



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 (Marwick, 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 persisting, 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, monocytes and macrophages are recruited to the area surrounding the bacilli, the bacilli slowly replicate and

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Table 1: Commonly used TB drugs and their targets

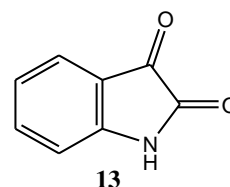
	Drug	MIC (µg/ml)	Effect on bacterial cell	Mechanism of action	Targets
First-line TB drugs	Isoniazid (1)	0.01-0.2	Bactericidal	Inhibition of cell wall mycolic acid synthesis and other multiple effects on DNA, lipids, carbohydrates, and NAD metabolism.	Multiple targets including acyl carrier protein reductase (InhA)
	Rifampin (2)	0.05-0.5	Bactericidal	Inhibition of RNA synthesis	RNA polymerase β subunit
	Pyrazinamide (3)	20-100 pH 5.5-6.0	Bacteriostatic/ Bactericidal	Disruption of membrane transport and energy depletion	Membrane energy metabolism
	Ethambutol (4)	1-5	Bacteriostatic	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl transferase
	Streptomycin (5)	2-8	Bactericidal	Inhibition of protein synthesis	Ribosomal S12 protein and 16S rRNA
Second-line TB drugs	Kanamycin (6)	1-8	Bactericidal	Inhibition of protein synthesis	16S rRNA
	Cycloserine (7)	5-20	Bacteriostatic	Inhibition of peptidoglycan synthesis	D-alanine racemase
	<i>p</i> -Aminosalicylic acid (8)	1-8	Bacteriostatic	Inhibition of folic acid and iron metabolism?	Unknown
	Ethionamide (9)	0.6-2.5	Bacteriostatic	Inhibition of mycolic acid synthesis	Acyl carrier protein reductase (InhA)
	Thioacetazone (11)	1	Bacteriostatic	Unknown	Unknown
	Quinolones (12)	0.2-4	Bactericidal	Inhibition of DNA synthesis	DNA gyrase

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).

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

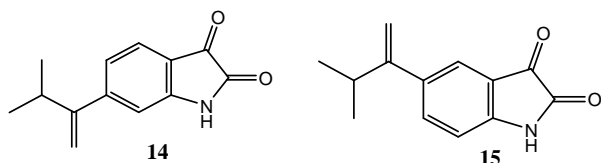
Isatin (1H-indoline-2,3-dione, **13**) is an endogenous indole found in the mammalian brain, peripheral tissues, and body fluids. It exhibits many neurophysiological and neuropharmacological effects (Fedchenko, 2008). It is a versatile compound with a diversity of effects including antibacterial (Pandeya & Sriram, 1998; Sarangapani & Reddy, 1994; Varma & Nobles, 1975; Loncle, 2004; Papakonstantinou-Garoufalias, 2002; Vicini, 2002), anticonvulsant (Sridhar, 2002; Varma, 2004; Popp, 1989; Küçükgülzel, 2003), antifungal (Loncle, 2004; Papakonstantinou-Garoufalias, 2002; Vicini, 2002; Pandeya, 1999 a-c), antiviral (Varma & Nobles, 1967; Singh, 1983; Logan, 1975; Zhou, 2006), anti-HIV (Pandeya, 1998; Pandeya, 1999 e; Pandeya, 2000 a,b), antiprotozoal (Imam & Varma, 1975; Varma &

Khan, 1977), antihelminthic (Sarciron, 1993; El-Sawi, 1998), anti-TB (Karah, 1998; Sriram, 2005 a; Küçükgülzel, 1999; Kaymakçioğlu, 2002; Patole, 2003; Maccari, 2005; Cocco, 1999; Karalı, 2002; Rando, 2002), anticancer (Holla, 2000), antimycobacterial (Pandeya, 2005), antimalarial (Pal, 1991; Chianzu, 2005; Melnyk, 2007) and anti-inflammatory activities (Todeschini, 1998; Gaston, 1996).

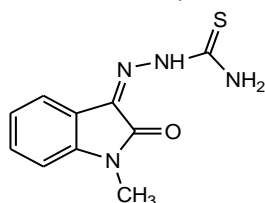


Isatin was first obtained by Erdman and Laurent in **1841** as a product from the oxidation of indigo by nitric and chromic acids (Da Silva, 2001). In nature, isatin is found in plants of the genus *Isatis* (Guo & Chen, 1986), in *Calanthe discolor* (Yoshikawa, 1998) and in *Couroupita guianensis* (Bergman, 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

(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).



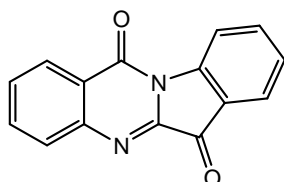
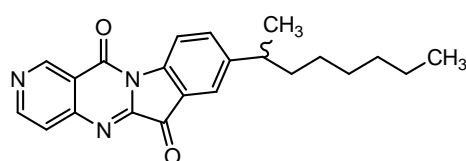
In recent years, Schiff and Mannich bases of isatin are reported to exhibit broad-spectrum chemotherapeutic properties such as antiviral (Sriram & Yogeewari, 2003; Pirrung, 2005; Bal, 2005), anti-TB (Karah, 1998; Sriram, 2005), antifungal and antibacterial activities (Pandeya, 1999; Pandeya, 2000). Methisazone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

**16**

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 H₃₇Rv (1mg/l) (Mitscher & Baker 1998).

**17****17a**

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 H₃₇Rv 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).

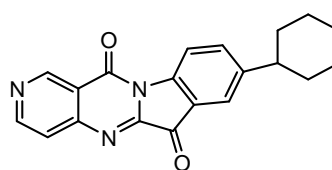
In a continuation of the previous study, another series of isatin derivatives (**20**) has been synthesized. The synthesized compounds were screened against MTB strain H₃₇Rv. Among the synthesized compounds, three compounds (**20 n**, **20 o** and **20 p**) showed complete inhibition (100%) of MTB in 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).

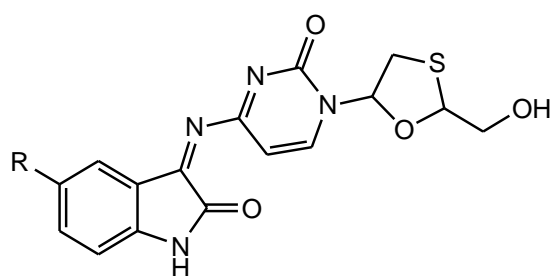
Extended series of the foregoing derivatives with 5-methyl isatin moiety has been synthesized. The synthesized compounds were also screened against MTB strain H₃₇Rv. Surprisingly, the only active three compounds (**21j**, **21k** and **21l**) showed complete inhibition (100%) of MTB in the primary screening. The MIC of these compounds was found to be 3.13 µg/ml (Sriram, 2005d).

5-Flouroisatin derivatives were also synthesized (**22**), and the synthesized compounds were screened against MTB strain H₃₇Rv. 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).

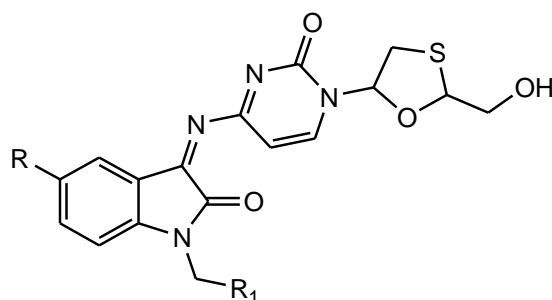
All the compounds (**23a-l**) exhibited greater than 90% inhibition against MTB H₃₇Rv strain at 6.25 µg/ml in the

**17b**

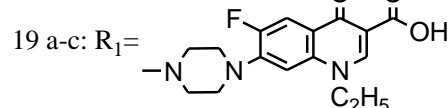
**18a-c**

R=H, Cl, F

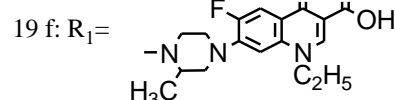
18 R= a, H ; b, F ; c, Cl .

**19a-h**

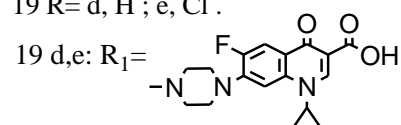
19 R= a, H ; b, Cl ; c, F .



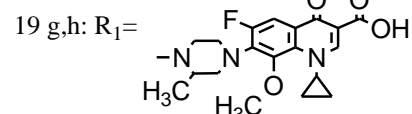
19 R=f, Cl .



19 R= d, H ; e, Cl .

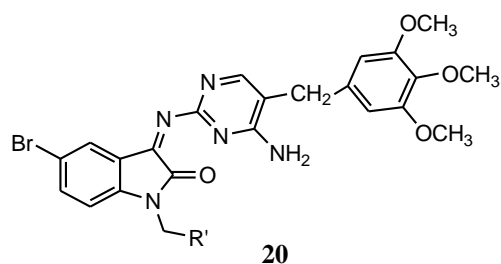
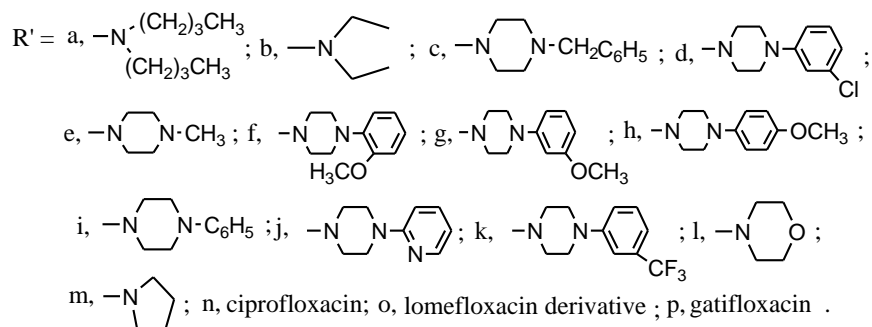


19 R= g, Cl ; h, F .



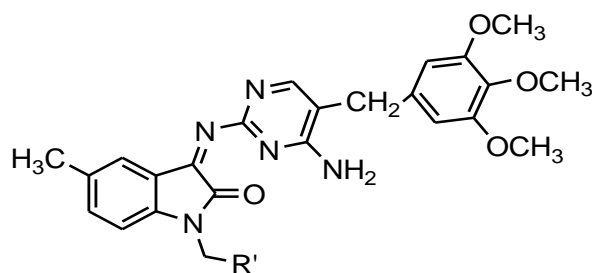
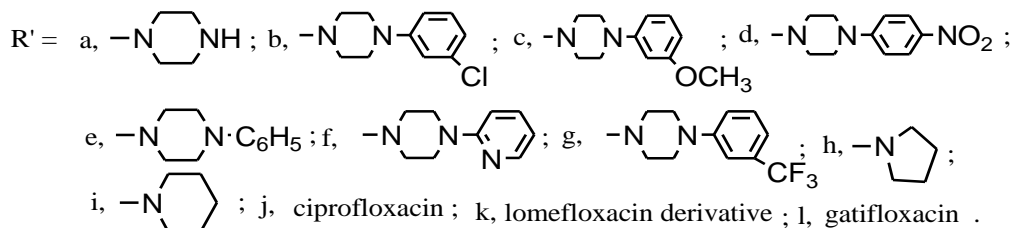
primary level screening. These compounds were further screened at the secondary level at and below 6.25 $\mu\text{g/ml}$ for determination of MIC value. Two compounds, **23b** and **23k**, showed promising activity at the secondary level screening with a MIC value of 1.56 and

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 $\mu\text{g/ml}$. Compounds **23g**, **23i**, **23j** and **23k** did not interfere with the

**20**

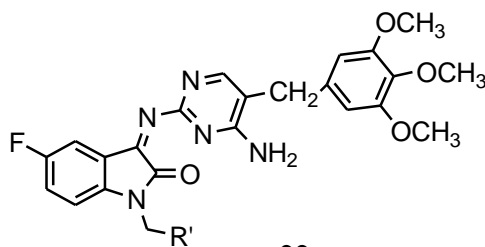
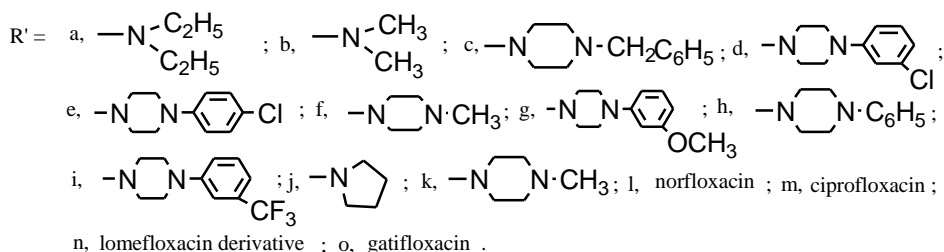
0.78 $\mu\text{g/ml}$ respectively. Compound **23k** demonstrated a pronounced decrease of bacterial load in lung and spleen tissues compared to the control and better than

supercoiling reaction at the same concentration, but showed some degree of resistance to this process

**21**

when compared to the control, i.e. supercoiling in the absence of drugs (Sriram,2006b).

bacterial count in spleen. The ability of compounds **24g**, **24h** and **24k** to inhibit DNA gyrase isolated from

**22**

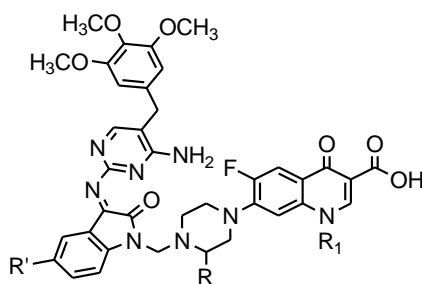
The observed anti-TB activities of aminopyrimidinoinisatin and fluoroquinolones encouraged further derivatization of isatin fluoroquinolones. Consequently, various Mannich bases of 7-ciprofloxacin with 5-substituted isatins have been synthesized (**24a-l**) and evaluated for antimycobacterial activity *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 isatinimino fluoroquinolones, 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



R' = CH₃, Cl, Br, F .

R = H, CH₃ .

R₁ = , -C₂H₅ .

23 a-l

a = R', Cl ; R, H ; R₁,

b = R', Cl ; R, CH₃ ; R₁, -C₂H₅

c = R', Cl ; R, CH₃ ; R₁,

d = R', Br ; R, H ; R₁,

e = R', Br ; R, CH₃ ; R₁, -C₂H₅

f = R', Br ; R, CH₃ ; R₁,

g = R', CH₃ ; R, H ; R₁,

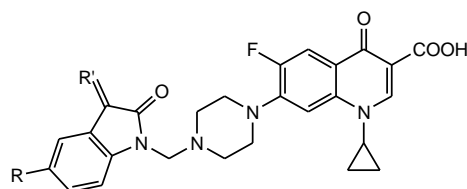
h = R', CH₃ ; R, CH₃ ; R₁, -C₂H₅

i = R', CH₃ ; R, CH₃ ; R₁,

j = R', F ; R, H ; R₁, -C₂H₅

k = R', F ; R, H ; R₁,

l = R', F ; R, CH₃ ; R₁,



24a-l

R = H, Cl, Br, CH₃ .

R' = O, -NNHCONH₂, -NNHCSNH₂ .

a = R = H, R' = O .

b = R = Cl, R' = O .

c = R = Br, R' = O .

d = R = CH₃, R' = O .

e = R = H, R' = -NNHCONH₂ .

f = R = Cl, R' = -NNHCONH₂ .

g = R = Br, R' = -NNHCONH₂ .

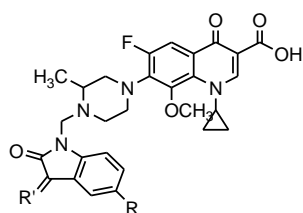
h = R = CH₃, R' = -NNHCONH₂ .

i = R = H, R' = -NNHCSNH₂ .

j = R = Cl, R' = -NNHCSNH₂ .

k = R = Br, R' = -NNHCSNH₂ .

l = R = CH₃, R' = -NNHCSNH₂ .



25a-p

R = H, Cl, F, CH₃ .

R' = =NNHCONH₂, =NNHCSNH₂, =NNHC-, =N--SO₂NH-

a = R, F; R', =NNHCONH₂

c = R, Cl; R', =NNHCONH₂

e = R, F; R', =NNHCSNH₂

g = R, Cl; R', =NNHCSNH₂

i = R, F; R', =NNHC-

k = R, Cl; R', =NNHC-

m = R, Cl; R', =N--SO₂NH-

o = R, H; R', =N--SO₂NH-

b = R, CH₃; R', =NNHCONH₂

d = R, H; R', =NNHCONH₂

f = R, CH₃; R', =NNHCSNH₂

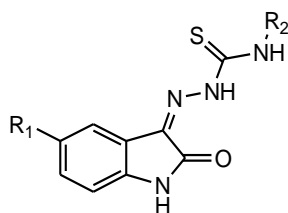
h = R, H; R', =NNHCSNH₂

j = R, CH₃; R', =NNHC-

l = R, H; R', =NNHC-

n = R, F; R', =N--SO₂NH-

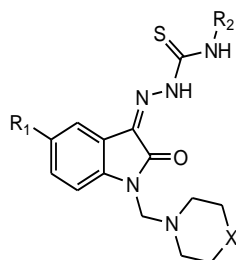
p = R, CH₃; R', =N--SO₂NH-

26 a-k R₁= F

26 a-k R₂= a, CH₃; b, C₂H₅; c, CH₂-CH=CH₂;
d, *n*-C₄H₉; e, *cyclo*-C₆H₁₁; f, C₆H₅CH₂;
g, C₆H₅; h, 4-CH₃C₆H₄; i, 4-ClC₆H₄;
j, 4-FC₆H₄; k, 4-NO₂C₆H₄ .

26 l-v R₁= NO₂

26 l-v R₂= l, CH₃; m, C₂H₅; n, CH₂-CH=CH₂;
o, *n*-C₄H₉; p, *cyclo*-C₆H₁₁; q, C₆H₅;
r, 4-CH₃C₆H₄; s, 4-BrC₆H₄; t, 4-ClC₆H₄;
u, 4-FC₆H₄; v, 4-NO₂C₆H₄ .



27 and 28

27a-r R₁= F

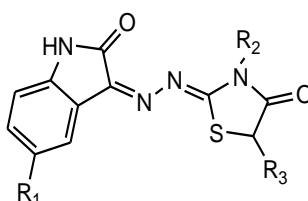
a= R₂, CH₃; X, O
b= R₂, CH₃; X, CH₂
c= R₂, C₂H₅; X, O
d= R₂, C₂H₅; X, CH₂
e= R₂, CH₂-CH=CH₂; X, O
f= R₂, CH₂-CH=CH₂; X, CH₂
g= R₂, *n*-C₄H₉; X, O
h= R₂, *n*-C₄H₉; X, CH₂
i= R₂, *cyclo*-C₆H₁₁; X, O

j= R₂, C₆H₅CH₂; X, O
k= R₂, C₆H₅CH₂; X, CH₂
l= R₂, C₆H₅; X, O
m= R₂, C₆H₅; X, CH₂
n= R₂, 4-CH₃C₆H₄; X, CH₂
o= R₂, 4-ClC₆H₄; X, O
p= R₂, 4-ClC₆H₄; X, CH₂
q= R₂, 4-FC₆H₄; X, O
r= R₂, 4-FC₆H₄; X, CH₂

28 a-l R₁= NO₂

a= R₂, CH₃; X, O
b= R₂, CH₂-CH=CH₂; X, O
c= R₂, CH₂-CH=CH₂; X, CH₂
d= R₂, *n*-C₄H₉; X, O
e= R₂, *cyclo*-C₆H₁₁; X, O
f= R₂, *cyclo*-C₆H₁₁; X, CH₂

g= R₂, C₆H₅; X, O
h= R₂, C₆H₅; X, CH₂
i= R₂, 4-CH₃C₆H₄; X, O
j= R₂, 4-CH₃C₆H₄; X, CH₂
k= R₂, 4-ClC₆H₄; X, O
l= R₂, 4-ClC₆H₄; X, CH₂



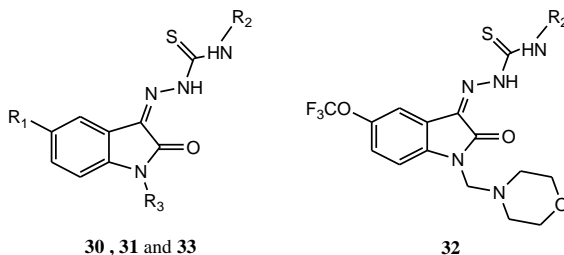
29 a-s

29 a-j R₁= NO₂ R₃= H

29 a-j R₂= a, CH₃; b, C₂H₅; c, CH₂-CH=CH₂;
d, *n*-C₄H₉; e, *cyclo*-C₆H₁₁; f, C₆H₅;
g, 4-CH₃C₆H₄; h, 4-BrC₆H₄; i, 4-ClC₆H₄;
j, 4-FC₆H₄ .

29 k-s R₁= NO₂ R₃= CH₃

29 k-s R₂= k, CH₂-CH=CH₂; l, *n*-C₄H₉; m, *cyclo*-C₆H₁₁;
n, C₆H₅; o, 4-CH₃C₆H₄; p, 4-BrC₆H₄;
q, 4-ClC₆H₄; r, 4-FC₆H₄; s, 4-NO₂C₆H₄ .



30 a-g R₁= CH₃, R₃= H

R₂= a, CH₂CH=CH₂; b, C₄H₉; c, C₆H₅CH₂; d, 4-FC₆H₄; e, 2-BrC₆H₄; f, 3-BrC₆H₄; g, 4-NO₂C₆H₄ .

30 h-t R₁= CF₃O, R₃= H

R₂= h, CH₃; i, C₂H₅; j, CH₂CH=CH₂; k, C₄H₉; l, *cyclo*-C₆H₁₁; m, C₆H₅CH₂; n, C₆H₅; o, 4-CH₃C₆H₄; p, 4-CH₃OC₆H₄; q, 4-FC₆H₄; r, 4-ClC₆H₄; s, 4-BrC₆H₄; t, 4-NO₂C₆H₄ .

31 a-i R₁ and R₃= CH₃

R₂= a, CH₃; b, C₂H₅; c, CH₂CH=CH₂; d, C₄H₉; e, C₆H₅CH₂; f, 4-FC₆H₄; g, 2-BrC₆H₄; h, 3-BrC₆H₄; i, 4-NO₂C₆H₄ .

31 j-u R₁= CF₃O; R₃= CH₃

R₂= j, CH₃; k, C₂H₅; l, CH₂CH=CH₂; m, C₄H₉; n, *cyclo*-C₆H₁₁; o, C₆H₅CH₂; p, C₆H₅; q, 4-CH₃C₆H₄; r, 4-FC₆H₄; s, 4-ClC₆H₄; t, 4-BrC₆H₄; u, 4-NO₂C₆H₄ .

32 a-m R₁= CF₃O

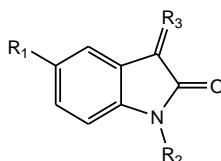
R₂= a, CH₃; b, C₂H₅; c, CH₂CH=CH₂; d, C₄H₉; e, *cyclo*-C₆H₁₁; f, C₆H₅CH₂; g, C₆H₅; h, 4-CH₃C₆H₄; i, 4-CH₃OC₆H₄; j, 4-FC₆H₄; k, 4-ClC₆H₄; l, 4-BrC₆H₄; m, 4-NO₂C₆H₄ .

33 a-g R₁= CH₃, R₃= H

R₂= a, CH₃; b, C₂H₅; c, *cyclo*-C₆H₁₁; d, C₆H₅; e, 4-CH₃C₆H₄; f, 4-ClC₆H₄; g, 4-BrC₆H₄ .

33 h-l R₁ and R₃= CH₃

R₂= h, *cyclo*-C₆H₁₁; i, C₆H₅; j, 4-CH₃C₆H₄; k, 4-ClC₆H₄; l, 4-BrC₆H₄ .

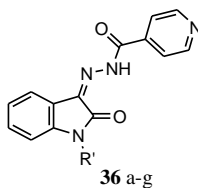


34 a-f R₃= N-NH-CS-NH₂

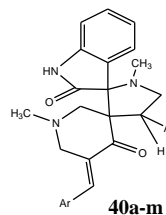
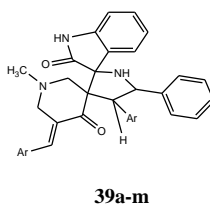
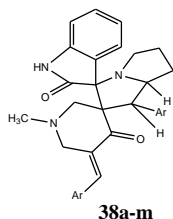
a=R₁, H; R₂, H
b= R₁, F; R₂, H
c=R₁, F; R₂, morpholino methyl
d= R₁, F; R₂, piperidino methyl
e= R₁, Br; R₂, piperidino methyl
f= R₁, Br; R₂, hydroxy methyl

35a-f R₃= 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



R'= a, H; b, CH₃; c, *n*-C₃H₇; d, allyl; e, propyl; f, benzyl; g, CH₂OH.



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 (Kara, 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 (Kara, 2007). Furthermore, the presence of Mannich bases with morpholino moiety of 5- nitroisatin derivatives seems to have a significant impact on the resultant anti-TB activity (Güzel, 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 (Güzel, 2008).

In vitro anti-TB activity of the synthesized compounds revealed a wide variety of activity (IC₉₀, 0.795–3.568 µg/ml) and compound **33 c** was the most potent one with IC₉₀ 0.795µg/ml (Güzel, 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 rifampin-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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