

Description

Technical Field

- 5 The present invention relates to substituted pyrazole derivatives, and particularly to 1,5-diaryl 3-substituted-pyrazoles that are pharmacologically active in alleviating inflammation, asthma, hypersensitivity, myocardial ischemia, dermatological conditions such as psoriasis, dermatitis and gastrointestinal inflammatory conditions such as inflammatory bowel syndromes, and to a method for synthesizing those pyrazole derivatives.

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Background

- Nonsteroidal anti-inflammatory drugs (NSAID's) such as indomethacin, naproxen, ibuprofen, tolectin, fenoprofen and the like have generally been shown to attenuate the biosynthesis of prostaglandins by inhibiting the activity of the enzyme cyclooxygenase. The prostaglandin end-products of the cyclooxygenase pathway are responsible for many of the early signs of inflammation including hyperalgesia, increases in vascular permeability leading to edema, and pyrexia. The activity and potency of the NSAID's in reducing these signs and symptoms is, for the most part, correlated with their ability to inhibit prostaglandin biosynthesis.

- 20 The other major pathway of arachidonic acid metabolism is the lipoxygenase pathway. Lipoxygenase products of arachidonate metabolism, the leukotrienes, hydroxyeicosatetraenoic acids (HETES) and hydroperoxyeicosatetraenoic acids (HPETES), have been shown or implicated to be involved in disease states including acute and chronic inflammation, arthritis, allergic and other hypersensitivity disorders, dermatological diseases such as psoriasis, acne, atopic dermatitis, contact sensitivity, eczema and others, cardiovascular disorders secondary to myocardial ischemia or infarction, thromboembolism or vasculitis or platelet aggregation, and hyperalgesic disorders, gynecological disorders such as dysmenorrhea, ocular inflammation, sperm motility or function, and others.

- Leukotriene B₄ (LTB₄), another product of the lipoxygenase pathway, as well as HETES and HPETES can mediate induction of other phlogistic substances such as thromboxanes and prostacyclin, is chemotactic to inflammatory cells and is hyperalgesic. Many of these mediators have been identified in skin, lungs, coronary circulation, eyes, gastrointestinal tract and other organs, and in the synovial fluid of rheumatoid arthritic patients. In chronic inflammatory conditions such as rheumatoid arthritis, it is believed to be the chronic influx of leukocytes, probably mediated by LTB₄, that is the eventual cause of joint erosion.

- It is believed that inhibitors of the lipoxygenase pathway could lead to a relatively permanent effect on inflammatory disorders such as rheumatoid arthritis since they could modulate the actual mechanisms of tissue and joint breakdown. Similarly, drugs that could inhibit prostaglandin synthesis via the cyclooxygenase pathway could modulate and reduce early manifestations of inflammation. Pharmacologically active compounds that can inhibit both enzyme pathways at similar concentrations (dual inhibitors) provide a more complete relief for patients suffering from arthritis, hypersensitivity, dermatological, cardiovascular, gastrointestinal, ocular, and gynecological disorders than present drugs that inhibit one pathway, but not the other as is the case for usually used NSAID's that are predominantly inhibitors of the cyclooxygenase (prostaglandin synthesis) pathway.

A number of 1,5-diaryl-3-substituted pyrazoles are reported in the literature. Some of these pyrazoles have been reported to have pharmacological activity.

- 45 For example Fulmer et al., *J. Het. Chem.*, 17:799-800 (1980) report the synthesis of 1,3,5-triaryl pyrazoles, as do Foote et al., *J. Het. Chem.*, 7:89-92 (1970), Beam et al., *J. Het. Chem.*, 9:183-185 (1972); Soliman et al., *J. Pharm. Sci.*, 70:606-610 (1981), and Barluenga et al., *J.C.S. Chem. Comm.*, 891 (1979). Soliman et al., *J. Pharm. Sci.*, 70:602-605 (1981) also report synthesis of 3-methyl-1,5-diarylpyrazoles in which the 1-position aryl is a phenylsulfonylurea or thiourea. Of the above reports, only the two reports by Soliman et al. discuss any pharmacological activity for the pyrazoles prepared or for analogs of those pyrazoles, and those materials are reported to have hypoglycemic activity.

- Virmani et al., *Indian J. Chem., Sect. B*, 17B: 472-477 (1979) report the synthesis of 3-omega-alkylaminoalkyl pyrazoles among other compounds. The 1,5-diaryl-3-substituted pyrazoles reported contained a phenyl group at the 1-position, a 4-nitrophenyl at the 5-position, and a (CH₂)_n-NHCH₃ group at the 3-position, where n is 3,4 or 5 (3-5). This report stated that the compounds prepared were screened for a number of biological activities, with nine of the ninety-four numbered compounds synthesized having mild anti-inflammatory activity, two others having diuretic activity and two others having weak anti-cancer activity. The above-discussed 1,5-diaryl-3-substituted pyrazoles were not among the compounds reported to have

any pharmacological activity.

Vereshchagin et al., *Zh. Org. Khim.*, 7:907-912 (1971) reported the synthesis of 1,5-diaryl-3-substituted pyrazoles. The 3-substituents were reported to be alkoxy alkylene in which the alkoxy radical was methoxy or phenoxy and the alkylene was methylene or isopropylene, while the 1,5-diaryl radicals were unsubstituted phenyl.

Jahn and Wagner-Jauregg, *Arzneim-Forsch. (Drug Res.)*, 24:494-499 (1974) reported the synthesis and some pharmacological activities of 1,5-diaryl-3-substituted-4,5-dihydropyrazoles. The aryl group at the 1-position for each reported compound was phenyl, while the 5-aryl substituent was reported to be phenyl, 4-methoxyphenyl, 3-methoxy-4-hydroxyphenyl, and 2-hydroxyphenyl. The before-mentioned pyrazoles were substituted at the 3-position by bonding to the 3-position of propionic acid or propiohydroxamic acid. These compounds were said to possess antirheumatic activity.

Shawali et al., *J. Het. Chem.*, 13:989-92 (1976); Shawali, *J. Het. Chem.*, 14:375-81 (1977); and Matsumoto et al., *Bull. Chem. Soc. Japan*, 47: 946-949 (1979) reported the synthesis of 1,5-diaryl-3-substituted pyrazoles, all of which also included a substituent other than hydrogen at the 4-position on the pyrazole ring. Exemplary 4-position substituents were reported to include cyano, amino, carboethoxy, and phenylcarbonyl. These reports included no mention of biological activity of the compounds reported. DE-A-2633992 discloses 1,4 diaryl derivatives.

A series of benzimidoylpyrazoles was reported by Shroff et al., *J. Med. Chem.*, 24:1521-1525 (1981). These compounds were reported to possess activities of sulfonyl urea and biguanide hypoglycemics.

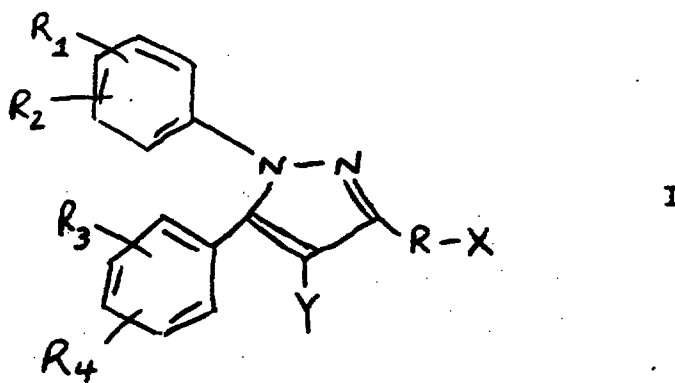
Biere et al., *Arch. Phar.*, 316:608-616 (1983) reported the synthesis of 1,4-diaryl-pyrazole-3-acetic acid derivatives, some of which also contained a an aryl substituent at the 5-position. The synthesized compounds were assayed for use as anti-inflammatory drugs in rats. The compounds assayed that also contained 5-position substituents were reported to be relatively inactive.

A further group of 1,5-diphenyl-4-substituted-pyrazole-3-acetic acids was reported by El-Sayed and Ohta, *Bull. Chem. Soc. Japan*, 46:1801-1803 (1973). Those compounds were utilized as intermediates in the synthesis of pyrazolo-[4,3-c]-pyridines. Another group of 1,5-diphenyl-4-substituted-pyrazoles, some of which also include methyl, phenyl and carboxymethyl groups at the 3-position, was reported in Al-Saleh et al., *J.C.S. Perkin I*, 642-645 (1981). The reports of El-Sayed and Ohta and those of Al-Saleh et al. make no mention of the pharmacological properties of the pyrazole derivatives reported. Another group of 1,5-diaryl-3,4-disubstituted pyrazoles and 4,5-dihydro-5-hydroxy pyrazoles was reported in Fusco and Croce, *Gazz. Chim. Ital.*, 101:703-272 (1971).

Summary of the Invention

The present invention contemplates 1,5-diaryl-3-substituted pyrazoles, their use and a method of their synthesis. The compounds of the present invention are pharmacologically active in alleviating inflammation, and inhibit the cyclooxygenase enzyme pathway, the lipoxygenase enzyme pathway, or preferably both pathways.

According to a first aspect of the present invention there is provided a compound having a structure that corresponds to the formula I:



wherein

R_1 , R_2 , R_3 and R_4 are the same or different and are individually selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, phenyl, halo, hydroxy, C_{1-8} alkylsulfonyl, C_{1-8} alkylthio, nitro,

trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid or where R₁R₂ or R₃R₄, taken together with the phenyl group to which they are attached, form a naphthyl;

R is a straight chained, saturated or unsaturated hydrocarbon that contains 2-16 carbon atoms;

Y is hydrogen, bromo, chloro or C₁₋₄ alkyl;

5 and X is selected from the group consisting of carboxy, hydroxy, acetoxy, alkanoyloxy, C₁₋₈ alkoxy, C₁₋₆ alkyl carbonyl, oximino, cyano, amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₆OH, -NHR₁₃, -C(R₁₄)=NNH-2thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)-C₁₋₈ alkyl;

wherein R₅ is selected from the group consisting of hydrogen, alkyl, C₁₋₈ alkoxy, NR₆R₇ and -O-NR₁₅R₁₆;

10 wherein R₆ and R₇ are the same or different and are selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, hydroxy, acyloxy, benzyloxy, 2-hydroxy C₁₋₈ alkyl, C₁₋₈ alkyl carboxy, phenyl, pyridyl, thiazolyl, dihydrothiazolyl, 5-tetrazolyl, ω-alkanoate, -OCO(CH₂)_n-COR₉ and -OCOR₁₀;

wherein R₈ is hydrogen, -CO-C₁₋₈ alkyl, -CO-t-butyl, -COC₇H₁₅, CO-phenyl, SO₂-C₁₋₈ alkyl, -COCO₂-C₁₋₈ alkyl, or -COCONHOH;

wherein R₉ is -OH, -ONa, dialkylamino and n is 2 or 3;

wherein R₁₀ is -CH₂NR₁₁R₁₂, -CH₂Cl, -CH₂O-C₁₋₈ alkyl, t-butyl, or

-CH-C₁₋₈ alkyl-CO₂ Q, wherein Q is C₁₋₈ alkyl or H;

wherein R₁₁ and R₁₂ are the same or different and are any of alkyl, cyclohexyl, or together form N-methylpiperazino;

wherein R₁₃ is hydrogen, -CO-C₁₋₈ alkyl, -CO-t-butyl, -COC₇H₁₅, -CO-phenyl, -SO₂-C₁₋₈ alkyl, -COCO₂-C₁₋₈ alkyl, -COCONHOH, -COCO₂H, COCON(C₁₋₈ alkyl)OH or PO(O-C₁₋₈ alkyl)₂;

wherein R₁₄ is hydrogen, C₁₋₈ alkyl, phenyl or t-butyl;

wherein R₁₅ and R₁₆ are the same or different and are selected from the group consisting of hydrogen,

25 C₁₋₈ alkyl and phenyl;

with the provisos that:

(a) when Y is bromo or chloro, X is -COOH, -CH₂OH or -C(O)-R₅ wherein R₅ is NR₆R₇ and R₆ is OH and R₇ is C₁₋₈ alkyl;

30 (b) at least one of R₁ and R₂ is other than hydrogen where (i) R-X is (CH₂)₂CO₂H or (CH₂)₂C(O)NHOH, and (ii) R₃ and R₄ are 4-methoxy, 3-methoxy-4-hydroxy, 2-hydroxy or hydrogen and

(c) at least one of R₁ and R₂ or of R₃ and R₄ is other than hydrogen where R-X together contains three saturated carbon atoms linked together by carbon-carbon bonds;

or the compound

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide,

35 Ethyl 3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamide-N-acetate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxyacetamido)propanamide 1/4 Hydrate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxy-N-methylacetamido) propanamide,

40 Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinate hemi-hydrate,

Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinate,

or

3-(3-Acetoacetoxypropyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole;

and pharmaceutically acceptable salts thereof.

45 Preferably, X is selected from the group consisting of hydroxy, carboxy, a carboxylate salt of a pharmaceutically acceptable cation, C(O)-NR₆R₇ wherein R₆ and R₇ are selected from the group consisting of hydrogen, hydroxyl, methyl, t-butyl, 2-hydroxyethyl and carboxymethyl.

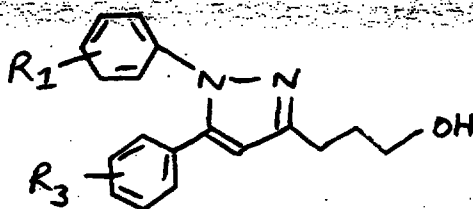
According to a second aspect of the present invention there is provided a pharmaceutical composition for topical, oral, parenteral or aerosol administration, comprising an effective amount of a substituted pyrazole compound of the formula I as defined above as active ingredient dispersed in a pharmaceutically acceptable carrier.

55 According to a third aspect of the present invention there is provided a substituted pyrazole compound of the formula I as defined above, but without the provisos, for use in alleviating inflammation, asthma, hypersensitivity, myocardial ischemia, dermatological conditions such as psoriasis, dermatitis and gastrointestinal inflammatory conditions such as inflammatory bowel syndromes.

According to a fourth aspect of the present invention there is provided a method of synthesising a 1, 5-diphenyl-3-(omega-substituted lower alkyl)-pyrazole of the formula I as defined above comprising reacting an arylhydrazine with a 1-aryl-(omega-substituted)-alkyl-1, 3-dione containing at least 4 carbons in the alkyl

chain, said reaction being carried out in a solvent that is substantially inert to said reaction conditions, and said omega-substituent being substantially inert to said reaction conditions, wherein said aryl groups are the same or different and are mono- or di-substituted phenyl wherein said phenyl substituents are selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, phenyl, halo, hydroxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy and naphthyl.

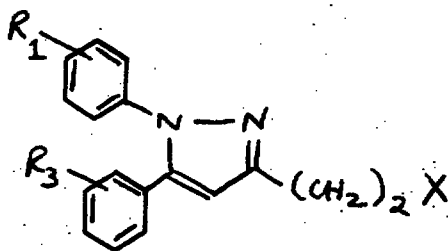
According to a fifth aspect of the present invention there is provided a compound having a structure that corresponds to the formula II:



II

wherein R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl, methyl and methoxy.

According to a sixth aspect of the present invention there is provided a compound having a structure that corresponds to the formula III:



III

wherein R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl, methyl, phenyl and methoxy; and

X is selected from the group consisting of carboxy, C(O)-R₅ wherein R₅ is selected from the group consisting of N(CH₃)OH, N(t-C₄H₉)OH, NHOH, ONH(CH₃) and ONH(t-C₄H₉).

In preferred practice, R₂ and R₄ are hydrogen, and R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl, lower alkyl and lower alkoxy, especially methoxy. R preferably contains two carbon atoms. It is also preferred that the X be hydroxyloweralkyl, carboxy, a hydroxamic acid or a N alkyl hydroxamic acid; i.e., that X be C(O)NR₆R₇ where R₆ is hydroxy and R₇ is hydrogen or lower alkyl or a N-alkyl hydroxamic acid; i.e. that X is -C(O)NR₆R₇ wherein R₆ is hydroxy or -OC(O)CH₂Z where Z is dialkylamino or -CH₂CO₂H and R₇ is hydrogen or lower alkyl.

The present invention also contemplates a pharmaceutical composition that comprises an anti-inflammatory amount of an above-described substituted pyrazole compound dispersed in a pharmaceutically acceptable carrier. The dose may be administered by topical, p.o., parenteral or aerosol routes. In preferred practice, that substituted pyrazole compound is capable of inhibiting both the cyclooxygenase and the lipoxygenase pathways in the amount present in the composition, when the composition is introduced into a mammal.

Further contemplated is a pharmaceutical composition for alleviating inflammation in a mammal exhibiting an inflammatory condition, wherein the pharmaceutical composition includes as the active ingredient an effective amount of an above-described substituted pyrazole compound dispersed in a pharmaceutically acceptable carrier for topical, oral, parenteral and aerosol administration.

A method for synthesizing a 1,5-diphenyl-3-(omega-substituted lower alkyl)pyrazole is also contemplated. In accordance with this method, an aryl hydrazine or its acid addition salt is reacted with a 1-aryl-(omega-substituted)-alkyl-1,3-dione containing at least 4 carbons in the alkyl chain. A polar solvent is used that is substantially inert to the reaction conditions, as is the omega-substituent of the alkyl 1,3-dione. The resulting 1,5-diaryl-3-(omega lower alkyl substituted) pyrazole is thereafter preferably recovered, although it

can be utilized in the form of its synthesis (crude form), as for further syntheses. Particularly preferred alkyl-1,3-dione derivatives contain 6 carbons in the alkyl chain and contain a hydroxy group as the omega-substituent.

The present invention provides several benefits and advantages.

5 A particular benefit of the invention is that it provides pharmacologically active compounds that are useful in treating inflammatory conditions.

A particular advantage of the present invention is that its synthetic method provides relatively high yields of 1,5-diaryl-3-(omega-substituted lower alkyl) pyrazole compounds.

Another benefit of the present invention is that some of its pharmacologically active compounds inhibit
10 the cyclooxygenase enzyme pathway, thereby providing a further means for studying that biological process.

Another advantage of the present invention is that some of its pharmacologically active compounds inhibit the lipoxigenase enzyme pathway, thereby providing a further means for studying that biological process.

15 Still further benefits and advantages of the present invention will be apparent to those skilled in the art from the detailed description and Examples that follow.

Detailed Description of the Invention

20 1,5-Diaryl-3-substituted pyrazole compounds, pharmaceutical compositions containing a substituted pyrazole compound as an active ingredient, a method of treating a mammal exhibiting an inflammatory condition and a method of synthesizing the substituted pyrazole compound are contemplated herein.

In the above formula, R_1 , R_2 , R_3 and R_4 are substituents on phenyl rings that substitute for hydrogen atoms at positions 1 and 5 of the pyrazole ring. It is preferred that at least one of R_1 and R_2 , and one of R_3
25 and R_4 be substituted at the 4-positions of their respective phenyl rings.

In examining the above structural formula to which the useful pyrazole compounds conform, it is noted that the R_1 , R_2 , R_3 and R_4 radicals and the X group can be a "lower" alkyl, "lower" alkoxy and the like. Groups and radicals referred to as "lower" denote that they possess 1 to about 6 carbon atoms. The same is true for "lower" groups and radicals that are substituents of the "lower" groups and radicals enumerated.

30 To the extent that X substituents are defined as being the same as those of R_1 , R_2 , R_3 and R_4 , those commonly defined substituents are discussed immediately below. Additional X substituents that are not common to X and R_1 , R_2 , R_3 and R_4 are discussed thereafter.

Lower alkyl radicals include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl,
35 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, octyl and the like.

Lower alkoxy radicals are oxygen ethers formed from a before-described lower alkyl group. Exemplary radicals include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, and the like.

Lower alkylthio radicals of R_1 , R_2 , R_3 and R_4 are sulfide ethers and are thus analogous to the oxygen ethers described above.

40 Halo radicals preferably include chloro and bromo, as well as fluoro and iodo.

Lower alkylsulfonyl radicals contain a before-described lower alkyl radical bonded to an SO_2 moiety that is itself also bonded to a phenyl ring. Exemplary lower alkylsulfonyl radicals thus include methylsulfonyl, ethylsulfonyl, 2-ethylbutylsulfonyl and the like.

An omega-trifluoromethyl lower alkoxy radical is a lower alkoxy radical as before described that additionally includes a trifluoromethyl group at a position farthest on the alkyl chain from the place of
45 bonding to the phenyl ring. Exemplary of such radicals are the 2,2,2-trifluoroethoxy.

Naphthyl and substituted naphthyl radicals can replace an aryl group herein at either the 1- or 2-positions to provide 1-naphthyl or 2-naphthyl substituents, respectfully. Substituents on the naphthyl radicals can be any of those described herein as being useful aryl substituents. Exemplary substituted 1-
50 and 2-naphthyls include 6-methoxy-2-naphthyl and the like.

Lower alkyl carboxy radicals are the before-described lower alkyl radicals that further include a carboxy group. Exemplary lower alkyl carboxy radicals include carboxymethyl, 2-carboxyhexyl and the like. Lower alkyl lower alkoxy carbonyl radicals are lower alkyl esters of lower alkyl carboxy radicals. Exemplary lower alkyl lower alkoxy carbonyl radicals include 3-isopropoxycarbonylpropyl, 4-hexyloxycarbonylpentyl and the
55 like.

A lower alkyl carbonyl radical contains a carbonyl group, a total of up to six carbon atoms, and with the portion of R to which it is linked, forms a ketone at the R/X junction. Exemplary lower alkyl carbonyl radicals include acetyl, propionyl 2-methylpropionyl, pentoyl and the like, which can also be named methyl carbonyl,

ethyl carbonyl, isopropylcarbonyl and butylcarbonyl, respectively.

Radicals in which X is C(O)-R₅ where in R₅ is lower alkoxy are carboxylic esters. These esters are preferably named by considering R-X to be a single substituent entity. Exemplary R₅ lower alkoxy groups are as before described, although methoxy and ethoxy are preferred. When R₅ is NR₆R₇ and ONR₁₅R₁₆, it is also useful to consider R-X as a substituent entity.

Lower hydroxy alkyl radicals of R₆ and R₇ are preferably 2-hydroxyethyl and 2-hydroxypropyl. Additionally useful lower hydroxy alkyl radicals include 4-hydroxybutyl and the like.

Substituted phenyl radicals that can comprise NR₆R₇ are the same as the substituted aryl groups described before wherein R₁, R₂, R₃ and R₄ comprise the substituents.

Pyridyl radicals are derivatives of pyridine and can be bonded to the nitrogen atom of NR₆R₇ at the 2-, 3- or 4-position relative to the pyridine nitrogen.

R in the structural formula above is a straight, saturated or unsaturated hydrocarbyl radical that contains 2 to about 16 carbon atoms. In particularly preferred practice, the R-X radical together contains three saturated carbon atoms linked together by carbon-carbon bonds. In other preferred embodiments, R is unsaturated and contains 7-16 carbon atoms.

R is a hydrocarbon radical and therefore contains no elements other than carbon and hydrogen. Consequently, any element present in R-X that is not hydrogen or carbon is, by definition, part of the X radical.

Pharmaceutically acceptable, non-toxic acid addition salts of 1,5-diaryl-3-substituted-pyrazole compounds are useful herein, and can be formed by treatment of the pyrazole with an appropriate acid. Exemplary inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric and the like acids. Exemplary organic acids include methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic and the like acids. Conversely, the acid addition salt form can be converted to the free base form by treatment with alkali.

1,5-Diaryl-3-substituted pyrazole compounds can include a carboxylic acid and/or a hydroxamic acid, as already noted. Basic salts of those carboxylic and hydroxamic acids are also contemplated, and are formed by treatment of the acid with an appropriate, non-toxic, pharmaceutically acceptable alkaline reagent to form a carboxylate or hydroxamate cation salt. Exemplary non-toxic, pharmaceutically acceptable cation salts of such carboxylic and hydroxamic acids include sodium, potassium, zinc, aluminum, calcium and magnesium. These salts also readily form in aqueous solutions of the carboxylic and hydroxamic acids.

In preferred practice, R₂ and R₄ are hydrogen, and R₁ and R₃ are selected from the group consisting of halo and lower alkoxy, especially methoxy. The preferred R₁ and R₃ substituents are preferably at the 4-positions of their respective aryl (phenyl) rings.

It is preferred that R contain two carbon atoms and that X be carboxy, hydroxymethyl, a hydroxamic acid (N-hydroxy amide) or a N-lower alkyl hydroxamic acid (N-hydroxy-N-lower alkyl amide).

Specific, particularly preferred 1,5-diaryl-3-substituted pyrazole compounds are named hereinbelow, followed by a parenthesized, underlined numeral for ease of identification and correlation with the syntheses and anti-inflammation study described in detail hereinafter.

The preferred species of this invention include:

1. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide, (3)
2. 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole, (2)
3. 5-(4-trifluoromethylphenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole, (56)
4. 1-(4-bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl) pyrazole, (35)
5. sodium 8-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-5(Z)-octenoate, (32)
6. sodium 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanoate, (13)
7. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide, (57)
8. N-carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanamide, (66)
9. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide (81)
10. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide (82)
11. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamide (83)
12. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-phenylpropanamide (84)
13. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propylamine (96)
14. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanal (11)
15. 5-(4-chlorophenyl)-3-(3-oximinopropyl)-1-(4-methoxyphenyl)pyrazole (26)
16. 3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl)pyrazole (55)

A pharmaceutical composition that comprises an anti-inflammatory amount of a before-discussed 1,5-diaryl-3-substituted pyrazole compound dispersed in a pharmaceutically acceptable carrier is also contemplated herein. The composition comprises a unit dosage of the substituted pyrazole compound.

The substituted pyrazole compounds of this invention are capable of inhibiting the lipoxigenase enzyme pathway and/or the cyclooxygenase (prostaglandin synthetase) enzyme pathway. In preferred practice, the substituted pyrazole compound of the pharmaceutical composition is capable of inhibiting both the lipoxigenase and the cyclooxygenase enzyme pathways in the amount at which that substituted pyrazole compound is present in the pharmaceutical composition, when that composition is introduced as a unit dose into an appropriate mammal such as a laboratory rat.

The term "unit dosage" and its grammatical equivalent is used herein to refer to physically discrete units suitable as unitary dosages for human patients and other warm blooded animals, each unit containing a predetermined effective, pharmacologic amount of the active ingredient calculated to produce the desired pharmacological effect in association with the required physiologically tolerable carrier, e.g., a diluent or a vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and are directly dependent on (a) the unique characteristics of the active ingredient, and (b) the limitations inherent in the art of compounding such an active ingredient for therapeutic use in humans and other animals. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, and the like, segregated multiples of any of the foregoing, as well as liquid solutions and suspensions.

The active ingredient is referred to herein as being dispersed in the carrier. Thus, the dispersion formed can be a simple admixture, a non-settling dispersion as in the case of certain emulsions, or as an ultimate dispersion, a true solution.

The amount of active ingredient that is administered *in vivo* depends on the age and weight of the mammal treated, the particular medical condition to be treated, the frequency of administration, and the route of administration. The dose range can be about 0.01 to about 500 milligrams per kilogram of body weight, more preferably about 0.1 to about 50 milligrams per kilogram of body weight and most preferably about 0.1 to about 25 milligrams per kilogram of body weight. The human adult dose is in the range of about 10 to about 2000 milligrams daily, given as a single dose or in 3 or 4 divided doses. Veterinary dosages correspond to human dosages with the amounts administered being in proportion to the weight of the animal as compared to adult humans.

As is seen from the data discussed hereinafter, orally administered unit doses containing about 1 to about 50 milligrams of a 1,5-diaryl-3-substituted pyrazole per kilogram of laboratory rat body weight (e.g., about 200 grams each) were useful in reducing inflammation. These results are contrary to those reported by Virmani et al., *Indian J. Chem., Sect. B*, 17:472-477 (1979) who reported compounds that are structurally similar to those described herein were not active as anti-inflammatory agents.

Physiologically tolerable carriers are well known in the art. Exemplary of liquid carriers are aqueous solutions that contain no materials in addition to the substituted pyrazole compound, or contain a buffer such as sodium phosphate at physiological pH value, saline and the like.

Liquid compositions can also contain liquid phases in addition to and to the exclusion of water. Exemplary of such additional liquid phases are glycerin and vegetable oils such as cottonseed oil.

Exemplary solid carriers (diluent) include those materials usually used in the manufacture of pills or tablets, and include corn starch, lactose, dicalcium phosphate, thickeners such as tragacanth and methylcellulose U.S.P., finely divided SiO₂, polyvinylpyrrolidone, magnesium stearate and the like. Antioxidants such as methylparaben and propylparaben can be present in both solid and liquid compositions, as can sweeteners such as cane or beet sugar, sodium saccharin, sodium cyclamate and the dipeptide methyl ester sweetener sold under the trademark NUTRASWEET™ (aspartame) by G. D. Searle Co.

A pharmaceutical composition for alleviating inflammation in a mammal exhibiting an inflammatory condition is also contemplated. The pharmaceutical composition includes a unit dose of an active ingredient that is the before-described substituted pyrazole compound dispersed in a pharmaceutically acceptable carrier. The pharmaceutical composition is preferably maintained within the mammal until the substituted pyrazole compound is cleared from the mammal's body by natural means such as excretion or metabolism.

The pharmaceutical composition can be administered orally, topically or by injection, by means well known in the art. In preferred practice, the composition is administered orally as a tablet, capsule or aqueous dispersion.

Inasmuch as a pharmaceutical composition can be administered 3 to 4 times daily (per 24 hour period), the method of alleviating inflammation can include administering the pharmaceutical composition a plurality of times into the treated mammal over a time period of weeks, months and years. The pharmaceutical composition is administered a plurality of times to the mammal over a time period of thirty days, in preferred practice.

A method for synthesizing a 1,5-diaryl-(omega-substituted lower alkyl) pyrazole constitutes yet another aspect of the present invention. Here, an aryl hydrazine or its acid addition salt is admixed in an inert polar

solvent with a 1-aryl-(omega-substituted)-alkyl-1,3-dione containing at least 4 carbons, and up to about 9 carbon atoms, in the alkyl chain to form a reaction mixture. The aryl hydrazine and the 1,3-alkyldione are preferably reacted in substantially stoichiometric amounts.

The omega-substituent of the 1-aryl-omega-substituted-alkyl-1,3-dione is substantially inert to the reaction conditions utilized for the cyclization reaction; i.e., the substituent does not itself react with any of the reactants or solvent during the cyclization reaction. Exemplary of useful substituents are hydroxy and lower alkoxy as before described. Hydroxy is particularly preferred as the omega substituent.

The aryl hydrazine and aryl-alkyl-1,3-dione are reacted in an inert polar solvent medium. Exemplary of such solvents are methanol, ethanol, isopropanol, pyridine, triethylamine and mixtures of those solvents.

The reaction mixture so formed is maintained with agitation, as by stirring, for a predetermined period of time for the 1-aryl-hydrazine and the 1-aryl-(omega-substituted)-alkyl-1,3-dione to react and form the desired 1,5-diaryl-3-(omega-substituted lower alkyl) pyrazole. The predetermined time period is typically about 1 to about 20 hours, depending upon the reactants, solvent and reaction temperature.

The cyclization reaction is normally carried out at ambient room temperature. The temperature typically rises somewhat during the cyclization, but is readily controlled. Temperatures above room temperature can also be utilized.

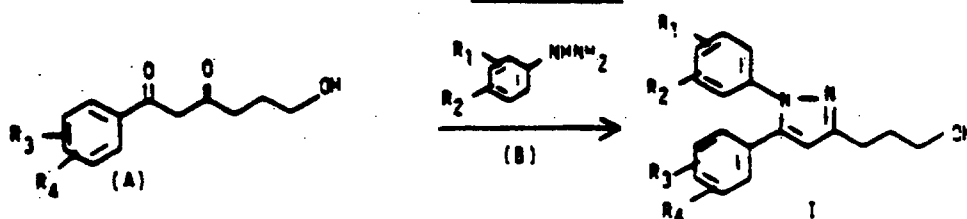
The resulting substituted pyrazole can be used as is in its crude form directly after the cyclization, as where a further reaction is to be carried out with it. Preferably however, the crude reaction product formed is recovered and purified as by crystallization or column chromatography prior to use in a further reaction or to alleviate inflammation.

Further reactions can be carried out on the omega-substituent of the pyrazole-3-lower alkyl group inasmuch as that substituent is substantially inert to the reaction conditions for cyclization and formation of the pyrazole ring, but need not be inert to all reaction conditions.

An exemplary, generalized reaction sequence is shown below in Scheme 1 where a 1-(R₃,R₄-disubstituted phenyl)-6-hydroxy-hexan-1,3-dione and R₁,R₂-disubstituted phenyl hydrazine hydrochloride are reactants (A) and (B), respectively, that react to form 1-(R₁,R₂-disubstituted phenyl)-5-(R₃,R₄-disubstituted phenyl)-3-(3-hydroxypropyl)-pyrazole, I, wherein R₁,R₂,R₃ and R₄ are as previously defined. The parenthesized numerals beneath the structural formula of I refer to compounds of that structure that are exemplified hereinafter.

The reaction sequence shown thereafter in Scheme 2 relates to reactions carried out with specific compounds and in which R* is the 1-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]methylene group (as shown hereinafter); R₁-R₇ are as before described; lower case letters adjacent to reaction arrows indicate reaction conditions discussed thereafter below; and underlined numerals indicate specific compounds whose syntheses are described in detail hereinafter.

Scheme 1



Scheme 2

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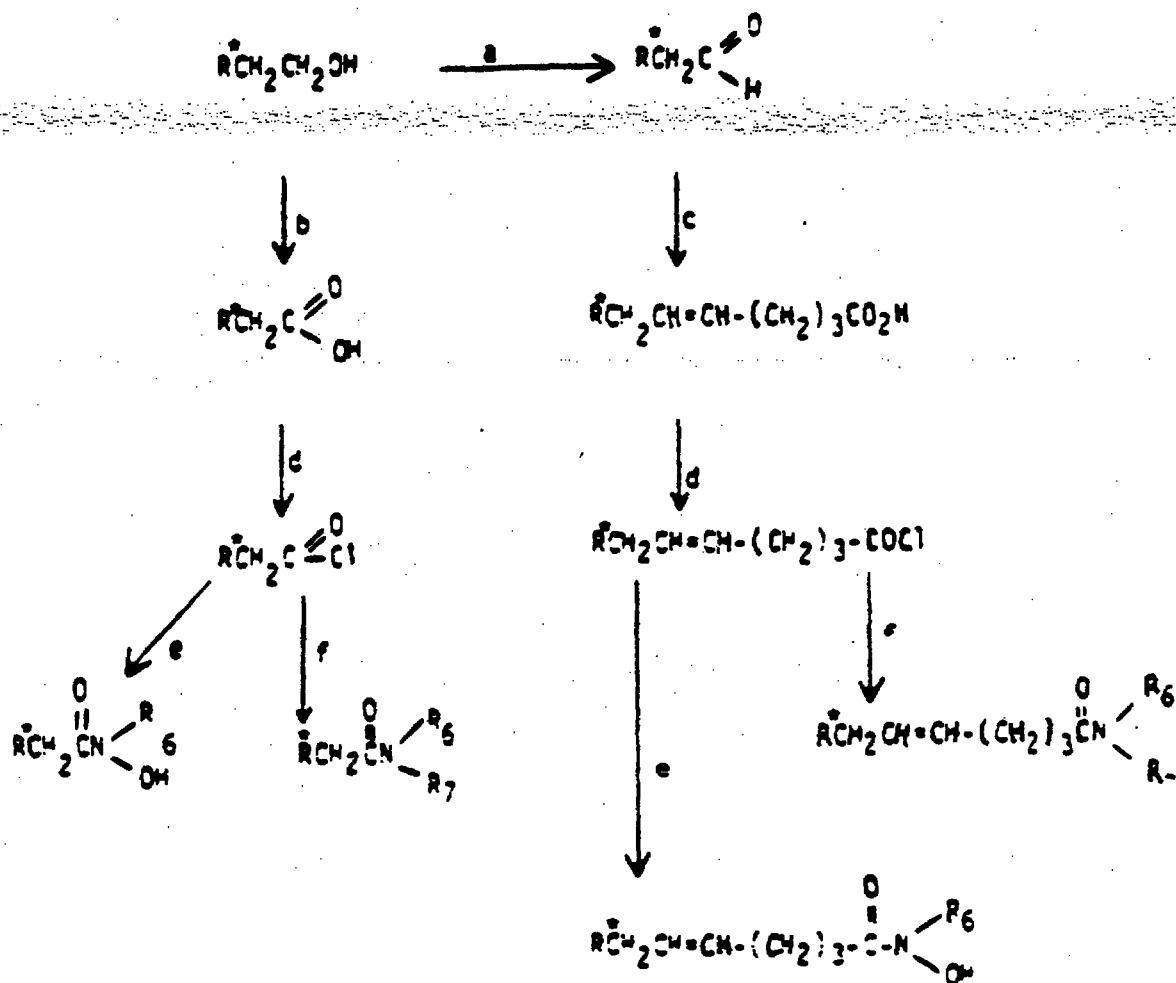
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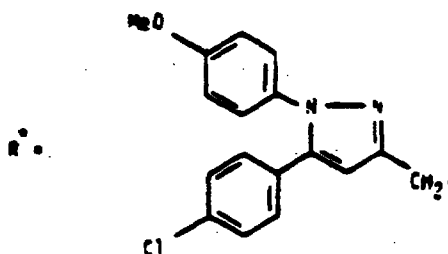
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a, pyridinium chlorochromate; b, Jones Reagent; c, lithium hexamethyldisilazide/ $BrPh_3P(CH_2)_4CO_2H$; d, oxalyl chloride; e, R_6NHOH ; f, R_6R_7NH .



Treatment of the appropriate aryl diketone A wherein R_3 and R_4 are defined as before with arylhydrazine B wherein R_1 and R_2 are defined as before gives the 1,5-diarylpyrazoles I that are isolated by recrystallization or chromatography on silica from the corresponding 1,3-diarylpyrazoles formed as minor products of the reaction.

The pyrazoles of formula I are oxidized to either the acid (e.g., 12) with, for example, Jones Reagent or to the aldehyde (e.g., 11) with, for example, pyridinium chlorochromate, as illustrated with compound 2; i.e., 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole. The olefinic acid 32 was obtained by

treatment of aldehyde 11 with (4-carboxylbutyl)triphenylphosphorane.

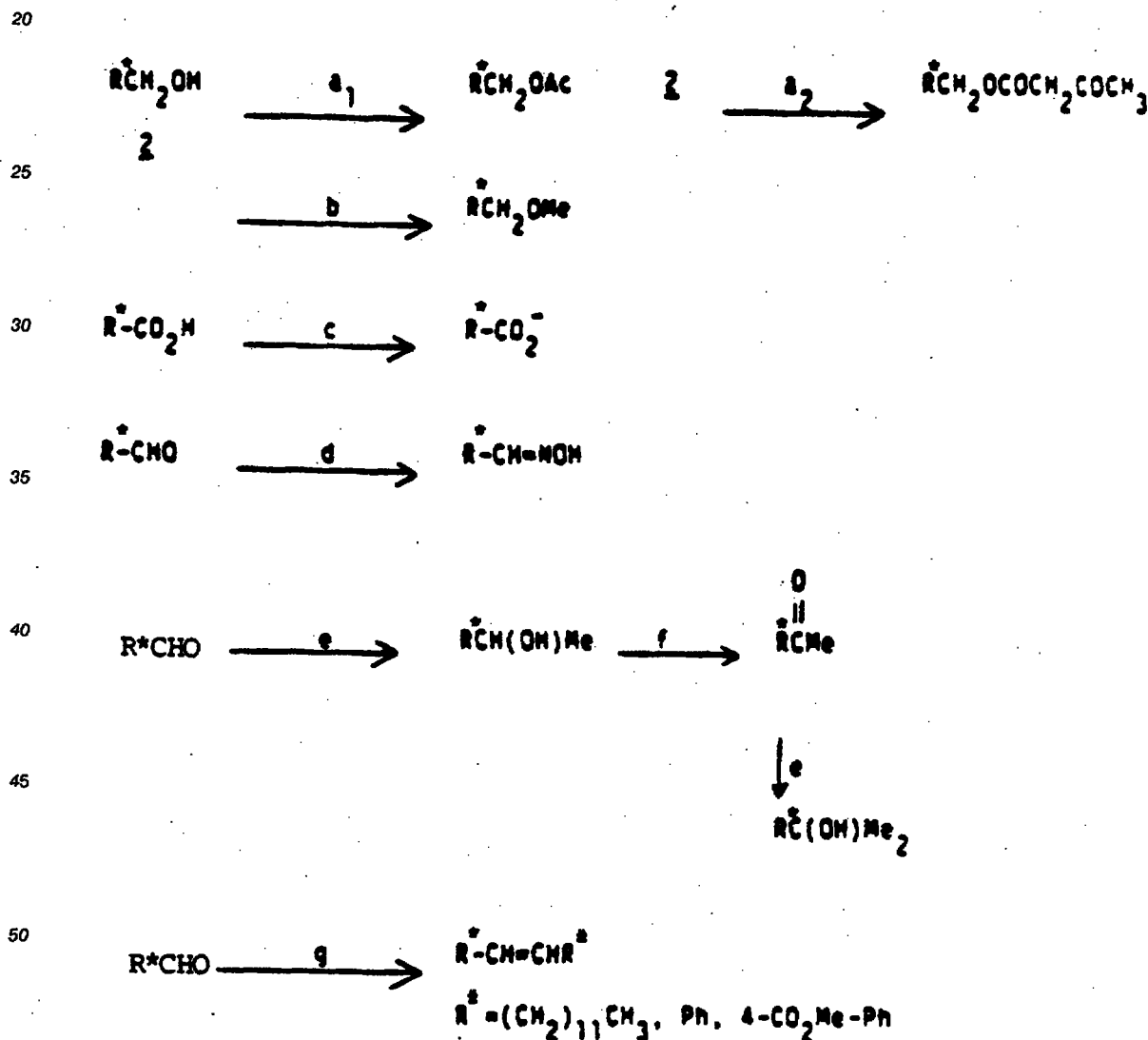
The appropriate acid chlorides were synthesized by treatment of acids of general formula 12 or 32 with oxalyl chloride in tetrahydrofuran (THF). The acid chlorides were then added as THF solutions to a solution of the appropriate alkylhydroxylamine hydrochloride [$R_6\text{NHOH}(\text{HCl})$] in THF/water/triethylamine (THF/ $\text{H}_2\text{O}/\text{Et}_3\text{N}$) to afford the alkylhydroxamic acids such as compounds 3, 58 and 41. The corresponding O-acylated products (e.g., 53 and 57) that may also form in the reaction were separated by either recrystallization or chromatography.

Similarly, treatment of the acid chlorides above with amines of general formula $R_6R_7\text{NH}$ gave amides such as 28, 65 and 38, where R_6 and R_7 are as before defined.

Oxidation of compound 65 with Jones Reagent as above gave acid 66.

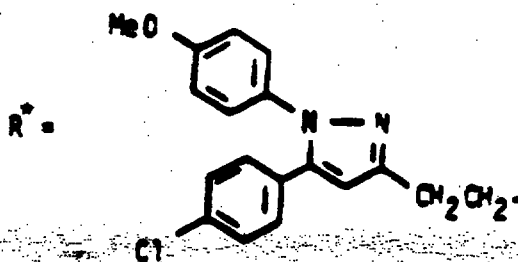
The remaining compounds of this invention were synthesized by standard methods from pyrazole alcohol 2, aldehyde 11 or acid 12 as shown in Scheme 3, below. The substituted pyrazole compounds with unsaturated side chains at the 3-position were prepared by reaction of aldehyde 11 with the appropriate Wittig reagent, as discussed specifically hereinafter and shown in Scheme 2, above. R_1 - R_7 , lower case letters and underlined numerals are as described for Schemes 1 and 2, before. R^* in Scheme 3 is the 1-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl-ethylene group, as shown.

Scheme 3



a_1 , acetic anhydride/pyridine, a_2 , 2,2,6-trimethyl-1,3-dioxen-4-one; b, NaH, methyl iodide; c, CH_2N_2 ; d, NH_2OH ; e, methyl magnesium bromide; f, pyridinium chlorochromate; g, lauryltriphenyl phosphonium bromide [$\text{BrPh}_3\text{P}(\text{CH}_2)_{11}\text{CH}_3$] benzyltriphenylphosphonium chloride [$\text{PhCH}_2^+\text{PPh}_3\text{Cl}^-$];

(4-methoxycarbonylphenyl)-triphenylphosphonium chloride $[4\text{-CO}_2\text{MePhCN}_2\text{P}^+\text{Ph}_3\text{Cl}^-]$.



Best Modes for Carrying Out the Invention

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Melting point (mp) were determined on a Thomas-Hoover apparatus, and are uncorrected. The infrared (IR) spectra were recorded on a Beckman Instruments IR-8 spectrophotometer and are expressed in reciprocal centimeters. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a Varian T-60A or an IBM
 20 WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. Parenthesized, underlined hydrogens were assigned to the resonance positions immediately before the parentheses. EI and CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph or a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer.

25 Example 1: 5-(4-Chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole (2).

4-Methoxyphenylhydrazine hydrochloride [35.0 grams (g), 0.20 moles] was added to CH_3OH [50 milliliters (ml)] containing pyridine (20 ml). An additional amount of CH_3OH (25 ml) was added to the thick
 30 resulting slurry. 1-(4-Chlorophenyl)-6-hydroxyhexan-1,3-dione (48.2g, 0.20 moles), was added neat, followed by more CH_3OH (25 ml). The slurry was stirred at room-temperature for 1.5 hours, after which times the mixture was concentrated and taken up in CHCl_3 (300 ml). The CHCl_3 solution was washed with 1N HCl (300 ml), dried (Na_2SO_4), filtered, and concentrated. The oil was decolorized (Norit) in hot diethyl ether (Et_2O) (300 ml). The Et_2O solution was cooled, and crystallization from Et_2O (300 ml) afforded 2 (49.4 g). From the filtrate was obtained additional 2
 35 (9.28 g), total yield 91%, mp $87.5 - 88^\circ$. NMR (CDCl_3) 1.7 - 2.3 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.55 (brs, 1H, OH), 2.80 (t, 2H, $J=7\text{Hz}$, CH_2), 3.75 (t, 2H, $J=6\text{Hz}$, CH_2O), 3.77 (s, 3H, OCH_3), 6.28 (s, 1H, $\text{C}_4\text{-H}$), 6.93 (ABq, 4H, $J=12, 9$, 4-OMe- C_6H_4), 6.9 - 7.3 (m, 4H, 4-Cl- C_6H_4); IR (KBr) 3320, 2920, 1495; MS, m/e 342 (M^+), 312, 298 (100%);

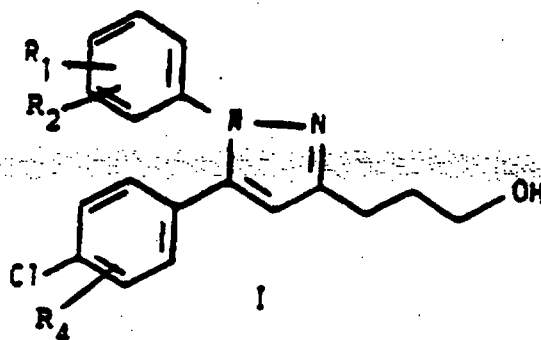
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Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_2$	C, 66.56;	H, 5.59;	N, 8.17
Found	C, 66.54;	H, 5.76;	N, 8.02

The following general procedure was used for the preparation of 1,5-diaryl-3-(3-hydroxypropyl)
 45 pyrazoles of Tables 1 and 2 that follow.

The appropriate aryl hydrazine or hydrazine hydrochloride B [10 millimoles (Mm)] was dissolved in a solution of methanol (25 ml) containing pyridine (1 ml). The appropriately substituted 1-aryl-1,3-dione A (10 Mm) was admixed in a single portion. In a short time, the mixture warmed slightly, darkened, and became homogeneous. After stirring at ambient temperature for a time period of from 2 to 20 hours, the reaction
 50 mixture was worked up as follows: the mixture was concentrated in vacuo and taken up in diethyl ether (250 ml); the ether solution was washed with aqueous 1N HCl (200 ml), decolorized, dried (Na_2SO_4), filtered through a pad of celite, and concentrated in vacuo. The crude material was either purified by column chromatography (silica gel 60, 70 - 230 mesh, about 250 g, and elution with ether) to give the desired 1,5-diarylpyrazoles (I) or recrystallized directly without chromatography. In some cases the isomeric 1,3-diaryl
 55 isomer was also isolated in varying minor amounts, and eluted before I from the column.

Table 1



Compound Number	R ₁	Melting point	Analysis ⁺ C, H, N			Mass spectrum m/e (M ⁺)
1	4-H	105.5 - 106.5°	x	x	x	312 (M ⁺)
2	4-OMe [#]	87 - 88°	x	x	x	342 (M ⁺)
4	4-Cl	85 - 87°	x	x	x	346 (M ⁺)
5	3-CF ₃	oil	x	x	x	380 (M ⁺)
35	4-Br	oil	x	x	x	390 (M ⁺)
36	4-SO ₂ CH ₃	95 - 97°	x	x	x	390 (M ⁺)
37	4-CH ₃	92 - 94°	x	x	x	326 (M ⁺)
42	3,4-diOMe	113 - 114°	x	x	x	372 (M ⁺)
46	3-OMe	oil	x	x	x*	342 (M ⁺)
47	4-SMe	82 - 84°	x	x	x	358 (M ⁺)
48	4-NO ₂	foam	x	x	x**	357 (M ⁺)
51	4-OC ₅ H ₁₁	oil	x	x	x	398 (M ⁺)
52	[6-MeO- naphth-2-yl]	foam	x	x	x	392 (M ⁺)
60	2-CF ₃	oil	x	x	x	-
61	4-OCH ₂ CF ₃	87 - 89°	x	x	x	410 (M ⁺)

Compound Number	R_1^S	Melting point	Analysis ⁺			Mass spectrum m/e (M ⁺)
			C	H	N	
8	3,4-diCl	oil	x	x	x	380 (M ⁺)
22	2-OCH ₃	78 - 82°	x	x	x	312 (M ⁺)
62	4-F	81 - 82°	x	x	x	330 (M ⁺)
69	4-NH ₂	210 - 213	x	x	x***	327 (M ⁺)
70	4-CON(OH)Me	98 - 100				385 (M ⁺)
71	4-iPr	oil	x	x	x	354 (M ⁺)

4* dihydrate

*** dihydrochloride, monohydrate

** 1/4 hydrate

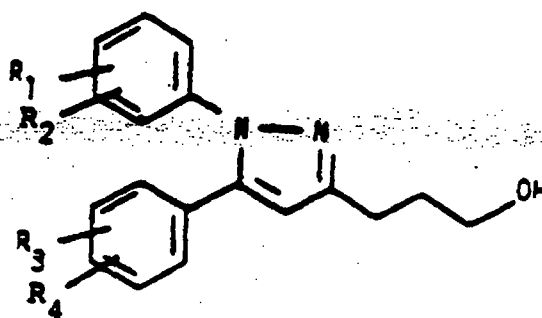
+ hemihydrate

Me = CH₃

\$ R₂ and R₄ = H except for compounds 42 and 8,
where R₂ = OMe and Cl, respectively.

+ analysis within experimental error for C, H & N.

Table 2



Compound Name	R ₁ ^S	R ₃	Melting point	Mass spectrum m/e (M ⁺)
9	H	H	oil	278 (M ⁺)
10	4-OMe [#]	H	oil	308 (M ⁺)
18	2-OMe	H	oil	308 (M ⁺)
21	4-Cl	H	oil	312 (M ⁺)
30	4-OMe	4-F	86-87.5°	326 (M ⁺)
50	3,4-diOMe	H	oil	338 (M ⁺)
54	4-OMe	4-Ph ^{##}	foam ^{**}	384 (M ⁺)
55	4-OMe	4-Me	94.5-96°	322 (M ⁺)
56	4-OMe	4-CF ₃	73-75°	376 (M ⁺)
68	4-OMe	3,4-diCl	56-58°	376 (M ⁺)

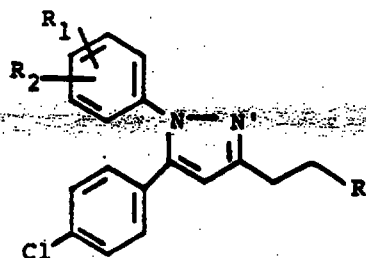
^{**}, &, # See Table 1 notes.

^{##} Ph = phenyl

^S R₂ and R₄ = hydrogen except for compounds 50 and 68, where R₂ = OMe and R₄ = Cl, respectively.

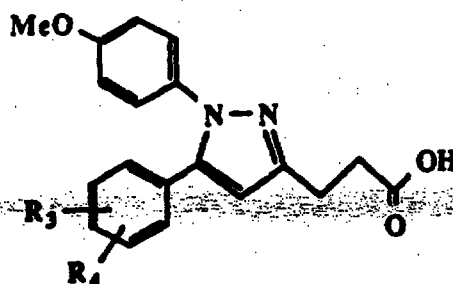
Compounds in which R₁, R₂, R₃ and R₄ are all other than hydrogen can be synthesized by the above procedure. For example, when the aryl hydrazine B is 3,4-dimethoxyphenylhydrazine and the 1-aryl-1,3-dione A is 3,4-dichloro-4,6-dioxohexanoic acid, 5-(3,4-dichlorophenyl)-1-(3,4-dimethoxyphenyl)-3-(3-hydroxypropyl)-pyrazole is obtained.

Table 2



Compound Number	R_1, R_2	R'	Melting Point	Analysis			Mass Spectrum $m/e (M^+)$
				C	H	N	
72	4-OEt	CO_2H	123-125°	x	x	x	370
73	4-OH	CO_2H	239-241°	x	x	x	342
74	3,4-diOMe	CO_2H	153-154°	x	x	x	386
75	4-OEt	CO_2Et	oil	x	x	x*	398
76	4-OEt	-CON(OH)Me	foam	x	x	x**	341
77	3,4-dioH	CO_2H	179-180°	x	x	x ^{4*}	358
78	3,4-diOMe	-CON(OH)Me	162-163°	x	x	x	415
103	2-OMe	- CO_2H	135-137°	x	x	x	356
104	2-OMe	-CON(OH)Me	145-147°	x	x	x	385

TABLE 2''



Compound Number	R ₃ , R ₄	Melting Point	Mass Spectrum	C, H, N
			(m/e)	
105 *	4-Me	145-147°	336(M ⁺)	XXX
106 *	3-Me	109-110°	336(M ⁺)	XXX
107 *	3,4-di-Me	141-142°	350(M ⁺)	XXX
109 *	2-Me	111-112°	336(M ⁺)	XXX
110 *	4-Et	137-138°	350(M ⁺)	XXX

Example 2: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propionic acid (12).

To a solution of the alcohol 2 [(0.92 g, 2.68 millimoles (mM)) in acetone (25 ml) was added a 2N H₂Cr₂O₇ (Jones Reagent) solution (3.02 ml, 6.04 mM) dropwise over a 10 minute time period. After stirring for 1 hour the reaction solution was decanted from the chromium precipitates on the sides of the reaction vessel. The reaction solution was concentrated in vacuo and taken up into ethyl acetate (EtOAc) (100 ml), washed with distilled H₂O until the washes were clear, dried (MgSO₄), filtered, and concentrated in vacuo. Crystallization from Et₂O: hexane afforded 12 (0.88 g, 92%) as an off-white crystalline solid, mp = 126 - 128°C.

NMR: (CDCl₃) 2.7 - 3.2 (m, 4H, -CH₂CH₂-), 3.80 (s, 3H, -OCH₃), 6.30 (s, 1H, C₄-H), 6.7 - 7.5 (m, 8H, aromatic), 7.5 - 8.5 (1H, -COOH); IR (KBr) 1700; MS, m/e 356 (M⁺), 312, 311 (100%).

Anal. Calcd. for C ₁₉ H ₁₇ ClN ₂ O ₃	C, 63.95;	H, 4.80;	N, 7.85
Found	C, 63.82;	H, 4.92;	N, 7.72.

Example 3: Sodium 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanoate monohydrate (13).

To the acid 12 (1.0169 g, 2.85 mM) was added a 1.00 N NaOH solution (2.85 ml, 2.85 mM) and distilled H₂O (15 ml). The reaction mixture was stirred until it was homogeneous, and then lyophilized to afford 13 - (1.08 g, 98%) as a white solid, with a mp greater than 300°C.

NMR (CD₃OD) 2.3 - 3.2 (m, 4H, -CH₂-CH₂-), 3.80 (s, 3H, -OCH₃), 6.47 (s, 1H, C₄-H), 6.7 - 7.4 (m, 8H, aromatic); IR (KBr) 3250, 1640.

Anal. Calcd. for C ₁₉ H ₁₆ ClN ₂ NaO ₃ ·H ₂ O	C, 57.51;	H, 4.57;	N, 7.06
Found	C, 57.19;	H, 4.33;	N, 6.98.

Example 4: 3-[5-(4-Chlorophenyl)-1-phenyl-3-pyrazolyl] propionic acid (17).

Following the procedure for compound 12 but substituting compound 1 for 2 afforded 17 (0.86 g, 68%) as a white crystalline solid, mp = 138 - 139°C.

NMR (CDCl₃) 2.6 - 3.2 (m, 4H, -CH₂-CH₂-), 6.30 (s, 1H, C₄-H); 6.4 - 7.5 (m, 10H, aromatic and -COOH). IR (KBr) 3460, 1740; MS, m/e 326 (M⁺), 282, 281 (100%).

Anal. Calcd. for C ₁₀ H ₁₅ ClN ₂ O ₂	C, 66.16;	H, 4.63;	N, 8.57
Found	C, 66.48;	H, 4.72;	N, 8.59

Example 5: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide (3).

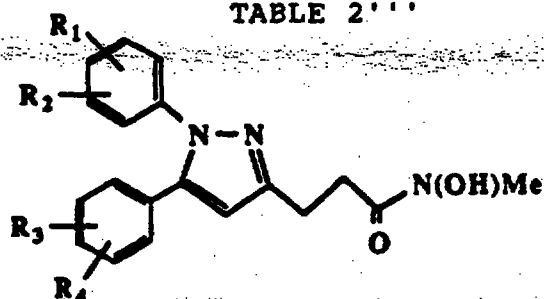
To a solution of the acid 12 (0.99 g, 2.77 mM) in tetrahydrofuran (THF) (20 ml) at 0°C, was added one drop of dimethyl formamide (DMF) and oxalyl chloride (0.29 ml, 33 mM). After 0.5 hours the cooling bath was removed and stirring was continued for an additional 0.5 hours. The reaction mixture was concentrated in vacuo to remove any excess oxalyl chloride, and the acid chloride of 12, was taken up into THF (10 ml).

To a solution of methylhydroxylamine hydrochloride (0.35 g, 4.16 mM) and triethylamine (Et₃N) (1.55 ml, 11.10 mM) in THF, H₂O (10 ml:5 ml) at 0°C, was added the THF solution of the acid chloride dropwise over a 5 minutes period. The cooling bath was removed, and the reaction mixture was stirred for 1 hour, diluted to 100 ml with EtOAc, washed with H₂O, dried (MgSO₄), filtered, and concentrated in vacuo. Chromatography (Baker silica gel, 45g) of the residue with EtOAc as eluent, followed by crystallization from Et₂O afforded pure 3 (0.70 g, 85%), mp = 113 - 115°C. Further recrystallization from ethyl acetate afforded white crystalline solid, m.p. 125-26°C.

NMR: (CDCl₃) 2.7 - 3.5 (m, 4H, -CH₂CH₂-), 3.18 (broad s, 3H, -N-CH₃), 3.83 (s, 3H, -OCH₃), 6.30 (s, 1H, C₄-H), 6.7 - 7.4 (m, 8H, aromatic), 10.67 (broad s, 1H, -N-OH); IR (KBr) 3160, 1640; MS, m/e 385 (M⁺), 339 (100%).

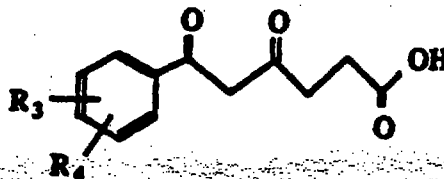
Anal. Calcd. for $C_{20}H_{20}ClN_3O_3$	C, 62.25;	H, 5.22;	N, 10.89
Found	C, 62.60;	H, 5.18;	N, 10.82.

TABLE 2



Compound				Mass	
Number	R1, R2	R3, R4	Melting Point	Spectrum (m/e)	C, H, N
111	4-OMe	4-Me	119-121°	365(M ⁺)	XXX*
112	4-Cl	4-OMe	158-160°	385(M ⁺)	XXX
113	4-OMe	4-OMe	104-105°	381(M ⁺)	XXX
114	4-OMe	4-H	foam	351(M ⁺)	XXX*
115	4-OMe	3-Me	137-138°	365(M ⁺)	XXX
116	4-OMe	3,4-di-Me	130-131°	379(M ⁺)	XXX
118	4-OMe	2-Me	117-118°	365(M ⁺)	XXX
119	4-OMe	4-Et	72-74°	379(M ⁺)	XXX
*1/2 hydrate					

TABLE 2"-AP



Compound Number	R3, R4	Melting Point	Mass Spectrum (m/e)	C, H
120	4-Me	139-141°	234(M ⁺)	XX
121	3-Me	92-94°	234(M ⁺)	XX
122	3,4-di-Me	98-100°	248(M ⁺)	XX
123	2-Me	139-140°	234(M ⁺)	XX
124	4-Et	114-115°	248(M ⁺)	XX
125	4-Cl	137-139°	254(M ⁺)	XX
126	4-F		238(M ⁺)	XX
127	3,4-di-Cl	87-90°	288(M ⁺)	XX
128	H	102-105°	220(M ⁺)	XX

The following general procedure was used for the preparation of the 1,5-diaryl-3-pyrazole propionic acids of Table 2".

A mixture of the appropriate 6-aryl-4,6-diketoheptanoic acid (0.1 Mole) from Table 2"-AP in methanol (750 ml) containing Et₃N (0.2 Mole) was treated with 4-methoxyphenylhydrazine hydrochloride (17.4 g, 0.1 Mole) at room temperature for 1 hour. If the reaction was incomplete at this point, it was refluxed until complete. The resulting darkened solution was evaporated *in vacuo* and taken up in Et₂O (700 ml); the ether solution was washed with aqueous 1N HCl (350 ml), brine, dried (Na₂SO₄), decolorized, evaporated *in vacuo* and recrystallized from Et₂O.

The compounds of Table 2" were synthesized directly from the appropriate 4,6-diketoheptanoic acid as described below.

Synthesis of 6-Aryl-4,6-diketoheptanoic acids.

The compounds of Table 2"-AP were synthesized by the following general procedure. To a reaction vessel containing anhydrous THF (250 ml) and diisopropylamine (14 ml, 0.1 Mole) stirring under nitrogen at 0°C was added by syringe, n-BuLi (1.6 M, 62.5 ml, 0.1 Mole). The vessel was then cooled to -78°C. Alternatively, lithium hexamethyldisilazide (0.1 Mole) may be employed as the base in place of lithium diisopropylamide.

The appropriately substituted acetophenone (0.1 Mole) in anhydrous THF (50ml) was added and the resulting solution allowed to stir for 30 minutes at -78° and succinic anhydride (4.0 g, 0.04 mole) in THF (100 ml) was added via syringe. The solution was allowed to stir for 1 hour at -78°, warmed to room temperature for 1 hour and poured into 5% HCl (250 ml). The mixture was extracted with Et₂O (2 X 300ml) and the combined ether extract was extracted with 10% NaOH (100 ml). The NaOH layer was separated

and acidified with 4N HCl, and reextracted with Et₂O (2 x 300 ml). The combined ether layers were dried (Na₂SO₄), filtered and concentrated in vacuo. The resultant residues were recrystallized from the appropriate solvent to give the compounds of Table 2" -AP.

5 Example 6: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide sodium salt monohydrate(3a).

To hydroxamic acid 3 (0.6052 g, 1.57 mM) was added 1.00 N NaOH solution (1.57 ml, 1.57 mM) and distilled H₂O (3 ml). The reaction mixture was stirred for 10 minutes at which time it was homogeneous.
10 Lyophilization afforded pure 3a (0.64 g, 97%) as a white hygroscopic solid, mp = 100 - 110 °C (decomposed).

NMR: (CD₃OD) 2.3 - 3.4 (m, 4H, -CH₂CH₂-), 2.92 (broad s, 3H, -NCH₃), 3.78 (s, 3H, -OCH₃), 6.47 (s, 1H, C₄-H), 6.7 - 7.6 (m, 8H, aromatic); IR (KBr) 3420, 1600; MS, m/e 384 (M⁺-Na).

15

Anal. Calcd. for C ₂₀ H ₁₉ ClN ₃ NaO ₃ ·H ₂ O	C,56.40;	H,4.97;	N,9.87
Found	C,56.24;	H,4.53;	N,9.70.

20 Example 7: 0-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] ethyl-carbonyl]-N-methylhydroxylamine (53).

The procedure to synthesize compound 3 was repeated on a twenty-fold scale.

Chromatography of the crude reaction mixture (Merck Silica Gel 60; 230 - 400 mesh, 150 g) with
25 CH₃OH:CHCl₃ (3 :97) as eluent, separated 3 from a mixture with the less polar component (2.5 g, R_f = 0.18).

Chromatography (Merck Silica Gel 60; 230 - 400 mesh, 75 g) of this mixture with Et₂O as eluent, and crystallization from Et₂O: hexane afforded 53 (0.81 g, 3.7%) as a white crystalline solid, mp = 80 - 81 °C (sharp).

30 NMR: (CDCl₃) 2.83 (d, 3H, J = 7.5 Hz, -NHCH₃), 2.6 - 3.3 (m, 4H, -CH₂CH₂-), 3.83 (s, 3H, -OCH₃), 6.33 (s, 1H, C₄-H), 6.7 - 7.4 (m, 4H, aromatic), 7.55 (q, J = 7.5 Hz, 1H, -NHCH₃); IR (KBr) 3200, 1740; MS (20 eV EI), m/e 356, 339 (100%), 311, 297.

35

Anal. Calcd. for C ₂₀ H ₂₀ ClN ₃ O ₃	C,62.25;	H,5.22;	N,10.89
Found	C,62.31;	H,5.21;	N,10.88.

40 Example 8: N-Carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanamide (66).

Following the procedure of Example 5, but substituting glycine for methylhydroxylamine hydrochloride afforded 66 (1.98 g, 67.4%), as a white crystalline solid, melting point = 185.5 - 187.5 °C.

45 NMR (DMSO-d₆) 2.4 - 2.7 (m, 2H, -CH₂CH₂CON-), 2.7 - 3.0 (m, 2H, -CH₂CH₂CON-), 3.78 (s, 3H, -OCH₃), 3.78 (d, J = 5.5 Hz, 2H, -NHCH₂COOH), 6.53 (s, 1H, C₄-H), 6.7 - 7.6 (m, 8H, aromatic), 8.29 (broad t, J = 5.5 Hz, 1H, CONH-CH₂COOH); IR (KBr) 3360, 1725, 1665; MS, m/e 413 (M⁺), 311 (100%).

50

Anal. Calcd. for C ₂₁ H ₂₀ ClN ₃ O ₇	C,60.94;	H,4.87;	N,10.15
Found	C,60.64;	H,4.87;	N,10.01.

Example 9: 3-[5-(4-Chlorophenyl)-1-phenyl-3-pyrazolyl]-N-hydroxy-N-methyl propanamide (67).

55 Following the procedure described in Example 5 but substituting compound 17 for compound 12 afforded 67 (1.24 g, 78.0%) as a white crystalline solid, mp = 155 - 156.5 °C.

NMR (CDCl₃) δ 2.5 - 3.5 (m, 4H, -CH₂CH₂-), 3.20 (s, 3H, -N(CH₃)OH), 6.33 (s, 1H, C₄H), 7.0 - 7.7 (m, 9H, aromatic), 10.37 (broad s, 1H, -N(CH₃)OH); IR (KBr): 3120, 1650; MS, m/e 355 (M⁺), 309 (100%).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$	C,64.13;	H,5.10;	N,11.81
Found	C,64.17;	H,5.45;	N,11.51.

5

Example 10: 3-[5-(4-Fluorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl propanamide (45).

Following the procedure described in Example 5, but substituting compound 30 for compound 12 afforded 45 (1.21 g, 83%) as an off-white crystalline solid, mp = 151 - 154 °C.

10 NMR ($CDCl_3$) 2.7 - 3.5 (m, 4H, $-CH_2CH_2-$); 3.20 (broad s, 3H, $-NCH_3$); 3.83 (s, 3H, $-OCH_3$); 6.30 (s, 1H, C_4-H); 6.7 - 7.4 (m, 8H, aromatic); 10.4 - 10.9 (broad s, 1H, $-NOH$); IR (KBr): 3140, 1650; MS (20 eV EI, m/e 369 (M^+), 340, 323 (100%).

15

Anal. Calcd. for $C_{20}H_{20}FN_3O_3$	C,65.03;	H,5.46;	N,11.38
Found	C,64.87;	H,5.59;	N,11.05.

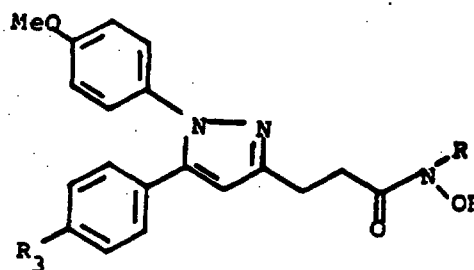
Example 11:

20

Following the procedure described in Example 5, the following compounds were synthesized.

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30



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Compound Number	R_3	R'	Melting Point	Analysis C. H. N	Mass Spectrum m/e (M^+)
81	Cl	iPr	80-83°	x x x*	413
82	Cl		74-76°	x x x	453
83	Cl	Et	113-114°	x x x	399
84	Cl		113.5-114.5	x x x	447
79	CF_3	Me	foam	x x x ^{2*}	419

60

* $1/2 C_6H_{14}$

2* $1/2 H_2O$

65

Example 12: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxypropanamide (29).

To a solution of the acid 12 (0.97 g, 2.72 mM) in THF (20 ml) at 0°C, was added one drop of DMF (catalyst) and oxalyl chloride (0.28 ml, 3.26 mM). After 0.5 hour the cooling bath was removed and stirring was continued for 0.5 hour. The reaction mixture was concentrated in vacuo to remove any excess oxalyl chloride, and the remaining crude acid chloride, of acid 12, was taken up in THF (10 ml).

To a solution of hydroxylamine hydrochloride (0.28 g, 4.08 mM) and Et₃N (1.52 ml, 10.9 mM) in THF:H₂O (10 ml:5 ml) at 0°C, was added the crude acid chloride solution, dropwise over a 5 minutes period. The cooling bath was removed, and the reaction mixture was stirred for 1 hour, diluted to 100 ml volume with EtOAc, washed with H₂O, dried (MgSO₄), filtered, and concentrated in vacuo. Crystallization from Et₂O afforded 29 (0.88 g, 87%) as a white crystalline solid, mp = 154 - 156°C.

NMR (CDCl₃) 2.4 - 3.4 (m, 4H, -CH₂CH₂-), 3.80 (s, 3H, -OCH₃), 6.30 (s, 1H, C₄-H), 6.3 - 7.5 (m, 9H, aromatic and -NH-). IR (KBr): 3260, 1665; MS, m/e 371 (M⁺), 353, 339, 311, 298 (100%).

15

Anal. Calcd. for C ₁₉ H ₁₈ ClN ₃ O ₃	C,61.37;	H,4.88;	N,11.30
Found	C,61.36;	H,5.05;	N,10.97.

20 Example 13:

0-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-N-tert-butylhydroxylamine (57); and 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide (58).

To a solution of the acid 12 (0.99 g, 2.77 mM) in THF (30 ml) at 0°C, was added one drop of DMF and oxalyl chloride (0.29 ml, 3.33 mM). After stirring for 0.5 hour the cooling bath was removed and stirring was continued for 0.5 hour. The reaction mixture was concentrated in vacuo to a volume of 10 ml, and added dropwise to a solution of N-(tert-butyl) hydroxylamine (HCl) (0.52 g, 4.16 mM) and Et₃N (1.56 ml, 11.1 mM) in THF:H₂O (12 ml:6 ml) at 0°C. The reaction mixture was stirred for 1 hour, diluted to 100 ml with EtOAc, washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. The residue was combined with that from a similar run on a 2.72 mM scale.

Chromatography (Merck Silica Gel 60; 230 - 400 mesh, 72 g) with Et₂O:hexane (4:1) as eluent afforded 57, crystallized from cold Et₂O:hexane (1.19 g, 51%) as a white crystalline solid, mp = 73 - 74.5°C and 58 recrystallized from EtOAc:Et₂O (0.63g, 27%) as a white crystalline solid, mp = 137 - 138°C.

Compound 57, NMR (CDCl₃) 1.10 (s, 9H, -C(CH₃)₃), 2.7 - 3.4 (m, 4H, -CH₂CH₂-), 3.80 (s, 3H, -OCH₃), 6.32 (s, 1H, C₄-H), 6.7 - 7.5 (m, 8H, aromatic); IR (KBr) 3480, 1730; MS (20eV EI), m/e 339 (100%), 311, 297.

50

Anal. Calcd. for C ₂₃ H ₂₆ ClN ₃ O ₃	C,64.55;	H,6.12;	N,9.82
Found	C,64.41;	H,6.19;	N,9.71.

Compound 58, NMR (CDCl₃) 1.25 (s, 9H, -C(CH₃)₃), 2.7 - 3.4 (m, 4H, -CH₂CH₂-), 3.83 (s, 3H, -OCH₃), 6.33 (s, 1H, C₄-H), 6.7 - 7.5 (m, 8H, aromatic), 10.08 (s, 1H, -N-OH). IR (KBr) 3460, 3130, 1620, 1590; MS (20eV EI), m/e 427 (M⁺), 339 (100%), 311, 297.

55

Anal. Calcd. for $C_{23}H_{20}ClN_3O_3$	C,64.55;	H,6.12;	N,9.82
Found	C,64.62;	H,6.38;	N,9.72.

5

Example 14: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanal (11).

To a suspension of pyridinium chlorochromate (10.02 g, 46.5 mM) in CH_2Cl_2 (500 ml) was added the alcohol 2, (5.09 g, 15.5 mM). After stirring overnight, the reaction mixture was concentrated in vacuo to a volume of about 200 ml, and diluted to 1 liter with Et_2O . This solution was filtered through celite, and the filter cake was washed with Et_2O (2 x 200 ml). The filtrate and the washes were combined and concentrated in vacuo. Chromatography (120g, Baker silica gel) of the residue with Et_2O :hexane (2:1) as eluent, and crystallization from Et_2O afforded pure 11, (0.88 g, 17%) as a white crystalline solid, mp. = 101 - 102 °C.

NMR ($CDCl_3$) 2.8 - 3.2 (m, 4H, $-CH_2CH_2CHO$), 3.85 (s, 3H, $-OCH_3$), 6.32 (s, 1H, C_4-H), 6.7 - 7.4 (m, 8H, aromatic), 9.93 (t, J = 1 Hz, 1H, $-CHO$); IR (KBr) 1715; MS, m/e 340 (M^+), 312 (100%).

20

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$	C,66.96;	H,5.03;	N,8.22
Found	C,66.72;	H,5.12;	N,8.13.

Example 15: Sodium 8-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-5(Z)-octenoate (32).

To a solution of hexamethyldisilazane (5.25 ml, 24.9 mM) in THF (125 ml) at +5 °C was added 1.46 M n-butyl lithium (n-BuLi) (16.3 ml, 23.8 mM). The cooling bath was removed after 15 minutes and (4-carboxybutyl)triphenylphosphonium bromide (5.17 g, 11.7 mM) was added. Stirring was continued for 45 minutes and the aldehyde 11 (3.61 g, 10.6 mM) was added. After stirring for 1 hour, the reaction solution was diluted to a 600 ml volume with EtOAc and extracted with H_2O (2 x 200 ml). The extracts were combined, acidified with 3N HCl, and extracted with EtOAc (2 x 200 ml). The EtOAc extracts were combined, dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography of the remaining residue (Baker silica gel, 160 g) with Et_2O as eluent afforded the acid (3.39 g, 75%) as a clear yellow oil.

To the neat acid (0.57 g, 1.34 mM) was added a 1.00 N NaOH solution (1.34 ml, 1.34 mM) and a small amount of water. After stirring overnight, the reaction solution was lyophilized to afford 32 (0.60 g, 95%) as a white solid.

Acid, NMR ($CDCl_3$) 1.4 - 3.1 (m, 10H, $-CH_2CH_2CH=CH(CH_2)_3COOH$), 3.80 (s, 3H, $-OCH_3$), 5.2 - 5.7 (m, 2H, $-CH=CH-$), 6.33 (s, 1H, C_4-H), 6.7 - 7.5 (m, 8H, aromatic); MS (20 eV EI), m/e 426 ($M+2$), 424 (M^+), 365, 351, 337, 298 (100%).

Compound 32, NMR (CD_3OD) 1.4 - 3.1 (m, 10H, $-CH_2CH_2CH=CH(CH_2)_3-$), 3.80 (s, 3H, $-OCH_3$), 5.2 - 5.7 (m, 2H, $-CH=CH-$), 6.45 (s, 1H, C_4-H), 6.7 - 7.5 (m, 8H, aromatic); IR (KBr) 3440, 1565; MS, m/e 423 ($M-Na$).

45

Anal. Calcd. for $C_{24}H_{24}ClN_2NaO_3(1.25 H_2O)$	C,61.40;	H,5.69;	N,5.97
Found	C,61.60;	H,5.46;	N,5.51.

Example 16: 8-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-5(Z)-octenamide (41).

Following the procedure described in Example 5, but substituting the acid for 12 afforded 41 (0.94 g, 62%) as a clear colorless oil.

NMR ($CDCl_3$) 1.5 - 3.5 (m, 14H, $-(CH_2)_2-CH=CH-(CH_2)_3CON(CH_3)OH$), 3.80 (s, 3H, $-OCH_3$), 5.3 - 5.7 (m, $-CH=CH-$, 2H), 6.30 (s, 1H, C_4-H), 6.7 - 7.4 (m, 8H, aromatic); IR (neat): 3160, 1630; MS (20 eV EI), m/e 455 ($M+2$), 453 (M^+), 407, 379, 365, 298 (100%).

55

Anal. Calcd. for $C_{25}H_{28}ClN_3O_3$	C,66.14;	H,6.22;	N,9.26
Found	C,65.78;	H,6.55;	N,8.93.

5

Example 17: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N,N-diethylpropanamide (28).

To a solution of the acid 12 (1.01 g, 2.83 mM) in THF (25 ml) at 0°C, was added one drop of DMF and oxalyl chloride (0.30 ml, 3.40 mM). After 0.5 hours the cooling bath was removed and stirring was continued for 0.5 hour. The reaction mixture was concentrated in vacuo to remove the excess oxalyl chloride, and the remaining acid chloride was diluted with THF (25 ml) and cooled to 0°C. To this solution diethylamine (1.17 ml, 11.32 mM) was added dropwise over a 5 minute period. After stirring for 1 hour, the reaction mixture was diluted to 100 ml with Et₂O, washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. Crystallization from Et₂O afforded 28 (0.98 g, 84%) as a yellow crystalline solid, mp = 111 - 112°C.

NMR (CDCl₃) 1.13, 1.17 (2t, J = 7Hz, 6H, -N(CH₂CH₃)₂), 2.5 - 3.8 (m, 8H, -CH₂CH₂- and -N(CH₂CH₃)₂), 3.80 (s, 3H, -OCH₃), 6.30 (s, 1H, C₄-H), 6.7 - 7.4 (m, 8H, aromatic); IR (KBr) 1630; MS (20eV EI), m/e 411 (M⁺), 311 (100%).

20

Anal. Calcd. for $C_{23}H_{26}ClN_3O_2$	C,67.06;	H,6.36;	N,10.20
Found	C,67.14;	H,6.34;	N,9.95.

Example 18: Compounds of Table 3.

25

Following the procedure of Example 17, but substituting NH₄OH, 4-aminophenol, O,N-dimethylhydroxylamine hydrochloride, 2-aminophenol, 2-aminothiophenol, 2-aminopyridine and ethanolamine for diethylamine gave the compounds of Table 3.

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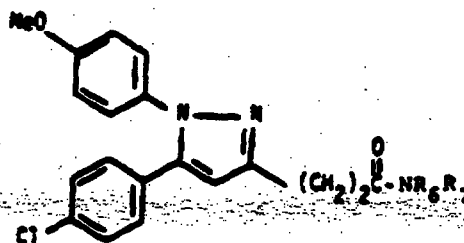
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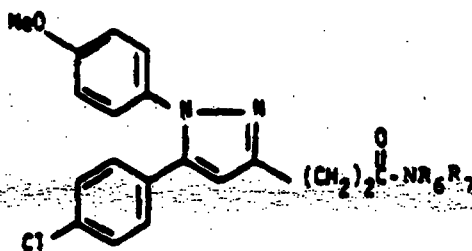
Table 3



Compound Number	NR_6R_7	Melting Point	Mass Spectrum m/e	C.H.N
31	$-\text{NH}_2$	145 - 146°	355 (M^+)	XXX
34	$-\text{NH}-\text{C}_6\text{H}_4-\text{OH}$	223 - 226°	447 (M^+)	XXX
44	$-\text{N}(\text{CH}_3)\text{OCH}_3$	136 - 137°	399 (M^+)	XXX
40	$-\text{NH}-\text{C}_5\text{H}_4\text{N}$	176 - 177°	432 (M^+)	XXX
63	$-\text{NH}-\text{C}_6\text{H}_3(\text{OH})_2$	198 - 200°	448 (M^+)	XXX
64	$-\text{NH}-\text{C}_6\text{H}_4-\text{SH}$	157.5 - 159°	468 (M^+)	XXX
65	$-\text{NHCH}_2\text{CH}_2\text{OH}$	115 - 118°*	399 (M^+)	XXX*

* 1/4 hydrate

In addition, following the procedure of Example 17, the following were synthesized.



Compound Number	NR_6R_7	Melting Point	Mass Spectrum m/e	C,H,N
85		227-228°	440 (M^+)	XXX*
86		187.5-189°	461 (M^+)	XXX*
87	$\text{H}-\text{N}-\text{CH}_2\text{CO}_2\text{Et}$	104-105.5°	441 (M^+)	XXX
88	$\text{H}-\text{N}-\text{CH}_2\text{CONHOH}$	160-162°	428 (M^+)	XXX*
89	$\text{H}-\text{N}-\text{CH}_2\text{CON(OH)Me}$	180-182°	442 (M^+)	XXX
90		235-237°	423 (M^+)	XXX*
100	$-\text{HN}-\text{CH}(\text{CO}_2\text{Et})\text{CH}_2\text{SH}$		487 (M^+)	XXX**
101	$-\text{HN}-\text{CH}(\text{CO}_2\text{Et})\text{CH}_2\text{SCH}_3$	93-96°	501 (M^+)	XXX

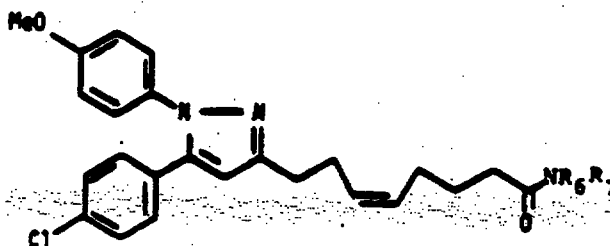
* 1/4 Hydrate

** 1/2 Hydrate

Example 19: Compounds of Table 4.

Following the procedure of Example 17 but substituting the acid for 12 and allowing the resulting acid chloride to react with NH_4OH and diethylamine, respectively gave the amides of Table 4.

Table 4



Compound		Mass	
Number	$-\text{NR}_6\text{R}_7-$	spectrum	C, H, N
38	$-\text{NH}_2^*$	423 (M^+)	XXX
39	$-\text{NEt}_2^*$	479 (M^+)	XXX

* Et = ethyl.

Example 20: 3-(3-Acetoxypropyl)-5-(4-chlorophenyl)-1-phenylpyrazole (7).

Compound 1 (1.00 g, 3.20 mM), acetic anhydride (1.0 ml, 11 mM), pyridine (1.0 ml, 12 mM) and CH_2Cl_2 (30 ml) were admixed and the admixture so formed was stirred overnight at room temperature, poured into H_2O (150 ml) and extracted with CH_2Cl_2 (25 ml). The extracts were dried (Na_2SO_4), filtered and concentrated to an oil (1.1 g). Chromatography (silica gel 60; 70 - 230 mesh, 150 g) and elution with Et_2O afforded 1.10 g (94%) of 7 as a colorless oil.

NMR (CDCl_3) 2.05 (s, 3H, CH_3CO), 1.8 - 2.4 (m, 2H, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.8 (dist t, $\text{J} \approx 8\text{Hz}$, CH_2-), 4.2 (t, 2H, $\text{J} = 6$, CH_2O), 6.32 (s, 1H, C_4-H), 7.1 - 7.5 (m, 9H, aromatic); IR (neat) 2960, 1740, 1600; MS, m/e 354 (M^+), 311, 281, 268 (100%).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{ClN}_2\text{O}_2$	C, 67.69;	H, 5.40;	N, 7.89
Found	C, 67.78;	H, 5.36;	N, 8.07.

Example 21: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl methyl ether (24).

To a suspension of NaH (0.135 g of 60% oil suspension, 3.37 mM) in THF (10 ml) at $+5^\circ\text{C}$ was added a solution of 2 (1.05 g, 3.06 mM) in THF (20 ml). After stirring for 30 minutes, methyl iodide (MeI) (0.21 ml, 3.37 mM) was added and the reaction mixture was left to stir overnight. After quenching with CH_3OH , the reaction mixture was concentrated in vacuo, the residue was taken up in EtOAc, washed with H_2O , dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (40g, Baker silica gel) with Et_2O as eluent afforded 24 (0.98 g, 90%) as a clear yellow oil.

NMR (CDCl_3) 1.8 - 2.4 (m, 2H, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$), 2.6 - 3.0 (m, 2H, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$), 3.35 (s, 3H, $-\text{CH}_2\text{OCH}_3$), 3.48 (t, $\text{J} = 7\text{Hz}$, 2H, $-\text{CH}_2\text{CH}_2\text{OCH}_3$), 3.78 (s, 3H, aromatic $-\text{OCH}_3$), 6.28 (s, 1H, C_4-H), 6.7 - 7.4 (m, 8H, aromatic); IR (neat) 1250, 830; MS, m/e 357 ($\text{M} + 1$, 100%), 323, 298.

Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{ClN}_2\text{O}_2$	C, 67.31;	H, 5.93;	N, 7.85
Found	C, 67.15;	H, 6.07;	N, 7.77.

Example 22: 5-(4-Chlorophenyl)-3-(3-hydroxybutyl)-1-(4-methoxyphenyl) pyrazole (20).

To a solution of methyl magnesium bromide (MeMgBr) (2.20 ml, 7.04 mM) in Et₂O (15 ml) at 0 °C was added a solution of the aldehyde 11 (1.60 g, 4.69 mM) in Et₂O (70 ml) dropwise over a 30 minute period. After stirring for 1 hour the reaction was quenched with a saturated, aqueous NH₄Cl solution. The reaction mixture was partitioned between EtOAc and H₂O. The EtOAc solution was dried (MgSO₄), filtered, and concentrated *in vacuo*. Chromatography (65g, Baker 40 gm silica gel) of their residue with Et₂O as eluent afforded 20 (1.33 g, 79%) as a clear light yellow oil.

NMR (CDCl₃) 1.25 (d, J = 6Hz, 3H, -CH(OH)-CH₃), 1.6 - 2.2 (m, 2H, -CH₂-CH(OH)-), 2.2 - 2.8 (m, 1H, -OH), 2.83 (t, J = 7Hz, 2H, CH₂), 3.78 (s, 3H, -OCH₃), 3.7 - 4.2 (m, 1H, -CH₂-CH(OH)-CH₃), 6.27 (s, 1H, C₄-H), 6.7 - 7.4 (m, 8H, aromatic); IR (neat) 3380; MS, m/e 356 (M⁺), 341, 312, 311, 298 (100%).

Anal. Calcd. for C ₂₀ H ₂₁ ClN ₂ O ₂	C,67.31;	H,5.93;	N,7.85
Found	C,67.38;	H,6.35;	N,7.61.

Example 23: 5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(3-oxobutyl)pyrazole (23).

To a suspension of pyridinium chlorochromate (3.65 g, 16.93 mM) in CH₂Cl₂ (20 ml) was added the alcohol 20, (3.02 g, 8.46 mM) in CH₂Cl₂ (15 ml). After stirring for 4 hours, the reaction solution was decanted from the chromium precipitates that were washed with EtOAc (2 x 150 ml). The reaction solution and the washes were combined, filtered through florisil, and concentrated *in vacuo*. Chromatography (120g, Baker 40 gm silica gel) with Et₂O:hexane (1:1 to 100% Et₂O) as eluent, followed by crystallization from Et₂O:hexane afforded 23, 2.09 g, 70%) as a white crystalline solid, mp = 85 - 86 °C.

NMR (CDCl₃) 2.20 (s, 3H, -CO-CH₃), 2.7 - 3.2 (m, 4H, -CH₂CH₂-), 3.78 (s, 3H -OCH₃), 6.25 (s, 1H, C₄-H), 6.7 - 7.4 (m, 8H, aromatic); IR (KBr) 1715; MS, m/e 355 (M⁺ + 1), 321, 311.

Anal. Calcd. for C ₂₀ H ₁₉ ClN ₂ O ₂	C,67.70;	H,5.40;	N,7.90
Found	C,67.41;	H,5.24;	N,7.90.

Example 24: 5-(4-Chlorophenyl)-3-(3-hydroxy-3-methylbutyl)-1-(4-methoxyphenyl) pyrazole (27).

To a solution of MeMgBr (1.32 ml of 3.2 M, 4.23 mM) in THF (15 ml) at 0 °C, was added a solution of the ketone 23, (1.00 g, 2.82 mM) in THF (25 ml) dropwise over a 20 minute period. After stirring for 1 hour, the reaction mixture was quenched with a saturated NH₄Cl solution, diluted to a 100 ml volume with Et₂O, washed with H₂O, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Chromatography of the residue (Baker silica gel, 45 g) with Et₂O as eluent, afforded 27, (0.68 g, 80% corrected for recovered starting material) as a colorless oil.

NMR (CDCl₃) 1.30 (s, 6H, -C(CH₃)₂OH), 1.7 - 2.2 (m, 2H, CH₂C-OH), 2.2 - 2.7 (broad s, 1H, -OH), 2.7 - 3.1 (m, 2H, CH₂), 3.78 (s, 3H, -OCH₃), 6.25 (s, 1H, C₄-H), 6.6 - 7.4 (m, 8H, aromatic); IR (neat) 3390, 1250; MS (20 eV EI), m/e 370 (M⁺), 355, 312 (100%), 311, 298.

Anal. Calcd. for C ₂₁ H ₂₃ ClN ₂ O ₂	C,68.01;	H,6.25;	N,7.55
Found	C,67.80;	H,6.30;	N,7.24.

Example 25: 5-(4-Chlorophenyl)-3-(3-oximinopropyl)-1-(4-methoxyphenyl) pyrazole (26).

To a solution of the aldehyde 11 (1.00 g, 2.93 mM) in EtOH (30 ml) was added hydroxylamine hydrochloride (0.31 g, 4.40 mM) and pyridine (0.47 g, 5.87 mM). After stirring overnight at room temperature, the reaction mixture was concentrated *in vacuo*. The remaining residue was taken up in CH₂Cl₂, washed H₂O, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Crystallization from Et₂O:hexane afforded 26, (0.67 g, 64%) as a white crystalline solid, mp = 134 - 135 °C.

NMR (CDCl₃) 2.5 - 3.3 (m, 5H, -CH₂CH₂- and =N-OH), 3.78 (s, 3H, -OCH₃), 6.30 (s, 1H, C₄-H), 6.5 -

7.4 (m, 9H, aromatic and $-\text{CH}_2-\text{CH}=\text{N}-\text{OH}$); IR (KBr) 3210; MS (20 eV EI), m/e 355 (M^+), 338 (100%), 311, 297.

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{ClN}_3\text{O}_2$	C,64.13;	H,5.10;	N,11.81
	Found C,63.79;	H,4.93;	N,11.53.

5

Example 28: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propionate (16)

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To a solution of the carboxylic acid 12 (0.40 g, 1.12 mM) in THF (10 ml) at 0°C , was added one drop of DMF and oxalyl chloride (0.12 ml, 1.35 mM). After stirring for 15 minutes the cooling bath was removed and stirring was continued for 1 hour. The reaction mixture was concentrated in vacuo (to remove the excess oxalyl chloride), taken up in THF (10 ml), and cooled to 0°C . To this solution was added the alcohol 2 (0.38 ml, 1.12 mM) and Et_3N (0.47 ml, 3.36 mM). After 15 minutes the cooling bath was removed and stirring was continued for 1 hour. The reaction mixture was diluted to 50 ml with Et_2O , washed with H_2O , dried (MgSO_4), filtered and concentrated in vacuo. Chromatography (Baker silica gel, 45 g) with Et_2O :hexane (9:1) as eluent, afforded 16 (59%) as a white semi-solid.

15

20

NMR (CDCl_3) 1.8 - 2.4 (m, 2H, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.5 - 3.3 (m, 6H, $-\text{CH}_2-\text{CH}_2\text{CH}_2\text{OCOCH}_2\text{CH}_2-$), 3.80 (s, 6H, 2- OCH_3), 4.25 (t, $J = 6.5\text{Hz}$, 2H, $-\text{CH}_2\text{CH}_2\text{OCO}-$), 6.27 + 6.33 (2s, 2H, 2 x C_4-H), 6.7 - 7.5 (m, 16H, aromatic); IR (KBr) 1730; MS (DCI), 681 ($\text{M} + 1$), 325.

25

Anal. Calcd. for $\text{C}_{38}\text{H}_{34}\text{Cl}_2\text{N}_4\text{O}_4$	C,66.96;	H,5.03;	N,8.22
	Found C,66.60;	H,4.90;	N,7.83.

Example 29: 3-[4-(4-Carbomethoxyphenyl)-3(E)-butenyl]-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole (25).

30

To a solution of hexamethyldisilazane (1.08 ml, 5.13 mM) in THF (50 ml) at $+5^\circ\text{C}$ was added n-BuLi (3.02 ml of 1.55 M, 4.68 mM). After 15 minutes

35

(4-carbomethoxyphenyl)triphenyl phosphonium chloride (2.19 g, 4.91 mM) was added, and the cooling bath was removed. After 30 minutes the aldehyde 11 (1.52 g, 4.46 mM) in THF (10 ml) was added, and the reaction mixture was stirred for an additional 0.5 hour. Concentration in vacuo of the reaction mixture and chromatography (Baker silica gel, 80 g) with Et_2O :hexane (1:1 to 100% Et_2O) as eluent afforded 25. Recrystallization from Et_2O afforded pure 25 (1.10 g, 48%) as a white crystalline solid, mp = $126 - 128^\circ\text{C}$.

40

NMR (CDCl_3) 2.5 - 3.1 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 3.80 (s, 3H, $-\text{OCH}_3$), 3.90 (s, 3H, $-\text{COOCH}_3$), 5.8 - 6.7 (m, 2H, $-\text{CH}=\text{CH}-$), 6.30 (s, 1H, C_4-H), 6.7 - 8.2 (m, 12H, aromatic); IR (KBr) 1725; MS, m/e 472 (M^+), 441, 297 (100%).

45

Anal. Calcd. for $\text{C}_{28}\text{H}_{25}\text{ClN}_2\text{O}_3$	C,71.10;	H,5.33;	N,5.92
	Found C,71.30;	H,5.22;	N,5.97.

Example 30: Methyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propionate (19).

50

To a solution of the acid 12 (0.98 g, 2.75 mM) in Et_2O (10 ml) and CH_2Cl_2 (15 ml) at 0°C , was added a CH_2N_2 solution in Et_2O (prepared from N-nitroso-N-methylurea, 40% $\text{KOH}/\text{Et}_2\text{O}$) until a persistent yellow color was observed in the reaction mixture. The reaction mixture was dried (MgSO_4), filtered and concentrated in vacuo. Crystallization from EtOAc :hexane afforded 19 (0.85 g, 83%) as a white crystalline solid, mp = $117 - 118^\circ\text{C}$.

55

NMR (CDCl_3) 2.5 - 3.4 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 3.70 (s, 3H, $-\text{COOCH}_3$), 3.80 (s, 3H, $-\text{OCH}_3$), 6.28 (s, 1H, C_4-H), 6.7 - 7.4 (m, 8H, aromatics). IR (KBr) 1730; MS, m/e 370 (M^+), 339, 311 (100%).

Anal. Calcd. for $C_{20}H_{19}ClN_2O_3$	C,64.77;	H,5.16;	N,7.56
Found	C,64.47;	H,5.15;	N,7.65.

5

Example 32: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propylamine (96).

To a suspension of $LiAlH_4$ (0.13 g, 3.5 mM) in THF (15 mL) was added a solution of the amide 31, (1.00 g, 2.81 mM) in THF (15 mL), dropwise, keeping the reaction temperature below reflux. The reaction mixture was heated to reflux, and refluxed for 17 hours, when it was quenched with 0.13 mL H_2O , 0.13 mL 20% NaOH solution and an additional 0.39 mL H_2O . The reaction mixture was filtered and concentrated in vacuo. The remaining residue was taken up into EtOAc (50 mL) and extracted with a 1.0 N HCl solution (2x25 mL). The aqueous extracts were combined and washed with EtOAc (25 mL), neutralized with a 2N NaOH solution, and extracted with EtOAc (2x50 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford the title compound (0.86 g, 90%) as a light yellow oil.

NMR ($CDCl_3$) 1.6-2.3 (m, 4H, $-CH_2CH_2CH_2NH_2$), 2.6-3.1 (m, 4H, $-CH_2CH_2CH_2NH_2$), 3.78 (s, 3H, $-OCH_3$), 6.27 (s, 1H, C_4-H), 6.6-7.5 (m, 8H, aromatic); IR (neat) 3380, 1520; MS (DCI), m/e 344 ($MH^+ + 2$), 342 (MH^+ , 100%).

20

Anal. Calcd. for $C_{19}H_{20}ClN_3O$	C,66.76;	H,5.90;	N,12.29.
Found	C,66.70;	H,5.97;	N,11.83.

25 Example 33: 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanenitrile (95).

To a suspension of compound 31, (7.75 g, 21.8 mM) in dry benzene (400 mL) was added $SOCl_2$ (4.78 mL, 65mM). The reaction mixture was heated to reflux for three days and then cooled at 0°C. Any excess $SOCl_2$ was decomposed with ice water. 50 mL of H_2O was added to the reaction mixture which was then neutralized with 50% NaOH, washed with H_2O (2x50mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Crystallization from Et_2O , Hexane afforded the title compound (6.43 g, 87%) as a light yellow crystalline solid, mp = 107-109°C.

NMR ($CDCl_3$) 2.4-3.2 (m, 4H, $-CH_2CH_2-$), 3.82 (s, 3H, OCH_3), 6.41 (s, 1H, C_4-H), 6.7-7.5 (m, 8H, aromatic); IR (KBr) 2250, 1510; MS(EI) m/e 339 ($M + 2$, 1Cl), 337 (M^+ , 100%).

35

Anal. Calcd. for $C_{19}H_{16}ClN_3O$	C,67.55;	H,4.77;	N,12.44
Found	C,67.23;	H,4.88;	N,12.21

40

Example 34

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-methyl-N-succinyloxy- propanamide.

To a solution of the hydroxamic acid 3 (5.0 g, 12.96 mM) in dry pyridine (13 mL) was added succinic anhydride (1.3 g, 12.99 mM) in pyridine (5 mL) and the resulting solution was stirred for 72 hours. The pyridine was removed in vacuo and the residue was triturated with hexane and recrystallized from Et_2O to afford pure 34 (6.21 g, 98%) as a white solid, mp = 146-147°C. MS, m/e 485 (M^+).

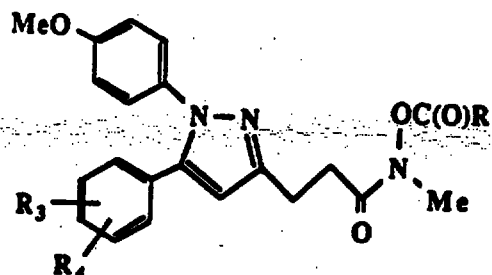
50

Anal. Calcd. for $C_{24}H_{24}ClN_3O_5$	C,59.32;	H,4.98;	N,8.65
Found	C,59.68;	H,4.97;	N,8.75.

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Employing a similar procedure, the compounds of Table 5 were synthesized.

TABLE 5



Compound Number	R ₃ , R ₄	R'	Melting Point	Mass Spectrum	
				(m/e)	C, H, N
130	4-Me	CH ₂ CH ₂ CO ₂ H	131-132°	465(M ⁺)	XXX
131	3,4-di-Me	CH ₂ CH ₂ CO ₂ H	124-125°	479(M ⁺)	XXX
132	4-Cl	CH ₂ CH ₂ CH ₂ CO ₂ H	glass	385(M-114)	XXX
133 *	4-Cl	CH ₂ CH ₂ CO ₂ Na	240°(dec)	507(M ⁺)	XXX

*Prepared as the sesquihydrate by treatment of compound prepared in Example 34 with 1N NaOH

Example 35

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N',N'-dimethylglycinyloxy-N-methylpropanamide (134)

Compound 3 (6.0 g, 15.55 mM) was added to a suspension of N,N-dimethyl-glycine (1.61 g, 15.61 mM) and N',N'-dicyclohexylcarbodiimide (3.21 g, 15.55mM) in dry pyridine (22 ml) under nitrogen and stirred for 44 hours. The solvent was removed in vacuo and the residue triturated with CH₂Cl₂, filtered, and the filtrate evaporated to dryness. Recrystallization from CH₂Cl₂/Et₂O afforded pure 35 (6.8 g, 93%) as a white solid, mp = 103-104°, MS, m/e 470 (M⁺).

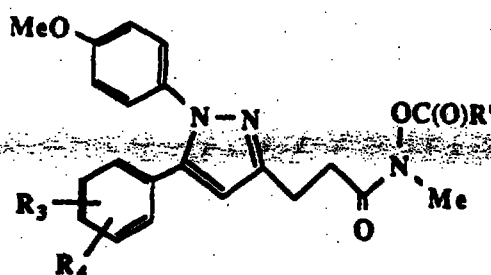
Anal. Calcd. for C ₂₄ H ₂₇ ClN ₄ O ₄	C, 61.20;	H, 5.78;	N, 11.90
Found	C, 61.26;	H, 5.94;	N, 11.79.

The oxalate salt of 35 was synthesized as the trihydrate as a white solid, mp = 114-115°.

Anal. Calcd. for C ₂₄ H ₂₇ ClN ₄ O ₄ • C ₂ H ₂ O ₄ • 3H ₂ O	C, 50.77;	H, 5.74;	N, 9.11
Found	C, 50.68;	H, 5.73;	N, 8.64

In a similar manner, the compounds of Table 6 were synthesized.

TABLE 6



Compound Number	R ₃ , R ₄	R'	Melting Point	Mass	C, H, N
				Spectrum (m/e)	
135	4-Cl	c-C ₅ H ₈ NHCO ₂ -t-Bu	155-156°	596 (M ⁺)	XXX
136	4-Cl	CH ₂ CH ₂ COMorpholine	108-109°	554 (M ⁺)	XXX
137	4-Cl	CH ₂ CH ₂ CONEt ₂	43-44°	540 (M ⁺)	XXX*
138	4-Me	CH ₂ NMe ₂	77-78°	450 (M ⁺)	XXX

*1/4 hydrate

Example 36

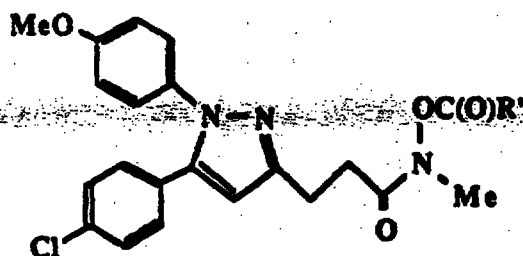
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] N-chloroacetyloxy-N-methylpropanamide (139)

To a solution of **3** (7.0 g, 18.14 mM) in anhydrous THF (125 ml) was added methylmorpholine (1.99 ml, 18.1 mM) and the resulting solution was cooled to -10° C under nitrogen. Chloroacetyl chloride (1.44 ml, 18.1 mM) was added and stirred for 10 minutes, filtered and the filtrate concentrated in vacuo. The residue was recrystallized from Et₂O to afford pure **36** (5.7 g, 68%) as a white solid, mp = 110-111°. MS, m/e 481 (M⁺).

Anal. Calcd. for C ₂₂ H ₂₁ Cl ₂ N ₃ O ₄	C, 57.15;	H, 4.58;	N, 9.09
Found	C, 57.42;	H, 4.55;	N, 8.99.

Employing a similar procedure to that of Example 36, the compounds of Table 7 were synthesized.

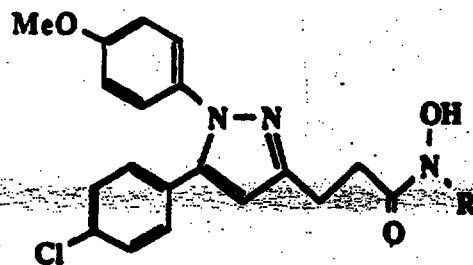
TABLE 7



Compound Number	<u>R'</u>	Melting Point	Mass Spectrum (m/e)	C,H,N
140	CH ₃	130-132°	427(M ⁺)	XXX
141	C(CH ₃) ₃	144-145°	469(M ⁺)	XXX
142	CH ₂ OMe	98-100°	457(M ⁺)	XXX*
*1/4 hydrate				

Following the procedure of Example 5, but using the appropriate hydroxylamine gave the compounds of Table 8.

TABLE 8



Compound Number	R'	Melting Point	Mass Spectrum (m/e)	C,H,N
143	CH ₂ CH ₂ Pyr	glass	695(M ⁺)	XXX*
144	CHMeCO ₂ Et	125-127°	471(M ⁺)	XXX
145	CHMeCO ₂ H	148-150°	443(M ⁺)	XXX
146	C ₈ H ₁₇	oil	483(M ⁺)	XXX

*1/2 hydrate

Example 37

3-[4-Bromo-5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propionic acid (147)

The acid 12 (3.57 g, 10 mM) and N-bromosuccinimide (1.78 g, 10 mM) were dissolved in a mixture of CCl₄ (150 ml) and CHCl₃ (20 ml) and allowed to stir for 16 hours. The solvents were evaporated in vacuo and the residue was dissolved in CHCl₃, washed with H₂O, dried (Na₂SO₄), filtered and evaporated to give an oil which was crystallized from Et₂O to afford pure 37 (2.18 g, 50%) as a white solid, mp = 147.5-148°. MS, m/e 435 (MH⁺).

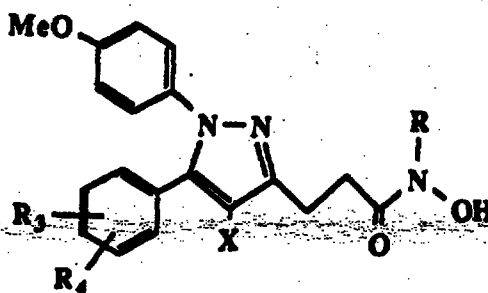
Anal. Calcd. for C ₁₉ H ₁₆ BrClN ₂ O ₃	C,52.37;	H,3.70;	N,6.43
Found	C,52.58;	H,3.69;	N,6.27.

Substitution of N-chlorosuccinimide for N-bromosuccinimide gave the corresponding 4-chloro derivative as a white solid, mp = 123.5-124.5°. MS, m/e 391(MH⁺) (Compound Number 182)

Anal. Calcd. for C ₁₉ H ₁₆ Cl ₂ N ₂ O ₃ · 1/4H ₂ O	C,57.66;	H,4.20;	N,7.08
Found	C,57.78;	H,4.12;	N,6.96.

Using the acids synthesized in Example 37 and following the procedure described in Example 5 gave the compounds of Table 9.

TABLE 9



Compound Number	X	R3, R4	R	Melting Point	Mass Spectrum	C, H, N
					(m/e)	
148	Br	4-Cl	Me	foam	463(M ⁺)	XXX
149	Cl	4-Cl	Me	foam	419(M ⁺)	XXX*
150	Br	4-Cl	H	150-151°	449(M ⁺)	XXX

*hydrate

Substituting Compound 2 for the acid 12 in Example 37 afforded 4-bromo-5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole, as an off-white solid, 87%, mp = 118.5-120°. MS, m/e 420 (M⁺) (Compound Number 183).

Anal. Calcd. for C ₁₉ H ₁₈ BrClN ₂ O ₂	C, 54.11;	H, 4.30;	N, 6.64
Found	C, 54.20;	H, 4.35;	N, 6.59

Following a similar procedure, but employing N-chlorosuccinimide gave 4-chloro-5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole as a tan solid; mp = 113-115°. MS, m/e 376 (M⁺) (Compound Number 184).

Anal. Calcd. for C ₁₉ H ₁₈ Cl ₂ N ₂ O ₂	C, 60.49;	H, 4.81;	N, 7.43
Found	C, 60.30;	H, 4.82;	N, 7.36

Example 38

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]hydroxyl-amine (151)

To a solution of the oxime 26 (2.70 g, 7.59 mM) in MeOH (50 ml), containing methyl orange (2 mg) as as indicator, was added a solution of NaBH₃CN (0.52 g, 8.4 mM) in MeOH (20 ml), and a solution of 2N HCl, simultaneously, at such a rate to maintain a pH of 3 to 4. The reaction was stirred for 3 hours at room temperature, acidified to pH 1 and concentrated in vacuo. The residue was diluted with H₂O (100 ml), adjusted to pH 8.5 with 5N NaOH, and extracted with EtOAc. The extracts were combined, dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was chromatographed on Merck Silica Gel 60 (90 g, 230-400 mesh) with EtOAc:MeOH (9:1) as eluent. Crystallization from Et₂O afforded pure 38 (1.64 g, 60%) as a white solid, mp = 91-93°. MS, m/e 357 (M⁺).

Anal. Calcd. for $C_{19}H_{20}ClN_3O_2$	C,63.77;	H,5.63;	N,11.74
Found	C,63.63;	H,5.74;	N,11.63.

5

Example 39

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]-N-hydroxy-acetamide (152)

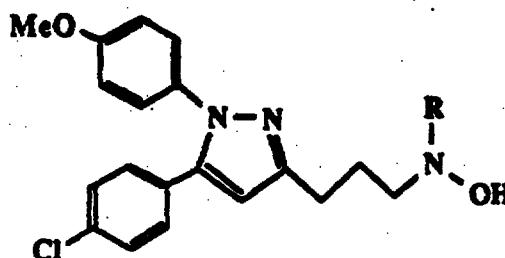
To a solution of hydroxylamine 38 (1.25 g, 3.49 mM) and Et₃N (0.97 ml, 6.9mM) in THF (35 ml) was added acetyl chloride (0.25 ml, 3.5 mM) and the reaction mixture stirred for 1 hour, diluted with EtOAc (165 ml), washed with H₂O, dried (Na₂SO₄), filtered and concentrated in vacuo to give a residue which was recrystallized from EtOAc:Et₂O to afford pure 39 (1.06 g, 76%) as a white crystalline solid, mp = 121-123°. MS, m/e 399 (M⁺).

15

Anal. Calcd. for $C_{21}H_{22}ClN_3O_3$	C,63.07;	H,5.55;	N,10.51
Found	C,62.83;	H,5.95;	N,10.43.

Following a similar procedure to that of Example 39 and employing the appropriate acyl chloride afforded the compounds of Table 10.

TABLE 10



35

Compound Number	R	Melting Point	Mass Spectrum (m/e)	C,H,N
153	CO-t-Bu	138-140°	441(M ⁺)	XXX
154	COC ₇ H ₁₅	90-91°	483(M ⁺)	XXX
155	COPh	foam	461(M ⁺)	XXX
156	SO ₂ CH ₃	173-175°	435(M ⁺)	XXX

50 Example 40

Ethyl N-[3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]-hydroxyoxamate (157)

Following a similar procedure to that of Example 39, but employing ethyl oxalyl chloride in place of acetyl chloride afforded 40 as a white foam; MS, m/e 457 (M⁺).

55

Anal. Calcd. for $C_{23}H_{24}ClN_3O_3$	C, 60.33;	H, 5.28;	N, 9.18
Found	C, 60.55;	H, 5.67;	N, 9.18.

5

Example 41

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]-N,N'-dihydroxyoxamide (158)

To a solution of hydroxylamine.HCl (0.25 g, 3.5 mM) and the ester 7C (0.81 g, 1.8 mM) in EtOH (17 ml) was added in 1N NaOEt solution (7.1 ml, 7.1 mM). After stirring for 2.5 hours the reaction mixture was acidified and concentrated in vacuo. The residue was diluted with $CHCl_3$, washed (H_2O), dried (Na_2SO_4), filtered and concentrated in vacuo. Crystallization from EtOAc:Et₂O afforded pure 41 as a white crystalline solid, mp = 145-146.5°. MS, m/e 444 (M^+).

15

Anal. Calcd. for $C_{21}H_{21}ClN_4O_5 \cdot 0.25 H_2O$	C, 56.13;	H, 4.82;	N, 12.47
Found	C, 56.16;	H, 4.76;	N, 12.32.

20 Example 42

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-ethyl amine (159)

To a solution of the acid 12 (1.0 g, 2.8 mM) in benzene (25 ml) was added Et₃N (0.39 ml, 2.8 mM) and diphenylphosphoryl azide (0.60 ml, 2.8 mM). After stirring overnight at room temperature, the reaction mixture was heated to 70°C for 1.5 hours, cooled and concentrated in vacuo. Dioxane (2 ml), followed by a solution of concentrated HCl (0.3 ml) in dioxane (2 ml) was added, and the reaction mixture was heated to reflux for 2 hours, cooled and diluted to 50 ml with EtOAc. The organic solution was washed with 0.25N NaOH solution, and extracted with 1N HCl. The extracts were combined, basified with 5N NaOH, and extracted with EtOAc, dried, filtered and concentrated in vacuo. Crystallization from Et₂O afforded pure 42 - (0.62 g, 68%) as a light yellow crystalline solid, mp = 95-97°. MS, m/e 327 (M^+).

30

Anal. Calcd. for $C_{18}H_{18}ClN_3O$	C, 65.95;	H, 5.53;	N, 12.82
Found	C, 66.14;	H, 5.57;	N, 13.10.

35

Example 43

Ethyl 2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-ethylamine-N-oxoacetate (160)

To a solution of the amine 42 (3.24 g, 9.8 mM) and Et₃N (1.56 ml, 10.9 mM) in THF (100 ml) was added ethyloxalyl chloride (1.1 ml, 9.8 mM). After stirring overnight the reaction mixture was diluted to 400 ml with EtOAc, washed with H_2O , dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed on Merck Silica Gel 60 (110 g, 230-400 mesh) with EtOAc:Hexane (3:1) as eluent. Crystallization from EtOAc:Hexane afforded pure 43 (3.6 g, 85%) as a white crystalline solid, mp = 93-94°. MS, m/e 427 (M^+).

45

Anal Calcd. for $C_{22}H_{22}ClN_3O_4$	C, 61.75;	H, 5.18;	N, 9.82
Found	C, 61.56;	H, 5.29;	N, 9.78

50

Example 44

Ethyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propylamine-N-oxoacetate (161)

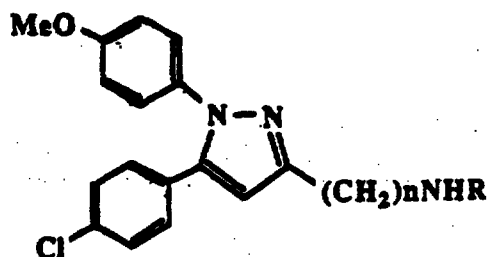
Following the procedure of Example 43, but substituting the amine 96 of Example 32 for the amine 42 afforded 44 as a yellow oil; MS, m/e 441 (M^+).

55

Anal. Calcd. for $C_{23}H_{24}ClN_3O_4$	C, 62.51;	H, 5.49;	N, 9.51
Found	C, 62.41;	H, 5.66;	N, 9.35.

The compounds of Table 11 were synthesized from compounds 43 or 44 by standard methods.

TABLE 11



Compound Number	n	R	Melting Point	Mass Spectrum (m/e)	C, H, N
162	3	COCON(Me)OH	111-113°	442(M ⁺)	XXX
163	2	COCON(Me)OH	110-111°	428(M ⁺)	XXX
164	3	COCONHOH	183-185°	428(M ⁺)	XXX
165	2	COCONHOH	188-189°	414(M ⁺)	XXX
166	3	COCO ₂ H	157-159°	413(M ⁺)	XXX

Example 45

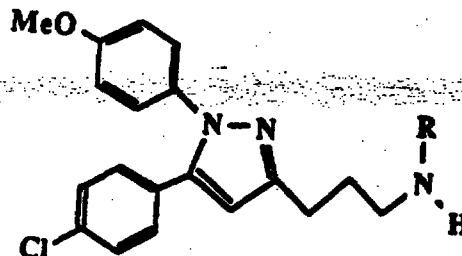
N-Acetyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl-amine (167)

To a solution of the amine 96 (0.96 g, 2.8 mM) and Et₃N (0.59 ml, 4.2 mM) in THF (25 ml) was added acetyl chloride (0.2 ml, 2.8 mM). After stirring for 1 hour the reaction mixture was diluted to 200 ml with EtOAc, washed with H₂O, dried, filtered and concentrated in vacuo. Crystallization from EtOAc:Et₂O afforded pure 45 (0.78 g, 72%) as an off-white crystalline solid, mp. = 129-131°. MS, m/e 383 (M⁺).

Anal. Calcd. for $C_{21}H_{22}ClN_3O_2$	C, 65.70;	H, 5.78;	N, 10.95
Found	C, 65.85;	H, 6.00;	N, 10.88.

Following the procedure of Example 45, but substituting trimethylacetyl chloride, methanesulfonyl chloride and diethyl chlorophosphate respectively for acetyl chloride gave the compounds of Table 12.

TABLE 12



Compound Number	R	Melting Point	Mass Spectrum (m/e)	C,H,N
168	CO-t-Bu	104-105°	425(M ⁺)	XXX
169	SO ₂ Me	108-110°	419(M ⁺)	XXX
170	PO(OEt) ₂	oil	477(M ⁺)	XXX*
*1/4 hydrate				

Example 46

N-Acetyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-propanamide (171)

A white slurry of compound 29 of Example 12 (5.0 g, 13.45mM) in CH₂Cl₂ (200 ml) and Et₃N (1.88 ml, 13.48 mM) was cooled to -10°C under nitrogen, and treated with acetyl chloride (0.91 ml, 12.8 mM). The mixture was allowed to stir at -10°C for 45 minutes, filtered and the filtrate concentrated in vacuo to give crude product which was purified via flash column chromatography (EtOAc) and recrystallized from Et₂O to afford 46 as a white solid, mp = 110-111°. MS, m/e 413 (M⁺).

Anal. Calcd. for C ₂₁ H ₂₀ ClN ₃ O ₄	C,60.94;	H,4.87;	N,10.15
Found	C,61.19;	H,5.15;	N, 9.77.

Example 47

N-Acetyl-N-acetoxy-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propanamide (172)

Following the procedure of Example 46, but employing 2 equivalents of acetyl chloride afforded 47 as a white solid, mp = 111-112°. MS, m/e 455 (M⁺).

Anal. Calcd. for C ₂₃ H ₂₂ ClN ₃ O ₅	C,60.59;	H,4.86;	N,9.22
Found	C,60.52;	H,5.12;	N,9.06.

Example 48

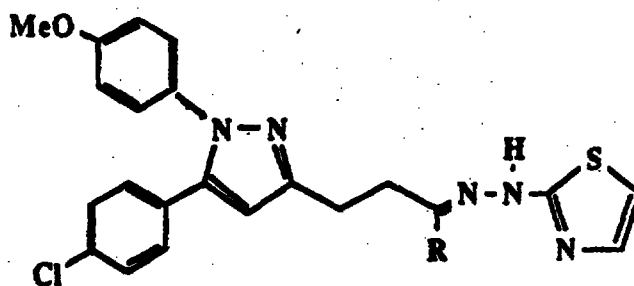
5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(3-oxobutyl)-pyrazole thiazol-2-yl hydrazone (173)

A solution of compound 23 (2.15 g, 6.06 mM) in EtOH (6.2 ml) and glacialacetic acid (0.2 ml) was warmed to 35° and 2-thiazolylhydrazine (0.698 g, 6.06 mM) was added. Stirring was continued for 80 minutes and the resulting brown solution was cooled to room temperature for 1 hour, then allowed to stand at -15°, filtered, and recrystallized from EtOH to afford 48 as a tan solid (1.22 g, 45%), mp = 128-129°. MS, m/e 451 (M⁺).

Anal. Calcd. for C ₂₃ H ₂₂ ClN ₅ S	C,61.12;	H,4.91;	N,15.50
Found	C,60.89;	H,4.81;	N,15.12.

Following the procedure of Example 48, but substituting the appropriate ketone from Table 15 or aldehyde 11 for compound 23 afforded the compounds of Table 13.

TABLE 13



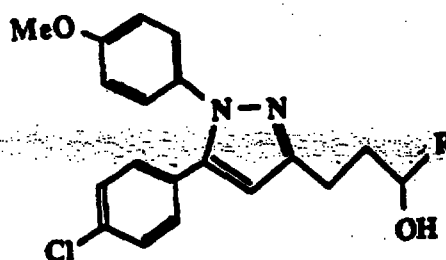
Compound Number	R	Melting Point	Mass Spectrum (m/e)	C, H, N
174	H	169-170°	437(M ⁺)	XXX
175	CH ₂ CH ₃	149-152°	465(M ⁺)	XXX*
176	Phenyl	104-105°	513(M ⁺)	XXX**

*1/4 hydrate

**1/2 hydrate

Following the procedure of Example 22, but substituting ethyl magnesium bromide, phenyl magnesium bromide and t-butyl magnesium chloride for methyl magnesium bromide gave the compounds of Table 14.

TABLE 14

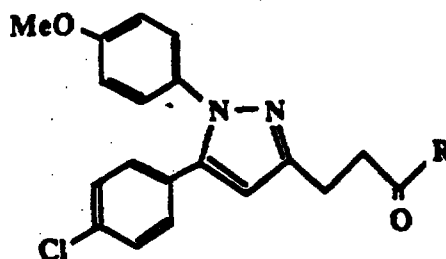


Compound Number	R	Melting Point	Mass Spectrum (m/e)	C,H,N
177	Et	84-85°	370(M ⁺)	XXX
178	Ph	107-108°	418(M ⁺)	XXX*
179	t-Bu	127-129°	398(M ⁺)	XXX*

*1/4 hydrate

Following the procedure of Example 23, but substituting the appropriate alcohol from Table 14 for compound 20 afforded the compounds of Table 15.

TABLE 15



Compound Number	R	Melting Point	Mass Spectrum (m/e)	C,H,N
180	Et	89-90°	368(M ⁺)	XXX
181	Ph	138-139°	416(M ⁺)	XXX

Example 49

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-ethyl carboxamidoxime (184)

To a suspension of nitrile 95 (1.0 g, 2.96 mM) in MeOH (6 ml) was added NaHCO₃ (0.50 g, 5.9 mM) and a solution of hydroxylamine.HCl (0.40 g, 5.9mM) in H₂O (5 ml). The reaction was heated to reflux for 16 hours, concentrated in vacuo and the residue partitioned between H₂O and CHCl₃. The CHCl₃ layer was dried (Na₂SO₄), filtered and concentrated in vacuo to a white foam. Crystallization from EtOAc afforded pure 49 (0.65 g, 59%) as a white crystalline solid, mp = 132-134°. MS, m/e 370 (M⁺).

10

Anal. Calcd. for C ₁₉ H ₁₉ ClN ₄ O ₂ • 0.25 H ₂ O	C,60.80;	H,5.24;	N,14.93
Found	C,60.73;	H,5.18;	N,14.74.

15 Example 50

N-Hydroxy-N-methyl-2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] ethylcarboximidamide Monohydrate (185)

Following the procedure of Example of 48, but substituting N-methylhydroxylamine.HCl for hydroxylamine.HCl afforded 50 as a white solid, mp = 106-110°. MS, m/e 384 (M⁺).

20

Anal. Calcd. for C ₂₀ H ₂₁ N ₄ O ₂ • H ₂ O	C,59.62;	H,5.75;	N,13.91
Found	C,59.62;	H,5.65;	N,13.61.

25

Following the procedure of Example 18, but substituting octylamine for diethylamine gave the following compound.

30

Compound Number	NR ₆ R ₇	Melting Point	Mass Spectrum	C,H,N
			(m/e)	
186	NHC ₈ H ₁₇	95-96°	467(M ⁺)	XXX

35

40 Example 51

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]-N-hydroxy-N-methylpropanamide (187)

5-Methyl-6-(4-methylphenyl)-4,6-dioxohexanoic acid

45 Following the procedure employed for the synthesis of the 4,6-dioxohexanoic acids of Table 2"-AP, but substituting 4'-methylpropiophenone for the appropriately substituted acetophenone gave the title compound 5-methyl-6-(4-methylphenyl)-4,6-dioxohexanoic acid.

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]propionic acid

50

Following the procedure employed for the synthesis of the pyrazole propionic acids of Table 2", but substituting compound 5-methyl-6-(4-methylphenyl)-4,6-dioxohexanoic acid for the appropriate 6-aryl-4,6-diketohexanoic acid gave 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]propionic acid.

55 3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]-N-hydroxy-N-methylpropanamide

Following the procedure of Example 5, but substituting the propionic acid compound obtained above for the acid 12 gave 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]-N-hydroxy-N-methyl-

propanamide the title compound.

IN VIVO ALLEVIATION OF INFLAMMATION

- 5 Polyarthritis was induced in Lewis strain laboratory rats (weight = about 200 grams) by injection of a suspension of *Mycobacterium butyricum* in mineral oil into the subplantar tissue of the mammal's hind paws. On day 10 after the injection, the rats were assigned to groups, and paw volumes and body weights were recorded. Paw volumes of the contralateral, uninjected hind paw were determined by mercury plethysmography. Per oral (p.o.) dosing began and continued for five consecutive days thereafter. On day 10 14 after the initial injection, approximately four hours after the final dose was administered, paw volumes and body weights were recorded and quantitated.

Anti-inflammatory activity of the substituted pyrazole compounds is expressed as the percent inhibition of paw volume increase. The results of this study for several compounds of the structure shown below are shown in Table 16, hereinafter.

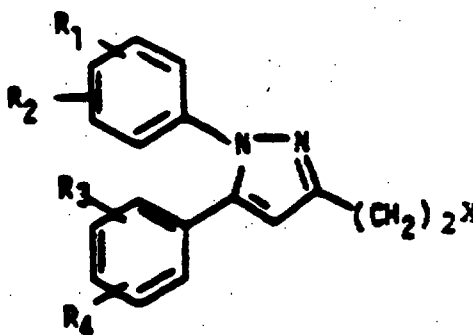


Table 16

In Vivo Alleviation of Inflammation
in Rats¹

	No.	R ₁ , R ₂ ²	R ₃ , R ₄ ³	X	%INH. p.o.* (mpk)
10	1	H	4-Cl	-CH ₂ OH	62% at 50
15	2	4-OMe	4-Cl	-CH ₂ OH	[ED ₅₀ =3.6]
	3	4-OMe	4-Cl	-CON(CH ₃)OH	[ED ₅₀ =4.1]
	4	4-Cl	4-Cl	-CH ₂ OH	68% at 50
	7	H	4-Cl	-CH ₂ OAc	54% at 50
20	8	3,4-diCl	4-Cl	-CH ₂ OH	41% at 50
	10	4-OMe	H	-CH ₂ OH	30% at 50
	11	4-OMe	4-Cl	-CHO	[ED ₅₀ =2.6]
25	12	4-OMe	4-Cl	-CO ₂ H	[ED ₅₀ =5.2]
	13	4-OMe	4-Cl	-CO ₂ Na	[ED ₅₀ =1.8]
	16	4-OMe	4-Cl	-CO ₂ (CH ₂) ₃ pyrazole	82% at 25
	17	H	4-Cl	-CO ₂ H	50% at 25
30	19	4-OMe	4-Cl	-CO ₂ Me	69% at 40
	20	4-OMe	4-Cl	-CH(OH)Me	19% at 40
	21	4-Cl	4-H	-CH ₂ OH	52% at 50
35	22	2-OMe	4-Cl	-CH ₂ OH	33% at 50
	23	4-OMe	4-Cl	-COCH ₃	53% at 40
	24	4-OMe	4-Cl	-CH ₂ OMe	64% at 25
	25	4-OMe	4-Cl	-CH=CH-  -CO ₂ Me	18% at 25
40	26	4-OMe	4-Cl	-CH=NOH	79% at 25
	28	4-OMe	4-Cl	-CONEt ₂	44% at 25
	29	4-OMe	4-Cl	-CONHOH	91% at 25
45	30	4-OMe	4-F	-CH ₂ OH	42% at 25
	31	4-OMe	4-Cl	-CONH ₂	75% at 25
	32	4-OMe	4-Cl	-CH=CH-(CH ₂) ₃ - CO ₂ Na	69% at 25
50	34	4-OMe	4-Cl	-CONH-  -OH	21% at 25

	35	4-Br	4-Cl	-CH ₂ OH	65% at 25
	36	4-SO ₂ Me	4-Cl	-CH ₂ OH	40% at 50
	37	4-CH ₃	4-Cl	-CH ₂ OH	41% at 25
5	38	4-OMe	4-Cl	-CH=CH-(CH ₂) ₃ -CONH ₂	40% at 40
	3a	4-OMe	4-Cl	-CON(CH ₃)ONa	65% at 10
	44	4-OMe	4-Cl	-CON(CH ₃)OMe	69% at 25
10	45	4-OMe	4-F	-CON(CH ₃)OH	51% at 25
	62	4-F	4-Cl	-CH ₂ OH	31% at 50
	47	4-SMe	4-Cl	-CH ₂ OH	48% at 25
	48	4-NO ₂	4-Cl	-CH ₂ OH	40% at 40
15	51	4-OC ₅ H ₁₁	4-Cl	-CH ₂ OH	6.4% at 30
	53	4-OMe	4-Cl	-CO ₂ NHMe	94% at 40
	54	4-OMe	4-Ph	-CH ₂ OH	36% at 25
20	55	4-OMe	4-Me	-CH ₂ OH	[ED ₅₀ =3.9]
	56	4-OMe	4-CF ₃	CH ₂ OH	[ED ₅₀ =3.0]
	57	4-OMe	4-Cl	CO ₂ NH(tBu)	87% at 25
	58	4-OMe	4-Cl	CON(tBu)OH	47% at 25
25	59	4-OMe	4-Cl	CH ₂ OCOCH ₂ COCH ₃	48% at 20
	60	2-CF ₃	4-Cl	CH ₂ OH	8% at 25
	65	4-OMe	4-Cl	CONHCH ₂ CH ₂ OH	21% at 15
30	66	4-OMe	4-Cl	CONHCH ₂ CO ₂ H	62% at 25
	67	4-H	4-Cl	CON(CH ₃)OH	30% at 40
	69	4-NH ₂	4-Cl	CH ₂ OH	17% at 15
	72	4-OEt	4-Cl	CO ₂ H	71% at 15
35	74	3,4-diOMe	4-Cl	CO ₂ H	17% at 40
	75	4-OEt	4-Cl	CO ₂ Et	73% at 40
	76	4-OEt	4-Cl	CON(CH ₃)OH	43% at 15
40	79	4-OMe	4-CF ₃	CON(CH ₃)OH	[ED ₅₀ =3.2]
	81	4-OMe	4-Cl	CON(OH)iPr	50% at 15
	82	4-OMe	4-Cl	CON(OH)cyclohexyl	54% at 15
	83	4-OMe	4-Cl	CON(OH)Et	42% at 15
45	84	4-OMe	4-Cl	CON(OH)Ph	27% at 40

50

55

	85	4-OMe	4-Cl	CONH-dihydrothiazoyl	40% at 40
	87	4-OMe	4-Cl	COHNCH ₂ CO ₂ Et	22% at 15
5	88	4-OMe	4-Cl	CONHCH ₂ CONHOH	36% at 15
	89	4-OMe	4-Cl	COHNCH ₂ CON(CH ₃)OH	57% at 15
	90	4-OMe	4-Cl	CONHtetrazole	32% at 15
	91	4-OMe	4-Cl	CON(OBz)COCH ₃	24% at 30
10	93	4-OMe	4-Cl	CH ₂ OCH ₂ CO ₂ H	17% at 15
	96	4-OMe	4-Cl	CH ₂ NH ₂	56% at 30
	100	4-OMe	4-Cl	CONHCH(CO ₂ Et)CH ₂ SH	58% at 15
15	101	4-OMe	4-Cl	CONHCH(CO ₂ Et)CH ₂ SMe	57% at 15
	102	4-OMe	4-Cl	CO ₂ NEt ₂	87% at 30
	103	2-OMe	4-Cl	CO ₂ H	55% at 10
	105	4-OMe	4-Me	CO ₂ H	87% at 10
20	106	4-OMe	3-Me	CO ₂ H	11% at 10
	107	4-OMe	3,4-di-Me	CO ₂ H	30% at 10
	109	4-OMe	2-Me	CO ₂ H	1% at 10
25	110	4-OMe	4-Et	CO ₂ H	51% at 10
	104	2-OMe	4-Cl	CON(CH ₃)OH	39% at 15
	111	4-OMe	4-Me	CON(CH ₃)OH	75% at 15
	112	4-Cl	4-OMe	CON(CH ₃)OH	[ED ₅₀ =16.3]
30	113	4-OMe	4-OMe	CON(CH ₃)OH	34% at 10
	114	4-OMe	4-H	CON(CH ₃)OH	5% at 15
	115	4-OMe	3-Me	CON(CH ₃)OH	35% at 10
35	118	4-OMe	2-Me	CON(CH ₃)OH	6% at 10
	119	4-OMe	4-Et	CON(CH ₃)OH	24% at 10
	133	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ CH ₂ CO ₂ H	[ED ₅₀ =4.7]
	130	4-OMe	4-Me	CON(CH ₃)OCOCH ₂ CH ₂ CO ₂ H	[ED ₅₀ =11.5]
40	132	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ CH ₂ CH ₂ CO ₂ H	30% at 10
	133	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ CH ₂ CO ₂ Na	75% at 10
	134	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ NMe ₂	[ED ₅₀ =12.5]

	135	4-OMe	4-Cl	CON(CH ₃)OCO-c-5H ₉ NHCO ₂ -t-Bu	1% at 10
	136	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ CH ₂ CO-Morpholine	38% at 10
5	137	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ CH ₂ CONEt ₂	54% at 10
	138	4-OMe	4-Me	CON(CH ₃)OCOCH ₂ NMe ₂	17% at 10
	139	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ Cl	[ED ₅₀ =6.0]
	140	4-OMe	4-Cl	CON(CH ₃)OCOCH ₃	77% at 15
10	141	4-OMe	4-Cl	CON(CH ₃)OCOC(CH ₃) ₃	17% at 10
	142	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ OMe	67% at 10
	143	4-OMe	4-Cl	CON(OH)Pyr	62% at 15
15	144	4-OMe	4-Cl	CON(OH)CHMeCO ₂ Et	55% at 10
	145	4-OMe	4-Cl	CON(OH)CHMeCO ₂ H	61% at 10
	146	4-OMe	4-Cl	CON(OH)C ₈ H ₁₇	29% at 10
	151	4-OMe	4-Cl	CH ₂ NHOH	42% at 25
20	152	4-OMe	4-Cl	CH ₂ N(OH)COCH ₃	40% at 10
	153	4-OMe	4-Cl	CH ₂ N(OH)CO-t-Bu	49% at 10
	154	4-OMe	4-Cl	CH ₂ N(OH)COC ₇ H ₁₅	11% at 10
25	155	4-OMe	4-Cl	CH ₂ N(OH)COPh	45% at 10
	156	4-OMe	4-Cl	CH ₂ N(OH)SO ₂ CH ₃	34% at 9
	157	4-OMe	4-Cl	CH ₂ N(OH)COCO ₂ Et	51% at 10
	158	4-OMe	4-Cl	CH ₂ N(OH)COCONHOH	[ED ₅₀ =33.4]
30	160	4-OMe	4-Cl	NHCOCO ₂ Et	9% at 15
	163	4-OMe	4-Cl	NHCOCON(Me)OH	28% at 15
	164	4-OMe	4-Cl	CH ₂ NHCOCONHOH	13% at 15
35	165	4-OMe	4-Cl	NHCOCONHOH	41% at 15
	171	4-OMe	4-Cl	CON(OH)COCH ₃	62% at 10
	172	4-OMe	4-Cl	CON(OAc)COCH ₃	83% at 15
40	173	4-OMe	4-Cl	C(Me)=NNH-2-Thiazoline	39% at 15

5	174	4-OMe	4-Cl	CH=NNH-2-Thiazoline	37% at 15
	175	4-OMe	4-Cl	C(Et)=NNH-2-Thiazoline	16% at 10
	176	4-OMe	4-Cl	C(Ph)=NNH-2-Thiazoline	6% at 15
	177	4-OMe	4-Cl	CH(OH)Et	16% at 15
	178	4-OMe	4-Cl	CH(OH)Ph	8% at 15
10	179	4-OMe	4-Cl	CH(OH)-t-Bu	36% at 10
	180	4-OMe	4-Cl	COEt	32% at 15
	181	4-OMe	4-Cl	COPh	30% at 15
	185	4-OMe	4-Cl	C(=NH)N(OH)Me	5% at 15
15	186	4-OMe	4-Cl	CONHC ₈ H ₁₇	37% at 10

20 *%INH.p.o. = Percentage inhibition of pad
 swelling from per oral dosages in the amount of
 substituted pyrazole compound shown, where "mpk" is
 25 milligrams per kilogram of rat bodyweight and "ED₅₀" is
 the effective dose to obtain a 50% inhibition of
 inflammation.

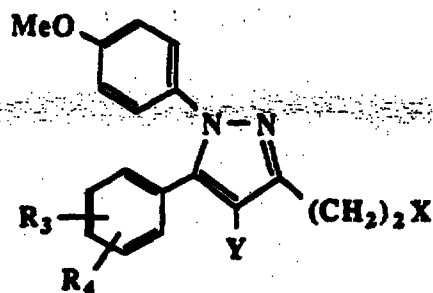
30 ¹Abbreviations for substituents are as utilized
 in previous Tables and reaction Schemes. Additionally tBu
 is tert-butyl and Ph is phenyl.

35 ²R₂ = hydrogen unless otherwise shown.

³R₄ = hydrogen unless otherwise shown.

In addition, the results for compounds of the structure shown below are shown in Table 17.

TABLE 17



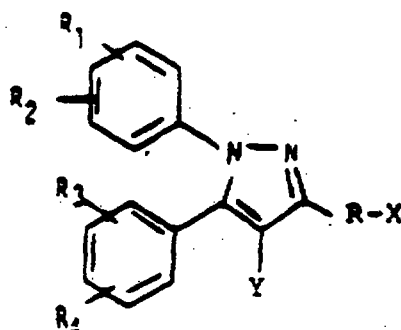
20	<u>No.</u>	<u>R3, R4</u>	<u>Y</u>	<u>X</u>	% INH. p.o.* (mpk)
	147	4-Cl	Br	CO ₂ H	79% at 15
25	182	4-Cl	Cl	CO ₂ H	71% at 15
	148	4-Cl	Br	CON(CH ₃)OH	15% at 40
	149	4-Cl	Cl	CON(CH ₃)OH	68% at 15
30	150	4-Cl	Br	CONHOH	70% at 15

The present invention has been described with respect to preferred embodiments. It will be clear to those skilled in the art that modifications and/or variations of the disclosed subject matter can be made without departing from the scope of the invention set forth herein.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound having a structure that corresponds to the formula I:



I

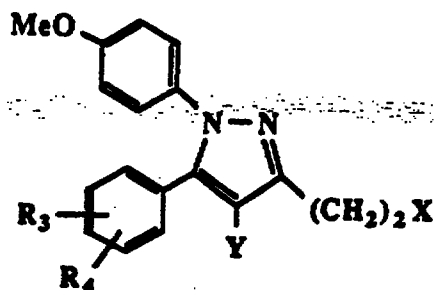
wherein

R₁, R₂, R₃ and R₄ are the same or different and are individually selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, phenyl, halo, hydroxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid or



In addition, the results for compounds of the structure shown below are shown in Table 17.

TABLE 17



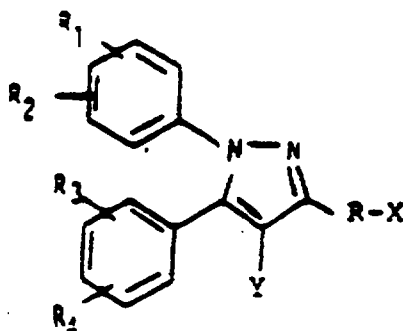
No.	R ₃ , R ₄	Y	X	% INH. p.o.* (mpk)
147	4-Cl	Br	CO ₂ H	79% at 15
182	4-Cl	Cl	CO ₂ H	71% at 15
148	4-Cl	Br	CON(CH ₃)OH	15% at 40
149	4-Cl	Cl	CON(CH ₃)OH	68% at 15
150	4-Cl	Br	CONHOH	70% at 15

The present invention has been described with respect to preferred embodiments. It will be clear to those skilled in the art that modifications and/or variations of the disclosed subject matter can be made without departing from the scope of the invention set forth herein.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound having a structure that corresponds to the formula I:



wherein

R₁, R₂, R₃ and R₄ are the same or different and are individually selected from the group consisting of hydrogen, C₁-₈ alkyl, C₁-₈ alkoxy, phenyl, halo, hydroxy, C₁-₈ alkylsulfonyl, C₁-₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁-₈ alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid or



where $R_1 R_2$ or $R_3 R_4$, taken together with the phenyl group to which they are attached, form a naphthyl;
 R is a straight chained, saturated or unsaturated hydrocarbon that contains 2-16 carbon atoms;

Y is hydrogen, bromo, chloro or C_{1-4} alkyl;

and X is selected from the group consisting of carboxy, hydroxy, acetoxo, alkanoyloxy, C_{1-8} alkoxy, C_{1-8} alkyl carbonyl, oximino, cyano, amino, $C(O)-R_5$, $-C(O)C(O)-R_5$, $-NR_6 OH$, $-NHR_{13}$, $-C(R_{14})-$
 5 $= NNH-2$ thiazolino, $-CH(OH)R_{14}$, $-C(=NH)N(OH)-C_{1-8}$ alkyl;

wherein R_5 is selected from the group consisting of hydrogen, alkyl, C_{1-8} alkoxy, $NR_6 R_7$ and $-O-NR_{15} R_{16}$;

wherein R_6 and R_7 are the same or different and are selected from the group consisting of
 10 hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, acyloxy, benzyloxy, 2-hydroxy C_{1-8} alkyl, C_{1-8} alkyl carboxy, phenyl, pyridyl, thiazolyl, dihydrothiazolyl, 5-tetrazolyl, ω -alkanoate, $-OCO(CH_2)_n-COR_9$ and $-OCOR_{10}$;

wherein R_8 is hydrogen, $-CO-C_{1-8}$ alkyl, $-CO-t$ -butyl, $-COC_7H_{15}$, CO -phenyl, SO_2-C_{1-8} alkyl, $-COCO_2-C_{1-8}$ alkyl, or $-COCONHOH$;

wherein R_9 is $-OH$, $-ONa$, dialkylamino and n is 2 or 3;

wherein R_{10} is $-CH_2NR_{11}R_{12}$, $-CH_2Cl$, $-CH_2O-C_{1-8}$ alkyl, t -butyl, or

$-CH-C_{1-8}$ alkyl- $CO_2 Q$, wherein Q is C_{1-8} alkyl or H ;

wherein R_{11} and R_{12} are the same or different and are any of alkyl, cyclohexyl, or together form N -methylpiperazino;

wherein R_{13} is hydrogen, $-CO-C_{1-8}$ alkyl, $-CO-t$ -butyl, $-COC_7H_{15}$, $-CO$ -phenyl, $-SO_2-C_{1-8}$ alkyl, $-COCO_2-C_{1-8}$ alkyl, $-COCONHOH$, $-COCO_2H$, $COCON(C_{1-8}$ alkyl) OH or $PO(O-C_{1-8}$ alkyl) $_2$;

wherein R_{14} is hydrogen, C_{1-8} alkyl, phenyl or t -butyl;

wherein R_{15} and R_{16} are the same or different and are selected from the group consisting of
 25 hydrogen, C_{1-8} alkyl and phenyl;

with the provisos that:

(a) when Y is bromo or chloro, X is $-COOH$, $-CH_2OH$ or $-C(O)-R_5$ wherein R_5 is $NR_6 R_7$ and R_6 is OH and R_7 is C_{1-8} alkyl;

(b) at least one of R_1 and R_2 is other than hydrogen where (i) $R-X$ is $(CH_2)_2CO_2H$ or $(CH_2)_2C(O)-NHOH$, and (ii) R_3 and R_4 are 4-methoxy, 3-methoxy-4-hydroxy, 2-hydroxy or hydrogen and

(c) at least one of R_1 and R_2 or of R_3 and R_4 is other than hydrogen where $R-X$ together contains
 30 three saturated carbon atoms linked together by carbon-carbon bonds;

or the compound

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]- N -cyclohexyl- N -hydroxypropanamide,

Ethyl 3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamide- N -acetate,

35 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]- N -(N -hydroxyacetamido)propanamide 1/4 Hydrate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] N -(N -hydroxy- N -methylacetamido) propanamide,

Ethyl N -[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinate hemi-
 40 hydrate,

Ethyl N -[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]- S -methyl-(R)-cysteinate, or

3-(3-Acetoacetoxypropyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole;

and pharmaceutically acceptable salts thereof.

45

2. The compound according to claim 1 wherein R_2 and R_4 are hydrogen, and R_1 and R_3 are selected from the group consisting of halo, trifluoromethyl, C_{1-8} alkyl and C_{1-8} alkoxy.

3. The compound according to claim 2 wherein R is straight chained, saturated and contains three carbon atoms bonded together by carbon-carbon bonds.
 50

4. The compound according to claim 3 wherein X is selected from the group consisting of hydroxy, carboxy, a carboxylate salt of a pharmaceutically acceptable cation, $C(O)-NR_6 R_7$ wherein R_6 and R_7 are selected from the group consisting of hydrogen, hydroxyl, methyl, t -butyl, 2-hydroxyethyl and carboxymethyl.
 55

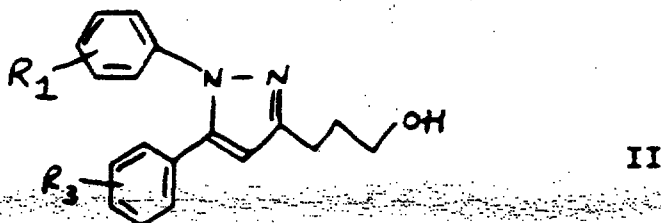
5. The compound according to claim 2 wherein R is unsaturated and contains 2-16 carbon atoms.



6. The compound according to claim 5 wherein X is carboxyl or a salt thereof.
7. A compound of claim 1 selected from the group consisting of N-carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxy-propanamide, and 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamide.
8. A compound of claim 1 selected from the group consisting of 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-phenyl-propanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propylamine, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanal, 5-(4-chlorophenyl)-3-(3-oximino-propyl)-1-(4-methoxyphenyl)-pyrazole and 3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl)-pyrazole.
9. A compound of claim 1 which is any one of the following individual compounds:
 - 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide;
 - 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole;
 - 5-(4-trifluoromethylphenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole;
 - 1-(4-bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl) pyrazole;
 - sodium 8-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] 5(Z)-octenoate;
 - sodium 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanoate;
 - 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] -N-tert-butyl-N-hydroxypropanamide;
 - 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl] -N-hydroxy-N-methyl propanamide;
 - 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl] -N-methyl-N-succinyloxypropanamide,
 - 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] -N'-N'-dimethylglycinyloxy-N-methylpropanamide;
 - N-[3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl] -N, N' -dihydroxyoxamide; or
 - N-acetyl-N-acetoxy [5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanamide.
10. A pharmaceutical composition for topical, oral, parenteral or aerosol administration, comprising an effective amount of a substituted pyrazole compound according to any one of claims 1 to 9 as active ingredient dispersed in a pharmaceutically acceptable carrier.
11. The pharmaceutical composition according to claim 10 wherein said substituted pyrazole compound is capable of inhibiting both the cyclooxygenase and lipoxigenase pathways in the amount present in the composition when said composition is introduced into a mammal.
12. A substituted pyrazole compound as defined in any one of claims 1 to 9 without the provisos or a pharmaceutical composition according to claim 10 or claim 11 for use in alleviating inflammation, asthma, hypersensitivity, myocardial ischemia, dermatological conditions such as psoriasis, dermatitis and gastrointestinal inflammatory conditions such as inflammatory bowel syndromes.
13. A method of synthesizing a 1, 5-diaryl-3-(omega-substituted lower alkyl)-pyrazole according to any one of claims 1 to 9 comprising reacting an arylhydrazine with a 1-aryl-(omega-substituted)-alkyl-1, 3-dione containing at least 4 carbons in the alkyl chain, said reaction being carried out in a solvent that is substantially inert to said reaction conditions, and said omega-substituent being substantially inert to said reaction conditions, wherein said aryl groups are the same or different and are mono- or di-substituted phenyl wherein said phenyl substituents are selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, phenyl, halo, hydroxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy and naphthyl.

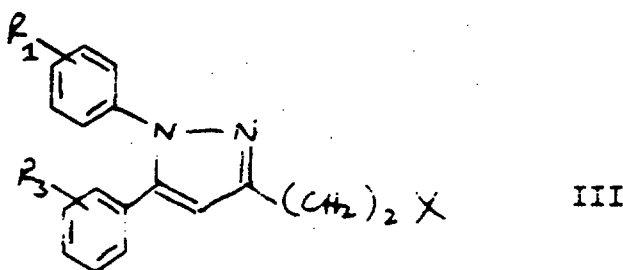


14. A compound having a structure that corresponds to the formula II:



wherein R_1 and R_3 are selected from the group consisting of halo, trifluoromethyl, methyl and methoxy.

15. A compound having a structure that corresponds to the formula III:



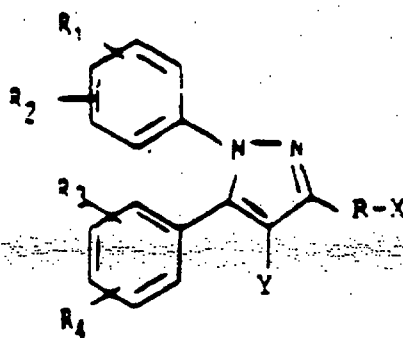
wherein R_1 and R_3 are selected from the group consisting of halo, trifluoromethyl, methyl, phenyl and methoxy; and

X is selected from the group consisting of carboxy, $C(O)-R_5$ wherein R_5 is selected from the group consisting of $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ and $ONH(t-C_4H_9)$.

- 35 16. A method of synthesizing a 1,5-diaryl-3-(omega-substituted alkyl)-pyrazole according to any one of claims 1 to 9 comprising a functional group modification step of converting a 1,5-diaryl-3-(omega substituted alkyl) pyrazole, wherein the omega substituent is a hydroxy, aldehyde, carboxy or acid chloride group, into a 1,5-diaryl-3-(omega substituted alkyl) pyrazole, wherein the omega substituent is a carboxy, hydroxy, acetoxo, alkanoyloxy, C_{1-8} alkoxy, C_{1-6} alkyl carbonyl, oximino, cyano, amino, $C(O)-R_5$, $-C(O)C(O)-R_5$, $-NR_8OH$, $-NHR_{13}$, $-C(R_{14})=NNH$ -thiazolino, $-CH(OH)R_{14}$, or $-C(=NH)N(OH)-C_{1-8}$ alkyl group in which R_5 , R_8 , R_{13} and R_{14} are as defined in claim 1.
- 40
17. A method according to claim 16 comprising reaction of a 1,5-diaryl-3-(omega acid chloride substituted alkyl)pyrazole with an alkylhydroxylamine compound of formula R_6NHOH wherein R_6 is as defined in claim 1, to give a 1,5-diaryl-3-(omega- $C(O)NR_6OH$ substituted alkyl)-pyrazole.
- 45
18. A method of preparing a pharmaceutical composition comprising dispersing a compound according to any one of claims 1 to 9 in a pharmaceutically acceptable carrier.

50 **Claims for the following Contracting States : AT, ES, GR**

1. A method of synthesizing a 1,5-diaryl-3-(omega-substituted lower alkyl)-pyrazole having a structure that corresponds to the formula I:



wherein

R_1 , R_2 , R_3 and R_4 are the same or different and are individually selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, phenyl, halo, hydroxy, C_{1-8} alkylsulfonyl, C_{1-8} alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl, C_{1-8} alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid or where R_1R_2 or R_3R_4 , taken together with the phenyl group to which they are attached, form a naphthyl;

R is a straight chained, saturated or unsaturated hydrocarbon that contains 2-16 carbon atoms;

Y is hydrogen, bromo, chloro or C_{1-4} alkyl;

and X is selected from the group consisting of carboxy, hydroxy, acetoxy, alkanoyloxy, C_{1-8} alkoxy, C_{1-6} alkyl carbonyl, oximino, cyano, amino, $C(O)R_5$, $-C(O)C(O)R_5$, $-NR_6OH$, $-NHR_{13}$, $-C(R_{14})=NNH-2$ thiazolino, $-CH(OH)R_{14}$, $-C(=NH)N(OH)-C_{1-8}$ alkyl;

wherein R_5 is selected from the group consisting of hydrogen, alkyl, C_{1-8} alkoxy, NR_6R_7 and $-ONR_{15}R_{16}$;

wherein R_6 and R_7 are the same or different and are selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, acyloxy, benzyloxy, 2-hydroxy C_{1-8} alkyl, C_{1-8} alkyl carboxy, phenyl, pyridyl, thiazolyl, dihydrothiazolyl, 5-tetrazolyl, ω -alkanoate, $-OCO(CH_2)_n-COR_9$ and $-OCOR_{10}$;

wherein R_8 is hydrogen, $-CO-C_{1-8}$ alkyl, $-CO-t$ -butyl, $-COC_7H_{15}$, CO -phenyl, SO_2-C_{1-8} alkyl, $-COCO_2-C_{1-8}$ alkyl, or $-COCONHOH$;

wherein R_9 is $-OH$, $-ONa$, dialkylamino and n is 2 or 3;

wherein R_{10} is $-CH_2NR_{11}R_{12}$, $-CH_2Cl$, $-CH_2O-C_{1-8}$ alkyl, t -butyl, or

$-CH-C_{1-8}$ alkyl- CO_2Q , wherein Q is C_{1-8} alkyl or H ;

wherein R_{11} and R_{12} are the same or different and are any of alkyl, cyclohexyl, or together form N -methylpiperazino;

wherein R_{13} is hydrogen, $-CO-C_{1-8}$ alkyl, $-CO-t$ -butyl, $-COC_7H_{15}$, $-CO$ -phenyl, $-SO_2-C_{1-8}$ alkyl, $-COCO_2-C_{1-8}$ alkyl, $-COCONHOH$, $-COCO_2H$, $COCON(C_{1-8} \text{ alkyl})OH$ or $PO(O-C_{1-8} \text{ alkyl})_2$;

wherein R_{14} is hydrogen, C_{1-8} alkyl, phenyl or t -butyl;

wherein R_{15} and R_{16} are the same or different and are selected from the group consisting of hydrogen, C_{1-8} alkyl and phenyl;

with the provisos that:

(a) when Y is bromo or chloro, X is $-COOH$, $-CH_2OH$ or $-C(O)R_5$ wherein R_5 is NR_6R_7 and R_6 is OH and R_7 is C_{1-8} alkyl;

(b) at least one of R_1 and R_2 is other than hydrogen where (i) $R-X$ is $(CH_2)_2CO_2H$ or $(CH_2)_2C(O)NHOH$, and (ii) R_3 and R_4 are 4-methoxy, 3-methoxy-4-hydroxy, 2-hydroxy or hydrogen and

(c) at least one of R_1 and R_2 or of R_3 and R_4 is other than hydrogen where $R-X$ together contains three saturated carbon atoms linked together by carbon-carbon bonds;

or the compound

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]- N -cyclohexyl- N -hydroxypropanamide,

Ethyl 3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamide- N -acetate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]- N -(N -hydroxyacetamido)propanamide 1/4 Hydrate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] N -(N -hydroxy- N -methylacetamido) propanamide,

Ethyl N -[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinate hemihydrate,

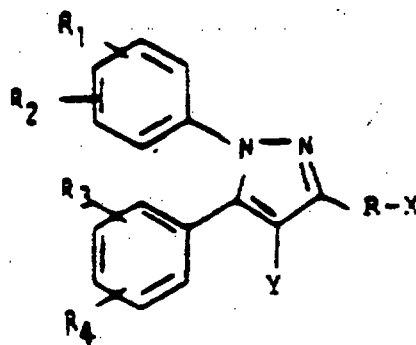


Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinate, or

3-(3-Acetoacetoxypropyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole;

and pharmaceutically acceptable salts thereof; the method comprising reacting an arylhydrazine with a 1-aryl-(omega substituted)-alkyl-1, 3-dione containing at least 4 carbons in the alkyl chain, said reaction being carried out in a solvent that is substantially inert to said reaction conditions, and said omega-substituent being substantially inert to said reaction conditions, wherein said aryl groups are the same or different and are mono- or di-substituted phenyl wherein said phenyl substituents are selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, phenyl, halo, hydroxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy and naphthyl.

2. A method of synthesising a 1,5-diaryl-3-(omega-substituted alkyl)-pyrazole having a structure that corresponds to the formula I:



wherein

R₁, R₂, R₃ and R₄ are the same or different and are individually selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, phenyl, halo, hydroxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid or where R₁R₂ or R₃R₄, taken together with the phenyl group to which they are attached, form a naphthyl;

R is a straight chained, saturated or unsaturated hydrocarbon that contains 2-16 carbon atoms;

Y is hydrogen, bromo, chloro or C₁₋₄ alkyl;

and X is selected from the group consisting of carboxy, hydroxy, acetoxy, alkanoyloxy, C₁₋₈ alkoxy, C₁₋₆ alkyl carbonyl, oximino, cyano, amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₈OH, NHR₁₃, -C(R₁₄)-=NNH-2thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)-C₁₋₈ alkyl;

wherein R₅ is selected from the group consisting of hydrogen, alkyl, C₁₋₈ alkoxy, NR₆R₇ and -O-NR₁₅R₁₆;

wherein R₆ and R₇ are the same or different and are selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, hydroxy, acyloxy, benzyloxy, 2-hydroxy C₁₋₈ alkyl, C₁₋₈ alkyl carboxy, phenyl, pyridyl, thiazolyl, dihydrothiazolyl, 5-tetrazolyl, ω-alkanoate, -OCO(CH₂)_n-COR₉ and -OCOR₁₀;

wherein R₈ is hydrogen, -CO-C₁₋₈ alkyl, -CO-t-butyl, -COC₇H₁₅, CO-phenyl, SO₂-C₁₋₈ alkyl, -COCO₂-C₁₋₈ alkyl, or -COCONHOH;

wherein R₉ is -OH, -ONa, dialkylamino and n is 2 or 3;

wherein R₁₀ is -CH₂NR₁₁R₁₂, -CH₂Cl, CH₂O-C₁₋₈ alkyl, t-butyl, or -CH-C₁₋₈ alkyl-CO₂ Q, wherein Q is C₁₋₈ alkyl or H;

wherein R₁₁ and R₁₂ are the same or different and are any of alkyl, cyclohexyl, or together form N-methylpiperazino;

wherein R₁₃ is hydrogen, -CO-C₁₋₈ alkyl, -CO-t-butyl, -COC₇H₁₅, -CO-phenyl, -SO₂-C₁₋₈ alkyl, -COCO₂-C₁₋₈ alkyl, -COCONHOH, -COCO₂H, COCON(C₁₋₈ alkyl)OH or PO(O-C₁₋₈ alkyl)₂;

wherein R₁₄ is hydrogen, C₁₋₈ alkyl, phenyl or t-butyl;

wherein R₁₅ and R₁₆ are the same or different and are selected from the group consisting of hydrogen, C₁₋₈ alkyl and phenyl;

with the provisos that:



(a) when Y is bromo or chloro, X is -COOH, -CH₂OH or -C(O)-R₅ wherein R₅ is NR₆R₇ and R₆ is OH and R₇ is C₁₋₈ alkyl;

(b) at least one of R₁ and R₂ is other than hydrogen where (i) R-X is (CH₂)₂CO₂H or (CH₂)₂C(O)-NHOH, and (ii) R₃ and R₄ are 4-methoxy, 3-methoxy-4-hydroxy, 2-hydroxy or hydrogen and

(c) at least one of R₁ and R₂ or of R₃ and R₄ is other than hydrogen where R-X together contains three saturated carbon atoms linked together by carbon-carbon bonds;

or the compound

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide,

Ethyl 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanamide-N-acetate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-(N-hydroxyacetamido)propanamide 1/4 Hydrate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxy-N-methylacetamido) propanamide,

Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinate hemi-hydrate,

Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinate, or

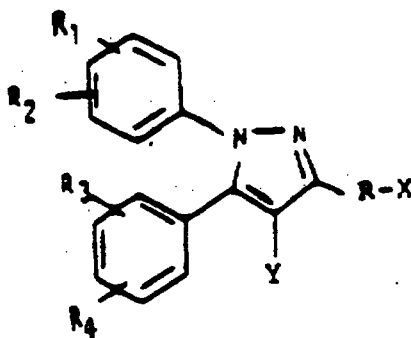
3-(3-Acetoacetoxypropyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole;

and pharmaceutically acceptable salts thereof;

the method comprising a functional group modification step of converting a 1,5-diaryl-3-(omega substituted alkyl) pyrazole, wherein the omega substituent is a hydroxy, aldehyde, carboxy or acid chloride group, into a 1,5-diaryl-3-(omega-substituted alkyl) pyrazole, wherein the omega substituent is a carboxy, hydroxy, acetoxy, alkanoyloxy, C₁₋₈ alkoxy, C₁₋₆ alkyl carbonyl, oximino, cyano, amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₆OH, -NHR₁₃, -C(R₁₄)=NNH-thiazolino, -CH(OH)R₁₄, or -C(=NH)N(OH)-C₁₋₈alkyl group.

3. A method according to claim 2 comprising reaction of a 1,5-diaryl-3-(omega acid chloride substituted alkyl)pyrazole with an alkylhydroxylamine compound of formula R₆NHOH to give a 1,5-diaryl-3-(omega-C(O)NR₆OH substituted alkyl)-pyrazole.

4. A method of preparing a pharmaceutical composition comprising dispersing in a pharmaceutically acceptable carrier a 1,5-diaryl-3-(omega substituted alkyl) pyrazole having a structure that corresponds to the formula I:



wherein

R₁, R₂, R₃ and R₄ are the same or different and are individually selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, phenyl, halo, hydroxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylthio, nitro, trifluoromethyl, omega-trifluoromethyl C₁₋₈ alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid or where R₁R₂ or R₃R₄, taken together with the phenyl group to which they are attached, form a naphthyl;

R is a straight chained, saturated or unsaturated hydrocarbon that contains 2-16 carbon atoms;

Y is hydrogen, bromo, chloro or C₁₋₄ alkyl;

and X is selected from the group consisting of carboxy, hydroxy, acetoxy, alkanoyloxy, C₁₋₈ alkoxy, C₁₋₆ alkyl carbonyl, oximino, cyano, amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₆OH, -NHR₁₃, -C(R₁₄)=NNH-2thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)-C₁₋₈ alkyl;

wherein R₅ is selected from the group consisting of hydrogen, alkyl, C₁₋₈ alkoxy, NR₆R₇ and -O-



NR₁₅R₁₆;

wherein R₆ and R₇ are the same or different and are selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₁₋₈ alkoxy, hydroxy, acyloxy, benzyloxy, 2-hydroxy C₁₋₈ alkyl, C₁₋₈ alkyl carboxy, phenyl, pyridyl, thiazolyl, dihydrothiazolyl, 5-tetrazolyl, ω-alkanoate, -OCO(CH₂)_n-COR₉ and -OCOR₁₀;

wherein R₈ is hydrogen, -CO-C₁₋₈ alkyl, -CO-t-butyl, -COC₇H₁₅, CO-phenyl, SO₂-C₁₋₈ alkyl, -COCO₂-C₁₋₈ alkyl, or -COCONHOH;

wherein R₉ is -OH, -ONa, dialkylamino and n is 2 or 3;

wherein R₁₀ is -CH₂NR₁₁R₁₂, -CH₂Cl, CH₂O-C₁₋₈ alkyl, t-butyl, or

-CH-C₁₋₈ alkyl-CO₂ Q, wherein Q is C₁₋₈ alkyl or H;

wherein R₁₁ and R₁₂ are the same or different and are any of alkyl, cyclohexyl, or together form N-methylpiperazino;

wherein R₁₃ is hydrogen, -CO-C₁₋₈ alkyl, -CO-t-butyl, -COC₇H₁₅, -CO-phenyl, -SO₂-C₁₋₈ alkyl, -COCO₂-C₁₋₈ alkyl, -COCONHOH, -COCO₂H, COCON(C₁₋₈ alkyl)OH or PO(O-C₁₋₈ alkyl)₂;

wherein R₁₄ is hydrogen, C₁₋₈ alkyl, phenyl or t-butyl;

wherein R₁₅ and R₁₆ are the same or different and are selected from the group consisting of hydrogen, C₁₋₈ alkyl and phenyl;

with the provisos that:

(a) when Y is bromo or chloro, X is -COOH, -CH₂OH or -C(O)-R₅ wherein R₅ is NR₆R₇ and R₆ is OH and R₇ is C₁₋₈ alkyl;

(b) at least one of R₁ and R₂ is other than hydrogen where (i) R-X is (CH₂)₂CO₂H or (CH₂)₂C(O)-NHOH, and (ii) R₃ and R₄ are 4-methoxy, 3-methoxy-4-hydroxy, 2-hydroxy or hydrogen and

(c) at least one of R₁ and R₂ or of R₃ and R₄ is other than hydrogen where R-X together contains three saturated carbon atoms linked together by carbon-carbon bonds;

or the compound

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide,

Ethyl 3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamide-N-acetate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-(N-hydroxyacetamido)propanamide 1/4 Hydrate,

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxy-N-methylacetamido) propanamide,

Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinate hemihydrate,

Ethyl N-[2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinate, or

3-(3-Acetoacetoxypropyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole;

and pharmaceutically acceptable salts thereof.

5. A method according to any one of claims 1 to 4 wherein R₂ and R₄ are hydrogen, and R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl, C₁₋₈ alkyl and C₁₋₈ alkoxy.

6. A method according to any one of claims 1 to 5 wherein R is straight chained, saturated and contains three carbon atoms bonded together by carbon-carbon bonds.

7. A method according to any one of claims 1 to 6 wherein X is selected from the group consisting of hydroxy, carboxy, a carboxylate salt of a pharmaceutically acceptable cation, C(O)-NR₆R₇ wherein R₆ and R₇ are selected from the group consisting of hydrogen, hydroxyl, methyl, t-butyl, 2-hydroxyethyl and carboxymethyl.

8. A method according to any one of claims 1 to 5 wherein R is unsaturated and contains 2-16 carbon atoms.

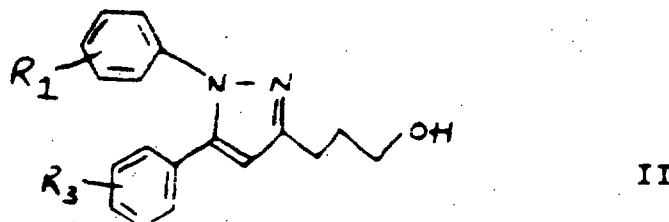
9. A method according to claim 8 wherein X is carboxyl or a salt thereof.

10. A method according to any one of claims 1 to 4 wherein the 1,5-diaryl-3-(omega substituted alkyl) pyrazole is selected from the group consisting of N-carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-



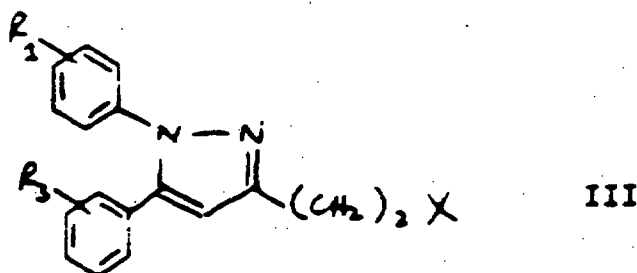
hydroxy-propanamide, and 3-[5-(4-chlorophenyl)-1-(4-methoxy-phenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamide.

11. A method according to any one of claims 1 to 4 wherein the 1,5-diaryl-3-(omega substituted alkyl) pyrazole is selected from the group consisting of 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-phenylpropanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propylamine, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanal, 5-(4-chlorophenyl)-3-(3-oximino-propyl)-1-(4-methoxyphenyl)-pyrazole and 3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl) pyrazole.
12. A method according to any one of claims 1 to 4 in which the 1,5-diaryl-3-(omega substituted alkyl) pyrazole is any one of the following individual compounds:
 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide;
 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole;
 5-(4-trifluoromethylphenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole;
 1-(4-bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl) pyrazole;
 sodium 8-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] 5(Z)-octenoate;
 sodium 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanoate;
 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide;
 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl propanamide;
 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methyl-N-succinyloxypropanamide;
 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N'-N'-dimethylglycinyloxy-N-methylpropanamide;
 N-[3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl]-N,N'-dihydroxyoxamide; or
 N-acetyl-N-acetoxy [5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanamide.
13. A method according to any one of claims 1 to 4 wherein the 1,5-diaryl-3-(omega substituted alkyl) pyrazole has a structure that corresponds to the formula II:



wherein R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl and methoxy.

14. A method according to any one of claims 1 to 4 wherein the 1,5-diaryl-3-(omega substituted alkyl) pyrazole has a structure that corresponds to the formula III:



wherein R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl, methyl, phenyl and methoxy; and

X is selected from the group consisting of carboxy, C(O)-R₅ wherein R₅ is selected from the group



consisting of $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ and $ONH(t-C_4H_9)$.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

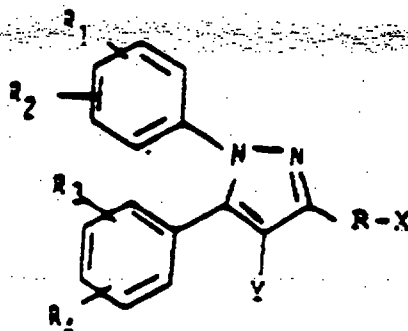
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1. Verbindung, die eine Struktur gemäß der Formel I aufweist:

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I

worin

R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und jeweils ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Phenyl, Halogen, Hydroxy, C_{1-8} -Alkylsulfonyl, C_{1-8} -Alkylthio, Nitro, Trifluormethyl, ω -trifluormethyl- C_{1-8} -Alkoxy, Amino, Acetamido, Carboxy, Alkylhydroxamsäure oder worin R_1R_2 oder R_3R_4 zusammengekommen mit der Phenylgruppe, an die sie gebunden sind, eine Naphthylgruppe bilden,

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R ein geradkettiger, gesättigter oder ungesättigter Kohlenwasserstoff ist, der 2 - 16 Kohlenstoffatome enthält,

Y gleich Wasserstoff, Brom, Chlor oder eine C_{1-4} -Alkylgruppe ist,

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und X ausgewählt ist aus der Gruppe bestehend aus Carboxy, Hydroxy, Acetoxy, Alkanoyloxy, C_{1-8} -Alkoxy, C_{1-6} -Alkylcarbonyl, Oximino, Cyano, Amino, $C(O)R_5$, $C(O)C(O)R_5$, NR_6OH , NHR_{13} , $-C(R_{14})=NNH^2$ Thiazolino, $-CH(OH)R_{14}$, $-C(=NH)N(OH)C_{1-8}$ -Alkyl,

worin R_5 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Alkyl, C_{1-8} -Alkoxy, NR_6R_7 und $-O-NR_{15}R_{16}$,

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worin R_6 und R_7 gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Hydroxy, Acyloxy, Benzyloxy, 2-Hydroxy- C_{1-8} -Alkyl, C_{1-8} -Alkylcarboxy, Phenyl, Pyridyl, Thiazolyl, Dihydrothiazolyl, 5-Tetrazolyl, ω -Alkanoat, $-OCO(CH_2)_n-COR_9$ und $-OCOR_{10}$,

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worin R_8 Wasserstoff, $-CO-C_{1-8}$ -Alkyl, $-CO-t$ -Butyl, $-COC_7H_{15}$, CO -Phenyl, SO_2-C_{1-8} -Alkyl, $-COCO_2-C_{1-8}$ -Alkyl oder $-COCONHOH$ ist,

worin R_9 gleich $-OH$, $-ONa$, Dialkylamino und n gleich 2 oder 3 ist,

worin R_{10} gleich $-CH_2NR_{11}R_{12}$, $-CH_2Cl$, $-CH_2O-C_{1-8}$ -Alkyl, t -Butyl oder

$-CH-C_{1-8}$ -Alkyl- CO_2Q ist, worin Q eine C_{1-8} -Alkylgruppe oder H ist,

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worin R_{11} und R_{12} gleich oder verschieden sind und eine Alkyl- oder Cyclohexylgruppe sind oder zusammen eine N -Methylpiperazingruppe bilden,

worin R_{13} gleich Wasserstoff, $-CO-C_{1-8}$ -Alkyl, $CO-t$ -Butyl, $-COC_7H_{15}$, $-CO$ -Phenyl, $-SO_2-C_{1-8}$ -Alkyl, $-COCO_2-C_{1-8}$ -Alkyl, $-COCONHOH$, $-COCO_2H$, $COCON(C_{1-8}-Alkyl)OH$ oder $PO(O-C_{1-8}-Alkyl)_2$ ist,

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worin R_{14} gleich Wasserstoff, C_{1-8} -Alkyl, Phenyl oder t -Butyl ist,

worin R_{15} und R_{16} gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_{1-8} -Alkyl und Phenyl,

mit der Maßgabe, daß:

(a) wenn Y gleich Brom oder Chlor ist, X gleich $-COOH$, $-CH_2OH$ oder $-C(O)R_5$ ist, worin R_5 gleich NR_6R_7 ist und R_6 gleich OH ist und R_7 eine C_{1-8} -Alkylgruppe ist,

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(b) mindestens einer der Reste R_1 und R_2 kein Wasserstoff ist, wenn (i) $R-X$ gleich $(CH_2)_2CO_2H$ oder $(CH_2)_2C(O)NHOH$ ist, und (ii) R_3 und R_4 gleich 4-Methoxy, 3-Methoxy-4-hydroxy, 2-Hydroxy oder Wasserstoff sind und

consisting of $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ and $ONH(t-C_4H_9)$.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

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1. Verbindung, die eine Struktur gemäß der Formel I aufweist:

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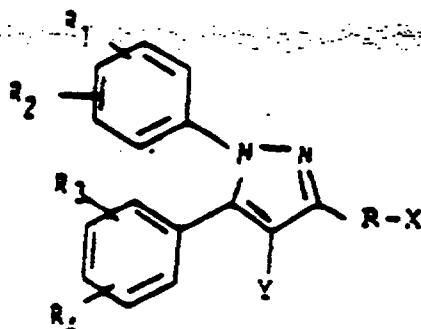
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worin

R₁, R₂, R₃ und R₄ gleich oder verschieden sind und jeweils ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C₁-₈-Alkyl, C₁-₈-Alkoxy, Phenyl, Halogen, Hydroxy, C₁-₈-Alkylsulfonyl, C₁-₈-Alkylthio, Nitro, Trifluormethyl, ω -trifluormethyl-C₁-₈-Alkoxy, Amino, Acetamido, Carboxy, Alkylhydroxamsäure oder worin R₁R₂ oder R₃R₄ zusammengekommen mit der Phenylgruppe, an die sie gebunden sind, eine Naphthylgruppe bilden,

R ein geradkettiger, gesättigter oder ungesättigter Kohlenwasserstoff ist, der 2 - 16 Kohlenstoffatome enthält,

Y gleich Wasserstoff, Brom, Chlor oder eine C₁-₄-Alkylgruppe ist,

und X ausgewählt ist aus der Gruppe bestehend aus Carboxy, Hydroxy, Acetoxy, Alkanoyloxy, C₁-₈-Alkoxy, C₁-₆-Alkylcarbonyl, Oximino, Cyano, Amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₆OH, -NHR₁₃, -C(R₁₄)=NNH-²Thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)-C₁-₈-Alkyl,

worin R₅ ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Alkyl, C₁-₈-Alkoxy, NR₆R₇ und -O-NR₁₅R₁₆,

worin R₆ und R₇ gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C₁-₈-Alkyl, C₁-₈-Alkoxy, Hydroxy, Acyloxy, Benzyloxy, 2-Hydroxy-C₁-₈-Alkyl, C₁-₈-Alkylcarboxy, Phenyl, Pyridyl, Thiazolyl, Dihydrothiazolyl, 5-Tetrazolyl, ω -Alkanoat, -OCO(CH₂)_n-COR₉ und -OCOR₁₀,

worin R₈ Wasserstoff, -CO-C₁-₈-Alkyl, -CO-t-Butyl, -COC₇H₁₅, CO-Phenyl, SO₂-C₁-₈-Alkyl, -COCO₂-C₁-₈-Alkyl oder -COCONHOH ist,

worin R₉ gleich -OH, -ONa, Dialkylamino und n gleich 2 oder 3 ist,

worin R₁₀ gleich -CH₂NR₁₁R₁₂, -CH₂Cl, -CH₂O-C₁-₈-Alkyl, t-Butyl oder

-CH-C₁-₈-Alkyl-CO₂ Q ist, worin Q eine C₁-₈-Alkylgruppe oder H ist,

worin R₁₁ und R₁₂ gleich oder verschieden sind und eine Alkyl- oder Cyclohexylgruppe sind oder zusammen eine N-Methylpiperazingruppe bilden,

worin R₁₃ gleich Wasserstoff, -CO-C₁-₈-Alkyl, CO-t-Butyl, -COC₇H₁₅, -CO-Phenyl, -SO₂-C₁-₈-Alkyl, -COCO₂-C₁-₈-Alkyl, -COCONHOH, -COCO₂H, COCON(C₁-₈-Alkyl)OH oder PO(O-C₁-₈-Alkyl)₂ ist,

worin R₁₄ gleich Wasserstoff, C₁-₈-Alkyl, Phenyl oder t-Butyl ist,

worin R₁₅ und R₁₆ gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C₁-₈-Alkyl und Phenyl,

mit der Maßgabe, daß:

(a) wenn Y gleich Brom oder Chlor ist, X gleich -COOH, -CH₂OH oder -C(O)-R₅ ist, worin R₅ gleich NR₆R₇ ist und R₆ gleich OH ist und R₇ eine C₁-₈-Alkylgruppe ist,

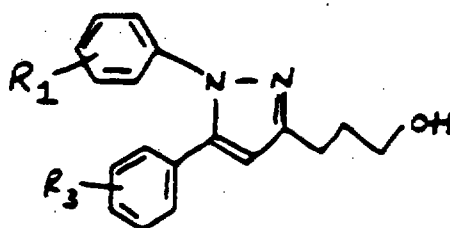
(b) mindestens einer der Reste R₁ und R₂ kein Wasserstoff ist, wenn (i) R-X gleich (CH₂)₂CO₂H oder (CH₂)₂C(O)NHOH ist, und (ii) R₃ und R₄ gleich 4-Methoxy, 3-Methoxy-4-hydroxy, 2-Hydroxy oder Wasserstoff sind und

(c) mindestens einer der Reste R_1 und R_2 oder der Reste R_3 und R_4 kein Wasserstoff ist, wenn R-X zusammen drei gesättigte Kohlenstoffatome enthält, die durch Kohlenstoff-Kohlenstoffbindungen miteinander verknüpft sind,
oder die Verbindung

- 5 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamid,
Ethyl-3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamid-N-acetat,
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-(N-hydroxyacetamido)propanamid 1/4 Hydrat,
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-(N-hydroxy-N-methylacetamido)propanamid,
10 Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinat-Hemihydrat,
Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinat
oder
3-(3-Acetoacetoxypropyl)-5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol
und pharmazeutisch verträgliche Salze davon.
- 15 2. Verbindung nach Anspruch 1, worin R_2 und R_4 Wasserstoff sind und R_1 und R_3 ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl, C_1-8 -Alkyl und C_1-8 -Alkoxy.
3. Verbindung nach Anspruch 2, worin R geradkettig und gesättigt ist und drei durch Kohlenstoff-Kohlenstoffbindungen miteinander verbundene Kohlenstoffatome enthält.
- 20 4. Verbindung nach Anspruch 3, worin X ausgewählt ist aus der Gruppe bestehend aus Hydroxy, Carboxy, einem Carboxylatsalz eines pharmazeutisch verträglichen Kations, $C(O)NR_6R_7$, worin R_6 und R_7 ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Hydroxyl, Methyl, t-Butyl, 2-Hydroxyethyl und Carboxymethyl.
- 25 5. Verbindung nach Anspruch 2, worin R ungesättigt ist und 2 - 16 Kohlenstoffatome enthält.
6. Verbindung nach Anspruch 5, worin X gleich Carboxyl oder ein Salz davon ist.
- 30 7. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus
N-Carboxymethyl-3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanamid,
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamid,
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamid und 3-[5-
35 (4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamid.
8. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-phenylpropanamid,
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propylamin, 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanal, 5-(4-Chlorophenyl)-3-(3-oximino-propyl)-1-(4-methoxyphenyl)-pyrazol
40 und 3-(3-Hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl)pyrazol.
9. Verbindung nach Anspruch 1, die eine der folgenden Einzelverbindungen ist:
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamid,
45 5-(4-Chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-pyrazol,
5-(4-Trifluormethylphenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazol,
1-(4-Bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl) pyrazol,
Natrium-8-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-5(Z)-oktenoat,
Natrium-3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanoat,
50 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamid,
3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamid,
3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methyl-N-succinyloxypropanamid,
3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N'-N'-dimethylglycinyloxy-N-methylpropanamid,
N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propyl]-N,N'-dihydroxyoxamid oder
55 N-Acetyl-N-acetoxy[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanamid.
10. Pharmazeutische Zusammensetzung zur topischen, oralen, parenteralen Verabreichung oder zur Verabreichung mittels eines Aerosols, umfassend eine wirksame Menge einer substituierten Pyrazolverbin-

ung nach einem der Ansprüche 1 bis 9 als aktiven Bestandteil, der in einem pharmazeutisch verträglichen Träger dispergiert ist.

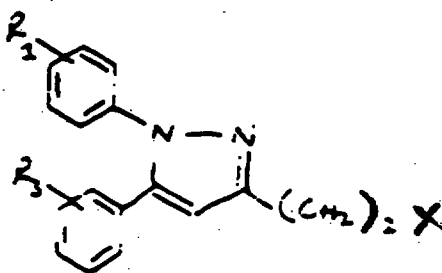
11. Pharmazeutische Zusammensetzung nach Anspruch 10, worin die substituierte Pyrazolverbindung in der Lage ist, sowohl den Cyclooxygenase-Weg als auch den Lipoxygenase-Weg in der in der Zusammensetzung vorliegenden Menge zu hemmen, wenn die Zusammensetzung in ein Säugetier eingeführt wird.
12. Substituierte Pyrazolverbindung nach einem der Ansprüche 1 bis 9 ohne die Maßgaben oder eine pharmazeutische Zusammensetzung nach Anspruch 10 oder Anspruch 11 zur Verwendung zur Linderung von Entzündung, Asthma, Hypersensitivität, myocardialer Ischämie, Hauterkrankungen wie Psoriasis, Dermatitis und entzündlichen gastrointestinalen Erkrankungen wie entzündliche Darmsyndromen.
13. Verfahren zur Synthese eines 1,5-Diaryl-3-(ω -substituierten Niedrig-Alkyl)pyrazols nach einem der Ansprüche 1 bis 9, umfassend das Umsetzen eines Arylhydrazins mit einem 1-Aryl-(ω -substituierten)-alkyl-1,3-dion, das mindestens 4 Kohlenstoffatome in der Alkylkette enthält, wobei die Umsetzung in einem Solvens durchgeführt wird, das bei den Reaktionsbedingungen im wesentlichen inert ist und wobei der ω -Substituent bei den Reaktionsbedingungen im wesentlichen inert ist worin die Arylgruppen gleich oder verschieden und mono-oder di-substituiertes Phenyl sind, worin die Phenyl-Substituenten ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C₁₋₈-Alkyl, C₁₋₈-Alkoxy, Phenyl, Halogen, Hydroxy, C₁₋₈-Alkylsulfonyl, C₁₋₈-Alkylthio, Nitro, Trifluormethyl, ω -Trifluormethyl-C₁₋₈-alkoxy und Naphthyl.
14. Verbindung, die eine Struktur entsprechend der Formel II aufweist:



II

worin R₁ und R₃ ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl, Methyl und Methoxy.

15. Verbindung, die eine Struktur gemäß der Formel III aufweist:



III

worin R₁ und R₃ ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl, Methyl, Phenyl und Methoxy und

X ausgewählt ist aus der Gruppe bestehend aus Carboxy, C(O)-R₅, worin R₅ ausgewählt ist aus der Gruppe bestehend aus N(CH₃)OH, N(t-C₄H₉)OH, NHOH, ONH(CH₃) und ONH(t-C₄H₉).

16. Verfahren zur Synthese eines 1,5-Diaryl-3-(ω -substituierten Alkyl)pyrazols nach einem der Ansprüche 1 bis 9, umfassend einen die funktionelle Gruppe modifizierenden Schritt, in dem ein 1,5-Diaryl-3-(ω -

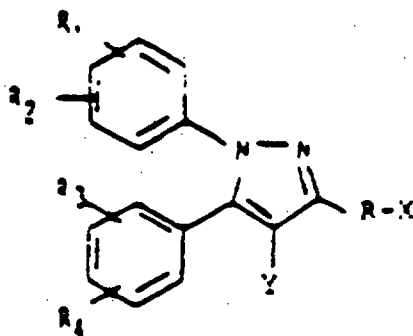
substituiertes Alkyl)pyrazol, worin der ω -Substituent eine Hydroxy-, eine Aldehyd-, eine Carboxy- oder eine Säurechloridgruppe ist, in ein 1,5-Diaryl-3-(ω -substituiertes Alkyl)pyrazol umgewandelt wird, worin der ω -Substituent eine Carboxy-, Hydroxy-, Acetoxy-, Alkanoyloxy-, C_{1-8} -Alkoxy-, C_{1-6} -Alkylcarbonyl-, Oximino-, Cyano-, Amino-, $C(O)-R_5$ -, $-C(O)C(O)-R_5$ -, $-NR_8OH$ -, $-NHR_{13}$ -, $-C(R_{14})=NNH$ -Thiazolino-, $-CH(OH)R_{14}$ - oder eine $-C(=NH)N(OH)-C_{1-8}$ -Alkylgruppe ist, in der R_5 , R_8 , R_{13} und R_{14} die in Anspruch 1 angegebene Bedeutung aufweisen.

17. Verfahren nach Anspruch 16, umfassend die Umsetzung eines 1,5-Diaryl-3-(ω -Säurechlorid substituierten Alkyl)pyrazols mit einer Alkylhydroxylaminverbindung der Formel R_6NHOH , worin R_6 die in Anspruch 1 angegebene Bedeutung aufweist, wobei man ein 1,5-Diaryl-3-($\omega-C(O)NR_6OH$ substituiertes Alkyl)pyrazol erhält.

18. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Dispergieren einer Verbindung nach einem der Ansprüche 1 bis 9 in einem pharmazeutisch verträglichen Träger.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Synthese eines 1,5-Diaryl-3-(ω -substituierten Niedrig-Alkyl)pyrazols, das eine Struktur gemäß der Formel I aufweist:



worin

R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und jeweils ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Phenyl, Halogen, Hydroxy, C_{1-8} -Alkylsulfonyl, C_{1-8} -Alkylthio, Nitro, Trifluormethyl, ω -trifluormethyl- C_{1-8} -Alkoxy, Amino, Acetamido, Carboxy, Alkylhydroxamsäure oder worin R_1R_2 oder R_3R_4 zusammengekommen mit der Phenylgruppe, an die sie gebunden sind, eine Naphthylgruppe bilden,

R ein geradkettiger, gesättigter oder ungesättigter Kohlenwasserstoff ist, der 2 - 16 Kohlenstoffatome enthält,

Y gleich Wasserstoff, Brom, Chlor oder eine C_{1-4} -Alkylgruppe ist,

und X ausgewählt ist aus der Gruppe bestehend aus Carboxy, Hydroxy, Acetoxy, Alkanoyloxy, C_{1-8} -Alkoxy, C_{1-6} -Alkylcarbonyl, Oximino, Cyano, Amino, $C(O)-R_5$ -, $-C(O)C(O)-R_5$ -, $-NR_8OH$ -, $-NHR_{13}$ -, $-C(R_{14})=NNH$ -2-Thiazolino-, $-CH(OH)R_{14}$ -, $-C(=NH)N(OH)-C_{1-8}$ -Alkyl,

worin R_5 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Alkyl, C_{1-8} -Alkoxy, NR_6R_7 und $-O-NR_{15}R_{16}$,

worin R_6 und R_7 gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_{1-8} -Alkyl, C_{1-8} -Alkoxy, Hydroxy, Acyloxy, Benzoyloxy, 2-Hydroxy- C_{1-8} -Alkyl, C_{1-8} -Alkylcarboxy, Phenyl, Pyridyl, Thiazolyl, Dihydrothiazolyl, 5-Tetrazolyl, ω -Alkanoat, $-OCO(CH_2)_n-COR_9$ und $-OCOR_{10}$,

worin R_8 Wasserstoff, $-CO-C_{1-8}$ -Alkyl, $-CO-t$ -Butyl, $-COC_7H_{15}$, CO -Phenyl, SO_2-C_{1-8} -Alkyl $-COCO_2-C_{1-8}$ -Alkyl oder $-COCONHOH$ ist,

worin R_9 gleich $-OH$, $-ONa$, Dialkylamino und n gleich 2 oder 3 ist,

worin R_{10} gleich $-CH_2NR_{11}R_{12}$, $-CH_2Cl$, $-CH_2O-C_{1-8}$ -Alkyl, t -Butyl oder

$-CH-C_{1-8}$ -Alkyl- CO_2 Q ist, worin Q eine C_{1-8} -Alkylgruppe oder H ist,

worin R_{11} und R_{12} gleich oder verschieden sind und eine Alkyl- oder Cyclohexylgruppe sind oder zusammen eine N-Methylpiperazylgruppe bilden,

worin R_{13} gleich Wasserstoff, $-\text{CO}-\text{C}_1-8\text{-Alkyl}$, $\text{CO}-t\text{-Butyl}$, $-\text{COC}_7\text{H}_{15}$, $-\text{CO}-\text{Phenyl}$, $-\text{SO}_2-\text{C}_1-8\text{-Alkyl}$, $-\text{COCO}_2-\text{C}_1-8\text{-Alkyl}$, $-\text{COCONHOH}$, $-\text{COCO}_2\text{H}$, $\text{COCON}(\text{C}_1-8\text{-Alkyl})\text{OH}$ oder $\text{PO}(\text{O}-\text{C}_1-8\text{-Alkyl})_2$ ist,

worin R_{14} gleich Wasserstoff, $\text{C}_1-8\text{-Alkyl}$, Phenyl oder $t\text{-Butyl}$ ist,

worin R_{15} und R_{16} gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, $\text{C}_1-8\text{-Alkyl}$ und Phenyl,

mit der Maßgabe, daß:

(a) wenn Y gleich Brom oder Chlor ist, X gleich $-\text{COOH}$, $-\text{CH}_2\text{OH}$ oder $-\text{C}(\text{O})-\text{R}_5$ ist, worin R_5 gleich NR_6R_7 ist und R_6 gleich OH ist und R_7 eine $\text{C}_1-8\text{-Alkyl}$ gruppe ist,

(b) mindestens einer der Reste R_1 und R_2 kein Wasserstoff ist, wenn (i) $\text{R}-\text{X}$ gleich $(\text{CH}_2)_2\text{CO}_2\text{H}$ oder $(\text{CH}_2)_2\text{C}(\text{O})\text{NHOH}$ ist, und (ii) R_3 und R_4 gleich 4-Methoxy, 3-Methoxy-4-hydroxy, 2-Hydroxy oder Wasserstoff sind und

(c) mindestens einer der Reste R_1 und R_2 oder der Reste R_3 und R_4 kein Wasserstoff ist, wenn $\text{R}-\text{X}$ zusammen drei gesättigte Kohlenstoffatome enthält, die durch Kohlenstoff-Kohlenstoffbindungen miteinander verknüpft sind,

oder die Verbindung

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamid,

Ethyl-3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamid-N-acetat,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-(N-hydroxyacetamido)propanamid 1/4 Hydrat,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxy-N-methylacetamido)propanamid, Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinat-Hemihydrat,

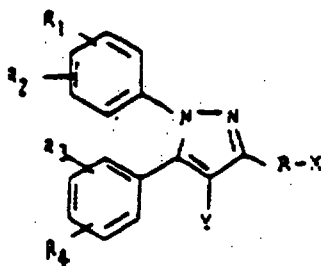
Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinat oder

3-(3-Acetoacetoxypropyl)-5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol

und pharmazeutisch verträgliche Salze davon,

wobei das Verfahren das Umsetzen eines Arylhydrazins mit einem 1-Aryl-(α -substituierten)-alkyl-1,3-dion, das mindestens 4 Kohlenstoffatome in der Alkylkette enthält, umfaßt, wobei die Umsetzung in einem Solvens durchgeführt wird, das bei den Reaktionsbedingungen im wesentlichen inert ist und wobei der α -Substituent bei den Reaktionsbedingungen im wesentlichen inert ist, worin die Arylgruppen gleich oder verschieden und mono- oder di-substituiertes Phenyl sind, worin die Phenyl-Substituenten ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, $\text{C}_1-8\text{-Alkyl}$, $\text{C}_1-8\text{-Alkoxy}$, Phenyl, Halogen, Hydroxy, $\text{C}_1-8\text{-Alkylsulfonyl}$, $\text{C}_1-8\text{-Alkylthio}$, Nitro, Trifluormethyl, -Trifluormethyl- $\text{C}_1-8\text{-alkoxy}$ und Naphthyl.

2. Verfahren zur Synthese eines 1,5-Diaryl-3-(α -substituierten Alkyl)-pyrazols, das eine Struktur gemäß der Formel I aufweist:



worin

R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und jeweils ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, $\text{C}_1-8\text{-Alkyl}$, $\text{C}_1-8\text{-Alkoxy}$, Phenyl, Halogen, Hydroxy, $\text{C}_1-8\text{-Alkylsulfonyl}$, $\text{C}_1-8\text{-Alkylthio}$, Nitro, Trifluormethyl, ω -trifluormethyl- $\text{C}_1-8\text{-Alkoxy}$, Amino, Acetamido, Carboxy, Alkylhydroxamsäure oder worin R_1R_2 oder R_3R_4 zusammengekommen mit der Phenylgruppe, an die sie gebunden sind, eine Naphthylgruppe bilden,

R ein geradkettiger, gesättigter oder ungesättigter Kohlenwasserstoff ist, der 2 - 16 Kohlenstoffatome enthält,

Y gleich Wasserstoff, Brom, Chlor oder eine $\text{C}_1-4\text{-Alkyl}$ gruppe ist,

und X ausgewählt ist aus der Gruppe bestehend aus Carboxy, Hydroxy, Acetoxy, Alkanoyloxy, C₁₋₈-Alkoxy, C₁₋₆-Alkylcarbonyl, Oximino, Cyano, Amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₈OH, -NHR₁₃, -C(R₁₄)=NNH-2Thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)-C₁₋₈-Alkyl,

worin R₅ ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Alkyl, C₁₋₈-Alkoxy, NR₆R₇ und -O-NR₁₅R₁₆,

worin R₆ und R₇ gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C₁₋₈-Alkyl, C₁₋₈-Alkoxy, Hydroxy, Acyloxy, Benzyloxy, 2-Hydroxy-C₁₋₈-Alkyl, C₁₋₈-Alkylcarboxy, Phenyl, Pyridyl, Thiazolyl, Dihydrothiazolyl, 5-Tetrazolyl, ω -Alkanoat, -OCO(CH₂)_n-COR₉ und -OCOR₁₀,

worin R₈ Wasserstoff, -CO-C₁₋₈-Alkyl, -CO-t-Butyl, -COC₇H₁₅, CO-Phenyl, SO₂-C₁₋₈-Alkyl, -COCO₂-C₁₋₈-Alkyl oder -COCONHOH ist,

worin R₉ gleich -OH, -ONa, Dialkylamino und n gleich 2 oder 3 ist,

worin R₁₀ gleich -CH₂NR₁₁R₁₂, -CH₂Cl, -CH₂O-C₁₋₈-Alkyl, t-Butyl oder

-CH-C₁₋₈-Alkyl-CO₂ Q ist, worin Q eine C₁₋₈-Alkylgruppe oder H ist,

worin R₁₁ und R₁₂ gleich oder verschieden sind und eine Alkyl- oder Cyclohexylgruppe sind oder zusammen eine N-Methylpiperazingruppe bilden,

worin R₁₃ gleich Wasserstoff, -CO-C₁₋₈-Alkyl, CO-t-Butyl, -COC₇H₁₅, -CO-Phenyl, -SO₂-C₁₋₈-Alkyl, -COCO₂-C₁₋₈-Alkyl, -COCONHOH, -COCO₂H, COCON(C₁₋₈-Alkyl)OH oder PO(O-C₁₋₈-Alkyl)₂ ist,

worin R₁₄ gleich Wasserstoff, C₁₋₈-Alkyl, Phenyl oder t-Butyl ist,

worin R₁₅ und R₁₆ gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C₁₋₈-Alkyl und Phenyl,

mit der Maßgabe, daß:

(a) wenn Y gleich Brom oder Chlor ist, X gleich -COOH, -CH₂OH oder -C(O)-R₅ ist, worin R₅ gleich NR₆R₇ ist und R₆ gleich OH ist und R₇ eine C₁₋₈-Alkylgruppe ist,

(b) mindestens einer der Reste R₁ und R₂ kein Wasserstoff ist, wenn (i) R-X gleich (CH₂)₂CO₂H oder (CH₂)₂C(O)NHOH ist, und (ii) R₃ und R₄ gleich 4-Methoxy, 3-Methoxy-4-hydroxy, 2-Hydroxy oder Wasserstoff sind und

(c) mindestens einer der Reste R₁ und R₂ oder der Reste R₃ und R₄ kein Wasserstoff ist, wenn R-X zusammen drei gesättigte Kohlenstoffatome enthält, die durch Kohlenstoff-Kohlenstoffbindungen miteinander verknüpft sind,

oder die Verbindung

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamid, Ethyl-3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamid-N-acetat,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-(N-hydroxyacetamido)propanamid 1/4 Hydrat, 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxy-N-methylacetamido)propanamid, Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinat-Hemihydrat,

Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinat oder

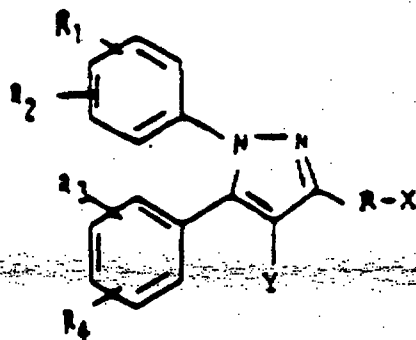
3-(3-Acetoacetoxypropyl)-5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol

und pharmazeutisch verträgliche Salze davon,

wobei das Verfahren einen eine funktionelle Gruppe modifizierenden Schritt umfaßt, in dem ein 1,5-Diaryl-3-(ω -substituiertes Alkyl)pyrazol, wobei der ω -Substituent eine Hydroxy-, eine Aldehyd-, eine Carboxy- oder eine Säurechloridgruppe ist, in ein 1,5-Diaryl-3-(ω -substituiertes Alkyl)pyrazol umgewandelt wird, wobei der ω -Substituent eine Carboxy-, eine Hydroxy-, eine Acetoxy-, eine Alkanoyloxy-, eine C₁₋₈-Alkoxy, eine C₁₋₆-Alkylcarbonyl-, eine Oximino-, eine Cyano-, eine Amino-, eine C(O)-R₅-, eine -C(O)C(O)-R₅-, eine -NR₈OH-, eine -NHR₁₃-, eine -C(R₁₄)=NNH-Thiazolino-, eine -CH(OH)R₁₄- oder eine -C(=NH)N(OH)-C₁₋₈-Alkylgruppe ist.

3. Verfahren nach Anspruch 2, umfassend die Umsetzung eines 1,5-Diaryl-3-(ω -Säurechlorid-substituierten Alkyl)-pyrazols mit einer Alkylhydroxylaminverbindung der Formel R₆NHOH, wobei man ein 1,5-Diaryl-3-(ω -C(O)NR₆OH substituiertes Alkyl)-pyrazol erhält.

4. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Dispergieren in einem pharmazeutisch verträglichen Träger eines 1,5-Diaryl-3-(ω -substituierten Alkyl)pyrazols, das eine Struktur entsprechend der Formel I aufweist:



worin

R_1 , R_2 , R_3 und R_4 gleich oder verschieden sind und jeweils ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_1 - 8 -Alkyl, C_1 - 8 -Alkoxy, Phenyl, Halogen, Hydroxy, C_1 - 8 -Alkylsulfonyl, C_1 - 8 -Alkylthio, Nitro, Trifluormethyl, ω -trifluormethyl- C_1 - 8 -Alkoxy, Amino, Acetamido, Carboxy, Alkylhydroxamsäure oder worin R_1R_2 oder R_3R_4 zusammengekommen mit der Phenylgruppe, an die sie gebunden sind, eine Naphthylgruppe bilden,

R ein geradkettiger, gesättigter oder ungesättigter Kohlenwasserstoff ist, der 2 - 16 Kohlenstoffatome enthält,

Y gleich Wasserstoff, Brom, Chlor oder eine C_1 - 4 -Alkylgruppe ist,

und X ausgewählt ist aus der Gruppe bestehend aus Carboxy, Hydroxy, Acetoxy, Alkanoyloxy, C_1 - 8 -Alkoxy, C_1 - 6 -Alkylcarbonyl, Oximino, Cyano, Amino, $C(O)-R_5$, $C(O)C(O)-R_5$, $-NR_6OH$, $-NHR_{13}$, $-C(R_{14})=NNH-2$ Thiazolino, $-CH(OH)R_{14}$, $-C(=NH)N(OH)-C_1$ - 8 -Alkyl,

worin R_5 ausgewählt ist aus der Gruppe bestehend aus Wasserstoff, Alkyl, C_1 - 8 -Alkoxy, NR_6R_7 und $-O-NR_{15}R_{16}$,

worin R_6 und R_7 gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_1 - 8 -Alkyl, C_1 - 8 -Alkoxy, Hydroxy, Acyloxy, Benzyloxy, 2-Hydroxy- C_1 - 8 -Alkyl, C_1 - 8 -Alkylcarboxy, Phenyl, Pyridyl, Thiazolyl, Dihydrothiazolyl, 5-Tetrazolyl, ω -Alkanoat, $-OCO(CH_2)_n-COR_9$ und $-OCOR_{10}$,

worin R_8 Wasserstoff, $-CO-C_1$ - 8 -Alkyl, $-CO-t$ -Butyl, $-COC_7H_{15}$, CO -Phenyl, SO_2-C_1 - 8 -Alkyl, $-COCO_2-C_1$ - 8 -Alkyl oder $-COCONHOH$ ist,

worin R_9 gleich $-OH$, $-ONa$, Dialkylamino und n gleich 2 oder 3 ist,

worin R_{10} gleich $-CH_2NR_{11}R_{12}$, $-CH_2Cl$, $-CH_2O-C_1$ - 8 -Alkyl, t -Butyl oder

$-CH-C_1$ - 8 -Alkyl- CO_2Q ist, worin Q eine C_1 - 8 -Alkylgruppe oder H ist,

worin R_{11} und R_{12} gleich oder verschieden sind und eine Alkyl- oder Cyclohexylgruppe sind oder zusammen eine N -Methylpiperazingruppe bilden,

worin R_{13} gleich Wasserstoff, $-CO-C_1$ - 8 -Alkyl, $CO-t$ -Butyl, $-COC_7H_{15}$, $-CO$ -Phenyl, $-SO_2-C_1$ - 8 -Alkyl, $-COCO_2-C_1$ - 8 -Alkyl, $-COCONHOH$, $-COCO_2H$, $COCON(C_1$ - 8 -Alkyl) OH oder $PO(O-C_1$ - 8 -Alkyl) $_2$ ist,

worin R_{14} gleich Wasserstoff, C_1 - 8 -Alkyl, Phenyl oder t -Butyl ist,

worin R_{15} und R_{16} gleich oder verschieden sind und ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C_1 - 8 -Alkyl und Phenyl,

mit der Maßgabe, daß:

(a) wenn Y gleich Brom oder Chlor ist, X gleich $-COOH$, $-CH_2OH$ oder $-C(O)-R_5$ ist, worin R_5 gleich NR_6R_7 ist und R_6 gleich OH ist und R_7 eine C_1 - 8 -Alkylgruppe ist,

(b) mindestens einer der Reste R_1 und R_2 kein Wasserstoff ist, wenn (i) $R-X$ gleich $(CH_2)_2CO_2H$ oder $(CH_2)_2C(O)NHOH$ ist, und (ii) R_3 und R_4 gleich 4-Methoxy, 3-Methoxy-4-hydroxy, 2-Hydroxy oder Wasserstoff sind und

(c) mindestens einer der Reste R_1 und R_2 oder der Reste R_3 und R_4 kein Wasserstoff ist, wenn $R-X$ zusammen drei gesättigte Kohlenstoffatome enthält, die durch Kohlenstoff-Kohlenstoffbindungen miteinander verknüpft sind,

oder die Verbindung

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]- N -cyclohexyl- N -hydroxypropanamid,

Ethyl-3-[5-(4-chlorophenyl)-1-methoxyphenyl)-3-pyrazolyl]propanamid- N -acetat,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]- N -(N -hydroxyacetamido)propanamid • 1/4 Hydrat,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]N-(N-hydroxy-N-methylacetamido)propanamid,
 Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-(R)-cysteinat-Hemihydrat,
 Ethyl-N-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethylcarbonyl]-S-methyl-(R)-cysteinat
 oder

5 3-(3-Acetoacetoxypropyl)-5-(4-Chlorophenyl)-1-(4-methoxyphenyl)pyrazol
 und pharmazeutisch verträgliche Salze davon

5. Verfahren nach einem der Ansprüche 1 bis 4, worin R_2 und R_4 gleich Wasserstoff sind und R_1 und R_3
 ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl, C_{1-8} -Alkyl und C_{1-8} -Alkoxy.

10

6. Verfahren nach einem der Ansprüche 1 bis 5, worin R geradkettig und gesättigt ist und drei durch
 Kohlenstoff-Kohlenstoffbindungen miteinander verbundene Kohlenstoffatome enthält.

15

7. Verfahren nach einem der Ansprüche 1 bis 6, worin X ausgewählt ist aus der Gruppe bestehend aus
 Hydroxy, Carboxy, einem Carboxylatsalz eines pharmazeutisch verträglichen Kations, $C(O)NR_6R_7$,
 worin R_6 und R_7 ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Hydroxyl, Methyl, t-
 Butyl, 2-Hydroxyethyl und Carboxymethyl.

20

8. Verfahren nach einem der Ansprüche 1 bis 5, wobei R ungesättigt ist und 2 - 16 Kohlenstoffatome
 enthält.

9. Verfahren nach Anspruch 8, worin X eine Carboxylgruppe oder ein Salz davon ist.

25

10. Verfahren nach einem der Ansprüche 1 bis 4, worin das 1,5-Diaryl-3-(ω -substituierte Alkyl)pyrazol
 ausgewählt ist aus der Gruppe bestehend aus

N-Carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanamid,
 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamid,
 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxy-propanamid und
 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamid.

30

11. Verfahren nach einem der Ansprüche 1 bis 4, worin das 1,5-Diaryl-3-(ω -substituierte Alkyl)pyrazol
 ausgewählt ist aus der Gruppe bestehend aus 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-
 N-hydroxy-N-phenyl-propanamid, 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propylamin, 3-
 [5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanal,

35

5-(4-Chlorophenyl)-3-(3-oximino-propyl)-1-(4-methoxyphenyl)-pyrazol und
 3-(3-Hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl)pyrazol.

40

12. Verfahren nach einem der Ansprüche 1 bis 4, in dem das 1,5-Diaryl-3-(ω -substituierte Alkyl)pyrazol eine
 der folgenden Einzelverbindungen ist:

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamid,

5-(4-Chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-pyrazol,

5-(4-Trifluormethylphenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazol,

1-(4-Bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl) pyrazol,

Natrium-8-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl-5(Z)-oktenoat,

45

Natrium-3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanoat,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamid,

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-propanamid,

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-methyl-N-succinyloxypropanamid,

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N'-N'-dimethylglycinyloxy-N-methylpropanamid,

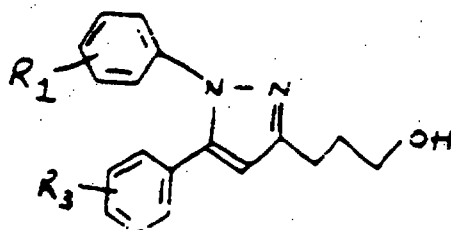
50

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl]-N,N'-dihydroxyoxamid oder

N-Acetyl-N-acetoxy[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanamid.

55

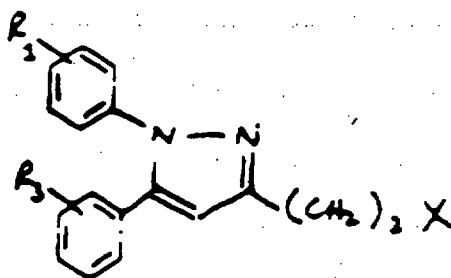
13. Verfahren nach einem der Ansprüche 1 bis 4, in dem das 1,5-Diaryl-3-(ω -substituierte Alkyl)pyrazol eine
 Struktur gemäß der Formel II aufweist:



II

10 worin R_1 und R_3 ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl und Methoxy.

14. Verfahren nach einem der Ansprüche 1 bis 4, in dem das 1,5-Diaryl-3-(ω -substituierte Alkyl)pyrazol eine Struktur gemäß der Formel III aufweist:



III

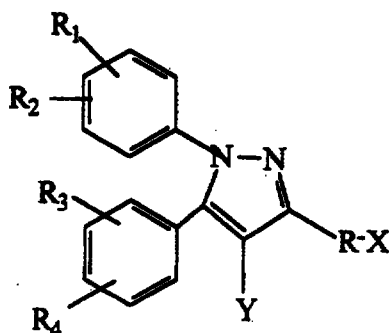
20 worin R_1 und R_3 ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl, Methyl, Phenyl und Methoxy, und

30 X ausgewählt ist aus der Gruppe bestehend aus Carboxy, $C(O)-R_5$, worin R_5 ausgewählt ist aus der Gruppe bestehend aus $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ und $ONH(t-C_4H_9)$.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

- 35 1. Composé ayant une structure qui correspond à la formule I :



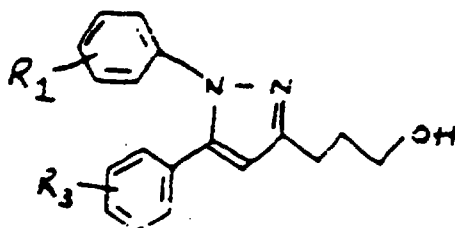
50 dans laquelle

R_1 , R_2 , R_3 et R_4 sont identiques ou différents et sont individuellement choisis dans le groupe formé par un hydrogène, un alkyle en C_{1-8} , un alcoxy en C_{1-8} , un phényle, un halo, un hydroxy, un alkyle en C_{1-8} sulfonyle, un thioalkyle en C_{1-8} , un nitro, un trifluorométhyle, un oméga-trifluorométhyle alcoxy en C_{1-8} , ou un amino un acétamido, un carboxy, un acide alkylhydroxamique ou R_1R_2 ou R_3R_4 , pris ensemble avec le groupe phényle auquel ils sont attachés, forment un naptyle ;

R est un hydrocarbure à chaîne linéaire, saturé ou insaturé qui contient 2-16 atomes de carbone ;

Y est un hydrogène, un bromo, un chloro ou un alkyle en C_{1-4} ;

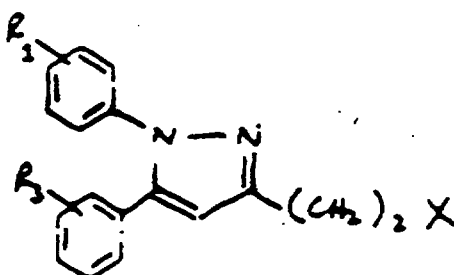
et X est choisi dans le groupe formé par un carboxy, un hydroxy, un acétoxy, un alcanoyloxy, un



II

10 worin R_1 und R_3 ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl und Methoxy.

14. Verfahren nach einem der Ansprüche 1 bis 4, in dem das 1,5-Diaryl-3-(ω -substituierte Alkyl)pyrazol eine Struktur gemäß der Formel III aufweist:



III

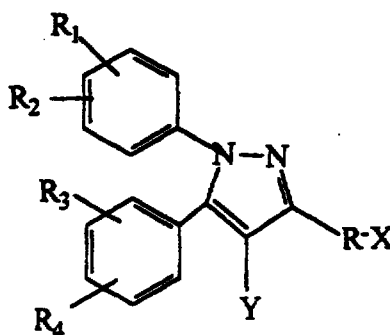
25 worin R_1 und R_3 ausgewählt sind aus der Gruppe bestehend aus Halogen, Trifluormethyl, Methyl, Phenyl und Methoxy, und

30 X ausgewählt ist aus der Gruppe bestehend aus Carboxy, $C(O)R_5$, worin R_5 ausgewählt ist aus der Gruppe bestehend aus $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ und $ONH(t-C_4H_9)$.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

35 1. Composé ayant une structure qui correspond à la formule I :



50 dans laquelle

R_1 , R_2 , R_3 et R_4 sont identiques ou différents et sont individuellement choisis dans le groupe formé par un hydrogène, un alkyle en C_{1-8} , un alcoxy en C_{1-8} , un phényle, un halo, un hydroxy, un alkyle en C_{1-8} sulfonyle, un thioalkyle en C_{1-8} , un nitro, un trifluorométhyle, un oméga-trifluorométhyle alcoxy en C_{1-8} , ou un amino un acétamido, un carboxy, un acide alkylhydroxamique ou $R_1 R_2$ ou $R_3 R_4$, pris ensemble avec le groupe phényle auquel ils sont attachés, forment un naphtyle ;

R est un hydrocarbure à chaîne linéaire, saturé ou insaturé qui contient 2-16 atomes de carbone ;

Y est un hydrogène, un bromo, un chloro ou un alkyle en C_{1-4} ;

et X est choisi dans le groupe formé par un carboxy, un hydroxy, un acétoxy, un alcanoyloxy, un



alcoxy en C₁₋₈, un alkyle en C₁₋₆, carbonyle, un oximino, un cyano, un amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₆OH, -NHR₁₃, -C(R₁₄)=NNH-2-thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)- alkyle en C₁₋₈ ;

dans lesquels R₅ est choisi dans le groupe formé par un hydrogène, un alkyle, un alcoxy en C₁₋₈, NR₆R₇ et -O-NR₁₅R₁₆ ;

5 dans lesquels R₆ et R₇ sont identiques ou différents et sont choisis dans le groupe formé par un hydrogène, un alkyle en C₁₋₈, un alcoxy en C₁₋₈, un hydroxy, un acyloxy, un benzyloxy, un 2-hydroxy alkyle en C₁₋₈, un alkyle en C₁₋₈ carboxy, un phényle, un pyridyle, un thiazolyle, un dihydrothiazolyle, un 5-tétrazolyle, un ω-alcanoate, -OCO(CH₂)_n -COR₉ et -OCOR₁₀ ;

10 dans lesquels R₈ est un hydrogène, -CO- alkyle en C₁₋₈, -CO-t-butyle, -COC₇H₁₅, -CO-phényle, SO₂-alkyle en C₁₋₈, -COCO₂- alkyle en C₁₋₈ ou -COCONHOH ;

dans lesquels R₉ est -OH, -ONa, un dialkylamino et n égal 2 ou 3 ;

dans lesquels R₁₀ est -CH₂NR₁₁R₁₂, -CH₂Cl, -CH₂O- alkyle en C₁₋₈, t-butyle, ou -CH- alkyle en C₁₋₈-CO₂ Q, dans lequel Q est un alkyle en C₁₋₈ ou H ;

15 dans lesquels R₁₁ et R₁₂ sont identiques ou différents et sont choisis parmi un alkyle, un cyclohexyle, ou ensemble forment un N-méthylpipérazino ;

dans lesquels R₁₃ est un hydrogène, -CO- alkyle en C₁₋₈, -CO-t-butyle, -COC₇H₁₅, -CO-phényle, -SO₂- alkyle en C₁₋₈, -COCO₂- alkyle en C₁₋₈, -COCONHOH, -COCO₂H, COCON(alkyle en C₁₋₈) OH ou PO(O- alkyle en C₁₋₈)₂ ;

dans lesquels R₁₄ est un hydrogène, un alkyle en C₁₋₈, un phényle ou un t-butyle ;

20 dans lesquels R₁₅ et R₁₆ sont identiques ou différents et sont choisis dans le groupe formé par un hydrogène, un alkyle en C₁₋₈ et un phényle ;

avec les conditions que :

(a) quand Y est un bromo ou un chloro, X est -COOH, -CH₂OH ou -C(O)-R₅ dans lequel R₅ est NR₆R₇ et R₆ est OH et R₇ est un alkyle en C₁₋₈ ;

25 (b) au moins une paroi R₁ et R₂ est différent de l'hydrogène où (i) R-X est (CH₂)₂CO₂H ou (CH₂)₂C(O)NHOH, et (ii) R₃ et R₄ sont des 4-méthoxy, 3-méthoxy-4-hydroxy, 2-hydroxy ou un hydrogène, et

(c) au moins un parmi R₁ et R₂ ou R₃ et R₄ est différent de l'hydrogène où R-X ensemble contient trois atomes de carbone saturés liés ensemble par des liaisons carbone-carbone ;

ou le composé

30 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide,

Ethyl 3-[5-(4-chlorophényl)-1-méthoxyphényl)-3-pyrazolyl] propanamide-N-acétate,

3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-(N-hydroxyacétamido)propanamide 1-4-hydrate,

35 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-(N-hydroxy-N-méthylacétamido) propanamide,

Ethyl N-[2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]éthylcarbonyl]-(R)-cystéinate hémi-hydrate,

Ethyl N-[2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]éthylcarbonyl]-S-méthyl-(R)-cystéinate, ou

40 3-(3-Adétoacétoxypropyl)-5-(4-chlorophényl)-1-(4-méthoxyphényl) pyrazole ;

et les sels pharmaceutiquement acceptables de ceux-ci.

2. Composé selon la revendication 1, dans lequel R₂ et R₄ sont un hydrogène, et R₁ et R₃ sont choisis dans le groupe formé par un halo, un trifluorométhyle, un alkyle en C₁₋₈ et un alcoxy en C₁₋₈.

3. Composé selon la revendication 2, dans lequel R est un hydrocarbure à chaîne linéaire, saturé et contient trois atomes de carbone liés ensemble par des liaisons carbone-carbone.

4. Composé selon la revendication 3, dans lequel X est choisi dans le groupe formé par un hydroxy, un carboxy, un sel carboxylate d'un cation pharmaceutiquement acceptable, C(O)-NR₆R₇ dans lequel R₆ et R₇ sont choisis dans le groupe formé par un hydrogène, un hydroxyle, un méthyle, un t-butyle, un 2-hydroxyéthyle et un carboxyméthyle.

5. Composé selon la revendication 2, dans lequel R est insaturé et contient de 2 à 16 atomes de carbone.

6. Composé selon la revendication 5, dans lequel X est un carboxyle ou un sel de celui-ci.



7. Composé selon la revendication 1, choisi dans le groupe formé par le N-carboxyméthyl-3-[5-(4-chlorophényl)-1'-(4-méthoxyphényl)-3-pyrazolyl] propanamide, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxy-propanamide, et le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-éthyl-N-hydroxypropanamide.

8. Composé selon la revendication 1, choisi dans le groupe formé par le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-N-phényl-propanamide, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]propylamine, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]propanal, le 5-(4-chlorophényl)-3-(3-oximino-propyl)-1-(4-méthoxyphényl)-pyrazole et le 3-(3-hydroxypropyl)-1-(4-méthoxyphényl)-5-(4-tolyl)pyrazole.

9. Composé selon la revendication 1 qui est l'un quelconque des composés individuels suivants :
 - 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-N-méthylpropanamide ;
 - 5-(4-chlorophényl)-3-(3-hydroxypropyl)-1-(4-méthoxyphényl) pyrazole ;
 - 5-(4-trifluorométhylphényl)-3-(3-hydroxypropyl)-1-(4-méthoxyphényl) pyrazole ;
 - 1-(4-bromophényl)-5-(4-chlorophényl)-3-(3-hydroxypropyl)pyrazole ;
 - sodium 8-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl 5(Z)-octénoate ;
 - sodium 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl] propanoate ;
 - 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide ;
 - 3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-N-hydroxy-N-méthyl propanamide ;
 - 3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-N-méthyl-N-succinyloxypropanamide ;
 - 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N'-N'-diméthylglycinyloxy-N-méthylpropanamide ;
 - N-[3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl] propyl]-N, N'-dihydroxyoxamide ; ou
 - N-acétyl-N-acétoxy [5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl] propanamide.

10. Composition pharmaceutique pour administration topique, orale, parentérale ou en aérosol, comprenant une quantité efficace d'un composé pyrazole substitué selon l'une des revendications 1 à 9, comme ingrédient actif dispersé dans un porteur pharmaceutiquement acceptable.

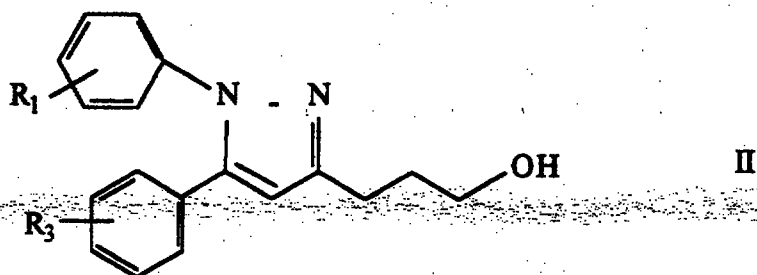
11. Composition pharmaceutique selon la revendication 10, dans laquelle ledit composé pyrazole substitué est capable d'inhiber à la fois les voies de synthèses cyclooxygénase et de lipoxygénase dans la quantité présente dans la composition quand ladite composition est introduite dans un mammifère.

12. Composé pyrazole substitué comme défini dans l'une quelconque des revendications 1 à 9 sans les conditions ou composition pharmaceutique selon la revendication 10 ou 11 pour utilisation dans le soulagement d'inflammation, d'asthme, d'hypersensibilité, ischémie du myocarde, d'état dermatologique tel que le psoriasis, la dermatite, et les états inflammatoires gastrointestinaux tels que les syndromes inflammatoires des intestins.

13. Procédé de synthèse de 1,5-diaryl-3-(oméga- alkyle inférieur substitué)-pyrazole selon l'une quelconque des revendications 1 à 9, comprenant la réaction d'une arylhydrazine avec un 1-aryl-(oméga-substitué)-alkyl-1, 3-dione contenant au moins 4 carbones dans la chaîne alkyle, ladite réaction étant mise en oeuvre dans un solvant qui est substantiellement inerte auxdites conditions de réaction, et ledit substituant oméga étant substantiellement inerte auxdites conditions de réaction, dans lequel lesdits groupes aryles sont identiques ou différents et sont des phényles mono-ou di-substitués dans lequel lesdits substituants phényles sont choisis parmi le groupe formé par un hydrogène, un alkyle en C₁₋₈, un alcoxy en C₁₋₈, un phényle, un halo, un hydroxy, un alkyle en C₁₋₈ sulfonyle, un alkyle en C₁₋₈ thio, un nitro, un trifluorométhyl, un oméga-trifluorométhyl alcoxy en C₁₋₈ et un naphthyle.

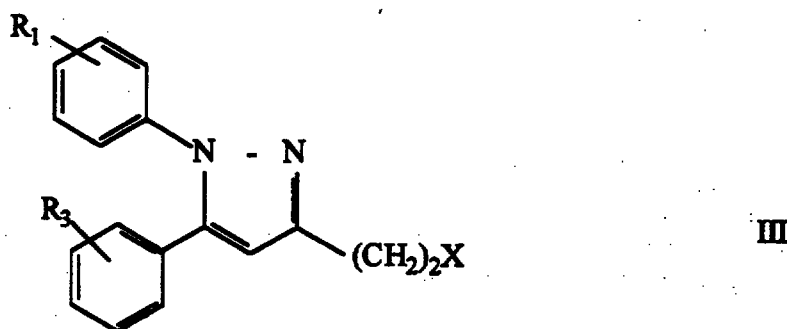


14. Composé ayant une structure qui correspond à la formule II :



15 dans laquelle R_1 et R_3 sont choisis dans le groupe formé par un halo, un trifluorométhyle, un méthyle et un méthoxy.

15. Composé ayant une structure qui correspond à la formule III :



dans laquelle R_1 et R_3 sont choisis dans le groupe formé par un halo, un trifluorométhyle, un méthyle, un phényle et un méthoxy ; et

X est choisi dans le groupe formé par un carboxy, $C(O)-R_5$ dans lequel R_5 est choisi dans le groupe formé par $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ et $ONH(t-C_4H_9)$.

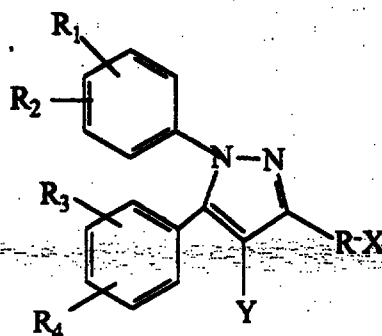
16. Procédé de synthèse d'un 1,5-diaryl-3-(alkyl oméga substitué)pyrazole selon l'une quelconque des revendications 1 à 9 comprenant une étape de modification de groupe fonctionnel de conversion d'un 1,5-diaryl-3-(alkyl oméga substitué) pyrazole, dans lequel le substituant oméga est un hydroxy, un aldéhyde, un carboxy ou un groupe chlorure d'acide, en un 1,5-diaryl-3-(alkyl oméga substitué) pyrazole, dans lequel le substituant oméga est un carboxy, un hydroxy, un acétoxy, un alkanoyloxy, un alcoxy en C_{1-8} , un alkyl en C_{1-6} carbonyle, un oximino, un cyano, un amino, $C(O)-R_5$, $-C(O)C(O)-R_5$, $-NR_6OH$, $-NHR_{13}$, $-C(R_{14})=NNH$ -thiazolino, $-CH(OH)R_{14}$, ou $-C(=NH)N(OH)-$ groupe alkyle C_{1-8} dans lequel R_5 , R_6 , R_{13} et R_{14} sont comme définis à la revendication 1.

17. Procédé selon la revendication 16, comprenant la réaction d'un 1,5-diaryl-3-(alkyl oméga substitué par un chlorure d'acide)-pyrazole avec un composé alkyl hydroxylamine de formule R_6NHOH pour donner un 1,5-diaryl-3-(alkyl oméga substitué par $-C(O)NR_6OH$)-pyrazole.

18. Procédé de préparation d'une composition pharmaceutique comprenant la dispersion d'un composé selon l'une quelconque des revendications 1 à 9 dans un porteur pharmaceutiquement acceptable.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé de synthèse d'un 1,5-diaryl-3-(alkyle inférieur oméga substitué)-pyrazole ayant une structure qui correspond à la formule I :



I

dans laquelle

R₁, R₂, R₃ et R₄ sont identiques ou différents et sont individuellement choisis dans le groupe formé par un hydrogène, un alkyle en C₁₋₈, un alcoxy en C₁₋₈, un phényle, un halo, un hydroxy, un alkyle en C₁₋₈ sulfonyle, un thio alkyle en C₁₋₈, un nitro, un trifluorométhyle, un oméga-trifluorométhyle, un alcoxy en C₁₋₈, un amino, un acétamido, un carboxy, un acide alkylhydroxamique ou R₁R₂ ou R₃R₄, pris ensemble avec le groupe phényle auquel ils sont attachés, forment un naphthyle ;

R est un hydrocarbure à chaîne linéaire, saturé ou insaturé qui contient 2-16 atomes de carbone ;

Y est un hydrogène, un bromo, un chloro ou un alkyle en C₁₋₄ ;

et X est choisi dans le groupe formé par un carboxy, un hydroxy, un acétoxy, un alcanoyloxy, un alcoxy en C₁₋₈, un alkyle en C₁₋₆ carbonyle, un oximino, un cyano, un amino, C(O)-R₅, -C(O)C(O)-R₅, -NR₆OH, -NHR₁₃,

-C(R₁₄)=NNH-2-thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)- alkyle en C₁₋₈ ;

dans lesquels R₅ est choisi dans le groupe formé par un hydrogène, un alkyle, un alcoxy en C₁₋₈, NR₆R₇ et -O-NR₁₅R₁₆ ;

dans lesquels R₆ et R₇ sont identiques ou différents et sont choisis dans le groupe formé par un hydrogène, un alkyle C₁₋₈, un alcoxy en C₁₋₈, un hydroxy, un acyloxy, un benzyloxy, un 2-hydroxy alkyle en C₁₋₈, un alkyle en C₁₋₈ carboxy, un phényle, un pyridyle, un thiazolyloxy, un dihydrothiazolyloxy, un 5-tétrazolyloxy, un ω-alcanoate, -OCO(CH₂)_n-COR₉ et -OCOR₁₀ ;

dans lesquels R₈ est un hydrogène, -CO-C₁₋₈ alkyle en C₁₋₈ -CO-t-butyle, -COC₇H₁₅, CO-phényle, SO₂-alkyle en C₁₋₈, -COCO₂- alkyle en C₁₋₈ ou -COCONHOH ;

dans lesquels R₉ est -OH, -ONa, un dialkylamino et n égal 2 ou 3 ;

dans lesquels R₁₀ est -CH₂NR₁₁R₁₂, -CH₂Cl, -CH₂O- alkyle en C₁₋₈, t-butyle, ou

-CH- alkyle en C₁₋₈ CO₂ Q, dans lequel Q est un alkyle en C₁₋₈ ou H ;

dans lesquels R₁₁ et R₁₂ sont identiques ou différents et sont choisis parmi un alkyle, un cyclohexyle, ou ensemble forment un N-méthylpipérazino ;

dans lesquels R₁₃ est un hydrogène, -CO- alkyle en C₁₋₈, -CO-t-butyle, -COC₇H₁₅, -CO-phényle, -SO₂- alkyle en C₁₋₈, -COCO₂- alkyle en C₁₋₈, -COCONHOH, -COCO₂H, COCON(alkyle en C₁₋₈) OH ou PO(O-alkyle en C₁₋₈)₂ ;

dans lesquels R₁₄ est un hydrogène, un alkyle en C₁₋₈, un phényle ou un t-butyle ;

dans lesquels R₁₅ et R₁₆ sont identiques ou différents et sont choisis dans le groupe formé par l'hydrogène, un alkyle en C₁₋₈ et le phényle ;

avec les conditions que :

(a) quand Y est un bromo ou un chloro, X est -COOH, -CH₂OH ou -C(O)-R₅ dans lequel R₅ est NR₆R₇ et R₆ est OH et R₇ est un alkyle en C₁₋₈ ;

(b) au moins un parmi R₁ et R₂ est différent de l'hydrogène où (i) R-X est (CH₂)₂CO₂H ou (CH₂)₂C(O)NHOH, et (ii) R₃ et R₄ sont un 4-méthoxy, un 3-méthoxy-4-hydroxy, un 2-hydroxy ou un hydrogène, et

(c) au moins un parmi R₁ et R₂ ou parmi R₃ et R₄ est différent de l'hydrogène où R-X ensemble contient trois atomes de carbone saturés liés ensemble par des liaisons carbone-carbone ;

ou le composé

3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide,

Ethyl 3-[5-(4-chlorophényl)-1-méthoxyphényl)-3-pyrazolyl] propanamide-N-acétate,

3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-(N-hydroxyacétamido)propanamide 14-hydrate,



3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-(N-hydroxy-N-méthylacétamido) propanamide,

Ethyl N-[2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]éthylcarbonyl]-(R)-cystéinate hémi-hydrate,

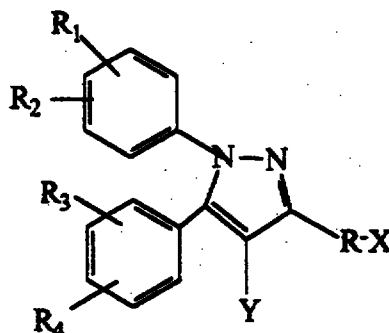
5 Ethyl N-[2-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]éthylcarbonyl]-S-méthyl-(R)-cystéinate, ou

3-(3-Adétoacétoxypropyl)-5-(4-chlorophényl)-1-(4-méthoxyphényl) pyrazole ;

et les sels pharmaceutiquement acceptables de ceux-ci;

le procédé comprenant la réaction d'une arylhydrazine avec un 1-aryl-oméga substitué)-alkyl-1, 3-
10 dione contenant au moins 4 carbones dans la chaîne alkyle, ladite réaction étant mise en oeuvre dans un solvant qui est substantiellement inerte auxdites conditions de réaction, et ledit substituant oméga étant substantiellement inerte auxdites conditions de réaction, dans lequel lesdits groupes aryles sont identiques ou différents et sont des phényl mono ou di-substitués dans lequel lesdits substituants phényles sont choisis parmi le groupe formé par l'hydrogène, un alkyle en C₁₋₈, un alcoxy en C₁₋₈, un
15 phényle, un halo, un hydroxy, un alkyle en C₁₋₈ sulfonyle, un thio alkyle en C₁₋₈, un nitro, un trifluorométhyle, un oméga-trifluorométhyle alcoxy en C₁₋₈ et un naphthyle.

2. Procédé de synthèse d'un 1,5-diaryl-3-(alkyle oméga substitué)pyrazole ayant une structure qui correspond à la formule I :



dans laquelle

35 R₁, R₂, R₃ et R₄ sont identiques ou différents et sont individuellement sélectionnés parmi le groupe formé par l'hydrogène, un alkyle en C₁₋₈, un alcoxy en C₁₋₈, un phényle, un halo, un hydroxy, un alkyle en C₁₋₈ sulfonyle, un thio alkyle en C₁₋₈, un nitro, un trifluorométhyle, un oméga-trifluorométhyle alcoxy en C₁₋₈, un amino, un acétamido, un carboxy, un acide alkylhydroxamique ou R₁ R₂ ou R₃ R₄, pris ensemble avec le groupe phényle auquel ils sont attachés, forment un naphthyle;

40 R est un hydrocarbure à chaîne linéaire, saturé ou insaturé qui contient 2-16 atomes de carbone;

Y est un hydrogène, un bromo, un chloro ou un alkyle en C₁₋₄ ;

et X est choisi parmi le groupe formé par un carboxy, un hydroxy, un acétoxy, un alcanoyloxy, un
alcoxy en C₁₋₈, un alkyle en C₁₋₆ carbonyle, un oximino, un cyano, un amino, C(O)-R₅, -C(O)C(O)-R₅,
-NR₈OH, -NHR₁₃,

45 -C(R₁₄)=NNH-2-thiazolino, -CH(OH)R₁₄, -C(=NH)N(OH)- alkyle en C₁₋₈ ;

dans lesquels R₅ est choisi parmi le groupe formé par un hydrogène, un alkyle, un alcoxy en C₁₋₈,
NR₆R₇ et -O-NR₁₅R₁₆ ;

dans lesquels R₆ et R₇ sont identiques ou différents et sont sélectionnés dans le groupe formé par
l'hydrogène, un alkyle en C₁₋₈, un alcoxy en C₁₋₈, un hydroxy, un acyloxy, un benzyloxy, un 2-
50 hydroxy alkyle en C₁₋₈, un alkyle en C₁₋₈ carboxy, un phényle, un pyridyle, un thiazolyle, un dihydrothiazolyle, un 5-tétrazolyle, un ω-alcanoate, -OCO(CH₂)_n-COR₉ et -OCOR₁₀ ;

dans lesquels R₈ est un hydrogène, un -CO-alkyle en C₁₋₈, -CO-t-butyle, -COC₇H₁₅, CO-phényle,
SO₂-alkyle en C₁₋₈, -COCO₂- alkyle en C₁₋₈ ou -COCONHOH ;

dans lesquels R₉ est -OH, -ONa, un dialkylamino et n égal 2 ou 3 ;

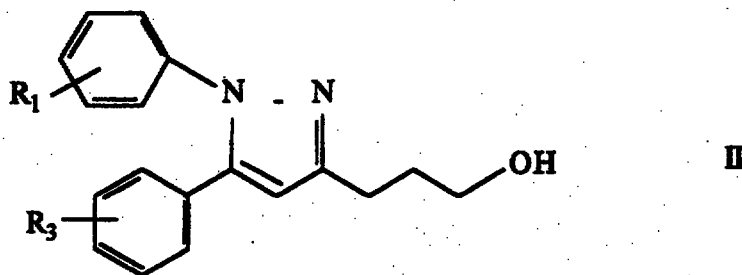
55 dans lesquels R₁₀ est -CH₂NR₁₁R₁₂, -CH₂Cl, -CH₂O- alkyle en C₁₋₈, t-butyle, ou

-CH- alkyle en C₁₋₈-CO₂ Q, dans lequel Q est un alkyle en C₁₋₈ ou H ;

dans lesquels R₁₁ et R₁₂ sont identiques ou différents et sont un alkyle, un cyclohexyle, ou ensemble forment le N-méthylpipérazino ;



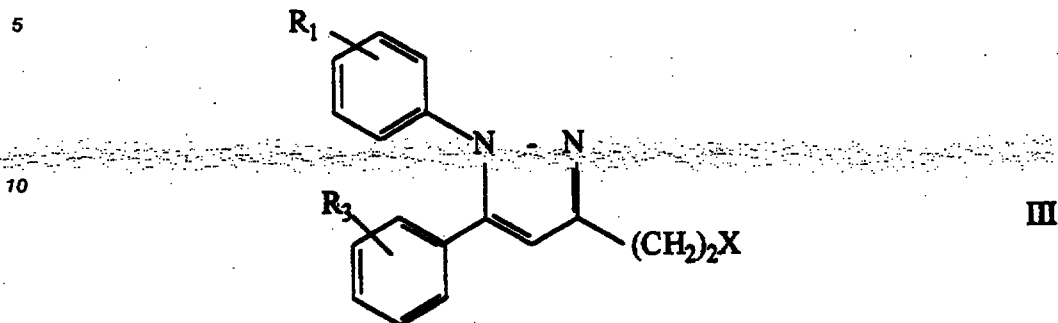
7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel X est choisi dans le groupe formé par un hydroxy un carboxy, un sel de carboxylate d'un cation pharmaceutiquement acceptable, $C(O)NR_6R_7$ dans lequel R_6 et R_7 sont choisis dans le groupe formé par un hydrogène, un hydroxyle, un méthyle, un t-butyle, un 2-hydroxyéthyle et un carboxyméthyle.
8. Procédé selon l'une quelconque des revendications 1 à 5 dans lequel R est insaturé et contient 2-16 atomes de carbone.
9. Procédé selon la revendication 8 dans lequel X est un carboxy ou un sel de celui-ci.
10. Procédé selon l'une quelconque des revendications 1 à 4 dans lequel le 1,5-diaryl-3-(alkyle oméga substitué) pyrazole est choisi dans le groupe formé par le N-carboxyméthyl-3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl] propanamide, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxy-propanamide, et le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-éthyl-N-hydroxypropanamide.
11. Procédé selon l'une quelconque des revendications 1 à 4, dans laquelle le 1,5-diaryl-3-(alkyle oméga substitué) pyrazole est choisi dans le groupe formé par le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-N-phényl-propanamide, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-propylamine, le 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]propanal, le 5-(4-chlorophényl)-3-(3-oximinopropyl)-1-(4-méthoxyphényl)-pyrazole et le 3-(3-hydroxypropyl)-1-(4-méthoxyphényl)-5(4-tolyl)pyrazole.
12. Procédé selon l'une quelconque des revendications 1 à 4 dans lequel le 1,5-diaryl-3-(alkyle oméga substitué) pyrazole est l'un quelconque des composés individuels suivants :
 - 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-hydroxy-N-méthylpropanamide ;
 - 5-(4-chlorophényl)-3-(3-hydroxypropyl)-1-(4-méthoxyphényl) pyrazole ;
 - 5-(4-trifluorométhylphényl)-3-(3-hydroxypropyl)-1-(4-méthoxyphényl) pyrazole ;
 - 1-(4-bromophényl)-5-(4-chlorophényl)-3-(3-hydroxypropyl)pyrazole ;
 - sodium 8-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-5(Z)octénoate ;
 - sodium 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]propanoate ;
 - 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide ;
 - 3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-N-hydroxy-N-méthyl propanamide ;
 - 3-[1-(4-méthoxyphényl)-5-(4-méthylphényl)-3-pyrazolyl]-N-méthyl-N-succinyloxypropanamide ;
 - 3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]-N'-N'-diméthylglycinyloxy-N-méthylpropanamide ;
 - N-[3-[5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl]propyl]-N, N'-dihydroxyoxamide ; ou
 - N-acétyl-N-acétoxy [5-(4-chlorophényl)-1-(4-méthoxyphényl)-3-pyrazolyl] propanamide.
13. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le 1,5-diaryl-3-(alkyle oméga substitué) pyrazole a une structure qui correspond à la formule II :



dans laquelle R_1 et R_3 sont choisis dans le groupe formé par un halo, un trifluorométhyle et un méthoxy.



14. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel le 1,5-diaryl-3-(alkyle oméga substitué) pyrazole a une structure qui correspond à la formule :



dans laquelle R_1 et R_3 sont choisis dans le groupe formé par un halo, un trifluorométhyle, un méthyle, un phényle et un méthoxy ; et

X est choisi dans le groupe formé par un carboxy, $C(O)-R_5$ dans lequel R_5 est choisi dans le groupe formé par $N(CH_3)OH$, $N(t-C_4H_9)OH$, $NHOH$, $ONH(CH_3)$ et $ONH(t-C_4H_9)$.