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Pharmacomodulation of a Sulfamide 5-HT$_6$ Receptor Ligand

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A series of *N*-ω-aminoalkyl- or *N*-ω-amidinoalkyl-2,4,6-triisopropyl benzenesulfonamides has been synthesized and their respective affinity indices on 5-HT$_6$ receptor determined. This evaluation clearly showed that the compounds possessing an arylpiperazine moiety or an amidine function exhibited good affinity for the model.

Keywords: 5-HT6 receptor; Ligand; Serotonin; Sulfamide

INTRODUCTION

Serotonin 5-HT$_6$ receptors are mainly localised in the central nervous system. Since some antipsychotic drugs exhibit high affinity for these receptor subtypes, a role of 5-HT$_6$ receptors has been suggested in schizophrenia. Moreover, the cholinergic central transmission appears to be modulated by 5-HT$_6$ receptors, a fact that suggests the interest of specific antagonists in the treatment of anxiety and memory alterations.[1]

Some ligands of this receptor subtype have been studied and are presented in Figure 1.

Apart from EMDT, these structures clearly differ from serotonin, the natural ligand, and the presence of an arylsulfonamide group with an arylpiperazine, amidine or guanidine moiety is noteworthy. Our previous work in this domain was the synthesis and evaluation of about twenty five arylamides and arylsulfamides.[2,3] Our lead compound, JR435, had a moderate affinity (Ki # 30 nM) but a good selectivity.

In order to obtain a higher affinity compound, pharmacomodulation at the level of the diamine moiety of JR435 was envisioned. This work led to structures (Figure 2) in which: (i) the diamine length was modified, (ii) the diamine was replaced by triamine, (iii) the terminal $-NH_2$ was replaced by a piperidine, an arylpiperazine, an amidine or a hydroxyl function and (iv) the sulfonamido nitrogen was methylated.

MATERIALS AND METHODS

General

FTIR spectra were recorded on a Perkin–Elmer 377 instrument (KBr pellets, ν: cm^{-1}). ^{1}H NMR spectra were recorded on a Bruker DMX spectrometer at 500 MHz. High resolution mass spectra (HRMS) were recorded at the "Centre Régional de Mesures Physiques de l'Ouest" on a ZabSpec Tof Micromass spectrometer using a LSIMS (Cs^+) or electrospray ionisation mode. Reagent-grade solvents were purchased from chemical suppliers and used directly without further purification unless otherwise specified. Merck silica gel 60 (70–230 mesh) was used as a solid phase for column chromatography. Thin-layer chromatography was performed on Merck silica gel 60 F254 (layer thickness: 0.22 mm). The compounds were visualised using UV light, ninhydrin or iodine. Their purity (>97%) was checked using ^{1}H NMR, HRMS and TLC.

Synthesis

N-(3-Aminopropyl)-2,4,6-triisopropylbenzene-sulfonamide, Hydrochloride (4)

Polymer **2** (0.5 g, 0.325 mmol) was suspended in anhydrous dichloromethane (5 mL). Next,

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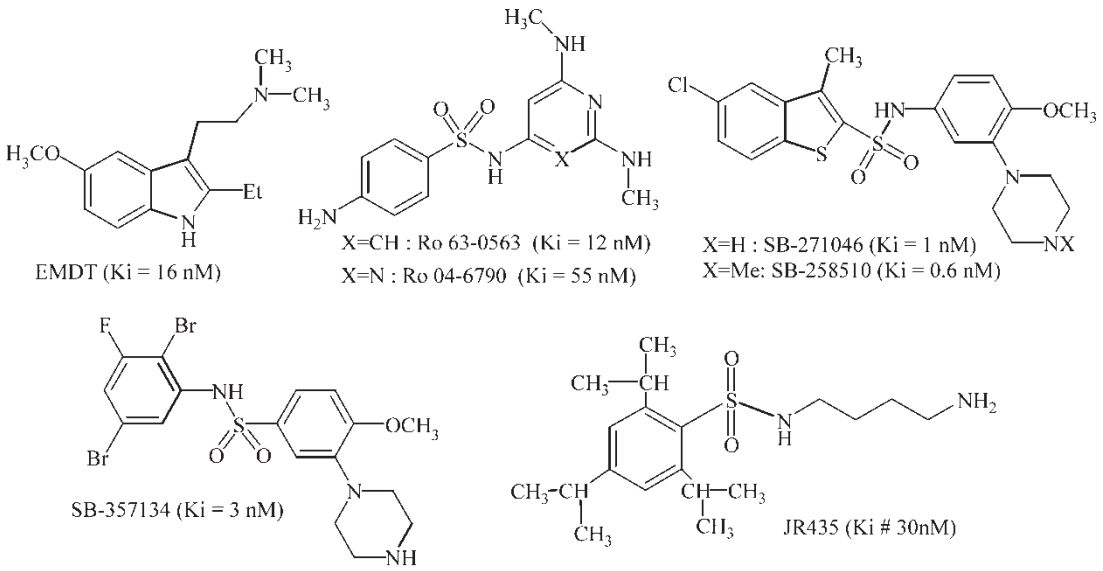


FIGURE 1 Ligands of 5-HT_6 receptor.

2,4,6-triisopropylbenzenesulfonyl chloride (0.19 g, 0.65 mmol) and *N*-methylmorpholine (0.065 g, 0.65 mmol) were dissolved separately in anhydrous dichloromethane (5 mL) and added to the suspension. Reaction at room temperature for 3 h gave the polymer **3** which was consecutively washed with dichloromethane (2 × 5 mL), tetrahydrofuran (2 × 5 mL), water (5 mL), tetrahydrofuran (2 × 5 mL) and diethyl ether (2 × 5 mL). Subsequently, the polymer **3** (0.5 g) was cleaved with trifluoroacetic acid (1 mL) and dichloromethane (1 mL) for 2 h at room temperature. The filtrate was reduced to dryness, dissolved in water (2 mL), made alkaline (10% NaOH) then extracted with dichloromethane (3 × 5 mL). After drying over potassium carbonate, the solvent was removed under reduced pressure. The hydrochloride salt was prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride salt was triturated in diethyl ether to yield **4** (91%). ^{1}H NMR (D_2O) δ (ppm): 1.04 (d, J = 5.7 Hz, 6H), 1.09 (d, J = 5.0 Hz, 12H), 1.85 (m, 2H), 2.73 (m, 1H), 2.93 (m, 2H), 2.99 (m, 2H), 3.90 (m, 2H), 7.14 (s, 2H). IR (KBr) cm^{-1}: 3203, 2953, 1601, 1509, 1314, 1144, 658. HRMS: [M + H]$^+$ $C_{18}H_{33}N_2O_2S$ calc. 341.2263, found. 341.2262.

N^1-(2,4,6-Triisopropylbenzenesulfonyl)spermidine, Hydrochloride (7)

A mixture of triethylamine (0.2 mL, 1.45 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (0.44 g, 1.45 mmol) in dichloromethane (5 mL) was added to a solution of N^4,N^8-di-*tert*-butyloxycarbonylspermidine **5** (0.5 g, 1.45 mmol) in the same solvent (10 mL). The solution was stirred for 18 h at room temperature, washed with water (3 × 15 mL), dried over sodium sulfate and concentrated under vacuum. Then the hydrochloride salt was prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride

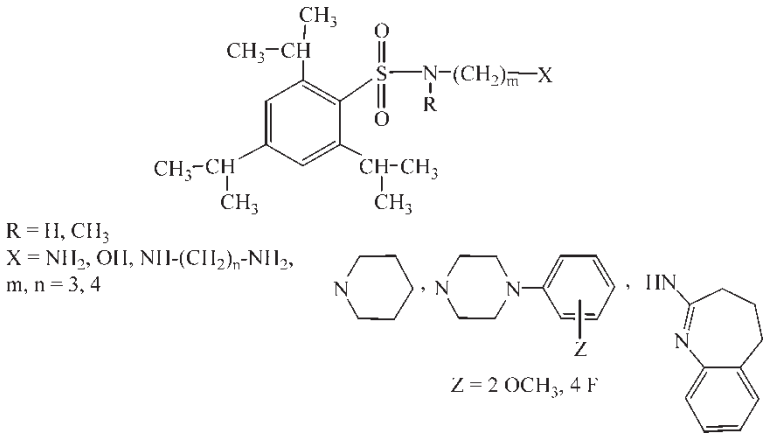


FIGURE 2 Pharmacomodulation of JR435.

salt **7** was triturated in diethyl ether and obtained as crystals in a 20% yield. ^{1}H NMR (D_2O) δ (ppm): 1.08 (d, $J = 7.0$ Hz, 6H), 1.14 (d, $J = 7$ Hz, 12H), 1.79 (t, $J = 3.5$ Hz, 4H), 1.95 (qt, $J = 6.6$ Hz, $J = 7.8$ Hz, 2H), 2.78 (qt, $J = 6.5$ Hz, $J = 7.0$ Hz, 1H), 3.20 (t, $J = 6.5$ Hz, 2H), 3.73 (t, $J = 6.7$ Hz, 2H), 3.11 (m, 4H), 3.95 (qt, $J = 6.7$ Hz, 2H), 7.18 (s, 2H). IR (KBr) cm^{-1}: 3233, 2987, 1321, 1150, 665. HRMS: $[M + H]^+$ $C_{22}H_{42}N_3O_2S$ calc. 412.2998, found. 412.2997.

N^8-(2,4,6-Triisopropylbenzenesulfonyl)spermidine, Hydrochloride (8)

The previous procedure was applied to a solution of N^1,N^4-di-*tert*-butyloxycarbonylspermidine **6** (0.5 g, 1.45 mmol). Compound **8** was obtained as crystals in 35% yield. ^{1}H NMR (D_2O) δ (ppm): 1.04 (m, 6H), 1.08 (m, 12H), 1.58 (m, 2H), 1.75 (m, 2H), 2.12 (m, 2H), 2.71 (m, 1H), 2.89 (m, 2H), 3.08 (m, 2H), 3.14 (m, 4H), 3.96 (m, 2H), 7.08 (s, 2H). IR (KBr) cm^{-1}: 3180, 2961, 1318, 1143, 660. HRMS: $[M + H]^+$ $C_{22}H_{42}N_3O_2S$ calc. 412.2998, found. 412.2988.

N-(4-Hydroxybutyl)-2,4,6-triisopropyl-benzenesulfonamide (9)

A solution of 2,4,6-triisopropylbenzenesulfonyl chloride (6.06 g, 20 mmol) in dichloromethane (10 mL) was added to a solution of 4-aminobutan-1-ol (1.78 g, 20 mmol) and diisopropylethylamine (2.58 g, 20 mmol) in dichloromethane (30 mL). The solution was stirred for 24 h at room temperature then washed with water (3 × 10 mL), dried over sodium sulfate and concentrated under reduced pressure. Then the residue was chromatographed using diethyl ether as eluent to yield **9** (47%). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.25 (d, $J = 4.7$ Hz, 6H), 1.27 (d, $J = 4.4$ Hz, 12H), 1.60 (m, 4H), 2.90 (qt, $J = 6.7$, $J = 7.0$, 1H), 3.00 (t, $J = 6.3$ Hz, 2H), 3.63 (t, $J = 5.7$ Hz, 2H), 4.16 (qt, $J = 6.7$ Hz, 2H), 7.16 (s, 2H). IR (KBr) cm^{-1}: 3474, 3185, 2952, 1461, 1308, 1190, 659. HRMS: $[M + H]^+$ $C_{19}H_{34}NO_3S$ calc. 356.2259, found. 356.2263.

N-[4-(Piperidin-1-yl)butyl]-2,4,6-triisopropyl-benzenesulfonamide, Hydrochloride (12)

A mixture of triethylamine (0.34 g, 3.4 mmol) and 4-nitrobenzenesulfonyl chloride (0.75 g, 3.4 mmol) in dichloromethane (5 mL) was added to a solution of **9** (0.60 g,1.7 mmol) in dichloromethane (15 mL). The solution was stirred for 24 h, washed with water (3 × 30 mL), dried over sodium carbonate and concentrated to dryness to give **10**. The crude compound **10** was then added to piperidine (0.85 mL) in tetrahydrofuran and heated to reflux for 24 h. Solvents were evaporated under reduced pressure and the residue was dissolved in water (30 mL) and extracted twice with 25 mL of dichloromethane. The combined organic layers were concentrated to dryness and the residue was chromatogaphed (90 CH_3OH, 10 CH_2Cl_2). The hydrochloride salt was then prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride salt was triturated in diethyl ether to yield **12** (5%). ^{1}H NMR (CD_3OD) δ (ppm): 1.17 (d, $J = 2.6$ Hz, 6H), 1.18 (d, $J = 2.2$ Hz, 12H), 1.52 (qt, $J = 6.8$ Hz, $J = 7.4$ Hz, 2H), 1.74 (m, 4H), 1.83 (m, 2H), 2.86 (m, 4H), 3.00 (m, 2H), 3.42 (m, 2H), 4.10 (qt, $J = 6.7$ Hz, 2H), 7.16 (s, 2H). IR (KBr) cm^{-1}: 2961, 2518,1454, 1312, 1152, 659 HRMS: $[M + H]^+$ $C_{24}H_{43}N_2O_2S$ calc. 423.3045, found. 423.3048.

N-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-2,4,6-triisopropylbenzenesulfonamide, Hydrochloride (19)

A solution of 2,4,6-triisopropylbenzenesulfonyl chloride (1.81 g, 6.0 mmol) in dichloromethane (10 mL) was added to a solution of triethylamine (0.6 g, 6.0 mmol) and **17** (1.3 g, 5.0 mmol) in dichloromethane (15 mL). The reaction mixture was stirred for 1 h and the solvents were evaporated under reduced pressure. Then, the residue was purified by column chromatography (95 CH_2Cl_2, 5 CH_3OH). The hydrochloride salt was prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride salt was triturated in diethyl ether to yield **19** (45%). ^{1}H NMR (CD_3OD) δ (ppm): 1.28 (m, 18H), 1.68 (qt, $J = 7.0$ Hz, 2H), 1.92 (m, 2H), 2.94 (qt, $J = 7.0$ Hz, 1H), 3.01 (t, $J = 6.7$ Hz, 2H), 3.28 (t, $J = 8.3$ Hz, 2H), 3.45 (m, 4H), 3.73 (m, 4H), 3.94 (s, 3H), 4.21 (qt, $J = 6.6$ Hz, 2H), 7.02 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 7.9$ Hz, 1H), 7.23 (t, $J = 7.8$ Hz, 2H), 7.27 (s, 2H). IR (KBr) cm^{-1}: 2953, 2429, 1602, 1458, 1260, 1151, 761. 659. HRMS: $[M + H]^+$ $C_{30}H_{48}N_3O_3S$ calc. 530.3416, found. 530.3403.

N-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}-2,4,6-triisopropylbenzenesulfonamide, Hydrochloride (20)

A solution of 2,4,6-triisopropylbenzenesulfonyl chloride (1.81 g, 6.0 mmol) in dichloromethane (10 mL) was added to a solution of triethylamine (0.6 g, 6.0 mmol) and **18** (1.25 g, 5.0 mmol) in dichloromethane (15 mL). The reaction mixture was stirred for 1 h and the solvents were evaporated under reduced pressure. Then, the residue was purified by column chromatography in diethyl ether. The hydrochloride salt was prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride salt was triturated in diethyl ether to yield **20** (41%). ^{1}H NMR (DMSO) δ (ppm): 1.20 (m, 18H), 1.48 (m, 2H), 1.78 (m, 2H), 2.84 (m, 2H), 2.93 (qt, $J = 6.7$ Hz, 1H),

3.09 (m, 4H), 3.23 (t, $J = 12.2$ Hz, 4H), 3.50 (d,$J = 11.45$ Hz, 2H), 3.71 (d, $J = 12.1$ Hz, 2H), 4.15 (qt, $J = 6.5$ Hz, 2H), 7.07 (m, 2H), 7.11 (t, $J = 8.6$ Hz, 2H), 7.24 (s, 2H). IR (KBr) cm^{-1}: 2960, 2428, 1510, 1454, 1237, 1148, 658, 530. HRMS: $[M + H]^+$ $C_{29}H_{45}N_3O_2FS$ calc. 518.3217, found. 518.3213.

N-(3-Cyanopropyl)-n-methyl-2,4,6-triisopropyl-benzenesulfonamide (24)

A solution of 2,4,6-triisopropylbenzenesulfonyl chloride (0.92 g, 3 mmol) in dichloromethane (5 mL) was added to a solution of triethylamine (0.34 g, 3.3 mmol) and **23** (0.3 g, 3.0 mmol) in dichloromethane (15 mL). After 18 h at room temperature, the mixture was washed with water (3×15 mL), dried and purified by column chromatography (CH_2Cl_2) to yield a white solid. (55%). ^{1}H NMR (CD_3OD) δ (ppm): 1.25 (m, 18H), 2.01 (qt, $J = 7.1$ Hz, 2H), 2.42 (t, $J = 7.3$ Hz, 2H), 2.73 (s, 3H), 2.90 (m, 1H), 3.34 (t, $J = 7.2$ Hz, 2H), 4.10 (m, 2H), 7.17 (s, 2H). IR (KBr) cm^{-1}: 2945, 2242, 1602, 1310, 1151, 738.

N^1-Methyl-N^1-(2,4,6-Triisopropylbenzene-sulfonamide)putrescine, Hydrochloride (25)

Compound **24** was dissolved in ethanol and hydrogenated under pressure (5 bars) in the presence of Raney nickel (1 g). After 36 h, the suspension was filtered off and concentrated to dryness. The hydrochloride salt was prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride salt was triturated in diethyl ether to yield **25** (13%). ^{1}H NMR (CD_3OD) δ (ppm): 1.27 (m, 18H), 1.74 (m, 4H), 2.74 (s, 3H), 2.95 (m, 1H), 2.99 (m, 2H), 3.29 (t, $J = 6.8$ Hz, 2H), 4.16 (qt, $J = 6.8$ Hz, 2H), 7.29 (s, 2H). IR (KBr) cm^{-1}: 3352, 2953, 1493, 1287, 1143, 726. HRMS (electrospray): $[M + H]^+$ $C_{20}H_{37}N_2O_2S$ calc. 369.2576, found. 369.2582.

N-[4-(4,5-Dihydro-3h-1-benzazepin-2-yl)-aminobutyl]-2,4,6-triisopropylbenzene-sulfonamide, Hydrochloride (28)

Mercury (II) chloride (0.37 g, 1.35 mmol) was added to a refluxing solution of 1,3,4,5-tetrahydro-2*H*-1-benzazepine-2-thione **27** (0.24 g, 1.35 mmol), triethylamine (0.52 g, 5.2 mmol) and **26** (0.48 g, 1.35 mmol) in tetrahydrofuran (20 mL). This suspension was heated for 2 h, concentrated to dryness, diluted with dichloromethane (25 mL) and filtered to remove the black mercury sulfide. The organic layer was washed with water (2×25 mL), dried over potassium carbonate and concentrated to dryness. The residue was chromatographed (CH_3OH) and the hydrochloride salt was prepared by treating the free amine with 1.5 M ethanolic HCl at 0°C. After 30 min, the corresponding hydrochloride salt was triturated in diethyl ether to yield **28** (25%). ^{1}H NMR (CD_3OD) δ (ppm): 1.24 (s, 6H), 1.25 (s, 12H), 1.70 (qt, $J = 6.7$ Hz, $J = 7.4$ Hz, 2H), 1.84 (qt, $J = 7.3$ Hz, 2H), 2.31 (qt, $J = 7.0$ Hz, 2H), 2.50 (t, $J = 7.0$ Hz, 2H), 2.80 (t, $J = 7$ Hz, 2H), 2.92 (qt, $J = 7.0$ Hz, 1H), 2.99 (t, $J = 6.7$ Hz, 2H), 3.50 (t, $J = 7.1$ Hz), 4.19 (qt, $J = 6.7$ Hz, 2H), 7.24 (s, 2H), 7.34 (m, 4 Hz). IR (KBr) cm^{-1}: 3388, 2960, 1594, 1145. HRMS: $[M + H]^+$ $C_{29}H_{44}N_3O_2S$ calc. 498.3154, found. 498.3136.

Pharmacological Characterisation of Drugs on Human 5-HT$_6$ Receptors

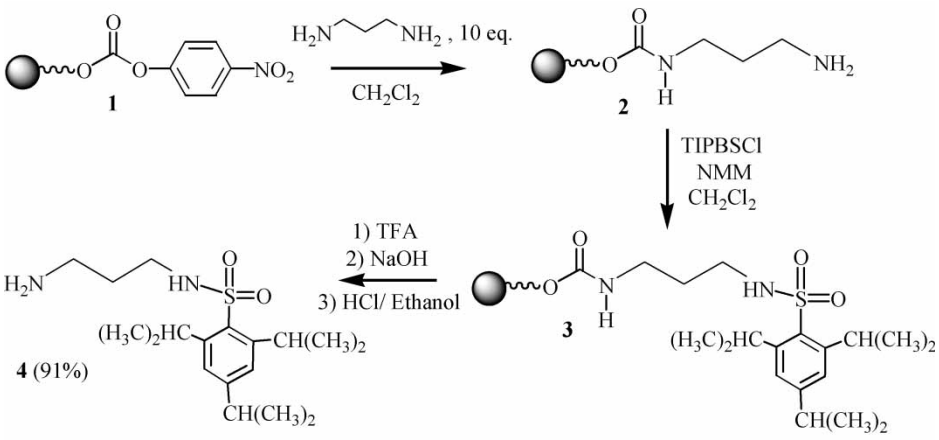
Drugs were evaluated through their ability to compete for the binding of [^{3}H]LSD on membranes of *sf9* cells transiently expressing the human 5-HT$_6$ receptors (CRM-044, NEN Life Sciences). In brief, 4 μg of proteins were incubated at 27°C for 90 min in duplicate in the absence or the presence of 10^{-6} or 10^{-8} M of each drug and 2 nM [^{3}H]LSD in 50 mM Tris–HCl buffer (pH 7.4) supplemented with 10 mM $MgSO_4$ and 0.5 mM EDTA. At the end of the incubation, the homogenates were then filtered through Whatman GF/A filters and washed five times with ice-cold 50 mM Tris–HCl buffer. Non-specific binding was parallely evaluated in the presence of 10^{-5} M clozapine. Radioactivity associated with protein was then quantified and expressed as the percentage of inhibition for each concentration of the drugs under study.

RESULTS AND DISCUSSION

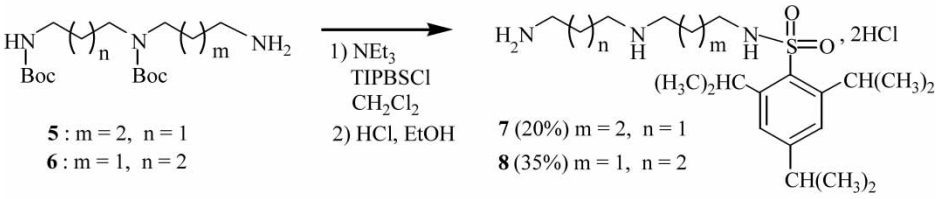
The target ω-aminoalkylsulfonamides were prepared by condensation of 2,4,6-triisopropylbenzene-sulfonyl chloride (TIPBSCl) with di- or triamines in the presence of a base: triethylamine (Et_3N), *N*-methylmorpholine (NMP) or diisopropylethylamine (DIPEA).

N-(3-Aminopropyl)sulfonamide **4** was obtained according to the previously described synthetic pathway used for JR435,[2] operating by solid phase synthesis (Scheme 1). Wang resin was first changed into its 4-nitrophenylcarbamate **1** that underwent aminolysis with 1,3-propanediamine, leading to the Wang-oxycarbonylpropanediamine **2**. After sulfonylation of its free $-NH_2$, the carbamate function was cleaved in TFA and its treatment with HCl/EtOH afforded **4** as its hydrochloride salt in a 91% yield.

Synthesis of the corresponding spermidine derivatives **7** and **8** (Scheme 2) was carried out starting from the diprotected (N^4,N^8- and N^1,N^4-di-*tert*-butoxycarbonyl)spermidines.[4,5] The yields after sulfonylation and Boc-hydrolysis remained nevertheless low: 20 and 35%, for the hydrochloride salts **7** and **8**, respectively.

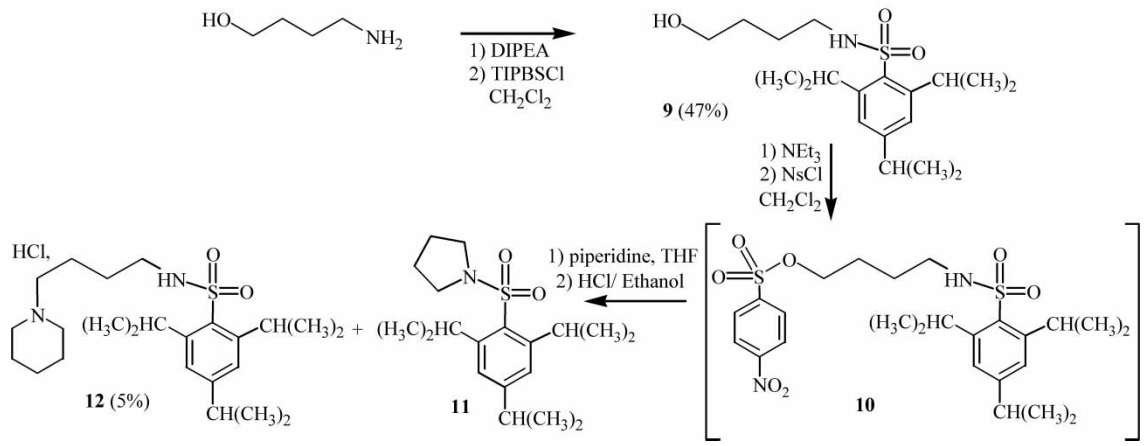


SCHEME 1 Solid-phase synthesis of **4**.

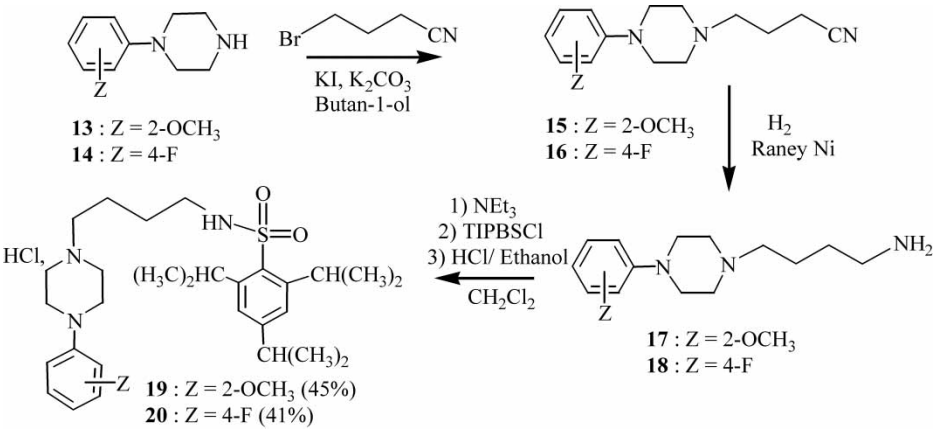


SCHEME 2 Synthesis of triamine derivatives **7** and **8**.

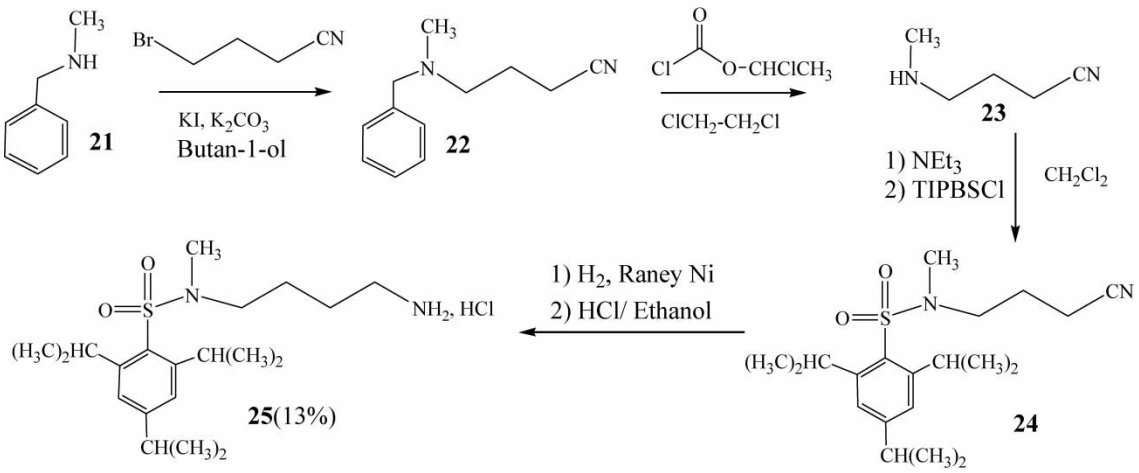
An alternative method consisted in introducing the ω-amine via a leaving group starting from 4-aminobutan-1-ol (Scheme 3). *N*-4-hydroxybutylsulfonamide **9** was transformed into its 4-nitrobenzenesulfonyl (Ns) derivative, but displacement of the nosyloxy group by piperidine afforded mainly sulfonamide **11**, resulting from intramolecular cyclisation and only traces (5%) of the desired *N*-4-piperidinobutylsulfonamide **12** was obtained. Due to the difficulties observed in the previous synthesis, the ω-aminobutyl chain was first created using 3-bromobutyronitrile[6,7] (Scheme 4). Nitriles **15** and **16** were then catalytically reduced (Raney nickel) into the corresponding amines **17** and **18** which underwent final sulfonylation with TIPBSCl in moderate yields (45 and 41%). A similar procedure was carried out to obtain the *N*-methyl derivative of JR435, **25** (Scheme 5). The tertiary 4-(*N*-benzyl-*N*-methylamino)butyronitrile **22** was transformed into its secondary amine according to Olofson.[8] Its sulfonylation into **24**, followed by nitrile reduction afforded **25**. Such a method avoids recourse to *N*-methylputrescine whose synthesis is not straightforward[9] and sulfonylation would afford a mixture of *N*,*N*′-sulfonamides.



SCHEME 3 Synthesis of derivatives **9** and **12**.



SCHEME 4 Synthesis of arylpiperazine derivatives **19** and **20**.

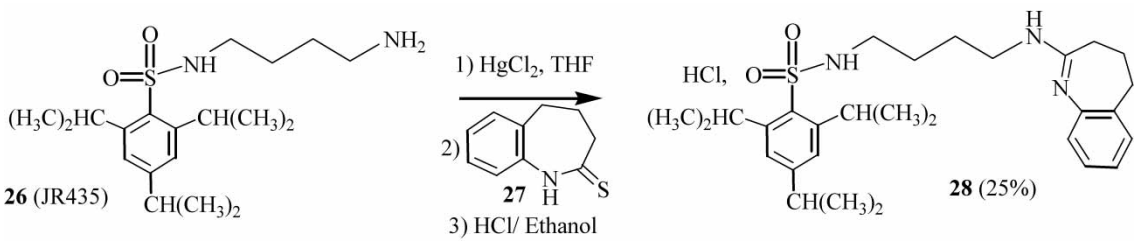


SCHEME 5 Synthesis of the N-methyl derivative of JR435, **25**.

Finally the ω-amidinosulfonamide **28** was obtained by aminolysis of the thiolactam group of the dihydrobenzazepinethione **27** in the presence of $HgCl_2$[10] (Scheme 6).

Pharmacology

In a preliminary pharmacological study, seven target benzenesulfonamides (**4**, **7**, **8**, **12**, **19**, **20**, **28**) and the intermediate ω-hydroxy derivative **9** were tested (Table I). Although the number of studied compounds is limited it is obvious that (i) replacement of the butyl chain by a propyl one induces a clear decrease of activity in **4**, (ii) the same dramatic effect was observed by introduction of a supplementary ω-aminoalkyl fragment as observed with **7** and **8**, (iii) replacement of the ω-amino group by a piperidinyl one was also unsatisfactory, (iv) only introduction of an arylpiperazinyl -present in the SB reference compounds- or an amidino moiety succeeded in maintaining a level of activity comparable with that of JR435 (compounds **19**, **20** and **28**), (v) lastly, the presence of an ω-cationic group seems to be critical for emergence of activity since



SCHEME 6 Synthesis of amidine **28**.

TABLE I Percentage inhibition (%) of [^{3}H]LSD binding to human 5-HT$_6$ receptors at 10^{-6} and 10^{-8} M

No.	10^{-6} M	10^{-8} M	No	10^{-6} M	10^{-8} M
JR435	97	10	**19**	80	10
4	54	0	**20**	69	32
7	15	10			
8	26	9	**28**	84	15
9	13	0			
12	39	0			

the ω-hydroxy compound **9** possesses no affinity for the studied model.

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