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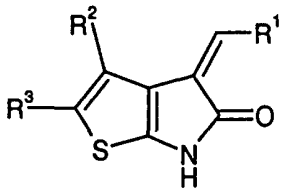
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(54) Title: THIENOPYRROLIDINONES



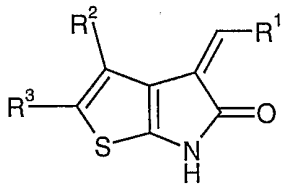
(I)

(57) Abstract: The present invention provides substituted thieno[2,3-b]pyrrolidin-5-ones of formula (I) wherein R^1, R^2, and R^3 have the values given in the specification. The compounds are useful as inhibitors of cellular production of tumour necrosis factor (TNF-α) and as antiproliferative agents and, therefore, may find use in the treatment of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases.

Thienopyrrolidinones

The present invention relates to bicyclic sulfur containing heteroaryls. More particularly, the invention is concerned with substituted thieno[2,3-b]pyrrolidin-5-one derivatives, a process for their manufacture and pharmaceutical preparations containing them. This invention is further directed to intermediates useful in the preparation of the foregoing compounds and to processes for the preparation of such compounds. In particular, the novel thienopyrrolidinones can inhibit or modulate the production of tumour necrosis factor (TNF-α) from cells. Compounds of the invention are also able to inhibit the proliferation of cells. These compounds and their pharmaceutically acceptable salts are useful as anti-inflammatory agents, particularly useful in the treatment of rheumatoid arthritis, neuro-degenerative diseases such as Alzheimer's, cardiovascular diseases and in cancer therapy. The invention is also directed to pharmaceutical compositions containing such compounds, and to methods for the treatment and/or control of the mentioned diseases.

In one aspect, the invention concerns thienopyrrolidinones of the general formula



I

wherein

R^1 represents a 5- or 6-membered monocyclic aromatic ring containing one or more hetero atoms independently selected from N, S and O, the remaining being carbon, and which ring may be benz-fused and which monocyclic or benz-fused aromatic ring is optionally substituted independently with one or more groups selected from lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted aryl-

lower alkyl, optionally substituted aryl-lower alkoxy, halogen, haloalkyl, nitro, hydroxy, cyano, $-C(O)R^7$, $-(CH_2)_nCO_2R^8$ or $-(CH_2)_nCONR^7R^8$,

wherein R^7 represents hydrogen, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, or lower alkyl optionally mono substituted by cycloalkyl, optionally substituted aryl or heterocyclyl and

R^8 represents hydrogen, cycloalkyl, heterocyclyl or lower alkyl optionally mono substituted by cycloalkyl, optionally substituted aryl, hydroxy, lower alkoxy, optionally substituted heteroaryl, heterocyclyl or hydroxy-loweralkoxy,

or, when R^7 and R^8 are both attached to nitrogen, R^7 and R^8 together with the nitrogen atom to which they are attached represent a 5- or 6-membered heterocycle optionally containing an additional heteroatom selected from N, S and O and optionally being substituted by lower alkyl, lower alkoxy or hydroxy-lower alkyl;

n is 0-3;

R^2 is H;

R^3 represents hydrogen, $-COR^4$, $-CONR^4R^5$, $-CONHOR^6$, cyano, halogen, $-CO_2R^5$, $-SO_2NR^4R^5$, $-OR^4$, lower alkyl optionally substituted independently by cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, hydroxy, $-CONR^4R^5$ or $-CO_2R^5$, or lower alkenyl optionally substituted independently by cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, hydroxy, $-CONR^4R^5$ or $-CO_2R^5$, wherein

R^4 represents hydrogen, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, or lower alkyl optionally mono substituted by cycloalkyl, optionally substituted aryl or heterocyclyl;

R^5 represents hydrogen, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl or lower alkyl optionally

substituted independently by -$CONH_2$, cycloalkyl, optionally substituted aryl, optionally substituted aryloxy, hydroxy, lower alkoxy, optionally substituted heteroaryl, heterocyclyl, hydroxy-loweralkoxy or -NR'R" wherein R' is hydrogen or lower alkyl optionally substituted by optionally substituted aryl and R" is -$COCH_3$, lower alkyl or optionally substituted aryl ;

R^6 represents hydrogen or heterocyclyl;

or, when R^4 and R^5 are both attached to nitrogen, R^4 and R^5 together with the nitrogen atom to which they are attached represent a 5- or 6-membered heterocycle optionally containing an additional heteroatom selected from N, S and O and optionally being independently substituted at one or more carbon and/or N-atoms by lower alkyl, lower alkoxy or hydroxy-lower alkyl;

and pharmaceutically acceptable salts thereof.

The compounds of the present invention, depending on the nature of the substituents, may posses one or more asymmetric carbon atoms. The invention extends to all such forms (enantiomers, diastereoisomers) and to mixtures thereof, including enantiomeric mixtures (racemates), diastereoisomeric mixtures and mixtures of both such mixtures.

As used herein, the term "lower alkyl" means a saturated straight-chain or branched-chain hydrocarbon containing from 1 to 7, preferably from 1 to 4, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, tert.butyl, n-pentyl, n-hexyl, n-heptyl and the like.

The term "lower alkoxy" means a lower alkyl group as defined earlier which is bonded via an oxygen atom, with examples of lower alkoxy groups being methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec.butoxy, tert-butoxy, n-pentoxy and the like.

The term "lower alkenyl" means a lower alkyl group as defined earlier which contains one double bond of either E or Z stereochemistries, for example ethenyl, prop-2-enyl, but-2-enyl, 2-ethenyl-butyl and the like.

The term "cycloalkyl" means a saturated cyclic hydrocarbon group of 3 to 8 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

The term "optionally substituted aryl" means a phenyl or an optionally partly saturated naphthyl group which is unsubstituted or optionally substituted with one or more, preferably one or two, substituents selected from halogen, lower alkoxy, haloalkyl, hydroxy, -COOR' (wherein R' is H, lower alkyl), nitro, amino, sulfamoyl, phenyl or lower alkyl optionally mono substituted by lower alkoxy or hydroxy, particularly by halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitro, amino or sulfamoyl. The term "partly saturated naphthyl" means a naphthyl group, to which one or two H_2 molecules were added. An example of a partially saturated naphthyl group is 1,2,3,4-tetrahydro-1-naphthyl.

The term "aryloxy" means a group R^a-O-, wherein R^a is optionally substituted aryl as defined before.

The term "optionally substituted heteroaryl" means an aromatic group of 5- or 6 ring atoms containing one or more, preferably one, two or three, hetero atoms independently selected from N, S and O, the remaining ring atoms being C and which aromatic group is optionally benz-fused. The heteroaryl is optionally substituted independently at one or more, preferably one or two, ring atoms by halogen, lower alkyl optionally substituted by lower alkoxy or hydroxy, lower alkoxy, haloalkyl, hydroxy, -COOR' (wherein R' is H, lower alkyl), nitro, amino, sulfamoyl or optionally substituted aryl; particularly by halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitro, amino or sulfamoyl. Examples of heteroaryl groups are pyrrolyl, pyrazolyl, thienyl, furanyl, pyridyl, pyrimidinyl, quinolyl, indolyl, benzofuranyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl and , if benz-fused, indolyl, benzofuranyl, or benzimidazolyl. Examples of substituted heteroaryl groups are 5-methyl-3H-imidazol-4-yl, 1-methyl-2-pyrrolyl, 3-methoxy-1H-pyrrol-2-yl, 3-phenyl-1H-pyrazol-4-yl, 3-(4-methoxyphenyl)-1H-pyrazol-4-yl, 3-methyl-1H-pyrazol-4-yl, 5-(2-nitro-phenyl)-2H-pyrazol-3-yl, 2-ethoxycarbonyl-3-(2-ethoxycarbonyl-ethyl)-4-ethoxycarbonylmethyl-pyrrol-5-yl or 2-ethoxycarbonyl-3,4-dimethyl-pyrrol-5-yl
and, if benz-fused, 5-methoxy-1H-indol-3-yl, 6-methyl-1H-indol-2-yl, 6-chloro-1H-benzimidazol-2-yl, 5-chloro-1H-benzimidazol-2-yl, 6-methoxy-1H-benzimidazol-2-yl, 1H-benzimidazol-2-yl or 6-chloro-1H-benzimidazol-2-yl.

The term "heterocyclyl" or "heterocycle" means, if not defined otherwise, a saturated, or partially unsaturated, cyclic group of 3- to 7, preferably 5- or 6, ring atoms in which one or more, preferably one, two or three, ring atoms are hetero atoms/groups selected from N, S, SO_2 and O, the remaining being C, which is linked via a carbon or nitrogen ring atom. The term "partially unsaturated cyclic group" means a cyclic group, from whose saturated form one or two H_2 molecules were removed. Examples of heterocyclyl groups are aziridinyl, pyrrolidinyl, tetrahydro-furanyl, tetrahydro-thienyl, tetrahydro-pyranyl, piperidinyl, piperazinyl, morpholinyl or tetrahydro-1,1-dioxo-3-thienyl.

The term "halogen" used alone or in combination as in "haloalkyl", means fluorine, chlorine, bromine or iodine.

The term "haloalkyl" means a lower alkyl group wherein one or more, preferably one or two, hydrogens are replaced by one or more halogen atoms, for example $-CH_2Cl$, $-CF_3$, $-CH_2CCl_3$, $-CH_2CF_3$.

The term "hydroxy-lower alkyl" means a lower alkyl group as defined earlier wherein a hydrogen atom is replaced by a hydroxy group. Examples of such groups are hydroxymethyl, 3-hydroxypropyl, 2-hydroxyethyl, 2-hydroxy-1,1-dimethyl-ethyl or 5-hydroxy-pentyl.

The term "hydroxy-lower alkoxy-" means a lower alkoxy group as defined before wherein a hydrogen has been replaced by hydroxy. An example of such a group is 2-(2-hydroxy-ethoxy)ethyl.

The compounds of formula I which are acidic form pharmaceutically acceptable salts with bases such as alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide and magnesium hydroxide), ammonium hydroxide and the like. The compounds of formula I which are basic form pharmaceutically acceptable salts with acids. As such salts there come into consideration not only salts with inorganic acids such as hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulfuric acid, nitric acid, phosphoric acid etc, but also salts with organic acids such as acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulfonic acid, p-toluenesulfonic acid etc.

In a preferred embodiment of the compounds of formula I the monocyclic aromatic ring in R^1 is a 5- or 6-membered ring, containing one, two, three or four heteroatoms, especially a 5-membered ring contaiing one, two, three or four heteroatoms. More preferably, the monocyclic ring is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thienyl or furanyl
and, if benz-fused, from benzimidazolyl or indolyl. Most preferably the monocyclic or benz-fused ring in R^1 is pyrrolyl, pyrazolyl, imidazolyl, and indolyl, in particular pyrrolyl and pyrazolyl. Particularly preferred monocyclic rings within R^1 are 1-H-imidazol-2-yl, 1H-imidazol-4-yl, 2-pyrrolyl and 1H-pyrazol-4-yl, and, if benz-fused, 1-H-indol-3-yl or 1H-indol-2-yl, preferably pyrrol-2-yl and 1H-pyrazol-4-yl.

In the preferred, more preferred, most preferred and particularly preferred embodiments of R^1 mentioned before, the monocyclic or benz-fused ring is preferably unsubstituted or substituted independently at one or more, preferably one or two, positions with lower alkyl, lower alkoxy, optionally substituted aryl or $(CH_2)_nCO_2R^8$ wherein n and R^8 are as defined above.

Within these preferred embodiments, when R^1 is substituted by -$(CH_2)_nCO_2R^8$, n is preferably 0-2 and R^8 is preferably lower alkyl, especially ethyl.

Most preferably the monocyclic or benz-fused ring in R^1 is substituted by lower alkyl, especially methyl; lower alkoxy, especially methoxy; optionally substituted aryl, especially phenyl, 2-nitrophenyl, or 4-methoxyphenyl; carbethoxy, carbethoxymethyl or carbethoxyethyl.

Particularly preferred R^1 groups are 1-H-imidazol-2-yl, 1H-imidazol-4-yl, 5-methyl-3H-imidazol-4-yl, 1-H-indol-3-yl, 5-methoxy-1H-indol-3-yl, 1H-indol-2-yl, 6-methyl-1H-indol-2-yl, 2-pyrrolyl, 1-methyl-2-pyrrolyl, 3-methoxy-1H-pyrrol-2-yl, 1H-pyrazol-4-yl, 3-phenyl-1H-pyrazol-4-yl, 3-(4-methoxyphenyl)-1H-pyrazol-4-yl, or 3-methyl-1H-pyrazol-4-yl, 5-(2-nitro-phenyl)-2H-pyrazol-3-yl, 2-ethoxycarbonyl-3-(2-ethoxycarbonyl-ethyl)-4-ethoxycarbonylmethyl-pyrrol-5-yl or 2-ethoxycarbonyl-3,4-dimethyl-pyrrol-5-yl, with 2-pyrrolyl and 1H-pyrazol-4-yl being most preferred.

In a preferred embodiment within the above R^1 embodiments R^3 is hydrogen, lower alkyl optionally substituted by hydroxy, -COR^4, -$CONR^4R^5$,

-CONHOR^6, cyano, -CO_2R^5, -$SO_2NR^4R^5$ or lower alkenyl optionally substituted by -CO_2R^5; more preferably R^3 is hydrogen, -$CONR^4R^5$, -CONHOR^6, -CO_2R^5 or cyano.

Within this preferred and more preferred embodiment, if R^3 is -$CONR^4R^5$ or -$SO_2NR^4R^5$, R^4 is preferably hydrogen or lower alkyl, especially methyl, preferably hydrogen, and R^5 is as defined above, more preferably R^5 is hydrogen, cycloalkyl (e.g. cyclooctyl), optionally substituted aryl (e.g. phenyl, 1,2,3,4-tetrahydro-1-naphthyl),
heterocyclyl (e.g. tetrahydro-1,1-dioxo-3-thienyl), lower alkyl (e.g. methyl, propyl, 2,2-dimethyl-1-methyl-propyl, 2-methyl-propyl) optionally substituted independently by one or more from -$CONH_2$ (e.g. 2-carbamoyl-ethyl), optionally substituted aryl (e.g. benzyl, 2-phenyl-butyl, 4-sulfamoylbenzyl), optionally substituted aryloxy (e.g. 2-phenoxy-ethyl), hydroxy (e.g. 3-hydroxypropyl, 2-hydroxyethyl, 5-hydroxy-pentyl, 2-hydroxy-1,1-dimethyl-ethyl), lower alkoxy (e.g. 2-methoxy-ethyl), optionally substituted heteroaryl (e.g. , furan-2-yl-methyl, 2-thiophen-2-yl-ethyl, 2-indol-3-yl-ethyl, pyridin-4-ylmethyl, 2-pyridin-2-yl-ethyl, pyridin-2-ylmethyl, 1H-benzimidazol-2-ylmethyl, 6-chloro-1H-benzimidazol-2-ylmethyl, 2-(5-chloro-1H-benzimidazol-2-yl)-ethyl, 6-methoxy-1H-benzimidazol-2-ylmethyl, 6-chloro-1H-benzimidazol-2-ylmethyl), heterocyclyl (e.g. tetrahydrofuran-2-yl-methyl, 3-morpholin-4-yl-propyl, 2-pyrrolidin-1-yl-ethyl), hydroxy-loweralkoxy (e.g. 2-(2-hydroxy-ethoxy)ethyl), or by -NR'R" wherein R' is hydrogen or lower alkyl optionally substituted by optionally substituted aryl and R" is -$COCH_3$, lower alkyl or optionally substituted aryl (e.g. 2-(N-(3-methylphenyl))-ethylamino)ethyl or 2-acetylamino-ethyl).

Preferably the lower alkyl in R^5 is mono- or di-substituted, especially mono-substituted, by one of the above mentioned groups. If disubstituted, the lower alkyl is preferably disubstituted by optionally substituted aryl (e.g. 1,2-diphenyl-ethyl) or by optionally substituted aryl and hydroxy-lower alkyl (e.g. 2-hydroxy-1(R)-phenylethyl).

If R^3 is -CONHOR^6, R^6 is preferably hydrogen.

If R^3 is -COR^4, R^4 is preferably lower alkyl, especially methyl.

If R^3 is -CO_2R^5, R^5 is preferably hydrogen or lower alkyl, especially methyl or tert-butyl.

If R^3 is lower alkenyl optionally substituted by $-CO_2R^5$, R^5 is preferably lower alkyl, especially methyl or ethyl.

Most preferably, R^3 is hydrogen, cyano or $-CONH_2$.

In another embodiment within this preferred R^3 embodiment where R^4 and R^5 together with the nitrogen atom to which they are attached represent a 5- or 6-membered heterocycle, the heterocycle is optionally independently substituted at one or two carbon and/or N-atoms. The heterocycle is preferably morpholino or pyrrolidinyl. Particular substituents are methyl or hydroxymethyl. An especially preferred heterocycle is morpholino and a preferred substituted heterocycle is 2(R)-(hydroxymethyl)-1-pyrrolidinyl.

A preferred heterocyclyl substituent in R^6 is tetrahydro-pyran-2-yl.

A further embodiment of the compounds of the present invention is wherein R^1 is 1-H-pyrrol-2-yl and R^3 is hydrogen, cyano or $-CONR^4R^5$.

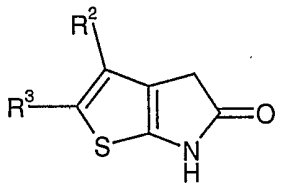
Particularly preferred compounds of the invention are:

(Z)-4,6-Dihydro-4-[(2-pyrrolyl)methylene]thieno[2,3-b]pyrrol-5-one,
(Z)-4,6-Dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one,
(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]-pyrrole-2-carboxamide, or
(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]-pyrrole-2-carbonitrile.

Other preferred compounds are
(Z)-4,6-Dihydro-4-[(3-methyl-1H-pyrazol-4-yl)methylene]thieno[2,3-b]pyrrol-5-one;
(Z)-4,6-Dihydro-4-[(3-phenyl-1H-pyrazol-4-yl)methylene]thieno[2,3-b]pyrrol-5-one; or
(Z)-4,6-Dihydro-4-[[3-(4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]-thieno[2,3-b] pyrrol-5-one.

In another aspect, the present invention relates to a process for the preparation of compounds of formula I. According to this process provided by the present invention, the compounds of formula I as described herein before and

their pharmaceutically acceptable salts are manufactured by a process which comprises reacting a compound of the general formula



II

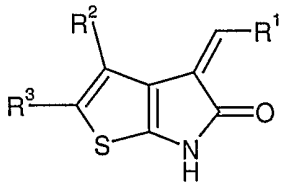
wherein R^2 and R^3 are as above,

with an aldehyde of the general formula

R^1-CHO III

wherein R^1 is as above,

to yield a compound of the general formula I



I

and, if desired, converting said compound into a pharmaceutically acceptable salt.

The reaction between compounds II and III is preferably effected in the presence of a base such as piperidine in a lower alkanol such as 2-propanol at a temperature between 0°C and the reflux temperature of the solvent, preferably at about 75°C.

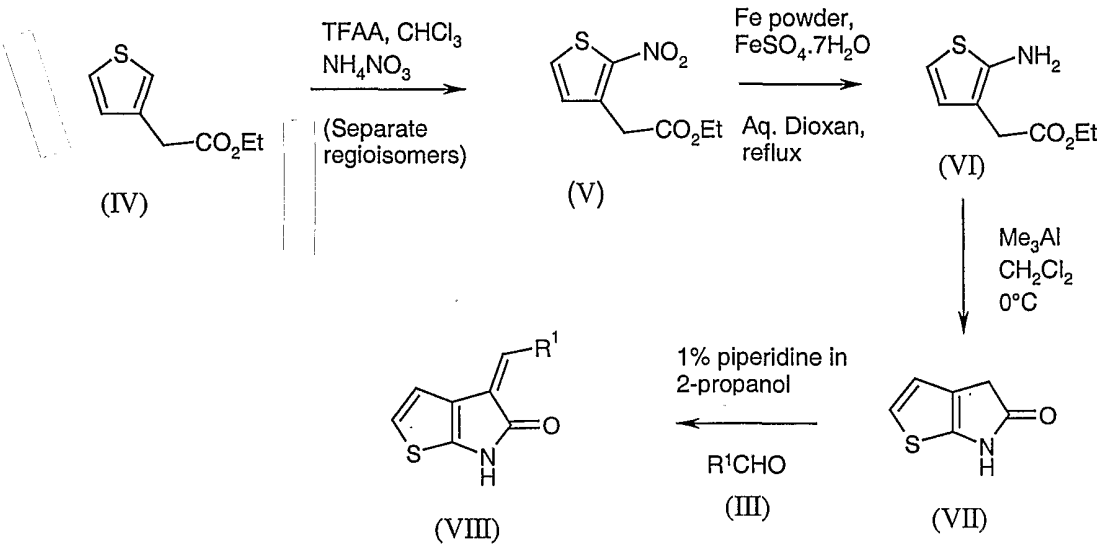
Starting materials of formula III are known compounds or analogues of known compounds that can be prepared in a similar manner to the known compounds. In particular, many compounds of formula III are commercially available, for example, from Sigma-Aldrich Company Ltd., Lancaster Synthesis Ltd. or Maybridge Chemical Company Ltd. (e.g. pyrrole-2-carboxaldehyde, Aldrich catalogue number P7, 340-4). Alternatively, starting materials of formula III may be prepared by adaptation of the methods in Vilsmeier et al., Chem. Ber., 60, 119, 1927, and Konvar et al., Tetrahedron Lett., 28, 955, 1987, for the introduction of a formyl group into appropriately substituted 5- or 6-membered

monocyclic aromatic rings containing one or more hetero atoms independently selected from N, S and O. 3-substituted pyyrole-2-carboxaldehydes, such as 3-methoxypyrrole-2-carboxaldehyde (used in Examples 13, 64, 65, 66 and 67), may also be prepared by photolytic ring-contraction of the corresponding 4-substituted pyridine-N-oxides as described in Campbell, S.E. et al., J. Chem. Soc. Perkin Trans. 1, 15, 2195-2202, 1997.

Acidic compounds of formula I can be converted into pharmaceutically acceptable salts by treatment with bases and basic compounds of formula I can be converted into pharmaceutically acceptable salts by treatment with acids. Such treatments can be carried out in a conventional manner.

Reaction schemes for manufacturing the compounds of the invention are as follows. Compounds of formula I where R^2 and R^3 are H and R^1 is a group as defined before, can be prepared according to scheme 1

Scheme 1



Having regard to Scheme 1, in the first step a compound of formula (IV) is reacted with a nitrating mixture, preferably with trifluoroacetic anhydride/ ammonium nitrate in a halogenated aliphatic hydrocarbon, especially chloroform. Suitably, the reaction is carried out at about 0°C to about 30°C.

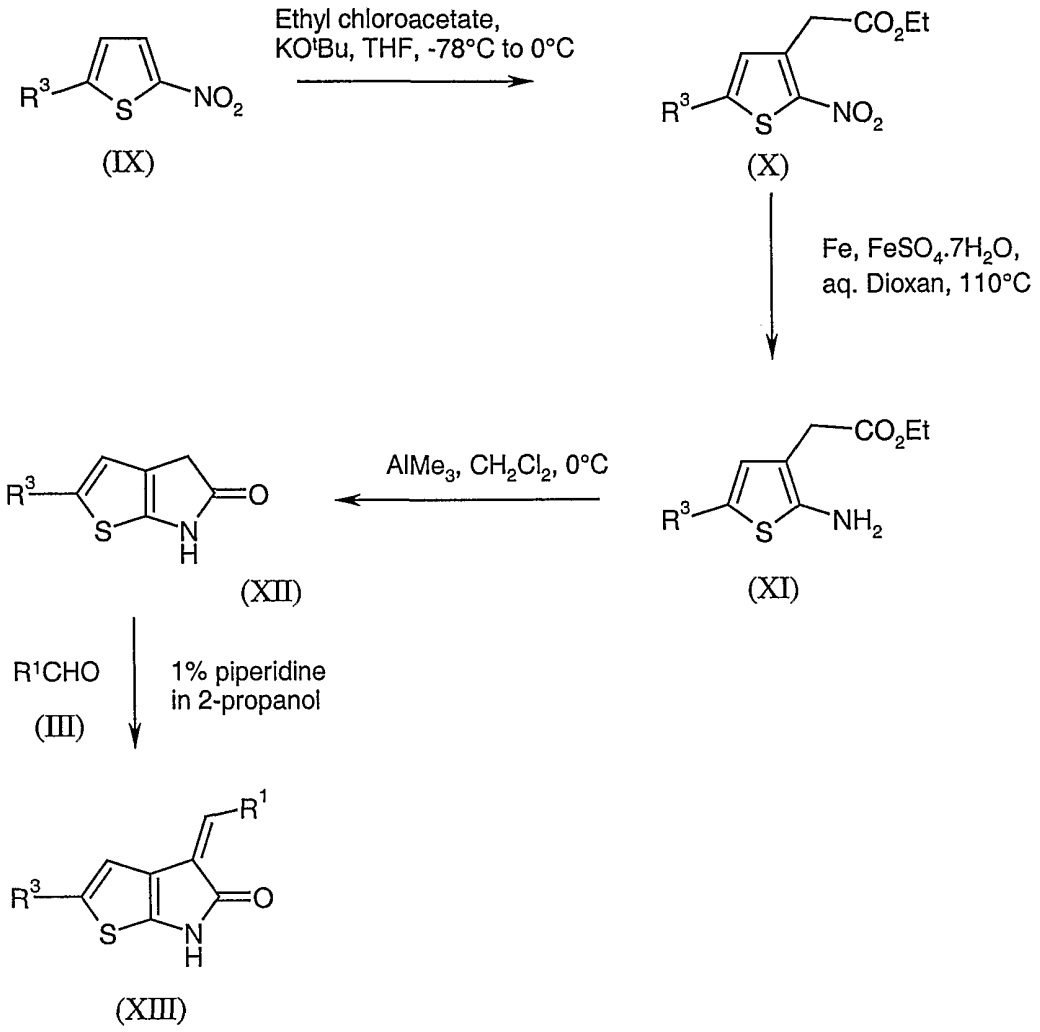
The next step comprises reduction of the compound of formula (V) to give the amine of formula (VI). This reduction is carried out using reduced iron powder, iron sulfate heptahydrate in aqueous dioxan solvent at about 90°C to about 115°C, preferably at about 110°C.

Reaction of the amine of formula (VI) with a Lewis Acid, preferably trimethylaluminium, yields the cyclised amide of formula (VII). The cyclisation is carried out in a solvent which is inert under the reaction conditions such as tetrahydrofuran or, preferably, a halogenated aliphatic hydrocarbon, especially dichloromethane, at about -78°C to about 30°C, preferably at about 0°C to about room temperature.

The next step comprises a reaction of a compound of formula (VII) with an aldehyde of formula (III) to give a compound of formula (VIII). This condensation is carried out with an organic base, preferably piperidine, in a lower alkanol such as 2-propanol at a temperature between 50°C and 100°C.

Compounds of formula I wherein R^1 is as described before, R^2 is H and R^3 is as described before, can be prepared according to scheme 2

Scheme 2



Having regard to Scheme 2, in the first step a compound of formula (IX) is reacted with ethyl chloroacetate to give a compound of formula (X). This reaction is conveniently carried out under inert atmosphere in a solvent which is inert under the reaction conditions, preferably a cyclic ether, especially tetrahydrofuran, at about -78°C to about 30°C, preferably at about -50°C to about room temperature.

The next step comprises reduction of the compound of formula (X) to give the amine of formula (XI). This reduction is carried out using reduced iron powder and iron sulfate heptahydrate in aqueous dioxan solvent at about 90°C to about 115°C, preferably at about 110°C.

Reaction of the amine of formula (XI) with a Lewis Acid, preferably trimethylaluminium, yields the cyclised amide of formula (XII). The cyclisation is carried out in a solvent which is inert under the conditions of the reaction such as tetrahydrofuran or, preferably, a halogenated aliphatic hydrocarbon, especially dichloromethane, at about -78°C to about 30°C, preferably at about 0°C to about room temperature.

The next step comprises a reaction of a compound of formula (XII) with an aldehyde of formula (III) to give a compound of formula (XIII). This condensation is carried out with an organic base, preferably piperidine in a lower alkanol such as 2-propanol at a temperature between 50°C and 100°C.

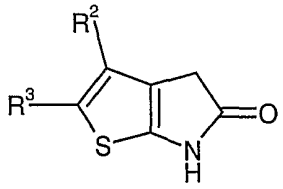
Starting materials of formula (IX) are known compounds or analogues of known compounds that can be prepared in a similar manner to the known compounds. In particular, compounds of formula (IX) are commercially available, for example, from Sigma-Aldrich Company Ltd., Lancaster Synthesis Ltd., or Maybridge Chemical Company Ltd. (e.g. 5-nitrothiophene carboxamide, used in Example 19, Maybridge catalogue number RF 01604), or prepared by adaptation of the methods provided in Crivello et al., JOC, 1981, 46(15), 3056 for the nitration of optionally substituted thiophene rings.

It will be apparent to one skilled in the art that it may be necessary or desirable to protect reactive functionality during the synthesis. More particularly, during the conversion of a compound of formula (IX) to a compound of formula (X) in scheme 2, when R^3 represents formyl (i.e. R^3 represents COR^4 and R^4 represents hydrogen) the formyl group must be in protected form. Suitable protection is, for example, the corresponding oxime, prepared by reaction with hydroxylamine. Subsequent removal of the protecting group may be effected by reaction with aqueous formaldehyde using acid catalysis. In the conversion of a compound of formula (XI) to a compound of formula (XII) in scheme 2, when R^3 represents carboxylic acid (i.e. R^3 represents CO_2R^5 and R^5 represents hydrogen) the carboxylic acid must be in protected form. Suitable protection is , for example, as an ester such as tert-butyl ester which may subsequently be removed by reaction with trifluoroacetic acid.

It will also be apparent that in addition to the general syntheses detailed in schemes 1 and 2, these processes may be combined with functional group interconversions to access the compounds of formula (I). For example, a

carboxylic acid present in R^1 or R^3 may be converted to an amide by methods known per se. Carboxylic acids may in turn be prepared from the corresponding carboxylic esters. In another example, a formyl group can be converted to a substituted alkenyl group by standard methods, for example by Wittig chemistry. These functional group interconversions may be carried out on compounds of formula (I) or intermediates in Schemes 1 or 2. Examples 23, 24, 66, 71, 72, 73, 74, 75 and 76 illustrate in more detail some of the functional group chemistry that may be performed.

Another aspect of the present invention are compounds of the general formula



II

wherein R^2 and R^3 are as defined above.

As mentioned earlier, the thienopyrrolidinones provided by the present invention are useful as inhibitors of cellular production of tumour necrosis factor (TNF-α) and as antiproliferative agents. These activities can be demonstrated by using procedures as described hereinafter.

The following assay may be used to demonstrate the ability of the compounds of the invention to inhibit LPS induced TNF-α production in THP-1 cells. The assay uses a modification of the methods described in Blifield et al., Transplantation, 51:498-503 (1991).

(a) Induction of TNF biosynthesis:

THP-1 cells were suspended in serum free culture medium LGM-3 (Clonetics, Bio Whittaker, UK, Cat. No. CC-3211), at a concentration of 5×10^5 cells/ml and then plated in 96 well-plates (0.2 ml aliquots in each well). Test compounds were dissolved in DMSO and then diluted with the culture medium such that the final DMSO concentration was 1%. Twenty five µl aliquots of test solution or only medium with DMSO (control) were added to each well giving a final DMSO concentration of 0.1%. The cells were incubated for 30 min. at 37°C. LPS (Sigma Chemical Company, UK) was added to the wells at a final

concentration of 2 μg/ml, and cells were incubated for an additional 4 hours. At the end of the incubation period, culture supernatants were collected and the amount of TNF-α present was determined using a commercial TNF-α ELISA assay as described below.

(b) ELISA Assay: Quantikine™ human TNF-α (R&D Systems Europe Ltd., UK) (Cat. No. DTA50 in 2000)

The assay was carried out according to the manufacturer's instructions with the following modifications. Assay plates were centrifuged at 200 g and a 200 μl sample added to each well. TNF-α standard was made up and diluted in LGM-3 culture medium. Samples in the ELISA plate were then incubated overnight at 4°C instead of 2 hours at 37°C. TNF-α production for each condition was calculated and expressed as a percentage of DMSO control to enable IC_{50} calculation.

The abbreviations used above are explained as follows:

LPS = lipopolysaccharide
TNF = tumour necrosis factor
LGM-3 = lymphocyte growth medium 3
DMSO = dimethyl sulfoxide
ELISA = enzyme linked immunoabsorbent assay

The following table illustrates IC_{50} values obtained according to the above assay for compounds of the invention:

Example No.	Name	IC_{50} (μM)
1	(Z)-4,6-Dihydro-4-[(1H-pyrrol-2-yl)methylene]-thieno [2,3-b] pyrrol-5-one	5.08
9	(Z)-4,6-Dihydro-4-[(3-phenyl-1H-pyrazol-4-yl)methylene]thieno[2,3-b]pyrrol-5-one	1.1
13	(Z)-4,6-Dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene] thieno [2,3-b]pyrrol-5-one	1.59
20	(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carbonitrile	3.69

The anti-proliferative activity of the compounds of the invention may be determined, for example, by use of the following assays:

The estrogen receptor negative epithelial breast carcinoma line (MDA-MB-435) can be purchased from American Type Cell Culture Collection (ATCC; Rockville, MD, USA, ATCC No. HTB-129) and grown in the medium recommended by ATCC. For analysis of the effect of the test compounds on growth of these cells, the cells are plated at 2000 cells per well in a 96-well tissue culture plate, and incubated at 37°C with 5% CO_2. The next day, the test compounds are dissolved in 100% dimethyl sulfoxide (DMSO) to yield a 10 mM stock solution. Each compound is diluted with sterile medium to 1 mM in a sufficient quantity to yield a final concentration of 120 μM. The compounds are then serially diluted in medium with 1.2% DMSO. One-fourth final volume of the diluted compounds is transferred to 96-well plates. Test compounds are assayed in duplicate. DMSO is added to a row of "control cells" such that the final concentration of DMSO in each well is 0.3%. Wells to which no cells are added serve as the "blank". Wells to which no inhibitor is added serve as "no inhibitor control". The plates are returned to the incubator, and 5 days post addition of test compound, are analysed as described below.

3(4,5-Dimethylthiazole-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (thiazolyl blue; MTT) is added to each well to yield a final concentration of 1 mg/ml. The plates are then incubated at 37°C for 3 hours. The plates are centrifuged at 1000 rpm for 5 minutes prior to aspiration of the MTT-containing medium. The MTT-containing medium is then removed and 100 μl of 100% ethanol is added to each well to dissolve the resulting formazan metabolite. To ensure complete dissolution, plates are shaken for 15 minutes at room temperature. Absorbencies are read in a microtiter plate reader (Molecular Dynamics) at a wavelength of 570 nm with a 650 nm reference. Percent inhibition is calculated by subtracting the absorbance of the blank (no cell) wells from all wells, then subtracting the division of the average of the controls from 1.00. Inhibitory concentrations (IC_{50}) are determined from the linear regression of a plot of the logarithm of the concentration versus the percent inhibition.

The colon carcinoma line SW480 can also be obtained from the ATCC (ATCC No. CCL-228) and tested according to the same protocol provided above

with the following modification: cell line SW480 is plated at 1000 cells per well and analysed at 4 days post addition of test compound.

In another aspect of the present invention, the compounds of formula (I) are suitable for use as therapeutically active compounds, particularly for use in the treatment of neuro-degenerative diseases, cardiovascular diseases, cancer or as anti-inflammatory agents.

In another aspect, the present invention relates to a medicament containing a compound of formula (I) and a therapeutically inert carrier material, especially a medicament for the control or prevention of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases. A further aspect is the use of a compound of the present invention for the manufacture of a medicament for the control or prevention of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases. In particular the compounds are useful in the treatment of inflammatory diseases, especially in connection with degenerative joint diseases such as rheumatoid arthritis and ostheoarthritis.

The compounds of formula (I) are inhibitors of cellular production of tumour necrosis factor (TNF-α). TNF-α is a proinflammatory cytokine implicated in the pathogenesis of rheumatoid arthritis (RA). Whilst a variety of cytokines are important in the pathogenesis of RA, TNF-α appears to play a pivotal role (Fox, David A., Arch. Intern. Med., Vol 160(4), 437-444, 2000). The specific causative agent of the pathological process of osteoarthritis (OA) has not been identified, but episodic inflammation at the clinical stage is well documented and believed to be involved in disease progression. TNF-α is a predominant proinflammatory cytokine synthesised during the OA process (Martel-Pelletier, J. et al., Frontiers in Bioscience, Vol 4, d694-703, 1999; Blackburn, Warren D. Jr., American Journal of Medicine, Vol 100(no. 2 part A), 24S-30S, 1996; Sipe, J. D. et al., Mediators of Inflammation, Vol 3(4), 243-256, 1994). Abnormal expression of TNF-α has also been implicated in Alzheimer's disease (Mattson, Mark P. et al., Brain Research Reviews, 23, 47-61, 1997) and in the pathophysiology of heart failure (Feldman, Arthur M. et al., Journal of the American College of Cardiology, 35(3), 537-544, 2000).

The compounds of the invention are also inhibitors of cellular proliferation. Cancer is characterised by dis-regulated cellular proliferation; therefore compounds of the invention are useful in the treatment of cancer.

The compounds of formula (I) and their pharmaceutically acceptable salts can be used as medicaments, for example in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, they can also be administered rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

For the manufacture of pharmaceutical preparations the compounds of formula (I) and their pharmaceutically acceptable salts can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like. Suitable carriers for the manufacture of injection solutions are, for example, water, alcohols, polyols, glycerine, vegetable oils and the like. Natural and hardened oils, waxes, fats, semi-liquid polyols and the like are suitable carriers for the manufacture of suppositories.

The pharmaceutical preparations can also contain preservatives, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for adjustment of the osmotic pressure buffers, coating agents or antioxidants.

Medicaments containing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a therapeutically acceptable carrier as well as a process for the manufacture of such medicaments are also objects of the present invention. This process comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof with a therapeutically inert carrier material and bringing the mixture into a galenical administration form.

As mentioned earlier, the compounds of formula (I) and the pharmaceutically acceptable salts thereof can be used in the control or prevention of illnesses, especially in the control or prevention of inflammatory diseases such as degenerative joint diseases, especially rheumatoid arthritis; in the treatment of

cardiovascular disorders; in the treatment of cancer such as invasive tumours, or the treatment of neuro-degenerative diseases. The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. In general, in the case of administration to adults, a daily dosage from about 0.1 mg/kg to about 50 mg/kg, preferably from about 0.5 mg/kg to about 5 mg/kg, should be appropriate, although the upper limit may be exceeded when this is found to expedient. The daily dosage can be administered as a single dosage or in divided dosages.

The following Examples illustrate the present invention. The structure of the products was confirmed by NMR spectroscopy and mass spectroscopy.

Example 1

(Z)-4,6-Dihydro-4-[(1H-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one

4,6-Dihydrothieno[2,3-b]pyrrol-5-one (30 mg, 0.22 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (2 ml). Pyrrole-2-carboxaldehyde (40 mg, 0.43 mmol) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (10 ml) and the precipitated solid was collected by filtration and washed with water to give 24 mg of (Z)-4,6-dihydro-4-[(1H2-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one as a red solid. MS(ES): m/e 217 [M+H].

The starting material was prepared as follows:

i) Preparation of ethyl 2-nitrothiophene-3-acetate

Method A: Ethyl thiophene-3-acetate, (10 g, 64.1 mmol) was dissolved in chloroform (90 ml) and trifluoroacetic anhydride (40 ml) at 0°C . Ammonium nitrate (5.2 g, 64.1 mmol) was added and the reaction mixture was stirred at 0°C for 1 hour then warmed slowly to room temperature for 2 hours. The reaction mixture was cooled in an ice-bath and diluted with dichloromethane (60 ml) and then water (50 ml). The aqueous phase was extracted with dichloromethane and the combined organic fractions were washed with saturated brine solution. The organic phase was dried over magnesium sulfate, evaporated to give a red/brown liquid which was chromatographed on silica gel using hexane/ethyl acetate (4:1) as

eluent to give 8.2 g of ethyl 2-nitrothiophene-3-acetate as a red/brown viscous oil. MS(ES): m/e 216 [M+H].

Method B: Potassium tertiary-butoxide (652 mg, 5.81 mmol) was dissolved in tetrahydrofuran (150 ml) and the solution cooled to –50°C. A solution of 2-nitrothiophene (250 mg, 1.94 mmol) (Avocado) and ethyl chloroacetate (0.22 ml, 1.94 mmol) (Aldrich) was added dropwise in dry tetrahydrofuran (4 ml) over 5 minutes. The reaction mixture was stirred at -50°C for 1 hour then quenched with acetic acid (0.5 ml), then washed with water (20 ml). The aqueous phase was extracted with ethyl acetate and the combined organic fractions were washed with saturated brine solution. The organic phase was dried over magnesium sulfate, evaporated to dryness and the residue chromatographed on silica gel using hexane/ethyl acetate (4:1) as eluent to give 261 mg of ethyl 2-nitrothiophene-3-acetate as a red/brown viscous oil. MS(ES): m/e 216 [M+H].

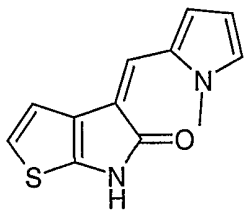
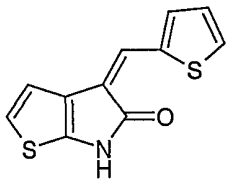
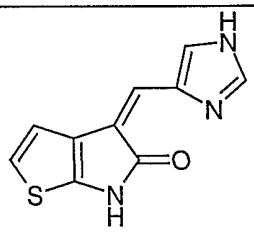
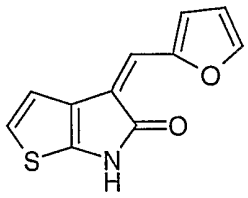
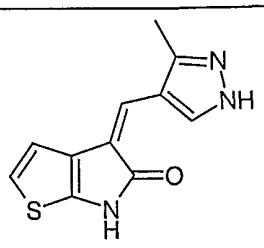
ii) Ethyl 2-nitrothiophene-3-acetate (4 g, 18.6 mmol) was dissolved in aqueous dioxan (40 ml, 4:1 dioxan/water) and treated with reduced iron powder (3.5 g, 62.7 mmol) and iron sulfate heptahydrate (400 mg, 1.44 mmol). The reaction mixture was heated at reflux for 2 hours then filtered through celite filter-aid and washed through with diethyl ether. The organic phase was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate and evaporated to a red/black liquid and then chromatographed on silica gel using hexane/ethyl acetate (3:1) as eluent to give 3.1 g of ethyl 2-aminothiophene-3-acetate. MS(ES): m/e 186 [M+H].

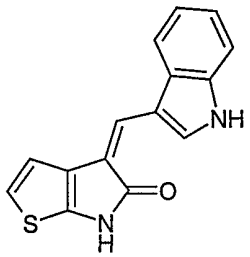
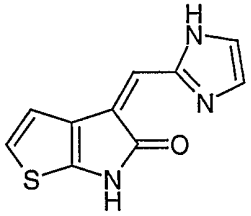
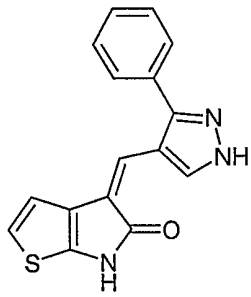
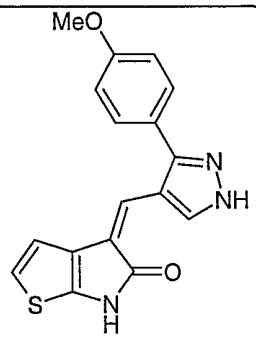
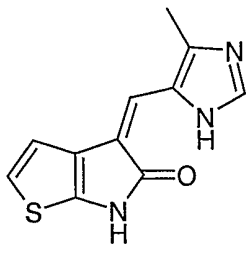
iii) Ethyl 2-aminothiophene-3-acetate (100 mg, 0.54 mmol) was dissolved in dry tetrahydrofuran (5 ml) and treated at –78°C with trimethylaluminium (2M in n-heptane, 0.59 mmol). The reaction mixture was allowed to warm slowly to room temperature over 4 hours, cooled to 0°C and quenched with saturated aqueous ammonium chloride solution. The solution was extracted with ethyl acetate and the organic phase dried over magnesium sulfate, evaporated to dryness and the residue chromatographed on silica gel using hexane/ethyl acetate (2:1) as eluent to give 45 mg of 4,6-dihydrothieno[2,3-b]pyrrol-5-one as a brown solid. MS(ES): m/e 140 [M+H].

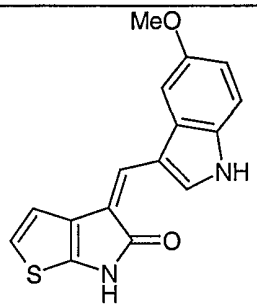
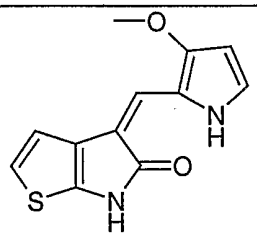
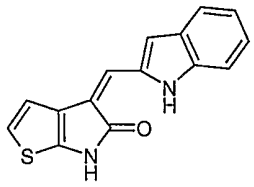
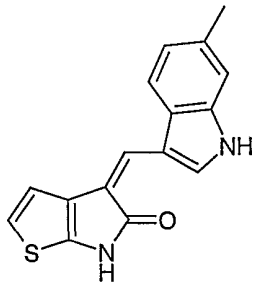
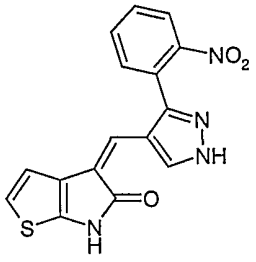
In a manner analogous to that described in Example 1, starting with 4,6-dihydrothieno[2,3-b]pyrrol-5-one (prepared as described in Example 1) and the

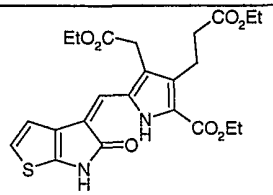
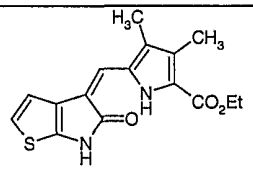
appropriate heterocyclic aldehyde, the compounds shown in Table 1 were also prepared.

Table 1

Example	Name	Structure	MS (ES)
2	(Z)-4,6-Dihydro-4-[(1-methyl-2-pyrrolyl)methylene]thieno[2,3-b]pyrrol-5-one		231
3	(Z)-4,6-Dihydro-4-[(2-thienyl)-methylene]thieno[2,3-b]pyrrol-5-one		234
4	(Z)-4,6-Dihydro-4-[(1H-imidazol-4-yl)methylene]thieno-[2,3-b]pyrrol-5-one		218
5	(Z)-4,6-Dihydro-4-[(2-furyl)-methylene]thieno[2,3-b]pyrrol-5-one		218
6	(Z)-4,6-Dihydro-4-[(3-methyl-1H-pyrazol-4-yl)methylene]-thieno[2,3-b]pyrrol-5-one		232

Example	Name	Structure	MS (ES)
7	(Z)-4,6-Dihydro-4-[(1H-indol-3-yl)methylene]thieno[2,3-b]pyrrol-5-one		267
8	(Z)-4,6-Dihydro-4-[(1H-imidazol-2-yl)methylene]thieno-[2,3-b]pyrrol-5-one		218
9	(Z)-4,6-Dihydro-4-[(3-phenyl-1H-pyrazol-4-yl)methylene]-thieno[2,3-b]pyrrol-5-one		294
10	(Z)-4,6-Dihydro-4-[(3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methylene]thieno[2,3-b]pyrrol-5-one		324
11	(Z)-4,6-Dihydro-4-[(5-methyl-3H-imidazol-4-yl)methylene]-thieno[2,3-b]pyrrol-5-one		232

Example	Name	Structure	MS (ES)
12	(Z)-4,6-Dihydro-4-[(5-methoxy-1H-indol-3-yl)methylene]thieno-[2,3-b]pyrrol-5-one		297
13	(Z)-4,6-Dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-thieno[2,3-b]pyrrol-5-one		279
14	(Z)-4,6-Dihydro-4-[(1H-indol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one		267
15	(Z)-4,6-Dihydro-4-[(6-methyl-1H-indol-3-yl)methylene]thieno-[2,3-b]pyrrol-5-one		281
16	(Z)-[5-(2-Nitro-phenyl)-2H-pyrazol-3-ylmethylene]-4,6-dihydro-thieno[2,3-b]pyrrol-5-one		339

Example	Name	Structure	MS (ES)
17	3-(2-Ethoxycarbonyl-ethyl)-4-ethoxycarbonylmethyl-5-(5-oxo-5,6-dihydro-thieno[2,3-b]pyrrol-4-ylidenemethyl)-1H-pyrrole-2-carboxylic acid ethyl ester		475
18	3,4-Dimethyl-5-(5-oxo-5,6-dihydro-thieno[2,3-b]pyrrol-4-ylidenemethyl)-1H-pyrrole-2-carboxylic acid ethyl ester		317

Example 19

(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide

5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide (30 mg, 0.17 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (2 ml). Pyrrole-2-carboxaldehyde (16 mg, 0.18 mmol) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (10 ml) and the precipitated solid was collected by filtration and washed with water to give 15 mg of (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide as a yellow/brown solid. MS(ES): m/e 260 [M+H].

The starting material was prepared as follows:

Method C:

i) Potassium tertiary-butoxide (1.96 g, 17.4 mmol) was dissolved in tetrahydrofuran (45 ml) and the solution cooled to –50°C. A solution of 5-nitrothiophene-2-carboxamide (1 g, 1.94 mmol) and ethyl chloroacetate (0.5 ml, 5.81 mmol) was added dropwise in dry tetrahydrofuran (12 ml) over 5 minutes. The reaction mixture was stirred at –50°C for 16 hours then quenched with acetic

acid (3 ml), then washed with water (20 ml). The aqueous phase was extracted with ethyl acetate and the combined organic fractions were washed with saturated brine solution. The organic phase was dried over magnesium sulfate, evaporated to dryness and the residue chromatographed on silica gel using hexane/ethyl acetate (4:1) as eluent to give 610 mg of ethyl 5-carbamoyl-2-nitrothiophene-3-acetate as a yellow/brown oil. MS(ES): m/e 259 [M+H].

ii) Ethyl 5-carbamoyl-2-nitrothiophene-3-acetate (600 mg, 2.33 mmol) was dissolved in aqueous dioxan (7 ml, 4:1 dioxan/water) and treated with reduced iron powder (1.55 g, 27.77 mmol) and iron sulfate heptahydrate (200 mg, 0.68 mmol). The reaction mixture was refluxed for 1 hour then filtered through celite filter-aid and washed through with ethyl acetate. The organic phase was washed with saturated sodium aqueous hydrogen carbonate and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate and evaporated to a red/black viscous oil and then chromatographed on silica gel using hexane/ethyl acetate (1:2) as eluent to give 510 mg of ethyl 2-amino-5-carbamoylthiophene-3-acetate. MS(ES): m/e 229 [M+H].

iii) Ethyl 2-amino-5-carbamoylthiophene-3-acetate (500 mg, 2.19 mmol) was dissolved in dry dichloromethane (20 ml) and treated at 0°C with trimethylaluminium (2M in heptane, 3.5 ml, 7.22 mmol). The reaction mixture was allowed to warm slowly to room temperature over 3 hours, cooled to 0°C and quenched with saturated aqueous ammonium chloride solution. The solution was extracted with ethyl acetate, the organic phase was dried over magnesium sulfate, evaporated to dryness and the residue chromatographed on silica gel using ethyl acetate as eluent to give 210 mg of 5,6-dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide as a pale grey solid. MS(ES): m/e 183 [M+H].

The procedure outlined in Method C was used for the synthesis of the starting material used in Example 20 (5-nitrothiophene-2-carbonitrile) which is an item of commerce. The starting materials used in Examples 21 and 22 can be prepared from the commercially available 5-nitrothiophene-2-carboxylic acid in a manner known per se. Method C was then used for preparation of the respective starting materials.

Example 20

(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carbonitrile

5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carbonitrile (32 mg, 0.2 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (1 ml). Pyrrole-2-carboxaldehyde (37 mg, 0.39 mmol) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (6 ml) and the precipitated solid was collected by filtration and washed with water to give 10 mg of (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carbonitrile as a yellow solid. MS(ES): m/e 242 [M+H].

Example 21

tert-Butyl (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylate

tert-Butyl 5,6-dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate (32 mg, 0.2 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (1 ml). Pyrrole-2-carboxaldehyde (0.39 mmol, 37 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (6 ml) and the precipitated solid was collected by filtration and washed with water to give 10 mg of tert-butyl (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylate as a yellow solid. MS(ES): m/e 317 [M+H].

Example 22

Methyl (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylate

Methyl 5,6-dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate (32 mg, 0.2 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (1 ml). Pyrrole-2-carboxaldehyde (37 mg, 0.39 mmol) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (6 ml) and the precipitated solid was collected by filtration and washed with water to give 10 mg of methyl (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-

2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylate as a yellow solid. MS(ES): m/e 275 [M+H].

Example 23

(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylic acid

tert-Butyl (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylate (150 mg, 0.47 mmol) was dissolved in dichloromethane (8 ml), cooled to 0°C, treated with trifluoroacetic acid (0.75 ml) and stirred for 2 hours warming to room temperature. The reaction mixture was evaporated to dryness and triturated with diethyl ether to give 70 mg of (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylic acid as a red solid. MS(ES): m/e 260 [M+H].

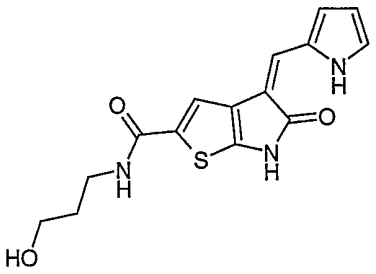
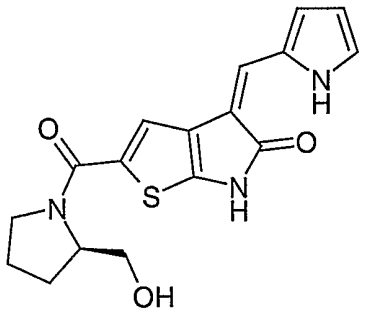
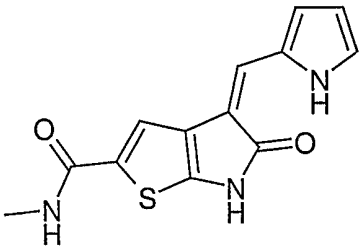
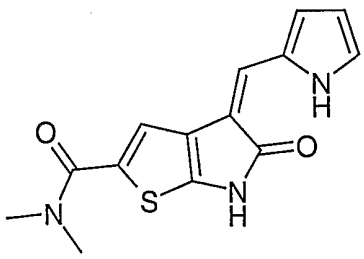
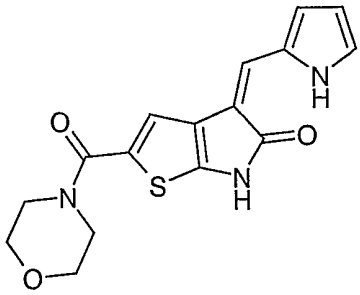
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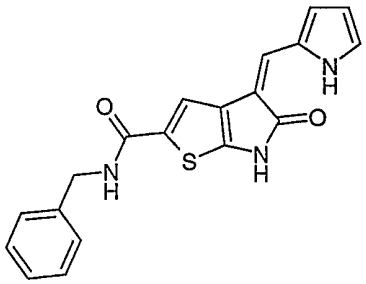
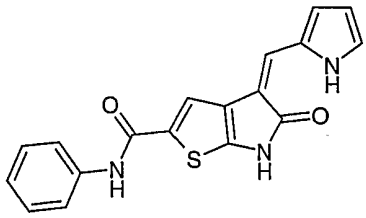
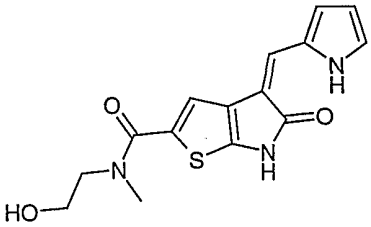
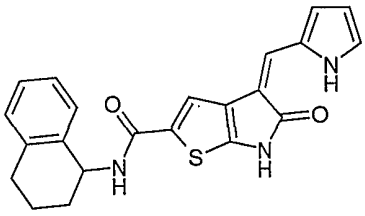
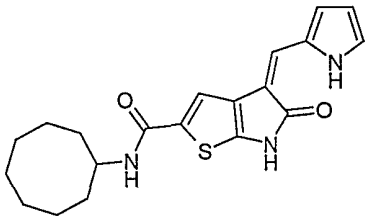
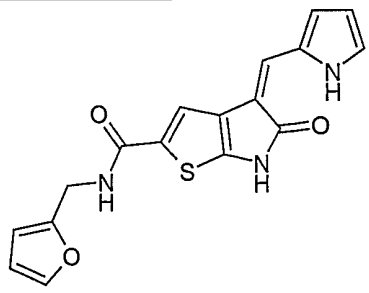
(Z)-5,6-Dihydro-5-oxo-N-propyl-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide

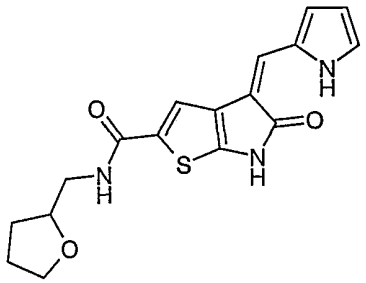
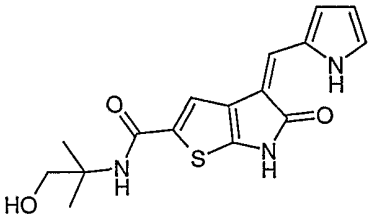
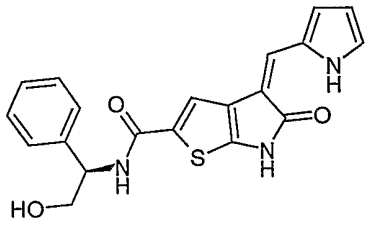
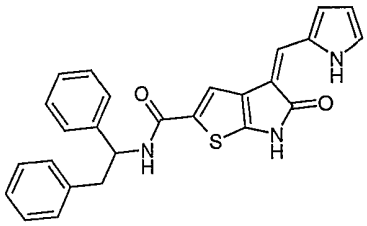
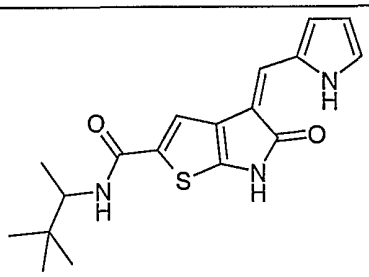
A solution of (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (30 mg, 0.12 mmol), 1-hydroxy-benzotriazole (18 mg, 0.13 mmol), propylamine (11 µl, 0.13 mmol), 1-(3-dimethoxyaminopropyl)-3-ethylcarbodiimide hydrochloride (25 mg, 0.13 mmol) and diisopropylethylamine (23 µl, 0.13 mmol) in dimethylformamide (1 ml) was stirred at room temperature for 3 hours then diluted with ethyl acetate and washed with 2M hydrochloric acid, saturated sodium bicarbonate and water. The resulting solution was dried over magnesium sulfate and evaporated to dryness. The residue was triturated with water/isopropyl alcohol to give 14 mg of (Z)-5,6-dihydro-5-oxo-N-propyl-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide as an orange solid. MS(ES): m/e 302 [M+H].

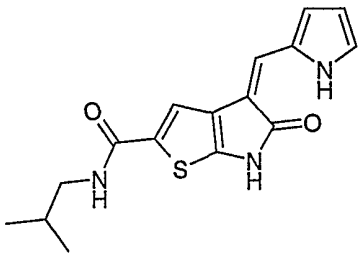
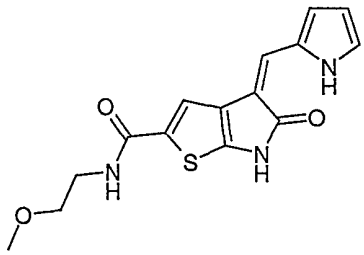
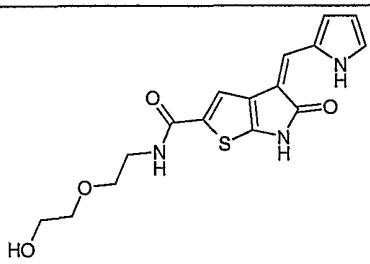
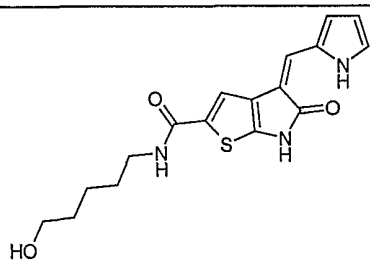
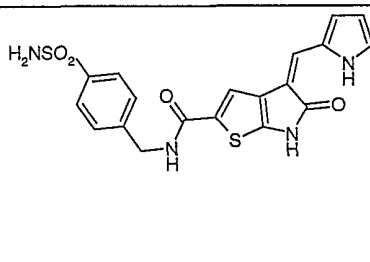
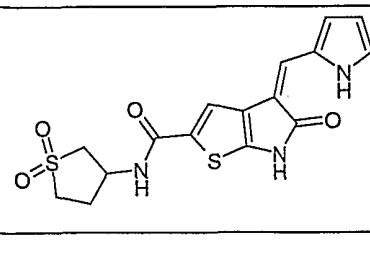
In a manner analogous to that described in Example 24, starting with (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylic acid and the appropriate amine the compounds shown in Table 2 were also prepared.

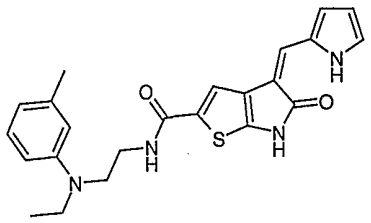
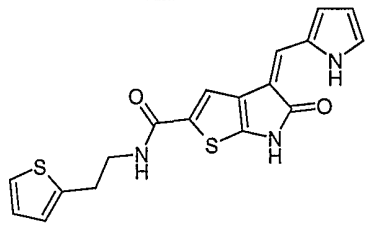
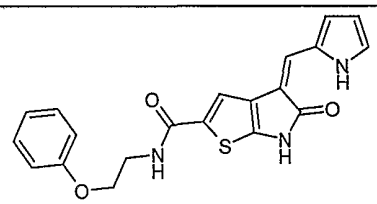
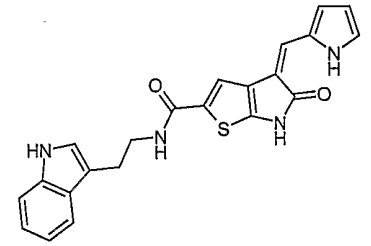
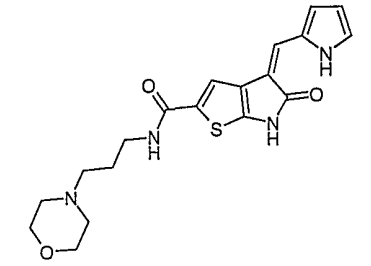
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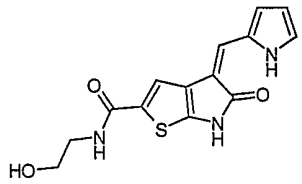
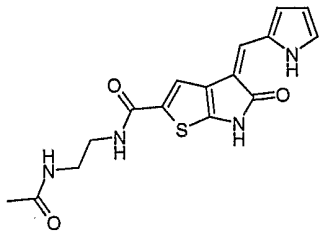
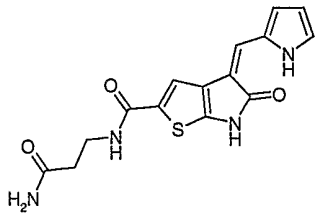
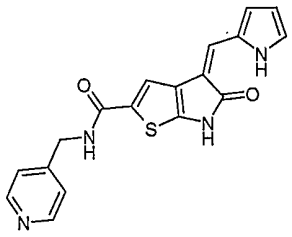
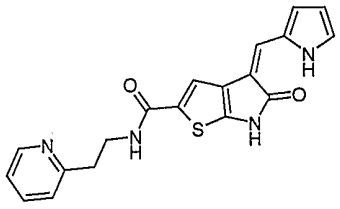
Example	Name	Structure	MS(ES)
25	(Z)-5,6-Dihydro-N-(3-hydroxypropyl)- 5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno-[2,3-b]pyrrole-2-carboxamide		318
26	(Z)-4,6-Dihydro-2-[[2(R)-(hydroxymethyl)-1-pyrrolidinyl]carbonyl]-4-[(1H-pyrrol-2-yl)-methylene]-5H-thieno-[2,3-b]pyrrol-5-one		343
27	(Z)-5,6-Dihydro-N-methyl-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		274
28	(Z)-5,6-Dihydro-N,N-dimethyl-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		288
29	(Z)-4,6-Dihydro-2-(morpholinocarbonyl)-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno-[2,3-b]pyrrole-2-carboxamide		330

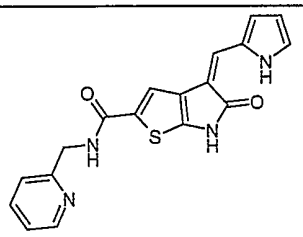
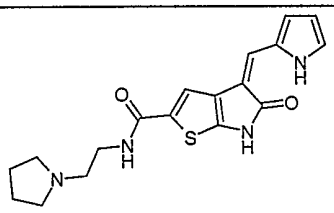
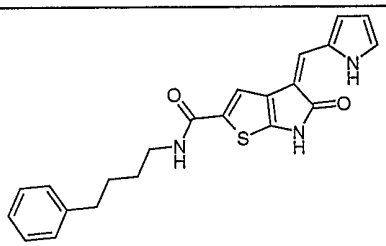
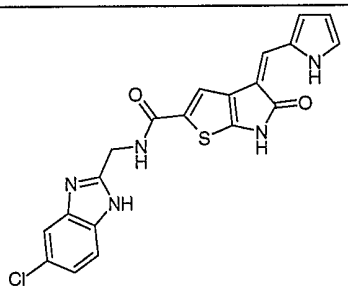
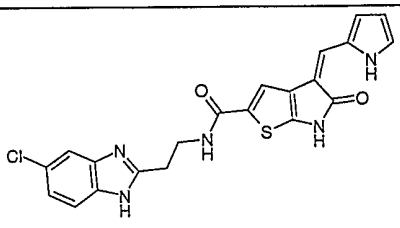
Example	Name	Structure	MS(ES)
30	(Z)- N-Benzyl-5,6-dihydro- 5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		350
31	(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno[2,3-b]pyrrole-2-carboxanilide		336
32	(Z)-5,6-Dihydro-N-methyl-N-(2-hydroxy-ethyl)- 5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		318
33	(Z)-5,6-Dihydro-N-(1,2,3,4-tetrahydro-1(RS)-naphthyl)-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		390
34	(Z)-N-Cyclooctyl-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		370
35	(Z)-N-(2-Furfuryl)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		340

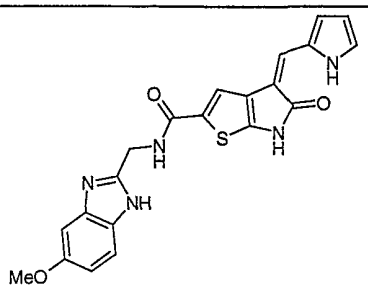
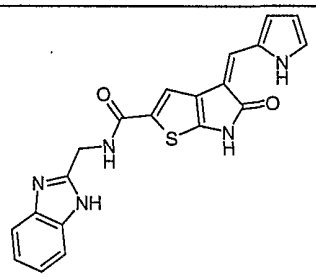
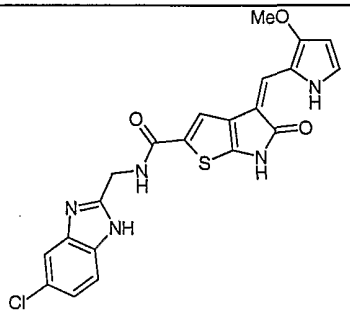
Example	Name	Structure	MS(ES)
36	(Z)-5,6-Dihydro-N-(tetrahydro-2(RS)-furfuryl)- 5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		344
37	(Z)-5,6-Dihydro-N-(2-hydroxy-1,1-dimethyl-ethyl)- 5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		332
38	(Z)-5,6-Dihydro-N-(2-hydroxy-1(R)-phenyl-ethyl)-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		380
39	(Z)-5,6-Dihydro-N-(1(RS),2-diphenylethyl)-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		440
40	(Z)-5,6-Dihydro-N-(2,2-dimethyl-1(RS)-methyl-propyl)- 5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		344

Example	Name	Structure	MS(ES)
41	(Z)-5,6-Dihydro-N-(2-methylpropyl)- 5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno-[2,3-b]pyrrole-2-carboxamide		316
42	(Z)-5,6-Dihydro-N-(2-methoxyethyl)-5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		318
43	(Z)-5,6-Dihydro-N-[2-(2-hydroxyethoxy)ethyl]-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		348
44	(Z)-5,6-Dihydro-N-(5-hydroxypentyl)-5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno-[2,3-b]pyrrole-2-carboxamide		346
45	(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-N-(4-sulfamoylbenzyl)-4H-thieno[2,3-b]pyrrole-2-carboxamide		429
46	(Z)-5,6-Dihydro-N-(tetrahydro-1,1-dioxo-3(RS)-thienyl)-5-oxo-4-[(1H-pyrrol-2-		378

Example	Name	Structure	MS(ES)
	yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		
47	(Z)-N-[2-(N-Ethyl-N-m-tolylamino)ethyl]-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		421
48	(Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-N-[2-(2-thienyl)ethyl]-4H-thieno[2,3-b]pyrrole-2-carboxamide		370
49	(Z)-5,6-Dihydro-5-oxo-N-(2-phenoxyethyl)-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide		380
50	(Z)-5,6-Dihydro-N-[2-(3-indolyl)ethyl]-5-oxo-4-[(1H-pyrrol-2-yl)-methylene]-4H-thieno-[2,3-b]pyrrole-2-carboxamide		403
51	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (3-morpholin-4-yl-propyl)-amide		387

Example	Name	Structure	MS(ES)
52	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (2-hydroxy-ethyl)-amide		304
53	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (2-acetylamino-ethyl)-amide		345
54	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (2-carbamoyl-ethyl)-amid		331
55	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (pyridin-4-ylmethyl)-amide		351
56	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (2-pyridin-2-yl-ethyl)-amide		365

Example	Name	Structure	MS(ES)
57	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (pyridin-2-ylmethyl)-amide		351
58	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide		357
59	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (2-phenyl-butyl)-amide		392
60	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (6-chloro-1H-benzimidazol-2-ylmethyl)-amide		424
61	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid [2-(5-chloro-1H-benzimidazol-2-yl)-ethyl]-amide		438

Example	Name	Structure	MS(ES)
62	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (6-methoxy-1H-benzimidazol-2-ylmethyl)-amide		420
63	(Z)-5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (1H-benzimidazol-2-ylmethyl)-amide		390
64	(Z)-4-(3-Methoxy-1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (6-chloro-1H-benzimidazol-2-ylmethyl)-amide		454

Example 65

tert-Butyl (Z)-5,6-dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate

tert-Butyl 5,6-dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate (915 mg, 3.8 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (10 ml). 3-Methoxypyrrole-2-carboxaldehyde (3.8 mmol, 480 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (15 ml) and the precipitated solid was collected by filtration and washed with water to give 530 mg of tert-butyl (Z)-5,6-dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate as a red solid. MS(ES): m/e 347 [M+H].

Example 66

(Z)-5,6-Dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylic acid

tert-Butyl (Z)-5,6-dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate (0.5 g, 1.45 mmol) was dissolved in dichloromethane (8 ml), cooled to 0°C, treated with trifluoroacetic acid (2 ml) and stirred for 3 hours warming to room temperature. The reaction mixture was evaporated to dryness and triturated with diethyl ether to give 300 mg of (Z)-5,6-dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylic acid as a red solid. MS(ES): m/e 291 [M+H].

Example 67

(Z)-5,6-Dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide

5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide (30 mg, 0.17 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (2 ml). Pyrrole-2-carboxaldehyde (0.19 mmol, 23 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (2 ml) and the precipitated solid was collected by filtration and washed with water to give 22 mg of (Z)-5,6-dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide as a red/brown solid. MS(ES): m/e 247 [M+H].

Example 68

(Z)-5,6-Dihydro-4-[(5-methyl-3H-imidazol-4-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide

5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide (30 mg, 0.17 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (2 ml). 4-Methyl-5-imidazole carboxaldehyde (0.18 mmol, 15 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into

an ice/water mixture (2 ml) and the precipitated solid was collected by filtration and washed with water to give 22 mg of (Z)-5,6-dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide as a yellow/brown solid. MS(ES): m/e 275 [M+H].

Example 69

(Z)-5,6-Dihydro-5-oxo-4-[(3-phenyl-1H-pyrazol-4-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide

5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide (30 mg, 0.17 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (2 ml). 3-Phenyl-1H-pyrazole-4-carboxaldehyde (0.18 mmol, 31 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (2 ml) and the precipitated solid was collected by filtration and washed with water to give 26 mg of (Z)-5,6-dihydro-5-oxo-4-[(3-phenyl-1H-pyrazol-4-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide as a yellow/brown solid. MS(ES): m/e 337 [M+H].

Example 70

(Z)-5,6-Dihydro-5-oxo-4-[[3-(4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide

5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxamide (25 mg, 0.14 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (2 ml). 3-(4-Methoxyphenyl)-1H-pyrazole-4-carboxaldehyde (0.15 mmol, 28 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (2 ml) and the precipitated solid was collected by filtration and washed with water to give 27 mg of (Z)-5,6-dihydro-5-oxo-4-[[3-(4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide as a brown solid. MS(ES): m/e 367 [M+H].

Example 71

(Z)-5-Oxo-4-[1H-pyrrol-2-ylmethylene]-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

A solution of (Z)-5,6-dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (250 mg, 0.95 mmol), 1-hydroxybenzotriazole (1.1 mmol, 150 mg), 1-(tetrahydro-pyran-2-yloxy) amine (1.25 mmol, 146 mg), 1-(3-dimethoxyaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1 mmol, 208 mg) and diisopropylethylamine (1.1 mmol, 190 mg) in dimethylformamide (4 ml) was stirred at room temperature for 3 hours then diluted with ethyl acetate and washed with 2M hydrochloric acid, saturated sodium bicarbonate and water. The resulting solution was dried over magnesium sulfate and evaporated to dryness. The residue was triturated with water/isopropyl alcohol to give 90 mg of (Z)-5-Oxo-4-[1H-pyrrol-2-ylmethylene]-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide as a brown solid. MS(ES): m/e 360 [M+H].

Example 72

(Z)-5-Oxo-4-[1H-pyrrol-2-ylmethylene]-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid hydroxamide

(Z)-5-Oxo-4-[1H-pyrrol-2-ylmethylene]-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (65 mg, 0.18 mmol) was dissolved in methanol (2 ml). 4-Toluene sulfonic acid (0.09 mmol, 15 mg) was added in one portion and the solution stirred at room temperature for 2 hours. The solvent was evaporated and the residue triturated with diethyl ether to give 10 mg of (Z)-5-Oxo-4-[1H-pyrrol-2-ylmethylene]-5,6-dihydro-4H-thieno[2,3-b]pyrrole-2-carboxylic acid hydroxamide as a brown solid. MS(ES): m/e 276 [M+H].

Example 73

(Z)-2-Hydroxymethyl-4-(1H-pyrrol-2-ylmethylene)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one

tert-Butyl 5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate (300 mg, 1 mmol) was dissolved in toluene (25 ml). Diisobutylaluminium hydride (1.5 mmol, 1.5 ml of a 1 M solution in toluene) was added dropwise and the reaction mixture stirred at room temperature for 2 hours. Methanol (1ml) was added and then diluted with ethyl acetate and washed with 2M hydrochloric acid, saturated sodium bicarbonate and water. The resulting solution was dried over magnesium sulfate and evaporated to dryness to give 70 mg of (Z)-2-hydroxymethyl-4- (1H-pyrrol-2-ylmethylene)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one as a red solid. MS(ES): m/e 247 [M+H].

Example 74

(Z)-2-Methyl-4-(1H-pyrrol-2-ylmethylene)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one

tert-Butyl 5,6-Dihydro-5-oxo-4H-thieno[2,3-b]pyrrole-2-carboxylate (300 mg, 1 mmol) was dissolved in dichloromethane (40 ml). Diisobutylaluminium hydride (2 mmol, 2 ml of a 1 M solution in dichloromethane) was added dropwise and the reaction mixture stirred at room temperature for 2 hours then diluted with ethyl acetate and washed with saturated sodium bicarbonate, saturated brine solution and water. The resulting solution was dried over magnesium sulfate and evaporated to dryness and chromatographed on silica gel using hexane/ethyl acetate (5:1) as eluent to give 10 mg of (Z)-2-methyl-4- (1H-pyrrol-2-ylmethylene)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one as a red solid. MS(ES): m/e 231 [M+H].

Example 75

(Z)-3-[5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrol-2-yl]-acrylic acid ethyl ester

3-(5-Oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-2-yl)-acrylic acid ethyl ester (30 mg, 0.13 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (1 ml). Pyrrole-2-carboxaldehyde (0.15 mmol, 14 mg) was added in one portion and the mixture heated at 75°C for 30 minutes. The reaction mixture was poured into an ice/water mixture (4 ml) and the precipitated solid was collected by filtration and washed with water to give 10 mg of (Z)-3-[5-Oxo-4-(1H-pyrrol-2-ylmethylene)-5,6-dihydro-4H-thieno[2,3-b]pyrrol-2-yl]-acrylic acid ethyl ester as a red solid. MS(ES): m/e 315 [M+H].

The starting material was prepared as follows:

Preparation of 3-(5-Oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-2-yl)-acrylic acid ethyl ester

i) A mixture of 5-nitrothiophene-2-carboxaldehyde (10 g, 64 mmol), hydroxylamine hydrochloride (9.4 g, 130 mmol) and sodium hydroxide (4.34 g, 107 mmol) in ethanol/water (150 ml, 2:1) was heated to reflux for 2 hours, then diluted with dichloromethane and washed with water. The organic layer was dried over magnesium sulfate and evaporated to dryness to give 8.8 g of 5-nitro-2-thiophenecarboxaldehyde oxime as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.54 (1H, d), 8.13 (1H, s), 8.16 (1H, d), 13.14 (1H, s).

ii) Potassium tertiary-butoxide (960 mg, 8.6 mmol) was dissolved in N,N-dimethylformamide (10 ml) and the solution cooled to –30°C. A solution of 5-nitro-2-thiophenecarboxaldehyde oxime (400 mg, 2.86 mmol) and ethyl chloroacetate (356 mg, 2.86 mmol) was added dropwise in dry N,N-dimethylformamide (5 ml) over 5 minutes. The reaction mixture was stirred at –30°C for 30 minutes then quenched with 2M HCl (50 ml), diluted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica gel using hexane/diethyl ether (1:2) as eluent to give 200 mg of ethyl-5-[(hydroxyimino)methyl]-2-nitro-3-thiopheneacetate as a tan solid. MS(ES): m/e 227 [M+H].

iii) A mixture of ethyl-5-[(hydroxyimino)methyl]-2-nitro-3-thiopheneacetate (1 g, 4.43 mmol) in aqueous formaldehyde (37%, 30 ml) and conc. sulfuric acid (0.1 ml) was refluxed for 30 minutes. The reaction mixture was cooled to room temperature then diluted with water and extracted with ethyl acetate. The organic phase was washed with saturated sodium hydrogen carbonate and saturated brine solution, dried over magnesium sulfate and evaporated to dryness and then chromatographed on silica gel using hexane/ethyl acetate (2:1) as eluent to give 500 mg of ethyl-5-nitrothiophene-4-acetate-2-carboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, t), 4.25 (2H, q), 7.71 (1H, s), 9.96 (1H, s).

iv) Ethyl-5-nitrothiophene-4-acetate-2-carboxaldehyde (350 mg, 1.44 mmol) was dissolved in dichloromethane, treated with (carbomethoxymethylene)-triphenylphosphorane (522 mg, 1.5 mmol) and heated to reflux for 1 hour. The reaction mixture was evaporated to dryness and then chromatographed on silica gel using hexane/diethyl ether (1:1) as eluent to give 250 mg of ethyl-4-[(ethoxycarbonyl)methyl]-5-nitro-2-thiopheneacrylate. MS(ES): m/e 314 [M+H].

v) Ethyl-4-[(ethoxycarbonyl)methyl]-5-nitro-2-thiopheneacrylate (230 mg, 0.74 mmol) was dissolved in aqueous dioxan (6 ml, 5:1 dioxan/water) and treated with reduced iron powder (0.4 g, 7.2 mmol) and iron sulfate heptahydrate (50 mg, 0.18 mmol). The reaction mixture was refluxed for 1 hour then filtered through celite and washed through with diethyl ether. The combined organics were then washed with saturated sodium hydrogen carbonate, saturated sodium chloride, dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica gel using hexane/ethyl acetate (2:1) as eluent to give 150 mg 3-(5-amino- 4-ethoxycarbonylmethyl-thiophen-2-yl)-acrylic acid ethyl ester. MS(ES): m/e 284 [M+H].

vi) Ethyl-4-[(ethoxycarbonyl)methyl]-5-amino-2-thiopheneacrylate (150 mg, 0.53 mmol) was dissolved in dichloromethane (20 ml), treated at room temperature with trimethyaluminium (2M in heptane, 1 ml, 2 mmol) and stirred for 1 hour. The reaction was quenched with water, diluted with ethyl acetate, washed with saturated brine solution and dried over magnesium sulfate. The organic phase was evaporated to dryness and the residue chromatographed on silica gel using hexane/ethyl acetate (2:1) as eluent to give 35 mg of 3-(5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-2-yl)-acrylic acid ethyl ester as a tan coloured solid. MS(ES): m/e 238 [M+H].

Example 76

(Z)-2-Acetyl-4,6-dihydro-4-[(1H-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one

2-Acetyl-4,6-dihydro-4-thieno[2,3-b]pyrrol-5-one (16 mg, 0.08 mmol) was dissolved in a solution of 1% piperidine in 2-propanol (1 ml). Pyrrole-2-carboxaldehyde (0.16 mmol, 17 mg) was added in one portion and the mixture heated at 75°C for 1 hour. The reaction mixture was poured into an ice/water mixture (3 ml) and the precipitated solid was collected by filtration and washed with water to give 7 mg of (Z)-2-Acetyl-4,6-dihydro-4-[(1H-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one as a red solid. MS(ES): m/e 259 [M+H].

The starting material was prepared as follows:

4,6-Dihydro-5H-thieno[2,3-b]pyrrol-5-one (70 mg, 0.5 mmol) was dissolved in boron trifluoride diethyletherate (4 ml) and treated with acetyl chloride (1.5 mmol, 0.11 ml) at room temperature. The reaction mixture was then heated to reflux for 3 hours, quenched with water, diluted with ethyl acetate and washed with 2M HCl solution. The organic phase was dried over magnesium sulfate, evaporated to dryness and the residue chromatographed on silica gel using hexane/ethyl acetate (1:1) as eluent to give 20 mg of 2-acetyl-4,6-dihydro-4-thieno[2,3-b]pyrrol-5-one as a brown solid. MS(ES): m/e 182 [M+H].

Example 77

Tablets containing the following ingredients may be produced in a conventional manner:

Ingredient	Per tablet
Thienopyrrolidinone derivative	10.0 mg
Lactose	135.0 mg
Microcrystalline cellulose	50.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg
Total weight	200.0 mg

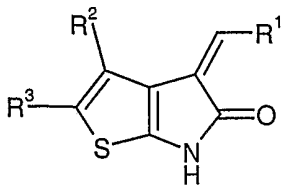
Example 78

Capsules containing the following ingredients may be produced in a conventional manner:

Ingredient	Per capsule
Thienopyrrolidinone derivative	10.0 mg
Lactose	155.0 mg
Pregelatinized starch	30.0 mg
Talc	5.0 mg
Capsule fill weight	200.0 mg

Claims

1. Compounds of the general formula



I

wherein

R^1 represents a 5- or 6-membered monocyclic aromatic ring containing one or more hetero atoms independently selected from N, S and O, the remaining being carbon, and which ring may be benz-fused and which monocyclic or benz-fused aromatic ring is optionally substituted independently with one or more groups selected from lower alkyl, lower alkoxy, optionally substituted aryl, optionally substituted aryl-lower alkyl, optionally substituted aryl-lower alkoxy, halogen, haloalkyl, nitro, hydroxy, cyano, $-C(O)R^7$, $-(CH_2)_nCO_2R^8$ or $-(CH_2)_nCONR^7R^8$,

wherein R^7 represents hydrogen, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, or lower alkyl optionally mono substituted by cycloalkyl, optionally substituted aryl or heterocyclyl and

R^8 represents hydrogen, cycloalkyl, heterocyclyl or lower alkyl optionally mono substituted by cycloalkyl, optionally substituted aryl, hydroxy, lower alkoxy, optionally substituted heteroaryl, heterocyclyl or hydroxy-loweralkoxy,

or, when R^7 and R^8 are both attached to nitrogen, R^7 and R^8 together with the nitrogen atom to which they are attached represent a 5- or 6-membered heterocycle optionally containing an additional heteroatom selected from N, S and O and optionally being substituted by lower alkyl, lower alkoxy or hydroxy-lower alkyl;

n is 0-3;

R^2 is H;

R^3 represents hydrogen, -COR^4, -$CONR^4R^5$, -CONHOR^6, cyano, halogen, -CO_2R^5, -$SO_2NR^4R^5$, -OR^4, lower alkyl optionally substituted independently by cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, hydroxy, -$CONR^4R^5$ or -CO_2R^5, or lower alkenyl optionally substituted independently by cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, hydroxy, -$CONR^4R^5$ or -CO_2R^5, wherein

R^4 represents hydrogen, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl, or lower alkyl optionally mono substituted by cycloalkyl, optionally substituted aryl or heterocyclyl;

R^5 represents hydrogen, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, heterocyclyl or lower alkyl optionally substituted independently by -$CONH_2$, cycloalkyl, optionally substituted aryl, optionally substituted aryloxy, hydroxy, lower alkoxy, optionally substituted heteroaryl, heterocyclyl, hydroxy-loweralkoxy or -NR'R'' wherein R' is hydrogen or lower alkyl optionally substituted by optionally substituted aryl and R'' is -$COCH_3$, lower alkyl or optionally substituted aryl ;

R^6 represents hydrogen or heterocyclyl;

or, when R^4 and R^5 are both attached to nitrogen, R^4 and R^5 together with the nitrogen atom to which they are attached represent a 5- or 6-membered heterocycle optionally containing an additional heteroatom selected from N, S and O and optionally being independently substituted at one or more carbon and/or N-atoms by lower alkyl, lower alkoxy or hydroxy-lower alkyl;

and pharmaceutically acceptable salts thereof.

2. Compounds according to Claim 1, wherein in R^1 the monocyclic aromatic ring is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thienyl or furanyl, and, if benz-fused, from benzimidazolyl or indolyl.

3. Compounds according to claim 1 or 2, wherein the monocyclic aromatic ring in R^1 is pyrrolyl.

4. Compounds according to Claims 1 to 3, wherein the monocyclic aromatic ring in R^1 is pyrazolyl.

5. Compounds according to any one of claims 1 to 4, wherein the monocyclic or benz-fused ring in R^1 is unsubstituted or substituted independently at one or more positions with lower alkyl, lower alkoxy, optionally substituted aryl or -$(CH_2)_nCO_2R^8$.

6. Compounds according to claim 5, wherein the monocyclic or benz-fused aromatic ring in R^1 is unsubstituted or substituted by methyl, phenyl, 2-nitrophenyl, p-methoxy-phenyl, methoxy, carbethoxy, carbethoxymethyl or carbethoxyethyl.

7. Compounds according to any one of claims 1-6, wherein R^1 is 2-pyrrolyl or 1H-pyrazol-4-yl.

8. Compounds according to any one of Claims 1-7, wherein R^3 is hydrogen, -COR^4, -$CONR^4R^5$, -$CONHOR^6$, cyano, -CO_2R^5, -$SO_2NR^4R^5$, lower alkyl optionally substituted by hydroxy or lower alkenyl optionally substituted by -CO_2R^5.

9. Compounds according to claim 8, wherein R^3 is hydrogen, -$CONH_2$ or cyano.

10. A compound according to Claim 1, which is (Z)-4,6-Dihydro-4-[(1H-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one.

11. A compound according to Claim 1, which is (Z)-4,6-Dihydro-4-[(3-methoxy-1H-pyrrol-2-yl)methylene]thieno[2,3-b]pyrrol-5-one.

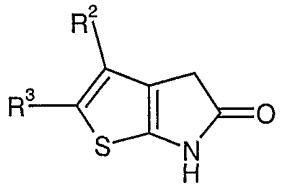
12. A compound according to Claim 1, which is (Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carboxamide.

13. A compound according to Claim 1, which is (Z)-5,6-Dihydro-5-oxo-4-[(1H-pyrrol-2-yl)methylene]-4H-thieno[2,3-b]pyrrole-2-carbonitrile.

14. A compound according to Claim 1, selected from

(Z)-4,6-Dihydro-4-[(3-methyl-1H-pyrazol-4-yl)methylene]thieno[2,3-b]pyrrol-5-one;
(Z)-4,6-Dihydro-4-[(3-phenyl-1H-pyrazol-4-yl)methylene]thieno[2,3-b]pyrrol-5-one; or
(Z)-4,6-Dihydro-4-[[3-(4-methoxyphenyl)-1H-pyrazol-4-yl]methylene]thieno[2,3-b]pyrrol-5-one.

15. Compounds of the general formula



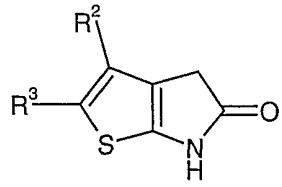
II

wherein R^2 and R^3 are as in Claim 1.

16. Compounds according to any one of Claims 1-14 and the pharmaceutically acceptable salts thereof for use as therapeutically active compounds, particularly for use in the treatment of neuro-degenerative diseases, cardiovascular diseases, cancer or as anti-inflammatory agents.

17. Compounds according to any one of Claims 1-14 and their pharmaceutically acceptable salts for use in the control or prevention of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases.

18. A process for the manufacture of the compounds of formula I according to Claim 1, which process comprises reacting a compound of the general formula



II

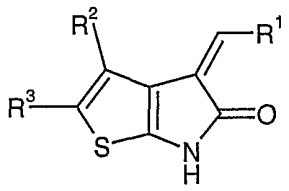
wherein R^2 and R^3 are as in Claim 1,

with an aldehyde of the general formula

R^1-CHO III

wherein R^1 is as in Claim 1,

to yield a compound of the general formula I



I

and, if desired, converting said compound into a pharmaceutically acceptable salt.

19. A medicament containing a compound according to any of Claims 1-14 or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier material.

20. A medicament for the control or prevention of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases containing a compound according to any one of claims 1-14 or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier material.

21. The use of a compound according to any one of Claims 1-14 or a pharmaceutically acceptable salt thereof in the control or prevention of illnesses, especially in the control or prevention of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases

22. The use of a compound according to any one of Claims 1-14 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the control or prevention of neuro-degenerative diseases, cardiovascular diseases, cancer or inflammatory diseases.

23. Compounds according to any one of Claims 1-14 and their pharmaceutically acceptable salts, whenever prepared by the process of Claim 18 or by an obvious chemical equivalent thereof.

24. The invention as herein before described, particularly with reference to the new compounds, intermediates, medicaments, uses and processes.

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INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 01/07423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61P35/00 A61K31/407

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D. WENSBO ET AL: "Indole-3-acetic acids and hetero analogs by one-pot synthesis including Heck cyclization " TETRAHEDRON , vol. 51, no. 37, 1995, pages 10323-10342, XP002182354 page 10327, compound 11a; page 10330, compound 19; page 10331, compound 20	1-24

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2001	27/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, A