Title: COMPOUNDS

Abstract: The use of a compound of the formula (I), or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof in the manufacture of a medicament for the treatment of Mycobacterium tuberculosis (M.tb).
COMPOUNDS

The present invention relates to chemical compounds, to their production as well as to pharmaceutical compositions containing them as well as to their use in therapy, in particular of tuberculosis.

Tuberculosis is the single largest infectious disease killer in the world that kills about 2 million people every year. Someone in the world is infected with TB every second and nearly 1% of the world population is newly infected with TB every year. Overall one third of the world’s population is infected with the TB bacillus and 5 to 10% of people who are infected with TB become sick or infectious at some time during their lifetime. Drugs in use today were discovered more than 40 years ago and since then there has been no major pharmaceutical research effort to discover and develop any new therapeutic agent. There is an urgent medical need to combat this disease with drugs that will be rapidly effective against drug-resistant as well as sensitive TB.

Combination therapy for TB includes four drugs, rifampicin, isoniazid, pyrizinamide and ethambutol, given for a minimum duration of six months. Use of multiple drugs helps in preventing the appearance of drug-resistant mutants and six months of treatment helps in preventing relapse. On the other hand, multiple drug therapy and the prolonged duration of therapy are major impediments to compliance.

Control programmes aimed at implementing “compliance” through DOTS (Directly Observed Therapy Service) exert a huge administrative burden on any treatment. At present, DOTS is available to only 25% of TB patients. WHO estimates that even a reduction to a 4-month therapy would allow DOTS to reach more than 50% of the TB patients world wide and thus have a direct advantage in TB control programmes.

Among the four anti TB drugs, rifampicin plays a major role in shortening the duration of therapy to six months and the duration increases to 18 months in case of rifampicin resistant TB.

The mechanism of RNA polymerase enzyme inhibition by Rifampicin is now well established. Drug resistance to Rifampicin maps almost exclusively to mutations in the rpoB gene encoding the beta subunit (Rifampicin binding site) of RNA polymerase, which shows that it acts in vivo via inhibition of RNA polymerase. Therefore RNA polymerase is
a valid drug target and inhibitors of RNA polymerase may be developed as highly potent drugs for TB.

Prokaryotic core RNA polymerase (RNAP) is composed of four distinct subunits: $\beta$, $\beta'$, $\omega$ and a $\alpha$ dimer. A fifth subunit, the $\sigma$ factor, reversibly associates with RNAP, forming the RNAP holoenzyme, and provides the promoter recognition function. The number of $\sigma$ factors encoded in a genome is quite variable. M. tuberculosis genome encodes 13 different putative $\sigma$ factors. It is generally observed that every $\sigma$ factor has its own specificity, allowing the initiation of transcription of different subsets of genes.

Therefore RNA polymerase being a multisubunit enzyme gives us the opportunity to find inhibitors, which can bind at various sites apart from the active site and thereby specifically inhibit the prokaryotic enzyme.

We have now unexpectedly found that certain carboxylic acid indole compounds have useful properties as RNA polymerase inhibitors in M. tuberculosis. Some of such compounds are described in our published patent application WO-00/46195 for use as inhibitors of the Monocyte Chemoattractant Protein-1 (MCP-1). MCP-1 is a chemokine and has been implicated in the physiology of a large number of inflammatory diseases. Other disease areas where MCP-1 may play a part are atherosclerosis, psoriasis, delayed-type hypersensitivity reactions of the skin, inflammatory bowel disease, multiple sclerosis and brain trauma. There is no anticipation or suggestion of their use in the treatment of infectious diseases such as tuberculosis.

Therefore according to the present invention we provide the use of a compound of the formula (I)
wherein X is a bond or CH₂

R¹ is hydrogen or C₁₅₋₂₀ alkyl or C₅₋₁₀ aryl or an optionally substituted C₅₋₁₀ aryl or C₅₋₁₀ heteroaryl ring;

R² is carboxy, cyano, -C(O) CH₂ OH, -CONHR⁸, -C(O)NH₂SO₂R⁹, tetrazol-5-yl, -(CH₂)₁₋₃ NR¹⁸R¹⁹, SO₃H or a group of formula (VI)

![Diagram](image)

where R⁸ is selected from hydrogen, C₁₋₁₀ alkyl or optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl group. R¹⁸ is a group -(CHR¹⁵)r-COOH where r is an integer of 1-3 and each R¹⁵ group is independently selected from hydrogen or C₁₋₁₀ alkyl; R⁹ is optionally substituted C₁₋₁₀ alkyl or optionally substituted C₅₋₁₀ aryl optionally substituted C₄₋₂₀ heterocyclyl; R¹⁰, R¹¹ and R¹² are independently selected from hydrogen, halogen or C₁₋₁₀ alkyl, or optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl; R¹⁸ and R¹⁹ are independently C₁₋₃ alkyl or taken together with the adjacent nitrogen atom R¹⁸ and R¹⁹ represent a morpholine or piperazine ring;

R³ is hydrogen, halogen or or optionally substituted C₁₋₁₀ alkyl or optionally substituted C₂₋₁₀ alkenyl or optionally substituted C₂₋₁₀ alkynyl or optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl or optionally substituted C₁₋₁₀ alkoxy or optionally substituted aralkyl of up to 15 carbon atoms or optionally substituted aralkyloxy of up to 15 carbon atoms or optionally substituted cycloalkyl of up to 7 carbon atoms;

R⁴ is a group NO₂, NHR¹⁴, NHCHR¹⁴ R¹⁵, NHCOR¹⁵, NH₂SO₂R¹⁵, NHC(X¹)NH₁⁶, or NHCONH SO₂R where X¹ is O or S, R¹⁴ is hydrogen or C₁₋₁₀ alkyl or optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl; R¹⁵ is optionally substituted C₁₋₁₀ alkyl, optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl and R¹⁶ is hydrogen, optionally substituted C₁₋₁₀ alkyl, or optionally...
substituted C₄₋₂₀ heteroaryl group, R¹⁷ is an optionally substituted C₁₋₁₀ alkyl, or optionally substituted C₄₋₂₀ heteroaryl group:

R⁵, R⁶ and R⁷ are independently selected from hydrogen, halogen, a functional group, an optionally substituted hydrocarbyl group or an optionally substituted heterocyclic group;

or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof in the manufacture of a medicament for the treatment of Mycobacterium tuberculosis (M.tb).

Compounds of formula (I) are inhibitors of M.tb RNA polymerase. In addition, they inhibit the growth of M.tb. As a result, these compounds can be used to treat tuberculosis disease.

In this specification the term ‘alkyl’ when used either alone or as a suffix includes straight chained or branched structures. These groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms “alkenyl” and “alkynyl” refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms, such as up to 10, up to 7, or up to 5 carbon atoms. Terms such as “alkoxy” comprise alkyl groups as are understood in the art and in particular alkyl groups as defined, more particularly of up to 6 carbon atoms.

The term “halo” includes fluoro, chloro, bromo and iodo.

References to aryl groups include aromatic carbocyclic groups such as phenyl and naphthyl.

The term “heterocyclyl” includes aromatic or non-aromatic rings, for example containing from 4 to 20, for example of up to 16, or up to 10 ring atoms, suitably from 5 to 8 ring atoms, such as 5, 6 or 7 ring atoms, in each case at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thieryl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoazolyl, benzothienyl or benzofuryl.

“Heteroaryl” refers to those groups described above which have an aromatic character. The term “arylalkyl” refers to aryl substituted alkyl groups of up to 20 carbon
atoms, such as up to 15 or up to 10 carbon atoms, in particular phenethyl or benzyl, more particularly benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any organic structure comprising carbon and hydrogen atoms. For example, these may be any one of alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl. In particular these may be C_{1-10} alkyl, such as C_{1-6} alkyl or C_{1-4} alkyl or C_{1-10} alkoxy, such as C_{1-6} alkoxy or C_{1-4} alkoxy.

The term "functional group" refers to reactive substituents. They may comprise electron-donating or electron-withdrawing. Examples of such groups include halo, cyano, nitro, C(O)_nR^{18}, OR^{18}, S(O)_nR^{18}, NR^{19}R^{20}, C(O)NR^{19}R^{20}, OC(O)NR^{19}R^{20}, -NR^{19}C(O)_nR^{18}, -NR^{18}CONR^{19}R^{20}, -N=CR^{19}R^{20}, S(O)_mNR^{19}R^{20} or -NR^{19}S(O)_mR^{18} where R^{18}, R^{19} and R^{20} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{19} and R^{20} together form an optionally substituted ring of up to 10, up to 7 or up to 5 ring atoms which optionally contains 1 or 2 further heteroatoms such as S(O)_m, oxygen and nitrogen, n is an integer of 1 or 2, m is 1 or 2.

In a further aspect of the invention we provide a compound of the formula (I) as defined above and with the proviso that R^4 is a group selected from NO_2, NHR^{14}, NHCHR^{14}R^{15}, NHC(X^1)NHR^{16}, and NHCONH SO_2R^{17} wherein X^1, R^{14}, R^{15}, R^{16} and R^{17} are as hereinbefore defined.

Suitably R^1 is an optionally substituted phenyl, pyridyl, naphthyl, furyl or thiényl ring, and in particular is a substituted phenyl or pyridyl or thiényl ring, such as a substituted phenyl or pyridyl ring, or a substituted phenyl ring.

Suitable optional substituents include alkyl, alkenyl, alkynyl, halo, haloalkyl including perhaloalkyl such as trifluoromethyl, mercapto, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, hydroxyalkoxy, alkoxyalkoxy, alkanoyl, alkanoyloxy, cyano, nitro, amino, mono- or di-alkyl amino, oximinio, sulphonamido, carbamoyl, mono or dialkylcarbamoyl or S(O)_mR^{21} where m is as defined above and R^{21} is hydrocarbyl.

Particular substituents include trifluoromethyl, C_{1-4}alkyl, halo, trifluoromethoxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, nitro, carbamoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanil, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, sulphonamido, carbamoylC_{1-4}alkyl, N-(C_{1-4}alkyl)carbamoylC_{1-4}alkyl, N-(C_{1-4}alkyl)carbamoyl-C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.
Additionally or alternatively, two such substituents together may form a divalent radical of the formula \(-O(CH_2)_4O^-\) attached to adjacent carbon atoms on a ring.

Preferred substituents for the ring in \(R^1\) are one or more non-polar substituents such as halo.

In particular, \(R^1\) is substituted by one or more halo groups such as two halo groups or three halo groups, particular two halo groups. Particular halo groups are chlorine, bromine and fluorine, such as chlorine and bromine, chlorine and fluorine, and bromine and fluorine. Chlorine is a particular halo group. A particular example of an \(R^4\) group is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chlorophenyl, 3-fluoro-phenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 3,5-dichlorophenyl.

Examples of groups \(R^2\) include carboxy, cyano, tetrazol-5-yl, \text{C(O)NH}_2SO_2R^9, \text{CONHR^8} where \(R^8\) is selected from alkyl, aryl, heteraryl and heterocyclic, or \(R^8\) is a group-(CHR\(^{13}\))\(_{-}\text{COOH}\) where \(r\) is an integer of 1-3 and each \(R^{13}\) group is independently selected from hydrogen or alkyl such as C\(_{1,4}\) alkyl; \(R^9\) is optionally substituted alkyl or optionally substituted aryl such as optionally substituted phenyl or is optionally substituted heterocyclic; or \(R^2\) is a group of formula (VI)

![Chemical structure](attachment:image.png)

(VI)

where \(R^{10}\), \(R^{11}\) and \(R^{12}\) are independently selected from hydrogen or alkyl, particularly C\(_{1,4}\) alkyl or a halogen.

Conveniently \(R^2\) is carboxy or a pharmaceutically acceptable salt or ester thereof; or \(-\text{C(O)NH}_2SO_2R^9\), or tetrazol-5-yl.

Conveniently \(R^2\) is carboxy or a pharmaceutically acceptable salt or ester, or a group of formula (VI) above.

Suitable groups \(R^3\) include hydrogen, fluoro, chloro, bromo, iodo, methyl, benzyl, cyano, trifluoromethyl, hydroxymethyl, alkoxymethyl such as C\(_{1,4}\) alkoxymethyl, methoxy, benzyloxy, carboxyalkoxy such as carboxymethoxy, methylsulphanil, methylsulphinyl, methylsulphonyl or carboxyC\(_{3,6}\)cycloalkyl, -(CHR\(^{22}\))\(_{-}\text{NR}^{23}\text{R}^{24}\) (where \(r\) is 0-2, each \(R^{22}\) is
independently hydrogen or alkyl, in particular C\textsubscript{1-4} alkyl, R\textsuperscript{23} and R\textsuperscript{24} are independently selected from H and C\textsubscript{1-4}alkyl or R\textsuperscript{23} and R\textsuperscript{24} together with the nitrogen to which they are attached form a 5 or 6 membered ring optionally containing one further heteroatom selected from O, N, S, S(O) or SO\textsubscript{2}. Suitably R\textsuperscript{23} and R\textsuperscript{24} together form a heterocyclic ring such as morpholino or piperazinyl.

Other such groups R\textsuperscript{3} include optionally substituted aryl groups, such as optionally substituted phenyl or naphthyl group. Suitable substituents for phenyl groups R\textsuperscript{3} include one or more groups selected from chlorine, fluorine, methyl, trifluoromethyl, trifluoromethoxy, amino, formyl, phenyl, methoxy, phenoxy or phenyl.

R\textsuperscript{3} may comprise a range of substituents as listed above, in particular, hydrogen or a small substituent group such as C\textsubscript{1-4}alkyl in particular methyl, or benzyl or trifluoromethyl, and is preferably hydrogen.

R\textsuperscript{4} may conveniently comprise a group NO\textsubscript{2}, NH\textsubscript{2}, NHSO\textsubscript{2} R\textsuperscript{15}, NHC(X\textsuperscript{1})NHR\textsuperscript{16}, or NHCH R\textsuperscript{14}R\textsuperscript{15} wherein R\textsuperscript{14}, R\textsuperscript{15}, R\textsuperscript{16} and X\textsuperscript{1} are as previously defined. More conveniently R\textsuperscript{14} is hydrogen. More conveniently R\textsuperscript{15}, R\textsuperscript{16} and R\textsuperscript{17} are independently optionally substituted aralkyl, aryl, heterocyclyl or heteroaryl, such as phenyl or pyridyl, especially phenyl, optionally substituted by one or more of halogen, CF\textsubscript{3}, OCF\textsubscript{3}, NO\textsubscript{2}, NH\textsubscript{2}, and C\textsubscript{1-6} alkyl.

Suitably, where R\textsuperscript{4} is a group NHCHR\textsuperscript{14}R\textsuperscript{15}, R\textsuperscript{14} is hydrogen or alkyl or aryl or an optionally substituted aryl or an optionally substituted heteroaryl ring such as an optionally substituted 5 or 6 member heteroaryl groups, R\textsuperscript{15} is hydrogen or alkyl or aryl or an optionally substituted aryl or an optionally substituted heteroaryl ring such as an optionally substituted 5 or 6 member heteroaryl groups.

Suitable optional substituents for hydrocarbyl groups R\textsuperscript{18}, R\textsuperscript{19} and R\textsuperscript{20} include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, arylxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or S(O)nR\textsuperscript{x} where n is as defined above and R\textsuperscript{x} is alkyl such as C\textsubscript{1-4} alkyl.

Suitable substituents for these hydrocarbyl or heterocyclic groups include those listed above for R\textsuperscript{18}, R\textsuperscript{19} and R\textsuperscript{20}.
Suitable optional substituents for the group $R^{14}$, $R^{15}$, $R^{16}$ and $R^{17}$ as they appear in the definition of $R^4$, include functional groups as hereinbefore defined, as well as aryl or heterocyclic groups, either of which may themselves be substituted by one or more functional groups or further aryl or heterocyclic groups.

Particular examples of substituents for groups $R^{15}$, $R^{16}$ and $R^{17}$ include one or more groups selected from halo such as chloro; hydroxy; cyano; amino; mono- or di-alkylamino; $C_{1-4}$ alkoxy; carboxy; sulphonamido; $\text{CONH}_2$; alkylamido where the alkyl moiety is optionally substituted for example with a functional groups such as carboxy; morpholino; pyridyl; pyrimidinyl; phenyl optionally substituted by halo such as chloro, hydroxy, alkoxy such as methoxy, carbamoyl, acyl such as acetyl, or hydroxyalkyl where the alkyl group suitably includes at least two carbon atoms, such as hydroxyethyl. Other examples of substituents for phenyl groups $R^{15}$ is alkanoylamino group such as methylylamino.

Where $R^{15}$, $R^{16}$ and/or $R^{17}$ is a heterocyclic group, or where $R^{16}$ and $R^{17}$ together form an optionally substituted heterocyclic ring, these may be substituted by functional groups such as halo or hydroxy, or by alkyl groups such as methyl or ethyl, or alkenyl or alkynyl groups any of which may be substituted, for example with hydroxy, as well as with further heteroaryl groups such as pyridyl. Particular examples of heterocyclic groups $R^{15}$, $R^{16}$ and/or $R^{17}$ are optionally substituted thiophenyl, optionally substituted imidazolyl, optionally substituted pyridyl.

Thus thiophenyl groups $R^{15}$, $R^{16}$ and/or $R^{17}$ may comprise pyridyl-thiophenyl, whilst an example of a substituted imidazolyl group for $R^{15}$, $R^{16}$ and/or $R^{17}$ is methylimidazolyl and halopyridyl in particular chloropyridyl is an example of a substituted pyridyl moiety for these groups.

Particular examples of $R^{15}$ include alkyl in particular methyl optionally substituted by a functional groups or, in particular, a heterocyclic group where the heterocyclic group may be optionally substituted by a functional group such as halo or hydroxy or by an alkyl group such as methyl. Preferably, $R^{15}$ is a substituted alkyl group. Where the substitutent is a functional group, it is preferably a group of formula $NR^{19}R^{20}$ where $R^{19}$ and $R^{20}$ are as defined above. Thus examples of substituted alkyl groups $R^{15}$ include morpholinomethyl or alkyl such as methyl substituted with a substituted alkyl amino group wherein the substituents include carboxy, alkanoyl, phenyl or alkyl sulphonyl.
Other examples of R\textsuperscript{15} are heterocyclyl groups which are optionally substituted for example by alkyl such as methyl, functional groups such as chloro or heterocyclyl groups such as pyridyl.

Particular examples of R\textsuperscript{16} and R\textsuperscript{17} are alkyl such as methyl.

Particular examples of substituents R\textsuperscript{5}, R\textsuperscript{6} and R\textsuperscript{7}, and where appropriate also R\textsuperscript{4} include hydrogen, hydroxy, halo, optionally substituted alkyl such as aralkyl, carboxyalkyl or the amide derivative thereof; alkoxy; arylox ; aralkyloxy; or an amino group which is optionally substituted with alkyl, aryl or aralkyl.

Particular examples of groups R\textsuperscript{5}, R\textsuperscript{6} and R\textsuperscript{7} are hydrogen, hydroxy, halogen, alkyl or alkoxy, such as hydrogen. In particular R\textsuperscript{6} and R\textsuperscript{7} are hydrogen. R\textsuperscript{5} may be hydrogen but in addition is suitably a small substituent such as hydroxy, halo or methoxy. Also R\textsuperscript{7} may be halogen such as chlorine or bromine, alkyl such as ethyl or methyl, alkoxy such as ethoxy or methoxy.

X is independently a bond or CH\textsubscript{2}, preferably CH\textsubscript{2}.

Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

An in vivo hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, such as C\textsubscript{1-6} alkyl esters for example, ethyl esters, C\textsubscript{1-6}alkoxymethyl esters for example methoxyethyl, C\textsubscript{1-6}alkanoylexymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C\textsubscript{3-4}cycloalkoxy-carbonyloxyC\textsubscript{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example
5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>4</sub> alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically acceptable esters of compounds of formula (I) are in vivo hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the in vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carbamoyacetil.

Esters which are not in vivo hydrolysable are useful as intermediates in the production of the compounds of formula (I) and therefore these form a further aspect of the invention.

Compounds of formula (I) are suitably prepared by methods such as those described in International Patent Application Nos. PCT/GB98/02340, PCT/GB98/02341, WO-01/51466, WO-01/51467, WO-00/46195 and by conventional literature methods.

In particular compounds of formula (I) where R<sup>4</sup> is NHCOR<sup>15</sup> or NHSO<sub>2</sub>R<sup>15</sup> can be prepared by reacting a compound of formula (VII)

![Diagram](image)

(VII)

where X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>7</sup> are as defined in relation to formula (I), R<sup>2</sup>' is a group R<sup>2</sup> as defined in relation to formula (I) or a protected form thereof, with a compound of formula (VIII)

Z-R<sup>22</sup>
(VIII)

where Z is a leaving group and \( R^{22} \) is a group \( \text{COR}^{15'} \) or \( \text{SO}_2R^{15'} \) where \( R^{15'} \) is group \( R^{15} \) as
defined in relation to formula (I) or a precursor thereof;
and thereafter if desired or necessary:

5 (i) converting a precursor group \( R^{15'} \) to a group \( R^{15} \) and/or converting a group \( R^{15} \) to a
different such group;
(ii) deprotecting a group \( R^{2'} \) to a group \( R^{2} \).

Suitable leaving groups \( Z \) include halo such as chloro.

The reaction is suitably effected in an organic solvent such as dichloromethane or
tetrahydrofuran in the presence of a base such as triethylamine or pyridine. Moderate
temperatures, for example from 0° to 50°C and conveniently ambient temperature, are
employed in the reaction.

Compounds of formula (I) where \( R^{4} \) is a group \( \text{NHC}(X^{1})\text{NHR}^{16} \) may be prepared
by a broadly similar method by the reaction of a compound of formula (VII) and a

compound of the formula (VII A)

\[
R^{16}\text{NC}(X^{1})
\]

(VII A)

where \( X^{1} \) and \( R^{16} \) are as defined above.

The reaction is suitably effected in an organic solvent such as dichloromethane or
chloroform in the presence of a base such as triethylamine or pyridine. Moderate
temperatures, for example from 0° to 50°C and conveniently ambient temperature, are
employed in the reaction.

Compounds of formula (I) where \( R^{4} \) is a group \( \text{NHCONHSO}_2R^{17} \) may be prepared
by a broadly similar method by the reaction of a compound of formula (VII) and a

compound of the formula (VII B)

\[
R^{17}\text{SO}_2\text{NCO}
\]

(VII B)

where \( R^{17} \) are as defined above.

The reaction is suitably effected in an organic solvent such as dichloromethane or
chloroform in the presence of a base such as triethylamine or pyridine. Moderate
temperatures, for example from 0° to 50°C and conveniently ambient temperature, are
employed in the reaction.
Compounds of formula (I) where R² is a group CONHSO₂R⁹ may be prepared by a broadly similar method by the reaction of a compound of formula (VII C) and a compound of the formula (VII D)

![Chemical Structure](image)

(VII C)

R² SO₂NH₂

(VII D)

where R¹, R³, R⁴, R⁵, R⁶, R⁷ and R⁹ are as defined above.

The reaction is suitably effected in an organic solvent such as dimethylformamide in the presence of a base such as DMAP and a coupling reagent like EDCI. Moderate temperatures, for example from 0° to 50°C and conveniently ambient temperature, are employed in the reaction.

Compounds of formula (I) where R⁴ is a group NHCHR¹⁴R¹⁵ may be prepared by a broadly similar reductive amination method of a compound of formula (VII) and a carbonyl compound of the formula (VIII)

OCR¹⁴R¹⁵

(VIII)

where R¹⁴ and R¹⁵ are as defined above.

This reductive amination reaction is suitably effected in an organic solvent such as methanol or ethanol in the presence of acetic acid and a reducing agent such as NaCNBH₃. Moderate temperatures, for example from 0° to 50°C and conveniently ambient temperature, are employed in the reaction.
Compounds of formula (VII) are suitably prepared from compound IX by the conversion of nitro group to amino group.

\[
\begin{align*}
\text{R}^2', \text{R}^3, \text{R}^5, \text{R}^6 \text{ and } \text{R}^7 & \text{ are as defined above} \\
\text{Compounds of formula (IX) can be prepared by reacting a compound of formula (X)}
\end{align*}
\]

\[
\begin{align*}
\text{with compound of formula (XI)} \\
\text{R}^1\cdot X \cdot Z^1
\end{align*}
\]

\[
\begin{align*}
\text{R}^1, \text{R}^3, \text{R}^5, \text{R}^6 \text{ and } \text{R}^7 & \text{ are as defined in relation to formula (I) and } \text{R}^2' \text{ is as defined in relation to formula (VII) and } X \text{ are as defined in relation to formula (I) and } Z^1 \text{ is a leaving group.}
\end{align*}
\]

Compounds of formula (XII)
can be prepared by reacting a compound of formula (XIII) with trimethylsilylazide or sodium azide in presence of dibutyltin oxide.

where $X, R^1, R^3, R^4, R^5, R^6, R^7$ and $R^9$ are as defined above.

The reaction is suitably effected in an organic solvent such as toluene. High temperatures, for example from 50°C to 120°C and conveniently refluxing conditions, are employed in the reaction.

Compounds of formula (XIII) can be prepared by reacting a compound of formula (XIV) with phosphorous oxychloride.

where $X, R^1, R^3, R^4, R^5, R^6, R^7$ and $R^9$ are as defined above.
The reaction is suitably effected by refluxing the solution of XIV in phosphorous oxychloride.

The compounds of the formula (XIV) can be prepared from the corresponding acids by conventional methods.

Compounds of formula (X) are either known compounds or they may be prepared from known compounds by conventional literature methods.

According to a further aspect of the invention there is provided a compound of the formula (I) as defined herein, or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of Tb.

According to a further aspect of the present invention there is provided a treatment method for M.Tb by inhibiting RNA polymerase, which comprises administering to said human or animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, or an in vivo hydrolysable ester thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt, or an in vivo hydrolysable ester thereof, in combination with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium
carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and
flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butandiol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a
conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients that may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in
treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of rats.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

**Materials and Methods:**

**Purification of native pure RNA polymerases:**

Due to operational hazards involved in handling and processing of *M. tuberculosis* cultures, this enzyme was purified in its native form from a closely related, non-pathogenic, surrogate species like *Mycobacterium bovis* BCG Pasteur-Meriux (PM). *M. tuberculosis* and *M. bovis* BCG (PM) share >99% amino acid sequence identity for all the four subunits of RNA polymerase. Purification methods were standardized to get the purified enzyme in its core form (without sigma subunit). The housekeeping sigma factor, σ A of *M. tuberculosis*, was cloned, expressed and purified from E.coli BL21DE3. Holoenzyme consisting of recombinant σA and core RNA polymerase from *M. bovis* BCG (PM) was reconstituted *in vitro* and used for the screening.

Native core RNA polymerase was purified as follows: Frozen cell pellet (40 g wet weight) was resuspended in 120 ml of TGED (25 mM Tris.Cl pH 8.0, 5 % w/v glycerol, 0.1 mM EDTA.Na2, 1 mM DTT, 1 mM PMSF and 1 mM NaN3) buffer and and passed through the French pressure cell (AMINCO Co.) for cell lysis using a single pass at 16,000 psi. After lysis, 120 ml of TGED was added and the viscosity of the lysate was reduced using a Branson sonifier. Sonication was performed using a macroprobe, at the output of 5 and 50% duty cycle, in 3 cycles of 5 min each. Cell debris was removed by centrifugation at 10,000 X g for 15 min. To the supernatant, 10% w/v polyethyleneimine (PEI) was added slowly while mixing to make the final concentration to 0.8% and mixed at 4°C for 5 min. Nucleic acid precipitate was removed by centrifugation at 6000 X g for 10 min., washed
with 200 ml of TGED buffer containing 0.5 M NaCl and the bound RNA polymerase was eluted in 200 ml of TGED buffer containing 1.0 M NaCl. Precipitate was removed by centrifugation as above and the supernatant was used for ammonium sulfate precipitation. Proteins in the supernatant were precipitated using 60% saturated ammonium sulfate solution and the precipitate was removed by centrifugation at 12,500 X g for 45 minutes. Ammonium sulfate pellet was resuspended gradually in buffer A (I) (TGED buffer at pH 7.6) and dialyzed overnight against the same buffer. Dialysate was clarified by centrifugation at 12,500 X g for 45 minutes and loaded onto 60 ml anion exchange chromatography column (DEAE Sepharose Fast Flow) equilibrated with buffer A (I). Flow rate used was 2.5 ml/min. OD was monitored at 260 and 280 nm. Column was washed with 120 ml of buffer A(I) and bound proteins were eluted with a five column volume gradient of 0 – 100 % B (TGED buffer, pH 7.6 plus 0.6 M NaCl). Fractions (10 ml each) were collected and checked for the enzyme activity. Desired fractions were pooled and loaded on 15 ml ds-DNA cellulose column after adjusting the conductivity to that of buffer A(D) (TGED buffer, pH 8.0 plus 150 mM NaCl). Flow rate used was 0.5 ml/min. OD was monitored at 260 and 280 nm. Column was washed with 30 ml (2 column volumes) of buffer A(D) and the bound proteins were eluted with a 5 column volume gradient of 0 – 100 % B (TGED buffer, pH 8.0 plus 600 mM NaCl). Active fractions were pooled, concentrated by ultrafiltration (NMWL of 10,000) and dialysed overnight against the predialysis buffer (50 mM Tris.Cl, pH 7.6, 50 mM KCl, 5 mM DTT, 1 mM NaN3, 1 mM PMSF, 5 % (v/v) glycerol) followed by the storage buffer (50 mM Tris.Cl, pH 7.6, 50 mM KCl, 5 mM DTT, 1 mM NaN3, 1 mM PMSF, 50 % (v/v) glycerol).

Recombinant M.tuberculosis σA containing plasmid, pARC 8171 was transformed into BL-21 (DE3) cells and grown in Terrific Broth with 50μg/ml of Kanamycin at 37°C on a shaker in baffled flasks and induced at an OD₆₀₀ of 0.6 with 100μM IPTG for 2 hours. Cells were pelleted and stored at -70°C until processed further. For the purification of σA, frozen cell pellet was resuspended in 1X PBS and the cells were lysed using a French Pressure Cell at 16000 psi. Cell lysate was centrifuged at 17,500Xg for 30 min at 4°C. SigmaA was present mostly in the form of inclusion bodies. This inclusion body pellet was resuspended in 1X PBS and purified using a discontinuous sucrose gradient (67%(3ml): 53%(3ml): 40%(4ml)). Two ml of the resuspended pellet overlayed on this gradient and centrifuged at 100,000Xg for 2 hrs. Inclusion bodies at the interface of 67% and 53 %
sucrose were removed using a syringe and washed twice with 0.5% Triton-X-100 in 1X PBS. Washed inclusion bodies were denatured with the denaturation buffer (50 mM Tris-Cl pH 8.0, 6 M Guanidine HCl, 10% Glycerol, 10 mM Magnesium Chloride, 10 mM Zinc Chloride, 1 mM EDTA, and 10 mM DTT) and the insoluble part was removed by centrifugation at 100,000 X g. Denatured Protein was refolded by dialysis against the renaturation buffer (50 mM Tris-Cl pH 8.0, 200 mM KCl, 20% Glycerol, 10 mM Magnesium Chloride, 10 mM Zinc Chloride, 1 mM EDTA, and 1 mM DTT) until the concentration of Guanidine HCl reached 25 mM or less. The insoluble protein was removed by centrifugation at 100,000 X g and the supernatant containing the refolded σA was dialysed against the storage buffer.

All the purified proteins were checked for the nuclease contamination and stored at -70°C.

**Enzyme Assay:**

In vitro transcription assay used for the screening of inhibitors was performed in 96 well Corning costar plates. Genomic DNA of the phage T4 was used as template. The assay buffer was composed of 50 mM Tris-Cl, pH 8.0, 50 mM KCl, 0.1 mM DTT, 12.5 mM MgCl2, 0.05 mM EDTA and 2% (v/v) glycerol. The assay mixture contained 2.5 μg/ml of core RNA polymerase, 5 μg/ml of recombinant σA, 20 μg/ml of T4 phage DNA, 500 μM (each) of ATP, GTP, UTP and 20 μM of [³H-CTP] in assay buffer. Holoenzyme was reconstituted by incubating core RNA polymerase with σA on ice for 10 minutes, before adding to the assay mixture. Additions to the 96 well plate were made in the following order- DNA followed by compound in 5% DMSO followed by the reconstituted holoenzyme and nucleotides in assay buffer. The assay plate was sealed with the plate sealer and incubated at 37°C for 30 min to 1 hr. Reaction was stopped by the addition of 10 ul of stop mix containing 140 mM EDTA and 1500 μg/ml of t-RNA. In order to precipitate the labelled RNA product, 215 ul of 12% TCA was added to each well and the plate was kept at 4°C for 1 hr. RNA precipitate was filtered onto GF-B membranes in 96 well MultiScreen plates. Unincorporated label was removed by three washes with 5% TCA and two washes with 95% ethanol. Plates were dried overnight at room temperature. Next day, 50 ul of the scintillation fluid (Optiphase) was added to each well and the plate was counted using Trilux.
When tested in the above enzyme assay all the exemplified compounds have an IC$_{50}$ of less than 50 µM.

The invention will now be illustrated but not limited by reference to the following Examples.
Example 1

N-{[(1-(3-chlorobenzyl)-4-nitro-1H-indol-2-yl) carbonyl] thiophene-2-sulfonamide

\[
\begin{align*}
\text{N} & \quad \text{O}^+ \quad \text{O}^- \\
\text{O} & \quad \text{N} \quad \text{S} \quad \text{O} \\
\text{Cl} & \quad \text{O} \\
\end{align*}
\]

1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxylic acid (0.3105mmol) was dissolved in THF, 4-Dimethyl amino pyridine (0.3726mmol), thiophene-2-sulfonamide (0.6211mmol), EDCI (0.3726mmol) (1-(3-(Dimethylamino) propyl)-3-ethylcarbodiimide hydrochloride), were added. The reaction was stirred for 4 hours. The progress of the reaction was monitored by TLC (30%ethylacetate in hexane) for the absence of starting indole-2-carboxylic acid. Removed THF under vacuum. Then the reaction mixture was partitioned between water and ethyl acetate. Combined organic extracts were dried over anhydrous NaSO4 and concentrated in vacuo and the residue purified by flash chromatography using hexane-40% ethyl acetate as eluent to give the desired end product in 65% yield. MS; (ES+) = 475.92/(ES-) = 473.95, 1HNMR(DMSO, ppm): 6.09(s, 2H, NCH2); 6.99-7.19(m, 2H,CH2); 7.25-7.39(m, 5H,); 7.48(d, 1H); 7.56-7.59(m, 2H); 7.98(s, 1H); 8.08(s, 1H).
Example 2
N-[(4-amino-1-(3-chlorobenzyl)-1H-indol-2-yl) carbonyl] thiophene-2-sulfonamide

N-[(1-(3-chlorobenzyl)-4-nitro-1H-indol-2-yl) carbonyl] thiophene-2-sulfonamide
(8.5393 mmol) was dissolved in ethanol, aqueous 2M ammonium chloride solution
(25.6179 mmol) and iron powder (17.0786 mmol) were added. The reaction was heated at
75°C for 4 hours, and then the progress of the reaction was monitored by TLC
(20%ethylacetate in hexane). Filtered the reaction mixture over celite and concentrated in
vacuo. Then the reaction mixture was partitioned between water and ethyl acetate.
Combined organic extracts were dried over anhydrous Na2SO4 and concentrated in vacuo
and the residue purified by flash chromatography using hexane-20% ethyl acetate as eluent
to give the desired end product in 84% yield. MS; (ES+)=445.98/(ES-)
=444.00,1HNMR(DMSO, ppm): 5.39(s, 2H, NH2); 6.09(s, 2H, NCH2); 6.99-7.19(m,
2H,CH2); 7.25-7.39(m, 5H,); 7.48(d, 1H); 7.56-7.59(m, 2H); 7.98(s, 1H); 8.08(s, 1H).
Example 3
1H-indole-2-carboxylic acid, 1-[(3-chlorophenyl) methyl]-4-[[4-(1,1-dimethylethyl) phenyl] sulfonyl] amino]-

Ethyl 4-amino-1- (3-chlorobenzyl)-1H-indole-2-carboxylate (0.6082 mmol) was dissolved in dry methylene chloride (5.0ml), 4-t-butyldimethylbenzene sulfonyl chloride (0.7299 mmol) and pyridine (0.7299 mmol) were added in a single portion. The reaction was stirred for 8 hours. Then the progress of the reaction was monitored by TLC (20% ethyl acetate in hexane) for the absence of starting 4-amino indole. Removed methylene chloride under vacuum and the residue purified by flash chromatography using hexane-20% ethyl acetate as eluent to give the corresponding ester product in 91% yield. Then the ester was taken for hydrolysis as described in example H protocol to yield the acid in 98% yield. MS; (ES+) =497.0; (ES-) =494.8; 1H NMR (DMSO, ppm): 1.25(s, 9H, C (CH3) 3); 5.75(s, 2H, NH2); 6.85-7.15(m, 3H,); 7.25-7.65(m, 9H); 10.35(s, 1H, NH); 13.1(s, 1H, COOH).
Example 4
1-(3-chlorobenzyl)-4-(((4-nitrophenyl) amino) carbonothioyl) amino)-1H-indole-2-carboxylic acid

Ethyl 4-amino-1- (3-chlorobenzyl)-1H-indole-2-carboxylate (0.6082 mmol) was dissolved in dry methylene chloride (5.0ml); p-nitrophenyl isothiocyanate (0.7299 mmol) and pyridine (0.7299 mmol) were added in a single portion. The reaction was stirred for 8 hours. Then the progress of the reaction was monitored by TLC (20%ethylacetate in hexane) for the absence of starting 4-amino indole. Removed methylene chloride under vacuum and the residue purified by flash chromatography using hexane-20% ethyl acetate as eluent to give the corresponding ester product in 94% yield. The ester obtained was taken for hydrolysis using example H protocol in 98% yield. MS; (ES+) =481.0;(ES-) =478.8; 1HNMR(DMSO, ppm): 5.85(s, 2H, NCH2); 7.0(s, 1H); 7.15-7.35(m, 5H,arom); 7.6-7.8(m, 4H,arom); 8.2-8.3(m, 2H,arom); 10.3(s, 1H,NH); 10.4(s, 1H,NH); 13.0(s, 1H,COOH).

The procedure described in above was repeated using the appropriate amino ester and corresponding thioisocyanates, isocyanates and sulfonlisocyanates. Then the corresponding ester products obtained were taken for hydrolysis. Thus there were obtained the compounds described in Examples 5 and 6 below.
Example 5
1-(3-chlorobenzyl)-4-(((4-isopropylphenyl) amino] carbonyl) amino)-1H-indole-2-carboxylic acid

92% yield. MS; (ES+) = 462.07; (ES-) = 460.08; 1HNMR(DMSO, ppm): 1.1-1.25(m, 6H, 2CH3); 2.75-2.85(m, 1H, CH); 5.9(s, 2H, NCH2); 7.0(d, 1H); 7.05-7.25(m, 5H, arom); 7.25-7.4(m, 3H, arom); 7.45-7.50(m, 2H, arom); 7.7(s, 1H, arom); 7.85(s, 1H, arom); 9.1(s, 1H, arom).
Example 6
1H-indole-2-carboxylic acid, 1-[(3-chlorophenyl) methyl]-4-[[[(phenylsulfonyl) amino]carbonyl]amino]-, ethyl ester

$$\text{N}$$

$$\text{O}$$

Cl

$$\text{N}$$

$$\text{O}$$

$$\text{O}$$

MS: ([ES+]) = 512.2; ([ES-]) = 509.8 1HNMR(DMSO, ppm): 1.25-1.35 (m, 3H, CH3); 4.15-4.35 (m, 2H, OCH2); 5.75 (s, 2H, NCH2); 6.85 (t, 1H); 7.05-7.15 (m, 2H, arom); 7.25-7.35 (m, 3H, arom); 7.5-7.75 (m, 5H, arom); 8.0 (d, 2H, arom); 9.05 (s, 1H, NH); 10.8 (s, 1H, NH).
**Example 7**

1-(3-chlorobenzyl)-4-([4-(trifluoromethoxy) benzyl] amino)-1H-indole-2-carboxylic acid

Ethyl 4-amino-1-(3-chlorobenzyl)-1H-indole-2-carboxylate (0.6082 mmol) was dissolved in dry methanol (5.0ml), 4-trifluoromethoxy benzaldehyde (0.7299 mmol) and glacial acetic acid (0.6082 mmol) were added in a single portion. The reaction was stirred for 1/2 hour, and then sodiumcyanoborohydride (0.6082 mmol) was added. Stirring was continued for a further 16 hours and then the progress of the reaction was monitored by TLC (20%ethylacetate in hexane) for the absence of starting 4-amino indole. Removed methanol under vacuum and the residue after ester hydrolysis was purified by flash chromatography using hexane-20% ethyl acetate as eluent to give the desired end product in 98% yield. MS; (ES+) =475.0; (ES-) =473.0; 1HNMR(DMSO, ppm): 4.3(d, 2H, CH2); 5.75(s, 2H, NCH2); 6.35(s, 1H,arom); 6.65-6.7(m, 2H, arom); 6.95-7.55(m, 10H, arom); 12.55(s, 1H, COOH).

The procedure described above was repeated using the appropriate amino indole ester compounds. Thus there were obtained the compounds described in Examples 8-29 below.
Example 8

1-(3-chlorobenzyl)-4-[(4-isopropylbenzyl) amino]-1H-indole-2-carboxylic acid

94% yield. MS; (ES+) =433.2; (ES-) =431.2 1HNMR(DMSO, ppm): 1.05-1.30 (m, 6H, C (CH3) 2); 2.75-2.90(s, 1H, CH); 4.20(s, 2H, NCH2); 5.75(s, 2H, NCH2); 6.35(m, 3H, arom); 6.8-7.6(m, 10H, arom); 12.55(s, 1H, COOH).
**Example 9**

1-(3-chlorobenzyl)-4-[(4-(trifluoromethyl) benzyl) amino]-1H-indole-2-carboxylic acid

95% yield. MS; (ES+) = 459.2; (ES-) = 457.2; 1HNMR(DMSO, ppm): 4.45(d, 2H, NH2); 5.65(s, 2H, NH2); 6.35(s, 1H, arom); 6.65(m, 2H); 6.85(d, 1H, arom); 7.0(s, 1H,); 7.15(s, 1H); 7.2-7.25(m, 2H); 7.35(d, 1H); 7.5-7.7(m, 4H).
Example 10

1-(3-chlorobenzyl)-4-[(4-ethylbenzyl) amino]-1H-indole-2-carboxylic acid

95% yield. MS; (ES+) =419.2; (ES-) =417.2; 1H NMR (DMSO, ppm): 1.15 (t, 3H, CH3); 2.55-2.6 (m, 2H, CH2); 4.25 (s, 2H, NCH2); 5.57 (s, 2H, NCH2); 6.35 (m, 2H); 6.6 (d, 1H, CH, arom); 6.9 (d, 1H, arom); 7.05-7.15 (m, 4H, arom); 7.25-7.4 (m, 5H, arom).
Example 11
4-[(4-tert-butylbenzyl) amino]-1-(3-chlorobenzyl)-1H-indole-2-carboxylic acid

93% yield. MS: (ES+)=447.2; (ES-)=445.2; 1H NMR (DMSO, ppm): 1.25 (s, 9H, C (CH3) 3); 4.25(s, 2H, NCH2); 5.57(S, 2H, NCH2); 6.35(m, 2H); 6.6(d, 1H, CH, arom); 6.9(d, 1H, arom); 7.1(d, 1H, arom); 7.25-7.4(m, 8H, arom).
Example 12

4-[[6-chloro-1, 3-benzodioxol-5-yl) methyl] amino]-1-(3-chlorobenzyl)-1H-indole-2-carboxylic acid

96% yield. MS: (ES+) = 469.2; (ES-) = 466.8; 1H NMR (DMSO, ppm): 4.25 (s, 2H, NCH2); 5.7 (s, 2H, NCH2); 6.0 (s, 2H, CH2); 6.25 (s, 1H); 6.5 (s, 1H, CH, arom); 6.65 (d, 1H, arom); 6.8-6.9 (m, 2H, arom); 6.95-7.05 (m, 2H, arom); 7.15 (s, 1H, arom); 7.25-7.3 (m, 2H, arom); 7.45 (d, 1H, arom); 12.6 (s, 1H, COOH).
Example 13

4-[(biphenyl-4-ylmethyl) amino]-1-(3-chlorobenzyl)-1H-indole-2-carboxylic acid

89% yield. MS; (ES+) =467.2; (ES-) =465.2; 1H NMR (DMSO, ppm): 4.3 (s, 2H, NCH2); 5.75 (s, 2H, NCH2); 6.40 (s, 1H, arom); 6.55 (s, 1H, arom); 6.65 (d, 1H, arom); 6.95 (d, 1H, arom); 7.05-7.15 (m, 2H, arom); 7.15-7.25 (m, 2H, arom); 7.35-7.70 (m, 10H, arom); 12.55 (s, 1H, COOH).
Example 14
1-(5-Chloro-thiophen-2-yl methyl)-4-(4-isopropyl-benzylamino)-1H-indole-2-carboxylic acid

81% yield. MS; (ES+)=439.2, (ES-)=437.0; 1HNMR(DMSO-d6, ppm) 1.15(d, 6H, 2 X CH3); 2.85(q, 1H,CH); 4.35(d, 2H,CH2); 5.90(s, 2H, CH2); 6.0(d, 1H,NH); 6.65(s, 1H,arom); 6.8(d, 1H,arom); 6.95(m, 3H,arom); 7.15(d, 2H,arom); 7.3(d, 2H,arom); 7.4(s, 1H,arom).
Example 15

1-(3-chlorobenzyl)-4-[[5-(3-chlorophenyl)-2-furyl] methyl] amino)-1H-indole-2-carboxylic acid

93% yield. MS; (ES+) =491; (ES-) =489; 1HNMR(DMSO, ppm): 4.55(s, 2H, NCH2); 5.8(s, 2H, NCH2); 6.25(d, 1H, arom); 6.50(d, 1H, arom); 6.70-6.85(m, 2H, arom); 6.95-7.15(m, 4H, arom); 7.2-7.35(m, 3H, arom); 7.45(t, 1H, arom); 7.45(t, 1H, arom); 7.75-7.8(m, 2H, arom); 7.85(s, 1H, NH); 12.75(s, 1H, COOH). Purity by HPLC is 92.32%.
Example 16

1-(3-chlorobenzyl)-4-[(mesitylmethyl) amino]-1H-indole-2-carboxylic acid

90% yield. MS; (ES+) =433; (ES-) =431; 1HNMR(DMSO, ppm): 2.2-2.4(m, 9H, NCH2); 4.25(s, 2H, NCH2); 5.8(s, 2H, NCH2); 6.0(s, 1H, arom); 6.25(d, 1H, arom); 6.70(d, 1H, arom); 6.85-7.0(m, 3H, arom); 7.1-7.15(m, 2H, arom); 7.25-7.35(m, 2H, arom); 7.85(s, 1H, NH); 12.75(s, 1H, COOH).
Example 17
1-(3-chlorobenzyl)-4-[(4-pyrrolidin-1-ylbenzyl) amino]-1H-indole-2-carboxylic acid

88% yield. MS; (ES+) =460.08; (ES-)=458.11; 1HNMR(DMSO, ppm): 1.8-2.0(m, 4H); 3.15-3.25(m, 4H); 3.7(s, 2H, NCH2); 5.75(s, 2H, NCH2); 6.35-6.45(m, 2H); 6.55-6.90(m, 4H,arom); 7.0-7.15(m, 3H,arom); 7.2-7.35(m, 2H,arom); 7.6(d, 1H,arom).
Example 18
1-(3-chlorobenzyl)-4-[[4-(1,2,3-thiadiazol-4-yl) benzyl] amino]-1H-indole-2-carboxylic acid

88% yield. MS; (ES+) =473; (ES-) =475; 1HNMR(DMSO, ppm): 4.5(s, 2H,NCH2); 5.8(s, 2H, NCH2); 6.1(d, 1H); 6.7(d, 1H, arom); 6.9-7.05(m, 2H, arom); 7.1(s, 1H, arom); 7.15-7.35(m, 4H, arom); 7.55(d, 1H, arom); 7.7(s, 1H, arom); 8.1(d, 1H, arom); 9.6(s, 1H, arom).
Example 19
1-(3-chlorobenzyl)-4-[[4-(2-thienyl benzyl) amino]-1H-indole-2-carboxylic acid

89% yield. MS; (ES+) =472.93; (ES-) =471.03; 1HNMR(DMSO, ppm): 4.5(s, 2H,NCH2); 5.8(s, 2H, NCH2); 6.1(d, 1H); 6.7(d, 1H, arom); 6.7-6.95(m, 2H, arom); 7.05(d, 1H, arom); 7.1-7.15(m, 2H, arom); 7.2-7.3(m, 2H, arom); 7.4-7.55(m, 5H, arom); 7.55-7.65(m, 2H, arom).
Example 20

1-(3-chlorobenzyl)-4-[(3-chloro-4-fluorobenzyl) amino]-1H-indole-2-carboxylic acid

88% yield. MS; (ES+)=442.87, (ES-)=441.00; 1HNMR(DMSO, ppm): 4.4-4.45(m, 2H, NCH2); 5.8(s, 2H, NCH2); 6.0(d, 1H,arom); 6.7(d, 1H,arom); 6.9-7.1(m, 2H,arom); 7.1(s, 1H,arom); 7.25-7.5(m, 4H,arom); 7.6(d, 1H,CH); 7.7(s, 1H,NH); 12.8(bs, 1H,COOH).
Example 21
1-(3,5-Dichloro-benzyl)-4-(4-isopropyl-benzylamino)-1H-indole-2-carboxylic acid

90% yield. MS, (ES+)=467.2,(ES-)=465,1HNMR(DMSO-d6, ppm): 1.15(d, 6H, 2XCH3); 2.85(q, 1H,CH); 4.35(d, 2H,CH2); 5.8(s, 2H,CH2); 6.0(d, 1H,arom); 6.6(d, 1H,arom); 6.75(t, 1H,arom); 6.95(t, 2H,arom); 7.05(s, 2H,arom); 7.15(d, 2H,arom); 7.3(d, 2H,arom); 7.45(s, 1H,arom); 7.6(s, 1H,arom).

Example 22
4-[[3,5-bis (trifluoromethyl) benzyl] amino]-1-(3-chlorobenzyl)-1H-indole-2-carboxylic acid
94% yield. MS; (ES+) =527.20; (ES-)=524.80. 1H NMR(DMSO, ppm): 4.6(d, 2H, NCH2); 5.8(s, 2H,NCH2); 6.05(d, 1H,arom); 6.7(d, 1H,arom); 6.9-7.1(m, 4H,arom); 7.25-7.35(m, 2H,arom); 7.65(s, 1H,arom); 8.0(s, 1H,arom); 8.15(s, 2H,arom).

Example 23
1-(3-chlorobenzyl)-4-([(4-methoxy-1-naphthyl) methyl] amino)-1H-indole-2-carboxylic acid

92% yield. MS; (ES+) =471.20; (ES-)=469.0. 1H NMR(DMSO, ppm): 3.95(s, 3H, OCH3); 4.75(d, 2H, NCH2); 5.85(s, 2H,NCH2); 6.05(d, 1H,arom); 6.6(d, 1H,arom); 6.65(s, 1H,arom); 6.85-6.95(m, 2H,arom); 7.05(d, 1H,arom); 7.15(s, 1H,arom); 7.2-7.35(m, 2H,arom); 7.4-7.65(m, 4H,arom); 8.15-8.25(m, 2H,arom).
Example 24
1-(3-chlorobenzyl)-4-[(2-ethoxy-1-naphthyl) methyl] amino]-1H-indole-2-carboxylic acid

88% yield. MS; (ES+) = 485.20; (ES-) = 483.0. 1H NMR (DMSO, ppm): 1.4 (t, 3H, CH3); 4.25 (dd, 2H, OCH2); 4.75 (d, 2H, NCH2); 5.85 (s, 2H, NCH2); 6.35-6.5 (m, 2H, arom); 6.65 (d, 1H, arom); 6.95 (d, 1H, arom); 7.05-7.15 (m, 2H, arom); 7.2-7.55 (m, 5H, arom); 7.65 (s, 1H, arom); 7.8-7.95 (m, 2H, arom); 8.15 (d, 1H, arom).
Example 25

4-[[4-(benzyloxy)-2-methoxybenzyl] amino]-1-(3-chlorobenzyl)-1H-indole-2-carboxylic acid

96% yield. MS; (ES-) = 525.0.  1HNMR(DMSO, ppm): 3.85(s, 3H, OCH3); 4.30(s, 2H, NCH2); 5.05(s, 2H, OCH2); 5.85(s, 2H, NCH2); 6.35-6.65(m, 4H, arom); 6.85(t, 1H, arom); 7.0-7.15(m, 3H, arom); 7.2-7.5(m, 9H, arom). HPLC: 93.76%; 254nM.

Example 26

1-(3-chlorobenzyl)-4-[[4-isopropylbenzyl] amino]-7-methyl-1H-indole-2-carboxylic acid
75% yield MS:447(ES+), 1H NMR(CDCl3, 1.30(d, 6H), 2.50(s, 3H), 2.85-2.30(m, 1H), 4.49(s, 2H), 6.05(s, 1H), 6.30(d, 1H), 6.60(d, 1H), 6.90-7.00(m, 2H), 7.10-7.30(m, 4H), 7.35-7.45(m, 2H), 7.55(s, 1H).

Example 27
1-(3-chlorobenzyl)-7-fluoro-4-[(4-isopropylbenzyl)amino]-1H-indole-2-carboxylic acid

70% yield. MS:451(ES+), 1H NMR(CDCl3, 1.30(d, 6H), 2.85-2.30(m, 1H), 4.40(s, 2H), 6.00(s, 1H), 6.20(d, 1H), 6.65-6.70(m, 2H), 7.05(s, 1H), 7.15-7.30(m, 4H), 7.35-7.40(m, 2H), 7.55(s, 1H).

Example 28
7-bromo-1-(3-chlorobenzyl)-4-[(4-isopropylbenzyl)amino]-1H-indole-2-carboxylic acid
65% yield. MS: 513.2 (ES+), 1H NMR (DMSO), 1.20 (d, 6H), 2.80-2.95 (m, 1H), 4.40 (d, 2H), 6.00 (d, 1H), 6.30 (s, 1H), 6.75 (d, 1H), 6.90 (s, 1H), 6.95-7.05 (t, 1H), 7.10-7.20 (m, 3H), 7.25-7.45 (m, 4H), 7.85 (s, 1H).

Example 29
7-chloro-1-(3-chlorobenzyl)-4-[(4-isopropylbenzyl)amino]-1H-indole-2-carboxylic acid

86% yield. MS: 465 (ES-), 1H NMR (DMSO), 1.20 (d, 6H), 2.75-2.95 (m, 1H), 4.40 (d, 2H), 6.05 (d, 1H), 6.25 (s, 1H), 6.75 (d, 1H), 6.90 (s, 1H), 7.00 (d, 1H), 7.20 (d, 2H), 7.25-7.40 (m, 4H), 7.90 (s, 1H).

Example 30
1-(3-chlorobenzyl)-N-(4-isopropylbenzyl)-2-(1H-tetrazol-5-yl)-1H-indol-4-amine
1-(3-chlorobenzyl)-4-[(4-isopropylbenzyl) amino]-1H-indole-2-carbonitrile (1.0mmol) was dissolved in toluene (10ml) and added trimethyl silylazide (2.0mmol) and dibutyl tin oxide (0.10mmol) were added. The reaction was heated to reflux for 24 hours, and then the progress of the reaction was monitored by TLC (20% ethylacetate in hexane). The reaction was then concentrated *in vacuo* to dryness and the residue obtained was partitioned between water and ethyl acetate. Combined organic extracts were dried over anhydrous NaSO4 and concentrated *in vacuo* and the residue purified by flash chromatography using hehane-20% ethyl acetate as eluent to give the desired end product in 33% yield.

**Example 31**

1H-indol-4-amine, 1-[(3-chlorophenyl) methyl]-2-(1H-tetrazol-5-yl)-

was prepared as per Example 30 protocol but starting from 4-amino-1-(3-chlorobenzyl)-1H-indole-2-carbonitrile.

MS; ((ES+))=325/(ES-)=323. 1HNMR (DMSO-d6); 5.90(s, 2H, -N-CH2); 6.30(d, 1H,NH2); 6.70(d, 1H,Aro); 6.90-7.0(m, 3H,Aro); 7.05(s, 1H,NH); 7.25-7.35(m, 3H,Aro); 7.60(s, 1H,Aro).
**Preparation of intermediates:**

**Ethyl 1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxylate**

Ethyl 4-nitro-1H-indole-2-carboxylate (0.5g) was dissolved in DMF and sodium hydride (0.116g) was added in a single portion. The reaction was stirred for 1/2 hour, and then 3-chlorobenzyl chloride (0.468g) was added drop wise. Stirring was continued for a further 8 hours and then the progress of the reaction was monitored by TLC (20%-ethylacetate in hexane) for the absence of starting indole. Removed DMF under vacuum then the reaction mixture was quenched by addition of cold water (5.0ml). Filter the solid *in vacuo*, to the solid was given n-hexane wash and dried *in vacuo* to give the desired product as a pale yellow solid (0.61 g, 74%). MS; (ES+) =358.8 1HNMR(CDCl3, ppm): 1.37-1.42(m, 3H,CH3); 4.34-4.41(m, 2H,CH2); 5.88(s, 2H,NCH2); 6.87-7.01(d, 1H); 7.17(s, 1H); 7.18-7.39(m, 2H); 7.42 (t, 1H); 7.63(d, 1H); 8.05 (s, 1H); 8.18(d, 1H).

The procedure described in Example 1 was repeated using the appropriate halides. Thus there were obtained the compounds described below.
Ethyl 1-[(5-chloro-2-thienyl) methyl]-4-nitro-1H-indole-2-carboxylate

\[
\text{O}^+\ \text{N}^-\ \text{O}^-
\]

68% yield; MS; (ES+) = 365.0: 1HNMR(DMSO, ppm): 1.30-1.45 (m, 3H, CH3); 4.35-4.45 (m, 2H, OCH2); 6.05 (s, 2H, NCH2); 6.95 (d, 1H, arom); 7.15 (d, 1H, arom); 7.65 (t, 1H, arom); 7.75 (s, 1H, arom); 8.2 (d, 1H, arom); 8.45 (d, 1H, arom).

Ethyl 1-(3,5-dichlorobenzyl)-4-nitro-1H-indole-2-carboxylate

\[
\text{O}^+\ \text{N}^-\ \text{O}^-
\]

72% yield; MS; (ES+) = 393.0: 1HNMR(DMSO, ppm): 1.30-1.45 (m, 3H, CH3); 4.35-4.45 (m, 2H, OCH2); 6.0 (s, 2H, NCH2); 7.05-7.10 (m, 2H, arom); 7.5-7.65 (m, 1H, arom); 7.85 (s, 1H, arom); 8.15-8.25 (m, 2H, arom).
Ethyl 4-nitro-1-(3-chlorobenzyl)-7-methyl-1H-indole-2-carboxylate

85% yield. MS:373((ES+)), 1H NMR(DMSO), 1.30(t, 3H), 2.30(s, 3H), 4.30-4.40(q, 2H), 6.10(s, 2H), 6.80(d, 1H), 6.95(d, 1H), 7.05 (d, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.65(d 1H).

Ethyl 4-nitro-1-(3-chlorobenzyl)-7-fluoro-1H-indole-2-carboxylate

80% yield. MS:377((ES+)), 1H NMR(DMSO), 1.30(t, 3H), 4.30-4.40(q, 2H), 6.10(s, 2H), 6.80(dd, 1H), 6.95(d, 1H), 7.05 (dd, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.65(d 1H).
Ethyl 4-nitro-1-(3-chlorobenzyl)-7-bromo-1H-indole-2-carboxylate

80% yield.  
MS:438((ES+)), 1H NMR(DMSO), 1.30(t,3H), 4.30-4.40(q, 2H), 6.00(s,2H), 6.75(d, 1H), 6.90(d, 1H), 7.00 (d, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.60(d 1H).

Ethyl 4-nitro-1-(3-chlorobenzyl)-7-chloro-1H-indole-2-carboxylate

85% yield. MS:393((ES+)), 1H NMR(DMSO), 1.30(t,3H), 4.30-4.40(q, 2H), 6.00(s,2H), 6.75(d, 1H), 6.90(d, 1H), 7.00 (d, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.60(d 1H).

The following compounds are prepared from the corresponding nitro compounds using the protocol of Example 2.
Ethyl 4-amino-1- (3-chlorobenzyl)-1H-indole-2-carboxylate

68% yield. MS; (ES+) =329.0 1HNMR(CDC13, ppm): 1.37-1.42(m, 3H, CH3); 4.27(s, 2H, NH2); 4.34-4.41(m, 2H, CH2); 5.73(s, 2H, NCH2); 6.38(d, 1H); 6.70(d, 1H); 6.91(d, 1H), 7.11-7.24(m, 4H); 7.36(s, 1H).

4-Amino-1- (5-chlorothiophen-2-ylmethyl)-1H-indole-2-carboxylic acid ethyl ester

75% yield. MS; ((ES+))=335.8, 1HNMR(DMSO-d6, ppm)- 1.25(t, 3H, -CH3); 4.4(q, 2H, -CH2-); 5.8(s, 2H, -CH2-); 6.2(d, 1H, Aro.); 6.8(d, 1H, Aro.); 7.0(m, 3H, Aro.); 7.4(s, 1H, Aro.).
4-Amino-1-(3,5-dichlorobenzyl)-1H-indole-2-carboxylic acid ethyl ester

\[
\begin{align*}
&\text{NH}_2 \\
&\text{Cl} \\
&\text{Cl} \\
\end{align*}
\]

78% yield. MS; ([ES+]=364.3, 1H NMR(DMSO-d6)-1.3(t, 3H, -CH3); 4.3(q, 2H, -CH2-); 5.75(s, 2H, -CH2-); 6.2(d, 1H, Aro.); 6.6(d, 1H, Aro.); 6.95(d, 1H, Aro.); 7.0(m, 2H, Aro.); 7.45(m, 1H, Aro.); 7.45(m, 1H, Aro.); 7.55(s, 1H, Aro.).

Ethyl 4-amino-1-(3-chlorobenzyl)-7-methyl-1H-indole-2-carboxylate

\[
\begin{align*}
&\text{NH}_2 \\
\end{align*}
\]

60% yield. MS:343([ES+]), 1H NMR(DMSO), 1.30(t, 3H), 2.30(s, 3H), 4.30-4.40(q, 2H), 6.00(s, 2H), 6.70(d, 1H), 6.90(d, 1H), 7.05 (d, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.60(d 1H).
Ethyl 4-amino-1-(3-chlorobenzyl)-7-fluoro-1H-indole-2-carboxylate

\[
\text{NH}_2
\]

\[
\text{HN}
\]

\[
\text{O}
\]

\[
\text{O}
\]

\[
\text{Cl}
\]

\[
\text{F}
\]

in 60% yield. MS:347((ES+)), 1H NMR(DMSO), 1.30(t, 3H), 4.30-4.40(q, 2H), 6.10(s, 2H), 6.80(dd, 1H), 6.95(d, 1H), 7.10 (dd, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.50(d 1H).

Ethyl 4-amino-1-(3-chlorobenzyl)-7-bromo-1H-indole-2-carboxylate

\[
\text{NH}_2
\]

\[
\text{HN}
\]

\[
\text{O}
\]

\[
\text{O}
\]

\[
\text{Br}
\]

\[
\text{Cl}
\]

70% yield. MS:408,410((ES+)), 1H NMR(DMSO), 1.30(t, 3H), 4.30-4.40(q, 2H), 6.10(s, 2H), 6.80(d, 1H), 6.95(d, 1H), 7.10 (d, 1H), 7.15(s, 1H), 7.30-7.40(m, 2H), 7.50(d 1H).
Ethyl 4-amino-1-(3-chlorobenzyl)-7-chloro-1H-indole-2-carboxylate

\[
\text{NH}_2
\]
\[
\text{Cl}
\]
70% yield. MS: 363 ((ES+)), 1H NMR (DMSO), 1.30 (t, 3H), 4.30-4.40 (q, 2H), 6.10 (s, 2H), 6.80 (d, 1H), 6.95 (d, 1H), 7.10 (d, 1H), 7.15 (s, 1H), 7.30-7.40 (m, 2H), 7.50 (d, 1H).

Yield: 70%

1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxylic acid

\[
\text{NO}_2
\]
\[
\text{Cl}
\]
Ethyl 1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxylate (0.806 mmol) was dissolved in ethanol and aqueous 2M sodium hydroxide solution (4.0ml) was added drop wise. The reaction was stirred for 16 hours, and then the progress of the reaction was monitored by TLC (20% ethylacetate in hexane). The reaction was then concentrated in vacuo to dryness and the residue dissolved in water. The solution was acidified to PH 3 by drop wise addition acetic acid, resulting in the precipitation of solid, which was filtered off.

Washed with water and dried in vacuo to give the desired end product in 95% yield. MS; (ES-) = 329.0. 1HNMR (DMSO, ppm): 6.05 (s, 2H, NCH2); 6.85-6.95 (m, 1H); 7.2 (s, 1H); 7.25-7.35 (m, 2H); 7.5-7.6 (t, 1H); 7.8 (s, 1H); 8.15-8.25 (m, 2H); 13.85 (bs, 1H).
1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxamide

1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxylic acid (1.5 mmol) was dissolved in ethyl acetate (30 ml) and thionyl chloride (15 mmol) was added drop wise. The reaction was heated at 65°C for 3 hours, and then the progress of the reaction was monitored by TLC (20% ethylacetate in hexane). The reaction was then concentrated in vacuo to dryness and the crude acid chloride obtained is taken for the next step.

The above crude acid chloride obtained is cooled to 0°C and ammonia solution was added drop wise. The reaction was stirred for ½ hour; resulting precipitation of yellow solid was filtered off. And dried in vacuo to give the desired end product in 95% yield. MS; (ES+) = 331.97/(ES-) = 329.03, 1HNMR(DMSO, ppm): 6.0 (s, 2H, NH2); 7.09 (d, 1H, CH, arom); 7.1 (s, 1H, CH, arom); 7.25-7.39 (m, 2H, arom); 7.50 (t, 1H, arom); 7.7 (s, 1H, arom); 7.90 (s, 1H, arom); 8.10 (d, 1H, arom) 8.15 (d, 1H, arom); 8.45 (s, 1H, arom).

1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carbonitrile

15
1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carboxamide (1.2 mmol) was dissolved in phosphorous oxychloride (3.0ml). The reaction was heated to reflux for 15 minutes, and then the progress of the reaction was monitored by TLC (20% ethylacetate in hexane). The reaction mixture was poured onto crushed ice and ammonia solution was added to maintain a basic pH. Then the reaction mixture was partitioned between aqueous and ethyl acetate (3x20ml). Combined organic extracts were dried over anhydrous NaSO4 and concentrated in vacuo and the residue purified by flash chromatography using hehane-20% ethyl acetate as eluent to give the desired end product in 95% yield.

**4-amino-1-(3-chlorobenzyl)-1H-indole-2-carbonitrile**

![Chemical Structure](image)

1-(3-chlorobenzyl)-4-nitro-1H-indole-2-carbonitrile was taken and the procedure described in Example 3 repeated. 92% yield.
4-amino-1-(3-chlorobenzyl)-1H-indole-2-carbonitrile (0.50 mmol) was taken and the procedure described in Example 4 repeated. 68.18% yield.

MS; (ES+) = 414/(ES-) = 412. HNMR (DMSO-d6); 1.20-1.30(d, 6H, 2CH3); 2.85-2.95(m, 1H, CH); 4.45(s, 2H, -NH-CH2); 5.40(s, 2H, NH-CH2); 6.80(bs, 1H, NH); 7.0-7.15 (m, 2H, Arom); 7.20-7.40(m, 10H, Arom).
CLAIMS

1. The use of a compound of the formula (I)

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{R}^3 \quad \text{R}^4 \\
\text{R}^5 \quad \text{R}^6 \\
\text{R}^7 \quad \text{X} \\
\text{R}^8 \quad \text{R}^9
\end{array}
\]

wherein X is a bond or CH₂
R¹ is hydrogen or C₁-₁₀ alkyl or C₅-₁₀ aryl or an optionally substituted C₅-₁₀ aryl or C₅-₁₀ heteroaryl ring;
R² is carboxy, cyano, -C(O) CH₂ OH, -CONHR, -C(O)NHSO₂R⁹, tetrazol-5-yl, -(CH₂)₁₃ – NR¹⁸R¹⁹, SO₃H or a group of formula (VI)

\[
\begin{array}{c}
\text{R}^{10} \\
\text{R}^{11} \\
\text{R}^{12}
\end{array}
\]

where R⁸ is selected from hydrogen, C₁-₁₀ alkyl or optionally substituted C₅-₁₀ aryl or optionally substituted C₄-₂₀ heterocycyl group. R⁸ is a group-(CHR¹³)r-COOH where r is an integer of 1-3 and each R¹³ group is independently selected from hydrogen or C₁-₁₀ alkyl;
R⁹ is optionally substituted C₁-₁₀ alkyl or optionally substituted C₅-₁₀ aryl optionally substituted C₄-₂₀ heterocycyl; R¹⁰, R¹¹ and R¹² are independently selected from hydrogen, halogen or C₁-₁₀ alkyl, or optionally substituted C₅-₁₀ aryl and optionally substituted C₄-₂₀ heterocycyl; R¹⁸ and R¹⁹ are independently C₁-₃ alkyl or taken together with the adjacent nitrogen atom R¹⁸ and R¹⁹ represent a morpholine or piperazine ring;
R³ is hydrogen, halogen or or optionally substituted C₁₋₁₀ alkyl or optionally substituted C₂₋₁₀ alkenyl or optionally substituted C₂₋₁₀ alkynyl or optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl or optionally substituted C₁₋₁₀ alkoxy or optionally substituted aralkyl of up to 15 carbon atoms or optionally substituted aralkyloxy of up to 15 carbon atoms or or optionally substituted cycloalkyl of up to 7 carbon atoms;

R⁴ is a group NO₂, NHR¹⁴, NHCHR¹⁴ R¹⁵, NHCOR¹⁵, NHSCO₂R¹⁵, NHC(X¹)NHR¹⁶, or NHCONH SO₂R where X¹ is O or S, R¹⁴ is hydrogen or C₁₋₁₀ alkyl or optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl; R¹⁵ is optionally substituted C₁₋₁₀ alkyl, optionally substituted C₅₋₁₀ aryl or optionally substituted C₄₋₂₀ heterocyclyl and R¹⁶ is hydrogen, optionally substituted C₁₋₁₀ alkyl, or optionally substituted C₄₋₂₀ heteroaryl group, R¹⁷ is an optionally substituted C₁₋₁₀ alkyl, or optionally substituted C₄₋₂₀ heteroaryl group;

R⁵, R⁶ and R⁷ are independently selected from hydrogen, halogen, a functional group, an optionally substituted hydrocarbyl group or an optionally substituted heterocyclic group;

or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof in the manufacture of a medicament for the treatment of Mycobacterium tuberculosis (M.t.b).

2. Use as claimed in claim 1 wherein in the compound of formula I, X is CH₂.

3. Use as claimed in claim 1 wherein in the compound of formula I, R¹ is hydrogen or C₁₋₁₀ alkyl or an optionally substituted C₅₋₁₀ aryl ring.

4. Use as claimed in claim 1 wherein in the compound of formula I, R² is carboxy or a group of formula (VI).

5. Use as claimed in claim 1 wherein in the compound of formula I, R³ is hydrogen, halogen, trifluoromethyl, C₁₋₄ alkyl, or optionally substituted phenyl or optionally substituted benzyl.
6. Use as claimed in claim 1 wherein in the compound of formula I, R\textsubscript{14} is hydrogen or C\textsubscript{1-10} alkyl; and R\textsubscript{15}, R\textsubscript{16} and R\textsubscript{17} are independently selected from hydrogen, optionally substituted C\textsubscript{1-10} alkyl and optionally substituted C\textsubscript{5-10} aryl.

7. Use as claimed in claim 1 wherein in the compound of formula I, R\textsuperscript{5}, R\textsuperscript{6} and R\textsuperscript{7} are independently selected from hydrogen, halogen, C\textsubscript{1-6} alkyl or C\textsubscript{1-6} alkoxy.

8. A compound of the formula (I) as defined in any one of claims 1-7 and provided that R\textsuperscript{4} is a group selected from NO\textsubscript{2}, NHR\textsuperscript{14}, NHCHR\textsuperscript{14} R\textsuperscript{15}, NH(X\textsuperscript{1})NHR\textsuperscript{16}, and NHCONH SO\textsubscript{2}R\textsuperscript{17}, wherein X\textsuperscript{1}, R\textsuperscript{14}, R\textsuperscript{15}, R\textsuperscript{16} and R\textsuperscript{17} are as defined in claim 1 above, or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof.

9. A compound of the formula (I) as defined in claim 8, or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy.

10. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 8, or a pharmaceutically acceptable salt, or an in vivo hydrolysable ester thereof, in combination with a pharmaceutically acceptable diluent or carrier.

11. A method for the treatment of Mycobacterium tuberculosis which comprises administering to a human or animal an effective amount of a compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt, or an in vivo hydrolysable ester thereof.

12. A process for the preparation of a compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof which process comprises:

(a) for compounds of formula (I) where R\textsuperscript{4} is NHCOR\textsuperscript{15} or NHSO\textsubscript{2}R\textsuperscript{15} by reacting a compound of formula (VII)
where $X$, $R^1$, $R^3$, $R^5$, $R^6$ and $R^7$ are as defined in claim 1, $R^{2^*}$ is a group $R^2$ as defined in claim 1 or a protected form thereof, with a compound of formula (VIII)

$$Z \cdot R^{2^*}$$

(VIII)

where $Z$ is a leaving group and $R^{2^*}$ is a group $\text{COR}^{15^*}$ or $\text{SO}_2R^{15^*}$, where $R^{15^*}$ is group $R^{15}$ as defined in claim 1 or a precursor thereof; and thereafter if desired or necessary:

(i) converting a precursor group $R^{15^*}$ to a group $R^{15}$ and/or converting a group $R^{15}$ to a different such group;

(ii) deprotecting a group $R^{2^*}$ to a group $R^2$; or

(b) for compounds of formula (I) where $R^4$ is a group $\text{NHC}(X^1)\text{NHR}^{16}$ by the reaction of a compound of formula (VII) with a compound of the formula (VII A)

$$R^{16} \text{NC}(X^1)$$

(VII A)

where $X^1$ and $R^{16}$ are as defined in claim 1; or

(c) for compounds of formula (I) where $R^4$ is a group $\text{NHCONHSO}_2R^{17}$ by the reaction of a compound of formula (VII) with a compound of the formula (VII B)

$$R^{17} \text{SO}_2\text{NCO}$$

(VII B)

wherein $R^{17}$ is as defined in claim 1; or
(d) for compounds of formula (I) where $R^2$ is a group $\text{CONHSO}_2R^9$ by the reaction of a compound of formula (VII C) with a compound of the formula (VII D)

(VII C)

$R^3\text{SO}_2\text{NH}_2$

(VII D)

where $R^1$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^9$ are as defined above; or

(e) for compounds of formula (I) where $R^4$ is a group $\text{NHCHR}^{14}\text{R}^{15}$ may be prepared by reductive amination of a compound of formula (VII) with a carbonyl compound of the formula (VIII)

(VIII)

$\text{OCR}^{14}\text{R}^{15}$

where $R^{14}$ and $R^{15}$ are as defined in claim 1.

13. A process as claimed in claim 12 for the preparation of compounds of the formula (I) as defined in any one of claims 2-8.