RTMP

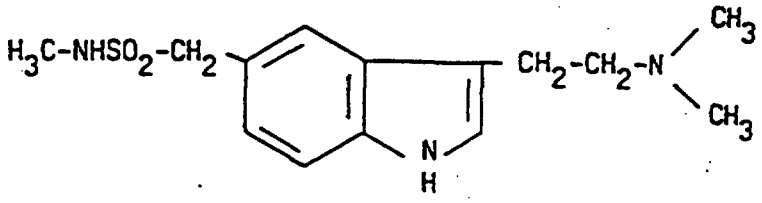
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INDOL DERIVATIVES FOR THE TREATMENT OF MIGRAINE

THIS INVENTION relates to new indol derivatives, methods for their preparation, compositions containing them and their use in medical treatment.

The mechanism involved in the genesis of a migraine attack is not known, but it has been demonstrated that the large intracranial vessels are distended during the headache phase. Some compounds like ergotamine and serotonine (5-Hydroxytryptamine; 5-HT), have a vasoconstrictor action in the carotid vascular bed by an agonistic action at the "5-HT_1-like" receptors. However, the lack of selectivity of these compounds is the cause of undesirable and potentially dangerous side-effects.

In British Patents 2124210A and 2162532A, new anti-migraine compounds have been disclosed and seem to stimulate more selectively a sub-population of "5-HT_1-like" receptors. Among these compounds, Sumatriptan of formula:

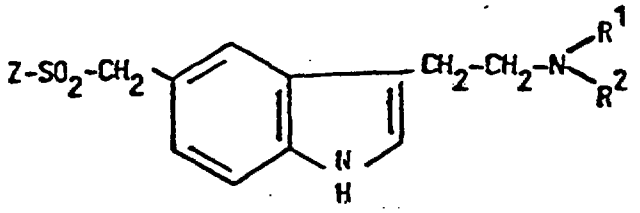


is available for migraine therapy. This compound presents a high affinity for 5-HT_{1D} receptor but it has also a very important affinity for 5-HT_{1A} receptor. This affinity for 5-HT_{1A} receptor, causes hypotension by a central nervous system action and other side effects.

We have now found that the introduction of a nitrogen ring in the methanesulfonyl group provides new anti-migraine compounds that present a greater affinity for 5-HT_{1A} receptor and therefore, less side-effects.

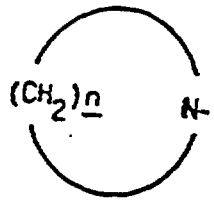
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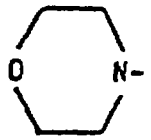
Accordingly, the present invention provides a compound of formula:

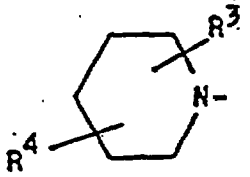


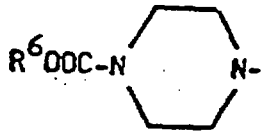
(I)

wherein R^1 and R^2 each represent a hydrogen atom or an alkyl group, Z represents a ring selected from:

II  n which n represents 4, 5 or 6;

III 

IV  in which R^3 represents hydrogen or an alkyl group R^4 represents an alkyl, methoxy, benzyl or R^5 NHCO group, R^5 being an alkyl group; and

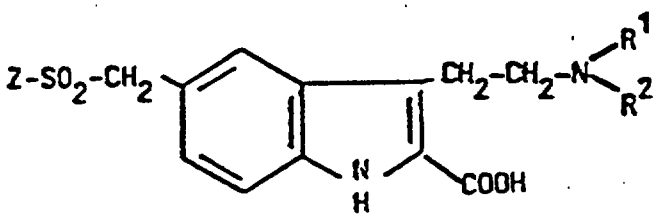
V  in which R^6 repreesents an alkyl group;

and pharmaceutically acceptable salts thereof.

The alkyl group mentioned in relation with the groups R^1, R^2, R^3, R^4, R^5 and R^6 in compounds of the invention, are usually "lower" alkyl, that is containing up to 6 and particularly up to 4 carbon atoms, the hydrocarbon chain being branched or straight.

The compounds of general formula I wherein R^1 and R^2 are alkyl groups and Z is II or V are preferred.

According to a feature of the present invention the indol derivatives of general formula I may be prepared by the process which comprises a decarboxylation of a carboxylic acid of general formula VI:



(VI)

(wherein the various symbols are as defined above). The reaction is preferably carried out in an inert organic solvent as quinoline, tri-n-butylamine, N,N-dimethylacetamide or pyridine, in the presence of a catalyst as copper powder, cupric oxide, cuprous oxide or other copper derivatives, at a temperature between 100 and 200°C.

The intermediates VI used in the preparation of the compounds of the invention, were prepared by known processes described in the literature (A. Gonzalez, Synth. Commun. (1991)), 21, 669; B.A. Howell, J. Chem. Ed. 176 (1984); H. Plieninger, Ber. (1950), 83, 268).

Indol derivatives of general formula I can be converted by methods known *per se* into acid addition salts with acids in appropriate solvents, for example acetone, alcohols, dioxane or tetrahydrofuran. Suitable acid addition salts are those derived from inorganic acids, for example the hydrochlorides and sulphates.

The experiments with usual test animals were conducted and evaluated in the following manner:

Dog saphenous vein

Isometric recordings were performed essentially as described by Humphrey *et al* (1988). Briefly, lateral saphenous vein ring preparations (3 mm. wide) removed from anaesthetized beagle dogs were suspended under 2g. resting tension, in 30 mL organ baths containing Krebs at 37°C. The experiments were carried out in the presence of 5-HT2, H1 and muscarinic antagonists and serotonin 1μM was used as quantitative reference standard.

(Humphrey P.P.A.; Feniuk W.; Perren M.J.; Connor H.E.; Oxford A.W.; Coates I.H. and Butina D. (1988). GR 43175, a selective agonist for the 5-HT1-like receptor in dog isolated saphenous vein. Br. J. Pharmac. 94, 1123-1132).

Binding to 5HT1D receptors

Assays were performed essentially as described by Bruinvels *et al*. Varying amounts of tested drugs were added to 0.25 mL final volume reaction that included 100μg of calf caudate nucleus membrane protein, 100 pM (Serotonin-5-O-Carboxymethyl-Glycyl[^{125}I]Tyrosinamide (^{125}I-GTI), 4 mM $CaCl_2$ and 50 mM Tris HCl buffer, pH 7.4. After incubation at 37°C for 30 minutes, samples were filtered under reduced pressure using glass fibre filters. The filters were washed with ice-cold buffer and dried. Non-specific binding was defined as that obtained in the presence of 10μM 5HT. Trapped radioactivity was quantified using a gamma counter. Displacement curves were constructed and the concentration displacing 50% of radioligand was calculated for each tested compound using non-linear regression. Data from at least three different assays run in duplicate was averaged.

(Bruinvels A.T.; Lery H.; Palacios J.M. and Hoyer D. 5-HT_{1D} binding sites in various species: similar pharmacological profile in dog, monkey, calf, guinea-pig and human brain membranes. Naunyn-Schmiedeberg's Arch. Pharmacol. (in press)).

Binding to 5HT1A receptors

Assays were performed essentially as described by Gozlan *et al* (1983). Varying amounts of tested drugs were added to 1 mL final volume reaction mixtures that included 100 μg of rat hippocampus membrane protein, 0.5 nM ^{3}H-8-OH-DPAT, 4 mM $CaCl_2$, 0.1% ascorbic acid, 10 μM pargyline and 50 mM Tris HCl buffer, pH 7.4. After incubation at 25°C for 30 minutes, samples were filtered under reduced pressure using glass fibre filters. The filters were washed with ice-cold buffer and dried. Non-specific binding was defined as that obtained in the presence of 10 μM 5HT. Radioactivity was quantified by scintillation counting and data was handled as described for the $5HT_{1D}$ binding assay. (Gozlan H.; El Mestikawy S.; Pichat L.; Glowinski J. and Hamon M. (1983). Identification of presynaptic serotonin autoreceptors using a new ligand:^{3}H-PAT. Nature 305, 140-142).

The results of the tests described above, using compounds according to the invention (see Examples below) and, as a comparison, Sumatriptan, are shown in Table I below:

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TABLE I. Results of different pharmacological test

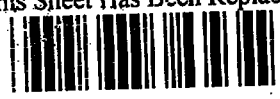
	Dog saphenous vein pD2	Binding IC50 nM		
		125I-GTI	3H-8-OH-DPAT	5HT1A/ 5HT1D
Sumatriptan	6.06 ± 0.01	10.4 ± 1	460 ± 67	44.2
1	6.06 ± 0.03	10.7 ± 0.4	825 ± 69	77.1
2	5.92 ± 0.10	6.9 ± 0.4	340 ± 0.5	49.3
11	6.47 ± 0.03	3.2 ± 0.3	850 ± 40	65.6

From results presented above it can be concluded that the novel compounds of this invention demonstrate binding selectivity for 5-HT1D receptors and vasoconstrictor capability mediated by an agonism on 5HT1D receptors. According to the results this invention provides compounds with potential interest for the treatment or prevention of migraine and other headache associated with vascular disorders (e.g. cluster headache and chronic paroxysmal hemicrania), with administration of substances or their withdrawal, and for the treatment or prevention of tensional cephaliar pain, movement disorders, depression and anxiety.

Thus, the present invention provides indol derivatives of the formula I and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such derivatives and salts thereof, for use in the treatment or therapy of the human body.

Accordingly, the indol derivatives of the formula I and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such derivatives and salts thereof, may be used in a method of treatment

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of disorders of the human body which comprises administering to a recipient in need of such therapy an effective amount of said derivatives or salts thereof or said compositions.

The present invention also provides pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, or a pharmacologically acceptable salt in association with a pharmaceutically acceptable carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, percutaneous or parenteral administration.

The pharmaceutically acceptable carriers or diluents which are admixed with the active compound, or compounds or salts of such compounds, to form the compositions of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions. Compositions of this invention are preferably adapted for administration parenteral and *per os*. In this case, the composition for oral administration may take the form of tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preeparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient,

together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 1 and 200 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

Effective doses are normally in the range of 10-600 mg of active ingredient per day.

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

EXAMPLE 1

To a solution of previously dried 1-[[2-carboxy-3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine (1.6 g; 0.0442 moles) in anhydrous quinoline (75 ml) and under atmosphere of nitrogen, cuprous oxide (160 mg; 0.0011 moles) was added. The reaction mixture was heated to 190°C for 15 minutes, stirred to room temperature, poured into a mixture of 1N hydrochloric acid (150 ml) and ethyl

acetate (50 ml), shaken and decanted. The aqueous solution was washed several times with ethyl acetate, then solid sodium bicarbonate was added until pH = 7.8, and washed with n-hexane to eliminate the quinoline. The aqueous solution was made alkaline with solid potassium carbonate and extracted with ethyl acetate. The organic solution was dried (Na_2SO_4), the solvent removed under reduced pressure when a dark oil was obtained (1.3 g; yield 92%). This product was purified by column chromatography with silica gel and methylene chloride:ethanol:ammonium hydroxide (60:8:1) as eluent and a white foam (0.8 g) of 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]pyrrolidine was obtained.

To a solution of the above product (0.8 g) in acetone (30 ml), a few drops of hydrogen chloride saturated dioxan solution, were added. The precipitated solid was collected by filtration, washed with acetone and dried to give 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]-pyrrolidine hydrochloride (0.75 g). Melting point 218-220°C.

Further indol derivatives of general formula I as set out in Table 2 below were prepared according to the process disclosed in Example 1 but using the appropriately substituted reactants VI.

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TABLE 2

COMPOUND No.	R^1 , R^2	Z	DERIVATIVE	M.P °C
1	$R^1=R^2=CH_3$	II; n=4	HCl	218-220
2	$R^1=R^2=CH_3$	II; n=5	HCl	225-227(d)
3	$R^1=R^2=CH_3$	II; n=6	hydrogen succinate	127-130(d)
4	$R^1=H; R^2=CH_3$	II; n=4	HCl	177-178
5	$R^1=R^2=CH_3$	III	HCl	231-232(d)
6	$R^1=R^2=CH_3$	IV; $R^3=H$; $R^4=4-CH_3$	hydrogen succinate	151-153
7	$R^1=R^2=CH_3$	IV; $R^3=H^4$ $=4-CH_3$	hydrogen succinate	170-172
8	$R^1=R^2=CH_3$	IV; $R^3=H$; R^4=methoxy	hydrogen succinate	143-145
9	$R^1=R^2=CH_3$	IV; $R^3=H$; R^4=benzyl	HCl	225-227
10	$R^1=R^2=CH_3$	IV; $R^3=H$; $R^4=H_3CNHCO$	base	161-163
11	$R^1=R^2=CH_3$	V; $R^6=C_2H_5$	base	170-171

EXAMPLE 2

20,000 Ampoules each containing 10 mg. of 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methanesulphonyl]piperidine hydrochloride (active ingredient) were preepared from the following formulation:

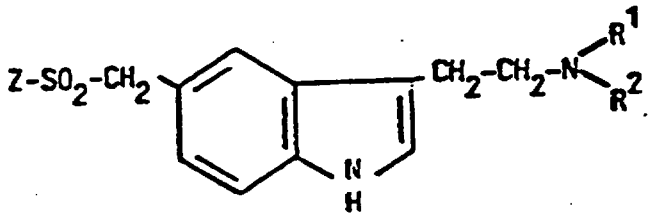
Active ingredient	200 g
Sodium chloride	200 g
Water injectable grade q.s.	40 litres

Procedure

The active ingredient and sodium chloride were dissolved in 40 litres of water, then passed through a bacteria-retaining filter and filled under sterile conditions into 2 ml glass ampoules in known manner.

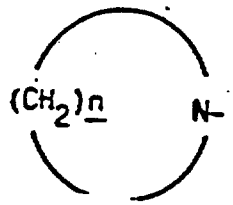
CLAIMS

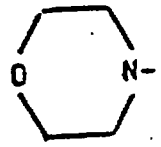
1. A compound of formula (I)

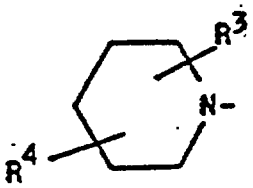


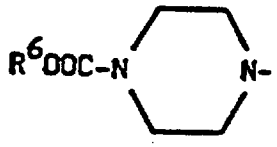
(I)

wherein R^1 and R^2 each represents a hydrogen atom or an alkyl group, Z represents a ring selected from:

II  in which n represents 4, 5 or 6;

III 

IV  in which R^3 represents hydrogen or an alkyl group and R^4 represents an alkyl, methoxy, benzyl or R^5 NHCO group, R^5 being an alkyl group; and

V  in which R^6 represents an alkyl group.

and pharmaceutically acceptable salts thereof.

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2. A compound according to claim 1 in which R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different is each hydrogen or a C_{1-6} alkyl group.

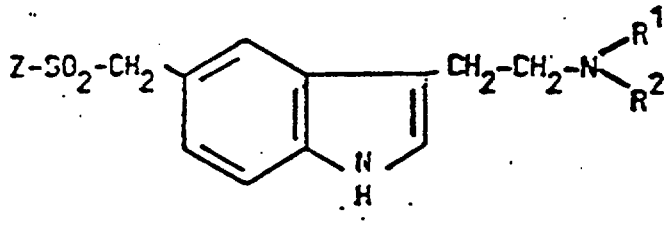
3. A compound according to claim 1 in which R^1 and R^2 which by the same or different is each C_{1-4} alkyl, and z is of the formula II.

4. 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methane-sulphonyl]pyrrolidoine;

1-[[3-(2-dimethylaminoethyl)-5-indolyl]methane-sulphonyl]piperidine; or

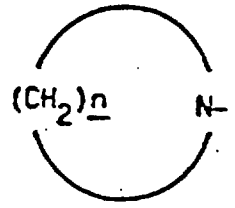
1-[[3-(2-dimethylaminoethyl)-5-indolyl]methane-sulphonyl]-4-ethoxycarbonyl piperazine;
or a hydrochloride salt thereof.

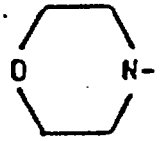
5. A process for the preparation of a compound of formula I



(I)

wherein R^1 and R^2 each represents a hydrogen atom or an alkyl group, z represents a ring selected from:

II  in which n represents 4, 5 or 6;

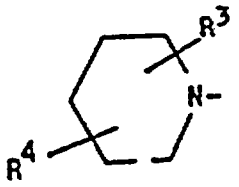
III 

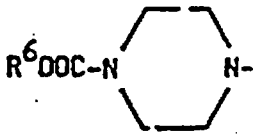
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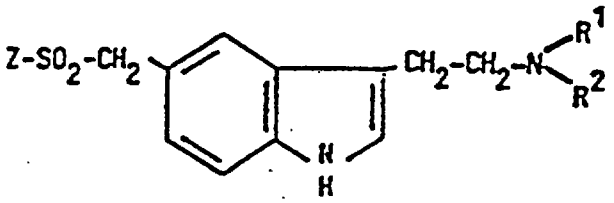
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IV  in which R^3 represents hydrogen or an alkyl group and R^4 represents an alkyl, methoxy, benzyl or R^5NHCO group R^5 being an alkyl group; and

V  in which R^6 represents an alkyl group.

and pharmaceutically acceptable salts thereof which process comprises a decarboxylation of a carboxylic acid of formula VI

(VI) 

wherein Z, R^1 and R^2 are as defined above.

6. A composition comprising a compound according to any one of claims 1 to 4 mixed with a pharmaceutically acceptable carrier or diluent.

7. A compound according to any one of claims 1 to 4 or a composition according to claim 6 for use in a method of treatment of the human or animal body.

8. Use of a compound according to any one of claims 1 to 4 or a composition according to claim 6 for the manufacture of a medicament for the treatment of headaches including migraines, movement disorders, depression or anxiety.

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9. A method of treating headaches including migraines, movement disorders, depression or anxiety which comprises administering to a human or animal subject in need of treatment of an effective amount of a compound according to claim 1.

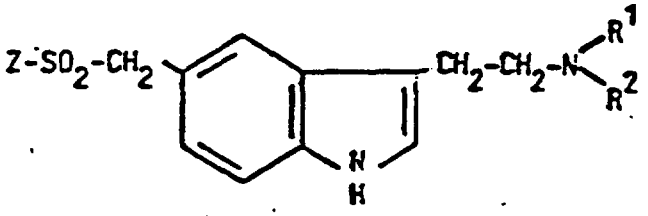
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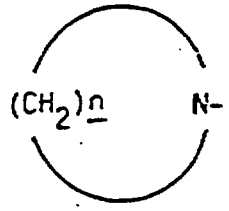
ABSTRACT

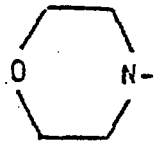
A compound of formula (I)

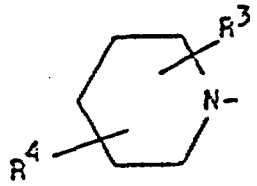


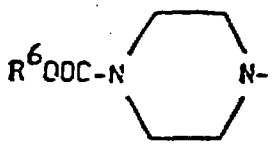
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and pharmaceutically acceptable salts thereof are useful in the treatment of migraine and other conditions. They are prepared by decarboxylation of the corresponding indolyl 2-carboxylic acid.

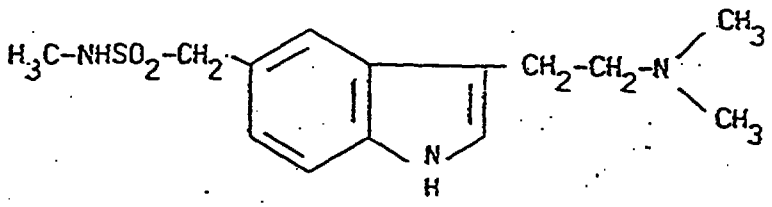
REPLACEMENT SHEET
Date 19 APR 1997

NEW INDOL DERIVATIVES

THIS INVENTION relates to new indol derivatives, methods for their preparation, compositions containing them and their use in medical treatment.

The mechanism involved in the genesis of a migraine attack is not known, but it has been demonstrated that the large intracranial vessels are distended during the headache phase. Some compounds like ergotamine and serotonine (5-Hydroxytryptamine; 5-HT), have a vasoconstrictor action in the carotid vascular bed by an agonistic action at the "5-HT_1-like" receptors. However, the lack of selectivity of these compounds is the cause of undesirable and potentially dangerous side-effects.

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We have now found that the introduction of a nitrogen ring in the methanesulfonyl group provides new anti-migraine compounds that present a greater affinity for 5-HT_{1D} receptor than for 5-HT_{1A} receptor and therefore, less side-effects.

REPLACEMENT SHEET
19 APR 1997
Date :.....

TABLE I. Results of different pharmacological test

	Dog saphenous vein, pD2	Binding IC50 nM		
		125I-GTI	3H-8-OH-DPAT	5HT1A/ 5HT1D
Sumatriptan	6.06 ± 0.01	10.4 ± 1	460 ± 67	44.2
1	6.06 ± 0.03	10.7 ± 0.4	825 ± 69	77.1
2	5.92 ± 0.10	6.9 ± 0.4	340 ± 0.5	49.3
11	6.47 ± 0.03	3.2 ± 0.3	850 ± 40	265.6

From results presented above it can be concluded that the novel compounds of this invention demonstrate binding selectivity for 5-HT1D receptors and vasoconstrictor capability mediated by an agonism on 5HT1D receptors. According to the results this invention provides compounds with potential interest for the treatment or prevention of migraine and other headache associated with vascular disorders (e.g. cluster headache and chronic paroxysmal hemicrania), with administration of substances or their withdrawal, and for the treatment or prevention of tensional cephaliar pain, movement disorders, depression and anxiety.

Thus, the present invention provides indol derivatives of the formula I and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such derivatives and salts thereof, for use in the treatment or therapy of the human body.

Accordingly, the indol derivatives of the formula I and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such derivatives and salts thereof, may be used in a method of treatment

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of disorders of the human body which comprises administering to a recipient in need of such therapy an effective amount of said derivatives or salts thereof or said compositions.

The present invention also provides pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, or a pharmacologically acceptable salt in association with a pharmaceutically acceptable carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, percutaneous or parenteral administration.

The pharmaceutically acceptable carriers or diluents which are admixed with the active compound, or compounds or salts of such compounds, to form the compositions of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions. Compositions of this invention are preferably adapted for administration parenteral and *per os*. In this case, the composition for oral administration may take the form of tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient

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TABLE 2

COMPOUND No.	R^1 , R^2	Z	DERIVATIVE	M.P °C
1	$R^1=R^2=CH_3$	II; n=4	HCl	218-220
2	$R^1=R^2=CH_3$	II; n=5	HCl	225-227(d)
3	$R^1=R^2=CH_3$	II; n=6	hydrogen succinate	127-130(d)
4	$R^1=H; R^2=CH_3$	II; n=4	HCl	177-178
5	$R^1=R^2=CH_3$	III	HCl	231-232(d)
6	$R^1=R^2=CH_3$	IV; $R^3=H$; $R^4=4-CH_3$	hydrogen succinate	151-153
7	$R^1=R^2=CH_3$	IV; $R^3=R^4=4-CH_3$	hydrogen succinate	170-172
8	$R^1=R^2=CH_3$	IV; $R^3=H$; R^4=methoxy	hydrogen succinate	143-145
9	$R^1=R^2=CH_3$	IV; $R^3=H$; R^4=benzyl	HCl	225-227
10	$R^1=R^2=CH_3$	IV; $R^3=H$; $R^4=H_3CNHCO$	base	161-163
11	$R^1=R^2=CH_3$	V; $R^6=C_2H_5$	base	170-171

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2. A compound according to claim 1 in which R^1, R^2, R^3, R^4, R^5 and R^6 which may be the same or different is each hydrogen or a C_{1-6} alkyl group.

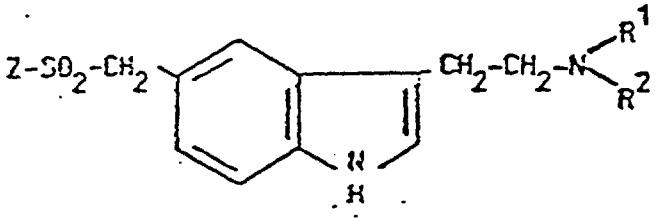
3. A compound according to claim 1 in which R^1 and R^2 which by the same or different is each C_{1-4} alkyl, and z is of the formula II.

4. 1-[[3-(2-dimethylaminoethyl)-5-indolyl]methane-sulphonyl] pyrrolidine;

1-[[3-(2-dimethylaminoethyl)-5-indolyl]methane-sulphonyl]piperidine; or

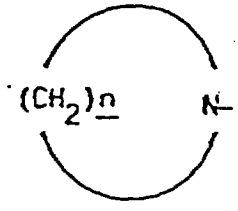
1-[[3-(2-dimethylaminoethyl)-5-indolyl]methane-sulphonyl]-4-ethoxycarbonyl piperazine;
or a hydrochloride salt thereof.

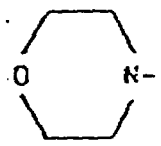
5. A process for the preparation of a compound of formula I



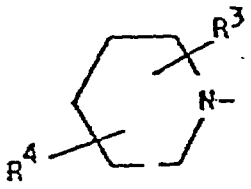
(I)

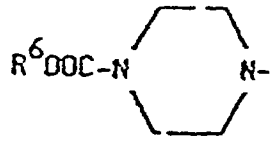
wherein R^1 and R^2 each represents a hydrogen atom or an alkyl group, z represents a ring selected from:

II  in which n represents 4, 5 or 6;

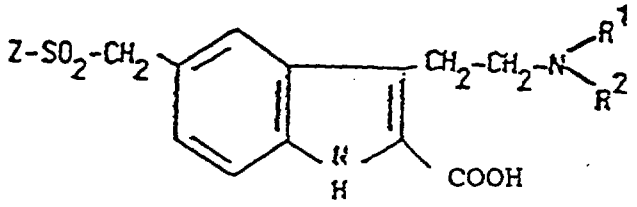
III 

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IV  in which R^3 represents hydrogen or an alkyl group and R^4 represents an alkyl, methoxy, benzyl or R^5NHCO group, R^5 being an alkyl group; and

V  in which R^6 represents an alkyl group.

and pharmaceutically acceptable salts thereof which process comprises a decarboxylation of a carboxylic acid of formula VI

(VI) 

wherein Z, R^1 and R^2 are as defined above.

6. A composition comprising a compound according to any one of claims 1 to 4 mixed with a pharmaceutically acceptable carrier or diluent.

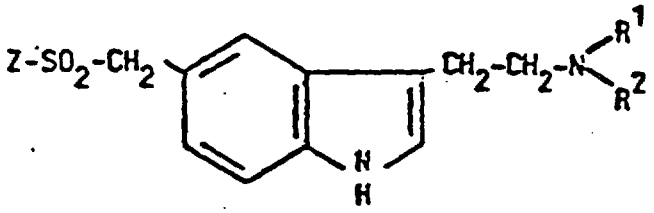
7. A compound according to any one of claims 1 to 4 or a composition according to claim 6 for use in a method of treatment of the human or animal body.

8. Use of a compound according to any one of claims 1 to 4 or a composition according to claim 6 for the manufacture of a medicament for the treatment of headaches including migraines, movement disorders, depression or anxiety.

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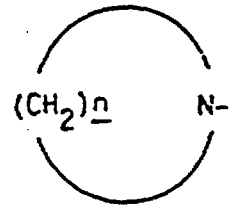
ABSTRACT

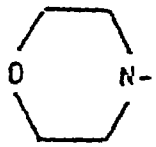
A compound of formula (I)

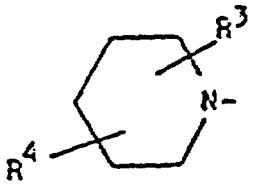


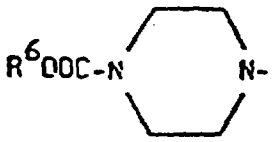
(I)

wherein R^1 and R^2 each represents a hydrogen atom or an alkyl group, Z represents a ring selected from:

II  in which n represents 4, 5 or 6;

III 

IV  in which R^3 represents hydrogen or an alkyl group and R^4 represents an alkyl, methoxy, benzyl or R^5 NHCO group, R^5 being an alkyl group; and

V  in which R^6 represents an alkyl group.

and pharmaceutically acceptable salts thereof are useful in the treatment of migraine and other conditions. They are prepared by decarboxylation of the corresponding indolyl 2-carboxylic acid.