Anti-Tubercular Activity of Isatin Derivatives

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ABSTRACT

Tuberculosis (TB) remains among the world’s great public health challenges. Worldwide resurgence of TB is due to two major problems: the acquired immunodeficiency syndrome (AIDS) epidemic, which started in the mid-1980s, and the outbreak of multidrug resistant tuberculosis (MDR-TB). Thus, there is an urgent need for anti-TB drugs with improved properties such as: Enhanced activity against MDR strains, reduced toxicity, shortened duration of therapy, rapid mycobactericidal mechanism of action and the ability to penetrate host cells and exert antimycobacterial effects in the intracellular environment. Indoline-2,3-dione (isatin) derivatives are reported to show anti-tubercular activities, accordingly, isatin is a versatile lead molecule for designing of potential anti-tubercular agent. The current review outlines isatin derivatives with potential anti-tubercular activity.

Keywords: Isatin; Indoline-2,3-dione; Isatin derivatives; Tuberculosis; Anti-tubercular.

1. Tuberculosis

Tuberculosis (TB) is a chronic bacterial infection, spread through the air, and caused by a bacterium called Mycobacterium tuberculosis (MTB) aerobic bacilli belonging to the Mycobacteriaceae, first identified in 1882 by Robert Koch, which can mainly attack the lungs, although can affect other organs as well (De Souza, 2006 a; De Souza, 2006 b; Swamy, 2007; Janin, 2007; Scior & Garces-Eisele, 2006; Ballell, 2005; Sriram, 2005). The cell wall of the bacilli has a high lipid content resulting in a high degree of hydrophobicity (Marrow, 1992; Daniel, 1991) that resists decolorization by acid alcohol after staining with basic fuchsin. For this reason, the organism is often referred to as an “acid-fast” bacillus (AFB). The bacillus thrives in environments where the oxygen tension is relatively high, such as the apices of the lung, the renal parenchyma, and the growing ends of bones (Daniel, 1991; Peloquin & Berning, 1994).

Currently TB is becoming again a worldwide problem and it was declared since 1993 by the World Health Organization (WHO), a global health emergency. The resurgence of TB became a serious world-wide problem during the period 1985–1992, particularly in people infected with the human immunodeficiency virus (HIV). However, there are also other problems that contribute to the increasing incidence of TB nowadays, such as immigration, increased trade, dense population, poor nutrition, poor sanitation, globalization, war, famine, poor patient compliance, and drug resistance issues caused by the emergence of multidrug resistant tuberculosis, MDR-TB, (De Souza, 2006 a; De Souza, 2006 b; Swamy, 2007; Janin, 2007; Scior, 2006; Ballell, 2005; Sriram, 2005). MDR-TB arises from inconsistent or partial treatment and the recent advent of extensively drug resistant tuberculosis, XDR-TB, (Berry & Kon, 2009).

At present, TB kills four people every minute somewhere in the world and accounts about two million deaths per year (Lourenço, 2008). According to the WHO, currently one-third of world’s population is infected with latent tuberculosis (WHO, 2006). Based on the trend over the past few years, a total of 225 million new cases and 79 million deaths are expected from tuberculosis between 1998 and 2030 (Rakesh, 2009). The problem is that the disease is not always active. Pathogenic mycobacteria stay nondividing in a persistent, a dormant state and are reactivated only during physiological stresses, after HIV infection, in the course of treatment with anti-inflammatory agents, immunosuppressive drugs or in otherwise immunocompromised individuals (Frieden, 2003). MTB is a multifaceted pathogen capable of causing both an acute disease processes as well as an asymptomatic latent infection. Some dormant bacteria persist for decades in host cells before resulting in reactivation of tuberculosis disease (Parrish & Dick, 1998). As more T cells, macrophages and macrophages are recruited to the area surrounding the bacilli, the bacilli slowly replicate and...
The current problem of tuberculosis therapy is the emergence of multi-drug resistant (MDR) strains, caused by the improper use of antibiotics in chemotherapy of TB patients. The WHO estimates that up to 50 million persons worldwide are infected with drug resistant strains of TB. In addition, 300,000 new cases of MDR-TB are diagnosed around the world each year and 79% of the MDR-TB cases now show resistance to three or more of the commonly used drugs (Székely, 2008). The current WHO-approved treatment for TB, known as directly observed therapy short course (DOTS), involves an intensive phase with three or four different drugs viz. isoniazid (INH, 1), rifampin (RIF, 2), pyrazinamide (PZA, 3), and ethambutol (EMB, 4) for a minimum of 6 months (Somu, 2006).

Most of the drugs in the current tuberculosis regime result from research performed over 50 years ago (Sacchettini, 2008). Hence, there is an urgent need to develop potent and fast acting anti-TB drugs with new modes of action to overcome the cross-resistance with current drugs and low toxicity profiles that can be tolerated for long treatment periods required for TB chemotherapy (Rakesh, 2009). Development of resistance to existing drugs is a constantly growing phenomenon that has concerned researchers throughout the world, and now has reached alarming levels for TB. This combined with the recent decline in the development of new drugs to combat them can be anticipated to lead to infectious diseases lacking ready treatment regimens (Snider, 1998).

2. Current TB drugs
The current TB drugs can be divided into two categories: First-line drugs and Second-line drugs. The first-line drugs include INH (1), RIF (2), PZA (3), EMB (4) and Streptomycin (SM, 5). The first-line drugs combine the greatest level of efficacy with an acceptable degree of toxicity. Designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. These drugs are best given as combination of preparations unless one of the components cannot be given because of resistance or intolerance (Mehta, 2003).

The second-line drugs include Kanamycin (6), Cycloserine (7), p-aminosalicylic acid (PAS, 8), Ethionamide (9), Prothionamide (10), Thiacetazone (11) and Fluoroquinolones (FQ, 12). The second-line drugs are potentially ototoxic and nephrotoxic, therefore no two drugs from this group should be employed simultaneously and they should not be used in combination with streptomycin (Petri, 2001). They are utilized in cases of resistance, re-treatment or intolerance to the first-line drugs (Lemke, 1995). They can also be categorized as either Bacteriostatic which include EMB (4) and PAS (8) or Bactericidal which include INH (1), RIF (2), SM (5) and FQ (12). The chemical structures and the targets of inhibition for the first-line and second-line TB drugs are shown in fig. 1 and table 1, respectively (Scior, 2002; Yepes, 2004). The mechanisms of action and resistance of TB drugs have been reviewed by Silva and Anisa (Silva & Anisa, 2007). These drugs can be grouped as cell wall synthesis inhibitors, nucleic acid synthesis inhibitors, protein synthesis inhibitors, and energy inhibitors.

3. Indoline-2, 3-dione (Isatin, 13)


Isatin was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids (Da Silva, 2001). In nature, isatin is found in plants of the genus Isatis (Guo & Chen, 1986), in Calanthe discolor (Yoshikawa, 1998) and in Couroupita guianensis (Bergman, 1985). It has also been found as a component of the secretion from the parotid gland of Bufo frogs (Wei, 1982), and in humans as it is a metabolic derivative of adrenaline (Ischia, 1988; Palumbo, 1989; Halket, 1991). Substituted isatins are also found in plants, for example the melosatin alkaloids

Table 1: Commonly used TB drugs and their targets

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (μg/ml)</th>
<th>Effect on bacterial cell</th>
<th>Mechanism of action</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (1)</td>
<td>0.01-0.2</td>
<td>Bactericidal</td>
<td>Inhibition of cell wall mycolic acid synthesis and other multiple effects on DNA, lipids, carbohydrates, and NAD metabolism.</td>
<td>Multiple targets including acyl carrier protein reductase (InhA)</td>
</tr>
<tr>
<td>Rifampin (2)</td>
<td>0.05-0.5</td>
<td>Bactericidal</td>
<td>Inhibition of RNA synthesis</td>
<td>RNA polymerase δ subunit</td>
</tr>
<tr>
<td>Pyrazinamide (3)</td>
<td>20-100 pH 5.5-6.0</td>
<td>Bacteriostatic/Bactericidal</td>
<td>Disruption of membrane transport and energy depletion</td>
<td>Membrane energy metabolism</td>
</tr>
<tr>
<td>Ethambutol (4)</td>
<td>1-5</td>
<td>Bacteriostatic</td>
<td>Inhibition of cell wall arabinogalactan synthesis</td>
<td>Arabinosyl transferase</td>
</tr>
<tr>
<td>Streptomycin (5)</td>
<td>2-8</td>
<td>Bactericidal</td>
<td>Inhibition of protein synthesis</td>
<td>Ribosomal 512 protein and 16S rRNA</td>
</tr>
<tr>
<td>Kanamycin (6)</td>
<td>1-8</td>
<td>Bactericidal</td>
<td>Inhibition of protein synthesis</td>
<td>16S rRNA</td>
</tr>
<tr>
<td>Cycloserine (7)</td>
<td>5-20</td>
<td>Bacteriostatic</td>
<td>Inhibition of peptidoglycan synthesis</td>
<td>D-alanine racemase</td>
</tr>
<tr>
<td>P- Aminosalicylic acid (8)</td>
<td>1-8</td>
<td>Bacteriostatic</td>
<td>Inhibition of folic acid and iron metabolism?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ethionamide (9)</td>
<td>0.6-2.5</td>
<td>Bacteriostatic</td>
<td>Inhibition of mycolic acid synthesis</td>
<td>Acyl carrier protein reductase (InhA)</td>
</tr>
<tr>
<td>Thioacetazone (11)</td>
<td>1</td>
<td>Bacteriostatic</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Quinolones (12)</td>
<td>0.2-4</td>
<td>Bactericidal</td>
<td>Inhibition of DNA synthesis</td>
<td>DNA gyrase</td>
</tr>
</tbody>
</table>

New drugs that offer improvements over current therapies are desperately needed (Glickman, 2006). New chemical entities with novel mechanisms of action will most likely possess activity against MDR-TB. However, these alone will not provide the breakthrough that is needed. The key to improving therapy is to develop new agents with potent sterilizing activity that will lead to a shortening of the duration of chemotherapy (Tomioka, 2002; Duncan & Barry, 2004).
(methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa* (Kapadia, 1977; Kapadia, 1980; Kapadia, 1993). Substituted isatins isolated as well, from fungi e.g.: 6-(3'-methylbuten-2'-yl) isatin (14) was isolated from *Streptomyces albus* (Grafe & Radics 1986) and 5-(3'-methylbuten-2'-yl) isatin (15) from *Chaetomium globosum* (Breinholt, 1996). Isatin has also been found to be a component of coal tar (Yan, 1992).

![Chemical structure of isatin](image)

In recent years, Schiff and Mannich bases of isatin are reported to exhibit broad-spectrum chemotherapeutic properties such as antiviral (Sriram & Yogeeswari, 2003; Pirrung, 2005; Bal, 2005), anti-TB (Karah, 1998; Sriram, 2005), antifungal and antibacterial activities (Pandeya, 1999; Pandeya, 2000). Methisazone (16) for example plays an important role as prophylactic agent against several viral diseases (Sethi, 2002).

![Chemical structure of methisazone](image)

Furthermore, it was recently reported that Schiff and Mannich bases of isatin are exhibiting significant anti-TB activity (Karal, 2007). Accordingly, isatin is a versatile lead molecule for potential bioactive agents. Special attention, however, will be paid in the following section for the anti-TB activity of isatin derivatives.

4. Isatin derivatives with potential Anti-TB activity

Diversity of isatin derivatives with potential anti-TB activities. Some of these derivatives are natural products, for example, tryptanthrin (17), an alkaloid from the Chinese herb *Strobilanthes cusia* showed potent activity against MTB H$_3$Rv (1mg/l) (Mitscher & Baker 1998).

![Chemical structure of tryptanthrin](image)

This finding stimulates the synthesis of several analogs of 17. Among the synthesized analogs, compounds 17a and 17b are approximately 100–fold more potent *in vitro* than 17 against MTB. Unfortunately, they have been extensively evaluated *in vivo* but failed to cure infected mice (Mitscher & Baker 1998).

Schiff and Mannich bases of isatin gained the major interest as potential anti-TB derivatives. In this regard, a series of Schiff bases of isatin with potential anti-TB activity against MTB were synthesized (18a–c), as well as their corresponding Mannich bases (19a–h). These derivatives were tested against MTB strain H$_3$Rv at a single concentration of 6.25 μg/ml. As a general pattern bases (19a–h) showed greater activity with inhibitory percentage range from 92–100%, however, compound 18b of the Schiff’s bases showed inhibitory activity of 82% (Sriram, 2005 b).

In a continuation of the previous study, another series of isatin derivatives (20) has been synthesized. The synthesized compounds were screened against MTB strain H$_3$Rv. Among the synthesized compounds, three compounds (20 n, 20 o and 20 p) showed complete inhibition (100%) of MTB in the primary screening at 6.25 μg/ml. In the secondary level screening the actual minimum inhibitory concentration (MIC) of these compounds were found to be 3.13 μg/ml (Sriram, 2005c). Extended series of the foregoing derivatives with 5-methyl isatoic anhydride has been synthesized. The synthesized compounds were also screened against MTB strain H$_3$Rv. Surprisingly, the only active three compounds (21j, 21k and 21l) showed complete inhibition (100%) of MTB in the primary screening. The MIC of these compounds was found to be 3.13 μg/ml (Sriram, 2005d).

5-Fluoroisatin derivatives were also synthesized (22), and the synthesized compounds were screened against MTB strain H$_3$Rv. Four compounds (22l–o) showed complete inhibition (100%) of MTB in the primary screening at 6.25 μg/ml. In the secondary level screening the actual MIC of these compounds were found to be 3.13 μg/ml (Sriram, 2004).

Further exploration for the anti-TB activity of the aminopyrimidinimino isatin derivatives was studied. Accordingly, a series of these analogs with fluoroquinolones has been synthesized (23) (Sriram, 2006 a).

All the compounds (23a–l) exhibited greater than 90% inhibition against MTB H$_3$Rv strain at 6.25 μg/ml in the
primary level screening. These compounds were further screened at the secondary level at and below 6.25 μg/ml for determination of MIC value. Two compounds, 23b and 23k, showed promising activity at the secondary level screening with a MIC value of 1.56 and the standard drug ciprofloxacin (Sriram, 2006). It was found that Compound 23a, 23c and 23f revealed inhibition of the supercoiling reaction catalyzed by the DNA gyrase enzyme at a concentration of 50 μg/ml. Compounds 23g, 23i, 23j and 23k did not interfere with the supercoiling reaction at the same concentration, but showed some degree of resistance to this process.

0.78 μg/ml respectively. Compound 23k demonstrated a pronounced decrease of bacterial load in lung and spleen tissues compared to the control and better than...
The observed anti-TB activities of aminopyrimidiniminoisatin and fluoroquinolones encouraged further derivatization of isatin fluoroquinolones. Consequently, various Mannich bases of 7-ciprofloxacin with 5-substituted isatins have been synthesized (24a–l) and evaluated for antimycobacterial activity in vitro against MTB H37Rv strain (Sriram, 2005d).

In the preliminary screening, all the compounds inhibited MTB with 95–100%. In the secondary level, five compounds 24a, g–i, and k showed most promising activity with MIC of <2 nM and all the compounds were more potent than parent compound ciprofloxacin (MIC = 6.04 nM) except 24l. Compound 24k was found to be the most active compound with MIC of 1.21 nM and was five times more potent than ciprofloxacin in vitro. The preliminary antimycobacterial evaluation results showed that compounds with bromo substitution in the C-5 position of isatinimino derivatives have shown promising results. Compound 24h was investigated in vivo and was found to be moderately active in reducing M. Smegmatis was tested. All the tested compounds revealed potent inhibitory activity compared to ciprofloxacin (Sriram, 2005d).

In order to optimize the anti-TB activity of isatiniminofluoroquinolones, Mannich bases of 7-gatifloxacin have been synthesized (25a–p) (Sriram, 2006b).

All compounds were screened for their antimycobacterial activity against MTB H37Rv strain and MDR-TB. Among the synthesized compounds, four compounds (25d, 25e, 25m and 25p) were more active (MIC < 0.2 µg/ml) and five compounds (25a, 25h, 25l, 25n and 25o) were equipotent (MIC = 0.2 µg/ml) to that of gatifloxacin against MTB. Compound 25d was found to be the most active compound in vitro with an MIC of 0.0125 µg/ml against MTB and was 16 times more potent than gatifloxacin (Sriram, 2006b). All compounds were more active with MIC of ≤ 0.78 µg/ml against MDR-TB, when compared to gatifloxacin (MIC 3.12 µg/ml). Compound 25d was found to be the most
23 a-l

\[ R' = \text{CH}_3, \text{Cl}, \text{Br}, \text{F} \]
\[ R = \text{H}, \text{CH}_3 \]
\[ R_1 = \text{CONH}_2 \]

24a-l

\[ R = \text{H}, \text{Cl}, \text{Br}, \text{CH}_3 \]
\[ R' = \text{CH}_3, \text{Cl}, \text{Br}, \text{F} \]
\[ R_1 = \text{CONH}_2, \text{CSNH}_2, \text{CONH} \]

25a-p

\[ R = \text{H}, \text{Cl}, \text{F}, \text{CH}_3 \]
\[ R' = \text{CONH}_2, \text{CSNH}_2, \text{SO}_2\text{NH} \]
26 a-k  $R_1=F$

26 a-k  $R_2=a, CH_3; b, C_2H_5; c, CH_2=CHCH_3; d, n-C_3H_7; e, cyclo-C_4H_9; f, C_6H_5; g, CH_2=CH_2; h, 4-CH_3C_6H_4; i, 4-ClC_6H_4; j, 4-FC_6H_4.$

26 i-v  $R_1=NO_2$

26 i-v  $R_2=I, CH_3; m, C_2H_5; n, CH_2=CH-CH_3; o, n-C_4H_9; p, cyclo-C_6H_11; q, ... C_6H_5; h, 4-CH_3C_6H_4; i, 4-ClC_6H_4; j, 4-FC_6H_4.$

29 a-s

29 a-j  $R_1=NO_2; R_3=H$

29 a-j  $R_2=a, CH_3; b, C_2H_5; c, CH_2=CHCH_3; d, n-C_3H_7; e, cyclo-C_4H_9; f, C_6H_5; g, 4-CH_3C_6H_4; h, 4-CH_3C_6H_4; i, 4-ClC_6H_4; j, 4-FC_6H_4.$

29 k-s  $R_1=NO_2; R_3=CH_3$

29 k-s  $R_2=k, CH_2=CHCH_3; l, n-C_4H_9; m, cyclo-C_4H_9; n, C_6H_5; o, 4-CH_3C_6H_4; p, 4-BrC_6H_4; q, 4-ClC_6H_4; r, 4-FC_6H_4; s, 4-NO_2C_6H_4.$
30 a-g R₁ = CH₃; R₂ = H
 R₃ = a, CH₂=CH₂; b, C₆H₅; c, C₆H₅CH₂;
d, 4-FC₆H₄; e, 2-BrC₆H₄; f, 3-BrC₆H₄; g, 4-NO₂C₆H₄.

30 b-t R₁ = CF₃O; R₂ = H
 R₃ = h, CH₂; i, C₆H₅; j, CH₂=CH₂; k, C₆H₅; l, cyclo-C₆H₄;
m, C₆H₅CH₂; n, C₆H₅; o, 4-CH₃C₆H₄; p, 4-CH₂OC₆H₄; q, 4-FC₆H₄;
r, 4-CIC₆H₄; s, 4-BrC₆H₄; t, 4-NO₂C₆H₄.

31 a-i R₁ and R₂ = CH₃;
 R₃ = a, CH₂; b, C₆H₅; c, CH₂=CH₂; d, C₆H₅; e, C₆H₅CH₂;
f, 4-FC₆H₄; g, 2-BrC₆H₄; h, 3-BrC₆H₄; i, 4-NO₂C₆H₄.

31 j-n R₁, CF₃O; R₂ = CH₃
 R₃ = j, CH₂; k, C₆H₅; l, CH₂=CH₂; m, C₆H₅; n, cyclo-C₆H₄;
o, C₆H₅CH₂; p, C₆H₅; q, 4-CH₃C₆H₄; r, 4-FC₆H₄; s, 4-CIC₆H₄;
t, 4-BrC₆H₄; u, 4-NO₂C₆H₄.

32 a-m R₁, CF₃O
 R₃ = a, CH₂; b, C₆H₅; c, CH₂=CH₂; d, C₆H₅; e, cyclo-C₆H₄;
f, C₆H₅CH₂; g, C₆H₅; h, 4-CH₂OC₆H₄; i, 4-CH₃C₆H₄;
j, 4-FC₆H₄; k, 4-CIC₆H₄; l, 4-BrC₆H₄; m, 4-NO₂C₆H₄.

33 a-g R₁ = CH₃; R₂ = H
 R₃ = a, CH₂; b, C₆H₅; c, cyclo-C₆H₄; d, C₆H₅;
e, 4-CH₂OC₆H₄; f, 4-CIC₆H₄; g, 4-BrC₆H₄.

33 h-i R₁ and R₂ = CH₃
 R₃ = h, cyclo-C₆H₄; i, C₆H₅; j, 4-CH₃C₆H₄; k, 4-CIC₆H₄; l, 4-BrC₆H₄.

34 a-f R₁ = N-NH-CS-NH₂
 a = R₁, H; R₂, H
 b = R₁, F; R₂, H
 c = R₁, F; R₂, morpholino methyl
d = R₁, F; R₂, piperidino methyl
e = R₁, Br; R₂, piperidino methyl
f = R₁, Br; R₂, hydroxy methyl

35 a-f R₁ = N-NH-CO-C₅H₄N
 a = R₁, H; R₂, H
 b = R₁, F; R₂, H
 c = R₁, F; R₂, morpholino methyl
d = R₁, F; R₂, piperidino methyl
e = R₁, Br; R₂, piperidino methyl
f = R₁, Br; R₂, hydroxy methyl

36 a-g R₁ = a, H; b, CH₃; c, n-C₃H₇; d, allyl; e, propyl; f, butyl; g, CH₂OH.

38a-m

39a-m

40a-m

Ar, a = phenyl; b = 4-chlorophenyl;
c = 4-methylphenyl; d = 4-methoxyphenyl;
e = 4-fluorophenyl; f = 2-chlorophenyl;
g = 2-methylphenyl; h = 2-methoxyphenyl;
i = 3-fluorophenyl; j = 2,4-dichlorophenyl;
k = 2-thienyl; l = 1-naphthyl; m = 2-furyl
potent (MIC 0.05 μg/ml). In the in vivo animal model 25d decreased the bacterial load in lung and spleen tissues. Furthermore, compound 25d was also found to be equally active as gatifloxacin in the inhibition of the supercoiling activity of wild-type M. tuberculosis DNA gyrase with IC₅₀ of 3.0 μg/ml (Sriram, 2006b).

Thiosemicarbazones of 5–fluoro and nitro isatin derivatives (26a–v, 27a–r, 28a–l and 29a–s) were synthesized and evaluated for in vitro anti–TB activity against MTB H₃7Rv (Karak, 2007).

It was observed that in isatin-3- thiosemicarbazones and its N-Mannich bases, most of 5-nitroisatin derivatives were more active than 5- fluoroisatin derivatives. Among the tested compounds, 26 r and 28e exhibited significant inhibitory activity with MIC of 6.25μg/ml (Karak, 2007). Furthermore, the presence of Mannich bases with morpholinoo moiety of 5- nitroisatin derivatives seems to have a significant impact on the resultant anti-TB activity (Guzel, 2008).

In the light of earlier study, new 5-methyl/ trifluoromethoxyisatin-3-thiosemicarbazone derivatives were synthesized (30−33), in order to optimized the anti-TB activity of these derivatives (Guzel, 2008).

In vitro anti-TB activity of the synthesized compounds revealed a wide variety of activity (MIC 0.795–3.568 μg/ml) and compound 33 c was the most potent one with IC₅₀ 0.795μg/ml (Guzel, 2008).

In another study isatin-3-thiosemicarbazone (34), isatin-3-isonicotinylhydrazone (35) and their derivatives revealed significant activity against MTB H₃7Rv. Derivatives of 5-fluoroisatin-3-isonicotinylhydrazone derivatives showed higher activity and have significant activity on rimifon-resistant strains of MTB (Hung, 2000).

3-Isonicotinylhydrazone of 1-alkyl isatin derivatives (36) have been synthesized and investigated against bovine, human sensitive and human resistant strains of MTB (Aboul-Fadl, 2003).

Compounds (36a, 36d, 36f and 36g) exhibited potent growth inhibitory activity against the tested strains close to the INH; however the later has no activity against human resistant strain (Aboul-Fadl, 2003).

In extension of the previous study, Mannich bases of isatin-3-isonicotinylhydrazone (37) have been synthesized. All the synthesized compounds were tested for their antitubercular activity against bovine MTB at a dose level of 10 μg/ml. The tested compounds exhibited comparable inhibitory activity against the tested TB strain compared to INH (Hussein, 2005).

Recently, several spiro–piperidin–4–ones of isatin was synthesized (38–40) (Kumar, 2008).

These compounds were evaluated for their in vitro and in vivo activity against MTB, MDR-TB, and Mycobacterium smegmatis. Compound 39e was found to be the most active in vitro with a MIC value of 0.07 μM against MTB and was 5.1 and 67.2 times more potent than INH and ciprofloxacin, respectively. In the in vivo study, compound 39e decreased the bacterial load in lung and spleen tissues (Kumar, 2008).

Conclusion

New drugs for TB are urgently needed. Unfortunately, there are few new drugs in the pipeline, making it unlikely that new compounds will be available to respond to the pressing need. Isatin is a versatile lead molecule for potential bioactive agents and its derivatives were reported to possess potent anti-TB activity. In the mean time no isatin derivative clinically used in anti-TB therapy, however, research will hopefully continue to shed light on ways to increase the therapeutic efficacy and specificity of isatins.

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