Title: TETRAHYDROBENZINDOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS 5-HT₂ RECEPTOR ANTAGONISTS

Abstract: The invention relates to compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein R¹ is halogen, C₆alkyl, hydroxy, C₆alkoxy, C₆alkylthio, C₆alkylsulphonyl, C₆alkylsulphonyl amino, mono- or di-C₆alkylamino, carboxyl, carboxamido, hydroxyC₆alkyl, mono- or di-C₆alkylaminocarboxyl, sulphonamido, C₆alkylsulphonylamino, aminoC₆alkyl, mono- or di-C₆alkylaminosulphonyl or C₆alkoxy-carbonyl; R² is hydrogen or C₆alkyl; n is 2, 3, 4, 5 or 6; A is nitrogen, carbon or CH, ..., is a single bond when A is nitrogen or CH or ...; is a double bond when A is carbon; X is nitrogen or CH; Y is O, S, NH or N-C₆alkyl, R³ is halogen, C₆alkyl, cyano, CF₃, C₆alkoxy-carbonyl, C₆alkoxy, hydroxy, amino, mono- or di-C₆alkylamino, acylamino, nitro, C₆alkoxy-carbonyl, C₆alkylthio, C₆alkylsulphonyl, C₆alkylsulphonyl, sulphanamoyl, mono- and di-C₆alkylsulphanamoyl, carboxamido, mono- and di-C₆alkylcarbamoyl, C₆alkylsulphonamido, arylsulphonamido, aryl, arylC₆alkyl, arylC₆alkoxy, arylxy and arylthio; m is 0, 1, 2 or 3, having 5-HT₂ antagonist activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.
Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
TETRAHYDROBENZINDOLONE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS 5-HT7 RECEPTOR ANTAGONISTS

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

Kikuchi et al. (J. Med. Chem., 1999, 42, 533) describes tetrahydrobenzindolone compounds as selective antagonists of the 5-HT7 receptor. Patent applications WO 98/00400, WO 99/33804 and WO 99/54303 also disclose tetrahydrobenzindolone compounds as 5-HT7 receptor antagonists. Such compounds are claimed to be useful in the treatment of various CNS diseases.

A structurally novel class of compounds has now been found which also possess 5-HT7 receptor activity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:

wherein:

- R1 is halogen, C1-alkyl, hydroxy, C1-alkoxy, C1-alkylthio, C1-alkylsulphonyl, C1-alkylsulphonyl, amino, mono-/di-C1-alkylamino, carboxy, carboxamido, hydroxy-C1-alkyl, mono-/di-C1-alkylaminocarbonyl, sulphonamido, C1-alkylsulphonylamino, mono-/di-C1-alkyl, mono-/di-C1-alkylaminosulphonyl or C1-alkoxy carbonyl;
- R2 is hydrogen, C1-alkyl or aryl C1-alkyl;
- p is 0, 1, 2 or 3;
- R3 is hydrogen or C1-alkyl;
- n is 2, 3, 4, 5 or 6;
- A is nitrogen, carbon or CH;
- --- is a single bond when A is nitrogen or CH or
- --- is a double bond when A is carbon;
- X is nitrogen or CH;
Y is O, S, NH or N-C₁₆-alkyl;
R₄ is halogen, C₁₆-alkyl, cyano, CF₃, C₃₋₇cycloalkyl, C₁₆-alkoxy, hydroxy, amino, mono- or di-C₁₆-alkylamino, acylamino, nitro, C₁₆-alkoxycarbonyl, C₁₆-alkythio, C₁₆-alkylsulphonyl, C₁₆-alkylsulphonylamino, sulfamoyl, mono- and di-C₁₆-alkylsulphamoyl, carbamoyl, mono- and di-C₁₆-alkylcarbamoyl, C₁₆-alkylsulphonamido, arylsulphonamido, aryl, aryIC₁₆-alkyl, aryIC₁₆-alkoxy, aryloxy and arylthio;
m is 0, 1, 2 or 3.

C₁₆-alkyl groups whether alone or as part of another group may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine. The term 'aryl', whether alone or as part of another group, is used herein to describe, unless otherwise stated, a group such as phenyl or naphthyl. Such aryl groups may be optionally substituted by one or more C₁₆-alkyl, halogen, CF₃ or C₁₆-alkoxy.

When p is one or more, R¹ is preferably halogen (particularly fluorine or chlorine) or a C₁₆-alkyl (particularly methyl). When p is 2 or 3 the groups R¹ may be the same or different. Preferably p is 0 or 1, most preferably 0.
Preferably R² is hydrogen.
Preferably n is 4 or 5, most preferably 4.
Preferably R³ is hydrogen.
Preferably X is N.
Preferably Y is O, S or NH;
When m is one or more, R⁴ is preferably halogen (particularly fluorine or chlorine), a C₁₆-alkyl (particularly methyl), C₁₆-alkoxy (particularly methoxy), CF₃ or hydroxy. A preferred site for substitution of R⁴ groups is at the 4, 5 or 6 position of the benzo fused heteroaryl ring. When m is 2 or 3 the groups R⁴ may be the same or different. Preferably m is 0 or 1.

Preferred compounds of this invention include examples E₁ – E₄₁ (as shown below) or a pharmaceutically acceptable salt thereof. Particularly preferred compounds of this invention include:

2a- {4-[4-((1H-Benimidazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(5-Methyl-1H-benimidazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a-4-{4-[(Benzoazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a-4-{4-[(Benzothiazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
5 2a-4-{4-(1H-Benzimidazol-2-yl)-piperazin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a-4-{4-(5-Fluoro-1H-benzimidazol-2-yl)-piperazin-1-yl]-butyl}-2a, 3, 4, 5-
tetrahydro-1H-benzo[c,d]indol-2-one,
2a-4-{5-(5-Fluoro-1H-benzimidazol-2-yl)-piperazin-1-yl]-penty]-2a, 3, 4, 5-
tetrahydro-1H-benzo[c,d]indol-2-one,
10 2a-4-(Benzothiazol-2-yl)-piperazin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a-4-[(Benzoazol-2-yl)-piperazin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
15 2a-4-{4-(1H-Benzimidazol-2-yl)-3,6-dihydro-1(2H)-pyridinyl]-butyl]-2a, 3, 4, 5-
tetrahydro-1H-benzo[c,d]indol-2-one,
2a-4-{4-(1H-Indol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one
or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. 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 coupling a compound of formula (II):

![Chemical structure](image)

(II)

in which \(R^1, R^2, p\) and \(n\) are as defined in formula (I) and \(L\) is a leaving group with a compound of formula (III):

![Chemical structure](image)

(III)

in which \(------\), \(R^3, R^4, A, X, m\) and \(Y\) are as defined in formula (I); and optionally thereafter if appropriate:
- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

Suitable leaving groups \(L\) include halogen, preferably chlorine or bromine, and \(-\text{OSO}_2\text{Ar}\) groups such as tosylate. The reaction of a compounds of formulae (II) and (III) is preferably carried out in a solvent such as dichloromethane or acetonitrile optionally in the presence of sodium iodide and a base such as potassium carbonate. Preferably, compounds of formula (II) and formula (III) are reacted together in the presence of a polymer supported base in a solvent such as DMF.

Those skilled in the art will appreciate that it may be necessary to protect certain 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).

Compounds of formulae (II) and (III) can be prepared using methods described herein, 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 5-HT7 receptor antagonist activity and are believed to be of potential use for the treatment or prophylaxis of CNS and other disorders such as anxiety, depression, obsessive compulsive disorder, schizophrenia, attention deficit disorders, sleep disorders (including disturbances of circadian rhythms), migraine, neurodegenerative disorders such as Parkinson's disease and Alzheimers disease, pain disorders, feeding disorders such as anorexia and bulimia, sexual dysfunction, ocular disorders, asthma, epilepsy, hypothalamic diseases, inflammation, renal disorders, hypotension, cardiovascular shock, stroke including neurodegeneration resulting from stroke, septic shock and gastrointestinal diseases such as spastic colon and IBS (irritable bowel syndrome).

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof for use in the treatment or prophylaxis of depression, anxiety, migraine and/or sleep disorders.

The invention further provides a method of treatment or prophylaxis of disorders where an antagonist of the 5-HT7 receptor is beneficial, particularly the aforementioned disorders, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which an antagonist of the 5-HT7 receptor is beneficial, particularly the aforementioned disorders.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) 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 infusible 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, tableting 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 times 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.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual
publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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

Example 1
2a-{4-[4-(1H-Benzimidazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E1)

Triazabicyclo[4.4.0]dec-5-ene bound to polystyrene cross-linked with 2% DVB (500 mg, 1.3 mmol) was added to a shaken solution of 4-benzimidazol-2-yl-piperidine\(^1\) (100 mg, 0.5 mmol) and 2a-(4-bromobutyl) 2a,3,4,5-tetrahydro-1H-benzo[c,d]indol-2-one\(^2\) (200 mg, 0.6 mmol) in DMF (10 ml). After 3 days the solution was decanted onto SCX resin and eluted with methanol (20 ml) followed by 1N methanolic-ammonia (20 ml). The methanolic-ammonia fraction was concentrated and the residue was purified by column chromatography (5% methanol-dichloromethane) to afford the title compound as a white foam (125mg, 58%).

LCMS (100%) Mass spectrum MH\(^+\) 429. \(^1\)H NMR: \(\delta\) DMSO 0.8-1.4 (5H, m), 1.6-2.2 (13H, m), 2.5-2.6 (1H, m), 2.7-2.9 (4H, m), 6.6 (1H, d), 6.7 (1H, d), 7.0-7.2 (3H, m), 7.3-7.4 (1H, m), 7.5-7.6 (1H, m), 10.1 (1H, s), 12.1 (1H, s).

Example 1a
Enantiomer 1 of 2a-{4-[4-(1H-benzimidazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E1a)
Racemic 2a-{4-[4-(1H-benzimidazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E1) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 30% ethanol-hexane, to afford the enantiomer 1 title compound as the faster running component with a retention time of 7.8 minutes.

Example 1b
Enantiomer 2 of 2a-{4-[4-(1H-benzimidazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E1b)
Racemic 2a-\{4-(1H-benzimidazol-2-yl)-piperidin-1-yl\}-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E1) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 30% ethanol-hexane, to afford the enantiomer 2 title compound as the slower running component with a retention time of 13.1 minutes.

**Example 2**

2a-\{4-(5-Methyl-1H-benzimidazol-2-yl)-piperidin-1-yl\}-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E2)

By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 4-(5-methyl)benzimidazol-2-yl-piperidine⁵ the title compound was obtained as a white solid.

Mass spectrum \( M^+ \) 444. § MeOD 1.0-1.5 (4H, m), 1.6-2.0 (4H, m), 2.1-2.5 (6H, m), 2.6 (3H, s), 2.7-2.8 (1H, m), 2.8-3.0 (1H, m), 3.0-3.3 (4H, m), 3.6-3.9 (3H, m), 6.7 (1H, d), 6.8 (1H, d), 7.1 (1H, App t), 7.4 (1H, dd), 7.6 (1H, d), 7.7 (1H, d).

**Example 2a**

Enantiomer 1 of 2a-\{4-(5-Methyl-1H-benzimidazol-2-yl)-piperidin-1-yl\}-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E2a)

Racemic 2a-\{4-(5-Methyl-1H-benzimidazol-2-yl)-piperidin-1-yl\}-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E2) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 30% ethanol-hexane, to afford the enantiomer 1 title compound as the faster running component with a retention time of 7.9 minutes.

**Example 2b**

Enantiomer 2 of 2a-\{4-(5-Methyl-1H-benzimidazol-2-yl)-piperidin-1-yl\}-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E2b)

Racemic 2a-\{4-(5-Methyl-1H-benzimidazol-2-yl)-piperidin-1-yl\}-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E2) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 30% ethanol-hexane, to afford the enantiomer 2 title compound as the slower running component with a retention time of 16.6 minutes.
Example 3
2a-4-[4-(Benzoxazol-2-yl)-piperidin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E3)

By an analogous procedure to that described for Example 1, replacing 4-
benzimidazol-2-yl-piperidine with 4-benzoxazol-2-yl-piperidine, the title compound
was obtained as a white solid.
LCMS (100%) Mass spectrum MH⁺ 430. 1H NMR: δ DMSO 0.7-1.3 (5H, m), 1.5-
2.1 (13H, m), 2.4-2.5 (1H, m), 2.6-2.9 (4H, m), 6.5 (1H, d), 6.6 (1H, d), 6.9 (1H, app t), 7.2-7.3 (2H, m), 7.5-7.6 (2H, m), 9.9 (1H, s).

Example 3a
Enantiomer 1 of 2a-4-[4-(Benzoxazol-2-yl)-piperidin-1-yl]-butyl]-2a, 3, 4, 5-
tetrahydro-1H-benzo[c,d]indol-2-one (E3a)
Racemic 2a-4-[4-(benzoxazol-2-yl)-piperidin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-
benzo[c,d]indol-2-one (E3) was subjected to preparative HPLC on a Chiralpak AD
column, eluting with 15% ethanol-hexane, to afford the enantiomer 1 title compound
as the faster running component with a retention time of 17 minutes.

Example 3b
Enantiomer 2 of 2a-4-[4-(Benzoxazol-2-yl)-piperidin-1-yl]-butyl]-2a, 3, 4, 5-
tetrahydro-1H-benzo[c,d]indol-2-one (E3b)
Racemic 2a-4-[4-(benzoxazol-2-yl)-piperidin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-
benzo[c,d]indol-2-one (E3) was subjected to preparative HPLC on a Chiralpak AD
column, eluting with 15% ethanol-hexane, to afford the enantiomer 2 title compound
as the slower running component with a retention time of 30 minutes

Example 4
2a-4-[4-(Benzothiazol-2-yl)-piperidin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-
benzo[c,d]indol-2-one (E4)
By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 4-benzothiazol-2-yl-piperidine\(^1\), the title compound was obtained as a white solid.

\[ \text{LCMS (100\%) MH}^+ 446. \]  \( ^1 \text{H NMR: } \delta \text{ CDCl}_3 1.0-1.2 \text{ (1H, m), 1.2-1.5 (5H, m), 1.8-2.3} \text{ (12H, m), 2.5-2.7 (1H, m), 2.8-3.1 (4H, m), 6.7 (1H, d), 6.8} \text{ (1H, d), 7.1 (1H, App t), 7.3 (1H, dd), 7.4 (1H, dd), 7.8 (1H, s), 7.8 (1H, d), 7.9} \text{ (1H, d).} \]

**Example 4a**

Enantiomer 1 of 2a-\{4-\{4-(benzothiazol-2-yl)-piperidin-1-yl\}-butyl\}-2a, 3, 4, 5-tetrahydro-1\(H\)-benzo[\(c\),\(d\)]indol-2-one (E4a)

Racemic 2a-\{4-\{4-(benzothiazol-2-yl)-piperidin-1-yl\}-butyl\}-2a, 3, 4, 5-tetrahydro-1\(H\)-benzo[\(c\),\(d\)]indol-2-one (E4) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 15% ethanol-hexane, to afford the enantiomer 1 title compound as the faster running component with a retention time of 21.5 minutes.

**Example 4b**

Enantiomer 2 of 2a-\{4-\{4-(Benzothiazol-2-yl)-piperidin-1-yl\}-butyl\}-2a, 3, 4, 5-tetrahydro-1\(H\)-benzo[\(c\),\(d\)]indol-2-one (E4b)

Racemic 2a-\{4-\{4-(benzothiazol-2-yl)-piperidin-1-yl\}-butyl\}-2a, 3, 4, 5-tetrahydro-1\(H\)-benzo[\(c\),\(d\)]indol-2-one (E4) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 15% ethanol-hexane, to afford the enantiomer 2 title compound as the slower running component with a retention time of 43 minutes.

**Example 5**

2a-\{4-\{4-(1\(H\)-Benzimidazol-2-yl)-piperazin-1-yl\}-butyl\}-2a, 3, 4, 5-tetrahydro-1\(H\)-benzo[\(c\),\(d\)]indol-2-one (E5)
By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 1-benzimidazol-2-yl-piperazine\(^4\), the title compound was obtained as a white foam.

LCMS (100%) MH\(^+\) 430. \(^1\)H NMR: \(\delta\) DMSO 1.0-1.2 (3H, m), 1.6-2.0 (7H, m), 2.5-3.8 (10H, m), 4.3-4.4 (2H, m), 6.6 (1H, d), 6.7 (1H, d), 7.0-7.1 (1H, App t), 7.2-7.3 (2H, m), 7.4-7.5 (2H, m), 10.1 (1H, s), 11.3 (1H, s).

**Example 6**

2a-{4-[4-(5-Fluoro-1H-benzimidazol-2-yl)-piperazin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E6)

By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 1-(5-fluoro)benzimidazol-2-yl-piperazine\(^5\), the title compound was obtained as a white solid.

LCMS (100%) MH\(^+\) 448. \(^1\)H NMR: \(\delta\) DMSO 0.9-1.3 (5H, m), 1.7-2.4 (11H, m), 2.5-2.8 (2H, m), 3.4-3.5 (4H, m), 6.6 (6.7 (3H, m), 6.9-7.2 (3H, m), 10.1 (1H, s), 11.4 (1H, s).

**Example 7**

2a-{5-[4-(5-Fluoro-1H-benzimidazol-2-yl)-piperazin-1-yl]-pentyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E7)

By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 1-(5-fluoro)benzimidazol-2-yl-piperazine\(^5\) and 2a-
(4-bromobutyl) 2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one with 2a-(5-bromopentyl) 2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one, the title compound was obtained as a white solid.

LCMS (100%) MH⁺ 462. ¹H NMR: δ CDCl₃ 1.1-1.8 (10H, m), 2.0-2.3 (4H, m), 2.5-2.6 (4H, m), 2.6-2.9 (2H, m), 3.5-3.6 (4H, m), 6.6-7.5 (8H, m).

Example 8

2a-{4-[4-(Benzothiazol-2-yl)-piperazin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E8)

By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 1-benzothiazol-2-yl-piperazine⁶, the title compound was obtained as a white solid.

LC/MS (97%) MH⁺ 447. ¹H NMR: δ DMSO 0.8-1.3 (5H, m), 1.6-1.8 (2H, m), 1.8-2.3 (4H, m), 2.3-2.4 (4H, m), 2.5-2.6 (1H, m), 2.8-2.9 (2H, m), 3.4-3.6 (4H, m), 6.6 (1H, d), 6.7 (1H, d), 7.0 (2H, App t), 7.2 (1H, app t), 7.4 (1H, d), 7.7 (1H, d), 10.1 (1H, s).

Example 9

2a-{4-[4-(Benzoazol-2-yl)-piperazin-1-yl]-butyl]-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E9)

By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 1-benzoazol-2-yl-piperazine⁷, the title compound was obtained as a white solid.

LC/MS (100%) MH⁺ 430. ¹H NMR: δ DMSO 0.8-1.4 (6H, m), 1.6-1.8 (2H, m), 1.8-2.2 (4H, m), 2.3-2.4 (4H, m), 2.6-2.7 (1H, m), 2.7-2.9 (1H, m), 3.4-3.6 (4H, m), 6.6 (1H, d), 6.7 (1H, d), 6.9-7.1 (3H, m), 7.2 (1H, d), 7.3 (1H, d), 10.1 (1H, s).
By analogous procedures to those described in Examples 1 - 9, using the appropriate piperidine or piperazine and 2a-(ω-bromoalkyl)-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one intermediates consistent with the final products, Examples 10 - 37 of Table 1 were prepared. $^1$H NMR and mass spectra were consistent with the structures given in Table 1.
Table 1

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Example 39

2a-{4-[4-(6-Fluorobenzoxazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E39)

By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 4-(6-fluorobenzoxazol-2-yl)-piperidine, the title compound was obtained as a white solid.

LCMS (100%) Mass spectrum MH\(^+\) 448 1H NMR: δ DMSO 0.9 – 1.0 (1H, m), 1.1 – 1.4 (4H, m), 1.6 – 2.3 (8H, m), 2.5 – 2.6 (1H, m), 2.7 – 3.0 (4H, m), 6.6 (1H, d), 6.7 (1H, d), 7.0 (1H, t), 7.2 (1H, td), 7.6 – 7.7 (2H, m), 10.1 (1H, s)

Example 39a

Enantiomer 1 of 2a-{4-[4-(6-Fluorobenzoxazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E39a)

Racemic 2a-{4-[4-(6-fluorobenzoxazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E39) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 10% ethanol-hexane, to afford the enantiomer 1 title compound as the faster running component with a retention time of 19 minutes.

Example 39b

Enantiomer 2 of 2a-{4-[4-(6-Fluorobenzoxazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E39b)

Racemic 2a-{4-[4-(6-fluorobenzoxazol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E39) was subjected to preparative HPLC on a Chiralpak AD column, eluting with 10% ethanol-hexane, to afford the enantiomer 2 title compound as the slower running component with a retention time of 29.5 minutes.

Example 40

2a-{4-[4-(1H-indol-2-yl)-piperidin-1-yl]-butyl}-2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one (E40)
By an analogous procedure to that described for Example 1, replacing 4-benzimidazol-2-yl-piperidine with 4-(indol-2-yl)-piperidine, the title compound was obtained as an off-white solid.

LCMS (100%) Mass spectrum MH+ 428  1H NMR: δ CDCl3 1.0 – 1.2 (1H, m), 1.2 – 2.2 (15H, m), 2.2 – 2.4 (2H, m), 2.6 – 2.8 (2H, m), 2.8 – 2.9 (1H, m), 2.9 – 3.0 (2H, m), 6.2 (1H, s), 6.7 (1H, d), 6.8 (1H, d), 7.0 – 7.2 (3H, m), 7.2 – 7.4 (2H, m), 7.5 (1H, d), 8.0 (1H, s)

Example 41

2a-[4-[4-(1H-Benzimidazol-2-yl)-3,6-dihydro-1(2H)-pyridinyl]-butyl]-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one (E41)

2-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-benzimidazole hydrochloride8 (0.07 g, 0.35 mmol) was added to a solution of diisopropylethylamine (0.06 ml, 0.35 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene bound to polystyrene crosslinked with 2% DVB (0.3 g, ~2.6 mmol base/g resin, 0.78 mmol) and 2a-(4-bromo-butyl)-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one2 (0.12 g, 0.39 mmol), in dimethylformamide (3 ml) and dichloromethane (1.5 ml), and the mixture stirred for 72 h. The reaction mixture was loaded onto an SCX cartridge and washed with methanol (50ml) and then 5% aqueous ammonia/methanol (25ml). The ammonia/methanol washing was concentrated in vacuo and the residue purified by column chromatography (5% then 10% methanol/chloroform) to give the title compound as a pale yellow solid (0.020 g, 13.4%).

LCMS (96%) Mass spectrum MH+ 427  1H NMR δ CDCl3 1.0 – 2.9 (21H, series of unassigned m's), 3.1 (2H, app br s), 6.5 (1H, m), 6.6 (1H, d), 6.8 (1H, d), 7.1 (1H, t), 7.2 (2H, m), 7.5 (2H, app br s), 8.4 (1H, s).
References

5. Prepared according to the general procedure of Orjales.

Pharmacological Data

[3H]-5-Carboxamidotryptamine binding to human 5-HT7 receptor clones expressed in HEK 293 cells *in vitro*.

The affinity of the compounds of this invention for the 5-HT7 receptor binding site can be determined by methods described in WO 97/29097. All compounds tested had a pKi greater than 6.0. Preferred examples had a pKi in the range 8.0 - 9.2.
Claims:

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

\[
\begin{array}{c}
\text{(I)} \\
\end{array}
\]

wherein:

- $R^1$ is halogen, $C_1$-$C_6$-alkyl, hydroxy, $C_1$-$C_6$-alkoxy, $C_1$-$C_6$-alkylthio, $C_1$-$C_6$-alkylsulphinyl, $C_1$-$C_6$-alkylsulphonyl, amino, mono- or di-$C_1$-$C_6$-alkylamino, carboxy, carboxamido, hydroxy-$C_1$-$C_6$-alkyl, mono- or di-$C_1$-$C_6$-alkylaminocarbonyl, sulphonamido, $C_1$-$C_6$-alkylsulphonylamino, amino-$C_1$-$C_6$-alkyl, mono- or di-$C_1$-$C_6$-alkylaminosulphonyl or $C_1$-$C_6$-alkoxycarbonyl;
- $R^2$ is hydrogen, $C_1$-$C_6$-alkyl or aryl-$C_1$-$C_6$-alkyl;
- $p$ is 0, 1, 2 or 3;
- $R^3$ is hydrogen or $C_1$-$C_6$-alkyl;
- $n$ is 2, 3, 4, 5 or 6;
- $A$ is nitrogen, carbon or CH,
- is a single bond when $A$ is nitrogen or CH or is a double bond when $A$ is carbon;
- $X$ is nitrogen or CH;
- $Y$ is O, S, NH or N-$C_1$-$C_6$-alkyl;
- $R^4$ is halogen, $C_1$-$C_6$-alkyl, cyano, CF$_3$, C$_3$-$C_7$-cycloalkyl, $C_1$-$C_6$-alkoxy, hydroxy, amino, mono- or di-$C_1$-$C_6$-alkylamino, acylamino, nitro, $C_1$-$C_6$-alkoxycarbonyl, $C_1$-$C_6$-alkylthio, $C_1$-$C_6$-alkylsulphinyl, $C_1$-$C_6$-alkylsulphonyl, sulphamoyl, mono- and di-$C_1$-$C_6$-alkylsulphamoyl, carbamoyl, mono- and di-$C_1$-$C_6$-alkylcarbamoyl, $C_1$-$C_6$-alkylsulphonamido, arylsulphonamido, aryl, aryl-$C_1$-$C_6$-alkyl, aryl-$C_1$-$C_6$-alkoxy, aryloxy and arylthio;
- $m$ is 0, 1, 2 or 3.

2. A compound according to claim 1 in which $X$ is nitrogen.
3. A compound according to claim 1 or claim 2 in which R² is hydrogen.

4. A compound according to any of the preceding claims in which n is 4 or 5.

5. A compound according to claim 1 which is a compound E1 - E41 (as described above) or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 which is

2a- {4-[4-(1H-Benzimidazol-2-yl)-piperidin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(5-Methyl-1H-benzimidazol-2-yl)-piperidin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(Benzoxazol-2-yl)-piperidin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(Benzothiazol-2-yl)-piperidin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(1H-Benzimidazol-2-yl)-piperazin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(5-Fluoro-1H-benzimidazol-2-yl)-piperazin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {5-[4-(5-Fluoro-1H-benzimidazol-2-yl)-piperazin-1-yl]-pentyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(Benzothiazol-2-yl)-piperazin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(Benzoxazol-2-yl)-piperazin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(1H-Benzimidazol-2-yl)-3,6-dihydro-1(2H)-pyridinyl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one,
2a- {4-[4-(1H-Indol-2-yl)-piperidin-1-yl]-butyl} -2a, 3, 4, 5-tetrahydro-1H-benzo[c,d]indol-2-one
or a pharmaceutically acceptable salt thereof.

7. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises coupling a compound of formula (II):
in which $R^1$, $R^2$, $p$ and $n$ are as defined in formula (I) and $L$ is a leaving group with a compound of formula (III):

(III)

in which $R^3$, $R^4$, $A$, $m$, $X$, and $Y$ are as defined in formula (I); and optionally thereafter if appropriate:
- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

8. A compound according to any one of claims 1 to 6 for use in therapy.

9. A compound according to any one of claims 1 to 6 for use in the treatment of depression, anxiety, migraine and/or sleep disorders.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

11. A compound of formula (I) as defined in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of the 5-HT$_7$ receptor is beneficial.

12. The use of a compound of formula (I) as defined in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of the 5-HT$_7$ receptor is beneficial.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

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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)

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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)

BEILSTEIN Data, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

### Patent family members are listed in annex.

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- **O** document referring to an oral disclosure, use, exhibition or other means
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**1** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search: 20 February 2001

Date of mailing of the international search report: 05/03/2001

Name and mailing address of the ISA:

European Patent Office, P.B. 5816 Patentlaan 2 NL – 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Hartrampf, G
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<td>EGLEN R.M. ET AL.: &quot;The 5-HT7 receptor: Orphan found&quot; TRENDS IN PHARMACOLOGICAL SCIENCES, GB, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 18, no. 4, 1 April 1997 (1997-04-01), pages 104-107, XP004058670 ISSN: 0165-6147 the whole document</td>
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### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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