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(72) TALLEY, JOHN J., US
(72) PENNING, THOMAS D., US
(72) COLLINS, PAUL W., US
(72) ROGIER, DONALD J., JR., US
(72) MALECHA, JAMES W., US
(72) MIYASHIRO, JULIE M., US
(72) BERTENSHAW, STEPHEN R., US
(72) KHANNA, ISH K., US
(72) GRANETS, MATTHEW J., US
(72) ROGERS, ROLAND S., US
(72) CARTER, JEFFERY S., US
(72) DOCTER, STEPHEN H., US
(72) YU, STELLA S., US
(71) G.D. SEARLE & CO., US

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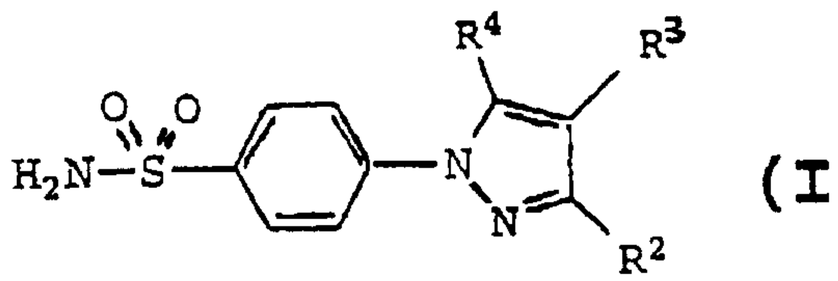
(54) **PYRAZOLYLE BENZENESULFONAMIDE SUBSTITUE ET LEURS COMPOSITIONS PHARMACEUTIQUES**

(54) **SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME**



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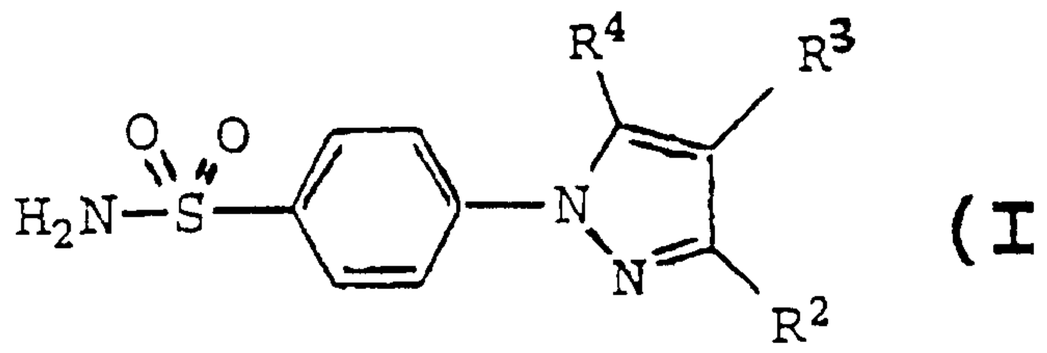
(57) The present invention is related to substituted pyrazolyl benzenesulfonamides of the Formula I (see formula I) wherein R2 is selected from hydrido, C1-C10-alkyl, C1-C6-haloalkyl, C1-C6-alkoxycarbonyl, cyano, carboxyl, C1-C6-cyanoalkyl, aminocarbonyl, C1-C6-alkylaminocarbonyl, C3-C7-cycloalkylaminocarbonyl, arylaminocarbonyl, C1-C6-carboxyalkylaminocarbonyl, aryl-C1-C6- alkoxycarbonyl-C1-C10-alkylaminocarbonyl, C1-C6-aminocarbonylalkyl, C1-C6-carboxyalkyl, C1-C6-alkoxycarbonylcyano-C2-C6-alkenyl and C1-C6-hydroxyalkyl; wherein R3 is selected from hydrido, C1-C10-alkyl, cyano, C1-C6-hydroxyalkyl, C3-C7-cycloalkyl, C1-C6-alkylsulfonyl, and halo; and wherein R4 is selected from optionally substituted C3-C10-cycloalkyl, C3-C10-cycloalkenyl and heterocyclic; provided R2 and R3 are not both hydrido, further provided that R4 is not triazolyl when R2 is methyl; and further provided that R4 is not substituted thienyl when R2 is trifluoromethyl; or a pharmaceutically-acceptable salt thereof. The invention is also related to pharmaceutical compositions containing such compounds.

ABSTRACT

The present invention is related to substituted pyrazolyl benzenesulfonamides of the Formula I



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wherein R^2 is selected from hydrido, C_1-C_{10}-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxycarbonyl, cyano, carboxyl, C_1-C_6-cyanoalkyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_7-cycloalkylaminocarbonyl, arylaminocarbonyl, C_1-C_6-carboxyalkylaminocarbonyl, aryl-C_1-C_6-alkoxycarbonyl-C_1-C_{10}-alkylaminocarbonyl, C_1-C_6-aminocarbonylalkyl, C_1-C_6-carboxyalkyl, C_1-C_6-alkoxycarbonylcyano-C_2-C_6-alkenyl and C_1-C_6-hydroxyalkyl;

wherein R^3 is selected from hydrido, C_1-C_{10}-alkyl, cyano, C_1-C_6-hydroxyalkyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylsulfonyl, and halo; and

wherein R^4 is selected from optionally substituted C_3-C_{10}-cycloalkyl, C_3-C_{10}- cycloalkenyl and heterocyclic;

provided R^2 and R^3 are not both hydrido, further provided that R^4 is not triazolyl when R^2 is methyl; and further provided that R^4 is not substituted thienyl when R^2 is trifluoromethyl; or a pharmaceutically-acceptable salt thereof.

The invention is also related to pharmaceutical compositions containing such compounds.

C-2779/2

SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

FIELD OF THE INVENTION

This invention is in the field of anti-inflammatory pharmaceutical agents and specifically relates to compounds and compositions containing such compounds.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase II (COX II)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

Pyrazoles have been described for use in the treatment of inflammation. U.S. Patent No. 5,134,142 to Matsuo et al describes 1,5-diaryl pyrazoles, and specifically, 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl pyrazole, as having anti-inflammatory activity.

U.S. Patent No. 3,940,418 to R. Hamilton describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. In addition, R. Hamilton [*J. Heterocyclic Chem.*, 13, 545 (1976)] describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. U.S. Patent No. 5,134,155 describes fused tricyclic pyrazoles having a saturated ring bridging the pyrazole and a phenyl radical as HMG-CoA reductase inhibitors. European publication EP 477,049, published Mar. 25, 1992, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]amides as having antipsychotic activity. European publication EP 347,773, published Dec. 27, 1989, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]propanamides as immunostimulants. M. Hashem et al [*J. Med. Chem.*, 19, 229 (1976)] describes fused tricyclic pyrazoles, having a saturated ring bridging the pyrazole and a phenyl radical, as antibiotics.

Certain substituted pyrazolyl-benzenesulfonamides have been described in the literature as synthetic intermediates. Specifically, 4-[5-(4-chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound as an intermediate for compounds having hypoglycemic activity [R. Soliman et al, *J. Pharm. Sci.*, 76, 626 (1987)]. 4-[5-[2-(4-Bromophenyl)-2*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound and described as potentially having hypoglycemic activity [H. Mokhtar, *Pak. J. Sci. Ind. Res.*, 31, 762 (1988)]. Similarly, 4-[4-bromo-5-[2-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]-3-

methyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared [H. Mokhtar et al, *Pak. J. Sci. Ind. Res.*, 34, 9 (1991)].

The phytotoxicity of pyrazole derivatives is described [M. Cocco et al, *Il. Farmaco-Ed. Sci.*, 40, 272 (1985)], specifically for 1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3,4-dicarboxylic acid.

The use of styryl pyrazole esters for antidiabetes drugs is described [H. Mokhtar et al, *Pharmazie*, 33, 649-651 (1978)]. The use of styryl pyrazole carboxylic acids for antidiabetes drugs is described [R. Soliman et al, *Pharmazie*, 33, 184-5 (1978)]. The use of 4-[3,4,5-trisubstituted-pyrazol-1-yl]benzenesulfonamides as intermediates for sulfonylurea anti-diabetes agents is described, and specifically, 1-[4-(aminosulfonyl)phenyl]-3-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic acid [R. Soliman et al, *J. Pharm. Sci.*, 72, 1004 (1983)] : A series of 4-[3-substituted methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamides has been prepared as intermediates for anti-diabetes agents, and more specifically, 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide [H. Feid-Allah, *Pharmazie*, 36, 754 (1981)]. In addition, 1-(4-[aminosulfonyl]phenyl)-5-phenylpyrazole-3-carboxylic acid has been prepared from the above described 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide compound [R. Soliman et al, *J. Pharm. Sci.*, 70, 602 (1981)].

EP-A 0 418 845 and EP-A 0 554 826 disclose pyrazole compounds wherein the position 1 is substituted by a thiosulfinyl or thiosulfonyl aryl group.

US-A 4 146 721 is concerned with pyrazole-4-acids and derivatives thereof.

All these compounds are said to be antiinflammatory. C.A. Vol. 111, No. 235651b discloses 1-(4-sulfamyl-phenyl)-5-phenylethenyl derivatives as well as (2- methyl-3-bromo-4-p-chlorophenyl)-1-(4-sulfamyl-phenyl)pyrazoles.

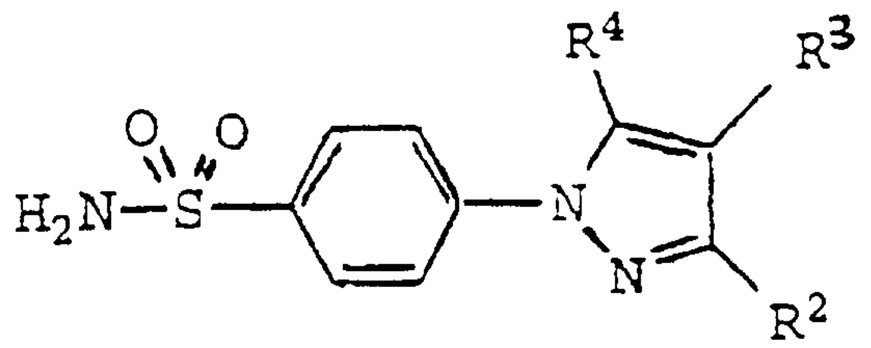
C.A. Vol. 114, No. 297194j discloses 1-(4-sulfamylphenyl)-4-(arylalkenyl)-pyrazole derivatives;

The same applies to the references C.A. Vol. 100, No. 34458d, also related to 1-(4-sulfamyl-phenyl)-4-(arylalkenyl)pyrazole derivatives.

From such compounds (i.e. the aryl alkenyl pyrazole derivatives) an antidiabetic activity has been indicated.

Description of the invention

A class of compounds useful as pharmaceutical agents is defined by Formula I:



(I)

wherein R^2 is selected from hydrido, C_1-C_{10}-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxycarbonyl, cyano, carboxyl, C_1-C_6-cyanoalkyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_7-cycloalkylaminocarbonyl, arylaminocarbonyl, C_1-C_6-carboxyalkylaminocarbonyl, aryl-C_1-C_6-alkoxycarbonyl-C_1-C_{10}-alkylaminocarbonyl, C_1-C_6-aminocarbonylalkyl, C_1-C_6-carboxyalkyl, C_1-C_6-alkoxycarbonylcyano-C_2-C_6-alkenyl and C_1-C_6-hydroxyalkyl;

wherein R^3 is selected from hydrido, C_1-C_{10}-alkyl, cyano, C_1-C_6-hydroxyalkyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylsulfonyl, and halo; and

wherein R^4 is selected from C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, C_1-C_6-alkylthio, C_1-C_6-alkylsulfonyl, cyano, nitro, C_1-C_6-haloalkyl, C_1-C_6-alkyl, hydroxyl, C_2-C_6-alkenyl, C_1-C_6-hydroxyalkyl, carboxyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylamino, C_1-C_{10}-dialkylamino, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, sulfamyl, five or six membered heterocyclic and amino; wherein aryl wherever occuring means phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl-,

provided R^2 and R^3 are not both hydrido, further provided that R^4 is not triazolyl when R^2 is methyl; and further provided that R^4 is not substituted thienyl when R^2 is trifluoromethyl; or a pharmaceutically-acceptable salt thereof.

The phrase "further provided", as used in the above description, is intended to mean that the denoted proviso is not to be considered conjunctive with any of the other provisos.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as antiinflammatory agents, such as for the

treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase II over cyclooxygenase I. Preferably, the compounds have a cyclooxygenase II IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase II inhibition over cyclooxygenase I inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase I IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Specifically preferred compounds of Formula (I) are the following:

4-[5-(1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-fluoro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-ethyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-methyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-chloro-1-methyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-dihydro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-fluoro-1-methyl-2,3-dihydro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(biphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,4-benzodioxan-6-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylcyclohexyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(methyl-1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methyl-1-cyclopentenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(benzofuran-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,3-benzodioxol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dimethyl-3-furyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-methyl-2-furyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-chloro-1-methyl-4-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dibromo-4-methylcyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methoxycyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dimethyl-3-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dichloro-3-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(benzofuran-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-indanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-methyl-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-dihydrobenzofuran-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-benzothienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydro-2H-1-benzopyran-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydro-2H-1-benzothiopyran-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-phenylethenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-1,3-benzodioxol-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyrazinyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(biphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,2,3,4-tetrahydronaphth-6-yl])-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-thiazolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-oxazolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cycloheptyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclopentenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methyl-3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylcyclohex-4-ene-1-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methoxy-2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten

carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical.

More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed

"heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include benzofuryl, 2,3-

dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The terms "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, or two alkyl radicals. More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl. The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. More preferred N-alkyl-N-arylaminosulfonyl radicals are "lower N-alkyl-N-arylsulfonyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower N-alkyl-N-aryl aminosulfonyl radicals include N-methyl-phenylaminosulfonyl and N-ethyl-phenylaminosulfonyl The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The terms "alkanoyl" or

"carboxyalkyl" embrace radicals having a carboxy radical as defined above, attached to an alkyl radical. The alkanoyl radicals may be substituted or unsubstituted, such as formyl, acetyl, propionyl (propanoyl), butanoyl (butyryl), isobutanoyl (isobutyryl), valeryl (pentanoyl), isovaleryl, pivaloyl, hexanoyl or the like. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes -(C=O)-. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. The term "alkylcarbonylalkyl", denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl, *tert*-butoxycarbonylethyl, and methoxycarbonylethyl. The term "aminocarbonyl" when used by itself or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", denotes an amide group of the formula $-C(=O)NH_2$. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one

alkyl radical and with two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. The term "aminocarbonylalkyl" embraces alkyl radicals substituted with aminocarbonyl radicals. The term "N-cycloalkylaminocarbonyl" denoted aminocarbonyl radicals which have been substituted with at least one cycloalkyl radical. More preferred are "lower cycloalkylaminocarbonyl" having lower cycloalkyl radicals of three to seven carbon atoms, attached to an aminocarbonyl radical. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an $-C(=NH)-NH_2$ radical. The term "cyanoamidino" denotes an $-C(=N-CN)-NH_2$ radical. The term "heterocyclicalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclicalkyl radicals are "lower heterocyclicalkyl" radicals having one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl, pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term

"cycloalkenyl" embraces unsaturated cyclic radicals having three to ten carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3-S-). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The terms "N-alkylamino" and "N,N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such as N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical. The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl

radical, respectively, to an amino group. The terms "N-arylaminoalkyl" and "N-aralkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aralkyl radical, respectively, and having the amino group attached to an alkyl radical. More preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical attached to one to six carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The terms "N-alkyl-N-arylaminoalkyl" and "N-aralkyl-N-alkylaminoalkyl" denote N-alkyl-N-arylamino and N-alkyl-N-aralkylamino groups, respectively, and having the amino group attached to alkyl radicals. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino or acetamido ($CH_3C(=O)-NH-$) where the amine may be further substituted with alkyl, aryl or aralkyl. The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio. The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. An example of "aralkylthio" is benzylthio. The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The term "haloaralkyl" embraces aryl radicals as defined above attached to haloalkyl radicals. The term "carboxyhaloalkyl" embraces carboxyalkyl radicals as defined above having halo radicals attached to the alkyl portion. The term "alkoxycarbonylhaloalkyl" embraces alkoxycarbonyl radicals as defined above substituted on a haloalkyl radical. The term "aminocarbonylhaloalkyl"

embraces aminocarbonyl radicals as defined above substituted on a haloalkyl radical. The term "alkylaminocarbonylhaloalkyl" embraces alkylaminocarbonyl radicals as defined above substituted on a haloalkyl radical. The term "alkoxycarbonylcyanoalkenyl" embraces alkoxycarbonyl radicals as defined above, and a cyano radical, both substituted on an alkenyl radical. The term "carboxyalkylaminocarbonyl" embraces aminocarbonyl radicals substituted with carboxyalkyl radicals, as defined above. The term "aralkoxycarbonylalkylaminocarbonyl" embraces aminocarbonyl radicals substituted with aryl-substituted alkoxycarbonyl radicals, as defined above. The term "cycloalkylalkyl" embraces cycloalkyl radicals having three to ten carbon atoms attached to an alkyl radical, as defined above. More preferred cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to lower alkyl radicals as defined above. Examples include radicals such as cyclopropylmethyl, cyclobutylmethyl, and cyclohexylethyl. The term "aralkenyl" embraces aryl radicals attached to alkenyl radicals having two to ten carbon atoms, such as phenylbutenyl, and phenylethenyl or styryl.

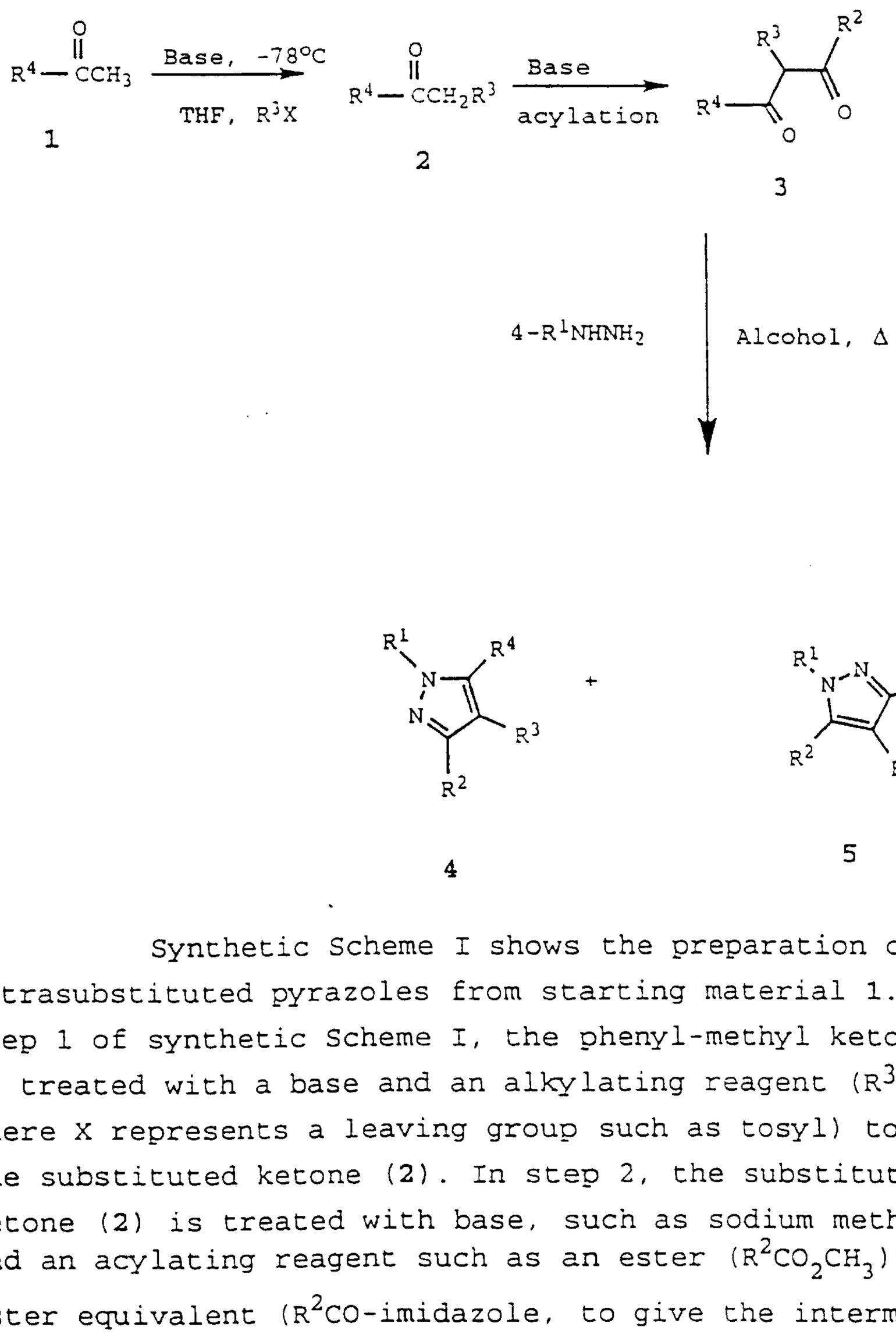
The present invention comprises a pharmaceutical composition for the treatment of inflammation and inflammation-associated disorders, such as arthritis, comprising a therapeutically-effective amount of a compound of Formula I, including those wherein R^4 is unsubstituted thienyl when R^2 is trifluoromethyl, in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-VIII, wherein the R^1-R^7 substituents are as defined for Formula I, above, except where further noted.

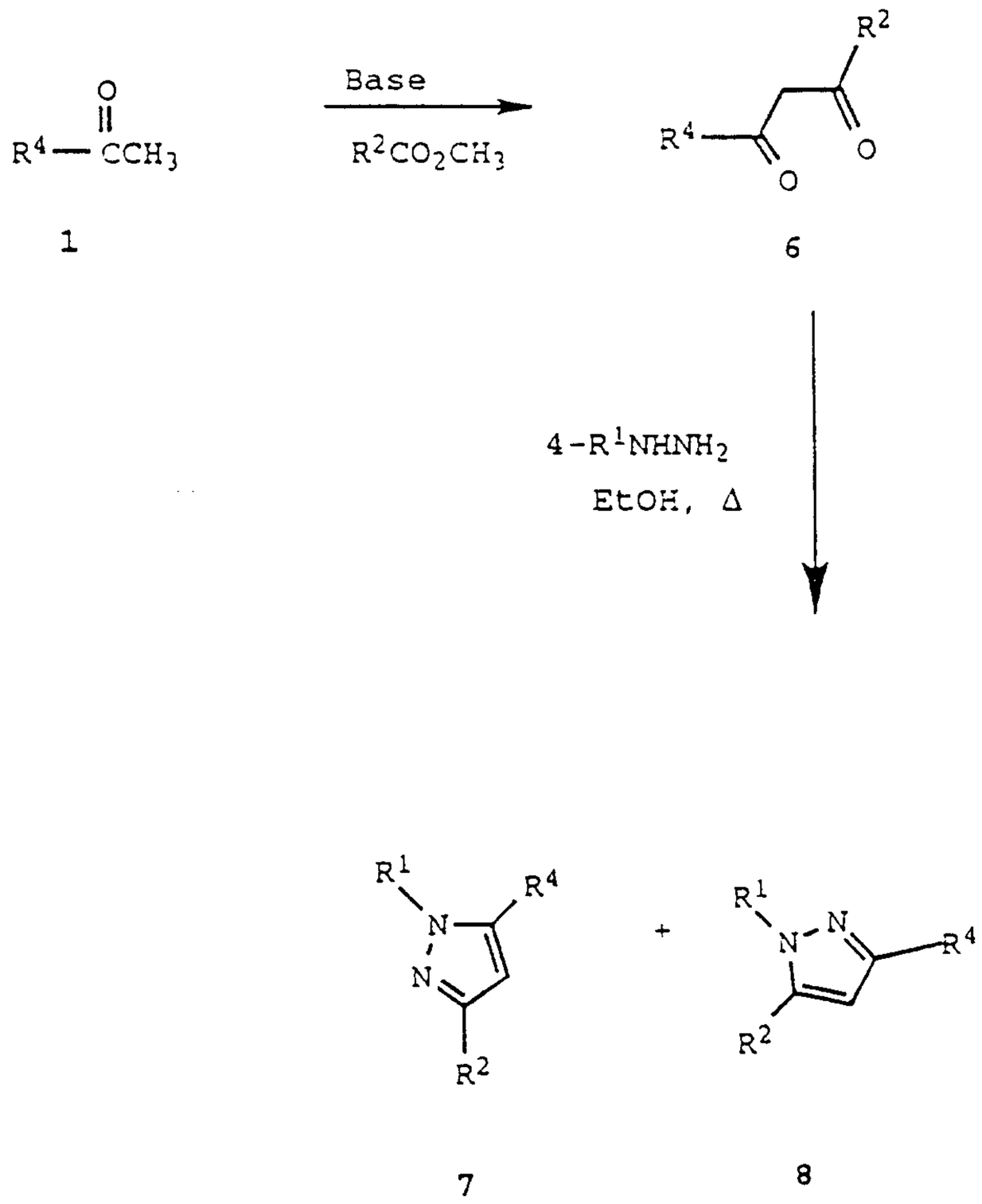
SCHEME I



Synthetic Scheme I shows the preparation of tetrasubstituted pyrazoles from starting material 1. In step 1 of synthetic Scheme I, the phenyl-methyl ketone (1) is treated with a base and an alkylating reagent (R^3X, where X represents a leaving group such as tosyl) to give the substituted ketone (2). In step 2, the substituted ketone (2) is treated with base, such as sodium methoxide, and an acylating reagent such as an ester ($R^2CO_2CH_3$), or ester equivalent (R^2CO-imidazole, to give the intermediate

diketone (3) in a procedure similar to that developed by Reid and Calvin, *J. Amer. Chem. Soc.*, **72**, 2948-2952 (1950). In step 3, the diketone (3) is reacted with a substituted hydrazine in acetic acid or an alcoholic solvent to give a mixture of pyrazoles (4) and (5). Separation of the desired pyrazole (4) can be achieved by chromatography or recrystallization.

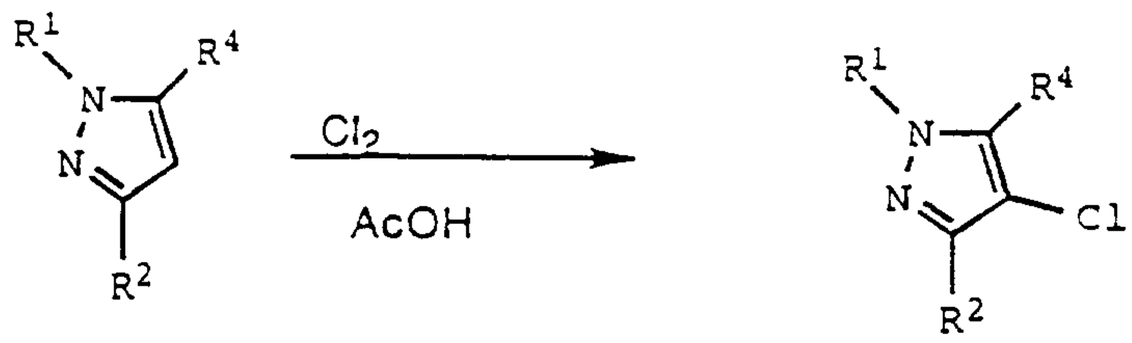
SCHEME II



Synthetic Scheme II shows the preparation of compounds embraced by Formula I, where R^3 is a hydrogen atom. In step 1, ketone (1) is treated with a base, preferably NaOMe or NaH, and an ester, or ester equivalent, to form the intermediate diketone (6) which is used without further purification. In step 2, diketone (6) in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the

free base of a substituted hydrazine at reflux for 10 to 24 hours to afford a mixture of pyrazoles (7) and (8). Recrystallization from diethyl ether/hexane or chromatography affords (7), usually as a light yellow or tan solid.

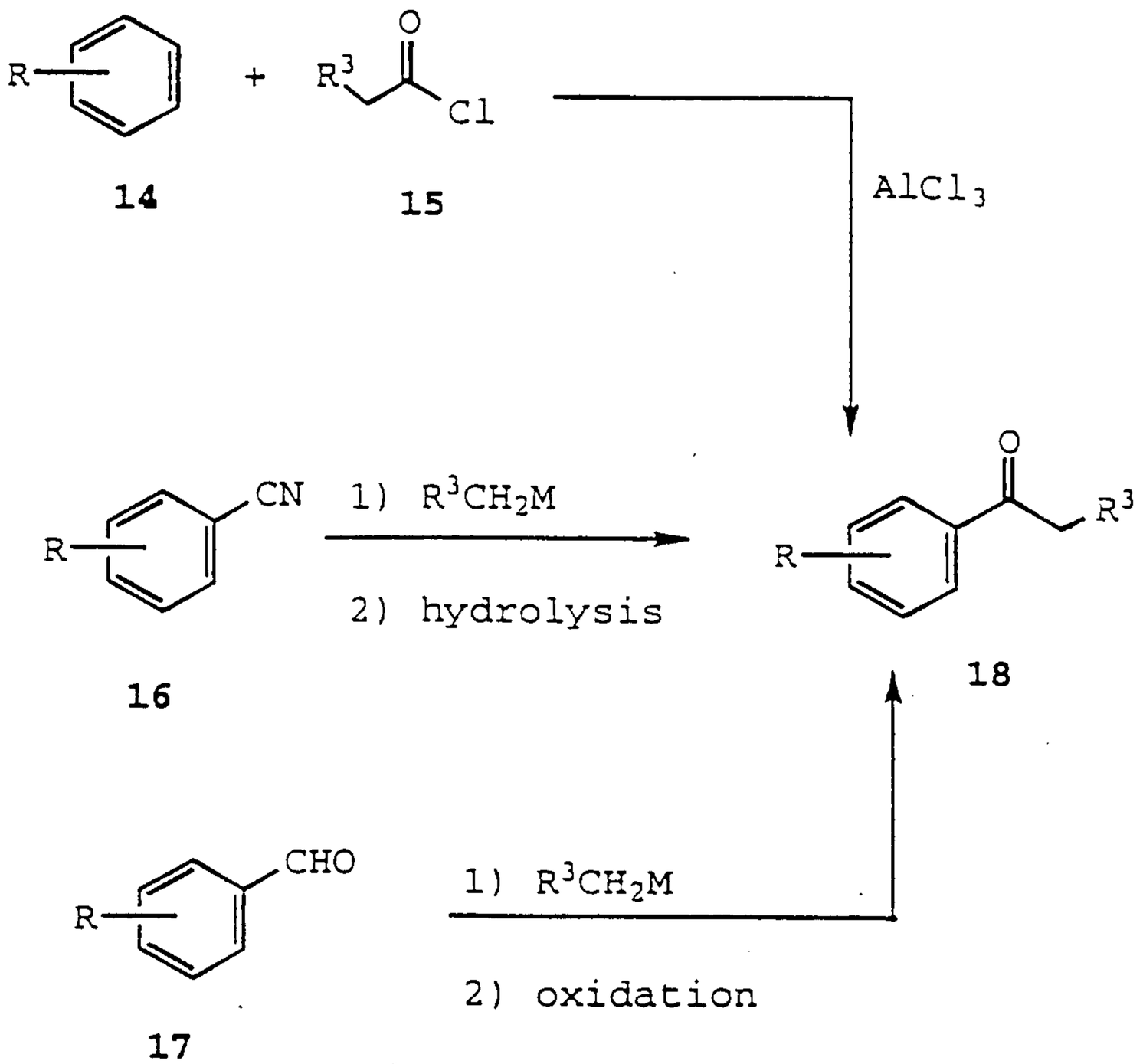
Scheme III



7 13

Synthetic Scheme III shows the preparation of pyrazole compounds (13), where R^3 is chlorine, from the available pyrazole compounds (7), where R^3 is hydrogen. Chlorination results from passing a stream of chlorine gas at room temperature through a solution containing (7).

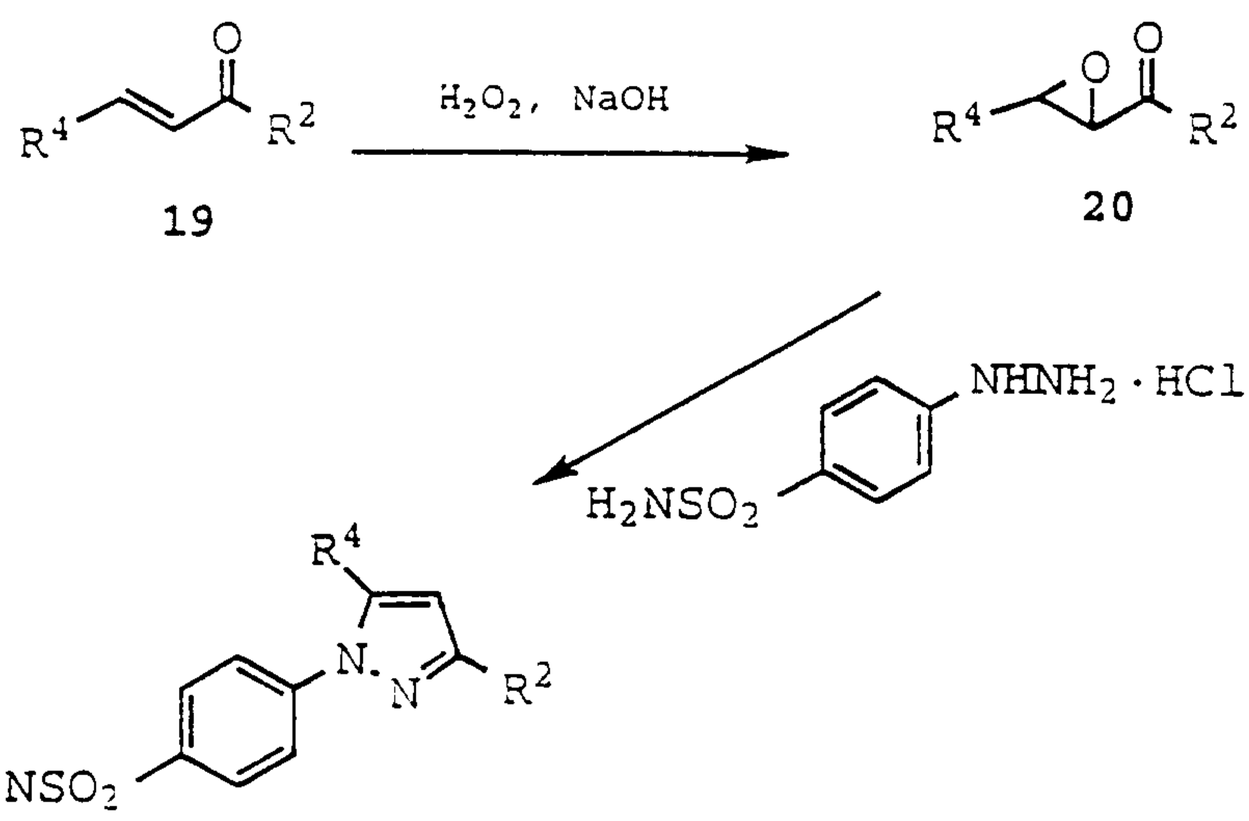
Scheme IV



14 15 16 17 18

Synthetic Scheme IV shows the preparation of substituted ketones 18 which are not commercially available as used in Scheme I. The ketones can be prepared by standard Friedel-Craft acylation of the starting substituted benzenes 14 with acid chlorides or anhydrides 15. Alternatively, the ketones can be prepared from phenylcarbonitriles 16 by standard organometallic techniques where M represents metals such as lithium, magnesium, and the like. An alternative organometallic route is shown from the aldehydes 17 where M represents metals such as lithium, magnesium, and the like. Oxidation with a suitable oxidizing agent, such as CrO_3, follows to produce the ketones.

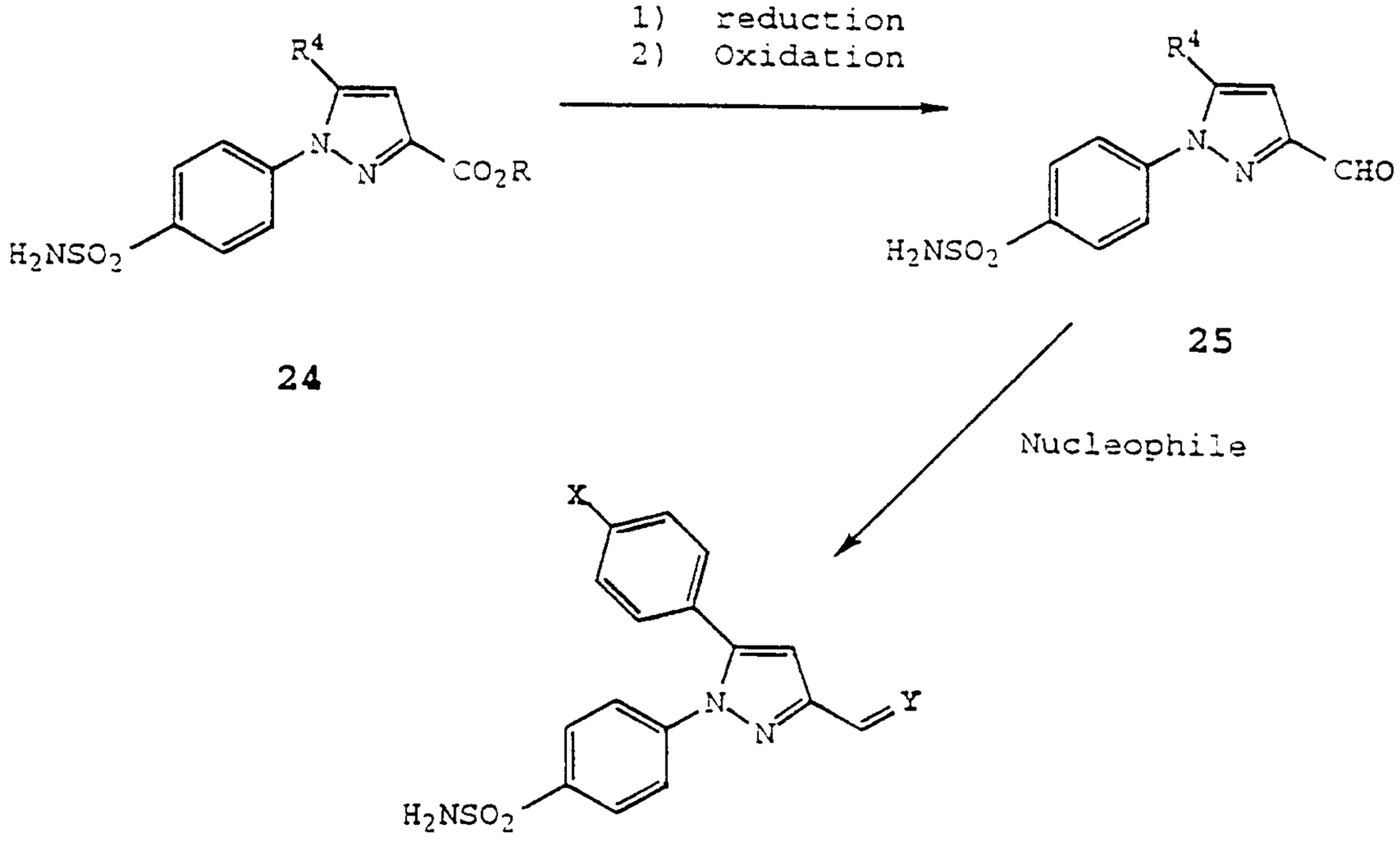
Scheme V



19 20 21

Synthetic Scheme V shows an alternative regioselective method of constructing the pyrazole 21. Commercially available enones 19 can be epoxidized to give epoxyketones 20, which are treated with 4-sulfonamidophenylhydrazine hydrochloride to provide the pyrazole 21.

Scheme VI



Synthetic Scheme VI shows the preparation of pyrazoles 26 from esters 24. Reduction of the ester 24 to the alcohol, preferably with lithium aluminum hydride (LAH) followed by oxidation, preferably with MnO_2, gives the aldehyde 25. Various nucleophiles (such as hydroxamates and 1,3-dicarbonyl compounds) can be condensed with the aldehyde to give the desired oximes or olefins 26.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I . These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention.

All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. HRMS is an abbreviation for High resolution mass spectrometry. In the following tables, "ND" represents "not determined".

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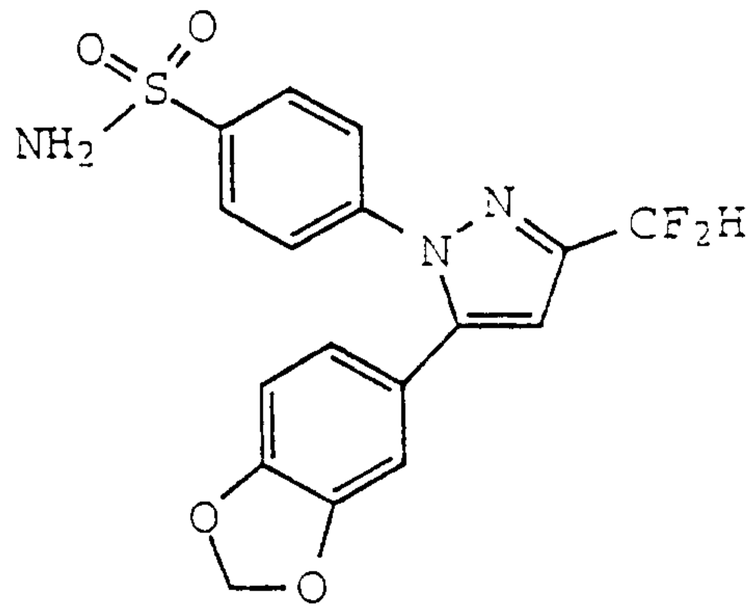
Example 1



4-[5-(1,3-Benzodioxol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1. Preparation of 1-(1,3-benzodioxol-5-yl)-4,4-difluorobutane-1,3-dione.

Ethyl difluoroacetate (1.72 g, 11 mmol) was dissolved in ether (25 mL). To the stirred solution was added 25% sodium methoxide (2.38 g, 11 mmol) followed by 3',4'-(methylenedioxy)acetophenone (1.64 g, 10 mmol). After stirring 16 hours, 1N HCl (25 mL) was added. The organic layer was collected and washed with water (2x25 mL), dried over magnesium sulfate, filtered, and concentrated. The resulting crude dione was used in the next step without further purification or characterization.

Step 2. Preparation of 5-(1,3-benzodioxol-5-yl)-4-[3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

1-(1,3-Benzodioxol-5-yl)-4,4-difluorobutane-1,3-dione from Step 1 (2.4 g, 10 mmol) was dissolved in ethanol (100 mL). To the stirred mixture was added 4-sulfonamidophenylhydrazine hydrochloride (2.46 g, 11 mmol) and heated to reflux for 16 hours. The mixture was cooled and water was added until crystals slowly appeared. Filtration yielded a light tan solid (3.3 g, 84 %): mp

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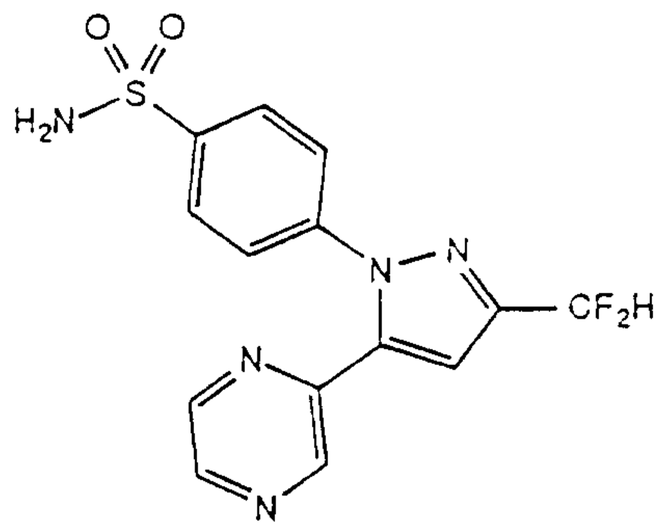
Example 2



4-[5-(2-Pyrazinyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

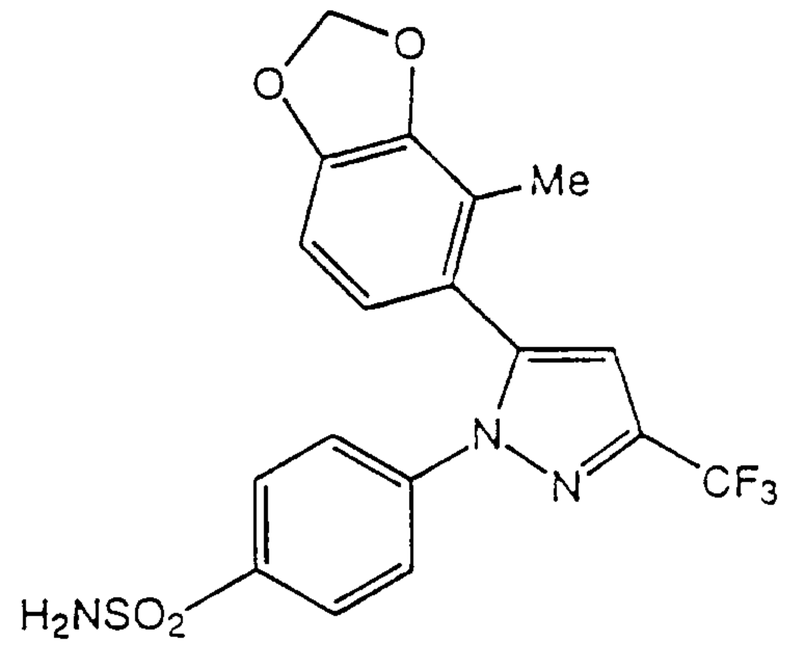
Step 1: Preparation of 4,4-difluoro-1-(2-pyrazinyl)-butane-1,3-dione.

Ethyl difluoroacetate (2.23 g, 18 mmol) was placed in a 100 mL round bottom flask and dissolved in ether (10 mL). To the stirred solution was added 25% sodium methoxide (4.68 g, 22 mmol) followed by acetylpyrazine (2.00 g,16 mmol). After two hours stirring at room temperature, a precipitate formed and THF (10 mL) was added to the reaction. The reaction was stirred an additional 25.9 hours, then treated with 3N HCl (10 mL). The organic layer was collected, washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* and recrystallized from methylene chloride/iso-octane to give the diketone as a brown solid (2.23 g, 68%); mp 103-110°C; ^1H NMR ($CDCl_3$) 300 MHz 14.00 (br s, 1H), 9.31 (d, J=1.4 Hz, 1H), 8.76 (d, J=2.4 Hz, 1H), 8.68 (dd, J=1.4 Hz 2.4 Hz, 1H), 7.20 (s, 1H), 6.03 (t, J=54.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) 300 MHz: -127.16 (d); M+ 200.

Step 2: Preparation of 4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

4-Sulfonamidophenylhydrazine hydrochloride (0.37 g, 1.65 mmol) was added to a stirred suspension of the diketone from Step 1 (0.30 g, 1.50 mmol) in ethanol (10 mL). The reaction was heated to reflux and stirred for 5.3 hours. The ethanol was removed *in vacuo*, and the residue was dissolved in ethyl acetate, washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a brown solid (0.36 g) which was recrystallized from ethyl acetate/ethanol/isooctane to give the pyrazole as a brown solid (0.20 g, 38%): mp 191-94°C; ^1H NMR (acetone d_6) 300 MHz 8.94(d, J=1.4 Hz, 1H), 8.62 (d, J=2.4 Hz, 1H), 8.52 (dd, J=1.4 Hz 2.4 Hz, 1H), 7.95 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H), 7.30 (s, 1H), 7.02 (t, J=54.6 Hz, 1H), 6.73 (br s, 2 H); ^{19}F NMR (acetone d_6) 300 MHz: -113.67 (d); M+ 351.

Example 3



4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Step 1: Preparation of 4-methyl-1,3-benzodioxole

11.6 g Adogen 464 and 7 mL of dibromomethane were refluxed in 50 mL of H_2O for 0.5 hours under argon. 3-Methylcatechol (8.89 g, 71.6 mmol) was added over 2 hours and the mixture refluxed for an additional 1 hour.

Distillation of the product from the reaction mixture afforded the title compound as a yellow oil: HRMS m/e 136.0524 (calc'd for $C_8H_8O_2$, 136.0524).

Step 2: Preparation of 5-acetyl-4-methyl-1,3-benzodioxole (A) and 6-acetyl-4-methyl-1,3-benzodioxole (B)

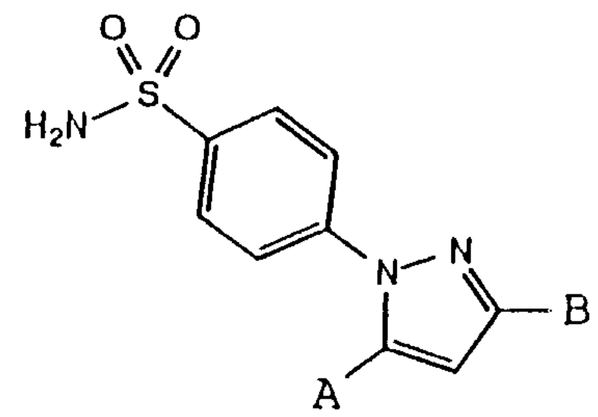
13.8 g of polyphosphoric acid and 5 mL of acetic anhydride were heated to 45°C under a drying tube of $CaSO_4$ until liquified. The product from Step 1 was added and the reaction was stirred at 45°C for 4.5 hours. The reaction was cooled to room temperature and quenched with 150 mL of ice water. The aqueous phase was washed with ethyl acetate (4x 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered to give the crude product as a red oil. The oil was chromatographed on silica gel eluting with 10% ethyl acetate/90% hexane to afford two products: A: Anal. calcd for $C_{10}H_{10}O_3$: C, 67.07; H, 5.66. Found: C, 67.41; H, 5.75, and B: MS, M^+ 178.

Steps 3 and 4: 4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

The title compound was prepared from product A using the procedures described in Example 2, Steps 1 and 2: White solid: Anal. calcd for $C_{18}H_{14}N_3O_4SF_3$: C, 50.82; H, 3.22; N, 9.88. Found: C, 50.71; H, 3.34; N, 9.55.

The following compounds in Table I were prepared according to procedures similar to that exemplified in Examples 2 and 3, with the substitution of the appropriate starting material.

TABLE I



Ex.	A	B	M.P.(°C)	Anal.
4	5-bromo-2-thienyl	CF_2H	168-169	M+Li 440/442
5	2-thienyl	CF_2H	190-191	M+Li 367
6	5-chloro-2-thienyl	CF_2H	168-170	M+ 389/391
7	1-cyclohexenyl	CF_2H	160-161	M+ 353.
8	1,4-benzodioxan	CF_2H	115-119	Calc. C,53.06; H,3.71; N, 10.32
				Obs. C,52.40; H,3.98; N,9.96
9	4-methylcyclohex-3-ene-1-yl	CF_2H	164-168	HRMS: 367.1194
10	2-methylcyclopenten-1-yl	CF_2H	165-166	HRMS: 353.1033
11	2,5-dimethyl-3-thienyl	CF_2H	125-127	Calc. C,50.12; H,3.94; N, 10.96
				Obs. C,50.21; H,3.92; N,11.00
12	2,5-dimethyl-3-furyl	CF_2H	139-142	Calc. C,52.31; H,4.12; N, 11.44
				Obs. C,52.07; H,4.16; N,11.37
13	5-methyl-2-furyl	CF_2H	177-179	Calc C,50.99; H,3.71; N, 11.89
				Obs. C,51.08; H,3.68; N, 11.95

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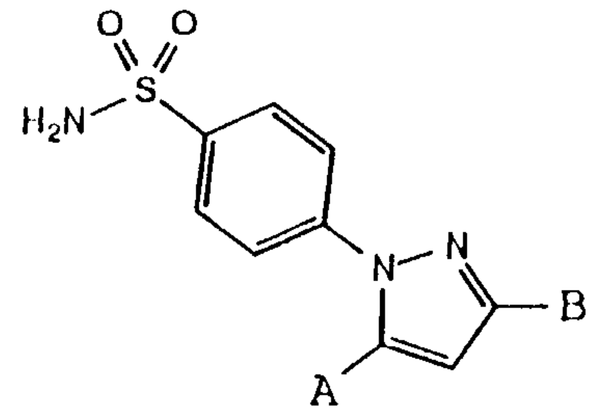
TABLE I (cont.)



Ex.	A	B	M.P.(°C)	Anal.
14	4-bromo-4-methylcyclohex-1-yl	CF_2H	175-178(dec)	HRMS: 448.0520
15	4-methylcyclohex-1-yl	CF_2H	190-192	HRMS: 369.1341
16	4-chloro-4-methylcyclohex-1-yl	CF_2H	197-199	HRMS: 403.0958
17	3,4-dibromo-4-methylcyclohex-1-yl	CF_2H	172-173	
18	2-methoxycyclohex-1-yl	CF_2H	177-179	HRMS: 386.1357
19	2-benzofuryl	CF_2H	215-217	Calc C,55.52; H,3.37; N,10.79
				Obs. C,55.52; H,3.32; N,10.85
20	2,5-dichloro-3-thien-yl	CF_2H	154-156	Calc. C,39.63; H, 2.14; N, 9.90
				Obs. C,39.63; H,2.13; N, 9.89
21	2-benzofuryl	CF_3	227-228	Calc. C, 53.07; H, 2.97; N, 10.31
				Obs. C, 53.02; H, 2.96; N, 10.39
22	5-chloro-2-thienyl	CF_3	161-165	HRMS: 406.9784

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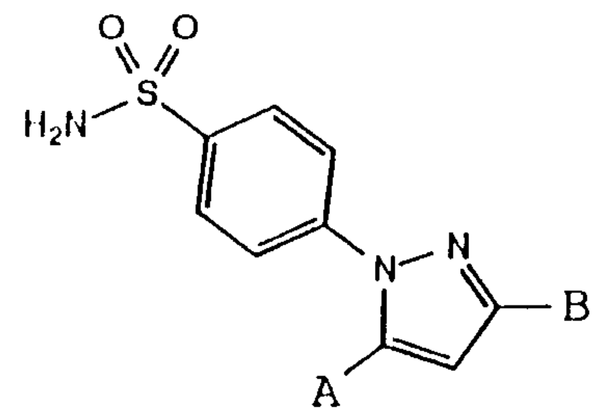
TABLE I (cont.)



Ex.	A	B	M.P.(°C)	Anal.
23	5-bromo-2-thienyl	CF_3	ND	Calc: C,37.18; H,2.01; N,9.29; Br, 17.67 Found: C, 37.25; H, 1.93; N, 9.45; Br, 17.40
24	5-indanyl	CF_3	118-120	Calc: C, 56.01; H, 3.96; N, 10.31 Found: C, 56.02; H, 4.06; N, 10.22
25	5-methylthien-2-yl	CF_3	188-190	Calc. C, 46.51; H, 3.12; N, 10.85 Found: C, 46.17; H, 3.10; N, 10.75
26	2,3-dihydrobenzofuryl	CF_3	152-153	Calc. C, 52.81; H, 3.45; N, 10.26 Found: C, 52.67; H, 3.78; N, 10.13
27	1-cyclohexenyl	CF_3	135-138	HRMS: 371.0918
28	6-tetrahydronaphthyl	CF_3	143-145	Calc. C, 57.00; H, 4.31; N, 9.97 Found: C, 56.72; H, 4.27; N, 9.90

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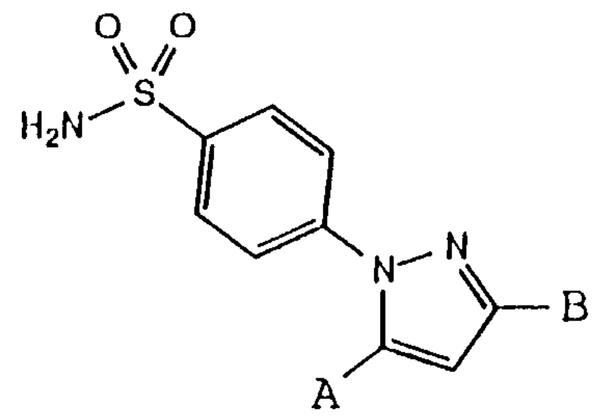
TABLE I (cont.)



Ex.	A	B	M.P.(°C)	Anal.
29	3-benzothienyl	CF_3	164-165	Calc. C, 51.06; H, 2.86; N, 9.92 Obs. C, 50.96; H, 2.73; N, 9.78
30	3,4-dihydrobenzopyranyl	CF_3	ND	HRMS : 423.0855
31	styryl	CF_3	166-167	Calc. C, 54.96; H, 3.59; N, 10.68 Obs. C, 54.77; H, 3.59; N, 10.47
32	4-methyl-1,3-benzodioxol-6-yl	CF_3	ND	Calc. C, 50.82; H, 3.22; N, 9.88 Obs. C, 50.64; H, 3.35; N, 9.72
33	3-pyridyl	CF_3	202-204	Calc. C, 48.91; H, 3.01; N, 15.21 Obs. C, 48.97; H, 3.16; N, 14.96
34	3,4-dihydrobenzothiopyranyl	CF3	ND	Calc. C,51.95; H, 3.67; N, 9.56 Obs. C, 51.98; H, 3.78; N, 9.48

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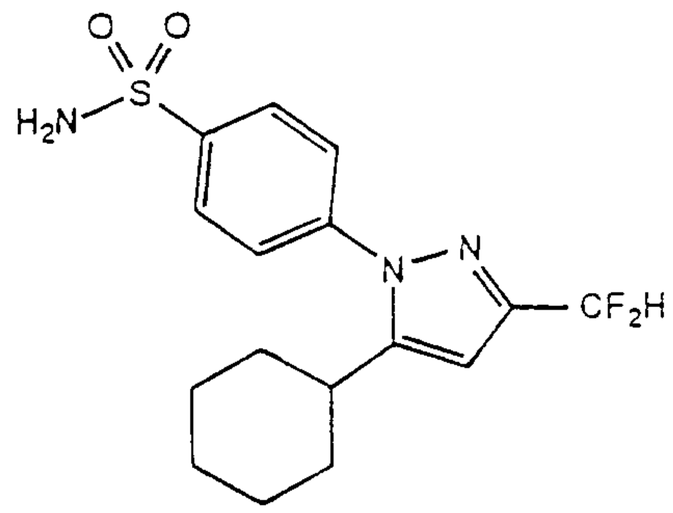
C-2779/2

Example 35



4-[5-(1-Cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

4-[5-(1-Cyclohexenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (Example 7) (0.31 g, 0.88 mmol) was dissolved in ethanol (15 mL), 10% palladium on charcoal was added, and the suspension was stirred at room temperature under hydrogen (36 psi) for 18.25 hours. The reaction was filtered through celite, and the ethanol removed *in vacuo* to give a white solid, which was recrystallized from methylene chloride/isooctane (0.31 g, 99%): mp 199-203°C; ^{1}H NMR (acetone-d_6) 300 MHz 8.05 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 6.69 (t, J=55.0 Hz 1 H), 6.47 (s, 1H), 5.02 (br s, 2H), 2.67 (m, 1H), 1.71-1.88(m, 5H), 1.24-1.43 (m, 5H); ^{19}F NMR (acetone-d_6) 300 MHz: -112.86 (d).

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar

injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in **Non-steroidal Anti-Inflammatory Drugs**, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table II.

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated

groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table XI.

TABLE II

Examples	RAT PAW EDEMA % Inhibition @ 10mg/kg body weight	ANALGESIA % Inhibition @ 30mg/kg body weight
35	18*	

.* Assay performed at 30 mg/kg body weight

Evaluation of COX I and COX II activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX II. The COX II inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

A 2.0 kb fragment containing the coding region of either human or murine COX-I or human or murine COX-II was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-I and COX-II in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x10e8) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10E7 - 10E8 pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 x 10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio] -1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX I and COX II activity:

COX activity was assayed as PGE_2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE_2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table III.

TABLE III

Example	Human COX II ID_{50} µM	Human COX I ID_{50} µM
1	<.1	1.1
3	.6	<.1
35	.1	>100

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly,

intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

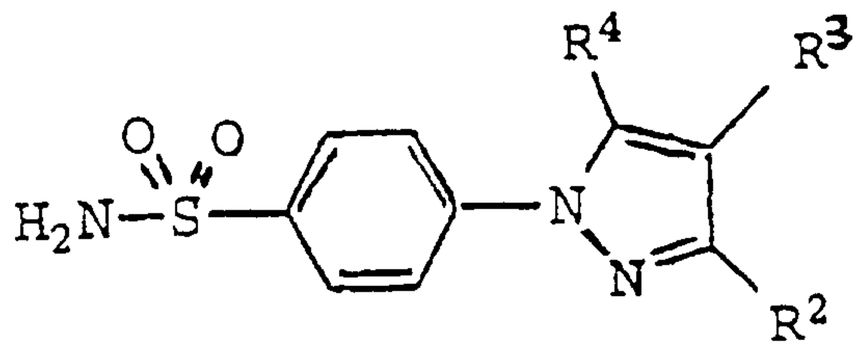
The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably from about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder,

cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Claims

1. A compound according to claim 1 having the Formula I



(I

wherein R^2 is selected from hydrido, C_1-C_{10}-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxycarbonyl, cyano, carboxyl, C_1-C_6-cyanoalkyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_7-cycloalkylaminocarbonyl, arylaminocarbonyl, C_1-C_6-carboxyalkylaminocarbonyl, aryl-C_1-C_6-alkoxycarbonyl-C_1-C_{10}-alkylaminocarbonyl, C_1-C_6-aminocarbonylalkyl, C_1-C_6-carboxyalkyl, C_1-C_6-alkoxycarbonylcyano-C_2-C_6-alkenyl and C_1-C_6-hydroxyalkyl;

wherein R^3 is selected from hydrido, C_1-C_{10}-alkyl, cyano, C_1-C_6-hydroxyalkyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylsulfonyl, and halo; and

wherein R^4 is selected from C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkenyl and heterocyclic; wherein R^4 is optionally substituted at a substitutable position with one or more radicals selected from halo, C_1-C_6-alkylthio, C_1-C_6-alkylsulfonyl, cyano, nitro, C_1-C_6-haloalkyl, C_1-C_6-alkyl, hydroxyl, C_2-C_6-alkenyl, C_1-C_6-hydroxyalkyl, carboxyl, C_3-C_7-cycloalkyl, C_1-C_6-alkylamino, C_1-C_{10}-dialkylamino, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, sulfamyl, five or six membered heterocyclic and amino; wherein aryl wherever occuring means phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl;

provided R^2 and R^3 are not both hydrido, further provided that R^4 is not triazolyl when R^2 is methyl; and further provided that R^4 is not substituted thienyl when R^2 is trifluoromethyl; or a pharmaceutically-acceptable salt thereof.

2. A compound according to Claim 1 selected from the group consisting of

4-[5-(1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-fluoro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-ethyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-methyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-chloro-1-methyl-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-dihydro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(7-fluoro-1-methyl-2,3-dihydro-1H-indol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(biphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,4-benzodioxan-6-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[3-(difluoromethyl)-5-(4-methylcyclohexyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(methyl-1-cyclohexenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methyl-1-cyclopentenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(benzofuran-2-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,3-benzodioxol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-(morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dimethyl-3-furyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-methyl-2-furyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-chloro-1-methyl-4-cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dibromo-4-methylcyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-methoxycyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,4-dimethyl-3-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,5-dichloro-3-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(benzofuran-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-indanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-methyl-2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2,3-dihydrobenzofuran-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-benzothienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydro-2H-1-benzopyran-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3,4-dihydro-2H-1-benzothiopyran-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-phenylethenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-1,3-benzodioxol-6-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methyl-1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyrazinyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(biphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1,2,3,4-tetrahydronaphth-6-yl])-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-thiazolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-oxazolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cyclopentyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(cycloheptyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(1-cyclopentenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(2-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methyl-3-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-pyridyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(3-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-cyclohexenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(4-methylcyclohex-4-ene-1-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-chloro-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(5-bromo-2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

4-[5-(6-methoxy-2-naphthyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

3. A pharmaceutical composition comprising a therapeutically-effective amount of a compound and a pharmaceutically-acceptable carrier or diluent, said compound selected from a family of compounds according to any of claims 1 or 2, including those wherein R^4 is unsubstituted thienyl when R^2 is trifluoromethyl.