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Review Article

An Insight into the Anti-Tubercular Potential of Schiff Bases

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ABSTRACT
Tuberculosis (TB) has been declared by WHO as a 'global public health emergency' and is amongst the worldwide health threats today. Despite over a decade of relentless drug development research, tuberculosis remains a major public health problem with a leading cause of infectious death worldwide. Worldwide resurgence of TB is due to its prevalence in synergy with the AIDS epidemic and the outbreak of multidrug resistant (MDR) TB. Hence the search for new promising drugs to combat the drug resistance and control the disease is clearly a priority. Schiff bases or azomethines are synthetically accessible and structurally diverse compounds, typically formed by simple condensation of a carbonyl group with a primary amine. Therapeutically, Schiff bases have been shown to be interesting moieties for the design of efficient antitubercular agents. In an effort to discover new and effective chemotherapeutic agent for the treatment of TB, the antimycobacterial activities of various Schiff bases and their complexes have been reported. This review enlightens a comprehensive review of the recent reports on the anti-tubercular potencies of Schiff bases and their metal complexes.

KEYWORDS: Schiff Bases; mycobacterium; tuberculosis; Isoniazid; antimycobacterial activity; MDR-TB.

INTRODUCTION

Tuberculosis (TB) is a major global health problem and is one of the oldest diseases known to humanity. Throughout history, TB has been among the world's most deadly epidemics [1]. More than a decade ago the World Health Organization declared tuberculosis "a global health emergency" [2]. Nevertheless, the disease remains the global health concern and the leading fatal infection affecting adults in developing nations [3]. Tuberculosis, also known as 'white plaque'[4], is an infectious epidemic caused by diverse species of mycobacteria, collectively termed the *tubercle bacilli* [5], which includes *Mycobacterium tuberculosis, M. bovis, M. africanum*, *M. caprae, M. microti, M. pinnipedii* and *M. canettii* [6]. It typically attacks the lung (termed as pulmonary tuberculosis) but can also act upon other organs (termed as extra-pulmonary tuberculosis).

About 1.5 million people, comprising of 1.1 million cases of HIV-negative and 0.4 million HIV-positive were killed by TB in 2014. The death includes 8.9 lakhs, 4.8 lakhs and 1.4 lakhs of men, women and children respectively. Globally, 9.6 million population are estimated to get infected by the disease including 1.0 million children. Among the 9.6 million new cases of TB

in 2014, the major cases (58%) were reported from the Western Pacific and South-East Asian regions. Of the global total, India, China and Indonesia had the major proportion of TB cases with 23%, 10% and 10% respectively. The higher toll due to TB is inadmissible, however with a timely diagnosis and correct therapy, the disease TB can be cured. [7].

The complex structure and characteristics of the mycobacterial cell wall, the lengthy treatment duration, multi-resistance and extensive drug resistance developed by the pathogen favors the recurrence of the infection and thus making difficult to treat the disease clinically. Moreover, the occurrence of TB in synergy with AIDS enhances the risk of infection by multi-fold [8] and the subsequent death toll escalated by 12% in the past two decades [9]. Hence, the unequivocal need is to discover new anti-TB drugs with enhanced activity with shorter duration of the therapy in drug resistant TB and to control the epidemic outbreak so as to completely eradicate this dreadful disease, prompted this review.

Schiff bases are one of the important classes of organic compounds which have many interesting properties and extensive applications in medicinal, agricultural, pharmaceutical fields and material science [10-13]. Structurally, a Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (>C=O) has been replaced by an azomethine group [14]. The first preparation of imines was reported in 1864, by Hugo Schiff [15]. The imine group present in such compounds has been shown to be indispensable to their biological activities [16,17]. The Schiff bases and their complexes were branded for their profound biological activities such as antimicrobial, antibacterial, antifungal, antiinflammatory, anticonvulsant, antitumor, antiproliferative, antioxidant, anti-tubercular and so on [18-27]. Since time, Schiff bases have been widely explored for industrial applications and pharmacological properties due to the importance of their medical assay as bactericide, antitumor and anticancer purposes. However, the biological activity of this class of compounds chiefly antitubercular activity deserves further investigation.

This article reviews the recent reports on the antitubercular potencies of Schiff bases and their metal complexes and enlightens the most noteworthy candidates exhibiting promising antimycobacterial activity.

IMPORTANCE OF SCHIFF BASES IN MEDICINAL CHEMISTRY AS ANTIMYCOBACTERIAL AGENT

A wide range of Schiff bases has been evaluated against various tubercular bacteria. This review describes the recent works reported in the past 10 years (2008–2018) in detail.

Cu(II) and Co(II) complexes of Schiff bases formed from 2-substituted carboxaldehydes *viz* pyrrole-2-carboxaldehyde (**1**), furan-2-carboxaldehyde (**2**), thiophene-2-carboxaldehyde (**3**) have been reported [28]. Proportion method was performed to test the antituberculosis activity of the synthesized ligands and complexes against H37Rv strain at 0.4-0.1 µg/mL. Enhanced activity was exhibited by most of the complexes than the reference isoniazid (INH) and the free ligands. The Co complex of ligand **1** exhibited outstanding activity (0.05 µg/mL) on 10^{-4} CFU/mL over the reference compound with highest activity (0.2µg/mL).

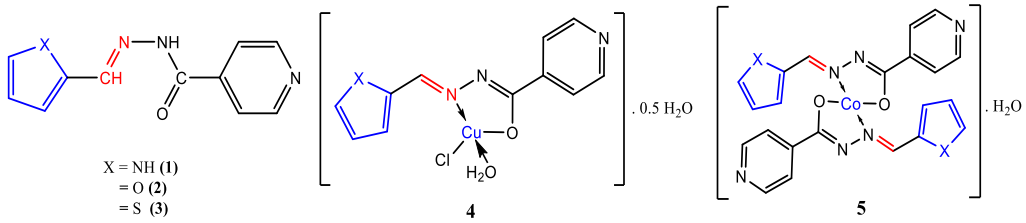


Fig. 1: Schiff bases formed from 2-substituted carboxyaldehydes

The antitubercular assays against *M. tuberculosis* of the Ag(I) and Zn(II) complexes of *N,N'*-bis(*trans*-cinnamaldehyde)ethane-1,2-diamine (EnCinn) **5** (fig. 2) have been reported [29]. The minimum inhibitory concentration (MIC) value of Ag complex **6** (22.7 µmol/L) was found to be closer to the reference silver sulfadiazine (SSD) (21.8 µmol/L), while the Zn

complex **7** was inactive. The ligand EnCinn showed no inhibition, witnessing the improvement in anti-TB activity upon complexation with Ag(I) and could afford new antitubercular drugs.

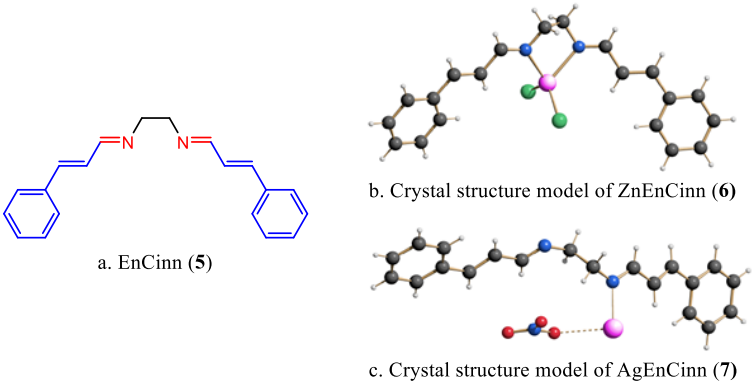


Fig. 2: Structure of Zn(II) and Ag(I) complexes of Schiff base (EnCinn)

Cu(II), Co(II) and Ni(II) complexes of mercapto pyrimidine Schiff bases having different substituents were synthesized by Jone Kirubavathy and Chitra [30]. The ligands **8** and **9** (fig. 3) were screened for the antituberculosis activity against *M. tuberculosis* strain (H37Rv) and pyrazinamide (MIC: 3.125 mg/mL), streptomycin (6.25 mg/mL), ciprofloxacin (3.125 mg/mL) were used as standards. The antituberculosis results established that ligand **8** has moderate activity than **9** having a bromo substituent with very low MIC value of 1.6 mg/mL which is even lower than the tested standards and hence found to be good against the strain. The Ni(II) complex with a MIC value of 25 mg/mL has lower activity than the ligands. Samina Khan Yusufzai *et al* [31] described the synthesis of 11 new thiazolyl coumarin derivatives **10a-k** (fig. 3) and evaluated their *in vitro* antibacterial activity against a few gram-positive, gram-negative bacteria and antituberculosis activity against *M. tuberculosis* H37Rv (ATCC 25618) by colorimetric microdilution assay technique. Nine of the synthesized compounds exhibited moderate anti-TB activity, and the highest activity with MIC values ranging between 31.25–62.5 µg/mL was observed for compound **10c** against all the strains including *Mycobacterium tuberculosis*.

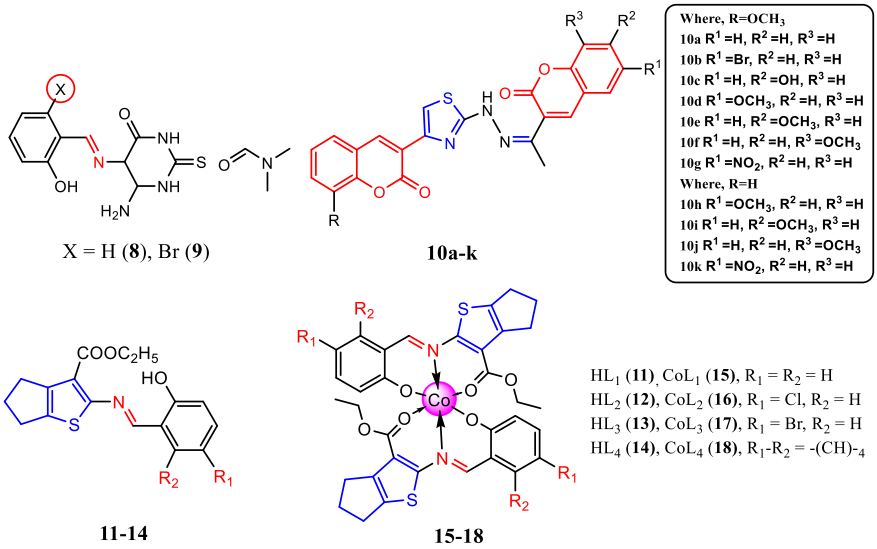


Fig. 3: Structure of mercapto-pyrimidine Schiff bases, thiazolyl coumarin Schiff bases, thiophene-3-carboxylate Schiff bases and its Co(II) complexes.

Schiff bases **11-14** derived from *o*-hydroxy benzaldehyde derivatives and ethyl-2-amino-5,6-dihydro-4H-cyclopenta-thiophene-3-carboxylate and their Co(II) complexes **15-18** (fig. 3) have

been reported by More *et al* [32]. The synthesized ligands and compounds were studied against *M. tuberculosis* (H37Rv strain ATCC No- 27294) by Microplate Alamar Blue Assay (MABA). The tested compounds shown moderate anti-TB activity with 100% inhibition against the strain at the concentration of 25 mg/mL. The Co(II) complexes and the Schiff base ligands displayed similar antitubercular activity which indicates that the metal ion did not involve in the inhibition course.

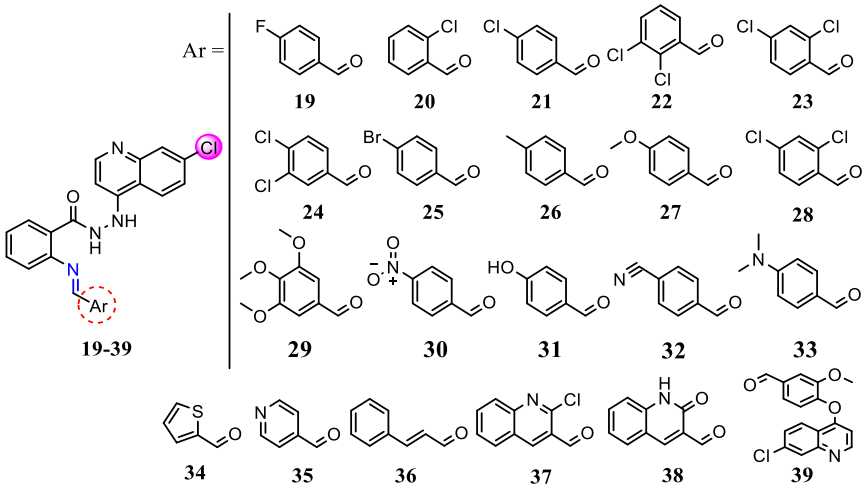


Fig. 4: Structure of (benzylideneamino)-N-(7-chloroquinolin-4-yl)benzohydrazide Schiff bases

The one-pot three component, catalyst free synthesis of (benzylideneamino)-N-(7-chloroquinolin-4-yl)benzohydrazide Schiff bases **19-39** (fig. 4) derived from 7-chloro-4-hydrazinylquinoline, isatoic anhydride, and aryl and/or hetero aryl aldehydes using water as reaction medium was described [33]. The synthesized Schiff bases were tested against *M. tuberculosis* (ATCC 27294) using MABA method with ciprofloxacin and pyrazinamide as standards. The compounds showed MIC ranging from 0.78 to 25 µM. The results demonstrated the effect of the nature and the position of the substituents on the inhibitory action. The Schiff bases with electron releasing groups (-CH_3, -OCH_3) at the para position of the phenyl ring of the aldehydes exhibited relatively good inhibitory activity. Compounds **26** and **27** were found to be more potent than the standards. Compounds bearing halogens at the meta and/or para position of the phenyl ring of the aldehyde were observed with relatively moderate activity.

Srinubabu Maddela and Ajitha Makula [34] presented a hybrid pharmacophore-based approach to design and synthesize a new series of isatin - quinoline hybrids **40a-j** and **41a-l** (fig. 5). All the synthesized hybrids were studied for *in vitro* anti-TB activity against *M. tuberculosis* using microdilution assay and their MIC values were reported. Compound **41h** possesses good inhibitory activity (0.09 µM) as compared to the reference drug, isoniazid (0.03 µM). The enhanced activity of the compound **41h** against poly and multi drug resistant strains was attributed to the presence of electron withdrawing group on the aromatic ring of isatin. Shivakumar *et al* [35] demonstrated that the antitubercular activity of the mononuclear Co(II), Ni(II) and Cu(II) complexes **43-45** of Schiff base **42**, derived from 8-formyl-7-hydroxy-4-methylcoumarin and 2-hydrazino-4 (coumarin-3-yl)thiazole (fig. 5) are relatively better than the ligand **42**. The result evident the increase in activity of the Schiff base ligands upon coordination.

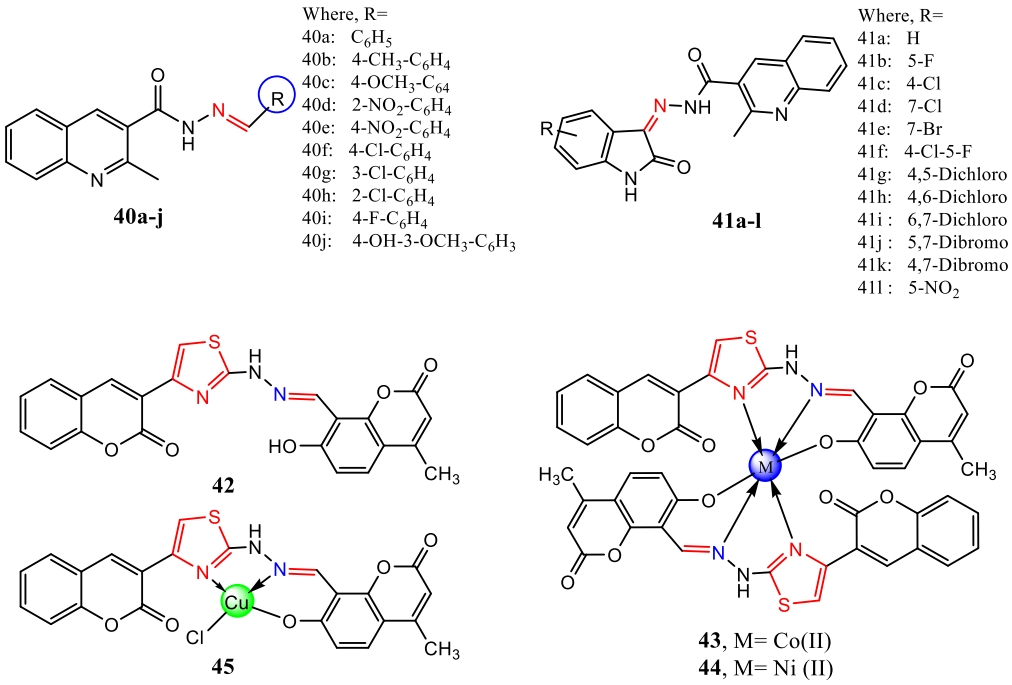
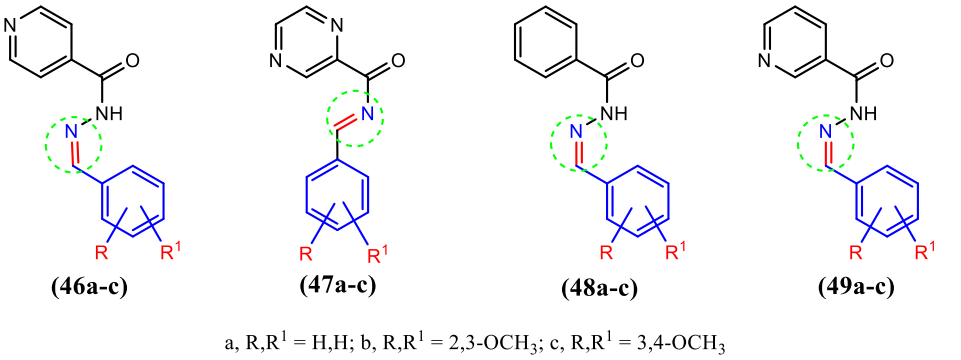
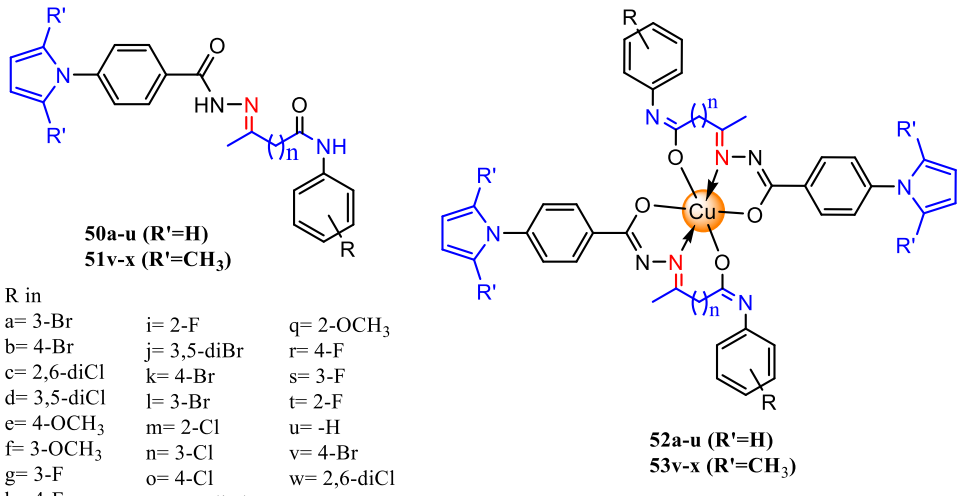


Fig. 5: Structure of novel isatin - quinoline analogs (40a-j, 41a-l) and coumarin Schiff base (42) and their metal complexes (42-44)



a, R,R^1 = H,H; b, R,R^1 = 2,3-OCH_3; c, R,R^1 = 3,4-OCH_3



R in

a= 3-Br	i= 2-F	q= 2-OCH_3
b= 4-Br	j= 3,5-diBr	r= 4-F
c= 2,6-diCl	k= 4-Br	s= 3-F
d= 3,5-diCl	l= 3-Br	t= 2-F
e= 4-OCH_3	m= 2-Cl	u= -H
f= 3-OCH_3	n= 3-Cl	v= 4-Br
g= 3-F	o= 4-Cl	w= 2,6-diCl
h= 4-F	p= 3,5-diCl	x= 4-OCH_3

Fig. 6: Structure of hydrazide based Schiff bases (46-49 a-c), novel pyrrolyl hydrazones (50a-u, 51v-x) and Copper complexes (52a-u, 53v-x)

Syed Tajudeen *et al* [36], described the synthesis, characterization, antitubercular, and antimicrobial activity of the 12 copper(II) complexes, with 12 different NO donor ligands (**46-49 a-c**) obtained in the scheme of various hydrazides namely isoniazid, pyrazinamide, benzhydrazide, and nicotinohydrazide with some dimethoxy benzaldehydes (fig. 6). Antitubercular activity observed by MIC, showed that the complex of **46b** exhibited the highest efficacy with >70% inhibition. The Cu(II) complexes of **46b** and **49b** reinforce the pharmacophoric contribution of isoniazid moiety to the mechanism of action against the *M. tuberculosis*. Joshi *et al* [37] assessed the *in vitro* antitubercular activity of novel pyrrolyl hydrazones **50a-u, 51v-x** and their copper complexes **52a-u, 53v-x** (fig. 6). The compounds **52b** and **52r** displayed the highest inhibition potential (0.8 µg/mL) quite close to the standard rifampicin (0.4 µg/mL), while others showed good to moderate activities with MIC values ranging from 1.6 to 100 µg/mL.

Three series of 6-aryl-2-methylnicotino hydrazides **54a**–**i**, *N*′-arylidene-6-(4-bromophenyl)-2-methylnicotino hydrazides **55a**–**f**, and *N*′-(unsubstituted/substituted 2-oxoindolin-3-ylidene)-6-(4-fluorophenyl)-2-methylnicotinohydrazides **56a**–**c** have been synthesized (fig. 7) by Wagdy M. Eldehna [38]. The results (table 1) of the *in vitro* antimycobacterial potential against *M. tuberculosis* showed that the isatin hydrazides **56a**–**c** were significantly more active than the parent hydrazide **54c**. Hydrazides **56b** and **56c** exhibited the highest activity among all the tested compounds with inhibition of the mycobacterium at 12.5 and 6.25 µg/mL, respectively. Compounds **56b** and **56c** were also devoid of apparent cytotoxicity to HepG2, HT-29, A549, MCF-7, and PC-3 cancer cell lines. The SAR study suggested that lipophilicity of the synthesized compounds is a vital component that accounts for their antitubercular activity.

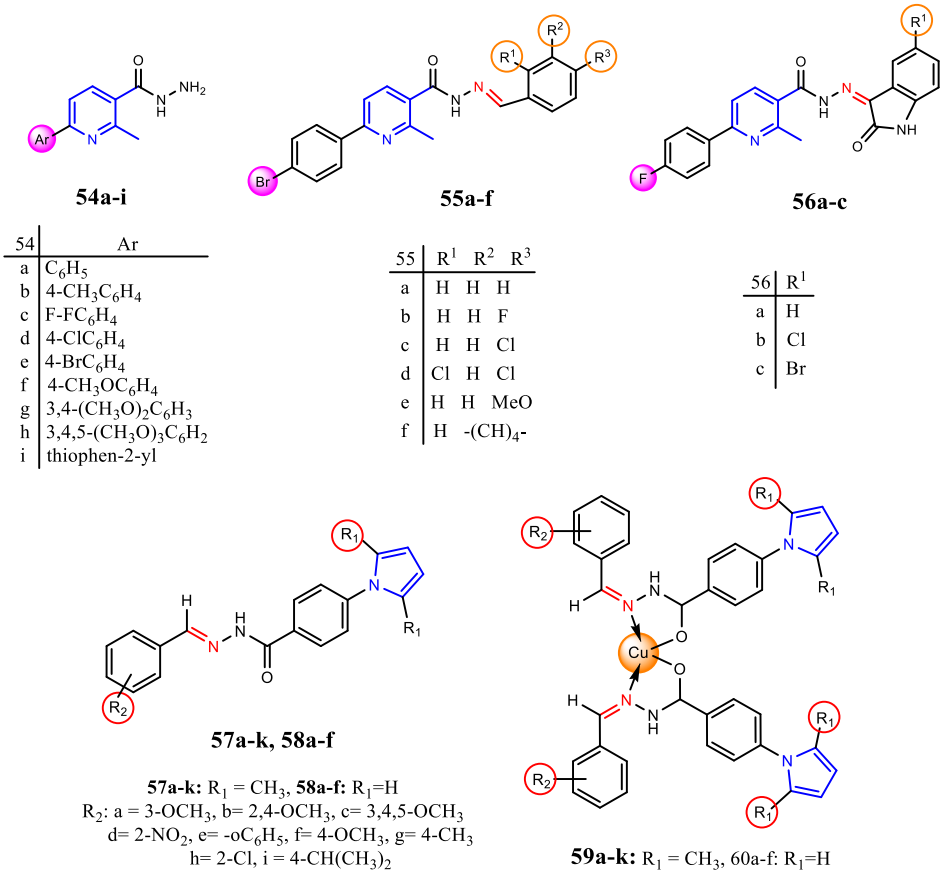
Table 1: Antitubercular activities, LogP measurements and drug-likeness model scores of nicotinic acid hydrazide derivatives.

Compd.	Ar	R_1	R_2	R_3	Mean of Inhibition %	MIC (µg/mL)	LogP	Drug-Likeness Model Score
54a	C_6H_5				42.52 ± 0.63	25	1.36	−0.1
54b	4-$CH_3C_6H_4$				36.33 ± 0.58	25	1.81	−0.36
54c	4-FC_6H_4				NA	NA	1.53	−0.06
54d	4-ClC_6H_4				12.45 ± 0.58	100	2.04	+0.05
54e	4-BrC_6H_4				20.63 ± 0.63	50	2.17	−0.25
54f	4-$CH_3OC_6H_4$				42.63 ± 0.16	25	1.42	−0.25
54g	3,4$(CH_3O)_2C_6H_3$				22.63 ± 0.16	50	1.01	+0.13
54h	3,4,5$(CH_3O)_3C_6H_2$				18.32 ± 0.72	50	0.99	+0.33
54i	thiophen-2-yl				22.63 ± 0.20	50	1.15	−0.10
55a		H	H	H	NA	NA	4.95	+0.12
55b		H	H	F	NA	NA	5.11	0.00
55c		H	H	Cl	NA	NA	5.63	+0.09
55d		Cl	H	Cl	13.57 ± 0.72	100	6.23	+0.13
55e		H	H	MeO	NA	NA	5.01	+0.09
55f		H	-$(CH)_4$-		14.32 ± 0.58	100	6.13	+0.46
56a		H			31.44 ± 0.58	25	3.54	+0.88
56b		Cl			52.63 ± 0.58	12.5	4.19	+0.62
56c		Br			77.42 ± 0.93	6.25	4.32	+0.41
Pyrazinamide					93.25 ± 0.63	3.21		
Isoniazid					-	0.75		

Note: NA= No Activity (>100 µg/mL).

Suresh *et al* [39] presented the synthesis of novel imidazole and benzimidazole based Schiff bases by both conventional and microwave assisted methods. Synthesized molecules were effective in inhibiting the enzyme Cyclopropane Mycolic acid Synthase-2 (1KPI), which is vital for the

growth of the cell wall of *M. tuberculosis*. Correlation was found between the docking score and *in vitro* activities of all the tested derivatives. A novel series of 4-(1*H*-pyrrol-1-yl)benzoic acid hydrazide based Schiff bases **57a-k, 58a-f** and their copper complexes **59a-k** were screened for antitubercular activity using MABA method with standard drugs, pyrazinamide and streptomycin (fig. 7). Compounds **57e**, **59c**, **59e**, and **60d** were remarkably active with MIC value of 3.12 µg/mL, whereas for compounds **57c**, **59b**, **59c**, and **59e**, the MIC value was 6.25 µg/mL, and the rest of compounds were moderately active. A noticeable rise in the activity was observed, when the hydrazones were coordinated with the copper metal, indicating the significance of the metal to enhance the antimycobacterial activity [40].



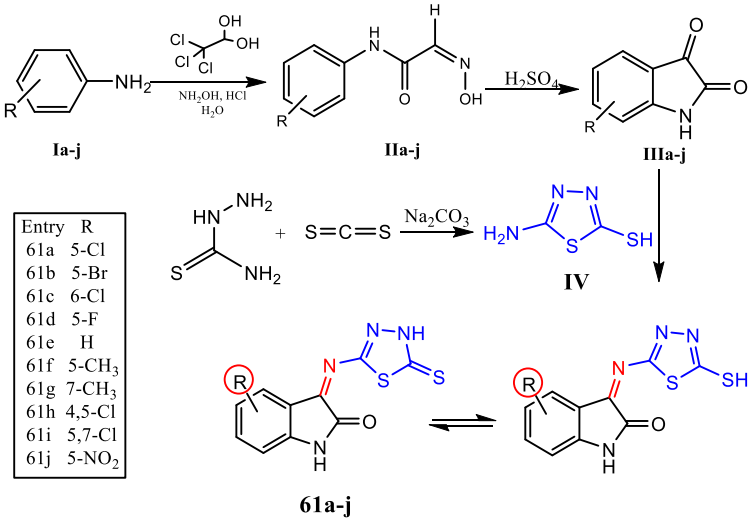
54	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	F-FC_6H_4
d	4-ClC_6H_4
e	4-BrC_6H_4
f	4-$CH_3OC_6H_4$
g	3,4-$(CH_3O)_2C_6H_3$
h	3,4,5-$(CH_3O)_3C_6H_2$
i	thiophen-2-yl

55	R^1	R^2	R^3
a	H	H	H
b	H	H	F
c	H	H	Cl
d	Cl	H	Cl
e	H	H	MeO
f	H	-$(CH)_4$-	

56	R^1
a	H
b	Cl
c	Br

Fig. 7: Structure of nicotinic acid hydrazide Schiff bases (55a–f, 56a–c), 4-(1*H*-pyrrol-1-yl)benzoic acid hydrazide Schiff bases (57a-k, 58a-f) and their Copper complexes (59a-k)

Shingade and Shirodkar [41] prepared Schiff bases **61a-j** by stirring isatins **IIIa-j** with 5-amino-1,3,4-thiadiazole-2-thiol **IV** (Scheme 1). The screening for the *in vitro* antimicrobial activity by agar well diffusion method and for *in vitro* antitubercular activity by BACTEC radiometric method against the strain *M. tuberculosis* H37Rv were reported. Compound **61d** revealed equipotent anti-TB activity compared to the reference streptomycin.



Scheme 1: Synthesis of isatin based Schiff bases (61a-j)

Suresh *et al* [42] designed a series of pyridine-3-carbohydrazide based Schiff bases (fig. 8) and docked against *M. tuberculosis* enzyme target diaminopimelate decarboxylase. Compounds with good docking score and multiple interactions were evaluated for antimycobacterial activity against the strain H37Rv by MABA method. The *in vitro* results have shown that the compound **62** displayed the inhibition activity with MIC >3.12 mcg/mL while **63, 64, 65, 66** and **67** exposed reasonable activity with MIC >50 mcg/mL. A series of Schiff base derivatives **68-76** (fig. 8) of isonicotinohydrazide (INH) and 1-oxide isonicotinohydrazide (hydrazide-hydrazones) were prepared by Velezheva [43] and investigated the *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv and also against a clinical isolate of INH-resistant *M. tuberculosis* (CN-40) with selective single INH resistance. INH-containing hydrazide-hydrazones **68-76** exhibited higher activity (except for **75**) than its corresponding *N*-oxide analog of INH. The antitubercular potential of Schiff bases **68-71** was found to be better than the standard drug ethambutol.

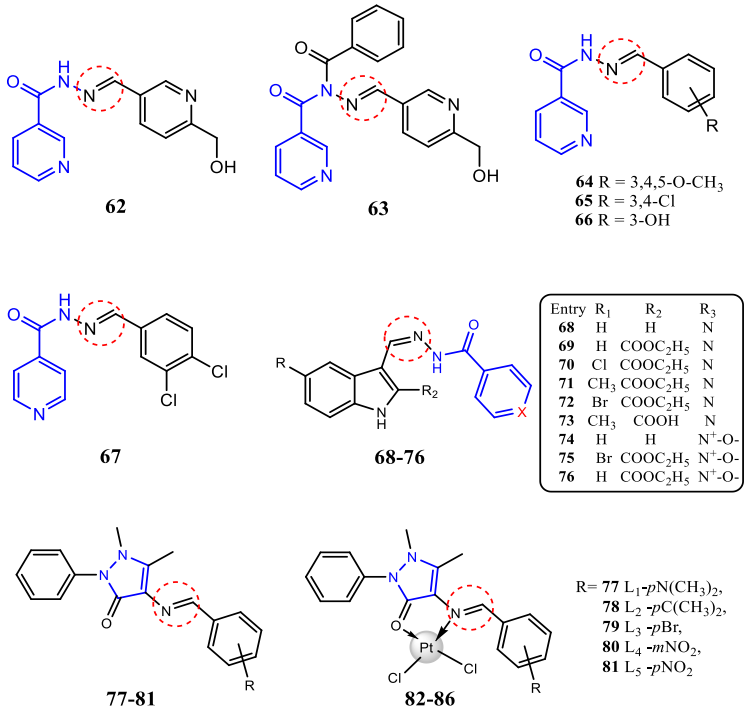
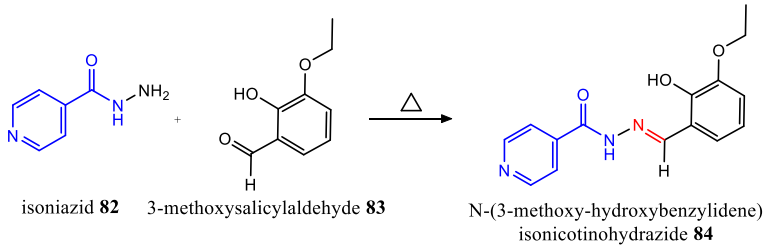


Fig. 8. Schiff bases derivatives of pyridine-3-carbohydrazide (62-67), isoniazid and 1-oxide isoniazid (68-76) and 4-aminoantipyrine (77-81), Pt(II) complexes (82-86)

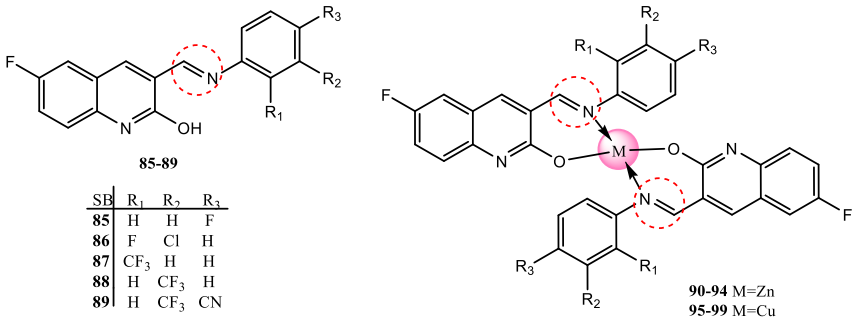
Schiff base **77-81** derived from 4-aminoantipyrine and substituted aldehydes and their platinum complexes **82-86** were synthesized (fig. 8) by Shiju *et al* [44]. The antimycobacterial activity of the ligands and the complexes were screened by resazurin microplate assay (REMA) against *Mycobacterium tuberculosis* with slight modification using rifampicin as the positive control. Schiff base ligands **77-81** exhibited no inhibitory action against the tubercular bacteria. All the synthesized Pt(II) complexes **82-86** displayed inhibitory potential to the bacterial growth at 100 µM concentration and the $[Pt(L_3)Cl_2]$ complex **84** was observed with comparatively better activity.

Elham Pahlavani *et al* [45] reported the synthesis, characterization, antimicrobial and antitubercular activity of novel Schiff base ligands *viz* N'-(3-ethoxy-2-hydroxybenzilidine) isonicotinohydrazide (Scheme 2). The antitubercular efficiency of the test compounds was assessed against *M. tuberculosis* H37Rv (at 512, 256, 128, 64, 32, 16, 8, 4, 2, and 1 µg/mL). The MIC of the compound **82** was found to be comparable with the standard, isoniazid.



Scheme 2: Synthesis of N'-(3-ethoxy-2-hydroxybenzilidine)isonicotinohydrazide

Schiff bases **85-89** yielded from 6-fluoro-2-hydroxyquinoline-3-carbaldehyde and their Zn(II) **90-94** and Cu(II) complexes **95-99** were tested against the strain H37Rv (fig. 9). Among the tested compounds **85, 87, 89, 90-94** showed promising activity. Moreover, the activity of the Zn complexes were found to be better than the Cu complexes [46].



SB	R_1	R_2	R_3
85	H	H	F
86	F	Cl	H
87	CF_3	H	H
88	H	CF_3	H
89	H	CF_3	CN

Fig. 9. Structure of quinoline-Schiff bases (85-89), Zn(II) complexes (90-94) and Cu(II) complexes (95-99)

The crystal structure and antitubercular assays of Ag(I) and Zn(II) complexes of Schiff base (ThioEn) (fig. 10) were described by da Silva *et al* [47]. The MIC, IC_{50} and subsequent SI values were established for the ligand ThioEn **100** and the Ag(I) complexes **101, 102** and Zn(II) complex **103** against *M. tuberculosis* (ATCC 27294) using standard drug, silver sulfadiazine (SSD) and pristine metal salts ($AgNO_3$ and $ZnCl_2$).

Pyrazolopyrimidine and pyrazolopyridine derivatives *via* the formation of Schiff base precursors **104a-c** were synthesized (fig. 11) and evaluated for their antitubercular activity and analgesic activity. It has been observed that the compounds **105c**, **106b**, **108a** and **108c** expressed the activity similar to that of standards (rifampicin 40 µg/mL and isoniazid 0.2 µg/mL) against the *M. tuberculosis* strain. The activities of the compounds **105b**, **107a**, **107c** and **108b** were moderate and a minor activity was displayed by compound **106a**, while the compound **105a** was inactive [48]. Joshi *et al* [49] developed the docking and 3D-QSARs model for the reported [50-53] anti-TB activity of 75 quinoline scaffolds. Structure–activity relationship (fig. 11) exposed that the quinoline moiety present in the scaffolds is responsible for exhibiting the antitubercular activity. The

methoxy group substitution at the 2nd position of quinoline moiety, an electronegative group at the 6th position and an electron donating group at the 7th position favours the activity.

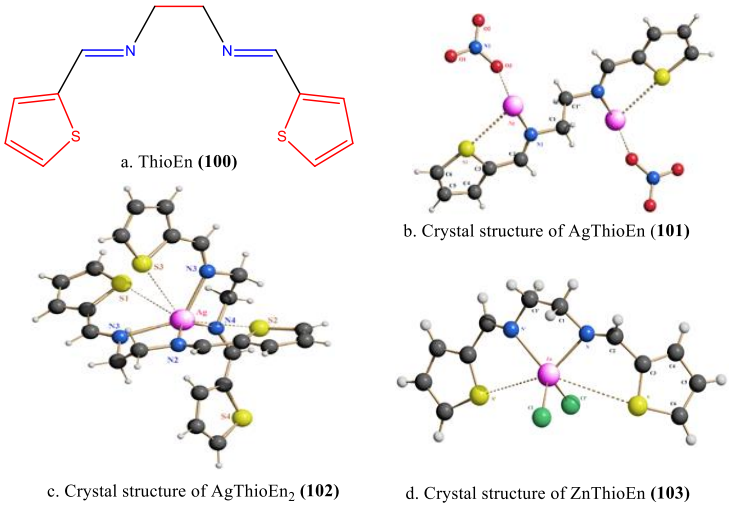


Fig. 10: Structure of Ag(I) and Zn(II) complexes of Schiff base (ThioEn)

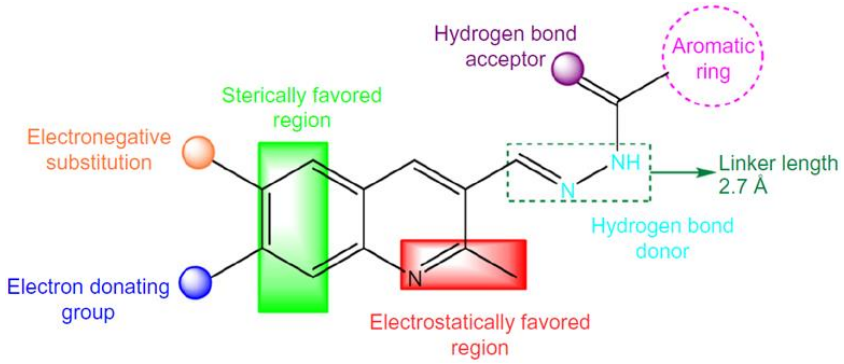


Fig. 11: Predicted structure–activity relationships of quinoline-based hydrazones [49]

The syntheses of a series of 4-(4-pyrrol-1-yl/2,5-dimethyl-4-pyrrol-1-yl) benzoic acid hydrazide analogs (fig. 12), some derived oxadiazoles and azines have been described [54]. The pyrrolyl-Schiff bases **109a** and **109c** presented appreciable activity with MIC of 0.4 µg/mL comparable to rifampicin. Most of them showed good activity against the mycobacterial strain with MIC ranging between 0.4 and 50 µg/mL at noncytotoxic concentrations. A varying degree of *in vitro* antimycobacterial potential was observed for Schiff bases of 3-amino-1-phenyl-4-[2-(4-phenyl-1,3-thiazol-2-yl) hydrazin-1-ylidene] -4,5-dihydro-1H-pyrazol-5-ones **110a-l** (fig. 12) against *M. smegmatis* and *M. tuberculosis*. All the 12 synthesized molecules **110a-l** showed good activity against *M. tuberculosis* strain with inhibition ranging from 6.48 µM to 53.59 µM. The compound **110h** exhibited outstanding antimycobacterial activity with MIC = 6.48 x 10^{-3} µM/mL that was 1.69 and 3.9 times more active than the reference drugs streptomycin and pyrazinamide (MIC=11.01 x 10^{-3}, 25.38 x 10^{-3} µM/mL), respectively [55].

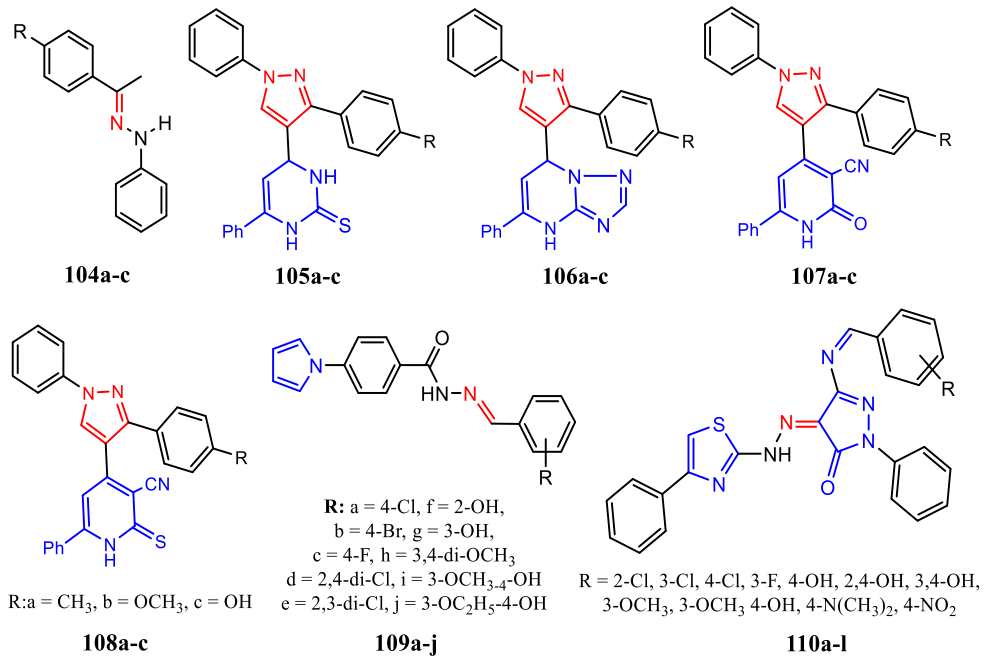
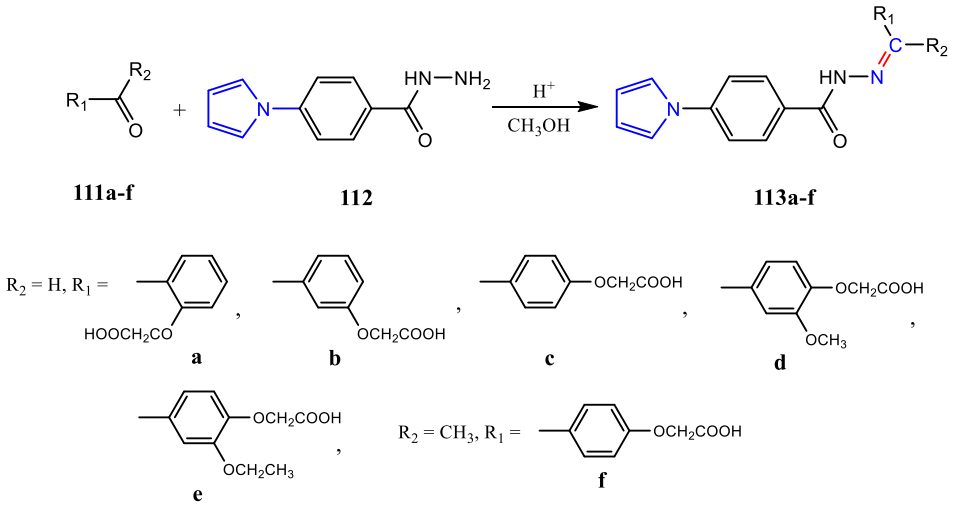
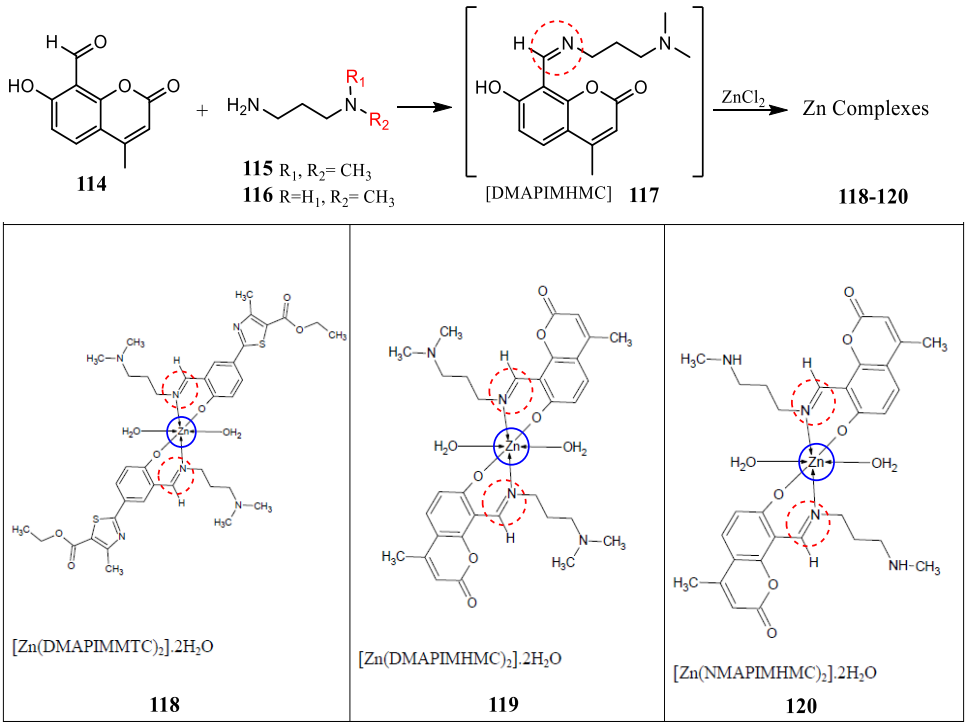


Fig. 12. Pyrazolopyrimidine and pyrazolopyridine derivatives of Schiff bases 104a-c, pyrrolyl-Schiff bases 109a-j, pyrazolone-Schiff bases 110a-l

Uttam *et al* [56] reported the synthesis of Schiff bases **113a-f** formed between substituted phenoxy aldehydes/ketones **111a-f** and 4-pyrrol-1-yl benzohydrazide **112** catalyzed by acetic acid in ethanolic medium (Scheme 3). The antimycobacterial potential was tested for **113a-f** against *M. tuberculosis* (H37Rv) by MABA assay using INH as reference and the results revealed promising activity for compounds **113d** and **113e**.



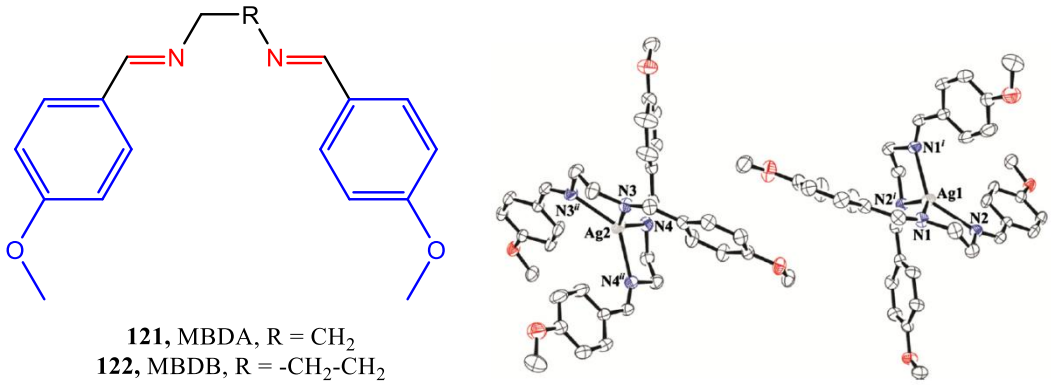
Scheme 3: Synthesis of Schiff bases 113a-f derived from 4-pyrrol-1-yl-benzohydrazide



Scheme 4: Synthesis of Zn(II) complexes (118-120) of chromene based Schiff base (117)

Yamgar *et al* [57] established the synthesis of some novel Zn complexes of Schiff bases obtained from 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde **114** and dimethylamino propylene diamine **115** and *N*-methylamino propylene diamine **(Scheme 4)**. The synthesized compounds were studied for the antitubercular activity. The zinc complexes **118-120** have shown moderate activity when compared with the standards pyrazinamide and streptomycin. This could be due to the poor permeability of the tested compounds into the bacterial cell wall.

The antimycobacterial analysis of Ag(I) complexes of two new Schiff bases (MBDA, **121** and MBDB, **122**) **(fig. 13)** obtained from ethylenediamine or 1,3-diaminopropane with *p*-anisaldehyde were reported [58]. The ligands **121** and **122** showed poor activity against the bacterial strain. However, the silver(I) complexes, AgMBDA **123a** and AgMBDB **123b** (MIC 27.8 and 23.5 $\mu molL^{-1}$ respectively), were found to be more effective than antibacterial agent silver sulfadiazine (SSD).



121, MBDA, R = CH_2
122, MBDB, R = $-CH_2-CH_2$

Fig. 13. Structure of Schiff bases (121, 122) and ORTEP representation of crystal structure of AgMBDA (123a) and AgMBDB (123b)

Malipeddi [59] demonstrated the synthesis of a series of Schiff bases **124a-l** obtained from 2-amino-5-aryl-5H-thiazolo[4,3-b]-l,3,4-thiadiazole and various aromatic aldehydes (fig. 14). Docking studies and *in vitro* anti-TB evaluation were carried out by MABA method at 0.1–100.0 µg/mL using streptomycin and pyrazinamide as standards. Compounds **124f**, **124h** and **124i** were observed with appreciable antitubercular potential compared to streptomycin.

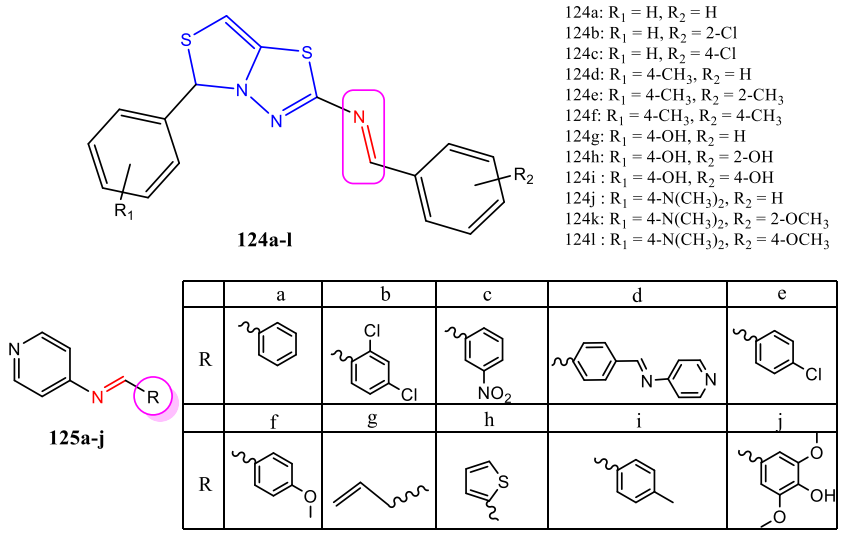
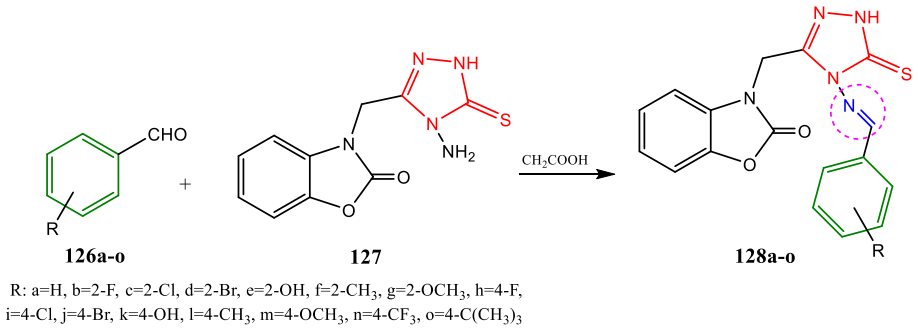
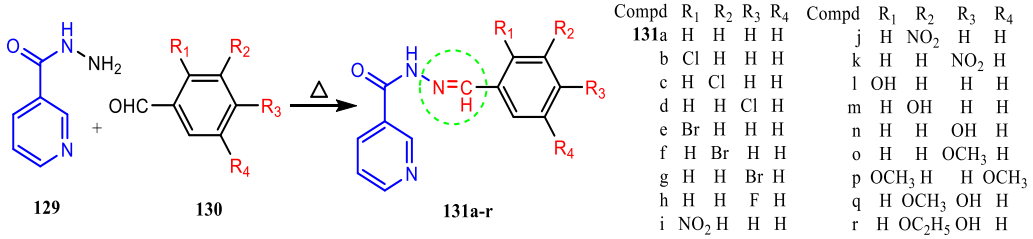


Fig. 14. Structure of thiazolidinones (124a-l) and pyridine-based Schiff bases (125a-j)

Sankar and Nandi [60] reported the synthesis of Schiff bases **125a-j** derived from 4-amino pyridine with different aldehydes and assessed the drug likeness properties (fig. 14). Docking studies with the target protein beta-ketoacyl acyl carrier protein synthase II (MtKasB) enzyme for *M. tuberculosis* revealed that the candidate **125d** with better docking score may have the ability to act as antitubercular compound. Onkol and Cicekli [61] derived new Schiff bases **128a-o** from 3-[(4-amino-5-thioxo-1,2,4-triazole-3-yl)methyl]-2(3H)-benzoxazolone **127** and aromatic aldehydes **126** by microwave irradiation (Scheme 5). Among the derivatives obtained, 4-bromophenylmethylidene derivative **128j** revealed significant antitubercular activity as well as antibacterial activity against *P. aeruginosa*.



Scheme 5: Synthesis of 1,2,4-triazoles based Schiff base (128a-o)



Scheme 6: Synthesis of nicotinic acid hydrazone derivatives (131a-r)

A novel series of nicotinic acid hydrazide derivatives as potential antimycobacterial agents has been developed [62] (Scheme 6). The *in vitro* antitubercular testing was performed by agar dilution method in Middlebrook 7H11 agar medium supplemented with OADC against the *M. tuberculosis*. The nicotinic acid hydrazide derivative **131a** with an unsubstituted phenyl ring displayed poor anti-TB activity with MIC > 25 µg/mL. The presence of -OCH_3 group in **131o** and -OH group in **131l, 131m** and **131n** showed no improvement in the activity. The derivatives **131q** and **131r** with both -OH and -OCH_3, -OC_2H_5 groups lead to considerable loss in the inhibition activity. The presence of electron withdrawing group (-NO_2) in the phenyl rings of **131i, 131j** and **131k** brought no change in the activity. However, the presence of -Cl group as a para substituent improved the anti-TB potential of **131d** in comparison to derivatives with *ortho* and *meta* -Cl substituents in **131b** and **131c**. The studies demonstrated that the presence of lipophilic electron withdrawing halogen groups at the *para* position of the phenyl ring improved the antimycobacterial activity.

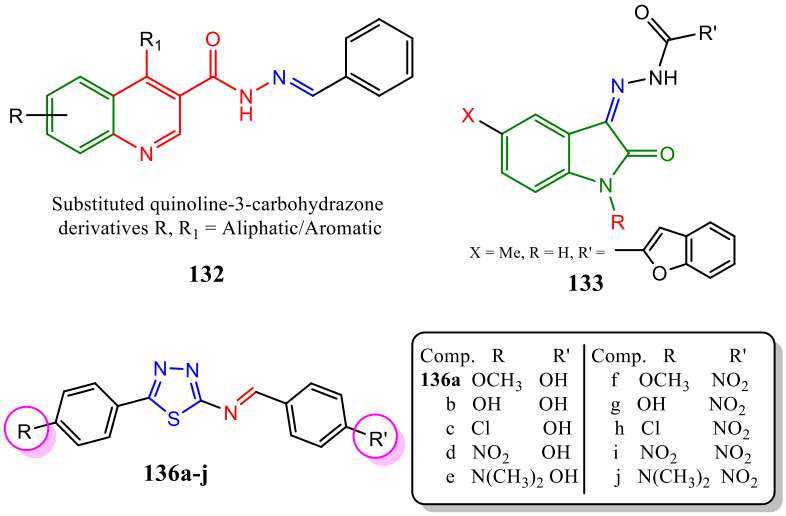
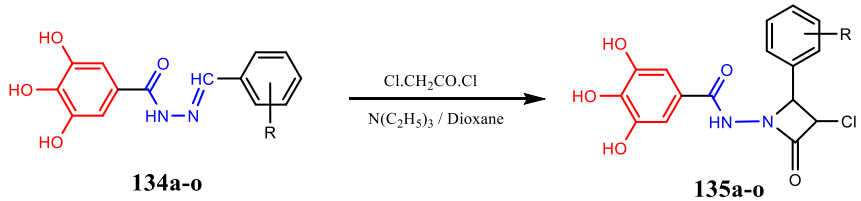


Fig. 15: Structure of substituted quinoline-3-carbohydrazones (132), Schiff bases of indoline-2,3-dione (133) and 1,3,4-thiadiazole based Schiff bases (136a-j)

Two reports on the design, synthesis and antimycobacterial evaluation of two different series of new quinoline-3-carbohydrazone derivatives with fused pyridine heterocycles **132**, (fig. 15) as potential antimycobacterial agents has been reported. [63,64]. Aboul-Fadl *et al* [65] reported the synthesis of a series of Schiff bases of indoline-2,3-dione and examined their *M. tuberculosis* gyrase inhibition potential. Promising inhibitory activity was explored by some of the Schiff bases, with IC_{50} values ranging from 50–157 µM relatively much higher than the positive control moxifloxacin. Highest activity was exposed by compound **133** (fig. 15), and hence can be utilized as a lead for future chemical optimization studies for the inhibitors of *M. tuberculosis* enzyme DNA gyrase. Ilango and Arunkumar [66] described the antitubercular potential of a series of new 4-aryl-3-chloro-*N*-(3,4,5-trihydroxybenzamido)-2-azetidinones, **135a-o,** synthesized from various Schiff bases of galloyl hydrazide **134a-o** (scheme 7).



Where, R= 2a H, 2b 2-OH, 2c 2-OH-3-OCH_3 , 2d 3-OH, 2e 4-OH, 2f 2-Cl, 2g 3-Cl, 2h 2-NO_2 , 2i 3-NO_2 , 2j 4-NO_2 , 2k 4-N-$(CH_3)_2$, 2l 3,4,5-$(OCH_3)_3$, 2m 3,4,-$(OCH_3)_2$, 2n 4-OCH_3 , 2o 4-Cl

Scheme 7: Synthesis of 4-aryl-3-chloro-*N*-(3,4,5-trihydroxy benzamido)-2-azetidinones (135a-o)

Table 2: *In vitro* anti-TB activity of the synthesized compounds

Compound	MIC (mg/mL)/Mycobacterium strain			
	M. intercellulari	***M. xenopi***	***M. cheleneo***	***M. smegmatis***
137a	NA	NA	NA	100
137b	200	NA	NA	200
137c	200	200	200	200
137f	0.625	0.625	0.625	0.625
138a	NA	NA	NA	200
138c	100	100	NA	NA
138f	50	50	50	50
INH	12.5	12.5	12.5	12.5

NA: no activity at 200 mg/mL

Schiff Bases of 2-amino-5-aryl-1,3,4-thiadiazole derivatives **136a-j** (fig. 15) were tested for antimycobacterial activity over *M. tuberculosis*. The compounds **136c, 136e, 136f** and **136i** responded positively at minimum concentration as compared to rest of the compounds [67]. Aboul-Fadl *et al* [68] inspected the *in vitro* antimycobacterial activity of Schiff bases of nalidixic acid carbohydrazide and isatin derivatives, **137(a-g), 138(a-g), 137(h-j)** and **138(h-j)** (fig. 16) against *M. cheleneo* (ATCC 35751), *M. intercellulari* (ATCC 35743), *M. xenopi* (ATCC 14470), and *M. smegmatis* (ATCC 35797) using INH as a reference drug by agar dilution method. The *in vitro* screening results (table 2) revealed that none of the compounds except **137f** displayed any considerable activity. The lonely active candidate **137f** (MIC: 0.625 mg/mL) was found to be 20 times more active than the first-line anti-TB drug isoniazid (MIC = 12.5 mg/mL).

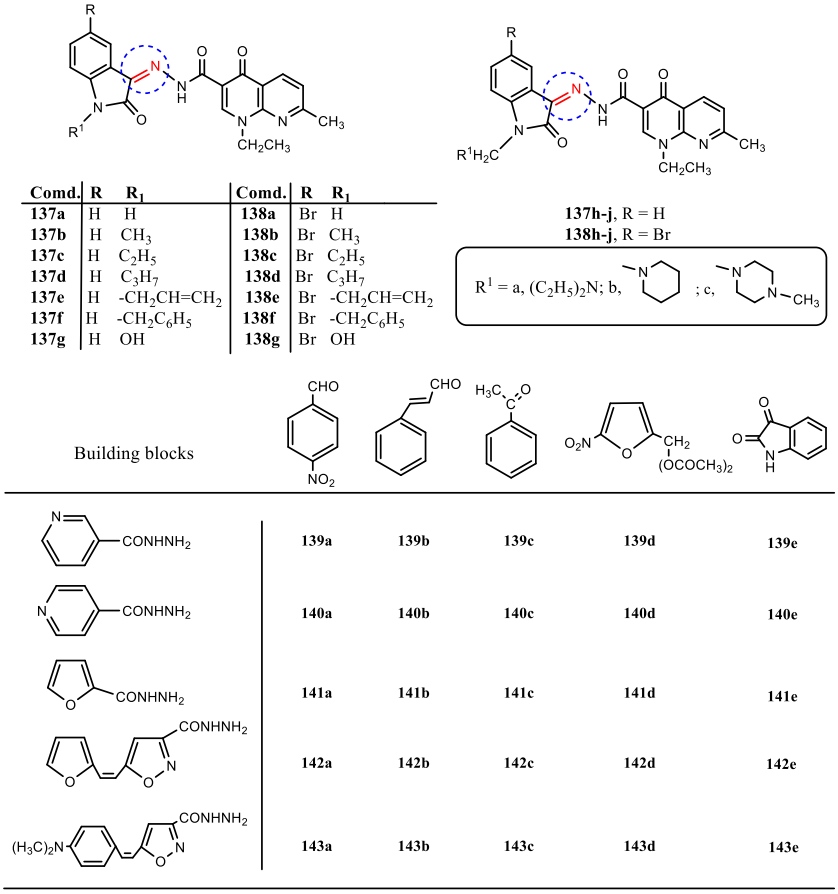


Fig. 16: Structure of Schiff bases of nalidixic acid carbohydrazide and isatin derivatives 137(a- g), 138(a-g), 139(a-c) and 140(a-c) and Schiff bases combinatorial library 139-143(a-e).

Abdel-Aal *et al* [69] reported the antimycobacterial efficiency of individual candidates of Schiff bases combinatorial library **139-143 a-e** against *M. tuberculosis* H37Rv at 6.25 mg/mL concentration (fig. 16). Compounds **140c** and **141d** exhibited 99% inhibitory activity on the tested strain and lower activity ranging from 35 to 84% was found with rest of the compounds. Sudeep K. Mandal *et al* [70] synthesized various imine derivatives of substituted 1,2,4-triazol-3-yl)benzene-1,2,3-triol **144-148** (fig. 17) and assessed their anti-TB activity against bacterial strain *M. tuberculosis* by MABA method using standard, rifampicin. A comparable activity was exhibited by compounds **146** and **148** with that of rifampicin and poor activity was exhibited by rest of the compounds.

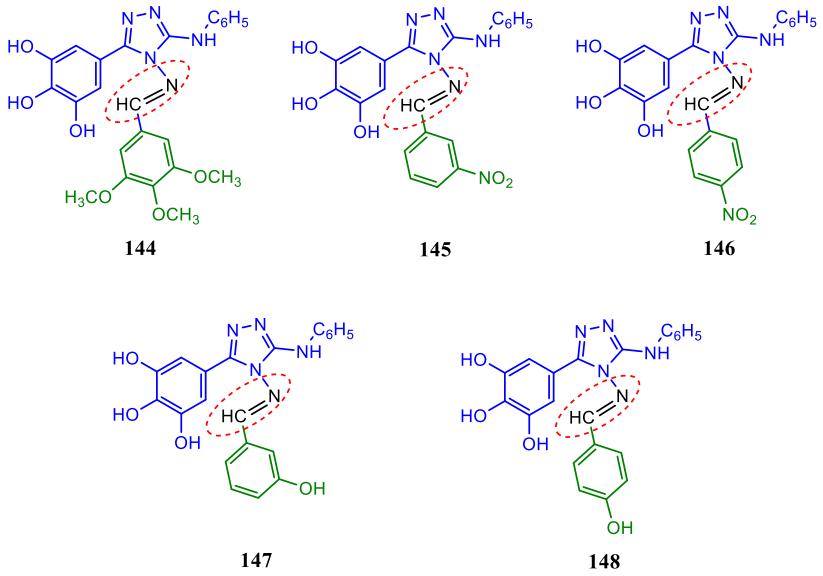


Fig. 17: Structure of Schiff bases of substituted 1,2,4-triazol-3-yl)benzene-1,2,3-triol

Hearn *et al* [71] developed a series of Schiff base derivatives **149a-z** and **150a-r** from the isoniazid and carbonyl precursors, which provides increase in lipophilicity to the drug and made it more effective against tuberculosis. The structural alteration of the INH framework described by Hearn *et al* **(fig. 18)**, provides a lipophilic adaptation of INH in which the hydrazine unit has been chemically blocked from the deactivating process of N2-acetylation by NATs. In a standard primary screen against *M. tuberculosis* strain H37Rv, all the compounds in the study were active and displayed MIC essential to inhibit growth of the strain by 90% of less than 6.25 µg/mL.

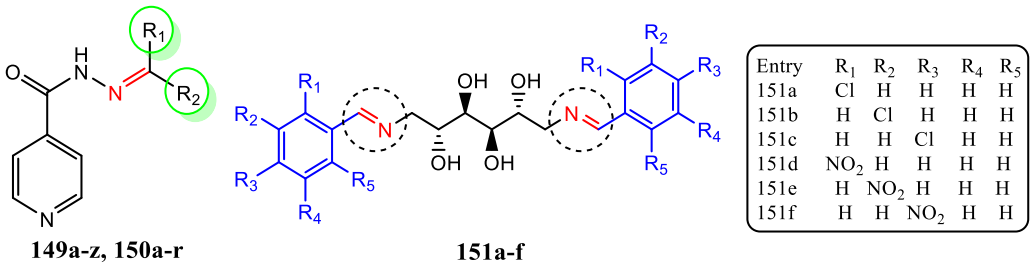


Fig. 18. Structure of isoniazid - Schiff bases (149a-z, 150a-r) and D-mannitol based Schiff bases (151a-f)

Marcelle de L. Ferreira *et al* [72] presented the synthesis of six Schiff bases **151a-f** derived from D-mannitol, 1,6-dideoxy-1,6-bis-{[(E)-arylmethylidene]amino}-D-mannitol (6: aryl= XC_6H_4: X = *o*-, *m*- and *p*- Cl or NO_2) (fig. 18), and screened the *in vitro* antibacterial activity using the Alamar blue susceptibility test against the strain *M. tuberculosis* (H37Rv). The results suggested that the Schiff bases with nitro substituents (**151d**: X = *o*-NO_2), (**151e**: X = *m*-

NO_2) and (**151f**: X = *p*-NO_2) with MIC values 12.5, 25.0 and 25.0 µg/mL, respectively exhibited promising activities when compared with the control ethambutol.

CONCLUSION

For the first time in 40 years, a portfolio of promising new compounds for the treatment of tuberculosis is on the horizon. A hopeful new era in tuberculosis drug development has been in progress. The emergence of multidrug resistance has necessitated the discovery and development of new structural classes of antitubercular candidates with promising activity against the drug resistant mycobacterial strains. In an effort to discover new and effective chemotherapeutic agent for the treatment of TB, the antimycobacterial activities of various Schiff bases and their complexes have been explored. Schiff bases of coumarin, isatin, chromene, oxadiazoles, substituted triazoles, hydrazides like isoniazid, pyrazinamide, benzhydrazide, and nicotinohydrazide are of great importance in the discovery of effective antimycobacterial drugs. For instance, the Schiff bases of nalidixic acid carbohydrazide and isatin derivative **137f** was found to be 20 times more potent than the first line antitubercular drug, isoniazid. However, the antimycobacterial activity of this Schiff bases deserves further investigation and there is plenty of room to explore new promising leads for the design of more competent anti-TB drugs to fight against the classic example of a disease of poverty - Tuberculosis.

ABBREVIATIONS

AIDS - Acquired Immuno Deficiency Syndrome, CFU- Colony Forming Unit, MtKasB - Beta-ketoacyl acyl carrier protein synthase II, 1KPI - Cyclopropane mycolic acid synthase II, DNA – Deoxy ribonucleic acid, HIV - Human Immuno Virus, INH - Isoniazid, MABA - Microplate Alamar Blue Assay, MIC - Minimum Inhibitory Concentration, QSAR – Qualitative structure-activity relationship, REMA - Resazurin microplate assay, SSD - Silver sulfadiazine, TB – Tuberculosis, WHO - World Health Organization.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in this research article.

REFERENCES

1. Van Wormer LM, Tuberculosis: The latest, CRNA 2000; 11(1): 15-19.
2. World Health Organization. TB: A global emergency. Geneva, Switzerland: WHO Report No. 14977, WHO; 1994.
3. Janin YL. Antituberculosis drugs: Ten years of research. Bioorg Med Chem 2007; 15(7): 2479–2513.
4. Grange JM. The genus Mycobacterium and the Mycobacterium tuberculosis complex, in tuberculosis: A comprehensive clinical reference. Pennsylvania:Saunders-Elsevier; 2009, p 44-59.
5. Satoskar RS, Bhandarkar SD, Ainapure SS. Pharmacology and Pharmacotherapeutics. Mumbai: Popular Prakashan; 2003, p 727-744.
6. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. JAMA 1999; 282(7): 677-686.
7. World Health Organisation. Global tuberculosis report. 2015. Available from : http://www.who.int/iris/handle/10665/191102
8. Ugwu DI, Ezema BE, Eze FU, and Ugwuja DI. Synthesis and structural activity relationship study of antitubercular carboxamides. Int J Med Chem 2014; 2014: 1-18.
9. Patole J, Shingnapurkar D, Padhye S, Ratledge C. Bioorg Med Chem Lett 2006; 16: 1514-1517.
10. Cerchiaro G, Aquilano K, Filomeni G, Rotilio G, Cirioio MR, Ferreira AMDC. Isatin Schiff base Copper(II) complexes and their influence on cellular viability. J Inorga Biochem 2005; 99: 1433-1440.
11. Vancoa J, Svajlenova O, Racanskac E, Muselika J, Valentova J. Antitradical activity of different Copper(II) Schiff base complexes and their effect on alloxan-induced diabetes. J Trace Elem Med Biol 2004, 18: 155- 161.
12. Marcell DL et al. Synthesis and antitubercular activity of novel Schiff bases from D-mannitol. Carbohydr Res 2009; 12: 2042-2047.
13. Nabel NA, Mohamed FZ. Structural and biological behaviors of some nonionic Schiff base amphiphiles and their Cu(II) and Fe(III) metal complexes. Colloids Surf. B 2008; 64: 179-183.

14. Schiff H. Mittheilungen aus dem universita tslaboratorium in Pisa: Eine neue reihe organischer basen. Justus Liebigs Ann Chem 1864; 131(1): 118–119.
15. Zheng Y et al. One pot synthesis of imines from aromatic nitro compounds with a novel Ni/SiO2 magnetic catalyst. Catal Lett 2009; 128: 465-474.
16. Atwood JL, Steed JW. Supramolecular Chemistry. New York: John Wiley & Sons; 2000.
17. Guo Z, Xing R, Liu S, Zhong Z, Ji X, Wang L. Antifungal properties of Schiff bases of chitosan, N-substituted chitosan and quaternized chitosan. Carbohydr Res 2007; 342(10): 1329-1332.
18. Pandeya SN, Sriram D, Nath G, Clercq E De. Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. Pharm Acta Helv 1999; 74: 11.
19. Pandeya SN, Sriram D, Nath G, Clercq E de. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin and its derivatives with triazole. Arzneimittel-Forsch 2000; 50: 55.
20. Singh WM, Dash BC. Synthesis of some new Schiff bases containing thiazole and oxazole nuclei and their fungicidal activity. Pesticides 1988; 22: 33-37.
21. Kelley JL, Linn JA, Bankston DD, Burchall CJ, Soroko FE, Cooper BR. 8-Amino-3-benzyl-1,2,4-triazolo[4,3-α]pyrazines: Synthesis and anticonvulsant activity. J Med Chem 1995; 38: 3676-3679.
22. Turan-Zitouni, Kaplancikli ZA, Ozdemir A, Chevallet P. Studies on 1,2,4-triazole derivatives as potential anti-inflammatory agents. Arch. Pharm Chem Life Sci 2007; 340: 586-590.
23. Tarafder MTH et al. Methyldithio-carbazate and its Schiff bases: Evaluation of bondings and biological properties. J Biochem Mol BioI Biophys 2002; 6: 85.
24. Chazin, EL et al. synthesis and biological evaluation of novel 6-hydroxybenzo[d][1,3]oxathiol-2-one Schiff bases as potential anticancer agents. Molecules 2015; 20: 1968-1983.
25. Barbuceanu, SF, Ilies DC, Saramet G, Uivarosi V, Draghici C, Radulescu V. synthesis and antioxidant activity evaluation of new compounds from hydrazine carbothioamide and 1,2,4-triazole class containing diarylsulfone and 2,4-difluorophenyl moieties. Int J Mol Sci 2014; 15: 10908-10925.
26. de Souza AO, Galetti FCS, Silva CL, Bicalho B, Parma MM, Fonseca SF. antimycobacterial and cytotoxicity activity of synthetic and natural compounds. Quím Nova 2007; 30(7): 1563-1566.
27. Aboul-Fadl T et al. Synthesis, antitubercular activity and pharmacokinetic studies of some Schiff bases derived from 1-alkylisatin and isonicotinic acid hydrazide. Arch Pharm Res 2003; 26(10): 778-784.
28. Dueke-Eze CU et al. Synthesis and anti-tuberculosis activity of some Copper(II) and Cobalt(II) complexes of substituted methylene isonicotinoyl hydrazide Schiff bases. J Chem Soc Nigeria 2018; 43(1): 24-30.
29. Amaral TC et al. Silver(I) and Zinc(II) complexes with symmetrical cinnamaldehyde Schiff base derivative: spectroscopic, powder diffraction characterization, and antimycobacterial studies. Polyhedron 2018; 146:166-171.
30. Jone Kirubavathy S, Chitra S. Structural, theoretical investigations and biological evaluation of Cu(II), Ni(II) and Co(II) complexes of mercapto-pyrimidine Schiff bases. J Mol Struct 2017; 1147: 797-809.
31. Samina KhanYusufzai et al. Design, characterization, in vitro antibacterial, antitubercular evaluation and structure–activity relationships of new hydrazinyl thiazolyl coumarin derivatives. Med Chem Res 2017; 22(6): 1139-1148.
32. Ganesh More, Darshana Raut K. Aruna, Sakina Bootwala. Synthesis, spectroscopic characterization and antimicrobial activity evaluation of new tridentate Schiff bases and their Co(II) complexes. J Saudi Chem Soc 2017; 21: 954-964.
33. Salve PS, Alegaon SG, Sriram D. Three-component, one-pot synthesis of anthranilamide Schiff bases bearing 4-aminoquinoline moiety as Mycobacterium tuberculosis gyrase inhibitors. Bioorg Med Chem Lett 2017; 27(8): 1859-1866.
34. Srinubabu Maddela, Ajitha Makula. Design, synthesis and docking study of some novel isatin- quinoline hybrids as

potential antitubercular agents. Anti Infect Agents 2016; 14: 53-62.
35. Shivakumar et al. Synthesis, characterization, thermal, fluorescence, in vitro anti-tuberculosis, anthemintic and DNA cleavage studies of mononuclear metal complexes of 2h-chromeme-2-one schiff base. J Chem Bio Phy Sci Sec A 2016; 6(3): 834-846.
36. Syed Tajudeen S, Geetha Kannappan. Schiff base–Copper(II) complexes: Synthesis, spectral studies and anti-tubercular and antimicrobial activity. Indian J Adv Chem Sci 2016; 4(1): 40-48.
37. Joshi SD et al. Synthesis, characterization and antitubercular activities of novel pyrrolyl hydrazones and their Cu-complexes. Eur J Med Chem 2016; 121: 21-39.
38. Wagdy M Eldehna, Mohamed Fares, Marwa M Abdel-Aziz, Hatem A Abdel-Aziz. Design, synthesis and antitubercular activity of certain nicotinic acid hydrazides. Molecules 2015; 20: 8800-8815.
39. Suresh et al. Design, synthesis, characterization and biological evaluation of some novel heterocyclic derivatives as anti-tubercular agents. Int J Appl Pharm Sci 2016; 3(2): 1-11.
40. Joshi SD et al. Molecular docking, synthesis, and antimycobacterial activities of pyrrolyl hydrazones and their Copper complexes. Res Rep Med Chem 2016; 6: 1-14.
41. Shingade SG, Shirodkar SS. Synthesis and antimicrobial screening of thiadiazole derivatives. J Adv Chem Sci 2016; 2(3): 309-312.
42. Ayyadurai Jerad Suresh, Rajendran Ravikumar, Parakkot Ramakrishnan Surya. Evaluation of few novel diaminopimelate decarboxylase inhibitors as antitubercular agents. World J Pharm Pharm Sci 2016; 5(5): 1785-1799.
43. Velezheva V, Brennan P, Ivanov P, Kornienko A, Lyubimov S, Kazarian K, Nikonenko B. Majorov K, Apt A. Synthesis and antituberculosis activity of indole-pyridine derived hydrazides, hydrazide-hydrazones, and thiosemicarbazones. Bioorg Med Chem Lett 2016; 26(3): 978-985.
44. Shiju C, Arish D, Bhuvanesh N, Kumaresan S. synthesis, characterization, and biological evaluation of Schiff base Platinum(II) complexes. Spectrochim Acta A Mol Biomol Spectrosc 2015; 145:213-222.
45. Elham Pahlavani et al. A study on antitubercular and antimicrobial activity of isoniazid derivative. Zahedan J Res Med Sci 2015; 17(7): 7-10.
46. Mustapha C Mandewale et al. Synthesis and anti-mycobacterium study of some fluorine containing Schiff bases of quinoline and their metal complexes. Der Pharma Chem 2015; 7(5): 207-215.
47. da Silva SA, Leite CQF, Pavan FR, Masciocchi N, Cuin A. Coordinative versatility of a Schiff base containing thiophene: Synthesis, characterization and biological activity of Zinc(II) and Silver(I) complexes. Polyhedron 2014; 79:170-177.
48. Savita R Shejale, Suhas S Awati1 et al. Synthesis, characterization and evaluation of antitubercular and analgesic activity of some novel pyrazolopyrimidine and pyrazolopyridine derivatives. Der Pharma Chem 2014; 6(2): 75-82.
49. Joshi SD et al. 3D-QSAR studies of quinoline Schiff bases as enoyl acyl carrier protein reductase inhibitors. Res Rep Med Chem 2014; 4: 59-75.
50. Joshi SD, More UA, Dixit SR, Dubey D, Tripathi A, Kulkarni VH. Discovering potent inhibitors against the enoyl-acyl carrier protein reductase (InhA) of mycobacterium tuberculosis: structure-based design, synthesis and antimicrobial activity of quinoline hydrazones. Indo Am J Pharm Res 2014; 4(2):864-877.
51. Joshi SD, Joshi A, Vagdevi HM, Vaidya VP, Gadaginamath GS. Microwave assisted synthesis of some new quinolinyl pyrrole derivatives as potential antibacterial and antitubercular agents. Ind J Heterocycl Chem 2010; 19: 221-224.
52. Pradeep Kumar MR, Joshi SD, Dixit SR, Kulkarni VH. Synthesis, antibacterial and antitubercular activities of some novel quinoline derivatives. Ind J Heterocycl Chem 2014; 23: 353-358.
53. Gemma S, Savini L, Altarelli M et al. Development of antitubercular compounds based on a 4-quinolylhydrazone scaffold. Further structure-activity relationship

studies. Bioorg Med Chem 2009; 17(16):6063-6072.
54. Joshi SD et al. Synthesis and molecular modeling studies of novel pyrrole analogs as antimycobacterial agents. J Saudi Chem Soc 2017; 21(1):42-57.
55. Sivakumar KK, Rajasekaran A. Synthesis, in-vitro antimicrobial and antitubercular screening of Schiff bases of 3-amino-1-phenyl-4-[2-(4-phenyl-1,3-thiazol-2-yl)hydrazin-1-ylidene]-4,5-dihydro-1H-pyrazol-5-one. J Pharm Bioall Sci 2013; 5:126-135.
56. Uttam et al. Antitubercular activity of pyrrole schiff bases on computational study of M. tuberculosis InhA. Int J Drug Des Discov 2013; 4(4): 1163-1173.
57. Yamgar et al. Synthesis, characterisation and antituberculosis activity of novel transition metal complexes of heterocyclic Schiff bases. Int J Adv Res 2013; 1(9): 1-21.
58. Paiva IL et al. Silver (I) complexes with symmetrical Schiff bases: Synthesis, structural characterization, DFT studies and antimycobacterial assays. Polyhedron 2013; 62: 104–109.
59. Malipeddi H. synthesis and antitubercular activity of some novel thiazolidinone derivatives. Trop J Pharm Res 2012; 11(4): 611-620.
60. Sankar VK, Nandi. Synthesis and docking studies of Schiff bases derived from 4-aminopyridine. J Pharm Sci Innov 2012; 1(5): 9-11.
61. Cicekli SU, Onkol T, Ozgen S, Fethi Sahin M. Schiff bases of 3-[(4-amino-5-thioxo-1,2,4-triazole-3-yl)methyl]2(3h)benzoxazolonederivatives. synthesis and biological activity. Rev Roum Chim 2012; 57(3): 187-195.
62. Narang RJ et al. Synthesis, antimycobacterial, antiviral, antimicrobial activities, and QSAR studies of nicotinic acid benzylidene hydrazide derivatives. Med Chem Res 2012; 21:1557-1576.
63. Eswaran S, Adhikari AV, Pal NK, Chowdhury IH. Design and synthesis of some new quinoline-3-carbohydrazone derivatives as potential antimycobacterial agents. Bioorg Med Chem Lett 2010; 20:1040-1044.
64. Thomas KD et al. Design, synthesis and docking studies of new quinoline-3-carbohydrazide derivatives as antitubercular agents. Eur J Med Chem 2011; 46: 5283-5292.
65. Aboul-Fadl T. Schiff bases of indoline-2,3-dione: potential novel inhibitors of Mycobacterium tuberculosis DNA gyrase. Molecules 2011; 16:7864-7879.
66. Ilango K, Arunkumar S. Synthesis, antimicrobial and antitubercular activities of some novel trihydroxy benzamido azetidin-2-one derivatives. Trop J Pharm Res 2011; 10(2):219-229.
67. Alok Pandey et al. Synthesis of Schiff bases of 2-amino-5-aryl-1, 3,4-thiadiazole and its analgesic, anti- inflammatory, anti-bacterial and anti-tubercular activity. Int J Chem Tech Res 2011; 3(1):178-184.
68. Tarek Aboul-Fadl Fayzah, A.S.Bin-Jubair, Omima Aboul-Wafa. Schiff bases of indoline-2,3-dione (isatin) derivatives and nalidixic acid carbohydrazide, synthesis, antitubercular activity and pharmacophoric model building. Eur J Med Chem 2010; 45:4578-4586.
69. Abdel-Aal WS et al. Pharmacophoric model building for antitubercular activity of the individual Schiff bases of small combinatorial library. Eur J Med Chem 2010; 45:1098-1106.
70. Sudeep K Mandal et al. Synthesis and antitubercular activity of some triazole derivatives of propyl gallate. Int J Pharm Sci Res 2010; 1(11): 465-472.
71. Michael J Hearn et al. Preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid. Eur J Med Chem 2009; 44:4169-4178.
72. Marcelle de L Ferreira et al. Synthesis and antitubercular activity of novel Schiff bases derived from D-mannitol. Carbohydr Res 2009; 344: 2042-2047.

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