SUBSTITUTED INDAZOLE DERIVATIVES AND THEIR USE AS INHIBITORS PHOSPHODIESTERASE (PDE) TYPE IV AND THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF)

Background of the Invention

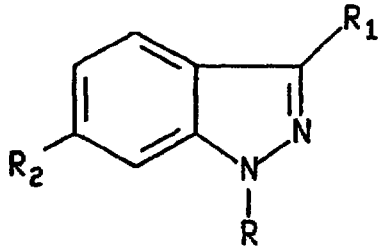
This invention relates to a series of novel indazole analogs that are selective inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF), and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airway disease, psoriasis, allergic rhinitis, dermatitis, and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF. This invention also relates to a method of using such compounds in the treatment of the foregoing diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Since the recognition that cyclic adenosine phosphate (AMP) is an intracellular second messenger, E.W. Sutherland, and T. W. Rall, Pharmacol. Rev., 12, 265, (1960), inhibition of the phosphodiesterases has been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized, J. A. Beavo et al., TiPS, 11, 150, (1990), and their selective inhibition has led to improved drug therapy, C. D. Nicholson, M. S. Hahid, TiPS, 12, 19, (1991). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release, M. W. Verghese et al., J. Mol. Cell Cardiol., 12 (Suppl. II), S 61, (1989) and airway smooth muscle relaxation (T.J. Torphy in "Directions for New Anti-Asthma Drugs," eds S.R. O'Donnell and C. G. A. Persson, 1988, 37 Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects.

TNF is recognized to be involved in many infectious and auto-immune diseases, W. Friers, FEBS Letters, 285, 199, (1991). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock, C. E. Spooner et al., Clinical Immunology and Immunopathology, 62, S11, (1992).

Summary of the Invention

The present invention relates to compounds of the formula I



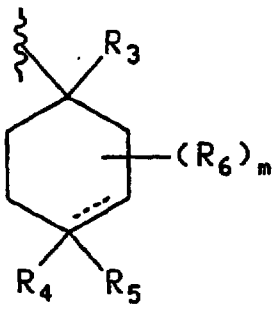
I

and to pharmaceutically acceptable salts thereof, wherein:

R is hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$(C_3-C_7 cycloalkyl) wherein n is 0 to 2, (C_1-C_6 alkoxy)C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_n$(C_3-C_9 heterocyclyl) wherein n is 0 to 2, or -$(Z')_b(Z'')_c$(C_6-C_{10} aryl) wherein b and c are independently 0 or 1, Z' is C_1-C_6 alkylene or C_2-C_6 alkenylene, and Z" is O, S, SO_2, or NR_9, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkoxy, trifluoromethyl, nitro, CO_2R_9, $C(O)NR_9R_{10}$, NR_9R_{10} and $SO_2NR_9R_{10}$;

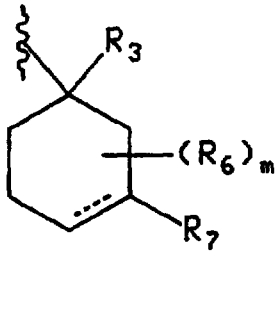
R_1 is hydrogen, C_1-C_7 alkyl, C_2-C_3 alkenyl, phenyl, C_3-C_7 cycloalkyl, or (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, wherein said alkyl, alkenyl and phenyl R_1 groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

R_2 is selected from the group consisting of



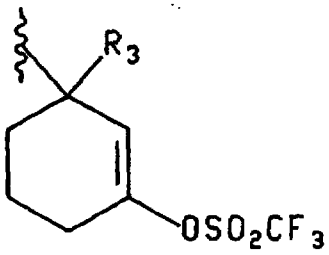
(Ia)

,



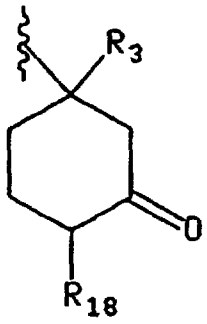
(Ib)

,



(Ic)

and



(Id)

;

wherein the dashed line in formulas (Ia) and (Ib) represent a single or double bond;

m is 0 to 4;

R_3 is H, halo, cyano, C_1-C_4 alkyl optionally substituted by 1 to 3 halo groups, $CH_2NHC(O)C(O)NH_2$, cyclopropyl optionally substituted by R_{11}, R_{17}, CH_2OR_9, NR_9R_{10}, $CH_2NR_9R_{10}$, CO_2R_9, $C(O)NR_9R_{10}$, $C{\equiv}CR_{11}$, C(Z)H or $CH{=}CR_{11}R_{11}$;

R_4 is H, $C(Y)R_{14}$, CO_2R_{14}, $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1$-C_4 alkyl), $CR_9R_{10}OR_{14}$, $CR_9R_{10}SR_{14}$, $CR_9R_{10}S(O)_nR_{15}$ wherein n is 0 to 2, $CR_9R_{10}NR_{14}R_{17}$, $CR_9R_{10}NR_{17}SO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)R_{14}$, $CR_9R_{10}NR_{17}CO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(NCN)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(CR_9NO_2)S(C_1$-$C_4$ alkyl), $CR_9R_{10}CO_2R_{15}$, $CR_9R_{10}C(Y)NR_{17}R_{14}$, $CR_9R_{10}C(NR_{17})NR_{17}R_{14}$, $CR_9R_{10}CN$, $CR_9R_{10}C(NOR_{10})R_{14}$, $CR_9R_{10}C(NOR_{14})R_{10}$, $CR_9R_{10}NR_{17}C(NR_{17})S(C_1$-$C_4$ alkyl), $CR_9R_{10}NR_{17}C(NR_{17})NR_{17}R_{14}$,

$CR_9R_{10}NR_{17}C(O)C(O)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(O)C(O)OR_{14}$, tetrazolyl, thiazolyl, imidazolyl, imidazolidinyl, pyrazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, CR_9R_{10}(tetrazolyl), CR_9R_{10}(thiazolyl), CR_9R_{10}(imidazolyl), CR_9R_{10}(imidazolidinyl), CR_9R_{10}(pyrazolyl), CR_9R_{10}(thiazolidinyl), CR_9R_{10}(oxazolyl), CR_9R_{10}(oxazolidinyl), CR_9R_{10}(triazolyl), CR_9R_{10}(isoxazolyl), CR_9R_{10}(oxadiazolyl), CR_9R_{10}(thiadiazolyl), CR_9R_{10}(morpholinyl), CR_9R_{10}(piperidinyl), CR_9R_{10}(piperazinyl), or CR_9R_{10}(pyrrolyl), wherein said heterocyclic groups and moieties for said R_4 substituents are optionally substituted by 1 to 3 R_{14} substituents;

R_5 is R_9, OR_9, CH_2OR_9, cyano, $C(O)R_9$, CO_2R_9, $C(O)NR_9R_{10}$, or NR_9R_{10}, provided that R_5 is absent when the dashed line in formula (Ia) represents a double bond;

or R_4 and R_5 are taken together to form =O or $=R_6$;

or R_5 is hydrogen and R_4 is OR_{14}, SR_{14}, $S(O)_nR_{15}$ wherein n is 0 to 2, $SO_2NR_{17}R_{14}$, $NR_{17}R_{14}$, $NR_{14}C(O)R_9$, $NR_{17}C(Y)R_{14}$, $NR_{17}C(O)OR_{15}$, $NR_{17}C(Y)NR_{17}R_{14}$, $NR_{17}SO_2NR_{17}R_{14}$, $NR_{17}C(NCN)NR_{17}R_{14}$, $NR_{17}SO_2R_{15}$, $NR_{17}C(CR_9NO_2)NR_{17}R_{14}$, $NR_{17}C(NCN)S(C_1\text{-}C_4$ alkyl), $NR_{17}C(CR_9NO_2)S(C_1\text{-}C_4$ alkyl), $NR_{17}C(NR_{17})NR_{17}R_{14}$, $NR_{17}C(O)C(O)NR_{17}R_{14}$, or $NR_{17}C(O)C(O)OR_{14}$;

each R_6 is independently selected from methyl and ethyl optionally substituted by 1 to 3 halo groups;

R_7 is OR_{14}, SR_{14}, $SO_2NR_{17}R_{14}$, $NR_{17}R_{14}$, $NR_{14}C(O)R_9$, $NR_{17}C(Y)R_{14}$, $NR_{17}C(O)OR_{15}$, $S(O)_nR_{12}$ wherein n is 0 to 2, $OS(O)_2R_{12}$, OR_{12}, $OC(O)NR_{13}R_{12}$, $OC(O)R_{13}$, OCO_2R_{13}, $O(CR_{12}R_{13})_mOR_{12}$ wherein m is 0 to 2, $CR_9R_{10}OR_{14}$, $CR_9R_{10}NR_{17}R_{14}$, $C(Y)R_{14}$, CO_2R_{14}, $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1\text{-}C_4$ alkyl), tetrazolyl, thiazolyl, imidazolyl, imidazolidinyl, pyrazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, wherein said R_7 heterocyclic groups are optionally substituted by 1 to 3 R_{14} substituents;

R_8 is $=NR_{15}$, $=NCR_9R_{10}(C_2\text{-}C_6$ alkenyl), $=NOR_{14}$, $=NOR_{19}$, $=NOCR_9R_{10}(C_2\text{-}C_6$ alkenyl), $=NNR_9R_{14}$, $=NNR_9R_{19}$, =NCN, $=NNR_9C(Y)NR_9R_{14}$, $=C(CN)_2$, $=CR_{14}CN$, $=CR_{14}CO_2R_9$, $=CR_{14}C(O)NR_9R_{14}$, $=C(CN)NO_2$, $=C(CN)CO_2(C_1\text{-}C_4$ alkyl), $=C(CN)OCO_2(C_1\text{-}C_4$ alkyl), $=C(CN)(C_1\text{-}C_4$ alkyl), $=C(CN)C(O)NR_9R_{14}$, 2-(1,3-dithiane), 2-(1,3-dithiolane), dimethylthio ketal, diethylthio ketal, 2-(1,3-dioxolane), 2-(1,3-dioxane), 2-(1,3-oxathiolane), dimethyl ketal or diethyl ketal;

each R_9 and R_{10} is independently hydrogen or C_1-C_4 alkyl optionally substituted by up to three fluorines;

each R_{11} is independently fluoro or R_{10};

each R_{12} is independently C_1-C_6 alkyl, C_2-C_3 alkenyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, C_6-C_{10} aryl, or C_3-C_9 heterocyclyl, wherein said R_{12} groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

each R_{13} is independently hydrogen or R_{12};

each R_{14} is independently hydrogen or R_{15}, or when R_{14} and R_{17} are as $NR_{17}R_{14}$ then R_{17} and R_{14} can be taken together with the nitrogen to form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N and S;

each R_{15} is independently C_1-C_6 alkyl or $-(CR_9R_{10})_nR_{16}$ wherein n is 0 to 2 and R_{16} and said C_1-C_6 alkyl are optionally substituted by 1 to 3 substituents independently selected from halo, nitro, cyano, $NR_{10}R_{17}$, $C(O)R_9$, OR_9, $C(O)NR_{10}R_{17}$, $OC(O)NR_{10}R_{17}$, $NR_{17}C(O)NR_{17}R_{10}$, $NR_{17}C(O)R_{10}$, $NR_{17}C(O)O(C_1$-C_4 alkyl), $C(NR_{17})NR_{17}R_{10}$, $C(NCN)NR_{17}R_{10}$, $C(NCN)S(C_1$-C_4alkyl), $NR_{17}C(NCN)S(C_1$-C_4alkyl), $NR_{17}C(NCN)NR_{17}R_{10}$, $NR_{17}SO_2(C_1$-C_4 alkyl), $S(O)_n(C_1$-C_4 alkyl) wherein n is 0 to 2, $NR_{17}C(O)C(O)NR_{17}R_{10}$, $NR_{17}C(O)C(O)R_{17}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, and C_1-C_2 alkyl optionally substituted with one to three fluorines;

each R_{16} is independently C_3-C_7 cycloalkyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, thienyl, thiazolyl, quinolinyl, naphthyl, or phenyl;

each R_{17} is independently OR_9 or R_{10};

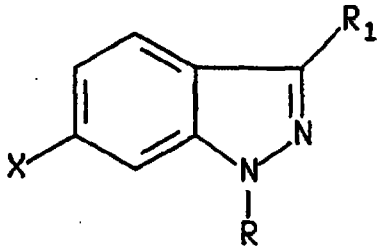
R_{18} is H, $C(Y)R_{14}$, CO_2R_{14}, $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1$-C_4 alkyl), $CR_9R_{10}OR_{14}$, $CR_9R_{10}SR_{14}$, $CR_9R_{10}S(O)_nR_{15}$ wherein n is 0 to 2, $CR_9R_{10}NR_{14}R_{17}$, $CR_9R_{10}NR_{17}SO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)R_{14}$, $CR_9R_{10}NR_{17}CO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(NCN)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(CR_9NO_2)S(C_1$-$C_4$ alkyl), tetrazolyl, thiazolyl, imidazolyl, imidazolidinyl, pyrazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, wherein said heterocyclic groups are optionally substituted by 1 to 3 R_{14} substituents;

R_{19} is $-C(O)R_{14}$, $-C(O)NR_9R_{14}$, $-S(O)_2R_{15}$, or $-S(O)_2NR_9R_{14}$;

each Y is independently =O or =S; and,

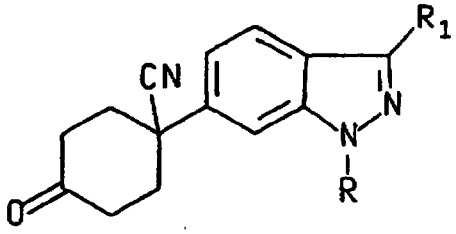
Z is =O, $=NR_{17}$, =NCN, $=C(CN)_2$, $=CR_9CN$, $=CR_9NO_2$, $=CR_9CO_2R_9$, $=CR_9C(O)NR_9R_{10}$, $=C(CN)CO_2(C_1\text{-}C_4$ alkyl) or $=C(CN)C(O)NR_9R_{10}$.

The invention also relates to intermediates that are useful in the preparation of compounds of formula I including compounds of the formula:



XXXX

and



XIX

wherein X is bromo, $-C(O)O(C_1\text{-}C_6$ alkyl), $-CH_2CN$, carboxy, $-CH_2OH$, or -C(O)H, and R and R_1 are defined as indicated above for the compound of formula I.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein "alkyl" is defined above.

The term "alkenyl", as used herein, unless otherwise indicated, includes unsaturated alkyl groups having one or more double bonds wherein "alkyl" is defined above.

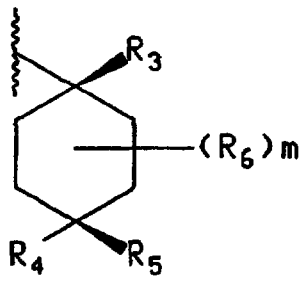
The term "cycloalkyl", as used herein, unless otherwise indicated, includes saturated monovalent cyclo hydrocarbon radicals including cyclobutyl, cyclopentyl and cycloheptyl.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "heterocyclyl", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with an oxo moiety. With reference to the R_4 substituent of formula Ia, the C_3-C_9 heterocyclic group can be attached to the C_1-C_6 alkyl group by a nitrogen or, preferably, a carbon atom. An example of a C_3 heterocyclic group is thiazolyl, and an example of a C_9 heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl and thiazolyl. Heterocyclic groups having a fused benzene ring include benzimidazolyl.

Where heterocyclic groups are specifically recited or covered as substituents for the compound of formula I, it is understood that all suitable isomers of such heterocyclic groups are intended. Thus, for example, in the definition of the substituent R_4, the term "thiazolyl" includes 2-, 4- or 5-thiazolyl; the term "imidazolyl" includes 2-, 4- or 5-imidazolyl; the term "pyrazolyl" includes 3-, 4- or 5-pyrazolyl; the term "oxazolyl" includes 2-, 4- or 5-oxazolyl; the term "isoxazolyl" includes 3-, 4- or 5-isoxazolyl, and so on. Likewise, in the definition of substituent R_{16}, the term "pyridyl" includes 2-, 3- or 4-pyridyl.

Preferred compounds of formula I include those wherein R_2 is a group of the formula (Ia) wherein R_3 and R_5 are cis as follows:



Other preferred compounds of formula I include those wherein R_2 is a group of the formula (Ia) wherein the dashed line represents a single bond and R_3 and R_4 are cis.

Other preferred compounds of formula I include those wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl.

Other preferred compounds of formula I include those wherein R_1 is C_1-C_2 alkyl optionally substituted by up to three fluorines, and, more preferably, those wherein R_1 is ethyl.

Other preferred compounds of formula I include those wherein R_2 is a group of formula (Ia) wherein the dashed line represents a single bond.

Other preferred compounds of formula I include those wherein R_2 is a group of formula (Ia) wherein the dashed line represents a single bond and R_3 is cyano.

Other preferred compounds of formula I include those wherein R_2 is a group of formula (Ia) wherein the dashed line represents a single bond, m is 0 and R_5 is hydrogen.

Other preferred compounds of formula I include those wherein R_2 is a group of formula (Ia) wherein the dashed line represents a single bond and R_4 is carboxy, $-CH_2OH$, or $-CH_2C(O)NH_2$.

Preferred compounds of formulas X, XIV, and XIX include those wherein R_1 is ethyl.

Other preferred compounds of formulas X and XIX include those wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl.

Specific preferred compounds include:

1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile;

Trans-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

Cis-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

1-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile;

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

Trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid;

Trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid;

1-(Cyclohexyl-3-ethyl-1H-indazole-6-yl)-cis-4-hydroxylmethylcyclohexane carbonitrile;

Cis-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide; and,

Trans-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula I. For example, pharmaceutically acceptable salts include sodium, calcium and potassium salts of carboxylic acid groups and hydrochloride salts of amino groups. Other pharmaceutically acceptable salts of amino groups are hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

Certain compounds of formula I may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula I, and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula I, the invention includes the use of a racemate, a single enantiomeric form, a single diastereomeric form, or mixtures thereof. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

The present invention further relates to a pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal comprising a pharmaceutically effective amount of a compound according to formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention further relates to a method for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) by administering to a patient an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof.

The present invention further relates to a pharmaceutical composition for the prevention or treatment of asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebal malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection (e.g. bacterial, viral or fungal infection) such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, autoimmune diabetes, systemic lupus erythematosis, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, or dermatitis, in a mammal, comprising a pharmaceutically effective amount of a compound according to formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

This invention further relates to a method of treating or preventing the foregoing specific diseases and conditions by administering to a patient an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof.

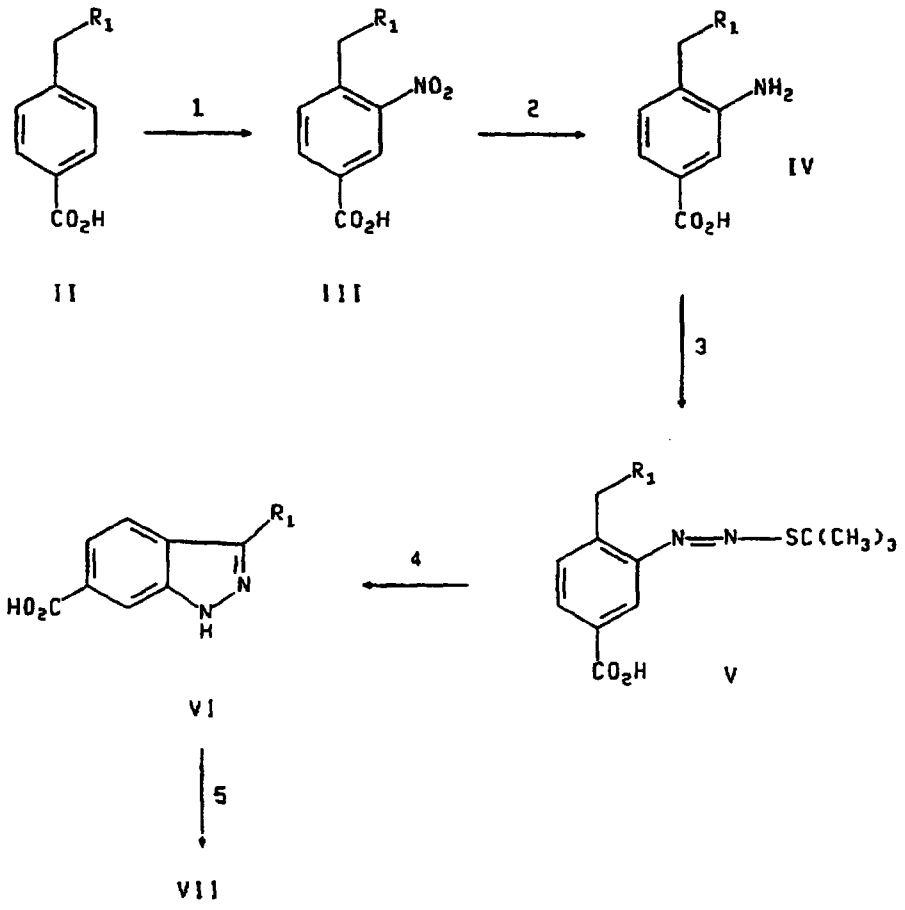
Certain "aminal" or "acetal"-like chemical structures within the scope of formula I may be unstable. Such structures may occur where two heteroatoms are attached to the same carbon atom. For example, where R is C_1-C_6 alkyl substituted by hydroxy, it is possible that the hydroxy may be attached to the same carbon that is attached to

the nitrogen atom from which R extends. It is to be understood that such unstable compounds are not within the scope of the present invention.

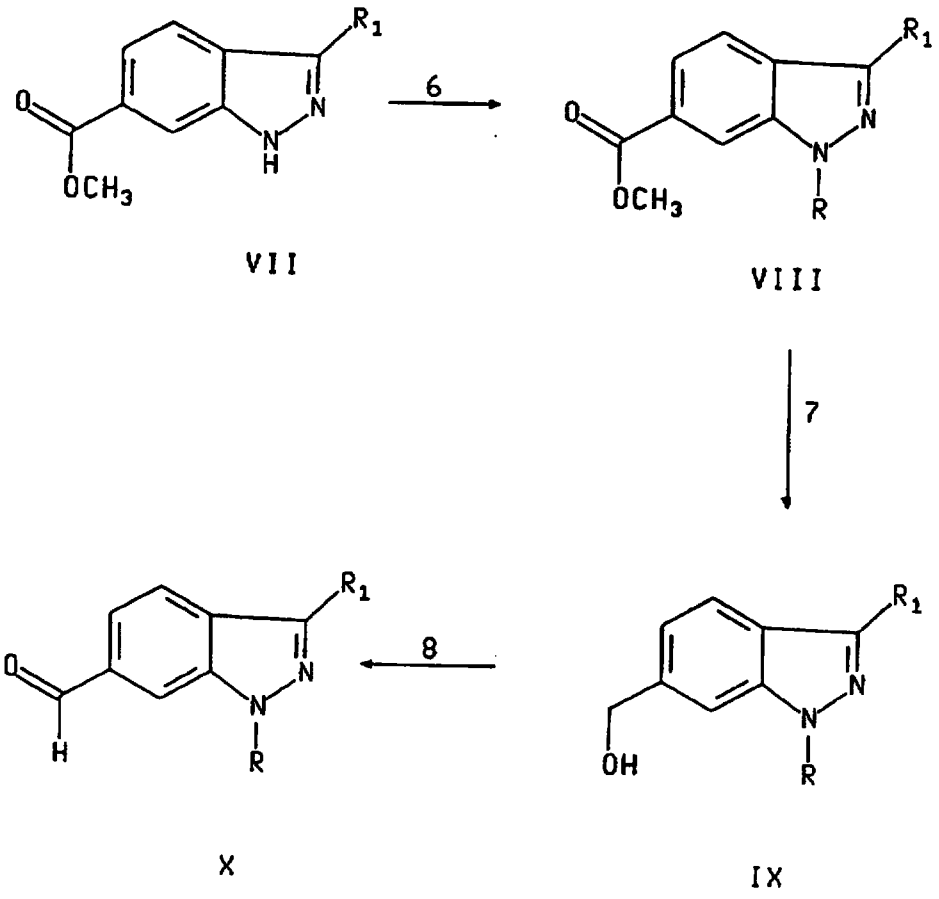
Detailed Description of the Invention

The following reaction schemes 1-4 illustrate the preparation of the compounds of the present invention. Unless otherwise indicated, R and R^1 in the reaction schemes are defined as above.

Scheme 1



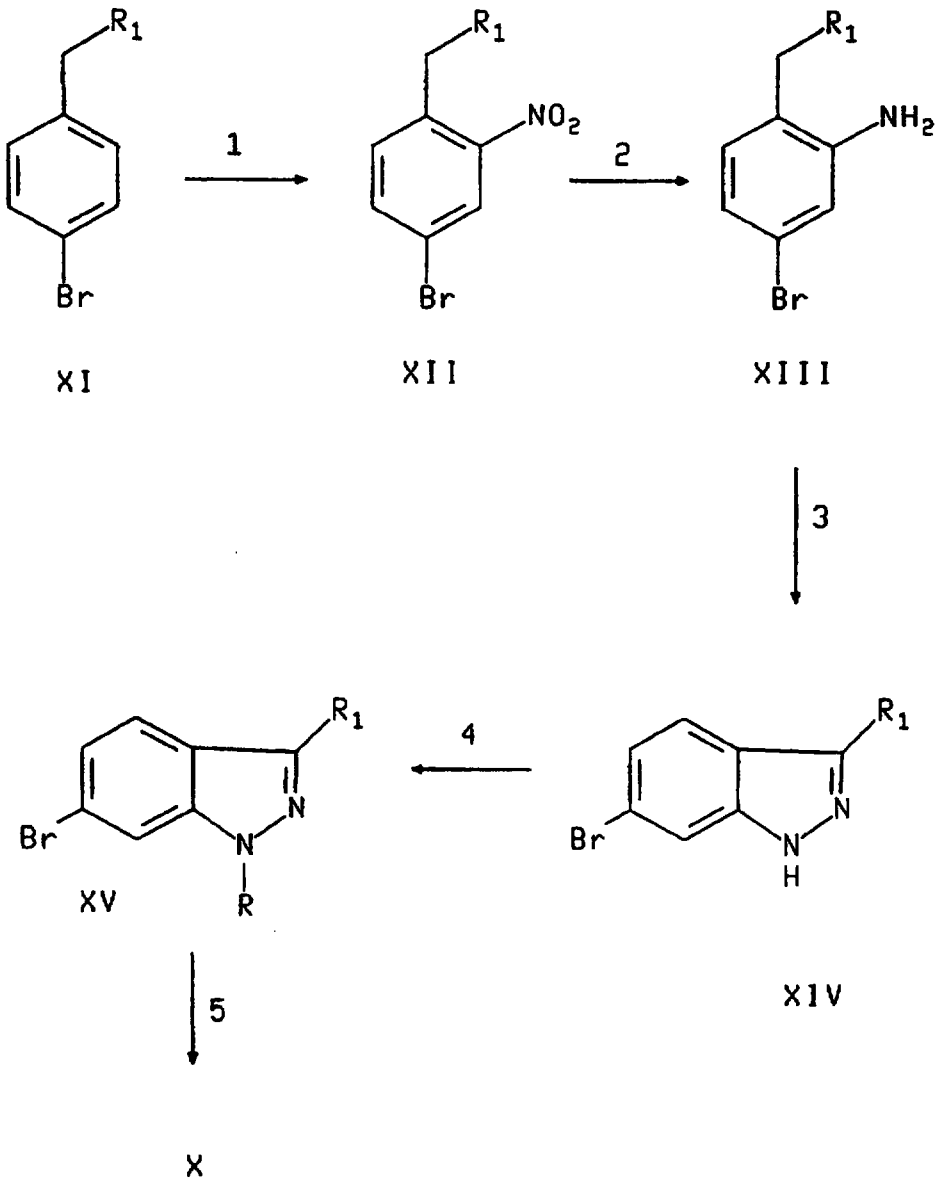
Scheme 1 continued



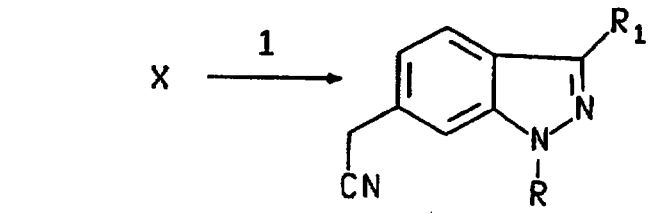
VII VIII

X IX

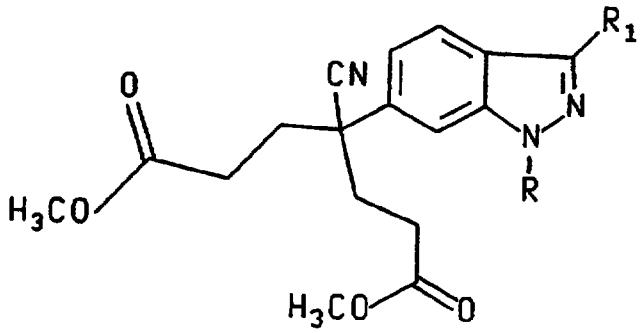
Scheme 2



Scheme 3



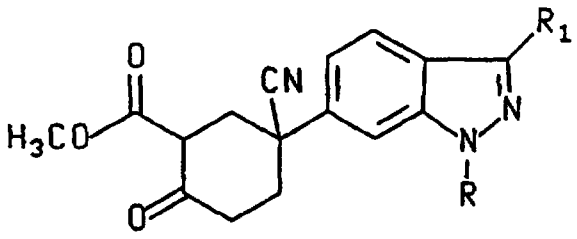
XVI



XVII

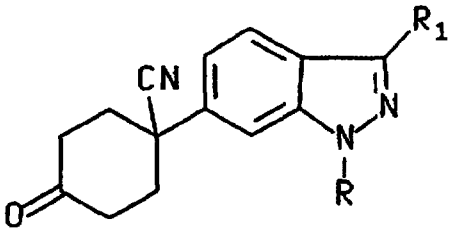
XVIII

Scheme 3 continued



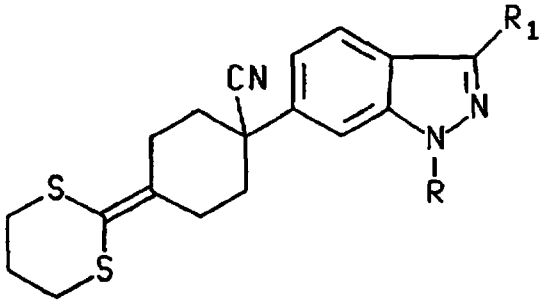
XVIII

↓ 4



XIX

↓ 5

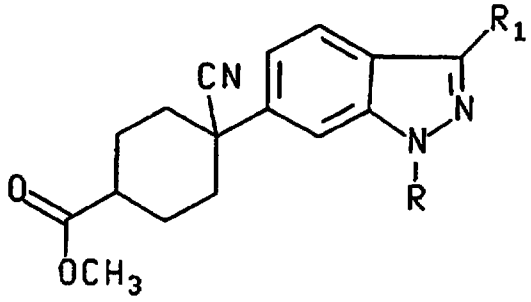


XX

↓ 6

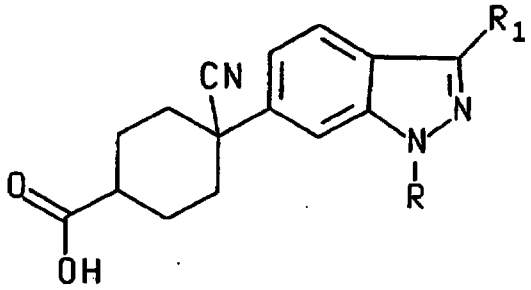
XXI

Scheme 3 continued



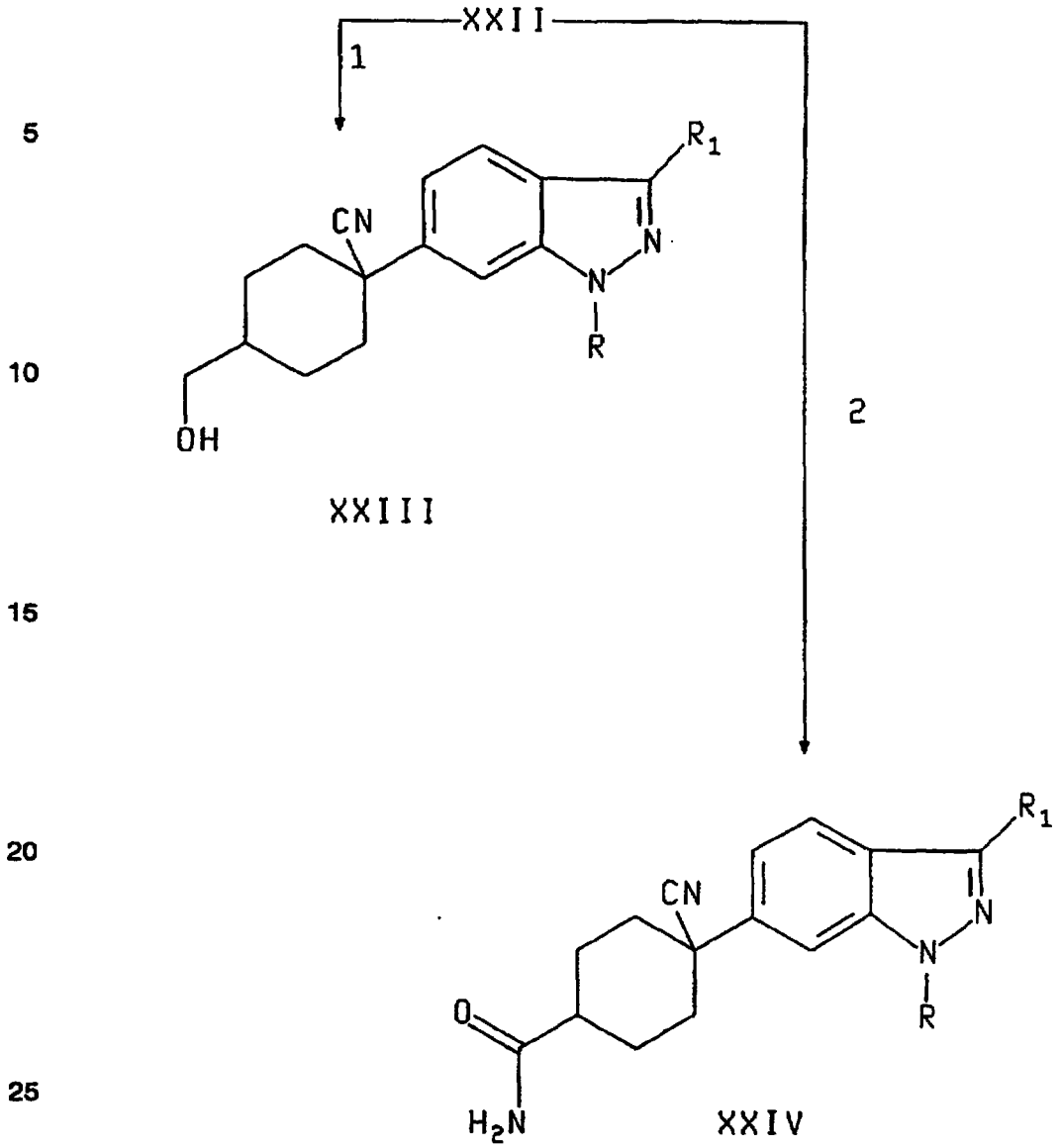
XXI

7



XXII

Scheme 4



The preparation of compounds of formula I can be carried out by one skilled in the art according to one or more of the synthetic methods outlined in schemes 1-4 above and the examples referred to below. In step 1 of scheme 1, the carboxylic acid of formula II, which is available from known commercial sources or can be prepared according to methods known to those skilled in the art, is nitrated under standard

conditions of nitration (HNO_3/H_2SO_4, 0°C) and the resulting nitro derivative of formula III is hydrogenated in step 2 of scheme 1 using standard hydrogenation methods (H_2-Pd/C under pressure) at ambient temperature (20-25°C) for several hours (2-10 hours) to provide the compound of formula IV. In step 3 of scheme 1, the amino benzoic acid of formula IV is reacted with a base such as sodium carbonate under aqueous conditions and gently heated until mostly dissolved. The reaction mixture is chilled to a lower temperature (about 0°C) and treated with sodium nitrate in water. After about 15 minutes, the reaction mixture is slowly transferred to an appropriate container holding crushed ice and a strong acid such as hydrochloric acid. The reaction mixture is stirred for 10-20 minutes and then added, at ambient temperature, to a solution of excess t-butyl thiol in an aprotic solvent such as ethanol. The reaction mixture is acidified to a pH of 4-5 through addition of an inorganic base, preferably saturated aqueous Na_2CO_3, and the reaction mixture is allowed to stir at ambient temperature for 1-3 hours. Addition of brine to the reaction mixture, followed by filtration, provides the sulfide of formula V.

In step 4 of scheme 1, the sulfide of formula V is converted to the corresponding indazole carboxylic acid of formula VI by reacting the sulfide of formula V with a strong base, preferably potassium t-butoxide, in dimethyl sulfoxide (DMSO) at ambient temperature. After stirring for several hours (1-4 hours), the reaction mixture is acidified with a strong acid, such as hydrochloric or sulfuric acid, and then extracted using conventional methods. In step 5 of scheme 1, the indazole carboxylic acid of formula VI is converted to the corresponding ester of formula VII by conventional methods known to those skilled in the art. In step 6 of scheme 1, the compound of formula VIII is provided through alkylation of the ester of formula VII by subjecting the ester to conventional alkylation conditions (strong base/various alkylating agents and, optionally, a copper catalyst such as $CuBr_2$) in a polar aprotic solvent, such as tetrahydrofuran (THF), N-methylpyrrolidinone or dimethylformamide (DMF), at ambient or higher temperature (25-200°C) for about 6-24 hrs, preferably about 12 hours. In step 7 of scheme 1, the compound of formula VIII is converted to the corresponding alcohol of formula IX by following conventional methods known to those skilled in the art for reducing esters to alcohols. Preferably, the reduction is effected through use of a metal hydride reducing agent, such as lithium aluminum hydride, in a polar aproptic solvent at a low temperature (about 0°C). In step 8 of scheme 1, the alcohol of formula IX is

oxidized to the corresponding aldehyde of formula X according to conventional methods known to those skilled in the art. For example, the oxidation can be effected through use of a catalytic amount of tetrapropylammonium perrutenate and excess N-methylmorpholine-N-oxide, as described in J. Chem. Soc., Chem. Commun., 1625 (1987), in an anhydrous solvent, preferably methylene chloride.

Scheme 2 provides an alternative method of preparing the aldehyde of formula X. In step 1 of scheme 2, the compound of formula XI is nitrated using conventional nitration conditions (nitric and sulfuric acid) to provide the compound of formula XII. In step 2 of scheme 2, the nitro derivative of formula XII is reduced to the corresponding amine of formula XIII according to conventional methods known to those skilled in the art. Preferably, the compound of formula XII is reduced to the amine of formula XIII using anhydrous stannous chloride in an anhydrous aprotic solvent such as ethanol. In step 3 of scheme 2, the amine of formula XIII is converted to the corresponding indazole of formula XIV by preparing the corresponding diazonium fluoroforates as described in A. Roe, Organic Reactions, Vol. 5, Wiley, New York, 1949, pp. 198-206, followed by phase transfer catalyzed cyclization as described in R. A. Bartsch and I. W. Yang, J. Het. Chem. 21, 1063 (1984). In step 4 of scheme 2, alkylation of the compound of formula XIV is performed using standard methods known to those skilled in the art (i.e. strong base, polar aprotic solvent and an alkyl halide) to provide the N-alkylated compound of formula XV. In step 5 of scheme 2, the compound of formula XV is subjected to metal halogen exchange employing an alkyl lithium, such as n-butyl lithium, in a polar aprotic solvent, such as THF, at low temperature (-50°C to 100°C (-78°C preferred)) followed by quenching with DMF at low temperature and warming to ambient temperature to provide the aldehyde compound of formula X.

Scheme 3 illustrates the preparation of a compound of formula XXII which is a compound of formula I wherein R_2 is a ring moiety of formula (Ia). In step 1 of scheme 3, the aldehyde moiety of the compound of formula X is converted to an appropriate leaving group, such as a halogen, mesylate or another leaving group familiar to those skilled in the art, followed by reacting the resulting compound with sodium cyanate in a polar solvent such as DMF to provide the compound of formula XVI. In step 2 of scheme 3, the compound of formula XVI is reacted under basic conditions with methyl acrylate (or related derivatives depending on the R_2 group to be added) in an aprotic

solvent such as ethylene glycol dimethyl ether (DME) at high temperature, preferably at reflux, to provide the compound of formula XVII. In step 3 of scheme 3, the compound of formula XVII is converted to the compound of formula XVIII using a strong base, such as sodium hydride, and a polar aprotic solvent, such as DMF or THF, at elevated temperature, preferably at reflux.

In step 4 of scheme 3, the compound of formula XVIII is decarboxylated using conventional methods, such as using sodium chloride in DMSO at a temperature of about 140°C, to provide the compound of formula XIX. In step 5 of scheme 3, derivatization of the compound of formula XIX to the corresponding dithian-2-ylidine cyclohexane carbonitrile of formula XX is done by reaction with 2-lithio-1,3-dithiane. In step 6 of scheme 3, the compound of formula XX is converted to the corresponding ester of formula XXI using mercury (II) chloride and perchloric acid in a polar protic solvent such as methanol. In step 7 of scheme 3, the compound of formula XXI is converted through hydrolysis to the corresponding carboxylic acid of formula XXII using a standard method of hydrolysis, such as using aqueous sodium hydroxide in a polar solvent, or any of numerous existing hydrolysis methods known to those skilled in art as described in T. Green and P.G.M. Wets, Protecting Groups in Organic Synthesis, 2nd Edition (John Wiley and Sons, New York (1991)). The synthetic steps described for scheme 3 are analogous to the synthetic methods provided for the preparation of corresponding catechol-containing compounds in PCT published applications WO 93/19751 and WO 93/17949.

Other compounds of formula I wherein R_2 is selected from moieties (Ia), (Ib), (Ic) and (Id), can be prepared from one or more of the intermediate compounds described in schemes I-III. In particular, the aldehyde of formula X or the keto compound of formula XIX can be used to prepare various compounds of formula I. Any of the various R_2 moieties of formulas (Ia), (Ib), (Ic) or (Id) can be introduced into one or more of the intermediate compounds referred to above using synthetic methods provided for corresponding non-indazole analogs in PCT published applications WO 93/19748, WO 93/19749, WO 93/09751, WO 93/19720, WO 93/19750, WO 95/03794, WO 95/09623, WO 95/09624, WO 95/09627, WO 95/09836, and WO 95/09837. For example, with reference to step 1 of scheme 4, the carboxylic acid of formula XXII can be converted to the alcohol of formula XXIII by reduction with various metal hydrides in a polar solvent as described in Example 9, referred to below, and in accordance with synthetic

methods provided for corresponding non-indazole analogs in PCT published applications publication numbers WO 93/19747, WO 93/19749 and WO 95/09836. Further, with reference to step 2 of scheme 4, the carboxylic acid of formula XXII can be converted to the corresponding carboxamide of formula XXIV through conversion to an intermediate acid chloride using conventional synthetic methods, and then reacting the acid chloride with ammonia in an aprotic solvent. Other carboxamide analogs of formula XXIV can be prepared through reaction of the acid chloride intermediate with various primary or secondary amines according to conventional methods known to those skilled in the art and as described in the PCT published applications referred to above.

Other compounds of formula I can be prepared from the intermediate compound of formula XIX in accord with synthetic methods provided for corresponding non-indazole analogs in the PCT published applications referred to above. Compounds of formula I wherein R_2 is a moiety of formula (Ia), and either R_4 or R_5 is H, can be prepared from the keto intermediate of formula XIX by reaction with a base such as lithium diisopropylamine in a polar aprotic solvent, such as THF, and excess N-phenyltrifluoromethylsulfonamide as described in PCT published application WO 93/19749 for corresponding non-indazole analogs. Compounds of formula I wherein R_2 is a moiety of formula Ia, R_4 is hydrogen, and R_5 is $-CO_2CH_3$ or $-CO_2H$, can be prepared from the keto intermediate of formula XIX through reaction with triflic anhydride in the presence of a tertiary amine base followed by reaction of the resulting triflate with (triphenylphosphine)palladium and carbon monoxide in the presence of an alcohol or amine to provide the methyl ester compounds of formula I wherein R_5 is $-CO_2CH_3$. The methyl ester compound can be hydrolyzed to obtain the corresponding carboxylic acid compound by employing standard methods for hydrolysis such as sodium or potassium hydroxide in aqueous methanol/tetrahydrofuran. Such synthetic methods are further described in PCT published application WO 93/19749 for corresponding non-indazole analogs.

Other compounds of formula I can be prepared from the intermediate compound of formula XIX in accord with synthetic methods described for corresponding non-indazole analogs in the published PCT applications referred to above. Compounds of formula I wherein R_2 is a moiety of formula (Ia), R_5 is hydrogen, and R_4 is hydroxy, can be prepared through reaction of the intermediate of formula XIX with an appropriate

reducing agent such as lithium borohydride, diamyl borane, lithium aluminum tris(t-butoxide), or sodium borohydride in a suitable non-reacting solvent such as 1,2-dimethoxy ethane, THF or alcohol. Compounds of formula I wherein R_2 is a moiety of formula (Ia), R_5 is hydrogen and R_4 is $-NH_2$, $-NHCH_3$, or $-N(CH_3)_2$, can be prepared by reacting the intermediate of formula XIX with an ammonium salt, such as ammonium formate, methylamine hydrochloride or dimethylamine hydrochloride, in the presence of sodium cyanoborohydride in an appropriate solvent such as alcohol.

Alternatively, compounds of formula I wherein R_2 is a moiety of formula Ia, R_4 amino, and R_5 is hydrogen, can be prepared by reacting the corresponding alcohol of formula I (R_4 = OH, R_5 = H) with a complex of an azadicarboxylate ester in the presence of an imide or phthalimide followed by reaction in an alcoholic solvent such as ethanol. Compounds of formula I wherein R_2 is a moiety of formula (Ia), R_5 is H, and R_4 is $-SR_{14}$ can be prepared by reacting the corresponding compound wherein R_4 is a leaving group such as mesylate, tosylate, bromine or chlorine, with a metal salt of mercaptan such as $NaSR_{14}$ in an appropriate aprotic solvent. Corresponding compounds of formula I wherein R_4 is -SH can be prepared by reacting the corresponding alcohol (R_4 = OH) with a complex of a phosphine, such as triphenyl phosphine, and an azidocarboxylate ester in the presence of thiolacetic acid followed by hydrolysis of the resulting thiolacetate. Furthermore compounds of this structure wherein R_4 is hydroxy can be interconverted using a standard alcohol inversion procedure known to those skilled in the art. The foregoing compounds of formula I wherein R_2 is a moiety of formula (Ia), R_5 is hydrogen, and R_4 is hydroxy, -SH or $-NH_2$, can be converted to various other compounds of formula I through one or more synthetic methods described in PCT published applications WO 93/19751 and WO 93/19749 for corresponding non-indazole analogs.

Compounds of formula I wherein R_2 is a moiety of formula (Ia) and the dashed line indicates a double bond can be prepared from the intermediate of formula XIX by following one or more synthetic methods provided for the preparation of corresponding non-indazole analogs in PCT published application WO 93/19720. Compounds of formula I wherein R_2 is a moiety of formula (Ia), and R_4 and R_5 are taken together to form =O or $=R_8$, wherein R_8 is as defined above, can be prepared from the corresponding ketone intermediate of formula XIX following one or more synthetic methods provided for corresponding non-indazole analogs in PCT published application

WO 93/19750. Other compounds of formula I wherein R_2 is a moiety of formula (Ia) and R_4 and R_5 are taken together as $=R_8$ can be prepared from the intermediate of formula XIX following one or more synthetic methods provided for the preparation of corresponding non-indazole analogs in PCT published application WO 93/19748.

Compounds of formula I wherein R_2 is a moiety of formula (Ib) can be prepared from one or more of the intermediates referred to above, such as the bromoindazole intermediate of formula XV, following one or more synthetic methods provided for the preparation of corresponding non-indazole analogs in PCT published applications WO 95/09627, WO 95/09624, WO 95/09623, WO 95/09836 and WO 95/03794. Compounds of formula I wherein R_2 is a moiety of formula (Ic) can be prepared from the intermediate of formula XV following one or more of synthetic methods provided for the preparation of corresponding non-indazole analogs in PCT published applications WO 95/09624 and WO 95/09837. Compounds of formula I wherein R_2 is a moiety of formula (Id) can be prepared from the bromoindazole intermediate of formula XV employing one or more synthetic methods provided for the preparation of the corresponding catechol-containing analogs in PCT published applications WO 95/09627, WO 95/09623 and WO 95/09624.

Pharmaceutically acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3CO_2H, gluconic acid, tartaric acid, maleic acid and succinic acid. Pharmaceutically acceptable cationic salts of the compounds of this invention of formula I wherein, for example, R^3 is CO_2R^9, and R^9 is hydrogen, include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'- dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine, tromethamine, and diethanolamine.

For administration to humans in the curative or prophylactic treatment of inflammatory diseases, oral dosages of a compound of formula I or a pharmaceutically acceptable salt thereof (the active compounds) are generally in the range of 0.1-1000 mg daily for an average adult patient (70 kg). Individual tablets or capsules should generally contain from 0.1 to 100 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1%

(w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For administration to humans for the inhibition of TNF, a variety of conventional routes may be used including orally, parenterally, topically, and rectally (suppositories). In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

For human use, the active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substance; for example, enough salts or glucose to make the solution isotonic.

Additionally, the active compounds may be administered topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The active compounds may also be administered to a mammal other than a human. The dosage to be administered to a mammal will depend on the animal species and the disease or disorder being treated. The active compounds may be administered to animals in the form of a capsule, bolus, tablet or liquid drench. The active compounds may also be administered to animals by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard

veterinary practice. As an alternative the compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

The ability of the compounds of formula I or the pharmaceutically acceptable salts thereof to inhibit PDE IV may be determined by the following assay.

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4°C. The supernatant is filtered twice through a 0.22 μm filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF Buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_{IV} activity determined by [^{3}H]cAMP hydrolysis and the ability of a known PDE_{IV} inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in dimethylsulfoxide (DMSO) at a concentration of 10 mM and diluted 1:25 in water (400 μM compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. The final DMSO concentration in the assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as the final concentrations in the assay tube).

i) 25 μl compound or DMSO (1%, for control and blank)

ii) 25 μl pH 7.5 Tris buffer

iii) [^{3}H]cAMP (1 μM)

iv) 25 μl PDE IV enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-

ethanesulfonic acid (HEPES)/0.1M naci, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an AFF-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melvile, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [^{3}H]cAMP is washed with 2 x 6 ml washing buffer, and [^{3}H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [^{3}H].

$$\% \text{ inhibition} = 1 - \frac{\text{average cpm (test compound - average cmp (blank)}}{\text{average cpm (control) - average cpm (blank)}}$$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [^{3}H]cAMP to [^{3}H]5'AMP.

The ability of the compounds I or the pharmaceutically acceptable salts thereof to inhibit the production TNF and, consequently, demonstrate their effectiveness for treating disease involving the production of TNF is shown by the following in vitro assay:

Peripheral blood (100 mls) from human volunteers is collected in ethylenediaminetetraacetic acid (EDTA). Mononuclear cells are isolated by FICOLL/Hypaque and washed three times in incomplete HBSS. Cells are resuspended in a final concentration of 1 x 10^6 cells per ml in pre-warmed RPMI (containing 5% FCS, glutamine, pen/step and nystatin). Monocytes are plated as 1 x 10^6 cells in 1.0 ml in 24-well plates. The cells are incubated at 37°C (5% carbon dioxide) and allowed to adhere to the plates for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds (10μl) are then added to the cells at 3-4 concentrations each and incubated for 1 hour. LPS (10μl) is added to appropriate wells. Plates are incubated overnight (18 hrs) at 37°C. At the end of the incubation period TNF was analyzed by a sandwich ELISA (R&D Quantikine Kit). IC_{50} determinations are made for each compound based on linear regression analysis.

The following Examples further illustrate the invention. In the following examples, "DMF" means dimethylformamide, "THF" means tetrahydrofuran, "DMSO" means dimethyl sulfoxide, and "DMAP" means 4-dimethylaminopyridine.

EXAMPLE 1

A. 3-Nitro-4-propyl-benzoic acid

9.44 g (57.5 mmol, 1.0 equiv.) of 4-propylbenzoic acid were partially dissolved in 50 mL conc. H_2SO_4 and chilled in an ice bath. A solution of 4.7 mL (74.7 mmol, 1.3 equiv) conc. HNO_3 in 10 mL conc. H_2SO_4 was added dropwise over 1-2 min. After stirring 1 hour at 0°C, the reaction mixture was poured into a 1 L beaker half full with ice. After stirring 10 minutes, the white solid which formed was filtered, washed 1 x H_20, and dried to give 12.01 g (100%) of the title compound: mp 106-109°C; IR (KBr) 3200-3400, 2966, 2875, 2667, 2554, 1706, 1618, 1537, 1299, 921 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.90 (t, 3H, J=7.4 Hz), 1.59 (m, 2H), 2.82 (m, 2H), 7.63 (d, 1H, J=8.0 Hz), 8.12 (dd, 1H, J=1.7, 8.0 Hz), 8.33 (d, 1H, J=1.7 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.2, 23.7, 34.2, 125.4, 130.5, 132.9, 133.6, 141.4, 149.5, 165.9; Anal. calcd for $C_{10}H_{11}NO_4 \cdot 1/4H_2O$: C, 56.20; H, 5.42; N, 6.55. Found: C, 56.12; H, 5.31; N, 6.81.

B. 3-Amino-4-propyl-benzoic acid

A mixture of 11.96 g (57.2 mmol) 3-nitro-4-propyl-benzoic acid and 1.5 g 10% Pd/C, 50% water wet, in 250 mL CH_3OH was placed on a Parr hydrogenation apparatus and shaken under 25 psi H_2 at ambient temperature. After 1 hour, the reaction mixture was filtered through celite, and the filtrate concentrated and dried to give 9.80 g (96%) of a pale yellow crystalline solid: mp 139.5-142.5°C; IR (Kbr) 3200-2400, 3369, 3298, 2969, 2874, 2588, 1690, 1426, 916, 864 cm^{-1}; ^1H NMR (300 Mhz, DMSO-d_6) δ 0.90 (t, 3H, J=7.2 Hz), 1.52 (m, 2H), 2.42 (m, 2H), 5.08 (br s, 2H), 6.96 (d, 1H, J=7.8 Hz), 7.05 (dd, 1H, J=1.7, 7.8 Hz), 7.20 (d, 1H, J=1.7 Hz); MS (CI, NH_3) m/z 180 ($M+H^+$, base); Anal. calcd for $C_{10}H_{13}NO_2 \cdot 1/3H_2O$: C, 64:85; N, 7.89; N, 7.56. Found: C, 64.69; H, 7.49; N, 7.86.

C. 3-Carboxy-6-propyl-benzenediazo t-butyl sulfide

A mixture of 8.80 g (49.1 mmol, 1.0 equiv) 3-amino-4-propyl-benzoic acid and 2.34 g (22.1 mmol, 0.45 equiv) sodium carbonate in 55 mL H_2O was heated gently with a heat gun until mostly dissolved. The reaction mixture was chilled in an ice bath, and a solution of 3.73 g (54.0 mmol, 1.0 equiv.) sodium nitrite in 27 mL H_2O was added dropwise. After 15 min., the reaction mixture was transferred to a dropping funnel and added over 10 minutes to a beaker containing 55 g of crushed ice and 10.6 mL concentrated HCl. After stirring 10 min., the contents of the beaker were transferred to a dropping funnel and added over 5 minutes to a room temperature solution of 5.31 mL

(47.1 mmol, 0.96 equiv) t-butyl thiol in 130 mL ethanol. The pH was adjusted to 4-5 by addition of saturated aqueous Na_2CO_3 solution, and the reaction mixture was allowed to stir 1 hour at ambient temperature. 200 mL brine were added, and the mixture was filtered. The solid was washed 1 x H_2O and dried overnight to give 12.25 g (89%) of a brown/rust colored powder (caution - stench): mp 102°C (dec); IR (KBr) 3200-2400, 2962, 2872. 2550, 1678, 1484, 1428, 1298, 1171 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, 3H, J=7.3 Hz), 1.48 (m, 2H), 1.55 (s, 9H), 2.42 (m, 2H), 7.29 (d, 1H, J=1.6 Hz), 7.50 (d, 1H, J=8.0 Hz), 7.86 (dd, 1H, J=1.7, 7.9 Hz), 13.18 (br s, 1H); MS (thermospray, NH_4OAc) m/z 281 (M+H+, base); Anal. calcd for $C_{14}H_{20}N_2O_2S$: C, 59.96; H, 7.19; N, 9.99. Found: C, 59.71; H, 7.32; N, 10.02.

D. 3-Ethyl-1H-indazole-6-carboxylic acid

A solution of 12.0 g (42.8 mmol, 1.0 equiv) 3-carboxy-6-propyl-benzenediazo t-butyl sulfide in 150 mL DMSO was added dropwise over 15 min. to a room temperature solution of 44.6 g (398 mmol, 9.3 equiv) potassium t-butoxide in 200 mL DMSO. After stirring 2 hours at ambient temperature, the reaction mixture was poured into 1.5 L of 0°C 1N HCl, stirred 5 min., then extracted 2 x 350 mL ethyl acetate. The ethyl acetate extracts (caution - stench) were combined, washed 2 x 250 mL H_2O, and dried over $MgSO_4$. Filtration, concentration of filtrate and drying gave a tan solid, which was triturated with 1 L of 1:3 Et_2O/Hexanes and dried to give 7.08 g (87%) of a tan crystalline powder: mp 248-251°C; IR (KBr) 3301, 3300-2400, 2973, 2504, 1702, 1455, 1401, 1219 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, 3H, J=7.6 Hz), 2.94 (q, 2H, J=7.6 Hz), 7.63 (dd, 1H, J=1.1, 8.4 Hz), 7.81 (d, 1H, J=8.4 Hz), 8.06 (d, 1H, J=1.1 Hz) 12.95 (br s, 1H); MS (CI, NH_3) m/z 191 (M+H+, base); Anal. calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.66; H, 5.42; N, 14.80.

E. 3-Ethyl-1H-indazole-6-carboxylic acid methyl ester

8.78 g (45.8 mmol, 1.1 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in one portion to a room temperature solution of 7.92 g (41.6 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid, 16.9 mL (416 mmol, 10 equiv) methanol and 5.59 g (45.8 mmol, 1.1 equiv) DMAP in 250 mL CH_2Cl_2. After 18 hours at room temperature, the reaction mixture was concentrated to 150 mL, diluted with 500 mL ethyl acetate, washed 2 x 100 mL 1N HCl, 1 x 100 mL H_2O, 1 x 100 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave 7.8 g of a brown solid, which was purified on a silica gel column (30% to 50% ethyl acetate/hexanes

gradient) to give 6.41 g (75%) of a tan solid: mp 107-108°C; IR (KBr) 3100-2950, 1723, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 1H), 7.7-7.8 (m, 2H), 3.96 (s, 3H), 3.05 (q, 2H, J=7.7 Hz), 1.43 (t, 3H, 7.7 Hz); MS (CI, NH_3) m/z 205 ($M+H^+$, base); Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.88; H, 6.01; N, 13.96.

F. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

1.17 g (29.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, was added in one portion to a room temperature solution of 5.7 g (27.9 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 125 mL anhydrous DMF. After 20 minutes, 3.89 mL (36.6 mmol, 1.3 equiv) cyclopentyl bromide were added dropwise, and the reaction was mixture allowed to stir overnight at room temperature. The mixture was then poured into 1 L H_2O and extracted 3 x 450 mL ethyl acetate. The organic extracts were combined, washed 3 x 400 mL H_2O, 1 x 200 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave an amber oil, which was purified on a silica gel column (10% ethyl acetate/hexanes, gravity) to give 5.48 g (72%) of a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1H, J=1.0 Hz), 7.7 (m, 2H), 5.00 (quintet, 1H, J=7.5 Hz), 3.97 (s, 3H), 3.01 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.8 (m, 2H), 1.39 (t, 3H, J=7.6 Hz); HRMS calcd for $C_{18}H_{20}N_2O_2$; 272.1526. Found: 272.15078.

G. (1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-methanol

7 mL (7.0 mmol, 1.0 equiv) lithium aluminum hydride, 1.0 M solution in THF, were added to a 0°C solution of 1.02 g (7.05 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 50 mL anhydrous THF. After 20 minutes, 1 mL methanol was added cautiously, then the reaction mixture was poured into 500 mL of 5% H_2SO_4 and extracted 3 x 50 mL ethyl acetate. The organic extracts were combined, washed 2 x 40 mL H_2O, 1 x 40 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate, and drying gave 1.58 g of a clear oil, which was purified on a silica gel column to give 1.53 g (89%) clear oil: IR ($CHCl_3$) 3606, 3411, 3009, 2972, 2875, 1621, 1490 cm^{-1}; ^1H NMR (300 Mhz, $CDCl_3$) δ 7.65 (d, 1H, J=8.0 Hz), 7.42 (s, 1H), 7.06 (dd, 1H, J=1.0, 8.2 Hz), 4.92 (quintet, 1H, J=7.7 Hz), 4.84 (s, 2H), 2.98 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 3H), 1.38 (t, 3H, J=7.6 Hz); MS (thermospray, NH_4OAc) m/z 245 ($M+H^+$, base); HRMS calcd for $C_{15}H_{20}N_2O$ + H: 245.1654. Found: 245.1675.

H. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde

106 mg (0.301 mmol, 0.05 equiv) tetrapropylammonium perruthenate (VII) were added to a room temperature suspension of 1.47 g (6.02 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-methanol, 1.06 g (9.03 mmol, 1.5 equiv) N-methylmorpholine N-oxide and 3.01 g 4A molecular sieves in 12 mL anhydrous CH_2Cl_2. After 30 minutes, the reaction mixture was filtered through a short column of silica gel (eluted with CH_2Cl_2). Fractions containing product were concentrated, and the residue chromatographed on a silica gel column (15% ethyl acetate/hexanes, flash) to give 924 mg (63%) of a pale yellow solid: mp 41°C; IR (KBr) 3053, 2966, 2872, 2819, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.93 (d, 1H, J=0.9 Hz), 7.77 (d, 1H, J=8.4 Hz), 7.60 (dd, 1H, J=1.2, 8.4 Hz), 5.00 (quintet, 1H, J=7.5 Hz), 3.01 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 2H), 1.39 (t, 3H, J=7.5 Hz); MS (CI, NH_3) m/z 243 ($M+H^+$, base); Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.17; H, 7.58; N, 11.79.

EXAMPLE 2

A. 4-Bromo-2-nitro-1-propyl-benzene

125 g (628 mmol, 1.0 equiv) 1-bromo-4-propyl-benzene were added in one portion to a 10°C solution of 600 mL concentrated H_2SO_4 and 200 mL H_2O. With vigorous mechanical stirring, a room temperature mixture of 43.2 mL (691 mmol, 1.1 equiv) conc. HNO_3 (69-71%, 16M) in 150 mL conc. H_2SO_4 and 50 mL H_2O was added dropwise over 30 minutes. The ice bath was allowed to warm to room temperature, and the reaction stirred at room temperature for 68 hours. The reaction mixture was poured into a 4 L beaker, loosely packed full with crushed ice. After stirring 1 hour, the mixture was transferred to a 4 L separatory funnel and extracted 4 x 800 mL isopropyl ether. The organic extracts were combined, washed 3 x 800 mL H_2O, 1 x 500 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave 150 mL of a yellow liquid, which was purified by silica gel chromatography (2 columns, 3 kg silica gel each, 2% ethyl acetate/hexanes) to afford 63.9 g (42%) of a yellow liquid. The desired regioisomer is the less polar of the two, which are formed in a 1:1 ratio. bp 108°C, 2.0 mm; IR ($CHCl_3$) 3031, 2966, 2935, 2875, 1531, 1352 cm^{-1}; ^1H NMR (300 MHZ, $CDCl_3$) δ 8.01 (d, 1H, J=2.1 Hz), 7.62 (dd, 1H, J=2.1, 8.3 Hz), 7.23 (d, 1H, J=8.3 Hz), 2.81 (m, 2H), 1.67 (m, 2H), 0.98 (t, 3H, J= 7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.94, 23.74, 34.43, 119.6, 127.4, 133.3, 135.7, 136.4, 149.8; GCMS (EI) m/z 245/243 (M^+.), 147 (base); HRMS calcd for $C_9H_{10}NO_2BR+H$: 243.9973. Found: 243.9954.

B. 5-Bromo-2-propyl-phenylamine

121 g (639 mmol, 3.0 equiv) of stannous chloride (anhydrous) were added in one portion to a room temperature solution of 51.9 g (213 mmol, 1.0 equiv) 4-bromo-2-nitro-1-propyl-benzene in 1200 mL absolute ethanol and 12 mL (6 equiv) H_2O. After 24 hours at room temperature, most of the ethanol was removed on a rotary evaporator. The residue was poured into a 4 L beaker, three-quarters full with crushed ice and H_2O. 150 g of NaOH pellets were added portionwise, with stirring, until the pH = 10 and most of the tin hydroxide has dissolved. The mixture was divided in half, and each half extracted 2 x 750 mL ethyl acetate. All four ethyl acetate extracts were combined, washed 1 x 500 mL each 1N NaOH, H_2O, and brine, then dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a yellow liquid, which was purified on a 1.2 kg silica gel column (1:12 ethyl acetate/hexanes) to give 41.83 g (92%) of a pale yellow liquid: IR ($CHCl_3$) 3490, 3404, 3008, 2962, 2933, 2873, 1620, 1491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.8-6.9 (m, 3H), 3.90 br s, 2H), 2.42 (m, 2H0, 1.62 (m, 2H), 0.99 (t, 3H, J=7.3 Hz); GCMS (EI) m/z 215/213 (M^+.), 186/184 (base); Anal. calcd for $C_9H_{12}NBr$: C, 50.49; H, 5.65; N, 6.54. Found: C, 50.77; H, 5.70; N, 6.50.

C. 6-Bromo-3-ethyl-1H-indazole

49.22 g (230 mmol, 1.0 equiv) 5-bromo-2-propyl-phenylamine were placed in a 3 L flask and chilled in an ice bath. A 0°C solution of 57.5 mL (690 mmol, 3.0 equiv) conc. HCl in 165 mL H_2O was added, and the resulting solid mass which formed was ground up until a fine white suspension resulted. 100 mL more H_2O were added, then a solution of 15.9 g (230 mmol, 1.0 equiv) sodium nitrite in 75 mL H_2O was added dropwise over 10 min. The ice bath was removed, and the reaction allowed to stir at room temperature for 30 minutes. The reaction mixture was then filtered through a sintered glass funnel, precooled to 0°C. The filtrate was chilled in an ice bath, and with mechanical stirring, a 0°C solution/suspension of 32.8 g (313 mmol, 1.36 equiv) ammonium tetrafluoroborate in 110 mL H_2O was added dropwise over 10 min. The thick white suspension which formed (aryl diazonium tetrafluoroborate salt) was allowed to stir 1.5 hours at 0°C. The mixture was then filtered, and the solid washed 1 x 200 mL 5% aq. NH_4BF_4 (cooled to 0°C), 1 x 150 mL CH_3OH (cooled to 0°C), then 1 x 200 mL Et_2O. Drying at high vacuum, room temperature for 1 hour gave 54.47 g (76%) of the diazonium salt, an off-white solid.

1500 mL of ethanol free chloroform was placed in a 3 L flask, then 34.16 g (348 mmol, 2.0 equiv) potassium acetate (powdered and dried) and 2.3 g (8.7 mmol, 0.05 equiv) 18-crown-6 were added. After 10 minutes the diazonium salt was added in one portion, and the reaction mixture allowed to stir at room temperature under nitrogen atmosphere for 18 hours. The mixture was then filtered, the solid washed 2 x with $CHCl_3$, and the filtrate concentrated to give 47 g of crude product (brown crystals). Silica gel chromatography (1.23 kg silica gel, ethyl acetate/hexanes gradient 15%, 20%, 40%) gave 21.6 g (55% for second step, 42% overall) of tan crystals: mp 112-114°C; IR (KBr) 3205, 3008, 2969, 2925, 1616, 1340, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 7.61 (d, 1H, J=1.3 Hz), 7.57 (d, 1H, J=8.4 Hz), 7.24 (dd, 1H, J=1.5, 8.6 Hz), 2.99 (q, 2H, J=7.6 Hz), 1.41 (t, 3H, J= 7.6 Hz); MS (CI, NH_3) m/z 227/225 ($M+H^+$, base); Anal. calcd for $C_9H_9N_2Br$: C, 48.02; H, 4.03; N, 12.45. Found: C, 48.08; H, 3.87; N, 12.45.

D. 6-Bromo-1-cyclopentyl-3-ethyl-1H-indazole

2.46 g (61.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, was added in 0.5 g portions to a 10°C solution of 13.17 g (58.5 mmol, 1.0 equiv) 6-bromo-3-ethyl-1H-indazole in 500 mL anhydrous DMF. The mixture was stirred at room temperature for 20 minutes, then a solution of 8.8 mL (81.9 mmol, 1.4 equiv) cyclopentyl bromide in 10 mL anhydrous DMF was added dropwise. After 18 hours, the reaction mixture was poured into 2 L H_2O and extracted 2 x 1L ethyl acetate. The organic extracts were combined, washed 2 x 750 mL H_2O, 1 x 500 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave 20.7 g of crude product, which was purified on a silica gel column (1.1 kg silica gel, 3% ethyl acetate/hexanes) to give 10.6 g (62%) of an amber liquid: IR ($CHCl_3$)2972, 2875, 1606, 1501, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, J=1.3 Hz), 7.52 (d, 1H, J=8.7 Hz), 7.17 (dd, 1H, J=1.5, 8.5 Hz), 4.83 (quintet, 1H, J=7.6 Hz), 2.96 (q, 2H, J=7.6 Hz), 2.15 (m, 4H), 2.0 (m, 2H), 1.65 (m, 2H), 1.36 (t, 3H, J = 7.7 Hz); MS (thermospray, NH_4OAc) m/z 295/293 ($M+H^+$, base); Anal. calcd for $C_{14}H_{17}N_2Br$: C, 57:35; H, 5.84; N, 9.55. Found: C, 57.48; H, 5.83; N, 9.90.

E. (1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde

11.6 mL (28.4 mmol, 1.0 equiv) n-BuLi, 2.45 M in hexanes, were added to a -78°C solution of 8.32 g (28.4 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole in 200 mL anhydrous THF. After 30 min. at -78°C, 8.8 mL (114 mmol, 4.0 equiv) anhydrous DMF was added dropwise, and the reaction mixture was allowed to stir an additional 30 min. at -78°C. The mixture was warmed to room temperature over 1 hour, then 125 mL 1N HCl was added. After stirring for 10 minutes, most of the THF was removed on a rotary evaporator. The residue was diluted with 500 mL H_2O, and extracted 2 x 250 mL ethyl acetate. The organic extracts were combined, washed 1 x 100 mL H_2O, 1 x 100 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on a silica gel column (15% ethyl acetate/hexanes, gravity) to give 4.70 g (68%) of a yellow crystalline solid: ^1H NMR (300 MHz, $CDCl_3$) identical to the spectrum of the compound from example 8.

F. (1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-acetonitrile

4.44 mL (35.0 mmol, 1.5 equiv) trimethylsilyl chloride were added dropwise to a room temperature suspension of 5.65 g (23.3 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde and 3.84 g (44.3 mmol, 1.9 equiv) lithium bromide in 115 mL anhydrous acetonitrile. After 15 minutes, the reaction mixture was cooled in an ice bath, and 6.84 mL (38.7 mmol, 1.66 equiv) 1,1,3,3-tetramethyldisiloxane were added dropwise, and the reaction was allowed to warm to room temperature over 2 hours. The reaction mixture was heated to reflux for 6 hours, then cooled to room temperature, diluted with 300 mL CH_2Cl_2, and filtered through Celite®. The filtrate was concentrated and dried at high vacuum, room temperature to give 13.08 g of a tan oily solid.

This solid was dissolved in 200 mL anhydrous DMF, 259 g (52.9 mmol, 2.27 equiv) sodium cyanide were added, and the mixture stirred at room temperature for 2 hours. The reaction mixture was then poured into 500 mL H_2O and extracted 3 x 200 mL ethyl acetate. The organic extracts were combined, washed 3 x 200 mL H_2O, 1 x 200 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a brown oil, which was purified on a silica gel column (10%-20% ethyl acetate/hexanes gradient) to give 2.98 g of impure product and 2.05 g of recovered (impure) starting material.

The recovered starting material was resubjected to the reaction conditions described above, using 50 mL 1,1,3,3-tetramethyldisiloxane, followed by 50 mL DMF

and 940 mg sodium cyanide. Silica gel chromatography gave 0.62 g of impure product, which was then combined with the 2.98 g lot of impure product and rechromatographed (10% ethyl acetate/hexanes) to give 3.27 g (55%) of a yellow oil: IR ($CHCl_3$) 3062, 2972, 2874, 2255, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H, J=8.3 Hz), 7.39 (s, 1H), 6.97 (dd, 1H, J=1.1, 8.4 Hz), 4.90 (quintet, 1H, J=7.6 Hz), 3.89 (s, 2H), 2.98 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 2H), 1.37 9t, 3H, J=7.4 Hz); MS (CI, NH_3) m/z 254 ($M+H^+$, base); Anal. calcd for $C_{16}H_{19}N_3$: C, 75.86; H, 7.56; N, 16.59. Found: C, 75.84; H, 7.94; N, 16.60.

G. 4-Cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-heptanedioic acid dimethyl ester

530 μL (1.26 mmol, 0.1 equiv) triton B, 40% in methanol, was added to a room temperature solution of 3.19 g (12.6 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-acetonitrile in 100 mL anhydrous acetonitrile. The reaction mixture was heated to reflux, and 11.3 mL (126 mmol, 10.0 equiv) methyl acrylate was added dropwise. After 15 minutes, the reaction mixture was cooled to room temperature, and concentrated on a rotary evaporator. The residue was diluted with 300 mL ether, washed 1 x 50 mL 1N HCl, 1 x 50 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a brown oil, which was purified on a silica gel column (20% ethyl acetate/hexanes, flash) to give 4.00 g (75%) of a yellow oil: IR ($CHCl_3$) 3031, 2972, 2955, 2874, 2250, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, J=8.5 Hz), 7.49 (s, 1H), 6.97 (d, 1H, J=8.5 Hz); 4.93 (quintet, 1H, J=7.6 Hz), 3.58 (s, 6H), 2.97 (q, 2H), J=7.7 Hz), 2.45 (m, 6H), 2.2 (m, 6H), 2.0 (m, 2H), 1.8 m, 2H), 1.37 (t, 3H, J=7.7 Hz); MS (CI, NH_3) m/z 426 ($M+H^+$, base); Anal. calcd for $C_{24}H_{31}N_3O_4$: C, 67.74; H, 7.34; N, 9.88. Found: C, 67.76; H, 7.40; N, 10.08.

H. (±)-5-Cyano-5-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-2-oxo-cyclohexane-carboxylic acid methyl ester

924 mg (23.1 mmol, 2.5 equiv) sodium hydride, 60% oil dispersion, was added in one portion to a room temperature solution of 3.93 g (9.24 mmol, 1.0 equiv) 4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-heptanedioic acid dimethyl ester in 100 mL anhydrous 1,2-dimethoxyethane. The reaction mixture was heated to reflux under nitrogen atmosphere for 1.5 hours, then cooled to room temperature. After 18 hours, the reaction mixture was quenched with 50 mL H_2O, poured into 200 mL ethyl acetate, and washed 1 x 100 mL 1N HCl. The aqueous layer was extracted 1 x 50 mL ethyl

acetate. The organic extracts were combined, washed 1 x 50 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on a silica gel column (10% ethyl acetate/hexanes) to give 2.78 g (76%) of a white amorphous solid: IR (KRr) 2954, 2871, 2240, 1663, 1619 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.27 (s, 1H), 7.70 (d, 1H, J=8.5 Hz), 7.57 (s, 1H), 7.15 (dd, 1H, J=1.6, 8.5 Hz), 4.93 (quintet, 1H, J=7.6 Hz), 3.78 (s, 3H), 3.05 (m, 1H), 2.98 (q, 2H, J=7.6 Hz), 2.9 (m, 1H), 2.75 (m, 1H), 2.6 (m, 1H), 2.35 (m, 2H), 2.2 (m, 4H), 2.0 (m, 2H), 1.75 (m, 2H), 1.38 (t, 3H, J=7.6 Hz); MS (CI, NH_3) m/z 394 ($M+H^+$, base); Anal. calcd for $C_{23}H_{27}N_3O_3$: C, 70.22; H, 6.92; N, 10.68. Found: C, 70.07; H, 7.01; N, 10.70.

I. 1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile. A mixture of 2.72 g (6.91 mmol, 1.0 equiv) (±)-5-cyano-5-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-2-oxo-cyclohexanecarboxylic acid methyl ester and 2.58 g (44.2 mmol, 6.4 eqiv) sodium chloride in 50 mL dimethyl sulfoxide and 4 mL H_2O was heated in 140°C oil bath under nitrogen atmosphere. After 3 hours, the reaction mixture was cooled to room temperature and allowed to stir for 72 hours. The reaction mixture was poured into 250 mL H_2O and extracted 2 x 150 mL ethyl acetate. The organic extracts were combined, washed 2 x 100 mL H_2O, 1 x 100 mL brine, and dried over Na_2SO_4. The crude product was purified on a silica gel column (20% ethyl acetate/hexanes) to give 1.82 g (78%) of a white crystalline solid: mp 81-89°C; IR (KBr) 2969, 2951, 2872, 2236, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 1H, J=8.5 Hz), 7.58 (s, 1H), 7.16 (dd, 1H, J = 1.5, 8.5 Hz), 4.93 (quintet, 1H, J=7.6 Hz), 3.0 (m, 4H), 2.7 (m, 4H), 2.45 (m, 2H), NH_4OAc) m/z 336 ($M+H^+$, base); Anal. calcd for $C_{21}H_{25}N_3O$: C, 75.20; H, 7.51; N, 12.53. Found: C, 74.06; H, 7.59; N, 12.41; HRMS calcd for $C_{21}H_{25}N_3O$ + H: 336.20778. Found 336.2088.

EXAMPLE 3

A. 1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-4-[1,3]dithian-2-ylidene-cyclohexane-carbonitrile

3.94 mL (9.84 mmol, 2.09 equiv) n-BuLi, 2.5 M in hexanes, was added dropwise to a 0°C solution of 1.88 mL (9.89 mmol, 2.1 equiv) 2-trimethylsilyl-1,3-dithiane in 80 mL anhydrous THF. After 25 minutes at 0°C, the reaction mixture was cooled to -78°C and a solution of 1.58 g (4.71 mmol, 1.0 equiv) 1-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile in 40 mL anhydrous THF was added. After 1 hours at -78°C, the reaction mixture was quenched by addition of 50 mL brine, then warmed to

room temperature, diluted with 100 mL H_2O, and extracted 1 x 100 mL CH_2Cl_2 and 1 x 50 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a clear oil, which was purified on a silica gel column (10% ethyl acetate/hexanes) to give 1.51 g (73%) of a white amorphous solid: IR (KBr) 2962, 2870, 2232, 1620, 1569, 1508, 1434, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, J=8.5 Hz), 7.53 (s, 1H), 7.15 (dd, 1H, J=1.5, 8.6 Hz), 4.92 (quintet, 1H, J=7.6 Hz), 3.36 (m, 2H), 3.0 (m, 6H), 2.42 (m, 2H), 2.34 (m, 2H), 2.2 (m, 6H), 2.0 (m, 4H), 1.8 (m, 2H), 1.37 (t, 3H, J=7.5 Hz); MS (CI, NH_3) m/z 438 ($M+H^+$, base); Anal. calcd for $C_{25}H_{31}N_3S_2$: C, 68.60; H, 7.14; N, 9.60. Found: C, 68.26; H, 7.29; N, 9.58.

B. Trans-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester and cis-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester

A mixture of 1.45 g (3.31 mmol, 1.0 equiv) 1-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-4-[1,3]dithian-2-ylidene-cyclohexane-carbonitrile, 3.59 g (13.2 mmol, 4.0 equiv) mercury (II) chloride and 1.48 mL (16.9 mmol, 5.1 equiv) 70% perchloric acid in 60 mL methanol was heated to reflux under nitrogen atmosphere. After 2 hours, the reaction mixture was cooled to room temperature, diluted with 250 mL CH_2Cl_2 and filtered through Celite®. The filtrate was washed 1 x 100 mL saturated aqueous $NaHCO_3$, 1 x 75 mL 10% aqueous sodium sulfite, 1 x 100 mL H_2O, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a clear oil, which was purified on a silica gel column (15% ethyl acetate/hexanes) to give 340 mg (27%) of trans isomer (less polar) as a white solid, and 794 mg (63%) of cis isomer (more polar) as a white solid:

data for trans isomer: mp 79-82°C; IR (KBr) 2973, 2949, 2890, 2871, 2235, 1721, 1618, 1484, 1453, 1217, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, J=8.4 Hz), 7.52 (s, 1Y), 7.14 (dd, 1H, J=1.4, 8.5 Hz), 4.93 (quintet, 1H, J=7.6 Hz), 3.74 (s, 3H), 2.97 (q, 2H, J=7.6 Hz), 2.85 (m 1H0, 2.3 (m, 2H), 2.2 (m, 10H), 2.0 (m, 2H), 1.75 (m, 2H), 1.37 (t, 3H, J= 7.6 Hz); MS (CI, NH_3) m/z 380 ($M+H^+$, base); Anal. calcd for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 73.05; H, 7.80; N, 11.03.

data for cis isomer: mp 112-114°C; IR (KBr) 3065, 2952, 2866, 2234, 1731, 1622, 1487, 1445, 1220; 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, J=8.5 Hz), 7.55 (s, 1H), 7.14 (dd, 1H, J=1.3, 8.4 Hz), 4.93 (quintet, 1H, J=7.6 Hz), 3.73 (s, 3H), 2.98 (q, 2H, J=7.6 Hz), 2.42 (m, 1H), 2.36 (m, 1H), 1.9-2.3 (m, 13H), 1.8 (m, 2H), 1.37 (t, 3H,

J=7.5 Hz); MS (CI, NH_3) m/z 380 ($M+H^+$, base); Anal. calcd for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.93; H, 7.56; N, 10.92.

EXAMPLE 4

Trans-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid

A mixture of 337 mg (0.888 mmol, 1.0 equiv) trans-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester in 10 mL methanol, 2 mL THF and 2.7 mL (2.66 mmol, 3.0 equiv) 1N NaOH was allowed to stir at room temperature. After 3 hours, the reaction mixture was concentrated on a rotary evaporator, diluted with 100 mL H_2O, acidified to pH 1, and extracted 2 x 70 mL ethyl acetate. The organic extracts were combined, washed 1 x 50 mL H_2O, 1 x 50 mL brine, and dried over Na_2SO_4. Filtration, concentration and drying gave a white solid, which was purified on a silica gel column (5% CH_3OH/CH_2Cl_2) to give 197 mg (61%) of a white amorphous solid: IR (KBr) 3200-2500, 3060, 2963, 2871, 2245, 1729, 1702, 1621, 1453, 1219 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.4 (br s, 1H), 7.77 (d, 1H, J=8.5 Hz), 7.69 (s, 1H), 7.20 (dd, 1H, J=1.3, 8.5 Hz); 5.17 (quintet, 1H, J=7.6 Hz), 2.90 (q, 2H, J=7.6 Hz), 2.75 (m, 1H), 1.9-2.3 (m, 16H), 1.7 (m, 2H), 1.28 (t, 3H, J=7.6 Hz); MS (CI, NH_3) m/z 366 ($M+H^+$, base); Anal. calcd for $C_{22}H_{27}N_3O_2$: C, 72.29; H, 7.45; N, 11.50. Found: C, 71.98; H, 7.75; N, 11.21.

EXAMPLE 5

Cis-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid.

A mixture of 831 mg (2.19 mmol, 1.0 equiv) cis-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester in 20 mL methanol, 4 mL THF and 6.6 mL (6.57 mmol, 3.0 equiv) 1N NaOH was allowed to stir at room temperature. After 1.5 hours, the reaction mixture was concentrated on a rotary evaporator, diluted with 100 mL H_2O, acidified to pH 1, and extracted 2 x 70 mL ethyl acetate. The organic extracts were combined, washed 1 x 50 mL H_2O, 1 x 50 mL brine, and dried over Na_2SO_4. Filtration, concentration and drying gave 0.80 g of a white solid, which was purified on a silica gel column (5% CH_3OH/CH_2Cl_2) to give 730 mg (91%) of a white crystalline solid. Recrystallization from ethyl acetate/hexanes gave 538 mg of white crystals: mp 197-199°C; IR (KBr) 3200-2600, 3061, 2961, 2948, 2939, 2871, 2245, 1732, 1625, 1451, 1255, 1185, 1169 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.35 (br s, 1H), 7.77 (d, 1H, J=8.6 Hz), 7.73 (s, 1H0, 7.27 (dd, 1H, J=1.5, 8.5 Hz), 5.13 (quintet,

1H, J=7.5 Hz), 2.90 (q, 2H, J=7.6 Hz), 2.42 (m, 1H), 2.30 (m, 2H), 1.7-2.1 (m, 14H), 1.29 (t, 3H, J=7.5 Hz); MS (CI, NH_3) m/z 366 ($M+H^+$, base); Anal. calcd for $C_{22}H_{27}N_3O_2$: C, 72.29; H, 7.45; N, 11.50. Found: C, 72.01; H, 7.60; N, 11.29.

EXAMPLE 6

A. 6-Bromo-1-cyclohex-2-enyl-3-ethyl-1H-indazole

2.12 g (52.9 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, was added in four portions over 10 min. to a room temperature solution of 11.35 g (50.4 mmol, 1.0 equiv) 6-bromo-ethyl-1H-indazole in 300 mL anhydrous DMF. After stirring 20 min., 9.0 mL (70.6 mmol, 1.4 equiv) 3-bromo-cyclohexene were added dropwise, and the reaction concentrated and dried at high vacuum, room temperature to give 7.52 g of an orange/yellow solid.

This solid was dissolved in anhydrous DMF, 1.56 g (31.8 mmol, 2.27 equiv) sodium cyanide were added, and the mixture stirred at room temperature for 2.5 h. The reaction mixture was then poured into 400 mL H_2O and extracted 3 x 200 mL ethyl acetate. The organic extracts were combined, washed 3 x 150 mL H_2O, 1 x 150 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on a silica gel column (5%-10% ethyl acetate/hexanes gradient) to give 1.40 g (38%) of a yellow/green oil; MS (CI, NH_3) 268 ($M+H^+$, base); Anal. calcd for $C_{17}H_{21}N_3$: C, 76.38; H, 7.92; N, 15.72. Found C, 76.43; H, 7.53; N, 15.39.

B. 6-Bromo-1-cyclohexyl-3-ethyl-1H-indazole

A mixture of 10.22 g (33.5 mmol, 1.0 equiv) 6-bromo-1-cyclohex-2-enyl-3-ethyl-1H-indazole and 1.5 g 10% Pt/C in 1 L cyclohexane was placed on a Parr® hydrogenation apparatus and shaken under 2-5 psi H_2 at room temperature. After 1 h, the reaction mixture was filtered through celite®, and the filtrate concentrated on a rotary evaporator and chromatographed (5% ethyl acetate/hexanes, flash) to give 9.70 g (94%) of a pale yellow oil: MS (CI, NH_3) m/z 309/307 ($M+H^+$, base); Anal. calcd for $C_{15}H_{19}N_2Br$: C, 58.64; H, 6.23; N, 9.12. Found: C, 58.56; H, 6.29; N, 8.77.

C. 1-Cyclohexyl-3-ethyl-1H-indazole-6-carbaldehyde

This compound was prepared according to the method of example 2.E., using 5.02 g (16.3 mmol, 1.0 equiv) 6-bromo-1-cyclohexyl-3-ethyl-1H-indazole as starting material to give 3.65 g (87%) of a pale yellow oil: MS (CI, NH_3) m/z 257 ($M+H^+$, base); Anal. calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.87; N, 10.93. Found: C, 75.00; H, 7.70; N, 10.74.

D. (1-(Cyclohexyl-3-ethyl-1H-indazol-6-yl)-acetonitrile

2.7 mL (21.0 mmol, 1.5 equiv) trimethylsilyl chloride were added dropwise to a room temperature suspension of 3.58 g (14.0 mmol, 1.0 equiv) 1-cyclohexyl-3-ethyl-1H-indazole-6-carbaldehyde and 2.31 g (26.6 mmol, 1.9 equiv) lithium bromide in 100 mL anhydrous acetonitrile. After 15 min., the reaction mixture was cooled in an ice bath, and 4.1 mL (23.2 mmol, 1.66 equiv) 1,1,3,3-tetramethyldisiloxane were added dropwise, and the reaction was allowed to warm to room temperature over 30 min. The reaction mixture was heated to reflux for 3 h, then cooled to room temperature, diluted with 300 mL CH_2Cl_2, and filtered through Celite®. The filtrate was concentrated and dried at high vacuum, room temperature to give 7.52 g of an orange/yellow solid.

This solid was dissolved in 100 mL anhydrous DMF, 1.56 g (31.8 mmol, 2.27 equiv) sodium cyanide were added, and the mixture stirred at room temperature for 2.5 h. The reaction mixture was then poured into 400 mL H_2O and extracted 3 x 200 mL ethyl acetate. The organic extracts were combined, washed 3 x 150 mL H_2O, 1 x 150 mL brine, and dried over Na_2SO_4. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on a silica gel column (5% - 10% ethyl acetate/hexanes gradient) to give 1.40 g (38%) of a yellow/green oil: MS (CI, NH_3) 268 ($M+H^+$, base); Anal. calcd for $C_{17}H_{21}N_3$: C, 76.38; H, 7.92; N, 15.72. Found: C, 76.43; H, 7.53; N, 15.39.

E. 4-Cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-heptanedioic acid dimethyl ester

This compound was prepared according to the method of example 2.G., using 1.33 g (4.98 mmol, 1.0 equiv) of (1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-acetonitrile as starting material, to give 1.38 g (63%) of a yellow oil; MS (CI, NH_3) m/z 440 ($M+H^+$, base); Anal. calcd for $C_{25}H_{33}N_3O_4$: C, 68.32; H, 7.57; N, 9.56. Found: C, 68.18; H, 7.52; N, 9.28.

F. 5-Cyano-5-(1-cyclohexyl-3-ethyl-1H-indazol-t-yl)-2-oxo-cyclohexanecarboxylic acid methyl ester

This compound was prepared according to the method of example 2.H., using 1.33 g (3.03 mmol, 1.0 equiv) 4-cyano-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-heptanedioic acid dimethyl ester as starting material, to give 983 mg (80%) of a white amorphous solid: MS (CI, NH_3) m/z 408 ($M+H^+$, base); Anal. calcd for $C_{24}H_{29}N_3O_3$: C, 70.75; H, 7.18; N, 10.31. Found: C, 70.75; H, 7.33; N, 10.19.

G. 1-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile. This compound was prepared according to the method of example 2.I., using 933 mg (2.29 mmol, 1.0 equiv) 5-cyano-5-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-2-oxocyclohexanecarboxylic acid methyl ester as starting material, to give 588 mg (74%) of a white amorphous solid: MS (CI, NH_3) m/z 350 ($M+H^+$, base); Anal. calcd for $C_{22}H_{27}N_3O$: C, 75.62; H, 7.79; N, 12.03. Found: C, 75.57; H, 7.90; N, 12.15.

EXAMPLE 7

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylicacid methyl ester and trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester

These compounds were prepared according to the method of example 3.B.,using 540 mg (1.20 mmol, 1.0 equiv) 1-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-[1,3]dithian-2-ylidene-cyclohexane-carbonitrile as starting material, to give 117 mg (25%) of trans isomer as a white oily solid, and 233 mg (50%) of cis isomer as a white crystalline solid:

Data for trans isomer: ^1H NMR (300 MHz, CDCl3) δ 7.68 (d, 1H, J=8.4 Hz), 7.50 (d, 1H, J=0.8 Hz), 7.13 (dd, 1H, J=1.6, 8.5 Hz), 4.34 (m, 1H), 3.74 (s, 3H), 2.98 (q, 2H, J+7.6 Hz), 2.85 (m, 1H), 2.35 (m, 2H), 1.9-2.2 (m, 12H), 1.8 (m, 2H), 1.55 (m, 2H), 1.37 (t, 3H, J=7.6 Hz); MS (CI, NH_3) m/z 394 ($M+H^+$, base); Anal. calcd for $C_{24}H_{31}N_3O_2$; C, 73.25; H, 7.95; N, 10.68. Fund: C, 73.07; H, 8.12; N, 10.89. Data for cis isomer: 1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, J=8.4 Hz), 7.53 (d, 1H, J=0.9 Hz), 7.14 (dd, 1H, J=1.6, 8.5 Hz), 4.34 (m, 1H), 3.74 (s, 3H), 2.98 (, 2H, J=7.6 Hz), 2.43 (m, 1H), 1.9-2.3 (m, 15H), 1.8 (m, 1H), 1.5 (m, 2H), 1.37 (t, 3H, JJ=7.6 Hz); MX (CI, NH_3) m/z 394 ($M+^+$, base); Ana. calcd for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.95; N, 10.68. Found: C, 73.17; H, 7.89; N, 10.43.

EXAMPLE 8

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid.

This compound was prepared according to the method of example 5, using 201 mg (0.511 mmol, 1.0 equiv) cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester as starting material, to give 178 mg (92%) of a white crystalline solid, which was recrystallized from ethyl acetate hexanes to give 153

mg of a white crystalline powder; mp 192-194°C; Anal. calculated for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.25; H, 7.99; N, 10.97.

EXAMPLE 9

1-(Cyclohexyl-3-ethyl-1H-indazole-6-yl)-cis-4-hydroxylmethylcyclohexane carbonitrile

To a stirred solution of the product from Example 8 (220 mg, 0.58 mmol.) in dry tetrahydrofuran (5 mL) at 0°C was added dropwise a solution of borane in tetrahydrofuran (1M, 1.3 mL, 1.3 mmol). The mixture was stirred at 0°C for one hour then quenched by the slow addition of methanol (1 mL). The mixture was poured into water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, washed with water (1 x 20 mL), brine (1 x 20 mL) dried over magnesium sulfate and concentrated to give an oil. A separate identical experiment was carried out using the product from Example 8 (100 mg, 0.26 mmol.) and borane in tetrahydrofuran (1M, 0.6 mL, 0.58 mmol.). The crude product from both experiments were combined and chromatographed on Silica Gel eluting with 2.5% methanol in methylene chloride (v/v) to give an oil. Recrystallization from ethyl acetate/hexanes yielded 214 mg white solid (67%) mp 117-9°C. mass spectrum (m/e) 367 (M+1, 20), 366 (M+, 100).

EXAMPLE 10

Cis-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide

A mixture of the product from Example 8 (150 mg, 0.4 mmol.) thionyl chloride (36 uL, 0.49 mmol) and dimethylformamide (5μL) in dry methylene chloride (3mL) was refluxed for four hours. The mixture was cooled to 0°C and dry ammonia gas was bubbled with chloroform (200 mL), washed with water (1 x 40 mL) dried over magnesium sulfate and concentrated to give a solid. Recrystallization from ethyl acetate/hexane yielded 125 mg white solid (83%) mp 180-2°C. mass spectrum (m/e) (M+1, 20), 379 (M+, 100).

EXAMPLE 11

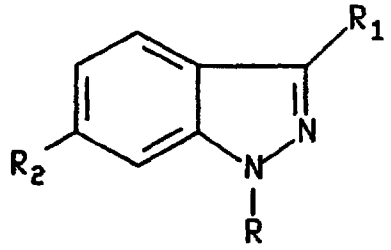
Trans-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide

The title compound was prepared in a manner analogous to the synthesis provided in Example 4. The melting point of the isolated product was 140-143°C.

CLAIMS

What is claimed is:

1. A compound of the formula I



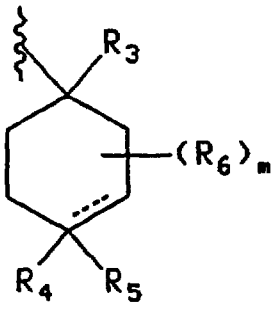
I

or a pharmaceutically acceptable salts thereof, wherein:

R is hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$(C_3-C_7 cycloalkyl) wherein n is 0 to 2, (C_1-C_6 alkoxy)C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_n$(C_3-C_9 heterocyclyl) wherein n is 0 to 2, or -$(Z')_b(Z'')_c$(C_6-C_{10} aryl) wherein b and c are independently 0 or 1, Z' is C_1-C_6 alkylene or C_2-C_6 alkenylene, and Z'' is O, S, SO_2, or NR_9, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkoxy, trifluoromethyl, nitro, CO_2R_9, $C(O)NR_9R_{10}$, NR_9R_{10} and $SO_2NR_9R_{10}$;

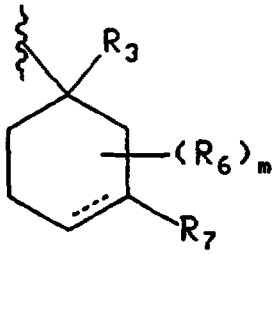
R_1 is hydrogen, C_1-C_7 alkyl, C_2-C_3 alkenyl, phenyl, C_3-C_7 cycloalkyl, or (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, wherein said alkyl, phenyl, and alkenyl R_1 groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

R_2 is selected from the group consisting of



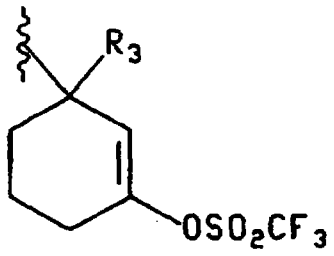
(Ia)

,



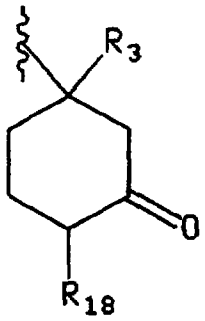
(Ib)

,



(Ic)

and



(Id)

;

wherein the dashed line in formulas (Ia) and (Ib) represent a single or double bond;

m is 0 to 4;

R_3 is H, halo, cyano, C_1-C_4 alkyl optionally substituted by 1 to 3 halo groups, $CH_2NHC(O)C(O)NH_2$, cyclopropyl optionally substituted by R_{11}, R_{17}, CH_2OR_9, NR_9R_{10}, $CH_2NR_9R_{10}$, CO_2R_9, $C(O)NR_9R_{10}$, $C{\equiv}CR_{11}$, C(Z)H or $CH{=}CR_{11}R_{11}$;

R_4 is H, $C(Y)R_{14}$, CO_2R_{14}, $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1$-C_4 alkyl), $CR_9R_{10}OR_{14}$, $CR_9R_{10}SR_{14}$, $CR_9R_{10}S(O)_nR_{15}$ wherein n is 0 to 2, $CR_9R_{10}NR_{14}R_{17}$, $CR_9R_{10}NR_{17}SO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)R_{14}$, $CR_9R_{10}NR_{17}CO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(NCN)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(CR_9NO_2)S(C_1$-$C_4$ alkyl), $CR_9R_{10}CO_2R_{15}$, $CR_9R_{10}C(Y)NR_{17}R_{14}$, $CR_9R_{10}C(NR_{17})NR_{17}R_{14}$, $CR_9R_{10}CN$, $CR_9R_{10}C(NOR_{10})R_{14}$, $CR_9R_{10}C(NOR_{14})R_{10}$, $CR_9R_{10}NR_{17}C(NR_{17})S(C_1$-$C_4$ alkyl), $CR_9R_{10}NR_{17}C(NR_{17})NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(O)C(O)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(O)C(O)OR_{14}$, tetrazolyl, thiazolyl, imidazolyl,

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imidazolidinyl, pyrazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, CR_9R_{10}(tetrazolyl), CR_9R_{10}(thiazolyl), CR_9R_{10}(imidazolyl), CR_9R_{10}(imidazolidinyl), CR_9R_{10}(pyrazolyl), CR_9R_{10}(thiazolidinyl), CR_9R_{10}(oxazolyl), CR_9R_{10}(oxazolidinyl), CR_9R_{10}(triazolyl), CR_9R_{10}(isoxazolyl), CR_9R_{10}(oxadiazolyl), CR_9R_{10}(thiadiazolyl), CR_9R_{10}(morpholinyl), CR_9R_{10}(piperidinyl), CR_9R_{10}(piperazinyl), or CR_9R_{10}(pyrrolyl), wherein said heterocyclic groups and moieties for said R_4 substituents are optionally substituted by 1 to 3 R_{14} substituents;

R_5 is R_9, OR_9, CH_2OR_9, cyano, $C(O)R_9$, CO_2R_9, $C(O)NR_9R_{10}$, or NR_9R_{10}, provided that R_5 is absent when the dashed line in formula (Ia) represents a double bond;

or R_4 and R_5 are taken together to form =O or $=R_8$;

or R_5 is hydrogen and R_4 is OR_{14}, SR_{14}, $S(O)_nR_{15}$ wherein n is 0 to 2, $SO_2NR_{17}R_{14}$, $NR_{17}R_{14}$, $NR_{14}C(O)R_9$, $NR_{17}C(Y)R_{14}$, $NR_{17}C(O)OR_{15}$, $NR_{17}C(Y)NR_{17}R_{14}$, $NR_{17}SO_2NR_{17}R_{14}$, $NR_{17}C(NCN)NR_{17}R_{14}$, $NR_{17}SO_2R_{15}$, $NR_{17}C(CR_9NO_2)NR_{17}R_{14}$, $NR_{17}C(NCN)S(C_1\text{-}C_4$ alkyl), $NR_{17}C(CR_9NO_2)S(C_1\text{-}C_4$ alkyl), $NR_{17}C(NR_{17})NR_{17}R_{14}$, $NR_{17}C(O)C(O)NR_{17}R_{14}$, or $NR_{17}C(O)C(O)OR_{14}$;

each R_6 is independently selected from methyl and ethyl optionally substituted by 1 to 3 halo groups;

R_7 is OR_{14}, SR_{14}, $SO_2NR_{17}R_{14}$, $NR_{17}R_{14}$, $NR_{14}C(O)R_9$, $NR_{17}C(Y)R_{14}$, $NR_{17}C(O)OR_{15}$, $S(O)_nR_{12}$ wherein n is 0 to 2, $OS(O)_2R_{12}$, OR_{12}, $OC(O)NR_{13}R_{12}$, $OC(O)R_{13}$, OCO_2R_{13}, $O(CR_{12}R_{13})_mOR_{12}$ wherein m is 0 to 2, $CR_9R_{10}OR_{14}$, $CR_9R_{10}NR_{17}R_{14}$, $C(Y)R_{14}$, CO_2R_{14}, $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1\text{-}C_4$ alkyl), tetrazolyl, thiazolyl, imidazolyl, imidazolidinyl, pyrazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, wherein said R_7 heterocyclic groups are optionally substituted by 1 to 3 R_{14} substituents;

R_8 is $=NR_{15}$, $=NCR_9R_{10}(C_2\text{-}C_6$ alkenyl), $=NOR_{14}$, $=NOR_{19}$, $=NOCR_9R_{10}(C_2\text{-}C_6$ alkenyl), $=NNR_9R_{14}$, $=NNR_9R_{19}$, =NCN, $=NNR_9C(Y)NR_9R_{14}$, $=C(CN)_2$, $=CR_{14}CN$, $=CR_{14}CO_2R_9$, $=CR_{14}C(O)NR_9R_{14}$, $=C(CN)NO_2$, $=C(CN)CO_2(C_1\text{-}C_4$ alkyl), $=C(CN)OCO_2(C_1\text{-}C_4$ alkyl), $=C(CN)(C_1\text{-}C_4$ alkyl), $=C(CN)C(O)NR_9R_{14}$, 2-(1,3-dithiane), 2-(1,3-dithiolane), dimethylthio ketal, diethylthio ketal, 2-(1,3-dioxolane), 2-(1,3-dioxane), 2-(1,3-oxathiolane), dimethyl ketal or diethyl ketal;

each R_9 and R_{10} is independently hydrogen or C_1-C_4 alkyl optionally substituted by up to three fluorines;

each R_{11} is independently fluoro or R_{10};

each R_{12} is independently C_1-C_6 alkyl, C_2-C_3 alkenyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, C_6-C_{10} aryl, or C_3-C_9 heterocyclyl, wherein said R_{12} groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

each R_{13} is independently hydrogen or R_{12};

each R_{14} is independently hydrogen or R_{15}, or when R_{14} and R_{17} are as $NR_{17}R_{14}$ then R_{17} and R_{14} can be taken together with the nitrogen to form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N and S;

each R_{15} is independently C_1-C_6 alkyl or $-(CR_9R_{10})_nR_{16}$ wherein n is 0 to 2 and R_{16} and said C_1-C_6 alkyl are optionally substituted by 1 to 3 substituents independently selected from halo, nitro, cyano, $NR_{10}R_{17}$, $C(O)R_9$, OR_9, $C(O)NR_{10}R_{17}$, $OC(O)NR_{10}R_{17}$, $NR_{17}C(O)NR_{17}R_{10}$, $NR_{17}C(O)R_{10}$, $NR_{17}C(O)O(C_1$-C_4 alkyl), $C(NR_{17})NR_{17}R_{10}$, $C(NCN)NR_{17}R_{10}$, $C(NCN)S(C_1$-C_4alkyl), $NR_{17}C(NCN)S(C_1$-C_4alkyl), $NR_{17}C(NCN)NR_{17}R_{10}$, $NR_{17}SO_2(C_1$-C_4 alkyl), $S(O)_n(C_1$-C_4 alkyl) wherein n is 0 to 2, $NR_{17}C(O)C(O)NR_{17}R_{10}$, $NR_{17}C(O)C(O)R_{17}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, and C_1-C_2 alkyl optionally substituted with one to three fluorines;

each R_{16} is independently C_3-C_7 cycloalkyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, thienyl, thiazolyl, quinolinyl, naphthyl, or phenyl;

each R_{17} is independently OR_9 or R_{10};

R_{18} is H, $C(Y)R_{14}$, CO_2R_{14}, $C(Y)NR_{17}R_{14}$, CN, $C(NR_{17})NR_{17}R_{14}$, $C(NOR_9)R_{14}$, $C(O)NR_9NR_9C(O)R_9$, $C(O)NR_9NR_{17}R_{14}$, $C(NOR_{14})R_9$, $C(NR_9)NR_{17}R_{14}$, $C(NR_{14})NR_9R_{10}$, $C(NCN)NR_{17}R_{14}$, $C(NCN)S(C_1$-C_4 alkyl), $CR_9R_{10}OR_{14}$, $CR_9R_{10}SR_{14}$, $CR_9R_{10}S(O)_nR_{15}$ wherein n is 0 to 2, $CR_9R_{10}NR_{14}R_{17}$, $CR_9R_{10}NR_{17}SO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)R_{14}$, $CR_9R_{10}NR_{17}CO_2R_{15}$, $CR_9R_{10}NR_{17}C(Y)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(NCN)NR_{17}R_{14}$, $CR_9R_{10}NR_{17}C(CR_9NO_2)S(C_1$-$C_4$ alkyl), tetrazolyl, thiazolyl, imidazolyl, imidazolidinyl, pyrazolyl, thiazolidinyl, oxazolyl, oxazolidinyl, triazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, wherein said heterocyclic groups are optionally substituted by 1 to 3 R_{14} substituents;

R_{19} is $-C(O)R_{14}$, $-C(O)NR_9R_{14}$, $-S(O)_2R_{15}$, or $-S(O)_2NR_9R_{14}$;

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each Y is independently =O or =S; and,

Z is =O, $=NR_{17}$, =NCN, $=C(CN)_2$, $=CR_9CN$, $=CR_9NO_2$, $=CR_9CO_2R_9$, $=CR_9C(O)NR_9R_{10}$, $=C(CN)CO_2(C_1\text{-}C_4$ alkyl) or $=C(CN)C(O)NR_9R_{10}$.

2. The compound of claim 1 wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl.

3. The compound of claim 2 wherein R_1 is $C_1\text{-}C_2$ alkyl optionally substituted by up to three fluorines.

4. The compound of claim 3 wherein R_1 is ethyl.

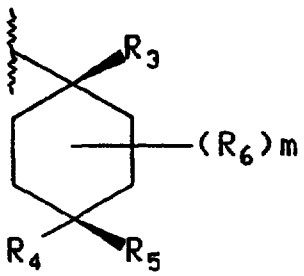
5. The compound of claim 3 wherein R_2 is a group of formula (Ia) wherein the dashed line represents a single bond.

6. The compound of claim 5 wherein R_3 is cyano.

7. The compound of claim 6 wherein m is 0 and R_5 is hydrogen.

8. The compound of claim 6 wherein R_4 is carboxy, $-CH_2OH$, or $-CH_2C(O)NH_2$.

9. The compound of claim 1 wherein R_2 is a group of formula (Ia) wherein R_3 and R_5 are cis as follows:



10. The compound of claim 1 wherein R_2 is a group of formula Ia wherein the dashed line represents a single bond and R_3 and R_4 are cis.

11. The compound of claim 1 selected from the group consisting of:

1-(1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile;

Trans-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

Cis-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

1-(1-Cyclohexyl-3-ethyl-1H-indazol-6-yl)-4-oxo-cyclohexanecarbonitrile;

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

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Trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid;

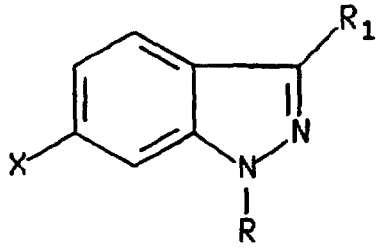
Trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid;

1-(Cyclohexyl-3-ethyl-1H-indazole-6-yl)-cis-4-hydroxylmethylcyclohexane carbonitrile;

Cis-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide; and,

Trans-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide.

12. A compound of the formula



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wherein R is hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$(C_3-C_7 cycloalkyl) wherein n is 0 to 2, (C_1-C_6 alkoxy)C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_n$(C_3-C_9 heterocyclyl) wherein n is 0 to 2, or -$(Z')_b(Z'')_c$(C_6-C_{10} aryl) wherein b and c are independently 0 or 1, Z' is C_1-C_6 alkylene or C_2-C_6 alkenylene, and Z'' is O, S, SO_2, or NR_9, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkoxy, trifluoromethyl, nitro, CO_2R_9, $C(O)NR_9R_{10}$, NR_9R_{10} and $SO_2NR_9R_{10}$;

R_1 is hydrogen, C_1-C_7 alkyl, C_2-C_3 alkenyl, phenyl, C_3-C_7 cycloalkyl, or (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, wherein said alkyl, phenyl, and alkenyl R_1 groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

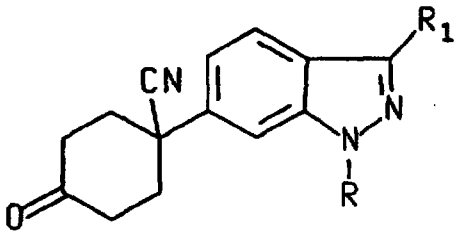
each R_9 and R_{10} is independently hydrogen or C_1-C_4 alkyl optionally substituted by up to three fluorines; and,

X is bromo, -C(O)O(C_1-C_6 alkyl), -CH_2CN, carboxy, -CH_2OH, or -C(O)H.

13. The compound of claim 12 wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl and R_1 is ethyl.

14. The compound of claim 13 wherein X is bromo.

15. A compound of the formula



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wherein R is hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$(C_3-C_7 cycloalkyl) wherein n is 0 to 2, (C_1-C_6 alkoxy)C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_n$(C_3-C_9 heterocyclyl) wherein n is 0 to 2, or -$(Z')_b(Z'')_c$(C_6-C_{10} aryl) wherein b and c are independently 0 or 1, Z' is C_1-C_6 alkylene or C_2-C_6 alkenylene, and Z'' is O, S, SO_2, or NR_9, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkoxy, trifluoromethyl, nitro, CO_2R_9, C(O)NR_9R_{10}, NR_9R_{10} and $SO_2NR_9R_{10}$;

R_1 is hydrogen, C_1-C_7 alkyl, C_2-C_3 alkenyl, phenyl, C_3-C_7 cycloalkyl, or (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, wherein said alkyl, phenyl, and alkenyl R_1 groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo; and,

each R_9 and R_{10} is independently hydrogen or C_1-C_4 alkyl optionally substituted by up to three fluorines.

16. The compound of claim 15 wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl and R_1 is ethyl.

17. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal comprising a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

18. A method for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.

19. A pharmaceutical composition for the prevention or treatment of asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebal malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft versus host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, autoimmune diabetes, systemic lupus erythematosis, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, or dermatitis, in a mammal, comprising a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

20. A method for treating asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebal malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, autoimmune diabetes, systemic lupus erythematosis, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, or dermatitis in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.

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Trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid methyl ester;

Cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid;

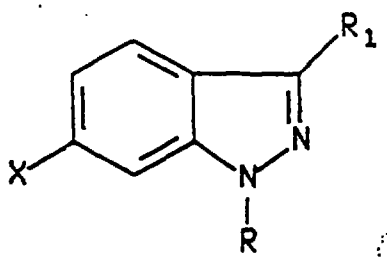
Trans-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)-cyclohexanecarboxylic acid;

1-(Cyclohexyl-3-ethyl-1H-indazole-6-yl)-cis-4-hydroxylmethylcyclohexane carbonitrile;

Cis-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide; and,

Trans-4-Cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cyclohexanecarboxylic acid amide.

12. A compound of the formula



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wherein R is hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$(C_3-C_7 cycloalkyl) wherein n is 0 to 2, (C_1-C_6 alkoxy)C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_n$(C_3-C_9 heterocyclyl) wherein n is 0 to 2, or -$(Z')_b(Z'')_c$(C_6-C_{10} aryl) wherein b and c are independently 0 or 1, Z' is C_1-C_6 alkylene or C_2-C_6 alkenylene, and Z'' is O, S, SO_2, or NR_9, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkoxy, trifluoromethyl, nitro, CO_2R_9, $C(O)NR_9R_{10}$, NR_9R_{10} and $SO_2NR_9R_{10}$;

R_1 is hydrogen, C_1-C_7 alkyl, C_2-C_3 alkenyl, phenyl, C_3-C_7 cycloalkyl, or (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, wherein said alkyl, phenyl, and alkenyl R_1 groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

each R_9 and R_{10} is independently hydrogen or C_1-C_4 alkyl optionally substituted by up to three fluorines; and,

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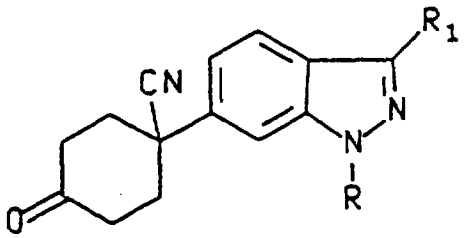
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X is bromo, -C(O)O(C_1-C_6 alkyl), -CH_2CN, carboxy, -CH_2OH, or -C(O)H provided that when X is has a meaning other than bromo, then R and R_1 may not both be hydrogen at the same time provided that when X has the meaning bromo, then R_1 is ethyl.

13. The compound of claim 12 wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl and R_1 is ethyl.

14. The compound of claim 13 wherein X is bromo.

15. A compound of the formula



XIX

wherein R is hydrogen, C_1-C_6 alkyl, -$(CH_2)_n$(C_3-C_7 cycloalkyl) wherein n is 0 to 2, (C_1-C_6 alkoxy)C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_n$(C_3-C_9 heterocyclyl) wherein n is 0 to 2, or -$(Z')_b(Z'')_c$(C_6-C_{10} aryl) wherein b and c are independently 0 or 1, Z' is C_1-C_6 alkylene or C_2-C_6 alkenylene, and Z'' is O, S, SO_2, or NR_9, and wherein said alkyl, alkenyl, alkoxyalkyl, heterocyclyl, and aryl moieties of said R groups are optionally substituted by 1 to 3 substituents independently selected from halo, hydroxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkoxy, trifluoromethyl, nitro, CO_2R_9, $C(O)NR_9R_{10}$, NR_9R_{10} and $SO_2NR_9R_{10}$;

R_1 is hydrogen, C_1-C_7 alkyl, C_2-C_3 alkenyl, phenyl, C_3-C_7 cycloalkyl, or (C_3-C_7 cycloalkyl)C_1-C_2 alkyl, wherein said alkyl, phenyl, and alkenyl R_1 groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo; and,

each R_9 and R_{10} is independently hydrogen or C_1-C_4 alkyl optionally substituted by up to three fluorines.

16. The compound of claim 15 wherein R is cyclohexyl, cyclopentyl, methylenecyclopropyl, isopropyl, phenyl or 4-fluoro-phenyl and R_1 is ethyl.

17. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal comprising a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

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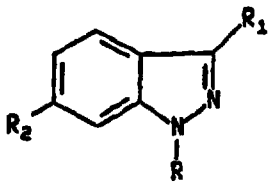
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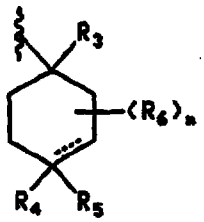
(54) Title: SUBSTITUTED INDAZOLE DERIVATIVES AND THEIR USE AS INHIBITORS PHOSPHODIESTERASE (PDE) TYPE IV AND THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF)

(57) Abstract

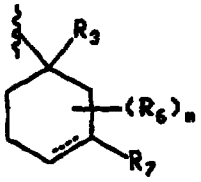
The invention relates to compounds of formula (I), and to pharmaceutically acceptable salts thereof, wherein R and R_1 are as defined herein. R_2 is selected from the group consisting of (Ia), (Ib), (Ic) and (Id). The invention further relates to intermediates for the preparation of the compounds of formula (I), and to pharmaceutical compositions containing, and methods of using, the compounds of formula (I), or pharmaceutically acceptable salts thereof, for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal.



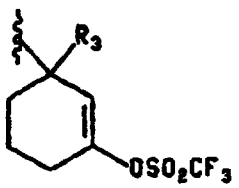
(I)



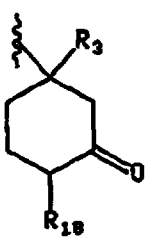
(Ia)



(Ib)



(Ic)



(Id)