Abstract: The patent discloses silicon analogs of piperine of formula I with increased antibacterial efficacy and their preparation thereof.
ANTITUBERCULAR COMPOUNDS AND PROCESS FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to silicon analogs of alkaloid of general formula I a molecule which has remarkable biological properties.

![General formula I](image)

Particularly, present invention relates to process for the preparation of silicon analogs of alkaloid of general formula I, which are expected to change physico-chemical properties of alkaloid, in particular lipophilicity and *in vivo* metabolism, which in turn may lead to improved drug candidates. More particularly, present invention relates to silicon analogs of alkaloid of general formula I useful for the treatment of *Mycobacterium tuberculosis*.

BACKGROUND AND PRIOR ART OF THE INVENTION

The alkaloid called piperine isolated from peppers possesses very interesting biological properties which can be used for treating various diseases like cancer, depression, inflammation and skin problems like vitiligo. However, piperine suffers from poor pharmacokinetics to become drug on its own.

Article titled "Synthesis and inhibitory effect of piperine derivates on monoamine oxidase" by Li-Hua Mua, Bo Wanga, Hao-Yang Ren, Ping Liu, Dai-Hong Guo, Fu-Meng Wang, Lin Bai, Yan-Shen Guo in Bioorganic & Medicinal Chemistry Letters 22 (2012) 3343-3348 relates to synthesis of piperine derivates and their evaluation in vitro for their monoamine oxidase (MAO) A and B inhibitory activity and selectivity. It also reports that most of the small amine moieties substituted on the piperidine ring proved to be potent and selective inhibitors of MAO-B rather than of MAO-A. 5-(3,4-methylenedioxyphenyl)-2E,4E-pentadienoic acid n-propyl amide showed the greatest MAO-B inhibitory activity (*IC*₅₀(MAO-B) = 0.045 µM) and good selectivity (*IC*₅₀(MAO-A) = 3.66 µM). The conjugated double bond and carbonyl group of piperine are proved to be an essential feature for piperine and related alkylamides to exhibit MAO-inhibitory activity.
Article titled, "Piperine as an inhibitor of Rvl258c, a putative multidrug efflux pump of Mycobacterium tuberculosis" by Sandeep Sharma, Manoj Kumar, Sujata Sharma, Amit Nargotra, Surrender Koul and Inshad Ali Khan in J Antimicrob Chemother 2010; 65: 1694-1701 reports The MIC of rifampicin was determined alone as well as in the presence of piperine (Table: A). The MIC of rifampicin was reduced by 4- to 8-fold in the presence of piperine. This reduction in the MIC was more prominent for M. tuberculosis rif as compared with M. tuberculosis H37Rv. However, piperine on its own did not show any antibacterial activity when tested up to 100 mg/L.

Table A: In vitro rifampicin/piperine combination studies

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC of piperine (mg/L)</th>
<th>MIC of rifampicin (mg/L)</th>
<th>Fold reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>&gt;1.00</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>H37Rv</td>
<td></td>
<td>0.06</td>
<td>8</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>&gt;0.10</td>
<td>128</td>
<td>8</td>
</tr>
<tr>
<td>rif</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>isolate</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>clinical</td>
<td></td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Article titled, "Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1)" by Fergal N.McNamara, Andrew Randall & Martin J.Gunthorpe in British Journal of Pharmacology (2005) 144, 781-790 relates to the effects of piperine in human body acting as a agonist at the receptor. It also reported that piperine exhibits a greater efficacy than capsaicin. The result further provided insight into the TRPV1-mediated effects of piperine on gastrointestinal function.

Article titled, 'Insecticide activity of piperine: Toxicity to eggs of Spodoptera frugiperda (Lepidoptera: Noctuidae) and Diatraea saccharalis (Lepidoptera: Pyralidae) and phytotoxicity on several vegetables" by W. S. Tavares, I. Cruz, F. Petacci, S. S. Freitas, J. E. Serrao and J. C. Zanuncio in Journal of Medicinal Plants Research Vol. 5(21), pp. 5301-5306, 9 October, 2011 reported that products made from piperine are important for the management of pests, but allelopathic studies for these products are also relevant. The result shows that piperine shows biological impact on eggs of S. frugiperda and D. saccharalis as well as in the germination and growth of plants.

Article titled, "The Place of the Bioisosteric Sila-Substitution in Drug Design" by Patrick Englebienne, Anne V. Hoonacker, C. V. Herst from Englebienne & Associates in research gate 2005 reports that the silicon bioisostere offers interesting benefits in drug
design. The altered bond length and angles of silicon over carbon in a new chemical entity can lead to its improved pharmacological potency, modify its selectivity toward a given target, or change its metabolic rate, respectively. The sila-substitution can also increase the lipophilicity of a compound and hence increase its tissue distribution, particularly through membranes including the blood brain barrier, although with the limitation of decreased water solubility. This review presents the synthetic methods currently available to effect a sila-substitution, along with its advantages and limitations in drug design.

Therefore it is the need of the time to develop novel analogs to increase the efficacy of piperine which suffers from poor pharmacokinetics to become drug on its own or it can be combined with any other drug.

OBJECTS OF INVENTION
Main object of the present invention is to provide silicon analogs of alkaloid of general formula I a molecule which has remarkable biological properties.

Another object of the present invention is to provide a process for the preparation of silicon analogs of alkaloid of general formula I, which are expected to change physico-chemical properties of alkaloid, in particular lipophilicity and in vivo metabolism, which in turn may lead to improved drug candidates.

Another object of the present invention is to provide silicon analogs of alkaloid of general formula I useful for the treatment of various diseases like cancer, depression, inflammation etc.

Another object of the present invention is to provide silicon analogs of alkaloid of general formula I useful for the treatment or prevention of Tuberculosis or Mycobacterium tuberculosis.

SUMMARY OF THE INVENTION
Accordingly, present invention provides a compound of general formula I

\[
\text{General Formula I}
\]
wherein
R₁, R₂ each are individually selected from H, hydroxy, alkoxy or
R¹ and R² may form alicyclic or aromatic ring which may additionally contain one or two hetero atoms;
R³, R⁴ each are individually selected from alkyl, aryl, alkoxy, halo or
R³ and R⁴ may form alicyclic ring which may additionally contain an hetero atom;
m, n = 0, 1, 2.
In an embodiment of the present invention, the alkoxy group has C₁ to C₅ carbon atoms.
In another embodiment of the present invention, the alicyclic ring is 3 to 8 membered alicyclic ring.
In yet another embodiment of the present invention, the aromatic ring is 3 to 8 membered aromatic ring.
In yet another embodiment of the present invention, the alkyl group has C₁ to C₅ carbon atoms.
In yet another embodiment of the present invention, the aryl group has 1 or 2 rings.
In yet another embodiment of the present invention, the hetero atom is selected from O, S or N.
In yet another embodiment of the present invention, the halo atom is chromo or bormo atom.
In yet another embodiment of the present invention, representative compounds comprising:

In yet another embodiment of the present invention, said compound are useful for the treatment of tuberculosis.
In yet another embodiment, present invention provides a process for the preparation of compound of general formula I according to claim 1 comprising the steps of:
   a) adding coupling agent and organic base to a solution of carboxylic acid precursor of general formula II in dry DCM at 0°C temperature;
b) adding silapiperidine salt of general formula III to the mixture of step (a) and stirring at temperature in the range of 20 to 25°C for period in the range of 7 to 9 h;

c) quenching the mixture of step (b) by the addition of water and separating the organic layer followed by washing with saturated NaHCO₃, HCl;
d) drying the separated mixture of step (c) by the addition of Na₂SO₄ followed by concentrating and purifying by column chromatography using pet ether-ethyl acetate to obtain the compound 3 and 6 of general formula I;
e) adding 10% Pd/C in alcoholic solution of compound 3 and 6 of general formula I followed by stirring at temperature in the range of 20 to 25°C for period in the range of 50 to 70 min to obtain a mixture;
f) filtering the mixture followed by concentrating under reduced pressure to obtain compound 4 and 7 of general formula I.

In yet another embodiment of the present invention, coupling agents used is selected from the group consisting of DCC (1,1'-Dicyclohexylcarbodiimide), EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide), HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), HBTU (O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate), HOBT (Hydroxybenzotriazole).

In yet another embodiment of the present invention, organic base used is selected from the group consisting of triethyl amine, diisopropylethylamine.

In yet another embodiment of the present invention, yield of the compound of general formula I is in the range of 75-90%.

In yet another embodiment of the present invention, alcohol used is ethanol.

In yet another embodiment, present invention provides a pharmaceutical composition comprising compound of Formula I along with pharmaceutically acceptable ingredients against Mycobacterium tuberculi.
DETAILED DESCRIPTION OF THE INVENTION

Present invention provides silicon analogs of piperine of general formula I which has remarkable biological properties and is expected to show activities similar or better with improved pharmacokinetics parameters. The introduction of Silicon atom, the novel compounds are expected to change physico-chemical properties, in particular lipophylicity and in vivo metabolism, which in turn may lead to improved drug candidates.

\[
\text{General formula I}
\]

Wherein,

- \(R^1, R^2\) each are individually selected from H, hydroxy, alkoxy or
- \(R^1\) and \(R^2\) may form alicyclic or aromatic ring which may additionally contain one or two hetero atoms;
- \(R^3, R^4\) each are individually selected from alkyl, aryl, alkoxy, halo or
- \(R^3\) and \(R^4\) may form alicyclic ring which may additionally contain an hetero atom;
- \(m, n = 0, 1, 2\).

- In a preferred aspect, alkoxy group has Cl to C5 carbon atoms.
- In another preferred aspect, the alicyclic ring is 3 to 8 membered alicyclic ring.
- In another preferred aspect, the aromatic ring is 3 to 8 membered aromatic ring.
- In another preferred aspect, the alkyl group has Cl to C5 carbon atoms.
- In yet another preferred aspect, the aryl group has 1 or 2 rings.
- In still another preferred aspect, the hetero atom is selected from O, S or N.
- In still another preferred aspect, the halo atom is chromo or bormo atom.

The present invention provides the synthesis for the preparation of analogs of piperine of general formula I with increased efficacy starting from the reaction of compound of general formula II with compound of general formula III and the said process comprises the steps of:
a) adding coupling agents like DCC, EDC, HATU, HBTU or HOBT and any organic base such as triethyl amine or diisopropylethylamine to a solution of carboxylic acid precursor general formula II in dry DCM at 0 °C;

$$\text{II}$$

b) adding silapiperidine salt of general formula III to the mixture of above and stirring it at room temperature for 8 h;

$$\text{III}$$

c) quenching the mixture of step (b) by the addition of water and separating the organic layer, by washing it with saturated NaHCO₃, IN HCl;

d) drying the separated mixture over Na₂SO₄ and concentrating it under reduced pressure to afford the crude mixture of desired product and

e) purifying the crude mixture of step (d) further by column chromatography using pet ether-ethyl acetate to obtain the compound of formula I in high yield.

A pharmaceutical composition is provided comprising a compound of general formula I or a stereoisomer, or ester or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, injections, gels and microspheres.

The present invention relates to administering 'an effective amount' of the 'composition of invention' to the subject in need of the same. Accordingly, compound of formula I and pharmaceutical compositions containing them may be administered using any amount, any form of pharmaceutical composition via any route of administration effective for treating the disease. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal.
Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient may take the form of one or more dosage units. The dosage forms can also be prepared as sustained, controlled, modified and immediate dosage forms.

Another embodiment of the present invention provides a pharmaceutical composition comprising a compound of Formula I along with pharmaceutically acceptable ingredients. Another embodiment of the present invention provides a pharmaceutical composition comprising a compound of Formula I along with pharmaceutically acceptable ingredients against Mycobacterium tuberculosis.

Another embodiment of the present invention provides a method of treating a patient with tuberculosis, said method comprising administering to the patient, a therapeutically effective amount of the compound of Formula I described as herein. Another embodiment of the present invention provides a method of treating a patient with tuberculosis, said method comprising administering to the patient, a therapeutically effective amount of any compound of Formula I described as herein in any of the embodiments of the invention. Another embodiment of the present invention provides use of a compound of Formula I described as herein in any of the embodiment of the present invention for the treatment or prevention of tuberculosis. Another embodiment of the present invention provides use of compound of Formula I for the preparation of a medicament. Another embodiment of the present invention provides use of the medicament as for the treatment of a disease.

Another embodiment of the present invention provides use of the medicament as for the treatment of a disease wherein the disease is selected from tuberculosis, cancer, inflammation, depression, etc. Another embodiment of the present invention provides a method of treating a patient with a disease, said method comprising administering to the patient, a therapeutically effective amount of the compound of formula I described as herein in any of the embodiments of the invention.

Another embodiment of the present invention a method of treating a patient with a disease, said method comprising administering to the patient, a therapeutically effective amount of the compound of formula I described as herein in any of the embodiments of
the invention, wherein the disease is selected from group comprising of tuberculosis, cancer, inflammation, depression, etc.

Another embodiment of the present invention a method of treating a patient with a disease, said method comprising administering to the patient, a therapeutically effective amount of the compound of formula I, wherein the disease is selected from group comprising of cancer, inflammation, depression, etc.

EXAMPLE 1
The following examples are given by way of illustration therefore should not be construed to limit the scope of the invention.

Preparation of (2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)-1-(4,4-dimethyl-1,4-azasilinan-1-yl)penta-2,4-dien-1-one (3)

To a solution of (2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoic acid, 1 (188 mg, 0.86 mmol) in dry DCM, EDC.HCl (215 mg, 1.1 mmol), HOBt (151 mg, 1.1 mmol) and diisopropylethylamine (0.45 mL, 2.6 mmol) at 0 °C was added. Then the silapiperidine salt, 2 (171 mg, 1.0 mmol) was added and stirred at RT (i.e. 27°C) for 8 h. The reaction was quenched by the addition of water and the organic layer was separated, washed with saturated NaHCO₃, IN HCl, dried over Na₂SO₄ and concentrated under reduced pressure. This crude mixture was purified by column chromatography using pet ether-ethyl acetate (70:30) to give the title compound (200 mg, 71 % yield) as a yellow viscous liquid.

IR  \text{\textit{\textmu}max (film): cm}^{-1} 2925, 1635, 1591, 1490, 1446, 1252;

H NMR (400 MHz, CDCl₃):  δ 7.44 (ddd, J = 14.2, 6.9, 2.8 Hz, 1H), 6.99 (s, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.79-6.75 (m, 3H), 6.46 (d, J = 14.7 Hz, 1H), 5.98 (s, 2H), 3.79 (t, J = 6.4 Hz, 2H), 3.71 (t, J = 6.2 Hz, 2H), 0.90-0.78 (m, 4H), 0.11 (s, 6H);

C NMR (100 MHz, CDCl₃): δ 165.7, 148.3, 148.2, 142.8, 138.4, 131.1, 125.5, 122.6, 120.1, 108.6, 105.7, 101.4, 45.6, 42.8, 15.7, 13.9, -2.9 (2C).
Example 2
Preparation of 5-(benzo[d][1,3]dioxol-5-yl)-1-(4,4-dimethyl-1,4-azasilinan-1-yl)pentan-1-one (4)

To a solution of 3 (50 mg, 0.15 mmol) in Ethanol 10 % Pd/C (5 mg) was added and stirred at RT (25°C) for 1 h under Hydrogen atmosphere. The reaction mixture was filtered through celite pad and the filtrate was concentrated under reduced pressure to give the title compound as a colourless liquid (50 mg, 99 % yield).

IR ν_{max} (film): cm\(^{-1}\) 3031, 1624, 1504, 1489, 1441;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 6.72-6.61 (m, 3H), 5.91 (s, 2H), 3.69 (t, J = 6.4 Hz, 2H), 3.56 (t, J = 6.4 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.34 (t, J = 6.5 Hz, 2H), 1.71-1.59 (m, 4H), 0.80-0.72 (m, 4H), 0.09 (s, 6H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 171.5, 147.4, 145.5, 136.2, 121.1, 108.8, 108.0, 100.7, 45.2, 42.1, 35.5, 33.0, 31.6, 25.0, 15.1, 13.6, -3.1 (2C).

20 Example: 3
(E)-3-(benzo[d][1,3]dioxol-5-yl)-1-(4,4-dimethyl-1,4-azasilinan-1-yl)prop-2-en-1-one (6)

To a solution of (E)-3-(benzo[d][1,3]dioxol-5-yl)acrylic acid (5), (300 mg, 1.56 mmol) in dry DCM, EDC.HCl (315 mg, 2.0 mmol), HOBt (274 mg, 2.0 mmol) and diisopropylethylamine (0.8 mL, 4.7 mmol) was added at 0 °C. Then the silapiperidine salt, 2 (285 mg, 1.7 mmol) was added and stirred at RT (30°C) for 8 h. The reaction was quenched by the addition of water and the organic layer was separated, washed with saturated NaHC03, IN HCl, dried over Na\(_2\)S0\(_4\) and concentrated under reduced pressure. This crude mixture was purified by column chromatography using pet ether-ethyl acetate (70:30) to give the title compound (360 mg, 77 % yield) as a crystalline white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.61 (d, J = 15.3 Hz, 1H), 7.05 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.81-6.73 (m, 2H), 5.99 (s, 2H), 3.81 (t, J = 6.3 Hz, 2H), 3.75 (t, J = 6.3 Hz, 2H), 0.90-0.83 (m, 4H), 0.12 (s, 6H);
\[ ^{13}C \text{NMR (100 MHz, CDC}_1\text{3): } \delta 165.5, 148.8, 148.1, 142.2, 129.9, 123.6, 115.5, 108.4, 106.3, 101.4, 45.5, 42.8, 15.6, 13.8, -3.0 \text{ (2C).} \]

Example: 4

\[ \text{3-(benzo[d][1,3]dioxol-5-yl)-1-(4,4-dimethyl-1,4-azasilinan-1-yl)propan-1-one (7)} \]

To a solution of 6 (100 mg, 0.33 mmol) in Ethanol was added 10 % Pd/C (10 mg) and stirred at RT (27°C) for 1 h under Hydrogen atmosphere. The reaction mixture was filtered through celite pad and the filtrate was concentrated under reduced pressure to give the title compound as a colourless liquid (100 mg, 100 % yield).

\[ ^{13}H \text{ NMR (400 MHz, CDC}_1\text{3): } \delta 6.73-6.67 \text{ (m, 3H), 5.91 (s, 2H), 3.70 (t, } J = 6.4 \text{ Hz, 2H), 3.54 (t, } J = 6.4 \text{ Hz, 2H), 2.90 (t, } J = 7.9 \text{ Hz, 2H), 2.58 (t, } J = 7.7 \text{ Hz, 2H), 0.78 (t, } J = 6.4 \text{ Hz, 2H), 0.65 (t, } J = 6.4 \text{ Hz, 2H), 0.08 (s, 6H);} \]

\[ ^{13}C \text{ NMR (100 MHz, CDC}_1\text{3): } \delta 170.7, 147.6, 145.8, 135.4, 121.2, 108.9, 108.2, 100.8, 45.2, 42.2, 35.1, 31.4, 15.0, 13.7, -3.1 \text{ (2C).} \]

ANTITUBERCULAR ACTIVITY

The compounds (3) and (6) were tested for antitubercular activity through inhibition of growth of the virulent strain of \textit{Mycobacterium tuberculosis H37Rv} using Alamar-Blue assay method. MIC values of the compounds against \textit{H37RV} were determined in 7H9-OADC media supplemented with 0.5% glycerol and 1 mg ml\(^{-1}\) tryptone at 37 °C in 96-well microtiter plates using the colorimetric resazurin microtiter assay, and growth was measured by visual readout, Rifampicin was used as a positive drug control.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC ((\mu)g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Piperine</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

ADVANTAGES OF THE INVENTION

a) Novel silicon analogs of piperine
b) Easy synthesis process
c) Increased efficacy
We claim:

1. A compound of general formula I

\[
\begin{align*}
R^1 & = \text{alkyl, aryl, alkoxy, halo or } \text{hetero atom} \\
R^2 & = \text{H, hydroxy, alkoxy or } \text{hetero atom} \\
R^3 & = \text{alkyl, aryl, alkoxy, halo or } \text{hetero atom} \\
R^4 & = \text{alkyl, aryl, alkoxy, halo or } \text{hetero atom} \\
m, n & = 0, 1, 2
\end{align*}
\]

General Formula I

wherein

2. The compound as claimed in claim 1, wherein the alkoxy group has C1 to C5 carbon atoms.

3. The compound as claimed in claim 1, wherein the alicyclic ring is 3 to 8 membered alicyclic ring.

4. The compound as claimed in claim 1, wherein the aromatic ring is 3 to 8 membered aromatic ring.

5. The compound as claimed in claim 1, wherein the alkyl group has C1 to C5 carbon atoms.

6. The compound as claimed in claim 1, wherein the aryl group has 1 or 2 rings.

7. The compound as claimed in claim 1, wherein the hetero atom is selected from O, S or N.

8. The compound as claimed in claim 1, wherein the halo atom is chromo or bormo atom.

9. The compound as claimed in claim 1, wherein representative compounds comprising:
10. The compound as claimed in claim 1, where said compound are useful for the
treatment of tuberculosis.

11. A process for the preparation of compound of general formula I according to
claim 1 comprising the steps of:

i. adding coupling agent and organic base to a solution of carboxylic
acid precursor of general formula II in dry DCM at 0°C
temperature;

\[
\begin{align*}
R^1 & \quad R^2 \\
\text{II} & \\
& \quad \text{OH}
\end{align*}
\]

ii. adding silapiperidine salt of general formula III to the mixture of
step (a) and stirring at temperature in the range of 20 to 25°C for
period in the range of 7 to 9 h;

\[
\begin{align*}
R^3 & \quad R^4 \\
\text{III} & \\
& \quad \text{NH}_2\text{HCl}
\end{align*}
\]

iii. quenching the mixture of step (b) by the addition of water and
separating the organic layer followed by washing with saturated
NaHCOa, HCl;

iv. drying the separated mixture of step (c) over Na_2SO_4 followed by
concentrating and purifying by column chromatography using pet
ether-ethyl acetate to obtain the compound 3 and 6 of general
formula I;

v. adding 10 % Pd/C in alcoholic solution of compound 3 and 6 of
general formula I followed by stirring at temperature in the range
of 20 to 25°C for period in the range of 50 to 70 min to obtain a mixture;
vi. filtering the mixture followed by concentrating under reduced pressure to obtain compound 4 and 7 of general formula I.

12. The process as claimed in claim 1, wherein coupling agents used is selected from the group consisting of DCC (JV,JV'-Dicyclohexycarbodiimide), EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide), HATU (1-[Bis(dimethylamino)methylene]-IH-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), HBTU (O-Benzotriazole-N,N,N^N'-tetramethyl-uronium-hexafluoro-phosphate), HOBT (Hydroxybenzotriazole).

13. The process as claimed in claim 1, wherein organic base used is selected from the group consisting of triethyl amine, disopropylethylamine.

14. The process as claimed in claim 1, wherein yield of the compound of general formula I is in the range of 75-90%.

15. The process as claimed in claim 1, wherein alcohol used is ethanol.

16. A pharmaceutical composition comprising a compound of Formula I along with pharmaceutically acceptable ingredients.

17. A pharmaceutical composition comprising compound of Formula I along with pharmaceutically acceptable ingredients against *Mycobacterium tuberculosis*.

18. A method of treating a patient with tuberculosis, said method comprising administering to the patient, a therapeutically effective amount of the compound of formula I as claimed in claim 1.

19. A method of treating a patient with tuberculosis, said method comprising administering to the patient, a therapeutically effective amount of compound as claimed in claim 9.

20. Use of the compounds as claimed in claims 1 to 9 for the treatment or prevention of tuberculosis.

21. Use of the compounds as claimed in claims 1 to 9 for the preparation of a medicament.

22. Use of the medicament as claimed in claim 20 for the treatment of a disease.

23. Use as claimed in claim 21, wherein the disease selected from tuberculosis, cancer, inflammation, depression, etc.

24. A method of treating a patient with a disease, said method comprising administering to the patient, a therapeutically effective amount of the compound as claimed in claims 1 to 9.

25. A method of treating a patient as claimed in claim 23, wherein the disease selected comprises of tuberculosis, cancer, inflammation, depression, etc.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07F7/08 A61K31/695 A61P31/06

ADD.

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)

C07F A61K A61P

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 practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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X Further documents are listed in the continuation of Box C. X See patent family 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 application or patent 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

Date of the actual completion of the international search

24 June 2014

Date of mailing of the international search report

02/07/2014

Name and mailing address of the ISA/

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Fax: (+31-70) 340-3016

Authorized officer

Eberhard, Michael
<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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