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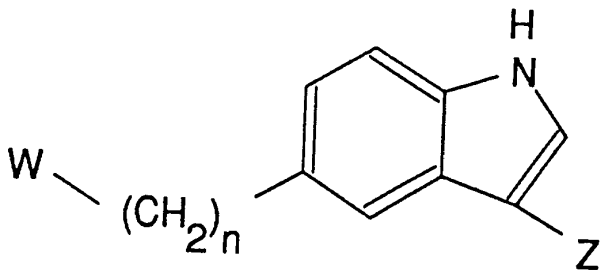
(54) **Indole derivatives as 5-HT1- like agonists.**

(57) The present invention is concerned with compounds of formula (I)




(I)

wherein
n is an integar of from 0 to 3;

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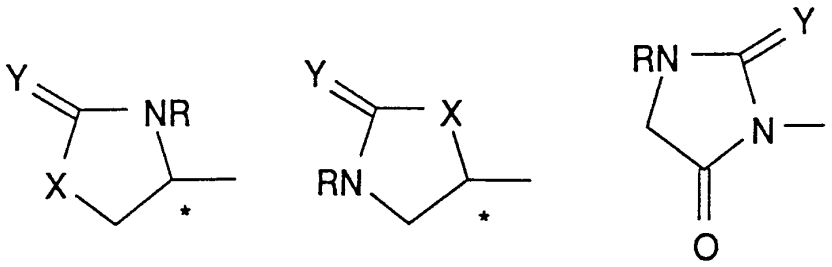
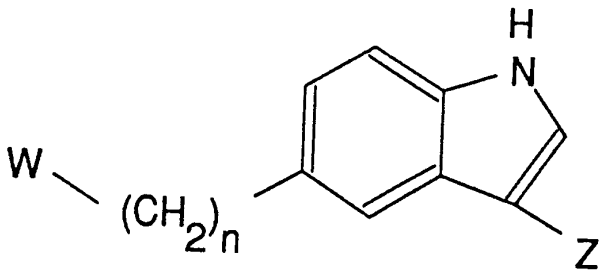


(i) (ii) (iii)

wherein R is hydrogen or $C_{1-4}$ alkyl, X is -O-, -S-, -NH-, or $-CH_2-$, Y is oxygen or sulphur and the chiral centre * in formula (i) or (ii) is in its (S) or (R) form or is a mixture thereof in any proportions; and
Z is a group of formula (iv), (v), or (vi)



(I)

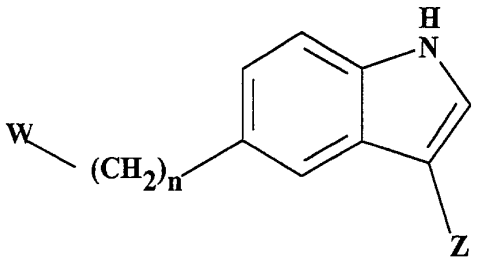
wherein $R^1$ and $R^2$ are independently selected from hydrogen and $C_{1-4}$ alkyl and $R^3$ is hydrogen or $C_{1-4}$ alkyl; and their salts, solvates and physiologically functional derivatives, with processes for their preparation, with medicaments containing them and with their use as therapeutic agents, particularly in the prophylaxis and treatment of migraine.

The present invention is concerned with new chemical compounds, their preparation, pharmaceutical formulations containing them and their use in medicine, particularly the prophylaxis and treatment of migraine.

Receptors which mediate the actions of 5-hydroxytryptamine (5-HT) have been identified in mammals in both the periphery and the brain. According to the classification and nomenclature proposed in a recent article (Bradley et al, Neuropharmac., 25, 563 (1986)), these receptors may be classified into three main types, viz. "5-$HT_1$-like", 5-$HT_2$ and 5-$HT_3$. Various classes of compounds have been proposed as 5-HT agonists or antagonists for therapeutic use, but these have not always been specific to a particular type of 5-HT receptor. European Patent Specification 0313397 describes a class of 5-HT agonists which are specific to a particular type of "5-$HT_1$-like" receptor and are effective therapeutic agents for the treatment of clinical conditions in which a selective agonist for this type of receptor is indicated. For example, the receptor in question mediates vasoconstriction in the carotid vascular bed and thereby modifies blood flow therein. The compounds described in the European specification are therefore beneficial in the treatment or prophylaxis of conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example, migraine, a condition associated with excessive dilation of the carotid vasculature. However, it is within the scope of the earlier application that the target tissue may be any tissue wherein action is mediated by "5-$HT_1$-like" receptors of the type referred to above.

We have now found a further class of compounds having exceptional "5-$HT_1$-like" receptor agonism and excellent absorption following oral dosing. These properties render the compounds particularly useful for certain medical applications, notably the prophylaxis and treatment of migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as "migraine".

According to the first aspect of the present invention, therefore, there is provided a compound of formula (I)

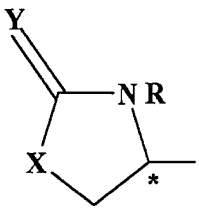


(I)

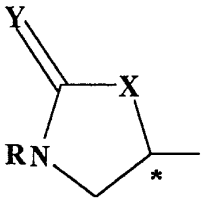
wherein

n is an integer of from 0 to 3;

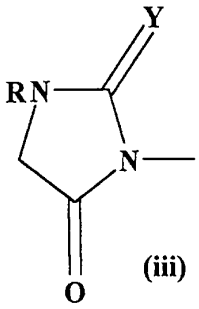
W is a group of formula (i), (ii), or (iii)



(i)



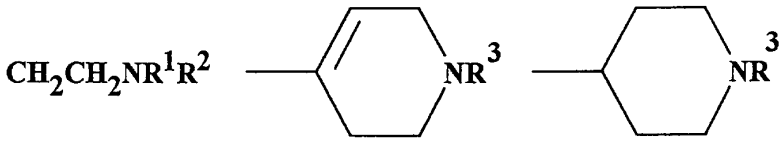
(ii)



(iii)

wherein R is hydrogen or $C_{1-4}$ alkyl, X is -O-, -S-, -NH-, or -$CH_2$-, Y is oxygen or sulphur and the chiral centre * in formula (i) or (ii) is in its (S) or (R) form or is a mixture thereof in any proportions; and

Z is a group of formula (iv), (v), or (vi)



(iv) (v) (vi)

wherein $R^1$ and $R^2$ are independently selected from hydrogen and $C_{1-4}$ alkyl and $R^3$ is hydrogen or $C_{1-4}$ alkyl;

and salts, solvates and physiologically functional derivatives thereof.

Compounds of formula (I) having particularly desirable properties for the treatment and prophylaxis of migraine include those wherein n is 1, W is a group of formula (i) and Z is a group of formula (iv) or (vi). Of these, compounds of formula (I) wherein n is 1, W is a group of formula (i) wherein R is hydrogen, X is -O- and Y is oxygen and Z is a group of formula (iv) or (vi) wherein $R^1$ = $R^2$ = hydrogen or methyl are particularly preferred.

Two compounds of formula (I) having exceptional properties for the treatment and prophylaxis of migraine are N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine and 3-(1-methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole in either their (S) or (R) form or as a mixture thereof in any proportions. The salts and solvates of these compounds, for example, the hydrate maleates, are particularly preferred.

Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, ie basic, compounds. Such salts must clearly have a physiologically acceptable anion. Suitable physiologically acceptable salts of the compounds of the present invention include those derived from acetic, hydrochloric, hydrobromic, phosphoric, malic, maleic, fumaric, citric, sulphuric, lactic, or tartaric acid. The succinate and chloride salts are particularly preferred for medical purposes. Salts having a non-physiologically acceptable anion are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, in vitro, situations.

According to a second aspect of the present invention, there is provided a compound of formula (I) or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof for use as a therapeutic agent, specifically as a "5-$HT_1$-like" receptor agonist, for example, as a carotid vasoconstrictor in the prophylaxis arid treatment of migraine. As indicated, however, target organs for the present compounds other than the carotid vasculature are within the scope of the present invention.

The amount of a compound of formula (I), or a salt or solvate thereof, which is required to achieve the desired biological effect will depend on a number of factors such as the specific compound, the use for which it is intended, the means of administration, and the recipient. A typical daily dose for the treatment of migraine may be expected to lie in the range 0.01 to 5mg per kilogram body weight. Unit doses may contain from 1 to 100mg of a compound of formula (I), for example, ampoules for injection may contain from 1 to 10mg and orally administrable unit dose formulations such as tablets or capsules may contain from 1 to 100mg. Such unit doses may be administered one or more times a day, separately or in multiples thereof. An intravenous dose may be expected to lie in the range 0.01 to 0.15mg/kg and would typically be administered as an infusion of from 0.0003 to 0.15mg per kilogram per minute. Infusion solutions suitable for this purpose may contain from 0.01 to 10mg/ml.

When the active compound is a salt or solvate of a compound of formula (I), the dose is based on the cation (for salts) or the unsolvated compound.

Hereinafter references to "compound(s) of formula (I)" will be understood to include physiologically acceptable salts and solvates thereof.

According to a third aspect of the present invention, therefore, there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula (I) and/or a pharmacologically acceptable salt or solvate thereof together with at least one pharmaceutical carrier or excipient. These pharmaceutical compositions may be used in the prophylaxis or treatment of clinical conditions for which a "5-$HT_1$-like" receptor agonist is indicated, for example, migraine. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or liquid and is preferably formulated with at least one compound of formula (I) as a unit dose formulation, for example, a tablet which may contain from 0.05 to 95% by weight of the active ingredient. If desired, other physiologically active ingredients may also be

incorporated in the pharmaceutical compositions of the invention.

Possible formulations include those suitable for oral, sublingual, buccal, parenteral (for example, subcutaneous, intramuscular, or intravenous), rectal, topical and intranasal administration. The most suitable means of administration for a particular patient will depend on the nature and severity of the condition being treated and on the nature of the active compound, but, where possible, oral administration is preferred.

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, or lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically, a flavoured base, such as sugar and acacia or tragacanth, and pastilles comprising the active compound in an inert base, such as gelatin and glycerin or sucrose and acacia.

Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient and one or more solid carriers forming the suppository base, for example, cocoa butter.

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethylene glycols, alcohols, and combinations thereof The active ingredient is typically present in such formulations at a concentration of from 0.1 to 15% w/w.

The formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

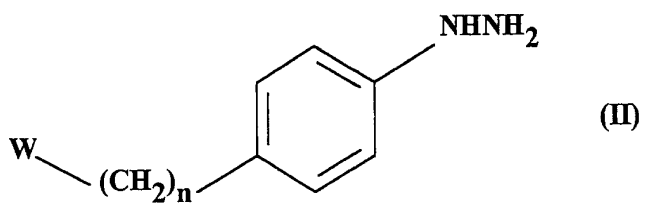
For example, a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

Aqueous solutions for parenteral administration are typically prepared by dissolving the active compound in sufficient water to give the desired concentration and then rendering the resulting solution sterile and isotonic.

Thus, according to a fourth aspect of the present invention, there is provided the use of a compound of formula (I) in the preparation of a medicament for the prophylaxis or treatment of a clinical condition for which a "5-$HT_1$-like" receptor agonist is indicated, for example, migraine.

According to a fifth aspect, there is provided a method for the prophylaxis or treatment of a clinical condition in a mammal, for example, a human, for which a "5-$HT_1$-like" receptor agonist is indicated, for example, migraine, which comprises the administration to said mammal of a therapeutically effective amount of a compound of formula (I) or of a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

According to a sixth aspect of the invention, compounds of formula (I) wherein Z is a group of formula (iv) may be prepared by reacting a compound of formula (II) (isolated or in situ - infra).




(II)

wherein n and W are as hereinbefore defined, with a compound of formula (III)

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