We, being the person identified below as the Applicant, request the grant of a patent to
the person identified below as the Nominated Person, for an invention described in the
accompanying standard complete specification.

Full application details follow:-

**Applicant:** ROUSSEL UCLAF

**Address:** 35, Boulevard des Invalides, 75007, Paris, France

**Nominated Person:** ROUSSEL UCLAF

**Address:** 35, Boulevard des Invalides, 75007, Paris, France

**Invention Title:** CHEMICAL COMPOUNDS

**Name(s) of actual Inventor(s):** Elizabeth Anne Kuo

**Address for service in Australia:** CALLINAN LAWRIE, 278 High Street, Kew 3101,
Victoria, Australia

**Attorney Code:** CL

**Convention Details**

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<th>Basic Applicant</th>
<th>Application Number</th>
<th>Country Code</th>
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<td>9300083.4</td>
<td>U.K.</td>
<td>GB</td>
<td>5 January 1993</td>
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LABORATORIES Ltd.

DATED this 30th day of November, 1993.

ROUSSEL UCLAF

By their Patent Attorneys:

CALLINAN LAWRIE
NOTICE OF ENTITLEMENT

We, ROUSSEL-UCLAF of 35, Boulevard des Invalides, 75007, Paris, France being the applicant and the person nominated for grant of patent in respect of Application for an invention entitled CHEMICAL COMPOUNDS state the following:-

STANDARD CONVENTION FILING

The person nominated for the grant of the patent is the assignee of the invention and of the priority right from ROUSSEL LABORATORIES LIMITED, who is the applicant for the basic application, and is, in turn, a person who would, of a patent were to be granted upon an application made by the said inventor, be entitled to have the patent assigned to it.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

Jeffrey A. Ryder
Patent Attorney for the Applicant

To: The Commissioner of Patents
Compounds of formula (I)

[wherein
A, B and E each represent a group =CH- or a nitrogen atom, with the proviso that at least one of A, B, or E represents a nitrogen atom;
R represents a cycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 6 carbon atoms or an alkynyl group containing 2 to 6 carbon atoms;
R2 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms;
R1 and R3, which may be the same or different, each represent a hydrogen atom, a halogen atom, a group NO2, a cyano group, a linear or branched alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a linear or branched alkoxy group containing 1 to 6 carbon atoms, a linear or branched alkylthio group containing 1 to 6 carbon atoms,
.../2]
a group -CO-R, (in which R, represents a hydrogen atom, a linear or branched alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 6 carbon atoms) or a group selected from -(CH₂)ₘCXₗ,
-O-(CH₂)ₘCXₗ, -S-(CH₂)ₘCXₗ, -O-(CXₗ)ₘCXₗ and
-S-(CXₗ)ₘCXₗ (wherein m represents 0, 1, 2 or 3 and X represents a halogen atom);
or R₁ and R₂ together represent a group -O-CH₂-O-;
and base addition salts thereof, possess anti-inflammatory and immulodulatory activity.
Processes for preparing them, intermediate compounds used in their preparation and compositions containing them are also described.
TO BE COMPLETED BY APPLICANT

Name of Applicant: ROUSSEL UCLAF
Actual Inventor(s): Elizabeth Anne Kuo
Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia
Invention Title: "CHEMICAL COMPOUNDS"

The following statement is a full description of this invention, including the best method of performing it known to me:-
The present invention relates to novel 2-cyano-3-5 hydroxy-propenamides, to processes for their preparation, to pharmaceutical compositions containing them and to their use as medicaments.

According to one aspect of the invention we provide compounds of general formula (I):

wherein A, B and E each represent a group =CH- or a nitrogen atom, with the proviso that at least one of A, B, or E represents a nitrogen atom;

R represents a cycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 6 carbon atoms or an alkynyl group containing 2 to 6 carbon atoms;

R1 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms;

R2 and R3, which may be the same or different, each represents a hydrogen atom, a halogen atom, a group NO2, a cyano group, a linear or branched alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a linear or branched alkoxy group containing 1 to 6 carbon atoms, a linear or branched alkylthio group containing 1 to 6 carbon atoms, a group -CO-R4 (in which R4 represents a hydrogen atom, a linear or branched alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 6 carbon atoms) or a group selected from -(CH2)m-CX3, -O-(CH2)m-CX3, -S-(CH2)m-CX3, -O-(CX2)m-CX3 and -S-(CX2)m-CX3 (wherein m represents 0, 1, 2 or 3 and X represents a halogen atom);
or \( R_2 \) and \( R_3 \) together represent a group \(-\text{O-CH}_2\text{-O-}\); and base addition salts thereof.

It will be understood that the invention extends to all tautomeric forms of the compounds of formula (I).

5 The term 'alkyl group containing 1 to 3 carbon atoms' as used herein denotes a methyl, ethyl, propyl or isopropyl group.

The term 'alkyl group containing 1 to 6 carbon atoms' as used herein denotes, for example, a methyl, ethyl, propyl or isopropyl group or a linear or branched butyl, pentyl or hexyl group.

The term 'cycloalkyl group containing 3 to 6 carbon atoms' as used herein denotes a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

The term 'alkoxy group containing from 1 to 6 carbon atoms' as used herein denotes, for example, a methoxy, ethoxy, propoxy or isoproproxy group or a linear or branched butoxy, pentyloxy or hexyloxy group.

The term 'alkylthio group containing from 1 to 6 carbon atoms' as used herein denotes, for example, a methylthio, ethylthio, propylthio or isopropylthio group or a linear or branched butylthio, pentylthio or hexylthio group.

The term 'halogen atom' as used herein includes a fluorine, chlorine, bromine or iodine atom and preferably refers to a fluorine, chlorine or bromine atom.

The term 'alkenyl group containing 2 to 6 carbon atoms' as used herein preferably denotes a group of formula

\[
\text{\lowercase{烃基}}
\]

The term 'alkynyl group containing 2 to 6 carbon atoms' preferably denotes a group of formula

\[
\text{\lowercase{烃基}}
\]

The following groups may be given as examples of the radicals \(-\text{CH}_2\mbox{-CX}_3\), \(-\text{O-CH}_2\mbox{-CX}_3\), \(-\text{S-CH}_2\mbox{-CX}_3\),
The group of formula

\[ -O-(CF_2)_n-CF_3 \text{ and } -S-(CF_2)_n-CF_3; \]
\[ -CF_3, \quad -(CH_2)_n-CF_3, \quad -(CH_2)_2-CF_3, \quad -(CH_2)_3-CF_3; \]
\[ -O-CF_3, \quad -O-(CH_2)_n-CF_3, \quad -O-(CH_2)_2-CF_3, \quad -O-(CH_2)_3-CF_3; \]
\[ -S-CF_3, \quad -S-(CH_2)_n-CF_3, \quad -S-(CH_2)_2-CF_3, \quad -S-(CH_2)_3-CF_3; \]
\[ -O-(CF_2)_n-CF_3, \quad -S-CF_2-CF_3. \]

includes, for example, the following groups:

- \( N-(2\text{-chloropyridine}-5\text{-yl})- \), \( N-(4\text{-methyl-5\text{-nitropyridine}-2\text{-yl})}- \), \( N-(5\text{-trifluoromethylpyridine}-2\text{-yl})- \), \( N-(5\text{-chloropyridine}-2\text{-yl})- \), \( N-(5\text{-bromopyridine}-2\text{-yl})- \), \( N-(5\text{-nitropyridine}-2\text{-yl})- \), \( N-(\text{pyridine}-4\text{-yl})- \), and \( N-(3,5\text{-dichloropyridine}-2\text{-yl})- \).

The base addition salts can be salts with inorganic or organic bases, for example salts formed with mineral bases, such as sodium, potassium, lithium, calcium, magnesium and ammonium salts, or salts formed with organic bases such as methylamine, propylamine, trimethylamine, diethylamine, triethylamine, \( N,N\text{-dimethylthanolamine} \), \( \text{tris(hydroxymethyl)}\text{-aminomethane} \), \( \text{ethanolamine} \), \( \text{pyridine} \), \( \text{picoline} \), \( \text{dicyclohexylamine} \), \( \text{morpholine} \), \( \text{benzylamine} \), \( \text{procaine} \), \( \text{lysine} \), \( \text{arginine} \), \( \text{histidine} \), and \( \text{N-methylglucamine} \).

Preferred compounds according to the invention are those wherein \( R \) represents a cyclopropyl group or a group of formula

\[ \text{or } \]

and \( A, B, E, R_1, R_2 \) and \( R_3 \) are as defined above.

Further preferred compounds according to the invention are those wherein \( R_1 \) represents a hydrogen atom or a methyl group; and \( R, A, B, E, R_2 \) and \( R_3 \) are as defined above.

Particularly preferred compounds according to the invention are those wherein
R₁ represents a hydrogen atom or a methyl group;
R₂ and R₃, which may be the same or different, each represent
a hydrogen, chlorine or bromine atom, or a cyano, nitro,
methyl, cyclopropyl, methoxy or methylthio group, a group
5 -CO-R₄ (in which R₄ represents a hydrogen atom, a methyl
group or a cyclopropyl group) or a group -(CH₂)ₘ-CF₃,
-O-(CH₂)ₘ-CF₃, -S-(CH₂)ₘ-CF₃, -O-(CF₂)ₘ-CF₃ or
-S-(CF₂)ₘ-CF₃ (in which m represents 0, 1, 2 or 3);
or R₂ and R₃ together represent a group -O-CH₂-CH₂-; and
10 A, B, E and R are as defined above.
More particularly preferred compounds according to the
invention are those wherein R represents a cyclopropyl group;
R₁ represents a hydrogen atom or a methyl group;
R₂ and R₃, which may the same or different, each represents a
15 hydrogen, chlorine or bromine atom or a methyl, nitro or
trifluoromethyl group;
A, B and E being as defined above.
Especially preferred compounds are:
2-cyano-3-cyclopropyl-3-hydroxy-N-(2-chloropyrid-5-yl)-2-
20 propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(4-methyl-5-nitropyrid-2-
yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(5-trifluoromethyl-pyrid-2-
yl)-2-propenamide;
25 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-chloropyrid-2-yl)-2-
propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(5-bromopyrid-2-yl)-2-
propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(5-nitropyrid-2-yl)-2-
propenamide;
30 2-cyano-3-cyclopropyl-3-hydroxy-N-(pyrid-4-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(3,5-dichloropyrid-2-yl)-2-
propenamide;
and base addition salts thereof.
The compounds according to the invention may, for
example, be prepared according to the following processes,
which processes constitute further features of the present
Compounds of formula (I) as defined above, may, for example, be prepared by either

a) reacting a compound of formula (II)

\[
\begin{align*}
\text{A} & \text{N} \\
\text{E} & \text{R}_1 \text{R}_2 \\
\text{R}_1 & \text{CN}
\end{align*}
\]

(wherein A, B, E, R₁, R₂ and R₃ are as defined above) with sodium hydride (where appropriate in the presence of a catalyst) and subsequently reacting the product with a compound of formula (III)

\[
\begin{align*}
\text{Hal} & \text{R}
\end{align*}
\]

(wherein Hal represents a halogen atom and R is as defined above); or

b) reacting a compound of formula (II) as defined above with a compound of formula (IIIₐ)

\[
\begin{align*}
\text{Hal} & \text{R}_\text{A}
\end{align*}
\]

(wherein Hal represents a halogen atom and Rₐ represents the group R as defined above additionally carrying a protecting group) to obtain a compound of formula (Iₐ)
(in which R<sub>1</sub>, A, B, E, R<sub>2</sub>, R<sub>3</sub> and R<sub>3</sub> are as defined above) and subsequently cleaving the protecting group to obtain a compound of formula (I) in which R is as defined above. Compounds of formula (I) as defined above wherein R represents a cycloalkyl group containing 3 to 6 carbon atoms may additionally be prepared by reacting a compound of formula (IV) in which A, B, E, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R are as defined above, with a strong base.

In the case of any of the processes above, if desired, the compound of formula (I) thereby obtained may subsequently be converted into a base addition salt thereof by conventional methods.

The reaction between the compound of formula (II) and sodium hydride is preferably effected in the presence of anhydrous organic solvent such as tetrahydrofuran or dichloromethane and, where appropriate, in the presence of a catalyst which is capable of solvating the sodium hydride such as, for example, imidazole.

The reaction between the product of the reaction of the compound of formula (II) and sodium hydride and the compound of formula (III) or (III<sub>a</sub>) is preferably effected in the presence of anhydrous organic solvent such as tetrahydrofuran.
or dichloromethane, at ambient or low temperature. In some cases the optimum temperature will be in the region of 25°C and in others in the region of 0°C; in others the optimum temperature will be between -80°C and -50°C.

The compound of formula (III) or (IIIA) is preferably an acid chloride or acid fluoride. As an example of the compound of formula (III) propynyl fluoride may be mentioned; this may be, for example, prepared by reaction of propionic acid with benzoyl fluoride and distilled into the subsequent reaction mixture.

Where the group RA represents a group R additionally carrying a protecting group, this protecting group may, for example, be an arylseleno group such as phenylseleno group.

The deprotection of such protecting group may, for example, be carried out by oxidation using, for example, a peroxide such as hydrogen peroxide, either in the absence of a solvent or in the presence of a mixture of organic solvents such as, for example, methanol/dichloromethane.

The reaction between the compound of formula (IV) and a strong base is preferably effected at the reflux temperature of the reaction medium.

The compounds of formula (II) may be prepared by reacting a compound of formula (V)

![Diagram](V)

in which A, B, E, R₁, R₂ and R₃ are as defined above, with cyanoacetic acid in the presence of dicyclohexylcarbodiimide or phosphorous pentachloride in the presence of an anhydrous organic solvent such as tetrahydrofuran or dichloromethane.

The reaction in the presence of both dicyclohexylcarbodiimide and anhydrous tetrahydrofuran is denoted Method A in the subsequent experimental description. The reaction in the presence of both phosphorous pentachloride and anhydrous
dichloromethane is denoted Method B in the subsequent experimental description.

The compounds of formula (IV) may be prepared by reaction of a compound of formula (V) as defined above with an acid chloride of formula (VI)

\[
\begin{align*}
\text{(IV)} \\
\text{(VI)}
\end{align*}
\]

according to a process analogous to that described in WO91/17748.

The acid chloride of formula (VI) can be prepared from the corresponding acid. The acid may, for example, be prepared according to the processes described in the literature; in particular mention can be made of European Patent No.326107.

The compounds of formula (I) are acidic in character. The base addition salts of the compounds of formula (I) can advantageously be prepared by reacting, in approximately stoichiometric proportions, an inorganic or organic base with the compound of formula (I). The salts can be prepared without intermediate isolation of the corresponding acidic compound.

The compounds according to the invention possess very interesting pharmacological properties. Of particular note is their remarkable anti-inflammatory activity. They inhibit both the inflammatory response caused by irritant agents, and delayed hypersensitivity reactions, by hindering activation of the immune cells by a specific antigen.

These properties are further illustrated in the experimental section.

The compounds of formula (I) and the base addition salts thereof are thus of use as medicaments.

According to a further aspect of the invention there is provided the use as medicaments of the compounds of formula
as defined above and pharmacologically acceptable base
addition salts thereof.

Preferred for use as medicaments are compounds according
to the invention wherein R represents a cyclopropyl group or
a group of formula:

\[
\text{or}
\]

A, B, E, R₁, R₂ and R₃ being as defined above.

Also preferred for use as medicaments are compounds
according to the invention wherein
R₁ represents a hydrogen atom or a methyl group; and
R, A, B, E, R₂ and R₃ are as defined above.

Particularly preferred compounds according to the
invention for use as medicaments are those wherein
R₁ represents a hydrogen atom or methyl group;
R₂ and R₃, which may the same or different, each represent a
hydrogen, chlorine or bromine atom or a cyano, nitro, methyl,
cyclopropyl, methoxy or methylthio group, a group \(-\text{CO-}R₄\) (in
which R₄ represents a hydrogen atom, a methyl group or a
cyclopropyl group) or a group \(-\text{(CH}_2\text{)}_m\text{-CF}_3\), \(-\text{O-}\text{(CH}_2\text{)}_m\text{-CF}_3\),
\(-\text{S-}\text{(CH}_2\text{)}_m\text{-CF}_3\), \(-\text{O-(CF}_2\text{)}_m\text{-CF}_3\) or \(-\text{S-(CF}_2\text{)}_m\text{-CF}_3\) (in which m
represents 0, 1, 2 or 3); or
R₂ and R₃ together represent a group \(-\text{O-CH}_2\text{-O-}\); and
A, B, E and R are as defined above.

Most particularly preferred compounds according to the
invention for use as medicaments are those wherein R
represents a cyclopropyl group;
R₁ represents a hydrogen atom or a methyl group;
R₂ and R₃, which may the same or different, each represents a
hydrogen, chlorine or bromine atom or a methyl, nitro or
trifluoromethyl group;
A, B and E being as defined above.
Especially preferred for use as medicaments are the following compounds:

2-cyano-3-cyclopropyl-3-hydroxy-N-(2-chloropyrid-5-yl)-2-propenamide;
5 2-cyano-3-cyclopropyl-3-hydroxy-N-(4-methyl-5-'itropyrid-2-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(5-trifluoromethyl-pyrid-2-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(5-chloropyrid-2-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(pyrid-4-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(3,5-dichloropyrid-2-yl)-2-propenamide;
and base addition salts thereof.

These medicaments are of use, for example, in the treatment of rheumatoid arthritis, chronic inflammatory diseases of immune or non-immune origin (e.g. graft-versus-host disease, transplantation reactions, uveitis) and cancer.

The usual dose varies depending on the compound used, the patient treated and the illness in question and can be, for example, from 0.1 mg to 200 mg per day via the oral route.

According to a further aspect of the invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of formula (I) as defined above or a pharmacologically acceptable base addition salt thereof in association with one or more pharmacologically acceptable diluents, carriers and/or excipients.

For use as medicaments, the compounds of formula (I) and their base addition salts can be incorporated into pharmaceutical compositions intended for the oral, rectal or parenteral route.

These pharmaceutical compositions can be, for example,
solid or liquid and can be in forms conventionally used in human medicine such as: plain or coated tablets, capsules (including gelatine capsules), granules, suppositories, solutions e.g. for injection; they can be prepared according to conventional methods. The active ingredient(s) can be incorporated with excipients to be conventionally used in pharmaceutical compositions such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and preservatives.

According to a further aspect of the invention, there is provided a method of treatment of rheumatoid arthritis, chronic inflammatory diseases of immune or non-immune origin and cancer in a human or animal subject which comprises administering to the subject an effective amount of a compound of formula (I) as defined above or a pharmacologically acceptable base addition salt thereof. The invention is further illustrated by the following non-limiting Examples.

PREPARATION OF STARTING MATERIALS FOR EXAMPLES 1-8

Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(2-chloropyrid-5-yl)-2-propenamide (example 1)

Method A

Cyanoacetic acid (5.95 g, 70.0 mmol) and dicyclohexyl-carbodiimide (14.44 g, 70.0 mmol) were added to a stirred solution of 5-amino-2-chloropyridine (9.00 g, 70.0 mmol) in anhydrous tetrahydrofuran (150 ml) at 0°C. The reaction was monitored by thin layer chromatography and when seen to be complete the reaction mixture was filtered and the filtrate evaporated to dryness. The resulting solid was triturated with anhydrous dichloromethane, filtered and dried in vacuo yielding N-(2-chloropyrid-5-yl)-2-cyanoacetamide (10.56 g 77%).

The starting materials for the following examples were made
According to this method from the appropriate substituted 2-
amino pyridine with the modifications indicated below:

Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(4-
methyl-5-nitropyrid-2-yl)-2-propenamide (example 2)

The product was purified by column chromatography
(Sorbsil C60 silica, 60% hexane/40% ethyl acetate) which
afforded N-(4-methyl-5-nitropyrid-2-yl)-2-cyanoacetamide
(51%).

Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-
trifluoromethylpyrid-2-yl)-2-propenamide (example 3)

The reaction was carried out using cyanoacetic acid (1.2
equivalents) and dicyclohexylcarbodiimide (1.2 equivalents)
which afforded N-(5-trifluoromethylpyrid-2-yl)-2-cyano-
acetamide (79%).

Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-
chloropyrid-2-yl)-2-propenamide (example 4)

The reaction was carried out using cyanoacetic acid (1
equivalent) and dicyclohexylcarbodiimide (1.1 equivalents) in
dichloromethane at reflux. Trituration with ethyl acetate
yielded N-(5-chloropyrid-2-yl)-2-cyanoacetamide (90%).

Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-
bromopyrid-2-yl)-2-propenamide (example 5)

Method B

Cyanoacetic acid (0.22 g, 2.60 mmol) was added to a
stirred solution of phosphorus pentachloride (0.54 g, 2.60
mmol) in anhydrous dichloromethane (8 ml) over a period of 1
minute. The resulting solution was refluxed for 30 minutes
and then the reaction vessel flushed through with nitrogen.
2-amino-5-bromopyridine (0.30 g, 1.73 mmol) was added and
reflux continued. The reaction was monitored by thin layer
chromatography and when complete the reaction mixture was
poured onto water (4 ml). After stirring for 30 minutes, N-
(5-bromopyrid-2-yl)-2-cyanoacetamide was filtered off and
dried in vacuo (0.27 g, 65%).

Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-
nitropyrid-2-yl)-2-propenamide (example 6)

N-(5-nitropyrid-2-yl)-2-cyanoacetamide was obtained from
2-amino 5-nitro pyridine using method B (42 %).

Starting material for 2-cyano 3-cyclopropyl 3-hydroxy N-(3,5-dichloropyrid-2-yl) 2-propenamide (example 8)
N-(3,5-dichloropyrid-2-yl) 2-cyano acetamide was obtained from 2-amino 3,5-dichloropyridine according to method B (29%).

PREPARATION OF EXAMPLES 1-8
EXAMPLE 1 : 2-cyano-3-cyclopropyl-3-hydroxy-N-(2-chloropyrid-5-yl)-2-propenamide

Method C

Sodium hydride (3.21 g 80 % dispersion in mineral oil, 107.1 mmol) was added portionwise to a stirred solution of N-(2-chloropyrid-5-yl)-2-cyanoacetamide (7.00 g, 35.7 mmol) in anhydrous tetrahydrofuran (200 ml) at 0°C. After stirring for one hour, cyclopropanecarbonyl chloride (48.6 ml, 53.6 mmol) was added. The progress of the reaction was followed by thin layer chromatography and when complete the reaction mixture was added to water (1.25 l), acidified to pH 1 by the addition of 35% hydrochloric acid and then stirred for 30 minutes. The resulting precipitate was filtered off and washed with water. It was then triturated with ethyl acetate, filtered and dried in vacuo yielding the title compound (7.91 g, 83%).

The following examples were made by this method with the modifications indicated :-
EXAMPLE 2 : 2-cyano-3-cyclopropyl-3-hydroxy-N-(4-methyl-5-nitropyrid-2-yl)-2-propenamide

Crystals from ethyl acetate/hexane (87 %).
EXAMPLE 3 : 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-trifluoromethyl-pyrid-2-yl)-2-propenamide

Crystals from ethyl acetate/40°-60° petroleum ether (86 %).
EXAMPLE 4 : 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-chloropyrid-2-yl)-2-propenamide

The reaction was carried out using sodium hydride (2.4 equivalents) with catalytic imidazole and cyclopropane-carbonyl chloride (1.2 equivalents). Recrystallisation from
The following statement is a full description of this invention, including the best method of performing it known to me:

**EXAMPLE 5**: 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-bromopyrid-2-yl)-2-propenamide

The reaction was carried out using sodium hydride (2.4 equivalents) with catalytic imidazole and cyclopropane-carbonyl chloride (1.2 equivalents) at 25°C. The title compound was triturated with diethyl ether, filtered and dried in vacuo (83%).

**EXAMPLE 6**: 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-nitropyrid-2-yl)-2-propenamide

The reaction was carried out using sodium hydride (2.4 equivalents) with catalytic imidazole and cyclopropane-carbonyl chloride (1.2 equivalents) at 25°C. The title compound was triturated with diethyl ether, filtered and dried in vacuo (89%).

**EXAMPLE 7**: 2-cyano-3-cyclopropyl-3-hydroxy-N-(pyrid-4-yl)-2-propenamide

Method D

5-cyclopropylisoxazole-4-carboxylic acid was made as described in the literature (EP 326 107 A1).

5-cyclopropylisoxazole-4-carboxylic acid (1.5 g, 9.75 mmol) and thionyl chloride (20 ml) were refluxed together for 90 minutes. The reaction mixture was evaporated in vacuo and the residue co-evaporated with toluene. The resulting acid chloride was dissolved in anhydrous dichloromethane (10 ml) and added to 4-aminopyridine (1.0 g, 9.75 mmol) suspended in anhydrous dichloromethane (50 ml). Pyridine (0.77 g, 9.75 mmol) was added and the reaction mixture stirred at room temperature for 90 minutes. The solid product was filtered off, dissolved in methanol (100 ml) and triethylamine (2 ml) was added. The reaction mixture was refluxed for one hour and then poured onto water (200 ml) and acidified to pH 1 by the addition of conc. hydrochloric acid. Standing at 4°C for sixteen hours afforded the title compound as a crystalline solid which was washed with water and dried in vacuo (0.67 g, 45%).

**EXAMPLE 8**: 2-cyano 3-cyclopropyl 3-hydroxy N-(3,5-dichloro-
-CO-R₄ (in which R₄ represents a hydrogen atom, a linear or branched alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 6 carbon atoms) or a group selected from -(CH₂)ₓ-CX₃, -O-(CH₂)ₓ-CX₃,
-S-(CH₂)ₓ-CX₃, -O-(CX₂)m-CX₃ and -S-(CX₂)m-CX₃ (wherein m represents 0, 1, 2 or 3 and X represents a halogen atom);
<table>
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<th>Ex</th>
<th>Ar</th>
<th>Method</th>
<th>m.pt °C</th>
<th>IR cm⁻¹</th>
<th>¹H NMR δ</th>
<th>Formula M.wt</th>
<th>Analysis % Calc Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>A + C</td>
<td>196-198</td>
<td>1170, 1955, 1500, 1275, 1100, 975, 885.</td>
<td>CDCl₃ 15.59[br, 1H, O-H]; 8.51[d, J=2.5Hz, 1H, Ar-H]; 8.00[d, d, J=8.0Hz, 2.5Hz, 2H, N-H, Ar-H]; 7.33(d, J=8.5Hz, 1H, Ar-H); 2.14[m, 1H, cyclopropyl-H]; 1.29[m, 4H, cyclopropyl-H].</td>
<td>C₁₂H₁₂ClN₂</td>
<td>54.66 3.82 15.94 13.45</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>A + C</td>
<td>178</td>
<td>(3400-2000)br, 1570, 1500, 1275, 1100, 985, 765.</td>
<td>DMSO-d₆ 13.14[br, 1H, O-H]; 11.86[vbrs, 1H, N-H]; 8.94[s, 1H, Ar-H]; 8.22[s, 1H, Ar-H]; 2.57[m, 3H, Ar-Me]; 2.22[m, 1H, cyclopropyl-H]; 1.29[m, 4H, cyclopropyl-H].</td>
<td>C₁₃H₁₂N₄O₄</td>
<td>54.16 4.20 19.44</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>A + C</td>
<td>202-203</td>
<td>(decomposition)</td>
<td>1395, 1250, 1225, 1075, 895.</td>
<td>CDCl₃ 15.38[br, 1H, O-H]; 8.60[e, 1H, Ar-H]; 8.38[brs, 1H, N-H]; 8.22[d, J=8.5Hz, 1H, Ar-H]; 7.95[d, J=8.5Hz, 1H, Ar-H]; 2.18[m, 1H, cyclopropyl-H]; 1.29[m, 4H, cyclopropyl-H].</td>
<td>C₁₃H₁₄F₃N₂</td>
</tr>
</tbody>
</table>
### TABLE I continued

<table>
<thead>
<tr>
<th>Ex</th>
<th>Ar</th>
<th>Method</th>
<th>m.pt °C</th>
<th>IR cm⁻¹</th>
<th>¹H NMR δ</th>
<th>Formula M.wt</th>
<th>Analysis % Calc Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Cl</td>
<td>A + C</td>
<td>223-225</td>
<td>DMSO-d⁶</td>
<td>12.59 (s, 1H, N-H); 8.24 (m, 2H, Ar-H); 7.77 (d, J=9.0 Hz, 2H, Ar-H); 2.20 (m, 1H, cyclopropyl-H); 0.73 (m, 4H, cyclopropyl-H).</td>
<td>C₁₂H₁₂ClIN-&lt;sub&gt;30&lt;/sub&gt;</td>
<td>54.66  3.02  15.94  13.45</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>B + C</td>
<td>202-203</td>
<td>(3300-1800)br, 3110, 2200, (1650-1530)br, 1145, 1005, 980, 770, 720.</td>
<td>C₁₂H₁₂BrIN-&lt;sub&gt;30&lt;/sub&gt;</td>
<td>46.78  3.27  13.64  25.93</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>O₂N</td>
<td>B + C</td>
<td>163-165</td>
<td>DMSO-d⁶</td>
<td>13.17 (s, 1H, N-H); 9.07 (d, J=3.0 Hz, 1H, Ar-H); 8.50 (dd, J=9.0 Hz, 3H, Ar-H); 8.30 (d, J=9.0 Hz, 3H, Ar-H); 2.22 (m, 1H, cyclopropyl-H); 0.77 (m, 4H, cyclopropyl-H).</td>
<td>C₁₂H₁₀N₂O₄</td>
<td>52.56  3.68  20.43</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>D</td>
<td>&gt;300</td>
<td>(3600-2200)br, 3430, 2180, 1630, 1225, 1185, 985, 815.</td>
<td>DMSO-d⁶</td>
<td>14.17 (brs, 1H, O-H); 13.51 (s, 1H, N-H); 8.53 (d, J=7.0 Hz, 2H, Ar-H); 8.04 (d, J=7.0 Hz, 2H, Ar-H); 2.25 (m, 1H, cyclopropyl-H); 0.80 (m, 4H, cyclopropyl-H).</td>
<td>C₁₂H₁₁N₃O₂</td>
</tr>
</tbody>
</table>
The compounds according to the invention may, for example, be prepared according to the following processes, which processes constitute further features of the present invention:

<table>
<thead>
<tr>
<th>Ex</th>
<th>Ar</th>
<th>Method</th>
<th>m.pt °C</th>
<th>IR cm⁻¹</th>
<th>¹H NMR δ</th>
<th>Formula M.wt</th>
<th>Analysis % Calc Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="" alt="Structure" /></td>
<td>B + C</td>
<td>222-224</td>
<td>3080, 3005, 2190, 1630, 1525, 1430, 1405, 1220, 1105, 990, 885.</td>
<td>DMSO-d₆ 13.76(s, 6H, OH); 9.50-11.0 (br s, 1H, NH); 8.62(d, J=1.6Hz, 1H, Ar-H); 8.42(d, J=1H, Ar-H); 7.22(s, 1H, cyclopropyl-H); 0.88(m, 4H, cyclopropyl-H).</td>
<td>C₁₂H₉Cl₃N₂ 296.12</td>
<td>48.34 3.04 14.09 23.79</td>
</tr>
</tbody>
</table>

TABLE I continued
group R as defined above additionally carrying a protecting group) to obtain a compound of formula (IA).

EXAMPLE 9:
Tablets corresponding to the following formula were prepared:
- Compound of Example 1: 20 mg
- Excipient for one tablet up to: 150 mg
(Detail of excipient: lactose, starch, talc, magnesium stearate).

EXAMPLE 10:
Tablets corresponding to the following formula were prepared:
- Compound of Example 2: 20 mg
- Excipient for one tablet up to: 150 mg
(Detail of excipient: lactose, starch, talc, magnesium stearate).

PHARMACOLOGICAL ACTIVITY
Biochemical test methods.
Test 1: Carrageenan rat paw oedema (PO-R)
- One hour after the oral administration of the test compounds or control vehicle to groups of rats (n=6-12, male CFHB, weight range 160-180 g) 1 mg of carrageenan dissolved in 0.2 ml of saline is injected into the right hind foot pad. Contralateral paws receive control saline injections. Paw oedema responses are assessed three hours later.

Test 2: Delayed type hypersensitivity mouse paw oedema (DTH-M)
- Groups of mice (n=8-10, male CD-1, weight range 25-30 g) are sensitized by the subcutaneous injection of 1 mg 30methylated bovine serum albumin (MBSA) in 0.2 ml volumes of saline/Freund's complete adjuvant (FCA) emulsion. Negative control groups receive injections of saline/FCA emulsion. DTH paw oedema responses are assessed twenty-four hours after the right hind foot pad challenge with 0.1 mg MBSA in 0.5 ml volumes of saline on day seven after sensitization. Contralateral paws receive control saline injections. The test compounds or control vehicles are orally administered daily on days four, five, six and twice on day seven, one hour before and six hours after MBSA challenge.
The reaction between the product of the reaction of the compound of formula (II) and sodium hydride and the compound of formula (III) or (III_A) is preferably effected in the presence of anhydrous organic solvent such as tetrahydrofuran.

Test 3: Delayed-type hypersensitivity rat paw oedema (DTH-R)

Groups of rats (n=8-12), male CFHB, weight range 160-180 g) are sensitized by the subcutaneous tail base injection of 0.1 ml volumes of FCA. Negative control groups receive injections of Freund's incomplete adjuvant. DTH paw oedema responses are assessed twenty-four hours after the right hind foot pad challenge with 0.1 mg MBSA in 0.4 mg Mycobacterium tuberculosis extract antigen in 0.2 ml volumes of saline on day seven after sensitization. Contralateral 10 paws receive control saline injections. The test compounds are orally administered daily on days four, five, six and twice on day seven, one hour before and six hours after antigenic challenge.

The results of these tests are given in Table II where the percentage inhibition of oedema formation is given. Doses are given in units of mg/kg p.o.

<table>
<thead>
<tr>
<th>Example</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% inhibition</td>
<td>Dose</td>
<td>% inhibition</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>50</td>
<td>Toxic</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>50</td>
<td>Toxic</td>
</tr>
<tr>
<td>6</td>
<td>-6</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>-43</td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>-15</td>
<td>50</td>
<td>9</td>
</tr>
</tbody>
</table>
The reaction in the presence of both dicyclohexylcarbodiimide and anhydrous tetrahydrofuran is denoted Method A in the subsequent experimental description. The reaction in the presence of both phosphorous pentachloride and anhydrous tetrahydrofuran is denoted Method B in the subsequent experimental description.

The claims defining the invention are as follows:

1. Compounds of formula (I):

   [Chemical structure diagram]

   [wherein
   A, B and E each represent a group =CH- or a nitrogen atom, with the proviso that at least one of A, B, or E represents a nitrogen atom;
   R represents a cycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 6 carbon atoms or an alkylnyl group containing 2 to 6 carbon atoms;
   R₁ represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms;
   R₂ and R₃, which may be the same or different, each represents a hydrogen atom, a halogen atom, a group NO₂, a cyano group, a linear or branched alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a linear or branched alkoxy group containing 1 to 6 carbon atoms, a linear or branched alkylthio group containing 1 to 6 carbon atoms, a group -CO-R₄ (in which R₄ represents a hydrogen atom, a linear or branched alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 6 carbon atoms) or a group selected from -(CH₂)ₘ-CX₃, -O-(CH₂)ₘ-CX₃, -S-(CH₂)ₘ-CX₃, -O-(CX₂)ₘ-CX₃ and -S-(CX₂)ₘ-CX₃ (wherein m represents 0, 1, 2 or 3 and X represents a halogen atom);
   or R₂ and R₃ together represent a group -O-CH₂-O-];
   and base addition salts thereof.

2. Compounds as claimed in claim 1 wherein R represents a cyclopropyl group or a group of formula
The compounds of formula (I) and the base addition salts thereof are thus of use as medicaments.

According to a further aspect of the invention there is provided the use as medicaments of the compounds of formula

and A, B, E, R₁, R₂ and R₃ are as defined in claim 1.

3. Compounds as claimed in claim 1 or claim 2 wherein R₁ represents a hydrogen atom or a methyl group; and R, A, B, E, R₂ and R₃ are as defined in claim 1.

4. Compounds as claimed in any one of claims 1 to 3 wherein R₁ represents a hydrogen atom or a methyl group; R₂ and R₃, which may be the same or different, each represent a hydrogen, chlorine or bromine atom, or a cyano, nitro, methyl, cyclopropyl, methoxy or methylthio group, a group -CO-R₄ (in which R₄ represents a hydrogen atom, a methyl group or a cyclopropyl group) or a group -(CH₂)ₙ-CF₃, -O-(CH₂)ₙ-CF₃, -S-(CH₂)ₙ-CF₃, -O-(CF₂)ₙ-CF₃ or -S-(CF₂)ₙ-CF₃ (in which n represents 0, 1, 2 or 3); or R₂ and R₃ together represent a group -O-CH₂-O; and R, A, B and E are as defined in claim 1.

5. Compounds as claimed in any one of claims 1 to 4 wherein R represents a cyclopropyl group; R₁ represents a hydrogen atom or a methyl group; R₂ and R₃, which may be the same or different, each represent a hydrogen, chlorine or bromine atom or a methyl, nitro or trifluoromethyl group; A, B and E being as defined in claim 1.

6. Compounds as claimed in any one of claims 1 to 5 selected from:

2-cyano-3-cyclopropyl-3-hydroxy-N-(2-chloropyrid-5-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(4-methyl-5-nitropyrid-2-yl)-2-propenamide;
2-cyano-3-cyclopropyl-3-hydroxy-N-(5-trifluoromethyl-
R₁ represents a hydrogen atom; R₂ and R₃, which may the same or different, each represents a hydrogen, chlorine or bromine atom or a methyl, nitro or trifluoromethyl group; A, B and E being as defined above.

A process for the preparation of a compound of formula as claimed in any one of claims 1 to 8 which comprises either

a) reacting a compound of formula (II)

(wherein A, B, E, R₁, R₂ and R₃ are as defined in claim 1) with sodium hydride (where appropriate in the presence of a catalyst) and subsequently reacting the product with a compound of formula (III)
their base addition salts can be incorporated into pharmaceutical compositions intended for the oral, rectal or parenteral route.

These pharmaceutical compositions can be, for example,

(II)

(wherein Hal represents a halogen atom and R is as defined in claim 1); or

b) reacting a compound of formula (II) as defined above with a compound of formula (IIIa)

(IIIa)

(wherein Hal represents a halogen atom and RA represents the group R as defined above additionally carrying a protecting group) to obtain a compound of formula (IA)

(IA)

(in which RA, A, B, E, R1, R2 and R3 are as defined above) and subsequently cleaving the protecting group to obtain a compound of formula (I) in which R is as defined above.

10. A process as claimed in claim 9 wherein the reaction between the product of the reaction of the compound of formula (II) and sodium hydride and the compound of formula (III) or (IIIa) is effected in the presence of anhydrous tetrahydrofuran or dichloromethane, at ambient or low temperature.

11. A process as claimed in claim 9 or claim 10 wherein the reaction between the compound of formula (II) and sodium hydride is effected in the presence of anhydrous tetrahydrofuran or dichloromethane and in the presence of imidazole as a catalyst.

12. A process as claimed in any one of claims 9 to 11 wherein if the group RA represents a group R1
with anhydrous dichloromethane, filtered and dried in vacuo yielding N-(2-chloropyrid-5-yl)-2-cyanoacetamide (10.56 g 77%).

The starting materials for the following examples were made additionally carrying a protecting group, this protecting group is an arylseleno group such as phenylseleno group.

13. A process for the preparation of a compound of formula (I) as claimed in any one of claims 1 to 8 wherein R represents a cycloalkyl group containing 3 to 6 carbon atoms which comprises reacting a compound of formula (IV)

in which A, B, E, R, R and R are as defined in claim 1 and R is as defined above, with a strong base.

14. A process as claimed in any one of claims 9 to 12 wherein the compound of formula (II) is prepared by reacting a compound of formula (V)

in which A, B, E, R, R and R are as defined in claim 1, with cyanoacetic acid.

15. A process as claimed in claim 14 wherein the reaction of the compound of formula (V) with cyanoacetic acid is effected in the presence of dicyclohexylcarbodimide or phosphorous pentachloride and in the presence
Starting material for 2-cyano-3-cyclopropyl-3-hydroxy-N-(5-nitropyrid-2-yl)-2-propenamide (example 6)

N-(5-nitropyrid-2-yl)-2-cyanacetamide was obtained from

of anhydrous tetrahydrofuran or dichloromethane.

16. A process as claimed in claim 13 wherein the compound of formula (IV) is prepared by reaction of a compound of formula (V) as defined in claim 14 with an acid chloride of formula (VI)

\[
\text{Cl} \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{R}
\end{array}
\]

(VI)

wherein \( R \) is as defined in claim 13.

17. A process as claimed in any one of claims 9 to 16 in which the compound of formula (I) thereby obtained is subsequently converted into a base addition salt thereof by conventional methods.

18. A process as claimed in claim 17 wherein the base addition salt of the compound of formula (I) is prepared by reacting, in approximately stoichiometric proportions, an inorganic or organic base with the compound of formula (I).

19. A process as claimed in any one of claims 9 to 18 substantially as herein described.

20. A process as claimed in any one of claims 9 to 18 substantially as herein described in any one of the Examples.

21. A compound of formula (I) or a base addition salt thereof as claimed in any one of claims 1 to 8 whenever prepared by a process as claimed in any one of claims 9 to 20.
The reaction was carried out using sodium hydride (2.4 equivalents) with catalytic imidazole and cyclopropane-carbonyl chloride (1.2 equivalents). Recrystallisation from
Standing at 4°C for sixteen hours afforded the title compound as a crystalline solid which was washed with water and dried in vacuo (0.67 g, 45%).

**EXAMPLE 8**: 2-cyano 3-cyclopropyl 3-hydroxy N-(2,5-dichloro-

acceptable base addition salt thereof.

DATED this 29th day of November 1993

ROUSSEL-UCLAF
By their Patent Attorneys
CALLINAN LAWRIE

[Signature]
Abstract

Chemical Compounds

Compounds of formula (I)

\[
\text{(I)}
\]

[wherein
A, B and E each represent a group =CH- or a nitrogen atom, with the proviso that at least one of A, B, or E represents a nitrogen atom;
R represents a cycloalkyl group containing 3 to 6 carbon atoms, an alkenyl group containing 2 to 6 carbon atoms or an alkynyl group containing 2 to 6 carbon atoms;
R represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms;
R, and R, which may be the same or different, each represents a hydrogen atom, a halogen atom, a group \(\text{NO}_2\), a cyano group, a linear or branched alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 6 carbon atoms, a linear or branched alkoxy group containing 1 to 6 carbon atoms, a linear or branched alkylthio group containing 1 to 6 carbon atoms, a group \(-\text{CO-R}_4\) (in which \(\text{R}_4\) represents a hydrogen atom, a linear or branched alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 6 carbon atoms) or a group selected from \(-\text{(CH}_2\text{)}_n\text{-CX}_3\), \(-\text{O-(CH}_2\text{)}_n\text{-CX}_3\), \(-\text{S-(CH}_2\text{)}_n\text{-CX}_3\), \(-\text{O-(CX}_2\text{)}_n\text{-CX}\) and \(-\text{S-(CX}_2\text{)}_n\text{-CX}\) (wherein \(m\) represents 0, 1, 2 or 3 and \(X\) represents a halogen atom); or \(R_1\) and \(R_2\) together represent a group \(-\text{O-CH}_2\text{-O-}\); and base addition salts thereof, possess anti-]
inflammatory and immulodulatory activity.

Processes for preparing them, intermediate compounds used in their preparation and compositions containing them are also described.