

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

595602

I-
We

FISONS plc, of
Fison House,
Princes Street,
Ipswich,
ENGLAND

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 2.2.90

hereby apply for the grant of a Standard Patent for an invention entitled:

"COMPOUNDS"

PYRAZOLE DERIVATIVES

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

<u>Number</u>	<u>Convention Country</u>	<u>Date</u>
86/11102	United Kingdom	7 May 1986
86/30906	United Kingdom	24 December 1986

LODGED AT SUB-OFFICE
- 7 MAY 1987
Melbourne

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 7th day of May, 1987.

H. M. Rimington

To: THE COMMISSIONER OF PATENTS

.....
(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.



COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention
entitled: "COMPOUNDS"

Insert full name(s) and address(es)
of declarant(s) being the appli-
cant(s) or person(s) authorized to
sign on behalf of an applicant
company.

I FINNBARR MURPHY
~~We~~ FISONS plc, of Fison House, Princes Street,
Ipswich, England

Cross out whichever of paragraphs
1(a) or 1(b) does not apply
1(a) relates to application made
by individual(s)
1(b) relates to application made
by company; insert name of
applicant company.

do solemnly and sincerely declare as follows:-

1. (a) ~~XXXX~~
We are ~~the applicant XXXX for the patent~~
or (b) I am authorized by

FISONS plc

Cross out whichever of paragraphs
2(a) or 2(b) does not apply

the applicant..... for the patent to make this declaration on ^{its} ~~their~~ behalf.

2(a) relates to application made
by inventor(s)
2(b) relates to application made
by company(s) or person(s) who
are not inventor(s); insert full
name(s) and address(es) of inven-
tor(s).

2. (a) ~~XXXX~~
~~XXXX~~ ~~the actual inventor XXXX of the invention~~
or (b)

Dr RICHARD ANTHONY APPLETON, of Fyrtle Field,
Wycomb, Nr Melton Mowbray, Leicestershire

Dr JOHN DIXON, of Church Farmhouse, Main Street,
Great Dalby, Nr Melton Mowbray, Leicestershire

Dr SIDNEY CLIFFORD BURFORD, of 51 Kirkstone Drive,
Loughborough, Leicestershire

~~XXXX~~
~~are~~ the actual inventor(s)..... of the invention and the facts upon which the applicant.....
~~is~~
~~XXXX~~ entitled to make the application are as follows:-

The inventors are employees of FISONS plc, and are
employed in a capacity where they are expected to
make inventions wherefor if a patent were
granted on an application made by the said
inventors, be entitled to have the patent
assigned to it.

State manner in which applicant(s)
derive title from inventor(s)

3. The basic application..... as defined by Section 141 of the Act ^{was} ~~were~~ made
in Great Britain..... on the 7 May 1986.....
by FISONS plc.....
in Great Britain..... on the 24 December 1986.....
by FISONS plc.....
in..... on the.....
by.....

4. The basic application..... referred to in paragraph 3 of this Declaration ~~XXXX~~
the first application..... made in a Convention country in respect of the invention the subject
of the application.

Insert place and date of signature.

Declared at Loughborough this Thirty First day of March 1987
England

Signature of declarant(s) (no
attestation required)

For FISONS plc.....

Note: Initial all alterations.

F Murphy By Power of Attorney

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-72584/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 595602

(54) Title
PYRAZOLE-3-AMINE DERIVATIVES

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(71) Applicant(s)
FISONS PLC

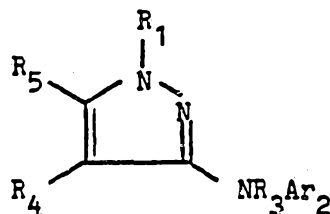
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DAVIES & COLLISON, MELBOURNE

(56) Prior Art Documents
AU 42275/85 C07D 231/38, 401/04
AU 75799/87 C07D 231/38, 235/30

(57) Claim

1. A pharmaceutical composition comprising a compound of formula I,



in which

R₁ represents hydrogen, alkyl, alkanoyl or alkyl substituted by Ar₁,

R₃, R₄ and R₅, which may be the same or different, each independently represent hydrogen, alkyl or

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(10) 595602

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Ar₃,

Ar₁, Ar₂ and Ar₃, which may be the same or different, independently represent phenyl or phenyl substituted by one or more of alkyl, hydroxy, alkoxy, NR₆R₇ or halogen,

R₆ and R₇, which may be the same or different, independently represent hydrogen or alkyl,

and pharmaceutically acceptable acid addition salts thereof,

in association with a pharmaceutically acceptable carrier, diluent or adjuvant.

10. A method of treatment of an inflammatory condition, which comprises administration of an effective amount of a compound of formula I as defined in Claim 1 to a patient suffering from such a condition.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

595602

Class

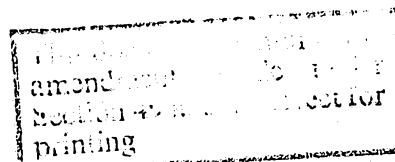
Int. Class.

Application Number: 72584/87
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:



Name of Applicant: FISONS plc

Address of Applicant: Fison House,
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Actual Inventor(s): Richard Anthony APPLETON
Sidney Clifford BURFORD
John DIXON

Address for Service: DAVIES & COLLISON, Patent Attorneys,
1 Little Collins Street, Melbourne, 3000.

Complete Specification for the invention entitled:

PYRAZOLE DERIVATIVES

~~"COMPOUNDS"~~

The following statement is a full description of this invention,
including the best method of performing it known to us :-



86/11102

This invention relates to new heterocyclic compounds, processes for their preparation and compositions containing them.

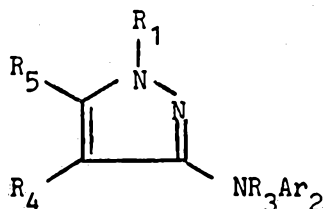
- 5 Chemical Abstracts, Vol 71, 1969, 22058Z describes several 3-aryl-5-methylpyrazol-3-amines but does not disclose any pharmaceutical uses of these compounds.

- 10 The Indian Journal of Chemistry, Section B, 1985 24(B), 472-6 describes several 3,5-diarylpirazol-3-amines but does not disclose any pharmaceutical uses of these compounds.

Pyrazole-3-amines are also described in Chemische Berichte, 1962 95 937-43, Chemische Berichte 1969, 100, 2577-2584, and in East German Patent 211343.

- 15 We have now found that certain pyrazol-3-amines have useful pharmacological properties.

According to the invention there are provided the compounds of formula I,



in which

- 25 R₁ represents hydrogen, alkyl, alkanoyl or alkyl

substituted by Ar_1 ,

R_3 , R_4 and R_5 , which may be the same or different, each independently represent hydrogen, alkyl or Ar_3 ,

5 Ar_1 , Ar_2 and Ar_3 , which may be the same or different, independently represent phenyl or phenyl substituted by one or more of alkyl, hydroxy, alkoxy, NR_6R_7 or halogen,

10 R_6 and R_7 , which may be the same or different, independently represent hydrogen or alkyl, and pharmaceutically acceptable acid addition salts thereof,

for use as a pharmaceutical.

According to the invention there are also provided
15 the novel compounds of formula I, as hereinbefore defined, provided that

i) when R_1 , R_3 and R_4 each represent hydrogen, and R_5 represents methyl, then Ar_2 does not represent phenyl or phenyl substituted by alkyl, alkoxy or halogen
20 and

ii) when R_1 , R_3 and R_4 each represent hydrogen and Ar_2 represents phenyl or phenyl substituted by alkyl, then R_5 does not represent phenyl or phenyl substituted by alkyl, alkoxy or halogen and

25 iii) when R_1 and R_3 represent hydrogen, and Ar_2

represents phenyl, then

(a) R_4 and R_5 do not both represent phenyl and

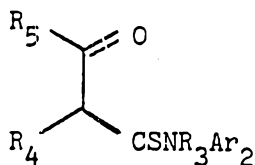
(b) R_5 does not represent hydrogen when R_4 represents alkyl,

5 and pharmaceutically acceptable acid addition salts thereof.

According to the invention there is further provided a process for the preparation of compounds of formula I or pharmaceutically acceptable acid addition salts thereof,

10 which comprises

(a) reacting a compound of formula II,



II

15 in which Ar_2 , R_3 , R_4 and R_5 are as defined

above,

with a compound of formula III,



III

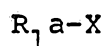
20 in which R_1 is as defined above, or

(b) producing a compound of formula I in which R_1

25 represents alkyl, alkanoyl or alkyl substituted by Ar_1 ,

- by reacting a corresponding compound of formula I in which R_1 represents hydrogen,
with a compound of formula IV,

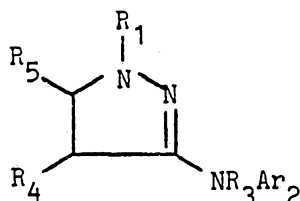
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IV

in which R_1a represents alkyl, acyl or alkyl substituted by Ar_1 and X represents a good leaving group,
(c) aromatising a compound of formula V,

10



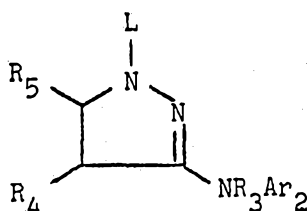
V

15

in which R_1 , R_3 , R_4 , R_5 and Ar_2 are as defined above,

(d) producing a compound of formula I in which R_1 represents hydrogen, by aromatising a compound of formula VI,

20



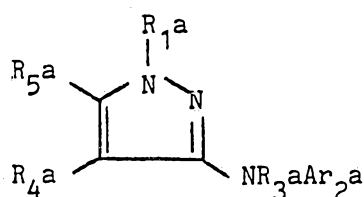
VI

25

in which L represents a leaving group and R_3 , R_4 ,

- R_5 and Ar_2 are as defined above, or
- (e) producing a compound of formula I in which one or more of Ar_1 , Ar_2 and Ar_3 is substituted by at least one -OH, by removing one or more protecting groups from a

5 corresponding compound of formula VII,



VII

10

in which R_1a , R_2a , R_3a , R_4a , R_5a and Ar_2a are as defined above, save that in addition R_1a may represent alkyl substituted by Ar_1a and any one of R_3a , R_4a or R_5a may represent Ar_3a , in which at

15 least one of Ar_1a , Ar_2a and Ar_3a bears at least one protected hydroxy group,

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable acid addition salt thereof or vice versa.

20

The cyclisation reaction (a) is preferably carried out in a polar solvent, eg ethanol, at a temperature of from about 25 to 75°C.

The process of reaction (b) is preferably carried out in a solvent. The solvent is preferably inert to the

25

reaction conditions, eg a polar, aprotic solvent such as

- 1,4-dioxan, dimethylformamide or N-methylpyrrolidone. The reaction may, if desired, be carried out in the presence of a non-nucleophilic base, eg sodium carbonate, sodium hydride or potassium t-butoxide. Good leaving groups that
- 5 X may represent include tosylate and halide, eg chloride, bromide and iodide. The reaction may be carried out at a temperature of from about 0 to 150°C.

- The aromatisation of process (c) may be carried out in the presence of an agent which is capable of accepting
- 10 hydrogen, for example palladium or charcoal. The aromatisation may be carried out by bubbling air or oxygen through a solution of the compound of formula V in an inert solvent, eg an halogenated hydrocarbon. However we prefer to carry out the aromatisation using an oxidising
- 15 agent, eg a metal oxide such as manganese dioxide. The oxidation is preferably carried out in a solvent which is inert to the reaction conditions, eg in an halogenated hydrocarbon, at a temperature of from about -70 to 150°C.

- Leaving groups that L may represent in the
- 20 aromatisation of process (d) include halogen, Oacetyl and especially arylsulphonyl, for example, tosyl. The aromatisation may be effected by heating. However we prefer to carry out the reaction in the presence of a base, eg a metal alkoxide in an alcohol. Sodium ethoxide
- 25 in ethanol is particularly suitable. The reaction may be

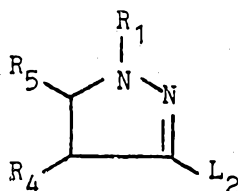
carried out at a temperature of from 40 to 150°C.

Protected hydroxy groups that Ar₁a, Ar₂a and Ar₃a may bear include alkyloxy, eg methoxy, acetoxy, trifluoroacetoxy and arylmethoxy, eg phenylmethoxy. Other
5 protecting groups are well known and include those described in Protective Groups in Organic Chemistry, ed JWF McOmie, Plenum Press (1973) and Protective Groups in Organic Synthesis, TW Greene, Wiley-Interscience (1981). Removal of the protecting group depends on the nature of
10 the protecting group; conventional techniques may generally be employed, including acidic or basic cleavage or hydrogenolysis. For example protecting alkyl or phenylalkyl groups may be removed using a protic acid, eg hydrochloric acid or hydrobromic acid at a temperature of
15 from 0 to 150°C, or a Lewis acid, eg by reacting with boron trihalide in a halocarbon solvent. When the protecting group is alkanoyl or haloalkanoyl, cleavage may be effected using a base, eg sodium hydroxide, in a suitable solvent, eg aqueous ethanol. Lewis bases, eg
20 pyridine hydrochloride, may be used to cleave alkyl or phenylalkyl groups. Arylmethyl groups, eg benzyl, may be removed by catalytic hydrogenation using a suitable catalyst, eg palladium, in a suitable solvent, eg ethanol or acetic acid. Further methods for the removal of
25 protecting groups are described in both McOmie and Greene,

loc. cit. Both McOmie and Greene also describe numerous methods for the application of protecting groups.

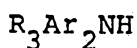
Compounds of formula V may be prepared by reacting a compound of formula VIII,

5



VIII

10 in which L_2 represents a leaving group and R_1 , R_4 and R_5 are as defined above, with a compound of formula IX,



IX

15

in which R_3 and Ar_2 are as defined above.

The reaction may be carried out by heating the two reactants with or without a solvent, eg at a temperature of 50 to 250°C. Suitable leaving groups that L_2 may represent include halogen, eg chlorine, NH_2 and hydroxy.

20

Compounds of formula VI may be prepared from compounds of formula V in which R_1 represents hydrogen by conventional techniques, for example when L represents p-toluenesulphonyl, compounds of formula VI may be

25

prepared by reacting a compound of formula V in which R_1

is hydrogen with p-toluenesulphonyl chloride in the presence of a base.

Compounds of formula VII may be prepared by processes analogous to those described in process a), b), c) or d).

- 5 Compounds of formulae II, III, IV, VIII and IX are either known, or may be made from known compounds using conventional techniques known per se.

- 10 The acid addition salts of the compounds of formula I may be prepared by reaction of the free base with an appropriate acid. The acid addition salts may be converted to the corresponding free base by the action of a stronger base.

The process as described above may produce the compound of formula I or an acid addition salt thereof.

- 15 It is also within the scope of this invention to treat any derivatives so produced to liberate the free compound of formula I, or to convert one derivative into another.

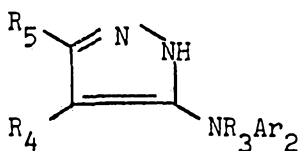
- 20 The compounds of formula I and the intermediates thereto may be isolated from their reaction mixtures using conventional techniques.

- 25 Pharmaceutically acceptable acid addition salts include, eg salts of mineral acids, such as hydrohalic acids, eg hydrochloric acid or hydrobromic acid, or organic acids such as formic, acetic or lactic acids. The acid may be polybasic, for example sulphuric, fumaric or

citric acid.

When R_1 represents hydrogen, compounds of formula I may exist in a tautomeric form, formula A,

5



These compounds are included in the scope of the
10 definition of the compounds of formula I.

The compounds of formula I, and pharmaceutically acceptable acid addition salts thereof, are useful because they possess pharmacological activity in animals. In particular, the compounds are useful as broad spectrum
15 anti-inflammatory agents as indicated in one or more of the following assay systems:

(a) Inhibition of lipoyxygenases, e.g. 5, 12 and 15 lipoyxygenase, in the presence of exogenous arachidonic acid and measurement of the enzyme activity by either a
20 modification of B A Jakschik et al, Biochemical and Biophysical Research Communications, 95(1), 103, (1980) using reverse phase HPLC to quantify the products or by a modification of the method of F F Sun et al, Prostaglandins 21 (2) 333 (1981) using uv absorption to
25 quantify product formation.

- (b) Inhibition of prostaglandin synthetase, utilising bovine seminal vesicle microsomes as the enzyme source after the method of Egan et al Biochemistry 17, 2230 (1978) using either radiolabelled arachidonic acid as substrate and product separation by thin layer chromatography and quantification by scintillation counting or unlabelled arachidonic acid as substrate and a specific radioimmunoassay kit (New England Nuclear) to measure prostaglandin E_2 produced.
- 10 (c) Inhibition of 5 lipoxygenase activity in intact human neutrophils stimulated by ionophore A23187 and supplemented with exogenous arachidonic acid after the method of P Borgeat and B Samuelsson, Proceedings New York Academy of Science 70 2148 (1979) using reverse phase HPLC to measure the products.
- 15 (d) Inhibition of formation of arachidonic acid metabolites by mouse peritoneal macrophages challenged in vitro with immune complexes by the method of Blackham et al, J. Pharm. Pharmac. (1985).
- 20 (e) Inhibition of PGE_2 formation and cell infiltration in the carrageenin sponge model by the method of Higgs et al, Eur. J. Pharmac. 66 81 (1980).
- (f) Inhibition of immune complex mediated inflammation in the mouse peritoneal cavity by the method of Blackham et al, J. Pharm. Methods (1985).
- 25

(g) Inhibition of carrageenin oedema in the rat by the method of Winter et al, Proc. Soc. Exp. Biol. 111 544 (1962).

5 (h) Inhibition of bronchial anaphylaxis in guinea pigs by the method of Anderson, Br. J. Pharmac. 77 301 (1982).

The compounds are indicated for use in the treatment or prophylaxis of inflammatory conditions in mammals, including man. Conditions that may be specifically mentioned are: rheumatoid arthritis, rheumatoid
10 spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions, inflamed joints;

eczema, psoriasis or other inflammatory skin conditions such as sunburn;

inflammatory eye conditions including conjunctivitis;
15 lung disorders in which inflammation is involved, eg asthma, bronchitis, pigeon fancier's disease and farmer's lung;

conditions of the gastrointestinal tract including aphthous ulcers, gingivitis, Crohn's disease (a condition
20 of the small, and sometimes also of the large intestine), atrophic gastritis and gastritis varialoforme (conditions of the stomach), ulcerative colitis (a condition of the large intestine and sometimes the small intestine) coeliac disease (a condition of the small intestine), regional
25 ileitis (a regional inflammatory condition of the terminal

ileum), peptic ulceration (a condition of the stomach and duodenum) and irritable bowel syndrome; pyresis, pain; and other conditions associated with inflammation, particularly those in which lipoxxygenase and cyclooxygenase products are a factor.

For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general satisfactory results are obtained when the compounds are administered at a daily dosage of from about 0.1mg to about 20mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man the total daily dose is in the range of from 7.0mg to 1,400mg and unit dosage forms suitable for oral administration comprise from 2.0mg to 1,400mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I, and pharmaceutically acceptable acid addition salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral, parenteral or topical administration.

According to our invention we also provide a pharmaceutical composition comprising preferably less than 80% and more preferably less than 50% by weight of a

- compound of formula I, or a pharmaceutically acceptable acid addition salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Examples of such adjuvants, diluents and carriers are:-
- 5 for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose; for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

10 Compositions in a form suitable for oral, ie oesophageal administration include tablets, capsules and dragees;

compositions in a form suitable for administration to the lung include aerosols, particularly pressurised aerosols;

15 compositions in a form suitable for administration to the skin include creams, eg oil-in-water emulsions or water-in-oil emulsion;

compositions in a form suitable for administration to the eye include drops and ointments.

20 We prefer the composition to contain up to 50% and more preferably up to 25% by weight of the compound of formula I, or of the pharmaceutically acceptable acid addition salt thereof.

25 The compounds of formula I and pharmaceutically acceptable acid addition salts thereof have the advantage

that they are less toxic, more efficacious, are longer acting, have a broader range of activity, are more potent, produce fewer side effects, are more easily absorbed, eg orally or have other useful pharmacological properties,

5 than compounds of similar structure.

When R_1 , R_3 , R_4 , R_5 , R_6 or R_7 represent alkyl or alkanoyl, the group preferably contains up to 10, more preferably up to six carbon atoms. Particular alkyl groups that R_1 , R_3 , R_4 , R_5 , R_6 and R_7 may
10 represent include saturated and unsaturated alkyl groups, for example, methyl, ethyl, 2-propenyl and butyl.

Particular NR_6R_7 groups that may substitute the N-phenyl include $-NH_2$, $-NHCH_3$ and $-N(CH_3)_2$.

Particular groups that R_1 may represent include
15 hydrogen, acetyl, benzyl, 4-alkoxybenzyl, methyl and isopropyl. We prefer R_1 to represent CH_2Ar_1 , alkyl or hydrogen. We particularly prefer R_1 to represent hydrogen when R_5 represents Ar_3 . Specific groups that Ar_1 may represent include phenyl and substituted by
20 hydroxy or alkoxy.

We prefer the phenyl group of Ar_2 to bear a substituent in the 2- or 4- position. We particularly prefer the phenyl group to bear an OH, alkoxy, eg methoxy or dialkylamino group in the 2- or 4- position. An
25 especially favoured group that Ar_2 may represent is

hydroxyphenyl, in particular 2- or 4-hydroxyphenyl. Ar_2 may be further substituted by groups selected from halogen, alkoxy and especially alkyl, eg methyl.

We prefer R_3 to represent alkyl and particularly
5 hydrogen.

We prefer R_4 to represent phenyl and particularly hydrogen.

Particular groups that R_5 may represent include hydrogen, methyl and Ar_3 . Particular groups that Ar_3
10 may represent include phenyl and hydroxyphenyl, eg 4-hydroxyphenyl.

Certain of the compounds of formula I possess one or more chiral centres and the invention also provides the compounds in the form of their individual optical isomers
15 or as racemic or other mixtures thereof. Certain of the compounds of formula I may also exist as stereoisomers and in these cases the invention provides all stereoisomeric forms. The various isomers may be prepared and/or separated using conventional processes known per se.

20 The invention will now be illustrated by the following Examples, in which temperatures are in degrees centigrade.

Examples

Example 1

25 N-(4-methoxyphenyl)-3(5)-phenyl-1H-pyrazol-5(3)-amine

Hydrazine hydrate (0.55ml) was added to a suspension of N-(4-methoxyphenyl)-3-phenyl-thiopropiolamide (2.7g) in ethanol (20ml) stirred at room temperature. After 2 hours, the mixture was heated to 60° for 2 hours then cooled to room temperature. The mixture was partitioned between ethyl acetate and dilute aqueous brine. The organic layer was collected and dried. The solvent was evaporated and the residue was recrystallised from ethanol to give the title compound, 1.1g m.p. 155-157°.

10 $C_{16}H_{15}N_3O$:

Requires: C = 72.45%, H = 5.66%, N = 15.85%

Found: C = 72.36%, H = 5.82%, N = 15.80%

Example 2

1-Acetyl-N-[4-methoxyphenyl]-1H-pyrazol-3-amine

15 The compound of Example 1 (1.0g), acetyl chloride (0.43g) and pyridine (0.43g) were stirred together at room temperature for 0.5 hr. The mixture was partitioned between ethyl acetate and aqueous brine. The organic layer was extracted, dried and chromatographed on silica eluting with 5% ethyl acetate/95% dichloromethane, to give the title produced as colourless crystals, 280 mg, mp 123-124°.

Example 3

N-[4-Methoxyphenyl]-1-phenylmethyl-1H-pyrazol-3-amine

25 a) 4,5-Dihydro-N-(4-methoxyphenyl)-1-phenylmethyl-1H-

pyrazol-3-amine

4,5-dihydro-1-phenylmethyl-1H-pyrazol-3-amine (24g)
(prepared by the method of H. Dorm, A. Otto, Chem Ber. 103
2505 (1970), p-anisidine (17.5g) and p-toluenesulphonic
5 acid (100mg) was heated at 170° under dry nitrogen until
evolution of ammonia ceased. The reaction mix was cooled,
purified by chromatography on SiO₂ eluting with
ether:pentane 1:1 to give the sub-title compound as
colourless cubes (13.3g).

10 b) N-(4-Methoxyphenyl)-1-phenylmethyl-1H-pyrazole-3-amine

To a stirred solution of the product of step a)
(13.3g) in dichloromethane (250ml) was added active
manganese dioxide in portions until all traces of starting
material had disappeared. The reaction mix was filtered,
15 evaporated to a gum and purified by chromatography on
silica, eluting with ether, to give the product,
mp 68-71°.

Example 4

4-(1-Phenylmethyl-1H-pyrazol-3-yl)aminophenol

20 The title pyrazole of Example 3 (6.3g) was heated on
a steam bath in a mixture of aqueous HBr (48%, 200ml) and
glacial acetic acid (25ml) for 6 hours. The reaction
mixture was cooled, poured into water, neutralised with
sodium bicarbonate, extracted with ethyl acetate, washed
25 with brine, dried and evaporated to give after

chromatography the title compound, 1.0g, mp 114-116°
(from cyclohexane/ethyl acetate).

Example 5

2-(1H-Pyrazol-3-yl)aminophenol

- 5 a) 4,5-Dihydro-N-(2-methoxyphenyl)-1-(4-toluenesulphonyl)-
1H-pyrazol-3-amine

A mixture of 4,5-dihydro-1-(4-toluenesulphonyl)-1H-pyrazol-3-amine (8.08g) (Organic Synthesis 48, 8, (1968)), o-anisidine (8.0g) and glacial acetic acid (80ml) was
10 heated on a steam bath for 4 hours. The reaction mixture was cooled, filtered and washed with ether to give the sub-title product, 7.6g, mp 176-9°.

- b) N-(2-Methoxyphenyl)-1H-pyrazol-3-amine

The product of step a) (7.5g) was added to a solution
15 of sodium ethoxide (60ml, prepared from 0.6g sodium), at a temperature of 60°. The mixture was refluxed for 10 minutes, cooled, added to water, extracted with ethyl acetate, dried and evaporated to give the sub-title compound as a purple oil, ms 189 (M⁺).

- 20 c) 2-(1H-Pyrazol-3-yl)aminophenol

The product of step b) (4.6g) was dissolved in 48% aqueous HBr (100ml) and refluxed for 8 hours. The mixture was poured onto water (750ml), neutralised with solid sodium bicarbonate, extracted with ethyl acetate, washed
25 with brine and evaporated to give the title compound as a

white crystalline solid, 0.49g, mp 163-4° (from ethyl acetate/cyclohexane).

Example 6

2-(1-Methyl-1H-pyrazol-3-yl)aminophenol

5 a) N-(2-Methoxyphenyl)-1-methyl-1H-pyrazol-3-amine

The pyrazole from Example 5 b) (4.0g) was added to a mixture of crushed potassium hydroxide pellets (4.7g) in dry dimethylsulphoxide, which had previously been stirred for 5 minutes under nitrogen at room temperature. After 10 stirring for 0.75 hours, methyl iodide (3.1g) was added to the red solution and stirring was maintained for a further 0.75 hours. The reaction mix was poured into water, extracted with ethyl acetate, the organic layer washed, dried, evaporated and chromatographed to give a light 15 brown oil.

b) 2-(1-Methyl-1H-pyrazol-3-yl)aminophenol hydrochloride

The pyrazole from step a) (1.7g) was dissolved in dichloromethane (30ml) under an atmosphere of nitrogen. Brown tribromide (8ml) in dichloromethane was added 20 dropwise and the mixture stirred at room temperature for 24 hours. After addition of dilute sodium bicarbonate, the organic phase was removed, dried and evaporated to give a pale oil, which was converted to the hydrochloride salt of the title compound, by trituration with ethereal 25 HCl, to give an off-white solid, 0.75g, mp 162-164°.

Example 7

4-(5-Phenyl-1H-pyrazol-3-yl)aminophenol

5 The title pyrazole from Example 1 (3g) was heated in a mixture of aqueous HBr (30%, 10ml) and glacial acetic acid (2ml) on a steam bath for 72 hours. The mixture was cooled, filtered and neutralised with dilute sodium bicarbonate to give the title compound as a colourless solid, 2.2g, mp 215-17° (from ethanol).

Example 8

10 The following compounds were prepared by methods analogous to those described in Examples 1 to 7 above:

(a) N-[4-Methoxyphenyl]-1-[1-methylethyl]-1H-pyrazol-3-amine, oil;

15 (b) N-[4-Methoxyphenyl]-1-methyl-1H-pyrazol-3-amine, mp 64-66°;

(c) 5-Methyl-N-phenyl-1-phenylmethyl-1H-pyrazol-3-amine, mp 97-98°;

(d) N-[4-Methoxyphenyl]-1H-pyrazol-3-amine, mp 95-96°;

(e) 5-Methyl-N-phenyl-1H-pyrazole-3-amine, mp 130-131°;

20 (f) N-[4-Methoxyphenyl]-5-methyl-1H-pyrazol-3-amine, mp 132-133°;

(g) N-[4-Methoxyphenyl]-1-methyl-5-phenyl-1H-pyrazol-3-amine, mp 107-108°;

25 (h) N-[4-Methoxyphenyl]-4,5-diphenyl-1H-pyrazol-3-amine, mp 190-191°.

- (i) 4-[3-(4-Methoxyphenylamino)-1H-pyrazol-5-yl]phenol,
mp 170-172°.
- (j) N-(4-Hydroxyphenyl)-1H-pyrazol-3-amine, mp 190-192°.
- (k) 4-(1-methylpyrazol-3-yl)aminophenol, mp 183-185°.
- 5 (l) 1-Methyl-N-(4-dimethylaminophenyl)-1H-pyrazol-3-amino,
mp 84-85°.
- (m) 4-(1-(4-Methoxyphenyl)methylpyrazol-3-yl)aminophenol,
mp 123-124°.

10

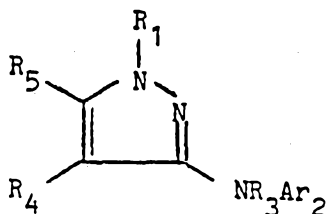
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition comprising a compound of formula I,



in which

10 R_1 represents hydrogen, alkyl, alkanoyl or alkyl substituted by Ar_1 ,

R_3 , R_4 and R_5 , which may be the same or different, each independently represent hydrogen, alkyl or Ar_3 ,

15 Ar_1 , Ar_2 and Ar_3 , which may be the same or different, independently represent phenyl or phenyl substituted by one or more of alkyl, hydroxy, alkoxy, NR_6R_7 or halogen,

R_6 and R_7 , which may be the same or different,
20 independently represent hydrogen or alkyl,

and pharmaceutically acceptable acid addition salts thereof,

in association with a pharmaceutically acceptable carrier, diluent or adjuvant.

- 25 2. A compound of formula I, as defined in Claim 1,

provided that

i) when R_1 , R_3 and R_4 each represent hydrogen, and R_5 represents methyl, then Ar_2 does not represent phenyl or phenyl substituted by alkyl, alkoxy or halogen
5 and

ii) when R_1 , R_3 and R_4 each represent hydrogen and Ar_2 represents phenyl or phenyl substituted by alkyl, then R_5 does not represent phenyl or phenyl substituted by alkyl, alkoxy or halogen and

10 iii) when R_1 and R_3 represent hydrogen, and Ar_2 represents phenyl, then

(a) R_4 and R_5 do not both represent phenyl and

(b) R_5 does not represent hydrogen when R_4 represents alkyl,

15 and pharmaceutically acceptable acid addition salts thereof.

3. A compound according to Claim 2, in which R_1 represents hydrogen, CH_2Ar_1 or alkyl.

4. A compound according to Claim 2 or Claim 3, in which
20 Ar_2 is phenyl substituted by an OH, alkoxy or dialkylamino group.

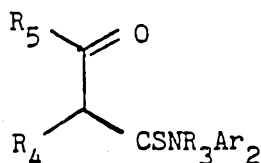
5. A compound according to any one of Claims 2, 3 or 4, in which Ar_2 represents hydroxyphenyl.

6. A compound according to any one of Claims 2, 3, 4 or
25 5, in which R_5 represents hydrogen or Ar_3 .

7. A compound according to Claim 2, wherein the compound of formula I is 4-(5-Phenyl-1H-pyrazol-3-yl)aminophenol or a pharmaceutically acceptable acid addition salt thereof.
8. A compound according to Claim 2, wherein the compound
5 of formula I is 4-(1-Phenylmethyl-1H-pyrazol-3-yl)aminophenol, 2-(1H-Pyrazol-3-yl)aminophenol, 2-(1-Methyl-1H-pyrazol-3-yl)aminophenol, or a pharmaceutically acceptable acid addition salt of any one thereof.
- 10 9. A compound according to Claim 2, wherein the compound of formula I is:
- N-(4-methoxyphenyl)-3(5)-phenyl-1H-pyrazol-5(3)-amine,
1-Acetyl-N-[4-methoxyphenyl]-1H-pyrazol-3-amine,
N-[4-Methoxyphenyl]-1-phenylmethyl-1H-pyrazol-3-amine,
15 N-[4-Methoxyphenyl]-1-[1-methyl]ethyl-1H-pyrazol-3-amine,
N-[4-Methoxyphenyl]-1-methyl-1H-pyrazol-3-amine,
5-Methyl-N-phenyl-1-phenylmethyl-1H-pyrazol-3-amine,
N-[4-Methoxyphenyl]-1H-pyrazol-3-amine,
20 5-Methyl-N-phenyl-1H-pyrazole-3-amine,
N-[4-Methoxyphenyl]-5-methyl-1H-pyrazol-3-amine,
N-[4-Methoxyphenyl]-1-methyl-5-phenyl-1H-pyrazol-3-amine,
N-[4-Methoxyphenyl]-4,5-diphenyl-1H-pyrazol-3-amine,
25 4-[3-(4-Methoxyphenylamino)-1H-pyrazol-5-yl]phenol,

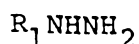
- N-(4-Hydroxyphenyl)-1H-pyrazol-3-amine,
 4-(1-Methylpyrazol-3-yl)aminophenol,
 1-Methyl-N-(4-dimethylaminophenyl)-1H-pyrazol-3-amino,
 4-(1-(4-Methoxyphenyl)methylpyrazol-3-yl)aminophenol,
 5 or a pharmaceutically acceptable acid addition salt of any
 one thereof.
10. A method of treatment of an inflammatory condition,
 which comprises administration of an effective amount of a
 compound of formula I as defined in Claim 1 to a patient
 10 suffering from such a condition.
11. A method of preparing a compound according to any one
 of Claims 2 to 9, which comprises
 (a) reacting a compound of formula II,

15



II

- in which Ar₂, R₃, R₄ and R₅ are as defined
 20 above,
 with a compound of formula III,

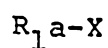


III

- 25 in which R₁ is as defined above, or

(b) producing a compound of formula I in which R_1 represents alkyl, alkanoyl or alkyl substituted by Ar_1 , by reacting a corresponding compound of formula I in which R_1 represents hydrogen,

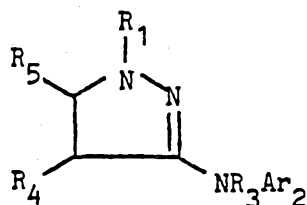
5 with a compound of formula IV,



IV

10 in which R_1a represents alkyl, alkanoyl or alkyl substituted by Ar_1 and X represents a good leaving group,

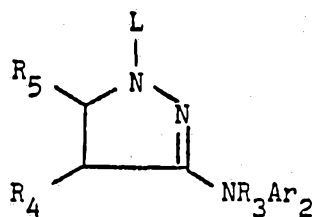
(c) aromatising a compound of formula V,



V

15 in which R_1 , R_3 , R_4 , R_5 and Ar_2 are as defined above,

20 (d) producing a compound of formula I in which R_1 represents hydrogen, by aromatising a compound of formula VI,



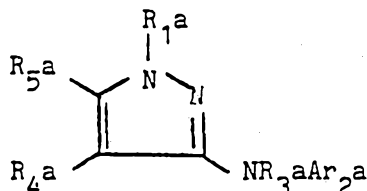
VI

5

in which L represents a leaving group and R_3 , R_4 , R_5 and Ar_2 are as defined above, or

(e) producing a compound of formula I in which one or more of Ar_1 , Ar_2 and Ar_3 is substituted by at least one -OH, by removing one or more protecting groups from a corresponding compound of formula VII,

10



VII

15

in which R_{1a} , R_{2a} , R_{3a} , R_{4a} , R_{5a} and Ar_{2a} are as defined above, save that in addition R_{1a} may represent alkyl substituted by Ar_{1a} and any one of R_{3a} , R_{4a} or R_{5a} may represent Ar_{3a} , in which at least one of Ar_{1a} , Ar_{2a} and Ar_{3a} bears at least one protected hydroxy group,

20

25

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable acid addition salt thereof or vice versa.

12. Compounds of formula 1, methods for their manufacture or pharmaceutical compositions or methods of treatment involving them, substantially as hereinbefore described with reference to the Examples.

DATED this 15th day of January, 1990

FISONS plc

by its Patent Attorneys

DAVIES & COLLISON

