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NOTICE OF ENTITLEMENT

We THE WELLCOME FOUNDATION LIMITED

of Unicorn House, 160 Euston Road, LONDON NW1 2BP, ENGLAND

being the Applicant and Nominated Person in respect of Australian Patent Application No. 11710/92

state the following:

James Leroy Kelley and Virgil Lee Styles are the actual inventors of the invention the subject of the Application.

The applicant and nominated person is the assignee of the invention from the actual inventors.

THE WELLCOME FOUNDATION LIMITED is the applicant of the application listed in the declaration under Article 8 of the PCT.

Convention priority is claimed from the following basic application referred to in the declaration under Article 8 of the PCT:

Application Number	**Application Date**	**Country**	**Country Code**
9101244.3	19 January 1991	Great Britain	GB

The basic application referred to in the declaration under Article 8 of the PCT was the first application made in a Convention country in respect of the invention the subject of the Application.

DATED this 9th day of July 1993

THE WELLCOME FOUNDATION LIMITED
By their Patent Attorney

GRIFFITH HACK & CO

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SUBSTITUTED (3) PHENYL-2-BUTENAMIDES THEIR PHARMACEUTICAL APPLICATIONS AND METHODS OF PREPARATION

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(71) Applicant(s)
THE WELLCOME FOUNDATION LIMITED

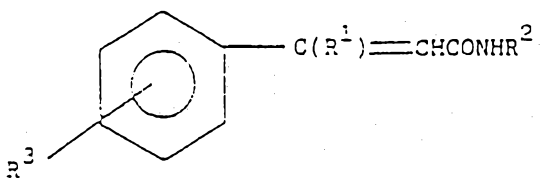
(72) Inventor(s)
JAMES LEROY KELLEY; VIRGIL LEE STYLES

(74) Attorney or Agent
GRIFFITH HACK & CO., GPO Box 4164, SYDNEY NSW 2001

(57) The present invention relates to 3-phenyl-2-alkenamide derivatives, physiologically functional derivatives thereof, pharmaceutical preparations containing them and the use of such compounds and preparations in therapy, particularly as muscle relaxants, anxiolytics and anti-convulsants.

CLAIM

1. A compound of formula (I):



(I)

wherein R^1 represents C_{1-6} alkyl, R^2 represents hydrogen or C_{3-6} cycloalkyl and R^3 represents one or more ring substituents selected from halogen and perhaloC_{1-4}alkyl;

with the following provisos that:

.../2

(i) when R^1 is methyl and R^2 is cyclopropyl then the or one of R^3 is in the 2-position; and

(ii) said compound of formula (I) is not 3-(4-chlorophenyl)-2-butenamide;

or a base salt or other physiologically functional derivative thereof.

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(71) Applicant *(for all designated States except US)*: THE WELLCOME FOUNDATION LIMITED [GB/GB]; Unicorn House, 160 Euston Road, London NW1 2BP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : KELLEY, James, Leroy [US/US]; 10928 Raven Rock Drive, Raleigh, NC 27614 (US). STYLES, Virgil, Lee [US/US]; 5807 Lake Elton Road, Durham, NC 27713 (US).

(74) Agent: GARRETT, M.; The Wellcome Foundation Limited, Langley Court, Beckenham, Kent BR3 3BS (GB).

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(54) Title: AMIDE DERIVATIVES AND THEIR THERAPEUTIC USE

(57) Abstract

The present invention relates to certain 3-phenyl-2-alkenamide derivatives, base salts and other physiologically functional derivatives thereof, pharmaceutical preparations containing them and the use of such compounds and preparations thereof in therapy, particularly as muscle relaxants, anxiolytics and anti-convulsants. Processes for the preparation of these 3-phenyl-2-alkenamides are also disclosed.

AMIDE DERIVATIVES AND THEIR THERAPEUTIC USE

The present invention relates to 3-phenyl-2-alkenamide derivatives, physiologically functional derivatives thereof, pharmaceutical preparations containing them and the use of such compounds and preparations in therapy, particularly as muscle relaxants, anxiolytics and anti-convulsants.

The hypnotic and sedative effects of certain 3-phenyl-2-alkenamide derivatives, usually referred to by their trivial chemical name cinnamamides, have been disclosed by Lott and Christiansen, J.Am. Pharm.Assoc., 23,788 (1934) and Van Heyningen et al., J.Med.Chem., 9,675 (1966) respectively.

In US patent no. 4,190,674 there is disclosed cinnamamide derivatives which are active in the treatment of convulsion of a mammal and their use in relaxing muscles, for example, treatment of increased skeletal muscle tone.

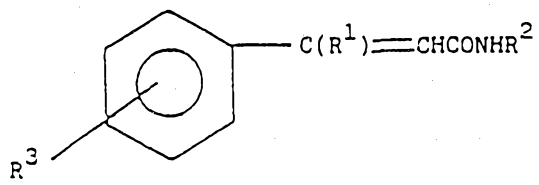
European patent specification no. 0381508 describes the use of certain cinnamamides for relaxing muscle tone, for example, in the treatment of muscle spasm or spastic paralysis such as cerebral injuries.

The major limiting side effects of many clinically effective muscle relaxants and anticonvulsants are the induction of sedation and incoordination in the recipient, which severely limits the usefulness of these compounds. Similar side effects have been found with drugs used in the treatment of anxiety, such as, benzodiazepines. Although these effects may be transient, patients on such therapy are often unable to drive or participate in certain occupations.

This side-effect liability of potential muscle relaxant compounds can be determined experimentally from studies on the efficacy and depressant potential of muscle relaxants (Drug Dev. Res., 2,383 (1982)).

We have now surprisingly found that certain 3-phenyl-2-alkenamides have potent muscle relaxant activity but with significantly reduced liability to the sedation and incoordination side-effects observed with known muscle relaxants. These compounds have also been found to have anxiolytic and anti-convulsant activity.

According to the present invention there is provided 3-phenyl-2-alkenamide derivatives of general formula (I):



(I)

wherein R^1 represents C_{1-6} alkyl, R^2 represents hydrogen or C_{3-6} cycloalkyl and R^3 represents one or more ring substituents selected from halogen (for example, Cl,Br,I,F) and perhaloC_{1-4}alkyl (for, example trifluoromethyl);

with the following provisos that:

(i) when R^1 is methyl and R^2 is cyclopropyl then the or one of R^3 is in the 2-position; and

(ii) said compound of formula (I) is not 3-(4-chlorophenyl)-2-butenamide;

or a base salt or other physiologically functional derivative thereof.

As used herein the term "alkyl" as a group or part of a group means a straight or branched chain alkyl group. Such alkyl groups preferably have 1 to 3 carbon atoms and are more preferably methyl or ethyl, most preferably methyl.

Preferred compounds of formula (I) include those wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or the or one of R^3 is a ring substituent at the 2-position, preferably bromo, chloro or iodo or a perhalomethyl, for example trifluoromethyl; or a base salt or other physiologically functional derivative thereof.

Particularly preferred compounds of formula (I) include those wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or R^3 is a single ring substituent at the 2-position, preferably bromo, chloro, iodo or trifluoromethyl; or a base salt or other physiologically functional derivative thereof.

The (E) isomers of compounds of formula (I) or a base salt or other physiologically functional derivative thereof are preferred.

Especially preferred compounds of formula (I) are:

1. (E)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide;

2. (E)-N-cyclopropyl-3-(2-(trifluoromethyl)phenyl))-2-butenamide;

3. (E)-N-cyclopropyl-3-(2-iodophenyl)-2-butenamide;

4. (E)-N-cyclopropyl-3-(2,3-dichlorophenyl)-2-butenamide;

5. (E)-3-(2-chlorophenyl)-N-cyclopropyl-2-butenamide; and

6. (E)-3-(2-bromophenyl)-2-butenamide.

The compounds of formula (I) above and their base salts, or other physiologically functional derivatives are hereinafter referred to as the compounds according to the invention.

It will be appreciated that the compounds of formula (I) may exist in various geoisomeric forms and as mixtures thereof in any proportions. The present invention includes within its scope the use of such geoisomeric forms or mixtures of geoisomers, including the individual E and Z isomers of the compounds of formula (I) as well as mixtures of such isomers, in any proportions.

By "other physiologically functional derivatives" is meant any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) the said compound or an active metabolite or residue thereof.

Examples of base salts according to the invention include salts, for example, derived from an appropriate base, such as alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium) salts, ammonium and NX_4^+ (wherein X is C_{1-4} alkyl).

For therapeutic use, salts of compounds of formula (I) will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable base. However, salts of bases which are not physiologically acceptable may also find use, for example in the preparation or purification of the compound. All base salts whether or not derived from a physiologically acceptable base are to be considered as being within the scope of the present invention.

According to further aspects of the invention there are provided the compounds according to the invention for use in medical therapy, in particularly for the treatment or prophylaxis of -

- conditions associated with abnormally raised muscle tone,
- convulsive states, and
- anxiety.

The compounds are thus of particular value in the relaxation of skeletal muscle in spastic, hypertonic and hyperkinetic conditions.

In particular the compounds may be used in the treatment and symptomatic relief of conditions such as spinal cord injury, parkinsonism, chorea, arthritis, athetosis, status epilepticus and tetanus and especially in the relief of muscle spasm in conditions such as myositis, spondylitis, cerebral palsy, cerebrovascular disease amd multiple sclerosis.

The compounds may also be used for the treatment of exertion-induced skeletal muscle spasm, for example, lower back pain.

Convulsive states for which the compounds may be employed include grand mal, petit mal, psychomotor epilepsy and focal seizure. The compounds according to the invention may also be used in the treatment of anxiety including generalised anxiety disorders, obsessive compulsive disorder, panic disorder, phobic anxiety, separation anxiety and post-traumatic stress disorder.

A further use of such compounds is as presurgical muscle relaxants and anti-anxiety agents.

In a further aspect of the present invention there is included:

a) a method for the treatment or prophylaxis of conditions associated with abnormally raised muscle tone, convulsive states or anxiety in a host, for example, a mammal including man, and mice which comprises treating said mammal with an effective non-toxic amount of a compound according to the invention.

b) use of a compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of conditions associated with abnormally raised muscle tone, convulsive states or anxiety.

The above compounds according to the invention may be employed in combination with other therapeutic agents for the treatment of the

conditions associated with abnormally raised muscle tone. Examples of such therapeutic agents include analgesics, such as, codeine, acetaminophen, phenacetin or ibuprofen.

The present invention further provides pharmaceutical formulations of the compounds according to the invention, also referred to herein as active ingredients, which may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). It will also be appreciated that the preferred route will vary with the conditions and age of the recipient, the nature of the disorder and the chosen active ingredient.

The amount required of the individual active ingredient for the treatment of, for example, increased muscle tone, convulsive states and anxiety of course depends upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician.

In general, for the foregoing conditions a suitable dose of a compound of formula (I) or a base salt or other physiologically functional derivatives thereof (estimated as the parent compound) is in the range of 0.05 to 100mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 50mg per kilogram body weight per day, most preferably in the range 0.5 to 20mg per kilogram body weight per day and optimally 3mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 1500mg, preferably 5 to 1000mg, and most preferably 10 to 700mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprises at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium

starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for oral use as described above may also include buffering agents designed to neutralize stomach acidity. Such buffers may be chosen from a variety of organic or inorganic agents such as weak acids or bases admixed with their conjugated salts.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injections solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render

the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, as liposomes or other microparticulate systems which are designed to target the compounds to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered, aqueous solution of, for example, 0.1 to 0.2M concentration with respect to the said compound. As one particular possibility, the active compound may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3/6, 318 (1986).

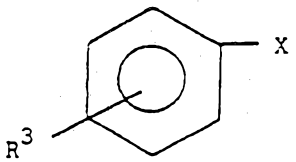
Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The compounds of formula (I) may be prepared in any conventional manner and in accordance with the present invention, may, for example, be prepared by any method hereinafter described.

Thus, the present invention further includes a process for the preparation of compounds of formula (I) and base salts, and other physiologically functional derivatives thereof which comprises:-

A) reacting a compound of formula (II)



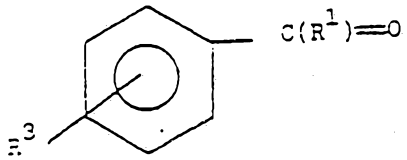
(II)

(wherein R^3 is as hereinbefore defined and X is a suitable leaving group, for example a halogen atom such as bromine or iodine or a sulphonate such as $CF_3S(O)_2O$- with a compound of formula (III)

$$R^1CH=CHCOR^4 \qquad \text{(III)}$$

(wherein R^4 represents $-NHR^2$ and R^1 and R^2 are as hereinbefore defined);

B) reacting a compound of formula (IV)



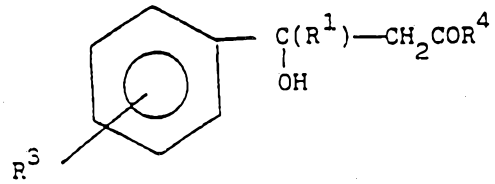
(IV)

(wherein R^1 and R^3 are as hereinbefore defined) with a Wittig reagent of formula (V)

$$YCH_2COR^4 \qquad (V)$$

(wherein R^4 is as hereinbefore defined and Y is $-P(=O)(OR)_2$ wherein R is a C_{1-4} alkyl, aryl or aralkyl group, or Y is a triarylphosphine) under Wittig conditions;

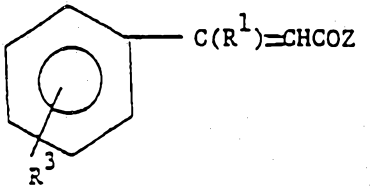
C) dehydrating a compound of formula (VII)



(VII)

(wherein R^1, R^3 and R^4 are as hereinbefore defined).

D) reacting a compound of formula (VIII)



(VIII)

(wherein R^- and R^3 are as hereinbefore defined and Z is a suitable leaving group, for example, a halogen atom, such as bromine or chlorine, azido, amino, or a ROC(O)O- group wherein R represents C_{1-6} alkyl, for example, $CH_3CH_2OC(O)O$- or an alkanoyloxy group, such as acetyloxy) with a compound of formula (IX)

$$H\text{-}R^4 \qquad (IX)$$

(wherein R^4 is as hereinbefore defined).

and thereafter, or simultaneously therewith, effecting one or more of the following optional conversions:-

(i) converting the compound of formula (I) so formed into a base salt, or other physiologically functional derivative thereof;

(ii) when a base salt, or other physiologically functional derivative of a compound of formula (I) is formed, converting the said derivative into a compound of formula (I), or a different derivative thereof.

In process A), a compound of formula (II), is reacted with a compound of formula (III), typically in the presence of a catalyst, such as a transition metal catalyst, for example, a palladium catalyst, in particular, palladium acetate, conveniently in the presence of an organic base such as triethylamine (TEA) and in a suitable polar solvent, for example, acetonitrile, dimethylformamide (DMF) or methanol, preferably at an elevated temperature. The reaction may be carried out in the presence of a phosphorus reagent such as tri-o-toluyl phosphine or another triarylphosphine.

Compounds of formula (II) may be obtained commercially or, may be prepared by methods known in the art for the synthesis of compounds of analogous structure and in this regard reference is made, by way of illustration only to the following texts:-

i) "Protective Groups in Organic Chemistry" ed. J.F.W.McOmie, Plenum Press (1973), ISBN 0-306-30717-0;

ii) "Compendium of Organic Synthetic Methods" ed. I.T.Harrison and S.Harrison, Wiley-Interscience, Vol.I (1971) ISBN 0.471-35550-X, Vol.II (1974) ISBN 0-471-35551-8 and Vol.III (ed. L.S.Hegedus and L.Wade) (1977) ISBN 0-471-36752-4; and

iii) Rodd's "Chemistry of Carbon Compounds" second edition, Elsevier Publishing Company.

Compounds of formula (III) wherein R^1 and R^4 are as hereinbefore defined may conveniently be prepared either directly from a compound of formula (III) wherein R^1 is as hereinbefore defined and R^4 represents hydroxy, for example, by treatment with the appropriate amine in the presence of a reagent such as dicyclohexylcarbodiimide (DCC) or by conversion of the latter compound of formula (III) to an activated derivative, such as an acid halide, for example, the acid chloride, or an acid anhydride. In the case of the acid chloride, by reaction with thionyl chloride, followed by reaction with the appropriate amine in the presence of an organic base such as TEA or an excess of the amine itself.

Compounds of formula (III) wherein R^1 is as hereinbefore defined and R^4 is hydroxy may be obtained commercially or by methods known to a skilled person.

In process B), a compound of formula (IV), is reacted with a Wittig reagent of formula (V), generally in the presence of a strong base such as sodium hydride or lithium hydride and conveniently in an inert

solvent, for example, dimethoxyethane (DME). The relative proportions of E and Z isomers in the compound of formula (I) so formed will depend on the nature of the alkyl, aryl or aralkyl group in the phosphorus-containing group of the Wittig reagent.

Compounds of formula (IV) may be obtained commercially or prepared by methods well known to a skilled person.

Compounds of formula (V) where Y and R^4 are as hereinbefore defined may be prepared by methods well known in the art, but are typically prepared from compounds of formula (V) wherein R^4 is as hereinbefore defined and Y is a suitable leaving group, for example, a halogen atom, such as chlorine or bromine, by treatment with a suitable phosphorylating agent such as a trialkylphosphite or a triarylphosphine. Compounds of formula (V) wherein R^4 is as hereinbefore defined and Y is a leaving group may be prepared from compounds of formula (V) wherein Y is the aforementioned leaving group and R^4 is another suitable leaving group, for example a halogen atom such as chlorine or bromine. Such compounds, for example, $ClCOCH_2Cl$, may be obtained from commercial sources or prepared by methods known to a skilled person or readily available from the chemical literature.

In process C), dehydration of a compound of formula (VII), may be effected with a suitable dehydrating agent, such as acetic anhydride, typically in the presence of an acid such as p-toluenesulphonic acid.

Compounds of formula (VII) may conveniently be prepared by reacting a compound of formula (IV) as defined in process B) with a compound of formula (V) wherein R^4 is as hereinbefore defined and Y is bromine, in the presence of zinc (Reformatski reaction). The compound of formula (VII) obtained may be isolated or dehydrated in situ.

Compounds of formula (V) wherein R^4 is as hereinbefore defined and Y is bromine may be prepared by methods analogous to those described above for the preparation of compounds of formula (V) wherein R^4 is as

hereinbefore defined and Y is a suitable leaving group, in this case bromine and compounds of formula (IV) may be obtained commercially or by methods known to a skilled person.

Process D) may be carried out by treating a compound of formula (VIII) with a compound of formula (IX), typically in an inert solvent such as THF or benzene.

Compounds of formula (IX) may be obtained commercially or made by methods well known to a skilled person.

Compounds of formula (VIII) wherein R^1, R^3 and Z are as hereinbefore defined may be prepared from compounds of formula (VIII) wherein R^1 and R^3 are as hereinbefore defined and Z is hydroxy, for example where Z is to be halogen, by treatment with a halogenating agent such as oxalyl chloride in an inert solvent such as benzene or, where Z is to be a ROC(O)O- group wherein R is as hereinbefore defined, by treatment with the appropriate alkylchloroformate in the presence of an organic base such as TEA and in an inert solvent such as THF. The compound of formula (VIII) obtained may be isolated or aminated <u>in situ</u>.

Compounds of formula (I) may also be prepared directly from a compound of formula (VIII) wherein R^1 and R^3 are as hereinbefore defined and Z is hydroxy by treatment with a compound of formula (IX) wherein R^4 is as hereinbefore defined in a suitable solvent.

Compounds of formula (VIII) where R^1 and R^3 are as hereinbefore defined and Z is hydroxy may conveniently be prepared by the hydrolysis of a compound of formula (VIII) wherein R^1 and R^3 are as hereinbefore defined and Z is a suitable leaving group, such as alkoxy, for example, (E)-methyl-3-(2-bromophenyl)-2-butenoate wherein R^1 is methyl, R^3 is 2-bromo and Z is methoxy, in the presence of a base such as sodium hydroxide or an acid such as hydrochloric acid and in a polar solvent, for example, ethanol. Compounds of formula (VIII) wherein Z is alkoxy may be made by the dehydration of a compound of

formula (VII) wherein R^1 and R^3 are as hereinbefore defined and R^4 = Z. Such compounds may be prepared by the Reformatski reaction described in process C) above.

The compound of formula (I) may be converted into a pharmaceutically acceptable base salt in a conventional manner, for example, by treatment with the appropriate base.

The present invention further includes the following novel intermediates which are of particular value for the preparation of compounds of formula (I) wherein R^1 and R^2 are as hereinbefore defined and R^3 is 2-bromo:-

1. (E)-3-(2-Bromophenyl)-2-butenoic acid.

2. (E)-Ethyl-3-(2-bromophenyl)-2-butenoate.

3. (E)-Methyl-3-(2-bromophenyl)-2-butenoate.

4. (E)-3-(2-Bromophenyl)-2-butenoylchloride.

The following examples illustrate the present invention but should not be construed as limitations thereof.

Example 1

Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

A) Preparation of 2-chloro-N-cyclopropylacetamide

A solution of chloroacetyl chloride (33.8g, 0.3moles) in 100ml of ethyl ether was added dropwise over 30 minutes to cyclopropyl amine (34.2g, 0.6moles, Aldrich) in 400ml of ethyl ether at 0°C with stirring. After and additional 30 minutes at this temperature, the ether was evaporated with a stream of nitrogen

while heating on a steam bath. The residue was dissolved in dichloromethane (400ml) and washed successively with 100ml portions of dilute hydrochloric acid (1N), aqueous sodium bicarbonate (5%), and distilled water. The volatiles were removed by spin evaporation in vacuo, and the residue was recrystallized from dichloromethane/hexanes to give 26.4g (66%) of 2-chloro-N-cyclopropylacetamide, m.p. 80-83°C.

Anal. Calcd. for C_5H_8ClNO: C, 44.96; H, 6.04; N, 10.48; Cl, 26.54
Found: C, 45.04; H, 6.06; N, 10.45; Cl, 26.52.

B) Preparation of Diethyl((cyclopropylcarbamoyl)methyl)phosphonate

2-Chloro-N-cyclopropylacetamide (20g, 0.15moles) was added in portions with stirring to triethyl phosphite (28g, 0.17moles, Aldrich) at 110°C. The solution was then heated to 155°C for 30 minutes, cooled to 125°C, and the volatiles were removed by distillation under aspirator vacuum (15mm Hg) at this temperature. The residual oil was stirred with pentane (200ml) while cooling in an ice bath to induce crystallization. Filtration gave 5.2g (14%) of diethyl((cyclopropylcarbamoyl)methyl)-phopsphonate as white crystals; m.p. 51-56°C. The liquor was concentrated and cooled to give 25.3g (71%) of a second crop; m.p. 50-56°C. Recrystallization from dichloromethane/hexanes gave the analytical sample, m.p. 55-57°C.

Anal. Calcd. for $C_9H_{18}NO_4P$: C, 45.96; H, 7.71; N, 5.95.
Found. C, 45.85; H, 7.76; N, 5.90.

C) Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

To an ice-cold, stirred suspension of NaH (80% dispersion in mineral oil, (0.67g, 28mmoles, Aldrich) in dimethoxyethane (25ml) was added a solution of diethyl((cyclopropylcarbamoyl)methyl)-phosphonate (5.0g, 21mmoles) in dimethoxyethane (60ml). After

1.5 hours, a solution of 2'-bromoacetophenone (4.0g, 20mmoles, Aldrich) in dimethoxyethane (60ml) was added, and the mixture was allowed to warm to room temperature overnight. The reaction mixture was poured into 1L of ice water and the mixture was extracted with dichloromethane. The residue was chromatographed on Silica Gel 60 using dichloromethane-ethyl acetate (9:1) as eluent. The fractions containing only (E)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide were combined and spin evaported in vacuo to give 2.2g of a colorless oil. Trituration with pentane gave 1.85g (33%) of (E)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide, m.p. 82-84°C; NMR (DMSO-d_6): 8.04 (d, 1H, J = 4.02 Hz, NH), 7.64-7.19 (m, 4H, Ar), 5.64 (d, 1H, J = 1.36 Hz, =CH), 2.68 (m, 1H, NCH), 2.36 (d, 3H, J = 1.17 Hz, CH_3), 0.68-0.35 (2m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 2.36, observed 4.9% nOe at 7.25 and 1.3% nOe at 5.64.

Anal. Calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00.
Found: C, 55.82; H, 5.09; N, 4.95.

Example 2

Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

(A) Preparation of (E)-N-Cyclopropyl-2-butenamide

Thionyl chloride (24mL, 0.33mol) was added dropwise during 15 minutes to a stirred solution of crotonic acid (25.8g, 0.30mol, Aldrich) in benzene (400mL) protected from moisture by a drying tube containing Drierite. The resulting clear solution was heated at reflux for 3 hours before a portion of the solvent (100mL) was removed by distillation (atmospheric pressure). The remaining solution was stirred, chilled (ice bath) and treated dropwise with cyclopropylamine (20.6g, 0.36mol, Aldrich) followed by triethylamine (41.8mL, 0.30mol). A white solid precipitated. Water (50mL) was added to the mixture and the resulting layers

were separated. The aqueous layer was saturated with NaCl and extracted with methylene chloride (5 x 100mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to a solid residue, which subsequently was subjected to bulb to bulb distillation (pot temperature 90-110°C) at 0.1 torr; yield, 31.2g (83%), m.p. 63-65°C; NMR (DMSO-d_6): δ 7.91 (br s, 1H, NH), 6.48-6.66 (m, 1H, -C<u>H</u>CH_3), 5.79 (d x d, <u>J</u> = 1.6, <u>J</u> = 15.2 Hz; 1H, -CHCO), 2.65 (m, 1H, NCH), 1.74 (d x d, J = 1.7, J = 6.8 Hz, 3H, CH_3), 0.39 and 0.60 (2 m's, 4H, CH_2CH_2).

Anal. Calcd. for $C_7H_{11}NO.0.1\ H_2O$: C, 66.22; H, 8.89; N, 11.03.
Found: C, 66.10; H, 8.90; N, 11.07.

(B) <u>Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide</u>

A stirred mixture of 1,2-dibromobenzene (Aldrich) (2.36g, 10.0mmol), (E)-<u>N</u>-Cyclopropyl-2-butenamide (1.30g, 10.0mmol), triethylamine (1.01g, 10.0mmol), tri-<u>o</u>-tolylphosphine (Aldrich) (0.24g, 0.8mmol), palladium acetate (Aldrich) (0.04g, 0.2mmol) and acetonitrile (25mL) was heated in a stoppered flask at 120°C for 18 hours. The mixture was cooled to ambient temperature, filtered, concentrated and chromatographed on Silica Gel 60 using ethyl acetate-hexanes (1:4 to 1:1 gradient) as eluent. Fractions containing only (E)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide were combined and spin evaporated <u>in vacuo</u> to give 1.2g (42.8%) of the product. An analytical sample obtained by recrystallization from dichloromethane/hexanes was identical to the compound prepared in Example 1 by mixed m.p. (82-84°C) and NMR.

Anal. Calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00;
Br, 28.52.
Found: C, 55.81; H, 5.06; N, 5.01; Br, 28.44.

Example 3

Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

A) Preparation of (E)-Ethyl 3-(2-Bromophenyl)-2-butenoate

A stirred mixture of 2'-bromoacetophenone (Aldrich) (14.7g, 74mmol), zinc powder (Mallinckrodt) (9.0g), ethyl bromoacetate (Aldrich) (18.5g, 111mmol), a crystal of iodine, benzene (100mL) and diethyl ether (100mL) was heated at reflux under nitrogen for 2 hours. The resulting grey suspension was cooled to ambient temperature, filtered and the filtrate was concentrated to a yellow foam. The residue was dissolved in acetic anhydride (50mL) with cooling, treated with p-toluenesulfonic acid (50mg, Aldrich) and heated at 70-80°C for 0.5 hours. The solution was cooled to ambient temperature, concentrated in vacuo and chromatographed on a Waters Prep 500 using ethyl acetate-hexanes (1:133) as eluent. Fractions containing only (E)-ethyl 3-(2-bromophenyl)-2-butenoate were combined and spin evaporated in vacuo to give 3.0g (15%) of a clear oil; NMR (DMSO-d_6): δ 7.67-7.23 (m, 4H, Ar), 5.72 (d, 1H, J=1.4 Hz, =CH), 4.13 (q, 2H, CH_2O), 2.37 (d, 3H, J=1.4 Hz, CH_3), 1.21 (t, 3H, CH_3CH_2O); steady-state nOe: irradiation at 2.37 δ, observed 2% nOe at 7.45 δ and 1% nOe at 5.72 δ.

Anal. Calcd. for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87; Br, 29.69.
Found: C, 53.61; H, 4.83; Br, 29.76.

B) Preparation of (E)-3-(2-Bromophenyl)-2-butenoic Acid

A mixture of (E)-ethyl 3-(2-bromophenyl)-2-butenoate (2.7g, 10.0mmol), ethanol (20mL) and 1N NaOH (11.0mL) was stirred overnight at ambient temperature. The solution was concentrated in vacuo, diluted with water (30mL) and extracted with diethyl ether. The aqueous layer was acidified by adding conc HCl

(1.2mL) and extracted with diethyl ether. The ether layer was dried over Na_2SO_4, filtered, concentrated and chromatographed on Silica Gel 60 using ethyl acetate-dichloromethane (1:4). The fractions containing only (E)-3-(2-bromophenyl)-2-butenoic acid were combined and concentrated to give white crystals (1.0g, 41.7%) of the product, m.p. 109-111°C; NMR (DMSO-d_6): δ 12.43 (br s, 1H, COOH), 7.67-7.22 (m, 4H, Ar), 5.66 (d, 1H, J=1.4 Hz, =CH), 2.34 (d, 3H, J=1.4 Hz, CH_3); steady-state nOe: irradiation at 2.34 δ, observed 1% nOe at 7.29 δ and 1% nOe at 5.66 δ.

Anal. Calcd. for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.14.
Found: C, 49.92; H, 3.77; Br, 33.21.

C) Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

A solution of (E)-3-(2-bromophenyl)-2-butenoic acid (1.0g, 4.0mmol) and oxalyl chloride (1.7g, 13.8mmol, Aldrich) in benzene (50mL) was refluxed for 2 hours and concentrated to give (E)-3-(2-bromophenyl)-2-butenoylchloride as a pale yellow oil; IR: 1773, 1611 cm^{-1}. Cyclopropylamine (0.9g, 16mmol, Aldrich) was added to the acid chloride in benzene (60mL), and the mixture was stirred overnight at room temperature. The solution was washed sequentially with saturated $NaHCO_3$ (50mL), 1N HCl (50mL) and brine (50mL), dried over Na_2SO_4, filtered and concentrated in vacuo to a cloudy oil (0.9g). Recrystallization from dichloromethane-hexanes gave white crystals (0.3g, 30%) of the product identical to the compound prepared in Example 1 by mixed m.p. (82-84°C) and NMR.

Anal. Calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00; Br, 28.52.
Found: C, 55.77; H, 5.02; N, 5.01; Br, 28.44.

Example 4

Preparation of (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

Ethyl chloroformate (Aldrich) (0.13g, 1.24mmol) was added dropwise to a stirred solution of (E)-3-(2-bromophenyl)-2-butenoic acid (0.30g, 1.24mmol), triethylamine (0.12g, 1.24mmol) and tetrahydrofuran (5mL) at 0°C. After 2h at 0°C, the precipitated triethylamine hydrochloride was removed by filtering and a solution of cyclopropylamine (71mg, 1.24mmol) in tetrahydrofuran (1mL) was added dropwise to the ice-cold filtrate. The mixture was stirred overnight at ambient temperature, concentrated and chromatographed on Silica Gel 60 using ethyl acetate-dichloromethane (1:19) as eluent. The fractions containing only (E)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide were combined and spin evaporated in vacuo to give 0.21g (60%) of the product. An analytical sample obtained by recrystallization from dichloromethane/ hexanes was identical to the compounds prepared in Example 1 by mixed m.p. (82-84°C) and NMR.

Anal. Calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00; Br, 28.52. Found: C, 55.71; H, 5.04; N, 5.01; Br, 28.60.

Example 5

Preparation of (Z)-3-(2-Bromophenyl)-N-cyclopropyl-2-butenamide

The fractions from Example 1C containing only (Z)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide were combined and spin evaporated in vacuo to give 1.7g of a white solid. Trituration with pentane gave 1.31g (23%) of (Z)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide, m.p. 144-146°C; NMR (DMSO-d_6): δ 7.82 (d, 1H, NH), 7.55-7.05 (m, 4H, Ar), 5.90 (d, 1H, J = 1.47 Hz, =CH), 2.48 (m, 1H, NCH), 1.97 (d, 3H, J = 1.47 Hz, CH_3) 0.57-0.27 (2m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 1.97, observed 8.2% nOe at 7.1 and 17.0% nOe at 5.90.

Anal. Calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00.
Found: C, 55.73; H, 4.99; N, 4.99.

Example 6

Preparation of (E)-N-Cyclopropyl-3-(2-(trifluoromethyl))phenyl)-2-butenamide

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 2'-bromoacetophenone in Example 1C with 2'-(trifluoromethyl)acetophenone (Aldrich). The chromatography solutions that contained (E)-N-cyclopropyl-3-(2-(trifluoromethyl))-2-phenyl)-2-butenamide were spin evaporated in vacuo. The solid was collected and recrystallized from ethanol-water to give 0.74g (10%) of (E)-N-cyclopropyl-3-(2-(trifluoromethyl))phenyl)-2-butenamide, m.p. = 114-116°C; NMR (DMSO-d_6): δ 8.06 (d, 1H, J = 4.16 Hz, NH), 7.76-7.36 (m, 4H, Ar), 5.62 (d, 1H, J = 1.31 Hz, =CH), 2.70 (m, 1H, NCH), 2.40 (d, 3H, J = 1.07 Hz, CH_3), 0.66-0.40 (2m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 2.40 δ, observed 4.9% nOe at 7.4 and 1.4% nOe at 5.628 δ.

Anal. Calcd. for $C_{14}H_{14}F_3NO$: C, 62.45; H, 5.24; N, 5.20.
Found: C, 62.37; H, 5.28; N, 5.19.

Example 7

Preparation of (E)-N-Cyclopropyl-3-(2,3-dichlorophenyl)-2-butenamide

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 2'-bromoacetophenone in Example 1C with 2',3'-(dichloro)acetophenone (Maybridge). The chromatography solutions that contained (E)-N-cyclopropyl-3-(2,3-dichlorophenyl)-2-butenamide were spin evaporated, and the solid was collected and dried; yield, 6.73g (47%), m.p. 111-113°C; NMR (DMSO-d_6): δ 8.08 (d, 1H, J = 4.06 Hz, NH), 7.62-7.21 (m, 3H, Ar), 5.69 (d, 1H, J =

1.22 Hz, =CH), 2.67 (m, 1H, NCH), 2.63 (d, 3H, J = 0.97 Hz, CH_3), 0.66-0.37 (2m's, 4H, CH_2CH_2).

Anal. Calcd. for $C_{13}H_{13}Cl_2NO$: C, 57.80; H, 4.85; N, 5.18; Cl, 26.25. Found: C, 57.71; H, 4.83; N, 5.13; Cl, 26.34.

Example 8

Preparation of (E)-3-(2-Chlorophenyl)-N-cyclopropyl-2-butenamide

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 2'-bromoacetophenone in Example 1C with 2'-chloroacetophenone (Aldrich). The chromatography solutions that contained (E)-3-(2-chlorophenyl)-N-cyclopropyl-2-butenamide were spin evaporated in vacuo. The solid was collected and dried; yield, 28.30g (32%), m.p. 92.5-94°C; NMR (DMSO-d_6): δ 8.05 (d, 1H, J = 3.86 Hz, NH), 7.48-7.22 (m, 4H, Ar), 5.68 (d, 1H, J = 1.28 Hz, =CH), 2.68 (m, 1H, NCH), 2.38 (d, 3H, J = 1.44 Hz, CH_3), 0.68-0.37 (2m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 2.38 δ, observed 4% nOe at 7.3 and 1% nOe at 5.68 δ.

Anal. Calcd. for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94; Cl, 15.04. Found: C, 66.34; H, 6.03; N, 5.90; Cl, 15.10.

Example 9

Preparation of (Z)-3-(2-Chlorophenyl)-N-cyclopropyl-2-butenamide

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 2'-bromoacetophenone in Example 1C with 2'-chloroacetophenone (Aldrich). The chromatography solutions that contained (Z)-3-(2-chlorophenyl)-N-cyclopropyl-2-butenamide were spin evaporated and the solid was collected and dried; yield, 3.52g (4%), m.p. 125-132°C; NMR (DMSO-d_6): δ 7.83 (d, 1H, NH), 7.38-7.06 (m, 4H, Ar), 5.92 (d, 1H, J = 1.45 Hz, =CH), 2.48 (m, 1H, NCH),

1.98 (d, 3H, J = 1.41 Hz, CH_3), 0.57-0.24 (2m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 1.98 δ, observed 5% nOe at 7.1 and 14% nOe at 5.92 δ.

Anal. Calcd. for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94; Cl, 15.04.
Found: C, 66.33; H, 6.04; N, 5.88; Cl, 15.11.

Example 10

Preparation of (E)-N-Cyclopropyl-3-(2-fluorophenyl)-2-butenamide

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 2'-bromoacetophenone in Example 1C with 2'-fluoroacetophenone (Aldrich). The chromatography solutions were spin evaporated, and the solid was collected and dried; yield, 8.50g (55%), m.p. 59-5.62°C; NMR (DMSO-d_6): δ 8.08 (d, 1H, J = 3.82 Hz, NH), 7.37-7.15 (m, 4H, Ar), 5.89 (d, 1H, J = 1.21 Hz, =CH), 2.67 (m, 1H, NCH), 2.40 (s, 3H, CH_3), 0.66-0.37 (2m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 2.49 δ, observed 5.3% nOe at 7.3 and 0.7% nOe at 5.89 δ.

Anal. Calcd. for $C_{13}H_{14}FNO$: C, 71.21; H, 6.44; N, 6.39.
Found: C, 71.30; H, 6.46; N, 6.35.

Example 11

Preparation of (E)-3-(3-Chlorophenyl)-N-cyclobutyl-2-butenamide

To a stirred, ice bath-cooled solution of (E)-3-(3-chlorophenyl)-2-butenoic acid (E. Van Heyningen et al. J.Med.Chem, 9, 675 (1966) (5.00g, 254mmole) and triethylamine (2.57g, 254mmole) in tetrahydrofuran (120ml) was added ethyl chloroformate (2.76g, 254mmole) in tetrahydrofuran (20ml). After 30 minutes cyclobutylamine (1.1g, 254mmole, Aldrich) in tetrahydrofuran (30ml) was added slowly. The reaction mixture was stirred at ambient temperature for 15 hours.

The reaction mixture was spin evaporated in vacuo, and the residue was partitioned between ethyl acetate and 5% aqueous sodium bicarbonate. The ethyl acetate layer was washed with 1N hydrochloric acid and brine. The ethyl acetate solution was dried (sodium sulfate) and spin evaporated in vacuo. The residual yellow solid was purified by flash chromatography on silica gel 60 (40-63 m, E. Merck No. 9385) using ethyl acetate-hexane (1:4) as eluent. The fractions that contained (E)-3-(3-chlorophenyl)-N-cyclobutyl-2-butenamide were combined and evaporated to give 3.93g (61%) of product, m.p. 89-90°C; NMR (DMSO-d_6): 8.2 (br d, 1H, NH), 7.54-7.35 (m, 4H, Ar), 6.21 (d, 1H, J = 1.3 Hz, =CH), 4.28 (m, 1H, NCH), 2.45 (d, 3H, J = 1.2 Hz, CH_3), 2.32-1.55 (m, 6H, $(CH_2)_3$); steady-state nOe: irradiation at 2.45, observed 18.1% nOe at 7.5 and -0.2% nOe at 6.21.

Anal. Calcd. for $C_{14}H_{16}ClNO$: C, 67.33: H, 6.46; N, 5.61.
Found: C, 67.34; H, 6.46; N, 5.58.

Example 12

Preparation of (E)-3-(2-Bromophenyl)-N-cyclobutyl-2-butenamide

This compound was prepared in an analogous manner to that of Example 3 with the replacement of cyclopropylamine in Example 3C with cyclobutylamine (Aldrich). The solid was recrystallized from dichloromethane-hexanes to give off white crystals (1.1g, 64%) of the product, m.p. 128-130°C; NMR (DMSO-d_6): δ 8.22 (d, 1H, J = 7.7 Hz, NH), 7.66-7.20 (m, 4H, Ar), 5.68 (d, 1H, J = 1.4 Hz, = CH), 4.25 (m, 1H, NCH), 2.36 (d, 3H, J = 1.3 Hz, CH_3), 2.20-1.58 (3 m's, 6H, $(CH_2)_3$); steady-state nOe: irradiation at 2.36 δ, observed 4% nOe at 7.24 δ and 1% nOe at 5.68 δ.

Anal. Calcd. for $C_{14}H_{16}BrNO$: C, 57.16; H, 5.48; N, 4.76; Br, 27.16.
Found: C, 57.08; H, 5.50; N, 4.72; Br, 27.08.

Example 13

Preparation of (E)-3-(2-Chlorophenyl)-N-cyclopropyl-2-pentenamide

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 2'-bromoacetophenone in Example 1C with 2'-choropropiophenone (B.L.Jenson, S.E. Burke and S.E.Thomas, Tetrahedron, 34, 1627-1631 (1978)). The chromatography solutions that contained (E)-3-(2-Chlorophenyl)-N-cyclopropyl-2-pentenamide were combined and spin evaporated in vacuo to give 6.60g (37%) of (E)-3-(2-Chlorophenyl)-N-cyclopropyl-2-pentenamide, m.p. = 148-150°C; NMR (DMSO-d_6): δ 8.06 (d, 1H, J = 3.9 Hz, NH), 7.50-7.22 (3 m's, 4H, Ar), 5.64 (s, 1H, =CH), 3.01 (q, 2H, J = 7.5 Hz, CH_2C=), 2.70 (m, 1H, NCH), 0.86 (t, 3H, J = 7.5 Hz, CH_3), 0.68-0.40 (2 m's, 4H, CH_2CH_2); steady-state mOe: irradiation at 3.01 δ, observed 19.7% nOe at 0.86 δ and 1.1% nOe at 5.64 δ.

Anal. Calcd. for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61; Cl, 14.19.
Found: C, 67.35; H, 6.48; N, 5.62; Cl, 14.12.

Example 14

Preparation of (E)-N-Cyclopropyl-3-(2-iodophenyl)2-butenamide

A) Preparation of Diisopropyl((cyclopropylcarbamoyl)methyl)-phosphonate

This compound was prepared (3.0 molar scale) in a manner analogous to that of Example 1B with the replacement of triethyl phosphite with triisopropylphosphite (Aldrich) and pentane with hexane: yield, 385g (48.7%) as a fluffy white solid, m.p. 58-60°C; the analytical sample was recrystallized from hexane.

Anal. Calcd. for $C_{11}H_{22}NO_4P$: C, 50.18; H, 8.42; N, 5.32
Found: C, 50.08; H, 8.44; N, 5.26.

B) Preparation of (E)-N-Cyclopropyl-3-(2-iodophenyl)-2-butenamide

This compound was prepared in an analogous manner to that of Example 1 with (Aldrich) the replacement of 2'-bromoacetophenone in Example 1C with 2'-iodoacetophenone (Aldrich) and the replacement of diethyl((cyclopropylcarbamoyl)methyl)phosphonate with diisopropyl((cyclopropylcarbamoyl)methyl)phosphonate. The chromatography solutions that contained (E)-N-cyclopropyl-3-(2-iodophenyl)-2-butenamide were spin evaporated in vacuo. The residue was recrystallized from dichloromethane-hexanes to give 1.7g (51%) of the product as white crystals, m.p. 120-122°C; NMR (DMSO-d_6): δ 8.04 (d, 1H, J = 4.0 Hz, NH), 7.88-7.00 (m, 4H, Ar), 5.57 (d, 1H, J = 1.4 Hz, =CH), 2.68 (m, 1H, CH), 2.34 (d, 3H, J = 1.3 Hz, CH_3), 0.68-0.35 (2 m's, 4H, CH_2CH_2); steady-state nOe: irradiation at 2.34 δ, observed 5% nOe at 7.04 δ and 1% nOe at 5.57 δ.

Anal. Calcd. for $C_{13}H_{14}INO$: C, 47.73; H, 4.31; N, 4.28; I, 38.79.
Found: C, 47.63; H, 4.33; N, 4.26; I, 38.86.

Pharmaceutical Formulations

In the following formulation Examples, the "Active Ingredient" may be any compound of formula (I) or base salt or other physiologically functional derivative thereof, for example, compounds of Examples 1 to 14.

Example 15

Tablet Formulations

The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Formulation A

	mg/tablet	mg/tablet
(a) Active ingredient	250	250
(b) Lactose B.P.	210	26
(c) Povidone B.P.	15	9
(d) Sodium Starch Glycollate	20	12
(e) Magnesium Stearate	5	3
	500	300

Formulation B

	mg/tablet	mg/tablet
(a) Active ingredient	250	250
(b) Lactose	150	-
(c) Avicel PH 101	60	26
(d) Povidone B.P.	15	9
(e) Sodium Starch Glycollate	20	12
(f) Magnesium Stearate	5	3
	500	300

Formulation C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following formulations, D and E, are prepared by direct compression of the admixed ingredients. The lactose in formulation E is of the direct compression type (Dairy Crest - "Zeparox").

Formulation D

	mg/tablet
Active ingredient	250
Pregelatinized Starch NF15	150
	400

Formulation E

	mg/tablet
Active ingredient	250
Lactose	150
Avicel	100
	500

Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the ingredients (below) with a solution of povidone followed by the addition of magnesium stearate and compression.

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.	28
(e)	Magnesium Stearate	7
		700

Example 16

Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of Formulation D in Example 15 above and filling into a two-part hard gelatin capsule. Formulation B (infra) is prepared in a similar manner.

Formulation B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Formulation C

	mg/capsule
(a) Active ingredient	250
(b) Macrogol 4000 B.P.	350
	600

Formulation D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules of formulation D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients a, b and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

	mg/capsule
(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose B.P.	125
(d) Ethyl Cellulose	13
	513

Example 17

Injectable Formulation

Active ingredient	0.200 g
95% Ethanol and PEG 400, 1:1 ratio	
Sterile water	q.s. to 10 mL

The active ingredient is dissolved in 95% Ethanol and PEG 400 (1:1). The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile 10 mL amber glass vial (type 1) and sealed with sterile closures and overseals.

Example 18

Syrup

Active ingredient	0.25 g
Sorbitol Solution	1.50 g
Glycerol	2.00 g
Sodium Benzoate	0.005 g
Flavor, Peach 17.42.3169	0.0125 mL
Purified Water	q.s. to 5.00 mL

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbitol solution and finally the flavor. The volume is made up with purified water and mixed well.

Example 19

Suppository

mg/suppository

Active ingredient	250
Hard Fat, B.P. (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 M sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 M stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.02 g of the mixture is filled into suitable, 2 mL plastic molds. The suppositories are allowed to cool to room temperature.

Example 20

Pessaries

	mg/pessary
Active ingredient	250
Anhydrate Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

Example 21

Muscle Relaxant Activity

Muscle relaxant activity of compounds of formula (I) was determined using a Straub tail test based on that described by K.O. Ellis and J.F. Carpenter Neuropharmacol, 13, 211 (1974).
The Straub tail test result is reported as an ED_{50} in mg/kg. The ED_{50} is defined as the dose of compound administered, which prevents Straub tail in 50% of mice. The compound is administered by oral gavage (po) 60 min. prior to scoring.

The side effect potential of these compounds was determined using the mouse rotorod test as described by G.D. Novak and J.M.-Zwolshei, J.Pharmacological. Methods, 10, 175 (1983). Rotorod result is reported as ED_{50} in mg/kg. The ED_{50} is the dose which causes 50% of the animals to fail to maintain position on a cylinder rotating at 11 r.p.m.

Antagonism of morphine-induced Straub tail reflects muscle relaxant efficacy while failure in the rotorod test reflects sedation and incoordination. Determination of the ratio of rotorod failure to antagonism of morphine-induced Straub tail is a means of assessing side effect liability of muscle relaxants (G.D. Novak, Drug Dev. Res., 2, 383 (1982).

Compound of Example No.	Straub Tail p.o. ED_{50}, mg/kg.	Rotorod p.o. ED_{50}, mg/kg.	Rotorod/ Straub Tail ratio
1	25	45	1.8

Example 22

Anticonvulsant Activity

Anticonvulsant activity of compounds of formula (I) was determined using a method described by Mehta et al., J.Med.Chem., 24, 465 (1981).

The anticonvulsant activity is reported as an ED_{50} in mg/kg. The ED_{50} for protection against maximal electroshock-induced convulsions was the dose which prevented hind limb extension in 50% of the animals. The ED_{50} for protection against Metrazol-induced convulsions was the dose which prevented? convulsions in 50% of the animals.

Compound of Example No.	i.p. ED_{50}, mg/kg (rat) MES	MET
1	9.6	3.6

MES - maximal electroshock
MET - metrazol

Example 23

Anxiolytic Activity

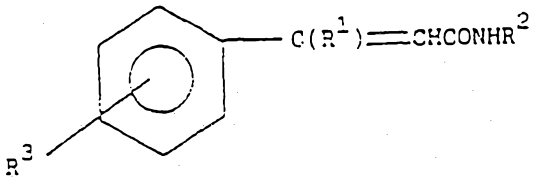
Anxiolytic activity of the compounds according to the invention was measured using method of Geller and Seifter, J.Psychopharmacolgia, 1, 482 (1960) as modified by Pollard and Howard, Psychopharmacology, 62, 117 (1979). Clinically efficacious anxiolytics increase punished responding. The anxiolytic activity of the compound is reported as

the dose necessary to produce a 50% increase in punished responding in rats.

Compound of Example No.	p.o. ED_{50}, mg/kg
1	16

CLAIMS

1. A compound of formula (I):



(I)

wherein R^1 represents C_{1-6} alkyl, R^2 represents hydrogen or C_{3-6} cycloalkyl and R^3 represents one or more ring substituents selected from halogen and perhaloC_{1-4}alkyl;

with the following provisos that:

(i) when R^1 is methyl and R^2 is cyclopropyl then the or one of R^3 is in the 2-position; and

(ii) said compound of formula (I) is not 3-(4-chlorophenyl)-2-butenamide;

or a base salt or other physiologically functional derivative thereof.

2. A compound according to claim 1 wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or the or one of R^3 as defined in formula (I) is in the 2-position; or a base salt or other physiologically functional derivative thereof.

3. A compound according to claims 1 or 2 wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or the or one of R^3 represents bromo, chloro, iodo or trifluoromethyl and is in the

2-position; or a base salt or other physiologically functional derivative thereof.

4. A compound according to any one of claims 1 to 3 wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or R^3 is as hereinbefore defined and is in the 2-position; or a base salt or other physiologically functional derivative thereof.

5. (E) isomers of compounds of formula (I) or a base salt or other physiologically functional derivative thereof according to any one of claims 1 to 4.

6. A compound according to claim 1 which compound is:-

1. (E)-N-cyclopropyl-3-(2-(trifluoromethyl)phenyl))-2-butenamide;

2. (E)-N-cyclopropyl-3-(2-iodophenyl)-2-butenamide;

3. (E)-N-cyclopropyl-3-(2,3-dichlorophenyl)-2-butenamide;

4. (E)-3-(2-chlorophenyl)-N-cyclopropyl-2-butenamide;

5. (E)-3-(2-bromophenyl)-2-butenamide;

or a base salt or other physiologically functional derivatives thereof.

7. (E)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide.

8. A base salt or other physiologically functional derivative of a compound according to any one of claims 1 to 7.

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9. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment or prophylaxis of the conditions associated with abnormally raised muscle tone.

10. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment or prophylaxis of convulsive states.

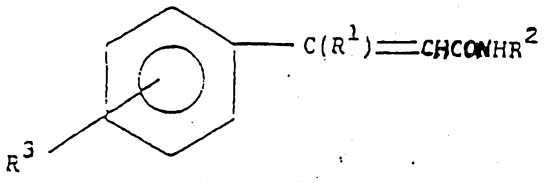
11. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of anxiety.

12. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 8, together with a pharmaceutically acceptable carrier therefor.

13. A formulation according to claim 12 adapted for oral administration.

14. A formulation according to claim 13 in the form of a tablet or capsule.

15. A process for the preparation of a compound of formula (I)



(I)

wherein R^1 represents C_{1-6} alkyl, R^2 represents hydrogen or C_{3-6} cycloalkyl and R^3 represents one or more ring substituents selected from halogen and perhaloC_{1-4}alkyl;

with the following provisos that:

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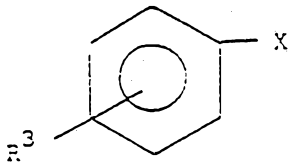
(i) when R^1 is methyl and R^2 is cyclopropyl then the or one of R^3 is in the 2- position; and

(ii) said compound of formula (I) is not 3-(4-chlorophenyl)-2-butenamide;

or a base salt or other physiologically functional derivative thereof, which process comprises:

A) reacting a compound of formula (II)



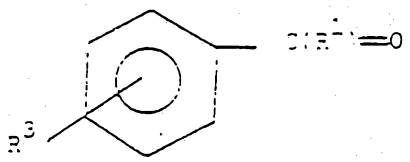
(II)

(wherein R^3 is as hereinbefore defined and X is a leaving group) with a compound of formula (III)

$$R^1CH=CHCOR^4 \qquad \text{(III)}$$

(wherein R^4 represents $-NHR^2$ and R^1 and R^2 are as hereinbefore defined);

B) reacting a compound of formula (IV)



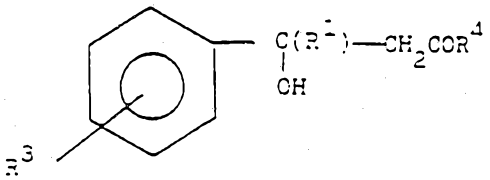
(IV)

(wherein R^1 and R^3 are as hereinbefore defined) with a Wittig reagent of formula (V)

$$YCH_2COR^4 \qquad (V)$$

(wherein R^4 is as hereinbefore defined and Y is $-P(=O)(OR)_2$ wherein R is a C_{1-4} alkyl, aryl or aralkyl group, or Y is a triarylphosphine) under Wittig conditions;

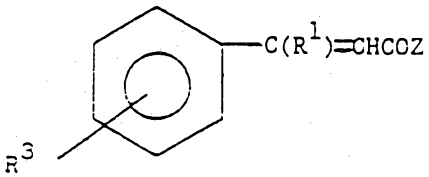
C) dehydrating a compound of formula (VII)



(VII)

(wherein R^1, R^3 and R^4 are as hereinbefore defined).

D) reacting a compound of formula (VIII)



(VIII)

(wherein R^1 and R^3 are as hereinbefore defined and Z is a leaving group) with a compound of formula (IX)

$$H\text{-}R^4 \qquad (IX)$$

(wherein R^4 is as hereinbefore defined).

and thereafter, or simultaneously therewith, effecting one or more of the following optional conversions:-

(i) converting the compound of formula (I) so formed into a base salt, or other physiologically functional derivative thereof;

(ii) when a base salt, or other physiologically functional derivative of a compound of formula (I) is formed, converting the said derivative into a compound of formula (I), or a different derivative thereof.

16. A process according to claim 15 for the preparation of a compound of formula (I) wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or the or one of R^3 as defined in formula (I) is in the 2-position; or a base salt or other physiologically functional derivative thereof.

17. A process according to claims 15 or 16 wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or the or one of R^3 represents bromo, chloro, iodo or trifluoromethyl and is in the 2-position; or a base salt or other physiologically functional derivative thereof.

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18. A process according to any one of claims 15 to 17 wherein R^1 represents methyl and/or, R^2 represents cyclopropyl and/or R^3 is as hereinbefore defined and is in the 2-position; or a base salt or other physiologically functional derivative thereof.

19. A process according to claim 15 for the preparation of (E) isomers of compounds of formula (I) or a base salt or other physiologically functional derivative thereof, according to any one of claims 15 to 18.

20. A process according to claim 15 for the preparation of a compound:-

1. (E)-N-cyclopropyl-3-(2-(trifluoromethyl)phenyl))-2-butenamide;

2. (E)-N-cyclopropyl-3-(2-iodophenyl)-2-butenamide;

3. (E)-N-cyclopropyl-3-(2,3-dichlorophenyl)-2-butenamide;

4. (E)-3-(2-chlorophenyl)-N-cyclopropyl-2-butenamide;

5. (E)-3-(2-bromophenyl)-2-butenamide;

or a base salt or other physiologically functional derivative thereof.

21. A process according to claim 16 for the preparation of (E)-3-(2-bromophenyl)-N-cyclopropyl-2-butenamide.

22. A process according to claim 15 wherein the product is isolated as a base salt or other physiologically functional derivative of formula (I) according to any one of claims 16 to 22.

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23. A method for the treatment or prophylaxis of conditions associated with abnormally raised muscle tone in a host, which comprises treating said host with an effective non-toxic amount of a compound according to claims 1 to 8.

24. A method for the treatment or prophylaxis of convulsive states in a host, which comprises treating said host with an effective non-toxic amount of a compound according to claims 1 to 8.

25. A method for the treatment or prophylaxis of anxiety in a host, which comprises treating said host with an effective non-toxic amount of a compound according to claims 1 to 8.

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26. Use of a compound of formula (I) or a base salt or other physiologically functional derivative thereof in a method of treatment or prophylaxis of conditions associated with abnormally raised muscle tone, convulsive states or anxiety in a host which method comprises treating said host with an effective non-toxic amount of a compound of formula (I) or a base salt or other physiologically functional derivative thereof as defined in claims 1 to 8.

27. A compound of formula (I) or a base salt or other physiologically functional derivative thereof substantially as herein described with reference to any one of examples 1 to 14.

28. A process of preparing a compound of formula (I) or a base salt or other physiologically functional derivative thereof substantially as herein described with reference to any one of examples 1 to 14.

29. A pharmaceutical formulation comprising a compound of formula (I) or a base salt or other physiologically functional derivative thereof substantially as herein described with reference to any one of examples 15 to 20.

30. A method of treatment or prophylaxis of conditions associated with abnormally raised muscle tone, convulsive states or anxiety in a host which comprises treating said host with an effective non-toxic amount of a compound of formula (I) substantially as herein described.

Dated this 24th day of May 1994
THE WELLCOME FOUNDATION LIMITED
By their Patent Attorneys
GRIFFITH HACK & CO



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00108

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 C 233/11 A 61 K 31/165

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 C 233/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	US,A,4190674 (E.M. GRIVSKY) 26 February 1980, see claims (cited in the application)	1-26
A	EP,A,0381508 (TAISHO PHARMACEUTICAL CO.) 8 August 1990, see claims (cited in the application)	1-26
A	Journal of Medicinal Chemistry, vol. 9, no. 5, September 1966, (Washington, US), E. VAN HEYNINGEN: "N-monoalkyl-beta-alkylcinnamamides as sedatives", pages 675-681, see page 675; examples 16,18-20; table II (cited in the application)	1-26
A	FR,A,2132547 (ETABLISSEMENTS CLIN-BYLA) 8 April 1972, see claims; table I	1-26

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" 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

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03-04-1992	11. 05. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Dagmar Frank

Form PCT/ISA/210 (second sheet) (January 1985)

Prime Dagmar FRANK

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers PL. SEE REMARK!! because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIMS 24-26 ARE DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200108 SA 55568

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4190674	26-02-80	GB-A-	1568401	29-05-80
		AT-B-	363926	10-09-81
		AT-B-	371801	10-08-83
		AU-A-	2183777	10-08-78
		BE-A-	851020	02-08-77
		CA-A-	1109076	15-09-81
		CH-A-	634551	15-02-83
		CH-A-	635820	29-04-83
		CH-A-	636849	30-06-83
		DE-A,C	2704365	04-08-77
		FR-A,B	2340303	02-09-77
		JP-C-	1330798	14-08-86
		JP-A-	52116437	29-09-77
		JP-B-	60056700	11-12-85
		NL-A-	7701088	05-08-77
		SE-B-	436870	28-01-85
		SE-A-	7701107	04-08-77
		SE-A-	8300432	28-01-83
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		JP-A-	2288823	28-11-90
FR-A- 2132547	24-11-72	None		