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(54) **Title:** SULFONAMIDE DERIVATIVES AS $5HT_7$ RECEPTOR ANTAGONISTS

(57) **Abstract**

The invention relates to compounds having $5HT_7$ antagonist activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

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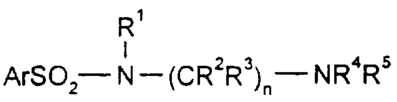
SULFONAMIDE DERIVATIVES AS 5HT7 RECEPTOR ANTAGONISTS

This invention relates to compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

EPA 0 021 580, EPA 0 076 072, FR 2694003, WO 9009170, EP 260901, US 4721809, US 4720580, US 4698445, US 4665227 and US 4794196 describe sulfonamide derivatives which are disclosed as having antiarrhythmic activity. It has now surprisingly been found that certain compounds disclosed in the above specifications, as well as structurally novel compounds, have $5HT_7$ receptor antagonist activity. $5HT_7$ receptor antagonists are believed to be of potential use in the treatment or prophylaxis of certain CNS disorders such as anxiety, depression, sleep disorders, migraine, Parkinson's disease, schizophrenia, pain, appetite disorders and other indications such as inflammation, spastic colon, renal disorders, hypotension, cardiovascular shock, septic shock and gastrointestinal diseases.

The present invention therefore provides, in a first aspect, use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



$$ArSO_2—\overset{R^1}{\overset{|}{N}}—(CR^2R^3)_n—NR^4R^5$$

(I)

wherein:

Ar is an optionally substituted mono- or bicyclic aromatic or heteroaromatic ring;

R^1 is C_{1-6} alkyl;

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl;

R^4 and R^5 are independently hydrogen, C_{1-6} alkyl, arylC_{1-6} alkyl or aryl or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 8-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, sulphur or oxygen; and

n is 2 to 4 in the manufacture of a medicament for the treatment of disorders in which antagonism of the $5HT_7$ receptor is beneficial.

C_{1-6} Alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably Ar is an optionally substituted mono- or bicyclic aromatic or heterocyclic ring. Preferred aromatic rings include phenyl and naphthyl. Preferred heteroaromatic groups include thiophene, quinoline and isoquinoline.

Optional substituents for aryl and heterocyclic groups include C_{1-6} alkyl optionally substituted by NR^7R^8, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, optionally substituted aryl, arylC_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylthio, cyano, nitro, halogen, CF_3, C_2F_5, NR^7R^8, $CONR^7R^8$, NR^7COR^8, $S(O)_pNR^7R^8$, CHO, OCF_3, SCF_3, COR^9, CH_2OR^9, CO_2R^9 or OR^9 where p is 1 or 2 and R^7, R^8 and R^9 are independently hydrogen, C_{1-6} alkyl, optionally substituted aryl or optionally substituted arylC_{1-6}alkyl;

Preferably Ar is a naphthyl group, a substituted phenyl group, or a dibromothienyl group.

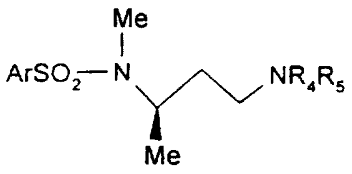
Suitably R^1 is C_{1-6} alkyl. Examples of R^1 groups include methyl and ethyl groups. Preferably R^1 is methyl.

Suitably R^2 and R^3 are independently hydrogen or C_{1-6} alkyl. Preferably R^2 and R^3 are hydrogen or methyl. More preferably one of R^2 and R^3 is hydrogen and the other is methyl attached to the carbon atom of the side chain adjacent to the sulfonamide nitrogen.

Suitably R^4 and R^5 are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 8-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen or oxygen. Preferably R^4 and R^5 form an optionally substituted 5- to 8-membered heterocyclic ring, in particular an optionally substituted 6-membered ring. Optional substituents for such rings, which can be present on carbon and nitrogen atoms can be selected from suitable groups listed above and include C_{1-6} alkyl. Most preferably R^4 and R^5 form a piperidine ring substituted by a methyl group.

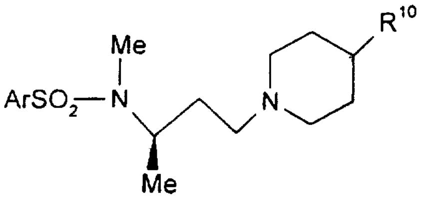
Suitably n is 2 to 4. Preferably n is 3.

Certain compounds of formula (I) are novel and all novel compounds of formula (I) and salts thereof form a further aspect of the invention. Preferred novel compounds are those of formula (i):



(i)

in which Ar, R^4 and R^5 are as defined in formula (I). Most preferred novel compounds are those of formula (ii):



(ii)

where Ar is a naphthyl group, a substituted phenyl group, or a dibromothienyl group and R^{10} is hydrogen, C_{1-6} alkyl, cycloC_{3-6} alkyl, arylC_{1-6} alkyl, CF_3, C_2F_5 or C_{1-6} alkyloxy.

Particularly preferred compounds of the invention include:

N-Methyl-N-[1-methyl-3-(3-methylpiperidin-1-yl)propyl]-1-naphthalenesulfonamide,
N-Methyl-N-[1R-methyl-3-(3S-methyl-piperidin-1-yl)propyl]-1-naphthalene sulfonamide,
N-Methyl-N-[1R-methyl-3-(3R-methyl-piperidin-1-yl)propyl]-1-naphthalene sulfonamide,
N-Methyl-N-[3-[1-(2R-methylpiperidinyl)propyl]]-1-naphthlenesulfonamide,
N-Methyl-N-[3-[1-(2S-methylpiperidinyl)propyl]]-1-naphthalenesulfonamide,
(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-1-naphthalenesulfonamide,
(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-benzene sulfonamide,
(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-2-naphthalenesulfonamide,
N-Methyl-N-[1-methyl-3-(2S-methyl-1-piperidyl)propyl]-4,5-dibromo-2-thiophene sulfonamide,
N-Methyl-N-[1-methyl-3-(2R-methyl-1-piperidyl)propyl]-4,5-dibromo-2-thiophene sulfonamide,
(±) N-Ethyl-N-[3-[1-(piperidinyl)butyl]]-1-naphthalenesulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-1-naphthalene sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidine-1-yl)propyl]-2,3-dibromothiophene-5-sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3,4-dichlorobenzene sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-phenylpiperazin-1-yl)propyl]-1-naphthalene sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-phenylpiperazin-1-yl)propyl]-2,3-dibromothiophene-5-sulfonamide,

(±)-N-Methyl-N-[1-ethyl-3-(4-methylpiperidin-1-yl)propyl]-1-naphthalene sulfonamide,

N-Methyl-N-(4-piperidin-1-yl-butyl)-1-naphthalene sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3,4-dibromobenzene sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3-methylbenzene sulfonamide,

N-Methyl-N-[3-[1-(pyrrolidinyl)propyl]]-3-chlorobenzenesulfonamide,

N-Methyl-N-[3-[1-(morpholinyl)propyl]]-3-chlorobenzenesulfonamide,

N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-3-chlorobenzenesulfonamide,

N-Methyl-N-[3-[1-(pyrrolidinyl)propyl]]-4-bromobenzenesulfonamide,

N-Methyl-N-[3-[1-(morpholinyl)propyl]]-4-bromobenzenesulfonamide,

N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-4-bromobenzenesulfonamide,

N-Methyl-N-[3-[1-(morpholinyl)propyl]]-1-naphthalenesulfonamide,

N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-1-naphthalenesulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-bromo-4-chlorophenyl sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]4-chloro-3-vinylphenyl sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidine-1-yl)propyl]3-hydroxymethylphenyl sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-ethylphenyl sulfonamide,

and pharmaceutically acceptable salts thereof.

Other preferred compounds of the invention include those of examples 29 - 83 which are disclosed herein. The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

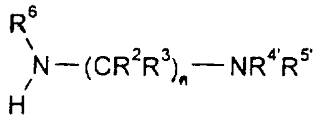
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

(a) the coupling of a compound of formula (II):

$$ArSO_2L$$

(II)

in which Ar is as defined in formula (I) and L is a leaving group with a compound of formula (III):

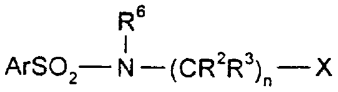


$$R^6(H)N-(CR^2R^3)_n-NR^{4'}R^{5'}$$

(III)

in which R^2 and R^3 are as defined in formula (I), $R^{4'}$ and $R^{5'}$ are R^4 and R^5 respectively or protected derivatives thereof, and R^6 is R^1 or hydrogen; or

(b) coupling a compound of formula (IV):



$$ArSO_2-N(R^6)-(CR^2R^3)_n-X$$

(IV)

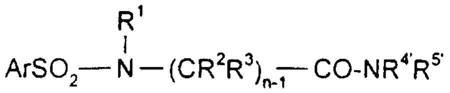
in which n, R^2, R^3 and R^6 are as defined above and X is a leaving group with a compound of formula (V):

$$HNR^{4'}R^{5'}$$

(V)

in which $R^{4'}$ and $R^{5'}$ are as defined above, or

(c) treating a compound of formula (VI):



$$ArSO_2-N(R^1)-(CR^2R^3)_{n-1}-CO\text{-}NR^{4'}R^{5'}$$

(VI)

in which n, R^1, R^2, R^3, $R^{4'}$ and $R^{5'}$ are as defined above with a reducing agent, and optionally thereafter if appropriate:

- removing any protecting groups;
- when R^6 is hydrogen converting to a group R^1;
- forming a pharmaceutically acceptable salt.

Suitable leaving groups L include halogen, in particular chloro. The reaction of a compounds of formulae (II) and (III) is preferably carried out in an inert solvent such as dichloromethane optionally in the presence of a base such as triethylamine.

For process (b), suitable leaving groups L include halogen, in particular chloro. For process (c) Suitable reducing agents include lithium aluminium hydride. Those skilled in the art will appreciate that it may be necesary to protect R^4 and R^5 groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

When R^6 is hydrogen it can be converted to a group R^1 using standard alkylation procedures, for example by reaction with an alkyl halide in the presence of a base such as sodium hydride.

Compounds of formulae (II), (III), (IV), (V) and (VI) are commercially available or may be prepared according to known methods or analogous to known methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_7$ receptor antagonist activity and are believed to be of potential use for the treatment or prophylaxis of certain CNS disorders such as anxiety, depression, sleep disorders, migraine, Parkinson's disease, schizophrenia, pain, appetite disorders and other indications such as inflammation, spastic colon, renal disorders, hypotension, cardiovascular shock, septic shock and gastrointestinal diseases.

. Preferably the compounds of the invention are used to treat CNS diseases.

Thus the invention also provides a compound of formula (i) and preferably a compound of formula (ii) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (i) and preferably a compound of formula (ii) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1
N-[1-Methyl-3-(3-methylpiperidin-l-yl)propyl]-l-naphthalenesulfonamide (D1)

To a cooled mixture of 1-methyl-3-(3-methylpiperidin-l-yl)propylamine [J.A.C.S. 1946 1911 **68**] (1g; 5.8mmol) and triethylamine (0.6g; 5.8mmol) was added dropwise with stirring a solution of 1-naphthalene sulfonyl chloride (1.3g; 5.8mmol) in anhydrous dichloromethane. After 24h, the solution was diluted with additional dichloromethane (50ml) and washed with water (×3), then dried and evaporated to give a yellow oil. The oil crystallised on standing, and the crystals were filtered off using n-pentane to afford the title compound (1.0g; 48%), m.p. 70-71°C

Description 2
Methanesulphonic acid 2R-benzyloxycarbonylaminopropyl ester (D2)

To a solution of N-Cbz-D-Alaninol (10g, 48 mmol) in dichloromethane (100 ml) at 0°C was added triethylamine (13.5 ml, 96 mmol) and methanesulphonic anhydride (12.5g, 72 mmol); stirring was continued at 0°C for 30 mins. The solution was diluted with additional dichloromethane (100 ml) and washed with saturated aqueous sodium bicarbonate (x2), dried over Na_2SO_4, filtered and concentrated to give a white solid (12.2g, 89%).

Found $MH^+ = 288$
$C_{12}H_{17}NO_5S$ + H requires 288

Description 3
3R-Benzyloxycarbonylaminobutyronitrile (D3)

To a solution of mesylate D2 (12.2g, 43 mmol) in dimethylformamide (200 ml) at room temperature was added sodium cyanide (3.1g, 63 mmol). Stirring was continued at room temperature for 48 hrs and then at 60°C for 2hrs. Reaction mixture was partitioned between saturated aqueous sodium bicarbonate (200 ml) and ether (2 x 500 ml). The organic solution was dried (Na_2SO_4), filtered and concentrated to give the nitrile (8.4g, 71%) as a yellow oil.

Found $MH^+ = 219$
$C_{12}H_{14}N_2O_2$ + H requires 219

Description 4
3R-Benzyloxycarbonylamino butyric acid (D4)

A solution of the nitrile D3 (6g, 27 mmol) in concentrated hydrochloric acid (60 ml) was heated to reflux for 18 hrs. The solution was then concentrated and azeotroped with toluene to give the crude amino acid which was dissolved in 5M NaOH (20 ml). The solution was cooled to 0°C, treated with benzyl chloroformate (5.9 ml, 40 mmol) dropwise and stirred at room temperature for 1 hr. The aqueous solution was washed with ether (50 ml) and then acidified with hydrochloric acid. The product was extracted with ether (3 x 100 ml) which was dried (Na_2SO_4), filtered and concentrated to give the title compound as a clear oil (1.9g, 27% over 2 steps).

Found M+Na = 260
$C_{12}H_{15}NO_4$+Na requires 260

Description 5
3R-Benzyloxycarbonylaminobutyric acid, 3S-methylpiperidin-1-yl amide (D5)

To a solution of the acid D4 (445 mg, 1.88 mmol) in dichloromethane (25 ml) at room temperature under argon was added oxalyl chloride (100 µl, 2.07 mmol) and DMF (1 drop). Stirring was continued at room temperature for 2 hrs. The solution was concentrated and the residue redissolved in dichloromethane (20 ml) before cooling to 0°C. A solution of 3(S)-methylpiperidine (186 mg, 1.88 mmol) in triethylamine (260 µl, 1.88 mmol) and dichloromethane (2 ml) was added and the reaction stirred for an additional 2hrs. The solution was diluted with dichloromethane (20 ml) and washed with saturated aqueous sodium bicarbonate (20 ml). The organic solution was dried (Na_2SO_4), filtered and concentrated and the residue purified on silica eluting with 70% ethyl acetate/petrol to afford the title compound (540 mg, 90%).

Found MH^+ = 319
$C_{18}H_{26}N_2O_3$ + H requires 319

Description 6
N-Methyl-N-[1R-methyl-3-(3S-methyl-piperidin-1-yl)propyl]amine (D6)

To a solution of the amide D5 (540 mg, 1.7 mmol) in THF (30 ml) was added lithium aluminium hydride (200 mg, 5.3 mmol) portionwise. The reaction was heated to reflux under argon for 3 hrs, cooled and then quenched by the cautious addition of water (0.2 ml), 10% aqueous sodium hydroxide (0.2 ml) and finally water (0.6 ml). The mixture was filtered, concentrated and then partitioned between 1N HCl (20 ml) and ether (2x20 ml). The aqueous layer was basified with 5N NaOH and extracted with ether (2 x 50 ml). The organic solution was dried (Na_2SO_4) filtered and concentrated to give the title compound (240 mg, 76%).

Found $MH^+ = 185$
$C_{11}H_{24}N_2+H$ requires 185

Description 7
Ethyl N-[3-(2R-methyl-1-piperidinyl)propyl]carbamate (D7)

A solution of (R)-3-[2-methyl-1-piperidinyl)propylamine (350 mg, 2.24 mmol) in dichloromethane (10 ml) was cooled (ice bath) and treated with triethylamine (0.34 ml, 2.46 mmol) and ethyl chloroformate (0.23 ml, 2.46 mmol) and stirred for 24 hours. Work up afforded the title compound (365 mg, 71%) as an oil.

$MH^+ = 229$ (62%).

Description 8
N-Methyl-3-(2R-methyl-1-piperidinyl)propylamine (D8)

The material from D7 (365 mg, 1.6 mmol) in tetrahydrofuran (10 ml) was treated with lithium aluminium hydride (182 mg, 3 eq.) and heated to reflux for 24 hours. Work up in the usual way afforded the title compound as an oil (200 mg, 73%)

$MH^+ = 171$ (100%).

Description 9
Ethyl N-[3-(2S-methyl-1-piperidinyl)propyl]carbamate (D9)

A solution of (S)-3-(2-methyl-1-piperidinyl)propylamine (500 mg, 3.2 mmol) dichloromethane (10 ml) was cooled (ice-bath) and treated with triethylamine (0.29 ml, 3.5 mmol) and ethyl chloroformate (0.33 ml, 3.5 mmol) and stirred for 24 hours. Work up afforded the title compound as an oil (524 mg, 72%).

$MH^+ = 229$ (100%)

Description 10
N-Methyl-3-(2S-methyl-1-piperidinyl)propylamine (D10)

The material from D9 (504 mg, 2.3 mmol) in tetrahydrofuran (30 ml) was treated with lithium aluminium hydride (262 mg, 6.9 mmol) and heated to reflux overnight. Work up in the usual way afforded the title compound as an oil (400 mg, 100%).

$MH^+ = 171$ (100%)

Description 11
1-(1-piperidinyl)-butan-3-one (D11)

A stirred, cooled (ice-bath) solution of methylvinylketone (10g, 0.14 mol) and piperidine (14.1 ml, 0.14 mol) in dichloromethane (150 ml) was treated with iron III chloride (anhydrous, 2.2g, 0.1 mol eq.) and stirred over a weekend. The mixture was filtered, the filtrate concentrated and the residue chromatographed on silica (flash 5% MeOH/DCM to 10% MeOH/DCM) to afford the title compound (19.8g, 91%)

$MH^+ = 156$ (100%)

Description 12
1-(1-piperidinyl)-3-butanone oxime (D12)

A suspension of D11 (19.8g, 0.127 mol) in water (200 ml) was treated with hydroxylamine hydrochloride (9.7g, 0.14 mol) and sodium carbonate (14.8g, 0.14 mol), heated to reflux for four hours and cooled. The solution was extracted into ether, the organics dried and concentrated to afford the title compound (13.6g, 63%) as an orange solid.

$MH^+ = 171$ (100%)

Description 13
(±) 1-(1-piperidinyl)-3-aminobutane (D13)

A suspension of lithium aluminium hydride (670 mg, 17.6 mmol) in tetrahydrofuran (20 ml) cooled by ice bath was treated dropwise with conc. sulfuric acid (0.45 ml) and stirred for 1 hour. A solution of D12 (1g, 5.88 mmol) in THF (5 ml) was added dropwise and the suspension heated to reflux overnight. Usual work up afforded the title compound (0.96 g, 100%).

Description 14

(±) Ethyl N-[3-(1-piperidinyl)-1-methylpropyl]carbamate (D14)

The title compound was prepared from D13 in a similar way to D7 (1.1g, 78%).

$MH^+ = 229$ (100%)

Description 15

(±) 1-Methyl-3-(1-piperidinyl)-N-methylaminopropane

The title compound was prepared from D14 in a similar way to D8 (0.71g, 87%).

$MH^+ = 171$ (100%).

Description 16

(±)-Methyl 3-N-Methylaminopentanoate (D16)

A 2M methanolic solution of methylamine (44 ml, 88 mmol) was added dropwise over 15 minutes to a stirred solution of methyl 2-pentenoate (5g, 44 mmol) in ethanol (50 ml). After 1h the reaction mixture was evaporated to dryness to afford the title compound (3.75g, 58%) as a colourless oil.

Found $MH^+ = 146$

$C_7H_{15}NO_2 + H$ requires 146

Description 17

(±)-3-N-Methylaminopentanol (D17)

Methyl 3-N-methylaminopentanoate D16 (3.67g; 25.3 mmol) in ether (20 ml) was added dropwise over 15 minutes to a stirred solution of lithium aluminium hydride (2.00g; 52.7 mmol) in ether (40 ml). After 72h the reaction mixture was cooled to 0°C and water (2.3 ml), 10% NaOH (3.5 ml) and finally water (4.7 ml) were added. The mixture was diluted with ether (50 ml), stirred for 1h, then filtered through kieselguhr. The filtrate was dried and evaporated to dryness to afford the title compound (2.96g; 100%) as a colourless oil.

Found $MH^+ = 118$
$C_6H_{15}NO + H$ requires 118

Description 18

(±) N-Methyl-N-[1-ethyl-3-chloropropyl)-1-naphthalenesulfonamide (D18)

A mixture of 1-naphthalenesulfonyl chloride (1.74g; 7.7 mmol), 3-N-methylamino pentanol D17 (0.36g, 3.1 mmol) and diisopropylethylamine (1.6 ml, 9.0 mmol) in toluene (30 ml) were stirred at reflux for 72h. After cooling to room temperature, the mixture was filtered through kieselguhr and evaporated to dryness. Purification by flash column chromatography afforded the title compound (0.69g, 69%) as a colourless oil.

Found $MH^+ = 326$
$C_{16}H_{20}SNO_2Cl+H$ requires 326

Description 19

1-(3-Aminopropyl)piperidine (D19)

A suspension of lithium aluminium hydride (13.75g; 0.36 mol) in dry THF (500 ml) at 0° under Ar was treated with conc. H_2SO_4 (9.2 ml) dropwise. After 1 hour at 0°, the suspension was treated with 1-piperidinepropionitrile (10g; 72 mmol) in dry THF (50 ml) and allowed to reach room temp. overnight. The reaction mixture was treated with diethyl ether (400 ml), cooled to 0° and treated with a solution of 10% NaOH (aq) (21 ml) in water (55 ml) dropwise. Allowed to reach room temp. and filtered through kieselguhr, washing the pad with diethyl ether (2x200 ml). The filtrate was evaporated *in vacuo* to a pale yellow liquid (8.1g; 79%).

$MH^+ = 143$
$C_8H_{18}N_2+H$ requires 143

Description 20

1-(3-Ethoxycarbonylamino)piperidine (D20)

A solution of 1-(3-aminopropyl)piperidine D19 (8.1g; 57 mmol) in dichloromethane (100 ml) at 0° was treated with triethylamine (11 ml; 79 mmol) and ethyl chloroformate (7.6 ml; 79 mmol) dropwise. Allowed to reach room temp. overnight, washed with H_2O (2x), dried and evaporated *in vacuo* to an orange oil (11.2g; 92%).

$MH^+ = 215$
$C_{11}H_{22}N_2O+H$ requires 215

Description 21
1-(3-Methylaminopropyl)piperidine (D21)

A solution of 1-(3-ethoxycarbonylamino)piperidine D20 (11.2g; 52 mmol) in dry THF (500 ml) at 0° under Ar was treated with lithium aluminium hydride (5.97g; 16 mmol) portionwise and heated at reflux overnight. Cooled to 0° and treated with a solution of 10% NaOH (aq) (9.1 ml) in H_2O (23 ml) dropwise followed by addition of diethyl ether (200 ml). The quenched reaction mixture was filtered through kieselguhr washing with diethyl ether. The filtrate was dried over Na_2SO_4 and evaporated *in vacuo* to an amber liquid (8.0g; 98%).

$MH^+ = 157$
$C_9H_{20}N_2+H$ requires 157

Example 1
N-Methyl-N-[1-methyl-3-(3-methylpiperidin-1-yl)propyl]-1-naphthalenesulfonamide hydrochloride (E1)

Sodium hydride (80mg; 3.2mmol) was added slowly to a stirred solution of sulfonamide D1 (0.91g; 2.5mmol) in dimethylformamide (28ml). After 1h, iodomethane (0.36g; 3.2mmol) in a small volume dimethylformamide was added dropwise, and allowed to stir at room temperature overnight. The solution was then concentrated, and dichloromethane (70ml) added, then washed with water (×2), aqueous sodium hydroxide, and finally water. The organic solution was then dried and evaporated to dryness. Formation of the hydrochloride salt was achieved by treatment with ethanolic HCl. (68%) m.p. 178°C

Found $MH^+ =375$
$C_{21}H_{30}N_2O_2S+H$ require 375

Example 2

N-Methyl-N-[1R-methyl-3-(3S-methyl-piperidin-1-yl)propyl]-1-naphthalene sulfonamide (E2)

To a solution of the amine D6 (230 mg, 1.25 mmol) in dichloromethane (5 ml) was added diisopropylethylamine (220 µl, 1.26 mmol) and 1-naphthylsulphonyl chloride (285 mg, 1.26 mmol). The reaction was allowed to warm to room temperature with stirring over 3 hrs. The solution was diluted with dichloromethane (15 ml) and washed with saturated aqueous sodium bicarbonate (10 ml). The organic solution was dried (Na_2SO_4), filtered and concentrated and the residue purified on silica eluting with ethyl acetate to afford the title compound (300 mg, 64%).

Found $MH^+ = 375$
$C_{21}H_{30}N_2O_2S + H$ requires 375

Example 3

N-Methyl-N-[1R-methyl-3-(3R-methyl-piperidin-1-yl)propyl]-1-naphthalene sulfonamide (E3)

The title compound was prepared using 3(R)methylpiperidine and a procedure similar to that in D5, D6 and E2.

Found $MH^+ = 375$
$C_{21}H_{30}N_2O_2S+H$ requires 375

Example 4

N-Methyl-N-[3-[1-(2R-methylpiperidinyl)propyl]]-1-naphthlenesulfonamide (E4)

A solution of D8 (200 mg, 1.17 mmol) and triethylamine (0.16 ml, 1 eq.) in dichloromethane (10 ml) cooled by ice-bath was treated with a solution of naphthalene-1-sulfonyl chloride (265 mg, 1eq) in dichloromethane. The solution was stirred overnight. Work up and chromatography (10% methanol/dichloromethane) afforded the title compound (156 mg, 37%).

$MH^+ = 361$ (100%)

Example 5

N-Methyl-N-[3-[1-(2S-methylpiperidinyl)propyl]]-1-naphthalenesulfonamide (E5)

A solution of D10 (400 mg, 2.3 mmol) and triethylamine (0.32 ml, 2.3 mmol) in dichloromethane (10 ml) cooled by ice bath, was treated with a solution of naphthalene-1-sulfonyl chloride (533 mg, 2.3 mmol) and stirred overnight. The solution was thoroughly washed (10% NaOH), dried and concentrated. Chromatography (10% MeOH/DCM) afforded the title compound (450 mg, 54%).

$MH^+ = 361$ (52%)

Example 6

(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-1-naphthalenesulfonamide (E6)

The title compound was prepared in a similar way to E4 using D15 (350 mg, 2 mmol), triethylamine (0.28 ml, 2 mmol) and 1-naphthalenesulfonyl chloride (0.46g, 64%).

$MH^+ = 361$ (100%)

Example 7

(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-benzene sulfonamide (E7)

The title compound was prepared from D15 (115 mg, 0.67 mmol) triethylamine (90 µl, 0.67 mmol) and benzenesulfonyl chloride (86 µl, 0.67 mmol) using a similar procedure to E4 (50 mg, 24%).

$MH^+ = 311$ (100%).

Example 8

(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-2-naphthalenesulfonamide (E8)

The title compound was prepared from D15 (115 mg, 0.67 mmol), triethylamine (90 µl, 0.67 mmol) and 2-naphthalenesulfonyl chloride (153 mg, 0.67 mmol) using a similar procedure to E4 (132 mg, 55%).

$MH^+ = 361$ (100%)

Example 9

N-Methyl-N-[1-methyl-3-(2S-methyl-1-piperidyl)propyl]-4,5-dibromo-2-thiophene sulfonamide (E9)

To a solution of 1-(3-methylaminobutyl)-2(S)-methylpiperidine (184 mg; 1.0 mmol) in dry dichloromethane (3 ml) containing diisopropylethylamine (174 μl; 1.0 mmol) was added 4,5-dibromo-2-thiophenesulphonyl chloride (341 mg; 1.0 mmol) and shaken at room temp. overnight. The reaction mixture was washed with H_2O and applied to a Waters sep-pak silica gel column, eluting with ethyl acetate to yield the title compound as a clear, colourless gum (300 mg; 61%).

$MH^+ = 489$
$C_{15}H_{24}Br_2N_2S_2O_2$+H requires 489

Example 10

N-Methyl-N-[1-methyl-3-(2R-methyl-1-piperidyl)propyl]-4,5-dibromo-2-thiophene sulfonamide (E10)

The procedure of Example 9 was employed. The reagents used were: 1-(3-methylamino butyl)-2(R)-methylpiperidine, 4,5-dibromo-2-thiophenesulphonyl chloride and diisopropylethylamine.

$MH^+ = 489$
$C_{15}H_{24}Br_2N_2S_2O_2$+H requires 489

Example 11

(±) N-Ethyl-N-[3-[1-(piperidinyl)butyl]]-1-naphthalenesulfonamide (E11)

1-Naphthalenesulphonyl chloride (0.15g, 0.7 mmoles) and (±) N-ethyl-4-(piperidinyl)-2-butylamine (0.12g, 0.7 mmoles) were mixed in dichloromethane (10 mL) and stirred at ambient temperature for 18 hrs. The mixture was then washed with saturated sodium hydrogen carbonate, dried (Na_2SO_4) and purified on silica gel eluting with 1-3% methanol/dichloromethane. This gave the title compound E11 (0.13g, 52%).

NMR ($CDCl_3$) δ: 1.05 (3H, d, J=8Hz), 1.15-2.19 (1H, m), 3.25-3.41 (2H, m), 3.81-3.95 (1H, m), 7.50-7.71 (3H, m), 7.91 (1H, d, J=10Hz), 8.05 (1H, d, J=10Hz), 8.29 (1H, d, J=10Hz), 8.69 (1H, d, J=10Hz).

$MH^+ = 375$

$C_{21}H_{30}N_2O_2S + H$ requires 375

Example 12

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-1-naphthalene sulfonamide

The title compound was prepared using 4-methyl piperidine in the methods described in D5, D6 and E2.

Found $MH^+ = 375$

$C_{21}H_{30}N_2O_2S+H$ requires 375

Example 13

N-Methyl-N-[1R-methyl-3-(4-methylpiperidine-1-yl)propyl]-2,3-dibromothiophene-5-sulfonamide (E13)

The title compound was prepared using 4-methylpiperidine and 2,3-dibromothiophene-5-sulphonyl chloride in the methods described in D5, D6 and E2.

Found $MH^+ = 487/489/491$

$C_{15}H_{24}Br_2N_2O_2S_2+H$ requires 487/489/491

Example 14

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3,4-dichlorobenzene sulfonamide (E14)

The title compound was prepared using 4-methylpiperidine and 3,4-dichlorophenyl sulphonyl chloride in the methods described in D5, D6 and E2.

Found $MH^+ = 393/395$

$C_{17}H_{26}Cl_2N_2O_2S+H$ requires 393/395

Example 15

N-Methyl-N-[1R-methyl-3-(4-phenylpiperazin-1-yl)propyl]-1-naphthalene sulfonamide (E15)

The title compound was prepared using 1-phenylpiperazine and 1-naphthylsulphonyl chloride in the methods described in D5, D6 and E2.

Found $MH^+ = 438$
$C_{25}H_{31}N_3O_2S+H$ requires 438

Example 16

N-Methyl-N-[1R-methyl-3-(4-phenylpiperazin-1-yl)propyl]-2,3-dibromothiophene-5-sulfonamide (E16)

The title compound was prepared using 1-phenyl piperazine and 2,3-dibromothiophene-5-sulphonyl chloride in the methods described in D5, D6 and E2.

Found $MH^+ = 550/552/554$
$C_{19}H_{25}Br_2N_3O_2S_2+H$ requires 550/552/554

Example 17

(±)-N-Methyl-N-[1-ethyl-3-(4-methylpiperidin-1-yl)propyl]-1-naphthalene sulfonamide (E17)

A mixture of D18 (0.67g, 2 mmol), 4-methylpiperidine (0.20g, 2 mmol), potassium carbonate (300 mg) and sodium iodide (25 mg) in acetonitrile (30 ml) were stirred at reflux for 48h. After cooling to room temperature, the mixture was filtered through kieselguhr and evaporated to dryness. Purification by flash column chromatography afforded the title compound (0.72g, 92%) as a yellow foam.

Found $MH^+ = 389$
$C_{22}H_{32}N_2O_2S+H$ require 389

Example 18

N-Methyl-N-(4-piperidin-1-yl-butyl)-1-naphthalene sulfonamide (E18)

To a solution of N-methyl-N-(4-piperidin-1-yl-butyl)amine (300 mg, 1.76 mmol) and diisopropylethylamine (325 µl, 1.86 mmol) in dichloromethane (5 ml) at 0°C was added 1-naphthylsulphonyl chloride. Stirring was continued at room temperature for 15 hrs. The solution was diluted with dichloromethane (20 ml) and washed with 10% aqueous sodium hydroxide (10 ml). The organic solution was dried (Na_2SO_4), filtered and concentrated and the residue purified on silica eluting with ethyl acetate to afford the title compound (500 mg, 78%).

Found $MH^+ = 361$
$C_{20}N_{28}N_2O_2S+H$ requires 361

Example 19

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3,4-dibromobenzene sulfonamide (E19)

The procedure of Example 9 was employed. The reagents used were: 1-[3-methylamino-3(R)-methylpropyl]-4-methylpiperidine, 3,4-dibromobenzenesulphonyl chloride and diisopropylethylamine.

$MH^+ = 483$
$C_{17}H_{26}Br_2N_2O_2S+H$ requires 483

Example 20

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3-methylbenzene sulfonamide (E20)

The procedure of E9 was employed using 1-[3-methylamino-3(R)-methylpropyl]-4-methylpiperidine, 3-methylbenzenesulfonyl chloride and diisopropylethylamine.

$MH^+ = 339$
$C_{18}H_{30}N_2O_2S+H$ requires 339.

Examples 21-28 were prepared by shaking a 1:1 mixture of the appropriate aryl sulphonyl chloride with the appropriate secondary amine in dichloromethane. After 10h, the resultant precipitate was filtered off and dried.

Example 21

N-Methyl-N-[3-[1-(pyrrolidinyl)propyl]]-3-chlorobenzenesulfonamide hydrochloride (E21)

M+H observed 317 and 319
$C_{14}H_{21}N_2O_2SCl$+H requires 317 and 319

Example 22
N-Methyl-N-[3-[1-(morpholinyl)propyl]]-3-chlorobenzenesulfonamide hydrochloride (E22)

M+H observed 333 and 335
$C_{14}H_{21}N_2O_3SCl$+H requires 333 and 335

Example 23
N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-3-chlorobenzenesulfonamide hydrochloride (E23)

M+H observed 346 and 348
$C_{15}H_{24}N_3O_2SCl$+H requires 346 and 348

Example 24
N-Methyl-N-[3-[1-(pyrrolidinyl)propyl]]-4-bromobenzenesulfonamide hydrochloride (E24)

M+H observed 361 and 363
$C_{14}H_{21}N_2O_2SBr$+H requires 361 and 363

Example 25
N-Methyl-N-[3-[1-(morpholinyl)propyl]]-4-bromobenzenesulfonamide hydrochloride (E25)

M+H observed 377 and 379
$C_{14}H_{21}N_2O_3SBr$+H requries 377 and 379

Example 26
N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-4-bromobenzenesulfonamide hydrochloride (E26)

M+H observed 390 and 392
$C_{15}H_{24}N_3O_2SBr$+H requires 390 and 392

Example 27

N-Methyl-N-[3-[1-(morpholinyl)propyl]]-1-naphthalenesulfonamide hydrochloride (E27)

M+H observed 349

$C_{18}H_{24}N_2O_3S$+H requires 349

Example 28

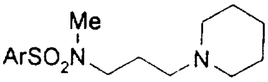
N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-1-naphthalenesulfonamide hydrochloride (E28)

M+H observed 362

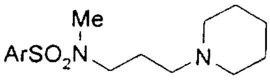
$C_{19}H_{27}N_3O_2S$+H requires 362

Examples 29-83 were prepared by the following generic procedure.

1-(3-Methylaminopropyl)piperidine D21 (1.0 mmol) was dissolved in dry dichloromethane (3 ml) containing diisopropylethylamine (1.0 mmol) and treated with a sulphonyl chloride (1.0 mmol). Shaken at room temp. overnight, washed with H_2O and purified by column chromatography eluting with ethyl acetate.



Example No.	Ar	MH$^+$
29	1-naphthyl	347
30	5-dimethylamino-1-naphthyl	390
31	phenylmethyl	311
32	4-bromophenyl	376
33	4-acetamidophenyl	354
34	2,1,3-benzoxadiazol-4-yl	339
35	2,1,3-benzothiadiazol-4-yl	355
36	2-thienyl	303
37	4-phenylsulphonylthienyl	443
38	4-(phenyl)phenyl	373
39	2,3-dibromo-5-thienyl	461
40	3-bromophenyl	376
41	3,5-dichlorophenyl	366
42	2,3,5,6-tetramethylphenyl	353
43	5-bromo-2,3-dichloro-4-thienyl	450
44	2-(trifluoromethyl)phenyl	365
45	2,3-dichlorophenyl	365
46	3-chloro-2-methylphenyl	345
47	2,3,4-trichlorophenyl	399
48	3,4-dichlorophenyl	365
49	8-quinolyl	348
50	phenyl	297
51	2-(2-pyridyl)-5-thienyl	380
52	3,4-dibromophenyl	455
53	3-(trifluoromethyl)phenyl	365
54	2-acetamido-4-methyl-5-thiazolyl	375
55	5-bromo-1-naphthyl	426



Example No.	Ar	MH+
56	2-bromophenyl	376
57	3-bromo-2-chloro-5-thienyl	416
58	4-bromo-2-chloro-5-thienyl	416
59	2-bromo-5-thienyl	382
60	2-chloro-5-thienyl	337
61	2-naphthyl	347
62	2,5-dibromo-3,6-difluorophenyl	491
63	2,5-dichloro-4-thienyl	371
64	5-chloro-3-methyl-2-benzothienyl	401
65	3-(phenyl)phenyl	373
66	4-methylphenyl	311
67	3-chlorophenyl	331
68	4-iodophenyl	423
69	4-t-butylphenyl	353
70	4-methoxyphenyl	327
71	3-methylphenyl	311
72	4-n-propylphenyl	339
73	4-chloro-2,5-dimethylphenyl	359
74	4-cyanophenyl	322
75	3-chloro-4-methylphenyl	345
76	3-vinylphenyl	322
77	3-ethylphenyl	324
78	4-vinylphenyl	322
79	4-ethylphenyl	324
80	4-fluorophenyl	314
81	3-(1-methoxyvinyl)phenyl	366
82	3-acetylphenyl	339
83	4-chlorophenyl	331, 333

Example 84

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-bromo-4-chlorophenyl sulfonamide.

The title compound was prepared using 4-methylpiperidine and 3-bromo-4-chlorophenyl sulfonyl chloride in the methods described in D5, D6 and E2.

Found MH^+ 437/439/441
$C_{17}H_{26}N_2O_2SClBr^{+H}$ requires 437/439/441

Example 85

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]4-chloro-3-vinylphenyl sulfonamide

A solution of E84 (50 mg, 0.11 mmol), vinyltributyltin (33 µl, 0.11 mmol) and tetrakistriphenylphosphine palladium (O) (10 mg) in triethylamine (15 µl, 0.11 mmol) and DMF (5 ml) was heated to 100°C under an argon atmosphere for 12 hours. The reaction mixture was cooled and concentrated and the residue purified on silica gel eluting with 5% methanol/dichloromethane to give the title compound.

Found $MH^+ = 385/387$
$C_{19}H_{29}ClN_2O_2S{+}H$ requires 385/387

Example 86

N-Methyl-N-[1R-methyl-3-(4-methylpiperidine-1-yl)propyl]3-hydroxymethylphenyl sulfonamide

A mixture of N-methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-carboxyphenyl sulfonamide (950mg, 2.6 mmol) and lithium aluminium hydride (350 mg, 9.2 mmol) in THF (40 ml) was stirred at room temperature for 3 hrs, cooled to 0°C and treated with a solution of water (0.35 ml), 10% aqueous sodium hydroxide (0.35 ml) and finally water (1.05ml). The quenched reaction mixture was filtered through kieselguhr washing with diethyl ether. The filtrate was dried with Na_2SO_4 and evaporated to afford the title compound (440 mg, 48%).

Found $MH^+ = 355$
$C_{18}H_{30}N_2O_3S{+}H$ requires 355

Example 87

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-ethylphenyl sulfonamide

A solution of E85 in ethanol was hydrogenated over platinum oxide for 3 hours. The reaction mixture was then filtered and concentrated to give the title compound.

Found $MH^+ = 353$
$C_{19}H_{32}N_2O_2S+H$ requires 353

Pharmacological Data

[^{3}H]-5-Carboxamidotryptamine binding to human 5-HT $_7$ receptor clones expressed in 293 cells *in vitro*.

The affinity of test drugs for the 5-HT $_7$ receptor binding site can be determined by assessing their ability to displace [^{3}H]-5-carboxamidotryptamine from 5-HT $_7$ receptor clones expressed in 293 cells (To *et al.*, 1995 and Sleight *et al.*, 1995).

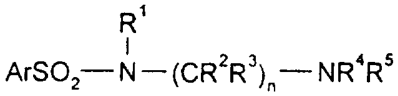
The cells suspension (400µl) was incubated with [^{3}H]-5-carboxamidotryptamine (0.5nM) in Tris HCl buffer (pH 7.4) at 37^{0}C for 45mins. Non-specific binding was measured in the presence of 5-hydroxytryptamine (10^{-6}M). Ten concentrations of test drug (10^{-11} to 10^{-5}M final concentration) were added in a volume of 50ul. The total assay volume was 500µl. Incubation was stopped by rapid filtration using a Tomtec cell harvester and radioactivity measured by scintillation counting on a Packard Topcount. The IC$_{50}$ values and pKi values were calculated by INFLEXION, a non-linear iterative curve fitting programme based in EXCEL (Bowen and Jerman, 1994).

Bowen, W. and Jerman, J. (1994). Br. J. Pharmacol.,112, 440P.
Sleight, A.J., Carolo, C.,Petit, N.,Zweingelstein, C. and Bourson, A. (1995). Mol. Pharmacol.,47, 99.
To, Z.P., Bonhaus, D.W., Eglen, R.M. and Jakeman, L.B. (1995). Br. J. Pharmacol.,15, 107.

- Testing Results: The compounds of Examples 1-83 have pKi's in the range <5.2 - 7.8

Claims:

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



$$ArSO_2-N(R^1)-(CR^2R^3)_n-NR^4R^5$$

(I)

wherein:

Ar is an optionally substituted mono- or bicyclic aromatic or heteroaromatic ring;

R^1 is C_{1-6} alkyl;

R^2 and R^3 are each independently hydrogen or C_{1-6} alkyl;

R^4 and R^5 are independently hydrogen, C_{1-6} alkyl, arylC_{1-6} alkyl or aryl or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 8-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, sulphur or oxygen; and

n is 2 to 4 in the manufacture of a medicament for the treatment of disorders in which antagonism of the $5HT_7$ receptor is beneficial.

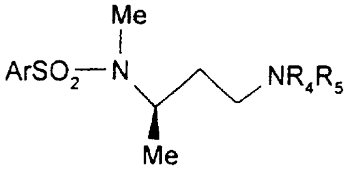
2. Use according to claim 1 in which Ar is a naphthyl group, a substituted phenyl group, or a dibromothienyl group.

3. Use according to claim 1 or 2 in which R^1 is methyl.

4 Use according to any one of claims 1 to 3 in which one of R^2 and R^3 is hydrogen and the other is methyl.

5 Use according to any one of claims 1 to 4 in which R^4 and R^5 form an optionally substituted 5- to 8-membered heterocyclic ring.

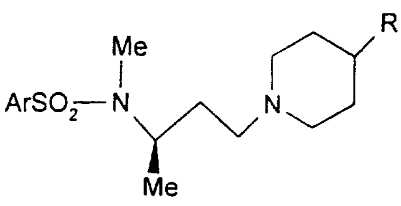
6. A compound of formula (i):



(i)

in which Ar, R^4 and R^5 are as defined in formula (I).

7. A compound of formula (ii):



(ii)

where Ar is a naphthyl group, a substituted phenyl group, or a dibromothienyl group and R^{10} is hydrogen, C_{1-6} alkyl, cycloC_{3-6} alkyl, arylC_{1-6} alkyl, CF_3, C_2F_5 or C_{1-6} alkyloxy.

8. A compound of formula (I) which is:

N-methyl-N-[1-methyl-3-(3-methylpiperidin-1-yl)propyl]-1-naphthalenesulfonamide,

N-Methyl-N-[1R-methyl-3-(3S-methyl-piperidin-1-yl)propyl]-1-naphthalene sulfonamide,

N-Methyl-N-[1R-methyl-3-(3R-methyl-piperidin-1-yl)propyl]-1-naphthalene sulfonamide,

N-Methyl-N-[3-[1-(2R-methylpiperidinyl)propyl]]-1-naphthlenesulfonamide,

N-Methyl-N-[3-[1-(2S-methylpiperidinyl)propyl]]-1-naphthalenesulfonamide,

(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-1-naphthalenesulfonamide,

(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-benzene sulfonamide,

(±) N-Methyl-N-[3-[1-(piperidinyl)butyl]]-2-naphthalenesulfonamide,

N-Methyl-N-[1-methyl-3-(2S-methyl-1-piperidyl)propyl]-4,5-dibromo-2-thiophene sulfonamide,

N-Methyl-N-[1-methyl-3-(2R-methyl-1-piperidyl)propyl]-4,5-dibromo-2-thiophene sulfonamide,

(±) N-Ethyl-N-[3-[1-(piperidinyl)butyl]]-1-naphthalenesulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-1-naphthalene sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidine-1-yl)propyl]-2,3-dibromothiophene-5-sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3,4-dichlorobenzene sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-phenylpiperazin-1-yl)propyl]-1-naphthalene sulfonamide,

N-Methyl-N-[1R-methyl-3-(4-phenylpiperazin-1-yl)propyl]-2,3-dibromothiophene-5-sulfonamide,

(±)-N-Methyl-N-[1-ethyl-3-(4-methylpiperidin-1-yl)propyl]-1-naphthalene sulfonamide,
N-Methyl-N-(4-piperidin-1-yl-butyl)-1-naphthalene sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3,4-dibromobenzene sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]-3-methylbenzene sulfonamide,
N-Methyl-N-[3-[1-(pyrrolidinyl)propyl]]-3-chlorobenzenesulfonamide,
N-Methyl-N-[3-[1-(morpholinyl)propyl]]-3-chlorobenzenesulfonamide,
N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-3-chlorobenzenesulfonamide,
N-Methyl-N-[3-[1-(pyrrolidinyl)propyl]]-4-bromobenzenesulfonamide,
N-Methyl-N-[3-[1-(morpholinyl)propyl]]-4-bromobenzenesulfonamide,
N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-4-bromobenzenesulfonamide,
N-Methyl-N-[3-[1-(morpholinyl)propyl]]-1-naphthalenesulfonamide,
N-Methyl-N-[3-[1-(N-methylpiperazinyl)propyl]]-1-naphthalenesulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-bromo-4-chlorophenyl sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]4-chloro-3-vinylphenyl sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidine-1-yl)propyl]3-hydroxymethylphenyl sulfonamide,
N-Methyl-N-[1R-methyl-3-(4-methylpiperidin-1-yl)propyl]3-ethylphenyl sulfonamide,
and pharmaceutically acceptable salts thereof.

9. A compound according to any one of claims 6 to 8 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 6 to 8 and a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 97/00446

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/12 A61K31/395 A61K31/445 A61K31/495 A61K31/54
C07C311/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 4 714 700 A (PATRICK CHOAY) 22 December 1987 see the whole document ---	1-10
X	EP 0 064 445 A (CHOAY S.A.) 10 November 1982 see the whole document ---	1-10
X	FR 2 313 918 A (CHOAY S.A.) 7 January 1977 see the whole document ---	1-19
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search 6 May 1997	Date of mailing of the international search report 20.05.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Luyten, H

INTERNATIONAL SEARCH REPORT

Inte   nal Application No
PCT/EP 97/00446

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