3}H]-LSD and [^{3}H]-5-CT from the cloned human receptor stably expressed in HEK293 cells was used in 5-HT_6R and 5-HT_7R binding experiments.[16]

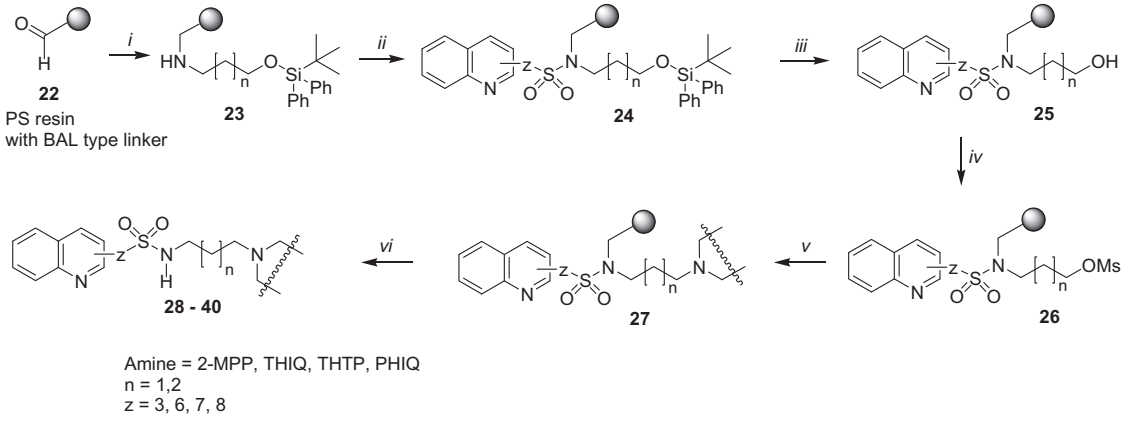
The functional activity of the selected compounds **54** and **55** at 5-HT_7 receptors was determined at CEREP (Le Bois l'Eveque, 86600 Celle L'Evescault, France) according to previously published methods.[17]

3.2. Pharmacological experiments

The potential antidepressant-like activity of compounds **54** and **55** was evaluated in the mouse forced swim test (FST) and their activity was compared with that of SB-269970.[18] The effect of the tested compounds on the spontaneous locomotor activity of mice was also investigated.

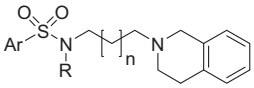
4. Results and discussion

Following the finding that compounds containing 1,2,3,4-tetrahydroisoquinoline (THIQ) and 2-methoxyphenylpiperazine (2-MPP) may be a source of 5-HT_7 receptor ligands,[19–23] we first evaluated a series of THIQ derivatives of N-unsubstituted (**11**–**17**) and *N*-(ω-aminoalkyl)substituted (**18**–**21**) arenesulfonamides for 5-HT_7 and



Scheme 2. Solid-phase synthesis for sulfonamide derivatives **28**–**40**: Reagents and conditions: (i) $TBDPSiO(CH_2)_3NH_2$ or $TBDPSiO(CH_2)_4NH_2$, $NaBH_3CN$, 1%AcOH/DMF, 60 °C, 15 h; (ii) Quinolinesulfonyl chloride, TEA, DCM, RT, 2 × 2 h; (iii) 1 M TBAF/THF, 12 h; (iv) $MeSO_2Cl$, Py, RT, 1 h; (v) secondary amine, anh. DMSO, 50 °C, 5 h; (vi) TFA/DCM, (80/20, v/v), 2 h.

Table 1
Binding affinities of the arene-sulfonamides **11**–**21** for 5-HT$_7$ receptors



11 - 21

Compd	*n*	Ar	R	K_i ± SEM (nM)
				5-HT$_7$
11	0	2-Naphthyl	H	78 ± 8
12	0	Phenyl	H	773 ± 94
13	1	2-Naphthyl	H	80 ± 6
14	1	Phenyl	H	270 ± 19
15	2	2-Naphthyl	H	64 ± 5
16	2	Phenyl	H	94 ± 11
17	2	1-Naphthyl	H	296 ± 31
18	0	Phenyl	$(CH_2)_3NH_2$	3010 ± 570
19	1	Phenyl	$(CH_2)_2NH_2$	267 ± 16
20	1	Phenyl	$(CH_2)_3NH_2$	335 ± 28
21	2	Phenyl	$(CH_2)_3NH_2$	235 ± 14

5-HT$_{1A}$ receptors. Introduction of the aminoalkyl fragment was suggested by preliminary docking to our 5-HT$_7$R homology models,[24] where potential interactions with Arg7.36 and/or Glu7.35 were observed. It was found, that 2-naphthalenesulfonamides **11**, **13** and **15** demonstrated almost the same affinity for the 5-HT$_7$ receptor, regardless of the spacer length. Their binding constant values ranged between 64 and 80 nM (Table 1). Interestingly, 2-naphthyl derivatives (**11**, **13**, **15**) were always more active than their benzenesulfonamide analogs (**12**, **14**, **16**). Among the benzenesulfonamides studied, compound **16** with a tetramethylene spacer had the highest 5-HT$_7$R affinity (K_i = 94 nM), whereas its trimethylene (**14**) and ethylene (**12**) analogs exhibited significantly lower affinities (K_i = 270 and 773 nM, respectively). The introduction of aminoalkyl substituents into the sulfonamide moiety of compounds **12**, **14** and **16** was not a profitable structure modification; their N-substituted analogs **18**–**21** showed a weaker 5-HT$_7$ receptor affinity (K_i = 235–3010 nM).

In view of literature data bioisosteric replacement of naphthyl ring with quinolinyl moiety may be beneficial for creation of additional hydrogen bonds in the receptor binding site being advantageous for ligand-receptor interaction[25,26] or may improve compound aqueous solubility facilitating compound bioavailability.[27,28]

As the following step, only three and four methylene linkers were used for a series of quinolinesulfonamides; besides THIQ, compounds with its bioisostere 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (THTP), the saturated analog perhydroisoquinoline (PHIQ), and 2-MPP were prepared.

In general, the new quinolinesulfonamides **28**–**40** displayed high-to-low binding affinities for 5-HT$_7$ (K_i = 55–1255 nM) and 5-HT$_{1A}$ (K_i = 3.7–4310 nM) receptors and practically did not bind to 5-HT$_6$ ones (Table 2). Of the tested compounds, only **29** and **33** exhibited affinity lower than 1000 nM for 5-HT$_{2A}$R. As regards amine fragments, the sulfonamides containing 2-MPP (**28**–**32**) showed the highest affinity for 5-HT$_7$ receptors (K_i <156 nM), being simultaneously devoid of selectivity for 5-HT$_{1A}$R (K_i <53 nM). The replacement of 2-MPP with THIQ and THTP decreased the affinity for both those subtypes (K_i = 88–506 nM), while the introduction of the fully saturated cycloaliphatic amine moiety—PHIQ (compounds **38**–**40**), dramatically shifted 5-HT$_{1A}$R and 5-HT$_7$R affinity to a μ-molar range.

Replacement of the 2-naphthyl ring of the THIQ derivative **15** with its β-position quinolinyl analogs, 3-quinolinyl or 6-quinolinyl, yielded compounds **33** and **34**, which were 3.5 times less potent 5-HT$_7$ ligands. Interestingly, the change of the 1-naphthyl ring of compound **17** to 8-quinolinyl (its α-position counterpart) gave compound **35** which displayed a threefold higher affinity for 5-HT$_7$ receptors.

2-Naphthalenesulfonamides containing 2-MPP fragments were previously described in the literature as multi-receptor ligands with high affinity for 5-HT$_{1A}$ receptors.[27] In comparison with these data, replacement of the 2-naphthyl ring with nitrogen-containing aromatic heterocycles differently influenced the 5-HT$_{1A}$ receptor affinity of the tested quinolinesulfonamides **28**–**32**; the rank order of 5-HT$_{1A}$ binding was 3-quinolinyl >6-quinolinyl >8-quinolinyl. It seemed that the nitrogen atom in the distal aromatic ring was unfavorable for an interaction with 5-HT$_{1A}$ receptors. The impact of the nitrogen position on the affinity for 5-HT$_7$ receptors was different: 8-quinolinyl >3-quinolinyl >6-quinolinyl. It was also observed that within the 2-MPP series, sulfonamides with four methylene linker displayed a decreased affinity for 5-HT$_{1A}$ receptors compared to their three methylene homologs (**30** vs **29**, and **32** vs **31**); on the other hand, an increased linker length was beneficial for 5-HT$_7$ receptor binding.

It was recently reported that substitution of the sulfonamide nitrogen mimicked the steric and lipophilic effects of the pyrrolidine fragment of the SB-series (e.g., SB-269970), being essential for 5-HT$_7$ selectivity.[10] N-alkylation of the sulfonamide may also improve the bioavailability, while suppression of the hydrophilic bond seems to be beneficial to brain permeation. Thus, as a successive step, we designed a series of the selected N-alkylated sulfonamide derivatives **49**–**55**. We chose 2-MPP and PHIQ as secondary amines to be bridged via tetramethylene and pentamethylene spacers with the quinolinesulfonamide fragment, since a longer spacer might also increase selectivity.[29]

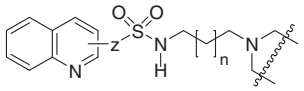
As expected, in the case of 2-MPP derivatives introduction of *N*-ethyl sulfonamide fragment increased affinity for 5-HT$_7$ receptors from two to fivefold (e.g., **29** vs **50**; **30** vs **51**, Tables 2 and 3). However, this modification did not increase selectivity for 5-HT$_7$ receptors. A kind of quinolinyl moiety did not influence 5-HT$_7$ receptor affinity of the N-substituted sulfonamides containing 2-MPP. With regard to the influence of the kind of quinolinyl moiety on 5-HT$_{1A}$ receptor affinity, it was found that within N-alkylated sulfonamides the rank order remained similar to that observed for unsubstituted derivatives **28**–**32** (3-quinolinyl >6-quinolinyl >8-quinolinyl). In consequence, *N*-ethyl sulfonamide derivatives containing 2-MPP were classified as dual 5-HT$_{1A}$/5-HT$_7$ ligands.

N-Alkylation of the PHIQ containing sulfonamide **40** resulted in **54**, which displayed high affinity for 5-HT$_7$ receptors, and good selectivity for 5-HT$_{1A}$ ones (S ratio—84). Unfortunately, elongation of the spacer up to pentamethylene unit (**55**) slightly decreased 5-HT$_7$R affinity and the 5-HT$_7$/5-HT$_{1A}$ selectivity ratio. These two interesting compounds (**54** and **55**) exhibited high 5-HT$_7$ receptor affinity and good selectivity over the 5-HT$_{1A}$ one, were also evaluated for α_1 receptors, since affinity of antidepressant drugs for these sites is considered as undesirable action, for example, cardiovascular effects (Table 3).[30]

At the successive stage, effects of the selected compounds **54** and **55** on intracellular cAMP levels were studied in CHO cells which stably expressed the human 5-HT$_7$ receptor.[17] The obtained results indicated that the compounds tested behaved like antagonists at the h5-HT$_7$R with K_B = 140 nM and K_B = 1.3 μM for **54** and **55**, respectively.

Those compounds were further pharmacologically evaluated in a mouse model of depression. Compound **54**, administered in a dose of 10 mg/kg, significantly reduced—by 22%—the immobility time of mice, whereas its analog **55**, given in doses of up to 20 mg/kg produced no effect in the FST in mice (Table 4). Compound **54** showed antidepressant-like activity similar to that of the selective 5-HT$_7$ receptor antagonist SB-269970, which exerted its effect characteristic of antidepressants in one medium dose (10 mg/kg), decreasing mouse immobility time by 33%. Those effects seemed to be specific, since **54** and SB-269970, used in a dose evoking antidepressant-like activity, did not change the locomotor

Table 2
Binding affinities of the quinolinesulfonamides **28**–**40** for 5-HT receptors

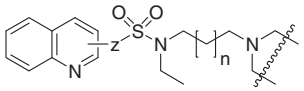


28 - 40

Compd	Ar	*n*	Amine[a]	K_i ± SEM (nM)				*S*[b]
				5-HT_{1A}	5-HT_6	5-HT_{2A}	5-HT_7	
28	3-Quinolinyl	2	2-MPP	3.7 ± 0.6	NT[c]	NT	79 ± 8	0.05
29	6-Quinolinyl	1	2-MPP	18 ± 2	825 ± 74	2842 ± 140	156 ± 26	0.1
30	6-Quinolinyl	2	2-MPP	40 ± 5	NT	NT	132 ± 18	0.3
31	8-Quinolinyl	1	2-MPP	37 ± 3	2159 ± 254	1640 ± 94	90 ± 7	0.4
32	8-Quinolinyl	2	2-MPP	53 ± 7	NT	NT	55 ± 4	0.9
33	3-Quinolinyl	2	THIQ	305 ± 18	590 ± 62	8635 ± 1245	228 ± 12	1.3
34	6-Quinolinyl	2	THIQ	233 ± 18	1518 ± 130	8246 ± 1678	224 ± 26	1
35	8-Quinolinyl	2	THIQ	271 ± 32	41858718	1462 ± 126	88 ± 7	3.0
36	3-Quinolinyl	2	THTP	986 ± 118	1082 ± 190	17390 ± 1620	506829	1.9
37	7-Quinolinyl	2	THTP	483 ± 47	2652 ± 320	17480 ± 3700	334 ± 48	1.4
38	3-Quinolinyl	2	PHIQ	1449 ± 208	NT	NT	995 ± 70	1.5
39	6-Quinolinyl	1	PHIQ	4310 ± 945	NT	NT	1420 ± 242	3.0
40	8-Quinolinyl	2	PHIQ	3565 ± 720	NT	NT	1255 ± 189	2.8

[a] 2-MPP—2-methoxyphenylpiperazine; THIQ—1,2,3,4-tetrahydroisoquinoline; THTP—4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine; PHIQ—perhydroisoquinoline.
[b] 5-HT_{1A}/5-HT_7 selectivity.
[c] NT = not tested.

Table 3
Receptor binding profile of the *N*-ethyl sulfonamide derivatives



49 - 55

Compd	Ar	*n*	Amine[a]	K_i ± SEM (nM)					*S*[b]
				5-HT_{1A}	5-HT_{2A}	5-HT_6	5-HT_7	α_1	
49	3-Quinolinyl	2	2-MPP	9.3 ± 1	NT[c]	NT	38 ± 3	NT	0.2
50	6-Quinolinyl	1	2-MPP	25 ± 2	1321 ± 98	1920 ± 186	29 ± 3	NT	0.9
51	6-Quinolinyl	2	2-MPP	21 ± 1	NT	NT	41 ± 6	NT	0.5
52	8-Quinolinyl	2	2-MPP	30 ± 4	NT	NT	37 ± 4	NT	0.8
53	3-Quinolinyl	2	PHIQ	325 ± 57	5093 ± 980	14460 ± 2950	187 ± 23	NT	1.7
54	8-Quinolinyl	2	PHIQ	1099 ± 113	6281 ± 1394	1950 ± 215	13 ± 1	155 ± 12	84.5
55	8-Quinolinyl	3	PHIQ	313 ± 42	1790 ± 222	4587 ± 580	33 ± 5	92 ± 8	9.5

[a] 2-MPP—2-methoxyphenylpiperazine; PHIQ—perhydroisoquinoline.
[b] 5-HT_{1A}/5-HT_7 selectivity.
[c] NT = not tested.

activity of mice measured during the time equal to the observation period in FST (i.e., from 2 to 6 min), and during 30-min experimental sessions (Table 2-SM). Our data on SB-269970 are in line with the results obtained by other authors[31–33] who found that SB-269970 used in a single, medium dose (10 mg/kg) shortened the time of mouse immobilization in both the tail suspension and the FST models. Both compound **54** and SB-269970 evoked U-shaped dose-response curves. The cause of such activity is difficult to explain.

A limited number of data concerning the in vivo activity of analog **54** do not permit us to find an explanation for the loss of an antidepressant-like effect after administration of its higher dose (20 mg/kg). It is noteworthy that SB-269970 can produce U-shaped dose-response effects in the animal models used to predict anxiolytic-like activity in mice and rats.[32] Similarly, the decrease in rat body temperature induced by the 5-$HT_{1A/7}$ receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin was inhibited by SB-269970, which showed a tendency to develop a bell-shaped dose-response relationship.[34] It is hypothesized that the potential antidepressant activity of **54** may result from the blockade of 5-HT_7 receptors, since sulfonamide **54** is a fairly selective 5-HT_7 receptor antagonist (Table 4).

5. Conclusions

Summing up, the paper presents the synthesis of two series of novel arene- (**11**–**17**) and quinoline- (**28**–**40**) sulfonamides and their N-alkylated analogs **18**–**21** and **49**–**55**. The study reveals that 5-HT_7 receptor affinity benefits from the increased distance between the basic center (embedded in PHIQ) and the terminal Ar group, as well as from the introduction of a hydrophobic fragment to the nitrogen of the sulfonamide group. The study also demonstrates that the kind of substitution and localization of the nitrogen atom in the aromatic ring of sulfonamide moiety affect 5-HT_7 and

Table 4
Effects of the tested compounds on immobility time in the forced swim test in mice

Treatment (mg/kg)	*n*	Immobility time (*s*)
		Mean ± SEM
Tween	9	165.2 ± 9.6
54 (5)	9	155.2 ± 12.1
54 (10)	8	128.1 ± 6.2*
54 (20)	8	182.3 ± 11.1
		$F(3,30) = 4.012$
		$P < 0.05$
Tween	9	165.2 ± 9.6
55 (5)	8	144.8 ± 5.6
55 (10)	9	158.6 ± 8.6
55 (20)	9	181.2 ± 9.9
		$F(3,30) = 3.368$
		$P < 0.05$
Tween	9	165.2 ± 9.6
SB-269970 (5)	10	136.1 ± 13.1
SB-269970 (10)	10	110.8 ± 10.4**
SB-269970 (20)	10	139.3 ± 8.1
		$F(3,34) = 5.172$
		$P < 0.01$

n—number of mice per group.
* $P < 0.05$.
** $P < 0.01$ versus respective tween group (Bonferroni post-hoc test).

5-HT_{1A} receptor affinity and selectivity. We have identified and pharmacologically evaluated the *N*-ethyl-substituted quinoline-sulfonamide **54** (5-HT_7R antagonist), which significantly reduces the duration of immobility in mice, when given in a dose comparable to that of SB-269970. The preliminary results concerning **54** as a potential antidepressant agent with 5-HT_7 receptor antagonistic activity are promising enough to warrant further detailed mechanistic studies.

6. Experimental

6.1. Materials and methods

Solution and solid-phase organic transformations and resin washes were carried out at ambient temperature, unless indicated otherwise. Organic solvents (from Aldrich and Chempur) were of reagent grade and were used without purification. BAL linker resin (loading 1.1 mmol/g) was purchased from Iris Chemicals. All other reagents were from Aldrich.

Purity of the synthesized compounds was confirmed by TLC performed on Merck silica gel 60 F_{254}aluminium sheets (Merck, Darmstadt, Germany). Spots were detected by their absorption under UV light (λ = 254 nm).

Analytical HPLC were run on a Waters Alliance HPLC instrument, equipped with a ChromolithSpeedROD column (4.6 × 50 mm). Standard conditions were eluent system A (water/0.1% TFA), system B (acetonitrile/0.1% TFA). A flow rate of 5 mL/min and a gradient of (0–100)% B over 3 min were used. Detection was performed on a PDA detector. Retention times (t_R) are given in minutes.

^{1}H NMR Spectra were recorded at 300 MHz (Varian BB 200 spectrometer) or at 60 MHz (Varian EM-360 L) using TMS (0.00 ppm) and chloroform-d_1, DMSO-d_6, or chloroform-d_1 mixed with methanol-d_4 (2–10%); *J* values are in hertz (Hz), and splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet).

Mass spectrometry analyses—Samples were prepared in acetonitrile/water (10/90 v/v) mixture. The LC/MS system consisted of a Waters Acquity UPLC, coupled to a Waters TQD mass spectrometer (electrospray ionization mode ESI-triple quadrupole (QqQ)). All other analyses were carried out using a Acquity UPLC BEH C18, 50 × 2.1 mm reversed-phase column. A flow rate of 0.3 mL/min and a gradient of (5–95)% B over 5 min was used. Eluent A: water/0.1% HCO_2H; eluent B: acetonitrile/0.1% HCO_2H. Nitrogen was used for both nebulizing and drying gas. LC/MS data were obtained by scanning the first quadrupole in 0.5 s in a mass range from 100 to 700 *m*/*z*; 10 scans were summed up to produce the final spectrum.

Elemental analyses were found within ±0.4% of the theoretical values.

Melting points (mp) were determined with a Buchi apparatus and are uncorrected.

Column chromatography separations were carried out on column with Merck Kieselgel 60 or Aluminium oxide 90, neutral (70–230 mesh). Purification of compounds synthesized on solid support was performed on silica gel (irregular particles 40–63 μm, Merck Kieselgel 60) filled synthesis reactors. The yields of the final compounds, after chromatographic purification, were calculated on the basis of the initial loading of the starting resins and are the overall yields of all reaction steps starting from these resins.

The following abbreviations were used: $CHCl_3$—chloroform; DCM—dichloromethane; DMF—dimethylformamide; TBAB—tetra-*n*-butylammonium bromide; TBAF—tetra-*n*-butylammonium fluoride; TFA—trifluoroacetic acid. The other abbreviations used were recommended by the IUPAC-IUB Commission (*Eur. J. Biochem.* **1984**, *138*, 9–37).

6.2. General procedure for the preparation of compounds 11–17 (Method A)

The starting *N*-(ω-aminoalkyl)-1,2,3,4-tetrahydroisoquinolines were synthesized by published procedures.[35,36] To the appropriate *N*-(ω-aminoalkyl-1,2,3,4-tetrahydroisoquinoline (6 mmol) and sodium hydroxide (7.2 mmol) in 20 cm^3 of water arylsulfonyl chloride (7.2 mmol) was added at the room temperature portionwise. The reaction mixture was stirred at 60 °C for 30 min then cooled down and after neutralization to pH = 7 (4 M HCl) was extracted with $CHCl_3$ (3 × 30 cm^3). The combined extracts were washed with water and dried (K_2CO_3). The solvent was evaporated and the sulfonamides were separated by column chromatography using SiO_2 and $CHCl_3$ followed by $CHCl_3$/MeOH = 49/1. Free bases were then converted into the hydrochloride salts in acetone by treatment with excess of Et_2O saturated with gaseous HCl.

6.2.1. *N*-[2-(1,2,3,4-Tetrahydroisoquinolin-2-yl)ethyl]-2-naphthalenesulfonamide (11)

Colorless crystals (53% yield), mp 107–172 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.3–3.2 (m, 6H), 3.1 (t, *J* = 6 Hz, 2H), 3.35 (s, 2H), 6.8 (b s, 1H), 6.95–7.3 (m, 4H), 7.45–8.1 (m, 6H), 8.45 (s, 1H). **11**·HCl: colorless crystals, mp 223–225 °C. Anal. ($C_{21}H_{22}N_2SO_2$·HCl) C, H, N.

6.2.2. *N*-[2-(1,2,3,4-Tetrahydroisoquinolin-2-yl)ethyl] benzenesulfonamide (12)

Pale yellow oil (39% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 2.3–2.9 (m, 6H), 3.1 (t, *J* = 6 Hz, 2H), 3.4 (s, 2H), 5.25 (b s, 1H), 6.8–7.2 (m, 4H), 7.4–7.7 (m, 3H), 7.8–8.1(m, 2H). **12**·HCl: colorless crystals, mp 213–215 °C. Anal. ($C_{17}H_{20}N_2SO_2$·HCl) C, H, N.

6.2.3. *N*-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propyl]-2-naphthalenesulfonamide (13)

Yellow oil (32% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.3–1.9 (m, 2H), 2.2–2.9 (m, 6H), 3.1 (t, *J* = 6 Hz, 2H), 3.4 (s, 2H), 6.6–7.3 (cluster, 5H), 7.3–8.0 (m, 6H), 8.35 (s, 1H). **13**·HCl: colorless crystals, mp 203–205 °C. Anal. ($C_{22}H_{24}N_2SO_2$·HCl) C, H, N.

6.2.4. *N*-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propyl] benzenesulfonamide (14)

Colorless crystals (65% yield), mp 114–116 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.5–1.9 (m, 2H), 2.3–2.9 (cluster, 6H), 3.1 (t, J = 6 Hz, 2H), 3.5 (s, 2H), 6.4 (b s, 1H), 6.8–7.3 (m, 4H), 7.3–7.6 (m, 3H), 7.6–8.0 (m, 2H). **14**·HCl: colorless crystals, mp 206–208 °C. Anal. ($C_{18}H_{22}N_2SO_2$·HCl) C, H, N.

6.2.5. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-2-naphthalenesulfonamide (15)

Pale yellow oil (58% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.35–1.9 (m, 4H), 2.2–3.1 (cluster, 8H), 3.5 (s, 2H), 6.8–8.0 (cluster, 11H), 8.3 (s, 1H). **15**·HCl: colorless crystals, mp 146–148 °C. Anal. ($C_{23}H_{26}N_2SO_2$·0.9HCl) C, H, N.

6.2.6. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl] benzenesulfonamide (16)

Pale yellow oil (74% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.4–1.9 (m, 4H), 2.4–3.2 (cluster, 8H), 3.65 (s, 2H), 6.7 (s, 1H), 6.8–7.7 (cluster, 9H). **16**·HCl: colorless crystals, mp 146–148 °C. Anal. ($C_{19}H_{24}N_2SO_2$·HCl) C, H, N.

6.2.7. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-1-naphthalenesulfonamide (17)

Pale yellow oil (67% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.15–1.75 (m, 4H), 2.2–3.2 (cluster, 8H), 3.55 (s, 2H), 6.9–7.7 (cluster, 8H), 7.8–8.3 (m, 3H), 8.6 (d, J = 8 Hz, 1 H). **17**·HCl: colorless crystals, mp 205–207 °C. Anal. ($C_{23}H_{26}N_2SO_2$·HCl) C, H, N.

6.3. General procedure for the preparation of compounds 18–21 (Method B)

To the slightly warm (60 °C) mixture of appropriate sulfonamide (5 mmol), finely powdered sodium hydroxide (0.35 g), potassium carbonate (0.35 g), TBAB (0.5 mmol) in toluene (30 mL) *N*-(ω-bromoalkyl)phthalimide (20% excess) in 10 mL of solvent was added dropwise with stirring. After the addition was completed (1 h) stirring was continued at the reflux for 17 h. The inorganic precipitate was filtered off and washed carefully with toluene. The filtrate was combined with washings, washed with water until neutral, dried ($MgSO_4$) and evaporated. The residue without purification was treated with hydrazine (100% excess) in EtOH (10 mL) and refluxed for 1 h. The reaction mixture was cooled down and treated with additional amount of ethanol (10 mL) and concentrated HCl (0.6 mL). Then the reaction mixture was refluxed for 4 h and left overnight at the room temperature. The precipitate was filtered off and the solvent was evaporated. The residue was purified by column chromatography (Al_2O_3, $CHCl_3/CH_3OH$ = 19/1). Free bases were then converted into the hydrochloride (**19**) or fumarate (**18**, **20**, **21**) salts in acetone.

6.3.1. *N*-(3-Aminopropyl)-N-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]benzenesulfonamide (18)

Pale yellow oil (32% yield); ^{1}H NMR (60 MHz, DMSO-d_6) δ (ppm): 1.4–1.9 (m, 2H), 2.3–3.4 (cluster, 10H), 3.1–3.4 (m, 4H), 3.6 (s, 2H), 7.1 (s, 4H), 7.5–7.8 (m, 3H), 7.8–8.0 (m, 2H). **18**·$C_4H_4O_4$·1.5H_2O: colorless crystals, mp 123–125 °C. Anal. ($C_{20}H_{27}N_3SO_2$·$C_4H_4O_4$·1.5H_2O) C, H, N.

6.3.2. *N*-(2-Aminoethyl)-N-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]benzenesulfonamide (19)

Pale yellow oil (100% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.4 (b s, 2H), 1.5–2.1 (m, 2H), 2.35–3.1 (cluster, 8H), 3.1–3.5 (m, 4H), 3.65 (s, 2H), 7.15 (s, 4H), 7.5–7.8 (m, 5H). **19**·2HCl·H_2O: colorless crystals, mp 148–150 °C. Anal. ($C_{20}H_{27}N_3SO_2$·2HCl·H_2O) C, H, N.

6.3.3. *N*-(3-Aminopropyl)-N-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]benzenesulfonamide (20)

Pale yellow oil (100% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.4–1.9 (m, 4H), 2.1 (s, 2H), 2.3–3.0 (cluster, 8H), 3.25 (t, J = 7 Hz, 4H), 3.55 (s, 2H), 7.1 (s, 4H), 7.3–7.7 (m, 3H), 7.7–8.0 (m, 2H). **20**·$C_4H_4O_4$·1.4H_2O: colorless crystals, mp 143–145 °C. Anal. ($C_{22}H_{29}N_3SO_2$·$C_4H_4O_4$·1.4H_2O) C, H, N.

6.3.4. *N*-(3-Aminopropyl)-N-[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)butyl]benzenesulfonamide (21)

Pale yellow oil (67% yield); ^{1}H NMR (60 MHz, $CDCl_3$) δ (ppm): 1.3–1.9 (m, 6H), 2.2 (s, 2H), 2.3–3.0 (cluster, 8H), 3.0–3.45 (m, 4H), 3.55 (s, 2H), 7.1 (s, 4H), 7.4–7.7 (m, 3H), 7.7–8.0 (m, 2H). **21**·2HCl·H_2O: colorless crystals, mp 58–60 °C. Anal. ($C_{22}H_{31}N_3SO_2$·–$C_4H_4O_4$·2H_2O) C, H, N.

6.4. General procedures for manual solid-phase synthesis of compounds 28–40

6.4.1. Preparation of amine-bound resin (23) via reductive amination

The BAL resin (2 g, 1.1 mmol) was divided into two reactors and was swelled in CH_2Cl_2 for 1 h, followed by DMF washes (3 × 10 mL). Then *O-tert*-butyldiphenylsilyl-3-aminopropanol hydrochloride[37] (1.92 g, 5.5 mmol, 5 equiv) and *O-tert*-butyldiphenylsilyl-4-aminobutanolhydrochloride[12] (2.0 g, 5.5 mmol, 5 equiv) were added (solubilized in a mixture of 1%AcOH in DMF, 2 mL each) to a resin. Subsequently, a resin was treated with a suspension of sodium cyanoborohydride ([$NaBH_3CN$] = 0.34 g, 5.5 mmol, 5 equiv) in a 1% AcOH in 8 mL of DMF.[38] The reactors were heated overnight at 60 °C. The resin was drained and washed with a mixture of 10% AcOH in DMF (1 × 10 mL), DMF (3 × 10 mL), MeOH (2 × 10 mL), and CH_2Cl_2 (3 × 10 mL). The amine resin product **3** was air-dried.

6.4.2. Sulfonylation of amine resin (23) with quinolinesulfonyl chlorides

The amine resin (0.1 g) was distributed to 5 mL polypropylene reactors. To the resin was added a solution of triethylamine in CH_2Cl_2 (0.33 M, 2 mL, 0.66 mmol, 6 equiv), followed by addition of quinolinesulfonyl chloride (75 mg, 0.33 mmol, 3 equiv). Sulfonylation was allowed to proceed at ambient temperature for 3 h. After draining of the resin and washing with CH_2Cl_2 (3 × 10 mL), the reaction was repeated. Then, the resin was drained again and washed with DMF (3 × 10 mL), MeOH (2 × 10 mL), and CH_2Cl_2 (3 × 10 mL).

6.4.3. Deprotection of the silyl ether with TBAF

The resin attached product **24** was swelled in CH_2Cl_2 for 30 min, then the drained resin was treated with THF (2 × 4 mL). Subsequently to the resin was added TBAF/THF (1 M, 2 mL, 18 equiv), and the reaction was allowed to proceed for 16 h. The drained resin was washed with THF (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), and air dried.

6.4.4. Mesylation of alcohol

The alcohol resin **25** was swelled in CH_2Cl_2 for 30 min, and then it was treated with a mixture of mesyl chloride (MsCl) in anhydrous pyridine (1 M, 2 mL, 2 mmol, 18 equiv), and rotated at room temperature for 1 h. The drained resin product **26** was washed with DMF (3 × 4 mL), H_2O (1 × 4 mL), MeOH (2 × 4 mL), and CH_2Cl_2 (3 × 4 mL).

6.4.5. *N*-Alkylation

The mesyl resin **26** was swelled in CH_2Cl_2 for 30 min, and to the resin was added a solution of secondary amine—2-MPP, THIQ, PHIQ in anhydrous DMSO (1 M, 2 mL, 2 mmol, 18 equiv), and the reac-

tion was heated to 80 °C for 6 h. The resulting resin product **27** was drained, washed with a mixture of 10% AcOH in DMF (2 × 4 mL), H_2O (1 × 4 mL), DMF (3 × 4 mL), MeOH (2 × 4 mL), and CH_2Cl_2 (3 × 4 mL), and air-dried.

6.4.6. Cleavage from the resin

The resin product was cleaved from the resin by the treatment with 80%TFA/CH_2Cl_2 (1.5 mL) over 2 h, washed with CH_2Cl_2 and the filtrates were collected and evaporated with a stream of nitrogen on Eva parallel evaporator. The crude residue was re-dissolved in CH_2Cl_2 or CH_2Cl_2/MeOH mixture, and purified using silica gel columns and mixture CH_2Cl_2/MeOH, to elute a pure product. The compounds were generally obtained as light yellow oil.

6.4.7. *N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-3-quinolinesulfonamide (28)

Yellow oil, 32 mg (64% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 98%, t_R = 1.10.^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.35–1.37 (m, 4H), 2.17–2.19 (m, 2H), 2.33–2.47 (m, 4H), 2.81–2.87 (m, 6H), 3.73 (s, 3H), 6.78–6.92 (m, 4H), 7.90–7.97 (m, 2H) 7.72–7.77 (m, 1H), 8.11–8.13 (d, 1H), 8.22–8.25 (d, 1H), 8.86–8.86 (m, 1H), 9.17–9.18 (m, 1H). MS calcd for $[M+H]^+$: $C_{24}H_{30}N_4O_3S$ *m*/*z*: 454.2, found 455.4.

6.4.8. *N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-6-quinolinesulfonamide (29)

Yellow oli, 29 mg (60% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 94%, t_R = 0.87. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.67–1.71 (m, 2H), 2.47–2.51 (m, 2H), 2.63 (br s, 4H), 3.13–3.17 (m, 6H), 3.86 (s, 3H), 6.85–7.05 (m, 5H), 7.52–7.56 (dd, 1H, *J* = 8.2 Hz, *J* = 4.4 Hz), 8.05–8.09 (dd, 1H, *J* = 8.9 Hz, *J* = 2.0 Hz), 8.21–8.29 (m, 2H), 8.42–8.43 (d, 1H), 9.04–9.06 (dd, 1H, *J* = 4.4 Hz, *J* = 1.8 Hz). MS calcd for $[M+H]^+$: $C_{23}H_{28}N_4O_3S$ *m*/*z*: 440.2, found 441.3.

6.4.9. *N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-6-quinolinesulfonamide (30)

Yellow oil, 29 mg (58% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 97%, t_R = 0.90. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.40–1.47 (m, 2H), 1.64–1.69 (m, 2H), 2.79–2.86 (m, 2H,), 2.98–3.08 (m, 6H), 3.41–3.44 (m, 4H), 3.77 (s, 3H), 6.85–7.03 (m, 4H), 8.00–8.15 (m, 1H) 7.79–7.84 (m, 1H), 8.18–8.18 (d, 1H), 8.31–8.34 (d, 1H), 8.61–8.62 (d, 1H), 8.81–8.83 (d, 1H), 9.14–9.16 (dd, 1H, *J* = 4.4 Hz, *J* = 1.5 Hz). MS calcd for $[M+H]^+$: $C_{24}H_{30}N_4O_3S$ *m*/*z*: 454.6, found 455.7.

6.4.10. *N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-8-quinolinesulfonamide(31)

Yellow oil, 30 mg (62% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 93%, t_R = 1.01.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.68–1.72 (m, 2H), 2.36–2.40 (m, 2H), 2.55 (br s, 4H), 2.95–3.06 (m, 6H), 3.86 (s, 3H), 6.84–7.02 (m, 5H), 7.53–7.58 (m, 1H), 7.64–7.69 (t, 1H), 8.04–8.07 (m, 1H), 8.27–8.30 (m, 1H), 8.44–8.47 (m, 1H), 9.02–9.04 (m, 1H). MS calcd for $[M+H]^+$: $C_{23}H_{28}N_4O_3S$ *m*/*z*: 440.2, found 441.2.

6.4.11. *N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-8-quinolinesulfonamide (32)

Yellow oil, 29 mg (58% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 92%, t_R = 1.09.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.68–1.72 (m, 2H), 2.36–2.48 (m, 4H), 2.55 (br s, 4H), 2.95–3.06 (m, 6H), 3.86 (s, 3H), 6.84–7.02 (m, 5H), 7.53–7.58 (m, 1H), 7.64–7.69 (t, 1H), 8.04–8.07 (m, 1H), 8.27–8.30 (m, 1H), 8.44–8.47 (m, 1H), 9.02–9.04 (m, 1H). MS calcd for $[M+H]^+$: $C_{24}H_{30}N_4O_3S$ *m*/*z*: 454.2, found 455.3.

6.4.12. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-3-quinolinesulfonamide (33)

Yellow oil, 21.2 mg (48% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1.15); initial LC/MS purity 91%, t_R = 1.04. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.41–1.43 (m, 4H), 2.27–2.29 (m, 2H), 2.49–2.51 (m, 2H), 2.66–2.70 (t, 2H), 2.86–2.88 (m, 2H), 3.39 (br s, 2H), 6.94–6.97 (m, 1H), 7.02–7.08 (m, 3H), 7.26–7.78 (td, 1H), 7.91–7.96 (m, 2H), 8.10–8.14 (dd, 1H),8.19–8.22 (dd, 1H), 8.83–8.84 (d, 1H), 9.15–9.16 (d, 1H). MS calcd for $[M+H]^+$: $C_{22}H_{25}N_3O_2S$ *m*/*z*: 395.2, found 396.4.

6.4.13. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-6-quinolinesulfonamide (34)

Yellow oil, 23 mg (53% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 93%, t_R = 0.82. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.43–1.48 (m, 2H), 1.74–1.81 (m, 2H), 2.80–2.86 (m, 2H), 2.94–2.98 (m, 1H), 3.05–3.15 (m, 4H), 3.18–3.23 (d, 1H), 3.57 (br s, 1H), 4.14–4.22 (q, 1H), 4.39–4.44 (dd, 1H), 7.14–7.21 (m, 4H), 7.79–7.82 (m, 1H), 8.15–8.18 (d, 1H), 8.30–8.34 (d, 1H),8.62 (s, 1H), 8.82 (br s, 1H), 9.14–9.15 (m, 1H). MS calcd for $[M+H]^+$: $C_{22}H_{25}N_3O_2S$ *m*/*z*: 395.2, found 396.4.

6.4.14. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-8-quinolinesulfonamide (35)

Yellow oil, 21.5 mg (49% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1.1); initial LC/MS purity 96%, t_R = 0.98. 1H NMR (300 MHz, DMSO) δ (ppm): 1.37–1.44 (m, 2H), 1.66–1.76 (m, 2H), 2.81–2.83 (m, 2H), 2.96–3.07 (m, 3H), 3.17–3.21 (d, 2H), 3.55–4.07 (m, 2H), 4.12–4.19 (m, 1H), 4.37–4.41 (m, 1H), 7.14–7.32 (m, 4H), 7.69–7.78 (m, 2H), 8.28–8.33 (m, 2H), 8.54–8.58 (m, 1H), 9.08–9.10 (dd, 1H, *J* = 4.4 Hz, *J* = 1.8 Hz). MS calcd for $[M+H]^+$: $C_{22}H_{25}N_3O_2S$ *m*/*z*: 395.2, found 396.4.

6.4.15. *N*-[4-(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-5-yl)butyl]-3-quinolinesulfonamide (36)

Yellow oil, 26 mg (59% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 94%, t_R = 0.87. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.65–1.71 (m, 4H), 2.55–2.59 (m, 2H, *J* = 10.8 Hz, *J* = 5.4 Hz), 2.84–2.88 (m, 2H, *J* = 11.5 Hz, *J* = 5.7 Hz), 2.99–3.06 (m, 4H), 3.49 (s, 2H), 6.65–6.66 (d, 1H), 7.11–7.13 (d, 1H), 7.61–7.66 (t, 1H), 7.81–7.86 (t, 2H), 8.13–8.16 (d, 1H), 8.30–8.31 (m, 1H), 8.96–8.97 (d, 2H). ESI $[M+H]^+$: $C_{20}H_{23}N_3O_2S_2$ *m*/*z* 402.13, found 402.0.

6.4.16. *N*-[4-(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-5-yl)butyl]-7-quinolinesulfonamide (37)

Yellow oil, 27 mg (61% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1); initial LC/MS purity 93%, t_R = 0.86. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.43–1.53 (m, 2H), 1.70–1.81 (m, 2H), 2.80–2.89 (m, 2H), 2.96–3.25 (m, 4H), 3.62–3.65 (m, 1H), 3.91 (m, 1H), 4.05–4.12 (m, 1H), 4.36–4.45 (m, 1H), 6.87–6.91 (m, 1H), 7.45–7.46 (d, 1H), 7.76–7.80 (q, 1H), 7.97–8.01 (dd, 1H), 8.06–8.10 (t, 1H, *J* = 11.2 Hz, *J* = 5.6 Hz), 8.27–8.30 (d, 1H), 8.48 (s, 1H), 8.61–8.63 (d, 1H), 9.10–9.11 (m, 1H). MS calcd for $[M+H]^+$: $C_{20}H_{23}N_3O_2S_2$ *m*/*z* 401.1, found 402.1.

6.4.17. *N*-[4-(1,2,3,4,4a,5,6,7,8,8a-Decahydroisoquinolin-2-yl)butyl]-3-quinolinesulfonamide (38)

Yellow oil, 21 mg (47% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1.3); initial LC/MS purity 89%, t_R = 1.10. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.88–3.11

(cluster 22H), 3.11–3.18 (m, 2H), 7.65–7.71 (t, 1H), 7.85–7.91 (m, 1H), 7.94–7.96 (d, 1H), 8.18–8.21 (d, 1H), 8.69 (s, 1H), 9.25–9.26 (d, 1H). MS calcd for $[M+H]^+$: $C_{22}H_{31}N_3O_2S$ *m/z*: 401.2, found 402.4.

6.4.18. *N*-[3-(1,2,3,4,4a,5,6,7,8,8a-Decahydroisoquinolin-2-yl)propyl]-6-quinolinesulfonamide (39)

Yellow oil, 24.8 mg (58% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1.3); initial LC/MS purity 92%, $t_R = 0.90$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.88–3.11 (cluster, 20H), 3.11–3.14 (m, 2H), 7.52–7.55 (m, 1H), 8.06–8.09 (m, 1H), 8.21–8.29 (m, 2H), 8.42 (s, 1H), 9.04–9.06 (m, 1H). MS calcd for $[M+H]^+$: $C_{21}H_{29}N_3O_2S$ *m/z*: 387.2, found 388.3.

6.4.19. *N*-[4-(1,2,3,4,4a,5,6,7,8,8a-Decahydroisoquinolin-2-yl)butyl]-8-quinolinesulfonamide (40)

Yellow oil, 21 mg (47% yield) following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/1.2); initial LC/MS purity 90%, $t_R = 1.09$.^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.84–3.52 (cluster 24H), 6.53 (br s, 1H), 7.59–7.69 (m, 2H), 8.07–8.10 (m, 1H), 8.29–8.32 (d, 1H, *J* = 7.9 Hz), 8.39–8.42 (d,1H, *J* = 7.2 Hz), 9.06 (s, 1H). MS calcd for $[M+H]^+$: $C_{22}H_{31}N_3O_2S$ *m/z*: 401.2, found 402.3.

6.5. General method for preparation of acetamides 41–44 (Method C)

Primary amines (1 mmol) obtained according to the method described by Gabriel were dissolved in a mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ (20 mL/10 mL).[35] Then to a vigorously stirred mixture, an acetic anhydride (1.5 mmol) was added in several portions. After addition of the acetic anhydride, a mixture was additionally stirred for 6 h at room temperature. Then, the layers were separated, inorganic phase was washed with CH_2Cl_2 (2×30 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and evaporated in vacuum.

6.5.1. *N*-{3-[4-(2-Methoxyphenyl)piperazyn-1-yl]propyl} acetamide (41)[10]

Obtained from 3-[4-(2-methoxyphenyl) piperazin-1-yl]propyl-1-amine (1.5 g, 6 mmol), as yellow oil, that crystalized upon standing (1.60 g, 92% yield). $t_R = 0.71$. ^1H NMR (300 MHz, CDCl3) δ (ppm): 2.03–2.06 (m, 3H), 2.11–2.19 (m, 2H), 3.08–3.12 (m, 4H), 3.39–3.62 (m, 8H), 3.86 (s, 3H), 6.87–7.10 (m, 4H), 7.27–7.41 (m, 1H). MS calcd for $[M+H]^+$: $C_{16}H_{25}N_3O_2$ *m/z*: 291.2, found 292.1.

6.5.2. *N*-{4-[4-(2-Methoxyphenyl)piperazyn-1-yl]butyl} acetamide (42)

Obtained from 4-[4-(2-methoxyphenyl) piperazin-1-yl]butyl-1-amine (1.2 g, 4.5 mmol), as yellow oil, that crystalized upon standing (1.32 g, 95% yield). $t_R = 0.75$. Mp 58–60 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.56–1.76 (m, 4H), 1.97 (s, 3H), 2.43–2.48 (t, 2H), 2.68 (br s, 4H), 3.12 (br s, 4H), 3.24–3.31 (m, 2H), 3.86 (s, 3H), 6.19 (s, 1H), 6.85–7.04 (m, 4H). MS calcd for $[M+H]^+$: $C_{17}H_{27}N_3O_2$ *m/z*: 305.2, found 306.2.

6.5.3. *N*-[4-(1,2,3,4,4a,5,6,7,8,8a-Decahydroisoquinolin-2-yl)butyl]acetamide (43)

Obtained from 4-(octahydro-isoquinolin-2-yl)-butyl-1-amine (1.26 g, 6 mmol), as yellow oil (1.37 g, 91% yield). $t_R = 0.72$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.79–3.34 (cluster, 24H), 3.82 (s, 3H), 6.14 (bs s, 1H). MS calcd for $[M + H]^+$: $C_{15}H_{28}N_2O$ *m/z*: 252.2, found 253.3.

6.5.4. *N*-[5-(1,2,3,4,4a,5,6,7,8,8a-Decahydroisoquinolin-2-yl)pentyl]acetamide (44)

Obtained from 5-(octahydro-isoquinolin-2-yl)-pentyl-1-amine (1 g, 4.4 mmol), as yellow oil, that crystalized upon standing (1.1 g, 93% yield). $t_R = 0.73$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.79–3.34 (cluster, 26H), 3.80 (s, 3H), 6.17 (bs s, 1H). MS calcd for $[M+H]^+$: $C_{16}H_{30}N_2O$ *m/z*: 266.2, found 267.3.

6.6. General method for preparation of secondary amines 45–48 (Method D)

Acetamides (1 mmol) were dissolved in anh. THF (10 mL); subsequently a suspension of $LiAlH_4$ in THF (2 N solution, 2 mmol) was added dropwise under argon atmosphere. The reaction mixture was warmed to reflux for 3–6 h. An excess of reactants was decomposed by addition of few drops of AcOEt, NaOH (1 N water solution, 1 equiv), and water. After filtration of the salts over Celite, a clear solution was dried over Na_2SO_4 and concentrated in vacuo. This yielded secondary amines, which were used without further purification.

6.6.1. Ethyl-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl} amine (45)[10]

Obtained from **41** (1.0 g, 3.43 mmol), as yellow oil (0.88 g, 91% yield). $t_R = 0.62$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.09–1.34 (t, 3H), 1.66–1.78 (m, 3H), 2.41–2.49 (m, 2H), 2.62–2.79 (m, 8H), 3.09 (br s, 4H), 3.86 (s, 3H), 6.84–7.02 (m, 4H). MS calcd for $[M+H]^+$: $C_{16}H_{27}N_3O$ *m/z*: 277.2, found 278.2.

6.6.2. Ethyl-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl} amine (46)

Obtained from **42** (1.0 g, 3.27 mmol), as yellow oil (0.92 g, 96% yield). $t_R = 0.64$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.13–1.20 (m, 3H), 1.52–1.63 (m, 4H), 2.41–2.56 (m, 2H), 2.61–2.75 (m, 8H), 3.10 (br s, 4H), 3.19–3.22 (t, 1H), 3.86 (s, 3H), 6.84–7.03 (m, 4H). MS calcd for $[M+H]^+$: $C_{17}H_{29}N_3O$ *m/z*: 291.2, found 292.2.

6.6.3. Ethyl-[4-(1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-2-yl)butyl]amine (47)

Obtained from **43** (1.2 g, 4.75 mmol), as yellow oil (1 g, 91% yield). $t_R = 0.63$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.82–3.16 (cluster,30H). MS calcd for $[M+H]^+$: $C_{15}H_{30}N_2$ *m/z*: 238.2, found 239.2.

6.6.4. Ethyl-[5-(1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-2-yl)pentyl]amine (48)

Obtained from **44** (1.0 g, 3.43 mmol), as yellow oil (0.86 g, 91% yield). $t_R = 0.66$. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.82–3.16 (cluster, 32H). MS calcd for $[M+H]^+$: $C_{16}H_{32}N_2$ *m/z*: 252.2, found 253.2.

6.7. General method for preparation of sulfonamides 49–55 (Method E)

Secondary amines (0.64 mmol, 1 equiv) obtained according to the method D were dissolved in a mixture of CH_2Cl_2 (generally 10 mL), followed by addition of triethylamine (1.3 mmol, 2 equiv). Then the mixture was cooled down (ice bath), and quinolinesulfonyl chloride (0.77 mmol, 1.2 equiv) was added, and the mixture was stirred for 2–5 h. After evaporation of the solvent, the crude product was purified on silica gel column chromatography using CH_2Cl_2/MeOH (9/0.7) for compounds **49**–**52**, and CH_2Cl_2/MeOH (9/1.2) for compounds **53**–**55**. The free base was converted to its hydrochloride salt by treatment with 4 N HCl in dioxane.

6.7.1. *N*-Ethyl-*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-3-quinolinesulfonamide (49)

Obtained from amine **46**, as yellow oil, 0.29 g (89% yield). $t_R = 1.24$. **49**·HCl: mp 182–184 °C. ^1H NMR (300 MHz, DMSO) δ(ppm) 1.03–1.08 (t, 3H), 1.55–1.62 (m, 2H), 1.69–1.75 (m, 2H),

3.07–3.10 (m, 6H), 3.19–3.29 (m, 4H), 3.40–3.47 (m, 4H), 3.78 (s, 3H), 6.86–7.04 (m, 4H), 7.75–7.81 (m, 1H), 7.94–7.99 (m, 1H), 8.13–8.16 (d, 1H), 8.26–8.29 (d, 1H),8.98–8.99 (d, 1H),9.20–9.21 (d, 1H), 10.97 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{26}H_{34}N_4O_3S$ *m*/*z*: 482.2, found 483.2. Anal. ($C_{26}H_{34}N_4O_3S$·HCl) C, H, N.

6.7.2. *N*-Ethyl-*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-6-quinolinesulfonamide (50)

Obtained from amine **45**, as an oil, 0.25 g (82% yield). t_R = 1.10. **50**·HCl: mp 190–192 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.02–1.06 (t, 3H),2.02–2.06 (m, 2H), 3.09–3.32 (m, 10H), 3.44–3.52 (m, 4H), 3.78 (s, 3H), 6.86–7.01 (m, 4H), 7.85–7.89 (m, 1H), 8.19–8.22 (d, 1H), 8.33–8.36 (d, 1H), 8.74 (s, 1H), 8.88–8.91 (d, 1H), 9.19–9.20 (d, 1H), 11.22 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{25}H_{32}N_4O_3S$ *m*/*z*: 468.2, found 469.2. Anal. ($C_{25}H_{33}ClN_4O_3S$·HCl) C, H, N.

6.7.3. *N*-Ethyl-*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-6-quinolinesulfonamide (51)

Obtained from amine **46**, as an oil, 0.28 g (86% yield). t_R = 1.26. **51**·HCl: mp 198–200 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.02–1.06 (t, 3H), 1.56–1.58 (m, 2H), 1.73 (br s 2H), 3.11 (br s 6H), 3.18–3.28 (m, 4H), 3.44–3.46 (m, 4H), 3.78 (s, 3H), 6.86–7.013 (m, 4H), 7.87–7.91 (m, 1H), 8.19–8.22 (m, 1H), 8.36–8.39 (d, 1H), 8.73–8.74 (d, 1H), 8.92–8.95 (d, 1H), 9.20–9.21 (d, 1H), 11.12 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{26}H_{34}N_4O_3S$ *m*/*z*: 482.2, found 483.2. Anal. ($C_{26}H_{34}N_4O_3S$·HCl) C, H, N.

6.7.4. *N*-Ethyl-*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-8-quinolinesulfonamide (52)

Obtained from amine amine **46**, as pale oil 0.2 g (81% yield). t_R = 1.28. **52**·HCl: mp 184–186 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.90–0.95 (t, 3H), 1.49–1.54 (m, 2H), 1.70 (br s, 2H), 3.05–3.07 (m, 6H), 3.33–3.46 (8H, m), 3.78 (s, 3H), 6.86–7.04 (m, 4H), 7.66–7.76 (m, 2H), 8.26–8.29 (m, 1H), 8.35–8.38 (m, 1H), 8.51–8.54 (m, 1H), 9.07–9.09 (m, 1H), 10.84 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{26}H_{34}N_4O_3S$ *m*/*z*: 482.2, found 483.2. Anal. ($C_{26}H_{34}N_4O_3S$·HCl) C, H, N.

6.7.5. *N*-Ethyl-*N*-[4-(1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-2-yl)butyl]-3-quinolinesulfonamide (53)

Obtained from amine **47**, as yellow oil 0.32 g (78% yield). t_R = 1.31. **53**·HCl: mp 172–174 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.89–0.92 (m, 5H), 1.17–1.21 (m, 3H), 1.44–1.62 (cluster, 11H), 2.81 (br s, 2H), 3.30–3.39 (m, 8H),7.67–7.73 (t, 1H), 7.88–7.93 (m, 1H), 7.9–7.96 (d, 1H), 8.21–8.24 (d, 1H), 8.70 (s, 1H), 9.24–9.26 (m, 1H) 11.02 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{24}H_{35}N_3O_2S$ *m*/*z*: 429.2, found 430.2. Anal. ($C_{24}H_{35}N_3O_2S$·HCl) C, H, N.

6.7.6. *N*-Ethyl-*N*-[4-(1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-2-yl)butyl]-8-quinolinesulfonamide (54)

Obtained from amine **46**, as yellow 0.34 g (78% yield). t_R = 1.24. **54**·HCl: mp 167–169 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.91–0.94 (m, 5H), 1.19–1.24 (m, 3H), 1.45–1.64 (cluster, 11H), 2.83 (br s, 2H), 3.32–3.41 (m, 8H),7.68–7.78 (m, 2H), 8.27–8.32 (m, 2H), 8.52–8.56 (d, 1H), 9.08–9.10 (d, 1H), 10.98 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{24}H_{35}N_3O_2S$ *m*/*z*: 429.2, found 430.2. Anal. ($C_{24}H_{35}N_3O_2S$·HCl) C, H, N.

6.7.7. *N*-Ethyl-*N*-[5-(1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinolin-2-yl)pentyl]-8-quinolinesulfonamide (55)

Obtained from amine **47**, as yellow oil 0.23 g (86% yield). t_R = 1.29. **55**·HCl: mp 178–180 °C. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.89–0.94 (m, 5H), 1.18–1.23 (m, 5H), 1.44–1.63 (cluster, 11H), 2.83 (br s, 2H), 3.31–3.40 (m, 8H), 7.75–7.65 (m, 2H), 8.25–8.28 (dd, 1H, J = 8.2 Hz, J = 1.3 Hz), 8.34–8.37 (dd, 1H, J = 7.4 Hz, J = 1.3 Hz), 8.50–8.53 (dd, 1H, J = 8.5 Hz, J = 1.5 Hz), 9.05–9.06 (dd, 1H, J = 4.1 Hz, J = 1.8 Hz), 10.2 (br s, $1H^+$). MS calcd for $[M+H]^+$: $C_{25}H_{37}N_3O_2S$ *m*/*z*: 443.3, found 444.4. Anal. ($C_{25}H_{37}N_3O_2S$·HCl)C, H, N.

7. In vitro pharmacology

7.1. Radioligand binding experiments

Compounds were tested in competition binding experiments for native 5-HT_{1A}, 5-HT_{2A} and adrenergic α_1 receptors as well as for cloned human 5-HT_6 and 5-HT_7 receptors, according to the previously published procedures.[14–16] The binding parameters are summarized in Table 1-SM. Following incubation, the receptor preparations were rapidly filtered under vacuum through GF/B glass fiber filters; the filters were washed extensively with an ice cold buffer using a harvester. Bound radioactivity was measured by scintillation counting using a liquid scintillation cocktail. Compounds (7–9 concentrations) were tested in triplicate. The inhibition constants (K_i) were calculated from the Cheng–Prusoff equation.[39] Results are expressed as means of at least three separate experiments.

7.2. Effects on adenylate cyclase activity

Adenylate cyclase activity is expressed as the percentage of the maximal effect obtained with 300 nM serotonin. The compounds were tested in 5 concentrations at 10^{-4}–10^{-9} in the h5-HT_7 antagonist effect. For the antagonists, the apparent dissociation constants (K_B) were calculated using the modified Cheng Prusoff equation ($K_B = IC_{50}/(1+(A/EC_{50}A))$, where A = concentration of reference agonist in the assay, and $EC_{50}A = EC_{50}$ value of the reference agonist).

8. In vivo pharmacology

8.1. Subjects

The experiments were performed on male Albino Swiss mice (22–26 g) purchased from a licensed breeder Staniszewska (Ilkowice, Poland). Mice were kept in groups of ten to Makrolon type 3 cages (dimensions 26 × 15 × 42 cm) in an environmentally controlled, experimental room (ambient temperature 21 ± 1 °C; relative humidity 50–60%; 12:12 light:dark cycle, lights on at 8:00). They were allowed to acclimatize with the environment for one week before commencement of the experiments. Standard laboratory food (Ssniff M-Z) and filtered water were freely available. All the experimental procedures were approved by the Local Ethics Commission at the Jagiellonian University in Kraków.

8.2. Experimental procedures

All the experiments were conducted in the light phase between 09.00 and 14.00 h. Each experimental group consisted of 7–10 animals/dose, and the animals were used only once in each test. The experiments were performed by an observer unaware of the treatment administered.

8.3. Forced swim test in mice

The experiment was carried out according to the method of Porsolt *et al.*[18] Briefly, mice were individually placed in a glass cylinder (25 cm high; 10 cm in diameter) containing 6 cm of water maintained at 23–25 °C, and were left there for 6 min. A mouse

was regarded as immobile when it remained floating on the water, making only small movements to keep its head above it. The total duration of immobility was recorded during the last 4 min of a 6-min test session.

8.4. Locomotor activity in mice

The locomotor activity was recorded with an Opto M3 multichannel activity monitor (MultiDevice Software v.1.3, Columbus Instruments). The mice were individually placed in plastic cages ($22 \times 12 \times 13$ cm), and then the crossings of each channel (ambulation) were counted from 2 to 6 min, that is, the time equal to the observation period in the forced swim test and during 30-min experimental sessions. The cages were cleaned up with 70% ethanol after each mouse.

8.5. Drugs

The following drugs were used: (2R)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl] pyrrolidine (hydrochloride, SB-269970, Tocris UK) and compounds **54**, **55**. SB-2699710, **54**, **55** were suspended in a 1% aqueous solution of Tween 80 immediately before administration. All the compounds were administered intraperitoneally at a volume of 10 ml/kg and were given 30 min before the test. Control animals received a vehicle injection according to the same schedule.

8.6. Statistics

All the data are presented as the mean ± SEM. The statistical significance of the results was evaluated by a one-way ANOVA, followed by Bonferroni Comparison Test.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.09.044.

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