(12) UK Patent Application (19) GB (11) 2 102 795 A

(21) Application No **8217152**
(22) Date of filing **14 Jun 1982**
(30) Priority data
(31) **8123595**
(32) **31 Jul 1981**
(33) **United Kingdom (GB)**
(43) Application published
9 Feb 1983
(51) **INT CL**^{3}
C07D 401/06
A61K 31/44
(C07D 401/06 209/04
213/36)
(52) Domestic classification
C2C 1343 1530 200 213
215 246 247 248 250 251
258 25Y 28X 30Y 350 366
367 37X 43X 54X 628 658
802 80Y AA BD TA
U1S 1320 C2C
(56) Documents cited
None
(58) Field of search
C2C
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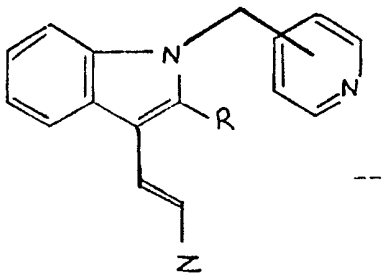
(54) **Indole derivatives**

(57) Compounds of the general formula:



---(I)

(wherein R is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl or phenyl; Z is CO_2H, $CO_2(C_1$-C_4 alkyl), $CONH_2$, CN or 5-tetrazolyl; and wherein the pyridine ring is attached at the 3 or 4 position) and the acid addition salts thereof are useful in the treatment of ischaemic heart disease, stroke, transient ischaemic attack, thrombosis, migraine and the vascular complications of diabetes.

The preparation of *1-(3-pyridylmethyl)-2-methylindole-3-carboxaldehyde* is described.

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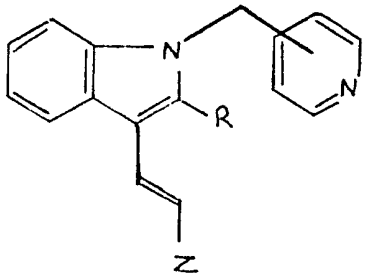
SPECIFICATION

Indole derivatives, process for their preparation and pharmaceutical compositions thereof

This invention relates to certain indole derivatives and in particular to a series of N-picolylindoles being substituted on the 3-position of the indole ring with certain acidic or polar groupings. Such compounds are able to selectively inhibit the action of the thromboxane synthetase enzyme without significantly inhibiting the action of the prostacyclin synthetase or cyclo-oxygenase enzymes. The compounds may thus be useful as therapeutic agents, for example, in the treatment of thrombosis, ischaemic heart disease, stroke, transient ischaemic attack, migraine and the vascular complications of diabetes.

Thus according to the invention, there are provided compounds of the general formula:



---(I)

wherein

R is hydrogen, C_1-C_4 lower alkyl, C_3-C_6 cycloalkyl or phenyl;

Z is CO_2H, CO_2(C_1-C_4 lower alkyl), $CONH_2$, CN or 5-tetrazolyl;

and wherein the pyridine ring is attached at the 3 or 4 position; and the pharmaceutically acceptable acid addition salts thereof.

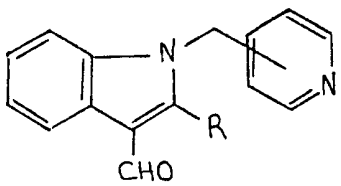
The invention also includes a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or salt together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of inhibiting the action of the thromboxane synthetase enzyme in an animal, including a human being, without significantly inhibiting the action of the prostacyclin synthetase or cyclo-oxygenase enzymes, which comprises administering to the animal an effective amount of a compound of the formula (I), or a pharmaceutically acceptable diluent or carrier.

Pharmaceutically acceptable acid addition salts of the compounds of the invention are salts with acids containing pharmaceutically acceptable anions, e.g. the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate and p-toluene sulphonate salts.

A preferred compound of the invention is 1-(3-pyridylmethyl)-2-methylindole-3-acrylic acid.

The compounds of the invention may be prepared by a number of different routes. In one process according to the invention the compounds of the formula (I) may be prepared from an indolecarboxaldehyde derivative of the formula:



--- (II)

wherein R is as previously defined. Attachment of the 3-substituent may be achieved by a number of methods, thus the aldehyde may be reacted with malonic acid in the presence of an organic base to yield the compounds of formula I wherein Z is CO_2H (Knoevenagel reaction). Alternatively, the aldehyde may be reacted with a Wittig reagent of the formula:

$$Ph_3P = CHCO_2R^1 \qquad \text{---(III)}$$

where R^1 is a C_1-C_4 lower alkyl group, to yield the compound of formula I wherein Z is CO_2 (C_1-C_4 lower alkyl). Conventional chemical transformation reactions can be used to convert the resulting acid or ester to compounds of formula I wherein Z is $CONH_2$, CN or tetrazolyl.

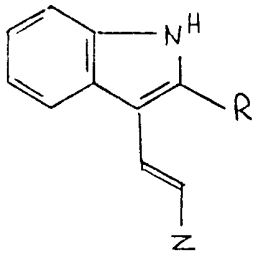
The reaction of the compound of formula (II) and malonic acid is conveniently performed with the

reactants, dissolved in pyridine with a small quantity of a secondary amine, usually piperidine, being added to catalyse the condensation. The reaction may be warmed with advantage to accelerate the reaction, a period of 6-12 hours at 50°C generally being sufficient to ensure complete reaction. The progress of the reaction can be monitored by thin layer chromatography and further malonic acid added and the heating continued as necessary to optimise the yield of the desired product.

The reaction mixture is finally worked-up in a conventional manner, for example by pouring the reaction mixture into excess water to precipitate the crude product which is further purified by conventional techniques. Thus the product can be taken up in dilute aqueous alkali and reprecipitated by acidification and the product may then be further purified, if desired, by chromatography or crystallization.

The reaction of the compound of formula (II) and the Wittig reagent of formula (III) may be performed in an entirely conventional manner, for example by heating the reactants together in an inert organic solvent e.g. toluene or xylene, for a period of several hours. The solvent is removed by evaporation and the product purified by conventional techniques, for example by solvent extraction, chromatography or crystallization.

In an alternative process the compound of the formula (I) may be prepared from a compound of the formula:



---(IV)

wherein R is as previously defined, and Z is CO_2 (lower alkyl), $CONH_2$ or CN, by reaction with a strong base (for example sodium hydride) to generate the anion, followed by addition of an appropriate halomethylpyridine derivative (for example 3 or 4-chloromethylpyridine).

This process is conveniently performed by dissolving the compound of formula (IV) in an inert organic solvent (for example N,N-dimethylformamide) and adding one equivalent of a strong base, usually an alkali metal hydride, for example sodium hydride, which may conveniently be used as a dispersion in a mineral oil. The reaction mixture is stirred at room temperature, a period of 1 hour generally being sufficient to ensure complete reaction. The halomethylpyridine may then be added, usually as a solution in the same solvent, in an amount of 1 equivalent or allowing a small excess. The reaction is allowed to proceed at room temperature; an overnight period generally being sufficient to ensure complete reaction, and the resulting 1-pyridylmethyl derivative is then isolated in a conventional manner, for example by solvent extraction, and may be further purified if desired, by crystallization or by chromatography.

Naturally certain of the groups Z may be obtained by chemical transformation reactions and these possibilities will be well known to those skilled in the art. Thus for example the compounds of the formula I where Z is a carboxyl group may be esterified with an appropriate lower aliphatic alkanol to give the esters where Z is CO_2 (C_1-C_4 lower alkyl). Reaction of the esters with concentrated ammonium hydroxide at room temperature for one or two hours yields the amides where Z is $CONH_2$. Dehydration of the amides, for example, using thionylchloride or phosphorus oxychloride yields the corresponding nitrile. Conversely, hydrolysis of the nitrile can be used to generate the compounds of formula I wherein Z is a carboxyl group. Compound where Z is 5-tetrazolyl are prepared from the nitrile by reaction with sodium azide and ammonium chloride.

All these reactions are quite conventional and methods for their performance and other possibilities and variations will be well known to those skilled in the art.

The pharmaceutically acceptable salts of the compounds of formula (I) may be prepared by mixing solutions containing equimolar amounts of the free base and appropriate acid and the required salt is collected by filtration, if insoluble, or by evaporation of the solvent.

The starting materials of formula (II) are prepared by an N-alkylation reaction from the known indole-3-carboxaldehydes. This reaction is achieved by treating the 3-carboxaldehyde with sodium hydride in N,N-dimethylformamide to generate the anion followed by addition of a halomethylpyridine derivative, e.g. chloromethylpyridine. Indole-3-carboxaldehydes and their preparation are described in The Chemistry of Heterocyclic Compounds, Indoles Part Three edited by W. J. Houlihan, page 361.

The starting materials of formula (IV) are prepared from the appropriate indolecarboxaldehyde by a similar process to that hereinbefore described for conversion of the compounds of formula (II) to compounds of the formula (I).

The compounds of formula (I) have been found to selectively inhibit the action of the thromboxane synthetase enzyme without significantly affecting the action of the prostacyclin synthetase or cyclo-oxygenase enzymes. Thus the compounds are of value in the treatment of a variety of clinical conditions which are characterised by an inbalance of prostacyclin/thromboxane A_2. For the reasons given below these conditions may include thrombosis, ischaemic heart disease, stroke, transient ischaemic attack, migraine

and the vascular complications of diabetes.

Research work has established that in most tissues the major product of the arachidonic acid metabolism is either of two unstable substances, thromboxane A_2 (TxA_2) or prostacyclin (PCI_2). (Proc. Nat. Acad. Sci. U.S.A., 1975, *72*, 2994, Nature 1976, *263*, 663; Prostaglandins, 1976, *12*, 897.) In most cases the prostaglandins PGE_2, $PGF_{2\alpha}$ and PGD_2 are comparatively minor by-products in this bio-synthetic pathway. The discovery of throxboxane A_2 and prostacyclin has significantly increased our understanding of vascular homeostasis; prostacyclin for instance is a powerful vasodilator and inhibitor of platelet aggregation, and in this last respect is the most potent endogenous substance so far discovered. The prostacyclin synthetase enzyme is located in the endothelial layer of the vasculature, and is fed by endoperoxides released by blood platelets coming into contact with the vessel wall. The prostacyclin thus produced is important for prevention of platelet deposition on vessel walls. (Prostaglandins, 1976, *12*; 685, Science, 1976, 17; Nature, 1978, *273*, 765.)

Thromboxane A_2 is synthetised by the thromboxane synthetase enzyme which is located in, for example, the blood platelets. Thromboxane A_2 is a powerful vasoconstrictor and pro-aggregatory substance. As such its actions are in direct opposition to those of prostacyclin. If, for any reason, prostacyclin formation by the vasculature is impaired, then the endoperoxides produced by platelets coming into contact with the vessel wall are converted into thromboxane, but are not coverted effectively into prostacyclin (Lancet, 1977, 18; Prostaglandins, 1978, *13*, 3.) Alteration of the prostacyclin/thromboxane balance in favour of the latter substance could result in platelet aggregation, vasospasm (Lancet, 1977, 479; Science, 1976, 1135; Amer. J. Cardiology, 1978, *41*, 787) and an increased susceptibility to atherothrombosis (Lancet (i) 1977, 1216). It is also known that in experimental atherosclerosis prostacyclin generation is suppressed and thromboxane A_2 production is enhanced (Prostaglandins, 1977, *14*, 1025 and 1035). Thus thromboxane A_2 has been implicated as the causitive agent in variant angina, myocardial infarction, sudden cardiac death and stroke (Thromb. Haemostasis, 1977, *38*, 132). Studies in rabbits have shown that ECG changes typical of these conditions were produced when freshly prepared thromboxane A_2 was injected directly into the animal's heart (Biochem. Aspects of Prostaglandins and Thromboxanes, Editors, N. Kharasch and J. Fried, Academic Press 1977 page 189). This technique is considered to represent a unique animal model of the heart attacks of coronary patients and has been used to show that administration of a compound believed to antagonise the effects of thromboxane A_2 protects the rabbits from the adverse consequences of thromboxane A_2 injection.

Another area where a PGI_2/TxA_2 imbalance is considered to be a contributory factor is that of migraine. The migraine headache is associated with changes in intra and extra-cerebral blood flow, in particular a pre-headache reduction of cerebral blood flow followed by dilation in both vascular areas during the headache phase.

Prior to the development of the headache, blood levels of 5-hydroxytryptamine are elevated, and this suggests the occurrence of *in vivo* aggregation and release of the amine from the platelet stores. It is known that the blood platelets of migraine patients are more prone to aggregate than are those of normal individuals (J. Clin. Pathol., 1971, *24*, 250; J. Headache, 1977, *17*, 101). Furthermore, it has now been postulated that not only is an abnormality of platelet function a major factor in the pathogenesis of migraine attacks but it is in fact their prime cause (Lancet (i), 1978, 501). Thus a drug that selectively modifies platelet function to inhibit thromboxane A_2 formation could be of considerable benefit in migraine therapy.

Abnormalities of platelet behaviour have also been reported in patients with diabetes mellitus (Metabolism, 1979, *28*, 394; Lancet 1978 (i) 235). Diabetic patients are known to be particularly susceptible to microvascular complications, atherosclerosis and thrombosis and platelet hyper-reactivity has been suggested as the cause of such angiopathy. Diabetic platelets produce elevated amounts of TxB_2 and malondialdehyde (Symposium "Diabetes and Thrombosis - Implications for Therapy", Leeds U.K., April 1979). Also it has been shown that in rats with experimental diabetes vascular prostacyclin production is impaired and TxA_2 synthesis from the platelets is elevated (IV International Prostaglandin Conference, Washington, DC, May 1979). Thus the imbalance between prostacyclin and TxA_2 is considered to be responsible for the microvascular complications of diabetes. A TxA_2 - synthetase inhibitor could, therefore, find clinical utility in preventing these vascular complications.

Aspirin and most other non-steroidal anti-inflammatory drugs inhibit the cyclo-oxygenase enzyme. The effect of this is to shut down the production of the PGG_2/H_2 enxoperoxides and by so doing to reduce both the prostacyclin and thromboxane A_2 levels. Aspirin and aspirin-like drugs have been evaluated clinically for prevention of stroke and heart attack (New England J. Med. 1978, *299*, 53; B.M.J. 1978, 1188; Stroke, 1977, *8*,301) and some encouraging results have been obtained with these drugs, however, it is clear that a compound which specifically inhibits thromboxane A_2 formation, leaving the biosynthesis of prostacyclin unimpaired would be more valuable in these clinical conditions (Lancet (ii), 1978, 780).

The effect of the compounds of the formula (I) on the thromboxane synthetase enzyme, and the prostacyclin synthetase and cyclo-oxygenase enzymes has been measured by the following *in vitro* enzymes assays:-

1. *Cyclo-oxygenase*

Ram seminal vesicle microsomes (Biochemistry, 1971, *10* 2372) are incubated with arachidonic acid (100 μM: 1 min : 22°C) to produce PGH_2 and aliquots of the reaction mixture injected into a stream of Krebs-bicarbonate at 37°C containing a mixture of antagonists (Nature, 1978, *218*, 1135) and indomethacin

(Brit. J. Pharmacol., 1972, *45*, 451) which is superfusing a spirally-cut rabbit aorta strip (Nature, 1969, *223*, 29). The ability of a compound to inhibit the enzyme is measured by comparing the increases in isometric tension produced by PGH_2 in the absence of the test compound, and following pre-incubation of the enzyme with the test compound for 5 minutes.

2. *Prostacyclin (PGI_2) Synthetase*

Pig aorta microsomes (Nature, 1976, *263*, 663) are incubated (30 sec.; 22°C) with PGH_2 produced as in 1 and aliquots bioassayed as in 1. PGI_2 production is assessed indirectly be measuring the decrease in PGH_2-induced tension (PGI_2 itself does not contract the aorta). This decreased can be prevented completely by pre-incubation of the enzyme with the selective PGI_2 synthetase inhibitor, 15-hydroperoxy-arachidonic acid (Prostaglandins, 1976, *12*, 715). The test compound is then preincubated with the enzyme for 5 minutes, and its ability to prevent the decreased in tension is measured.

3. *Thromboxane A_2 (TxA_2) Synthetase*

Indomethacin pre-treated human platelet microsomes (Science, 1976, *193*, 163) are incubated (2 min.; 0°C) with PGH_2 (produced as in 1) and aliquots of the reaction mixture superfused over two rabbit aorta spirals which are separated by a delay coil (2 min.). The latter is required to allow the selective decay of the more unstable thromboxane A_2 (Proc. Nat. Acad. Sci., 1975, *72*, 2994) thereby enabling the separate measurement of increased isometric tension due to the TxA_2 formed and the PGH_2 remaining. The test compound is pre-incubated with the enzyme for 5 minutes, and its ability to inhibit the thromboxane syntehtase enzyme is measured as its reduction of the TxA_2 component of the isometric tension.

Compounds of the invention tested in this way have been shown to be capable of selectively inhibiting the thromboxane synthetase enzyme.

In addition to the above, an *in vitro* assay for measuring the inhibition of human blood platelet aggregation has been described and this may be predictive of anti-thrombotic efficacy clincally (Lancet (ii), 1974, 1223; J. Exp. Med., 1967, *126*, 171). Both clinically effective agents aspirin and sulphinpyrazone show inhibitory activity *in vitro* against a variety of aggregating agents in this test.

A number of *in vivo* tests in animals have also been described for evaluating potential anti-thrombotic drugs.

Intravenous injection of arachidonic acid causes death in rabbits by causing platelet clumping and embolisation in the lungs. Again both the clinically effective aspirin (Agents and Actions, 1977, *1*, 481) and sulphinpyrazone (Pharmacology, 1976, *14*, 522) protect the rabbit from the lethal effect of the injection. Sulphinpyrazone has also been shown to prevent the aggregation of platelets in an extra corporeal loop of the abdominal aorta of rats *in vivo* (Throm. Diathes. Haem., 1973, *30*, 138).

For human use the compounds may be administered orally in the form of tablets or capsules containing a unit dose of the compound together with such excipients as maize starch, calcium carbonate, dicalcium phosphate, alginic acid, lactose, magnesium stearate, or talc. The tablets are typically prepared by granulating the ingredients together and compressing the resulting mixture to give tablets of the desired size. Capsules are typically prepared by granulating the ingredients together and filling them into hard gelatine capsules of the appropriate size to contain the desired dosage.

The compounds may also be administered parenterally, for example by intramuscular, intravenous or subcutaneous injection. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes such as tonic and pH adjusters. Such solutions are prepared by adding the compounds to distilled water and adjusting the pH to 3-6 using an acid such as citric, lactic or hydrochloric acid. Sufficient solutes such as dextrose or saline may be added to render the solution isotonic. The resulting solution may then be sterilized and filled into sterile glass vials of an appropriate size to contain the desired volume of solution. The compounds of the invention may also be administered by the infusion of a parenteral formulation as described above into a vein.

For oral administration to human patients, it is expected that the daily dosage level of a compound of the invention will be from 0.1 to 20 mg/kg per day for a typical adult patient (70 kg). For parenteral administration, it is expected that the daily dosage level of a compound of the formula (I) will be from 0.01 to 0.5 mg/kg per day, for a typical adult patient. Thus tablets or capsules can generally be expected to contain from 5 to 150 mg of the active compound for administration orally up to 3 times a day. Dosage units for parenteral administration can be expected to contain from 0.5 - 35 mg of the active compound. A typical vial could be a 10 ml vial containing 5 mg of the active compound in 6-10 ml of solution.

It should of course be appreciated that in any event the physician will determine the actual dosage which will be most suitable for the individual and it will vary with the age, weight and response of the patient. The above dosages are exemplary of the average patient, there may of course be individual cases where higher or lower dosage ranges are merited.

The preparation of compounds of the invention and pharmaceutical compositions thereof is illustrated by the following Examples:

Preparation 1

1-(3-Pyridylmethyl)-2-methylindole-3-carboxaldehyde

Sodium hydride (50% dispersion in mineral oil; 4.90 g) was added portionwise to a stirred solution of

2-methylindole-3-carboxaldehyde (16.0 g) in dry N,N-dimethylformamide (100 ml) at 0°C and the resulting mixture was stirred at room temperature for 1 hour. It was then cooled to 0°C and 3-chloromethylpyridine (13.0 g) in 20 ml of dry N,N-dimethylformamide was added over 5 minutes with stirring. The resulting mixture was stirred at room temperature for 2 hours and then poured into water (500 ml). The mixture was extracted several times with ethyl acetate and the combined extracts were extracted with 2N hydrochloric acid. The combined acid extracts were made just alkaline by the addition of solid sodium bicarbonate and the mixture was extracted several times with ethyl acetate. The combined ethylacetate extracts were dried (Na_2SO_4) and evaporated to give a solid which was crystallized from methanol/H_2O to give 1-(3-pyridylmethyl)-2-methylindole-3-carbonaldehyde (12.55 g), m.p. 132-134°C.

Found: C,76.51: H,5.83: N,11.64.
$C_{16}H_{14}N_2O$ requires: C,76.77: H,5.64: N,11.20%

Example 1

1-(3-Pyridylmethyl)-2-methylindole-3-acrylic acid

A mixture of 1-(3-pyridylmethyl)-2-methylindole-3-carboxaldehyde (2.50 g), malonic acid (1.5 g), pyridine (10 ml) and piperidine (3 drops) was heated at 50°C for 6 hours. A further 2.0 g of malonic acid was added and the mixture was heated at 50°C for a further 1 hour and then poured into water to give a gum. The supernatant was poured off and the gum was dissolved in the minimum volume of 0.5 N sodium hydroxide solution. The solution was filtered and acidified with acetic acid to give a solid which was washed with water and dried. The solid was chromatographed on silica gel. Elution with chloroform gave first some impurity followed by pure product. Evaporation of the product containing franctions gave a solid which was crystallized from ethyl acetate to give 1-(3-pyridylmethyl)-2-methylindole-3-acrylic acid (0.84 g), m.p. 195-196°C.

Found: C,73.57: H,5.56: N,9.35.
$C_{18}H_{16}N_2O_2$ requires: C,73.95: H,5.52: N,9.59%

Example 2

1-(3-Pyridylmethyl)-2-methylindole-3-acrylic acid (1 g) was added to distilled water (900 ml) and the pH adjusted to 5 with hydrochloric acid. Sodium chloride (18 g) was added and the solution made up to 2 litres. The final solution was sterilised by filtration through a bacteria-proof filter under aseptic conditions into 10 ml glass vials so as to comply with the test for sterility of Appendix 121 British Pharmacopea 1973.

Example 3

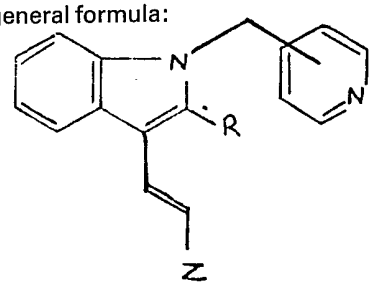
Capsules are compounded from the following ingredients:

	mg/capsule
1-(3-Pyridylmethyl)-2-methylindole-3-acrylic acid	20
Lactose	250
Maize starch	75
Magnesium stearate	5
	350 mg

The ingredients are thoroughly blended, granulated and then filled into hard gelatine capsules of the desired size.

CLAIMS

1. A compound of the general formula:



---(I)

wherein

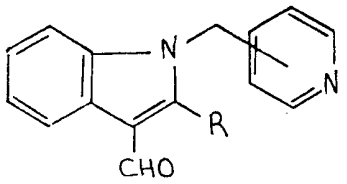
R is hydrogen, C_1-C_4 lower alkyl, C_3-C_6 cycloalkyl or phenyl;

Z is CO_2H, $CO_2(C_1$-C_4 lower alkyl), $CONH_2$, CN or 5-tetrazolyl;

and wherein the pyridine ring is attached at the 3 or 4 position; and the pharmaceutically acceptable acid addition salts thereof.

2. A compound as claimed in claim 1 wherein said compound is 1-(3-pyridylmethyl)-2-methylindole-3-acrylic acid.

3. A process for preparing a compound of the formula 1 as claimed in claim 1 which comprises reacting a compound of the formula:



--- (II)

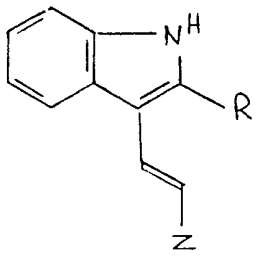
wherein R is as defined in claim 1,

with malonic acid in the presence of an organic base to yield the compounds of formula 1 where Z is CO_2H; or with a reagent of the formula:

$$Ph_3P = CHCO_2R^1 \qquad \text{--- (III)}$$

wherein R^1 is a C_1-C_4 lower alkyl group, to yield the compound of formula I wherein Z is $CO_2(C_1$-C_4 lower alkyl); and optionally using a conventional chemical transformation reaction to convert the resulting acid or ester to a compound of formula I wherein Z is $CONH_2$, CN or tetrazolyl; and optionally forming a pharmaceutically acceptable salt thereof.

4. A process for preparing a compound of the formula 1 as claimed in claim 1 which comprises reacting a compound of the formula:



---(IV)

wherein R is as previously defined and Z is $CO_2(C_1$-C_4 lower alkyl), $CONH_2$ or CN; with a strong base to generate the anion followed by addition of a 3 or 4-halomethylpyridine; and optionally using a conventional chemical transformation reaction to obtain those compounds where Z is CO_2H or 5-tetrazolyl; and optionally forming a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound of the formula (I) as claimed in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

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Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.