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AN OVERVIEW ON SCHIFF BASES AND ITS MEDICINAL CHEMISTRY POTENTIAL FOR NEW ANTITUBERCULAR DRUG MOLECULES RESEARCH

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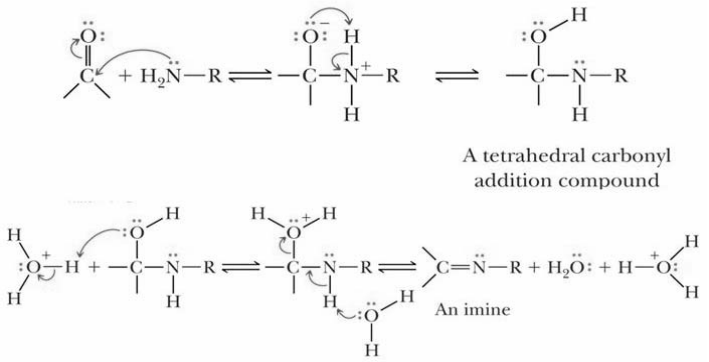
Schiff bases are the most widely used organic compounds, carrying an imine or azomethine group. Schiff bases derived from various heterocyclic compounds displayed a very broad range of biological activities such as anti-inflammatory, analgesic, antimicrobial, anticonvulsant, anticancer, antioxidant, anthelmintic and antitubercular. This review highlights the importance of schiff bases as potent antitubercular agents. There is an emergence need for new drugs to treat MDR and XDR tuberculosis.



INTRODUCTION

Schiff bases, named after Hugo Schiff and the very first preparation of imines are reported in 1864.[1] Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group. These are the condensation products of primary amines with carbonyl compounds.[2] Schiff bases act as the most important class of the widely used organic compounds and have a wide variety of applications in many fields including biological and inorganic chemistry. Schiff bases have gained importance both in medicinal chemistry and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory,[3] analgesic,[4] antimicrobial,[5-7] anti-convulsant,[8] anticancer,[9] antioxidant,[10] anthelmintic,[11] antitubercular,[12] and so onwards.

Schiff bases were also used as catalysts, intermediates in organic synthesis, dyes, pigments, polymer stabilizers,[13] and corrosion inhibitors.[14] Studies reveled that metal complexes have good biological activity than normal Schiff bases.[15] Improved biological activity was reported by coupling of transition metals into various Schiff bases.[16] In this review we are highlighting the most significant examples of compounds belonging to this class, which exhibit antitubercular activity to have been reported in the literature. Other pharmacological activities of Schiff bases are not included in this review.

Tuberculosis (TB) is one of the world's deadliest communicable diseases. In 2014, the World Health Organization (WHO) estimated 6 million new TB cases had recorded globally. In that 480,000 of them being affected by multidrug-resistant (MDR) Mycobacterium tuberculosis strains, including 400,000 deaths associated with co-infection with HIV.[17] And a serious concern is required in antitubercular therapy to treat the

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emergence of MDR strains, and more recently, the extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis is identified.[18,19] The magnitude and extent of drug-resistant strains have increased concern that TB may once again become an incurable disease.[20,21] Moreover, the increasing rate of incidence of the disease in immune compromised patients along with the longer durations of therapy insist the very urgent need for new drugs to extend the range of effective TB treatment.[22-24]

GENERAL SYNTHESIS OF SCHIFF BASE

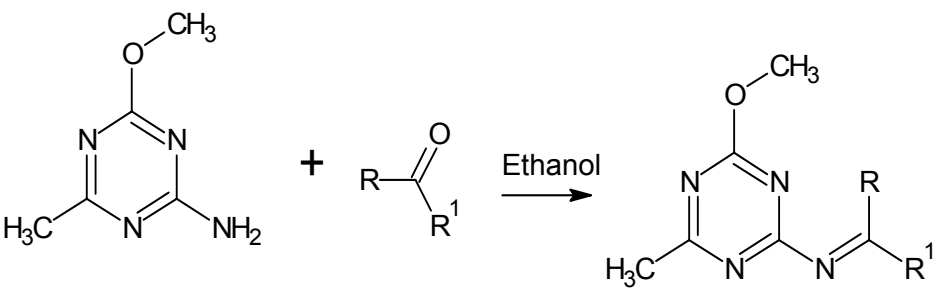
A Schiff base is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group is replaced by C=N-R group. The nucleophilic addition of an aromatic amine and a carbonyl compound forms a hemiaminal, which on dehydration gives an imine. The general method of formation is by condensation of aldehyde or ketone with a primary amine.[25]

SCHIFF BASES AS ANTI-TUBERCULAR AGENTS

The synthesis, characterization and in vitro biological evaluation of some novel 1,3,5-triazine–Schiff base conjugates as potential antimycobacterial agents have been reported by Vasudeva *et al.* A series of 1,3,5-triaizine-azomethine conjugates were synthesized by condensation of 4-methoxy-6-methyl-1,3,5-triazin-2-amine with a variety of aromatic/hetero-aromatic aldehydes and ketones in ethanol. These compounds were characterized by spectroscopic methods such as FTIR, ^{1}H NMR, ^{13}C NMR and LC mass spectral analysis, and screened for antimycobacterial activity using Microplate Alamar Blue assay (MABA). The compound 4 showed potent inhibitory activity with MIC value of 3.125µg/mL compared to other compounds. And other derivatives also showed satisfactory antimycobacterial activity. [26] [Scheme: 1, Table: 1]

Pramod and coworkers have reported the synthesis and antitubercular activity of some novel N-methyl triazolone derivatives. The methylation of triazole-5-one gives N-methyl triazolone initially, which then reacted with p-amino benzoic acid and converted to acids, and then to ester and to hydrazide. From this various Schiff bases are synthesised by reacting with respective aldehydes. The characterization of the compounds was done by IR, ^{1}H NMR and mass spectra. The compounds were screened for antitubercular activity. The compounds P4 and P5 showed significant inhibitory activity with MIC value of 6.25µg/mL and P1, P2, P3 showed moderate antitubercular activity. [27] [Scheme: 2, Table: 2]

Himaja *et al.* have reported the synthesis and antitubercular activity of some novel thiazolidinone derivatives. Intially 2-amino-5-aryl-5H-thiazolo[4,3-b]-l,3,4-thiadiazole were synthesized by mixing of aromatic aldehyde, thioglycolic acid and thiosemicarbazide. Sulphuric acid was added drop by drop to the mixture. Further thiadiazole derivative was converted to Schiff base by refluxing with aromatic aldehyde in ethanolic solution cointaing sulphuric acid. Schiff bases was converted to thiazolidinone derivatives by refluxing with thioglycollic acid in DMF solvent. The spectral characterization was done using methods such as FTIR, ^{1}H NMR and mass spectral analysis for the synthesized compounds and screened for their antitubercular activity. Schiff base series compounds 3f, 3h and 3i showed good antitubercular activity with MIC value of 3.125 µg/mL compared to standard streptomycin.[28] [Sceheme: 3, Table: 3]

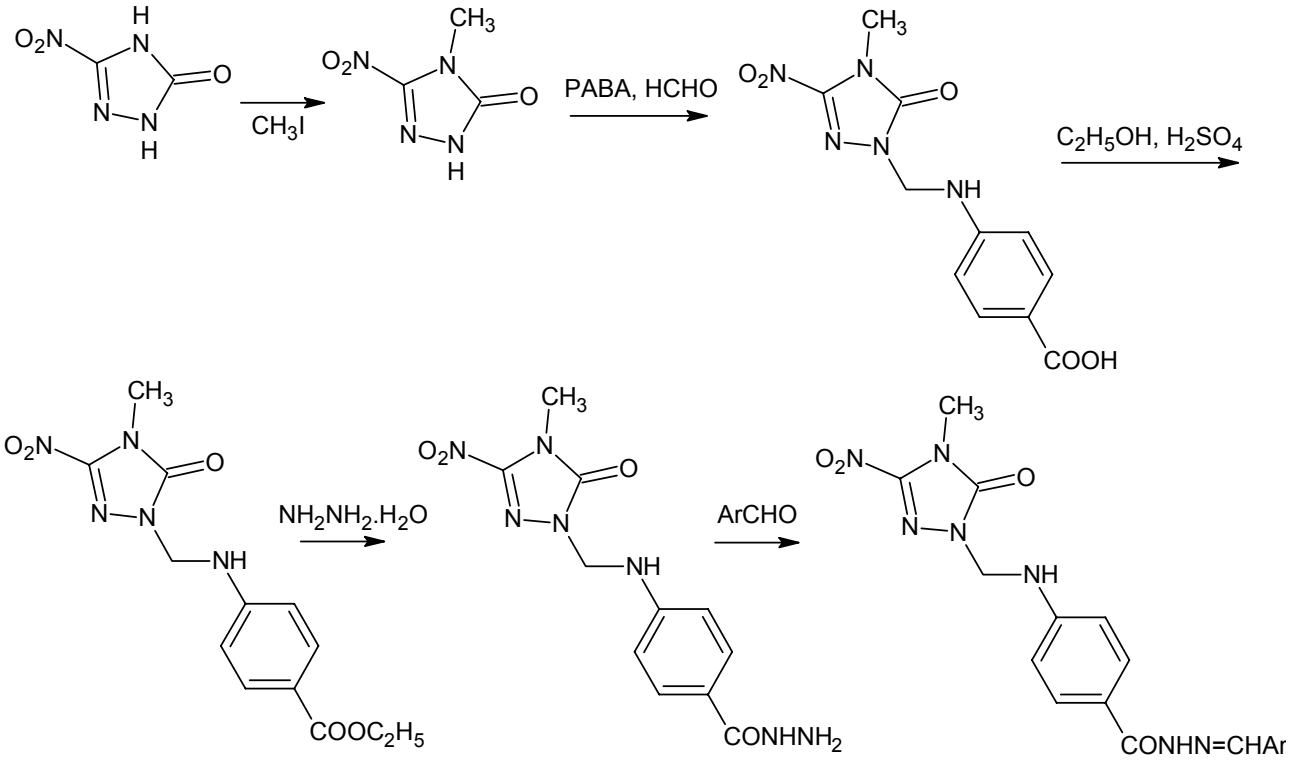


Scheme 1

Table 1

List of compounds with various substitutions of R andR^1

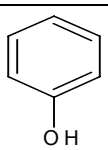
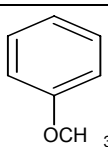
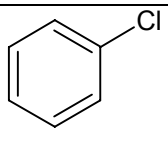
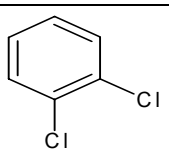
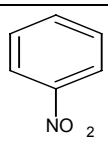
S.No	R	R^1	S.No	R	R^1
1.	H	C_6H_5	17.	CH_3	C_6H_5
2.	H	4-Me C_6H_4	18.	CH_3	4-Me C_6H_4
3.	H	4-N Me_2 C_6H_4	19.	CH_3	3-OMe C_6H_4
4.	H	3, 4, 5-triOMe C_6H_2	20.	CH_3	4-OMe C_6H_4
5.	H	3-OEt, 4-OH C_6H_3	21.	CH_3	2-OH C_6H_4
6.	H	3-NO_2 C_6H_4	22.	CH_3	4-OH C_6H_4
7.	H	4-Cl C_6H_4	23.	CH_3	2,4-diOH C_6H_3
8.	H	2,4-diCl C_6H_3	24.	CH_3	2,5-diOH C_6H_3
9.	H	3-Br C_6H_4	25.	CH_3	2-OH,5-Me C_6H_3
10.	H	4- Br C_6H_4	26.	CH_3	6-OH,5-Me C_6H_3
11.	H	2-OH, 3-Br, 5-ClC_6H_2	27.	CH_3	3-NO_2 C_6H_4
12.	H	4-Allyl-O C_6H_4	28.	CH_3	4-NO_2 C_6H_4
13.	H	Pyrrol-2-yl	29.	CH_3	Thiophen-2-yl
14.	H	Pyridin-3-yl	30.	CH_3	Pyridin-3-yl
15.	H	Indol-3-yl	31.	CH_3	Napthalen-2-yl
16.	H	Anthracen-9-yl	32.	CH_3	Fluoren-2-yl

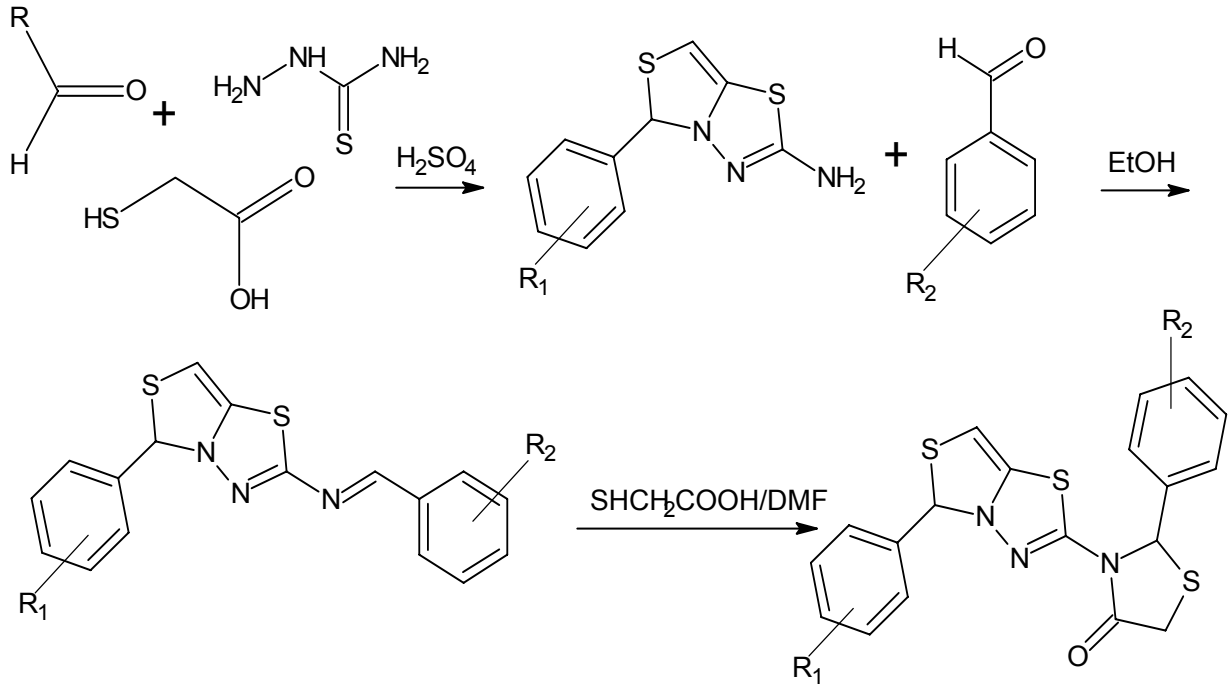


Scheme 2

Table 2

List of compounds with various substitutions

Ar					
Compound code	P1	P2	P3	P4	P5

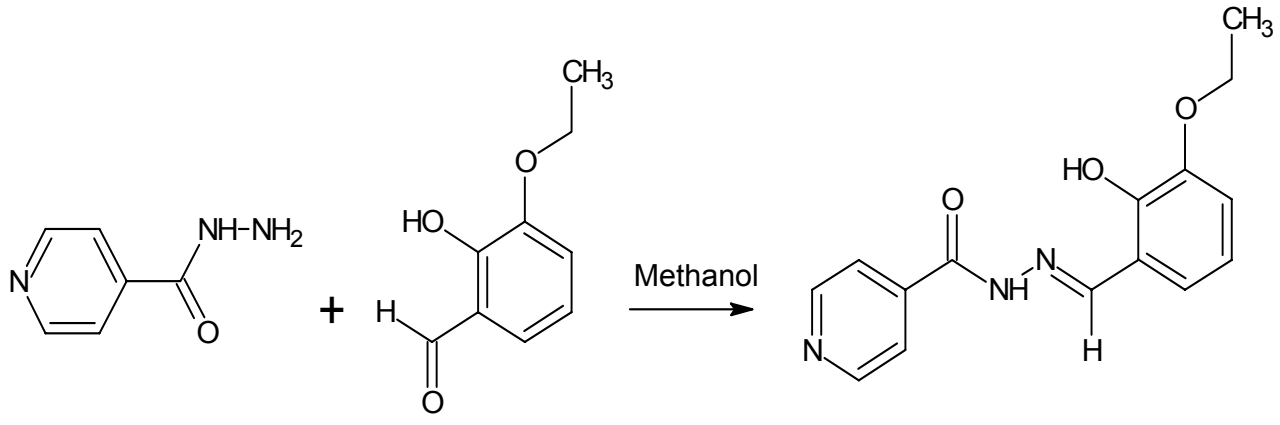


Scheme 3

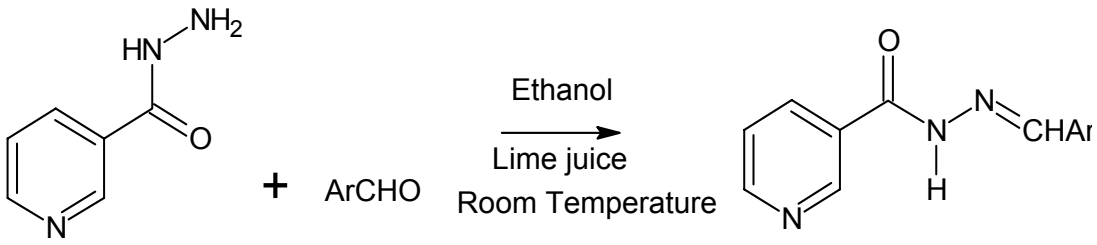
Table 3

List of compounds with various substitutions of R_1 and R_2

Compound code	R_1	R_2	Compound code	R_1	R_2
3a	H	H	4a	H	H
3b	H	2-Cl	4b	H	2-Cl
3c	H	4-Cl	4c	H	4-Cl
3d	4-CH_3	H	4d	4-CH_3	H
3e	4-CH_3	2-CH_3	4e	4-CH_3	2-CH_3
3f	4-CH_3	4-CH_3	4f	4-CH_3	4-CH_3
3g	4-OH	H	4g	4-OH	H
3h	4-OH	2-OH	4h	4-OH	2-OH
3i	4-OH	4-OH	4i	4-OH	4-OH
3j	4-$N(CH_3)_2$	H	4j	4-$N(CH_3)_2$	H
3k	4-$N(CH_3)_2$	2-OCH_3	4k	4-$N(CH_3)_2$	2-OCH_3
3i	4-$N(CH_3)_2$	4-OCH_3	4i	4-$N(CH_3)_2$	4-OCH_3



Scheme 4



Scheme 5

Table 4

List of compounds with various substitutions

Compound	Ar	Compound	Ar
2a	4-OH-3,5-$(OMe)_2$	2e	2-NO_2
2b	2-Cl-3-Quinolinyl	2f	3-NO_2
2c	2,4$(Cl)_2$	2g	4-NO_2
2d	4-Cl	2h	4-Br

Elham and coworkers synthesised N-(3-methoxy-hydroxybenzylidene) isonicotinohydrazide, an isoniazid derivative and studied its antitubercular and antimicrobial activity. The compound N-(3-ethoxy-2-hydroxybenzilidine) isonicotinohydrazide was synthesized by the addition of 3-ethoxysalicylaldehyde to a solution of isonicotinohydrazide in methanol and stirred. The structure of the compound was confirmed by FTIR, and ^{1}H NMR. The synthesized compound showed good antitubercular activity at concentration 4 μg/mL. [29] [Scheme: 4]

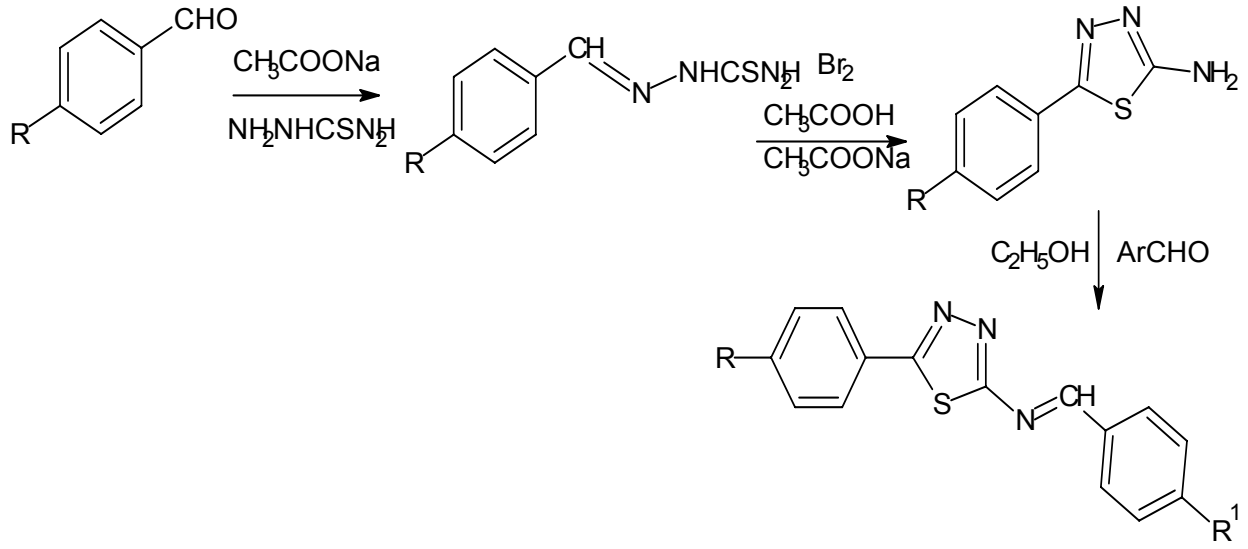
Vidya *et al.* have reported green synthesis of nicotinic acid hydrazide Schiff bases and its biological evaluation. The synthesis was carried out by dissolving nicotinic acid hydrazide in ethanol followed by addition of lemon juice with swirling and then aldehyde at room temperature. The compounds were characterized by spectroscopic methods such as FTIR and ^{1}H NMR. Most of the compounds showed better antitubercular activity with MIC values ranges from 0.8 to 3.12 μg/mL than the standard drugs pyrazinamide, streptomycin and ciprofloxacin against the strain H37RV.[30][Scheme: 5, Table: 4]

Alok and coworkers have reported the synthesis of Schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole and its analgesic, anti-inflammatory, antibacterial and antitubercular activity. Schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole were synthesized by the reaction of thiosemicarbazide with aldehyde which forms thiosemicarbazone initially, which then reacts with sodium acetate in glacial acetic acid and bromine added to this on magnetic stirrer. The obtained 2-amino-5-aryl-1, 3, 4-thiadiazole was further dissolved in alcohol and refluxed with aldehyde to form Schiff bases. The compounds were characterized by IR and ^{1}H NMR and subjected to antitubercular activity by rema plate method. Compounds 4c, 4e, 4f and 4i showed good response at MIC value of 2.5μg/mL compared to other synthesized compounds.[31] [Scheme 6, Table: 5]

Michael and coworkers have reported the preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid. Schiff bases are readily prepared in good yields, by condensation of isoniazid with the appropriate ketone or aldehyde in boiling alcohol. Synthesized compounds are characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. Compounds are screened for antitubercular activity, the compound 46 shows very significant inhibitory activity with MIC of less than 0.025μg/mL and compounds 3, 36, 42 and 46 also showed good inhibitory activity compared to other compounds.[32] [Scheme 7, Table: 6]

Sivakumar *et al.* have done 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. Synthesis of Schiff base was carried out by condensation of 3-amino-1-phenyl-4- [2- (4-phenyl-1, 3-thiazol-2-yl) hydrazin-1-ylidene]-4,5-dihydro-1H-pyrazol-5-one with corresponding aldehyde by glacial acetic acid in ethanol. Characterization of the compounds was done by elemental analysis, FTIR, 1H NMR and mass spectrometry. Synthesized compounds were subjected to antitubercular activity against *Mycobacterium tuberculosis* H37Rv by microplate Alamar Blue assay (MABA). Results revealed that compound TZP4h exhibited tremendous antitubercular activity with MIC value of 03.125μg/mL which was more active than the

standard drugs pyrazinamide and streptomycin. Other synthesized compounds with electron donating group on the phenyl ring TZP4g, TZP4i, TZP4j, and TZP4k showed appreciable antitubercular activity which was equipotent to pyrazinamide but less potent than Streptomycin.[33] [Scheme 8, Table: 7]

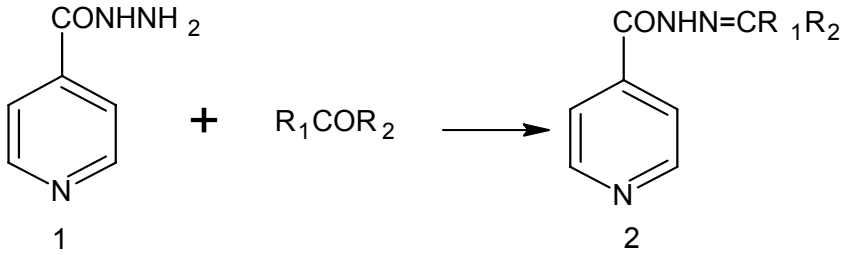


Scheme 6

Table 5

List of compounds with various substitutions of R andR^1

Compound code	R	R^1	Compound code	R	R^1
4a	OCH_3	OH	4f	OCH_3	NO_2
4b	OH	OH	4g	OH	NO_2
4c	Cl	OH	4h	Cl	NO_2
4d	NO_2	OH	4i	NO_2	NO_2
4e	$N(CH_3)_2$	OH	4j	$N(CH_3)_2$	NO_2



Scheme 7

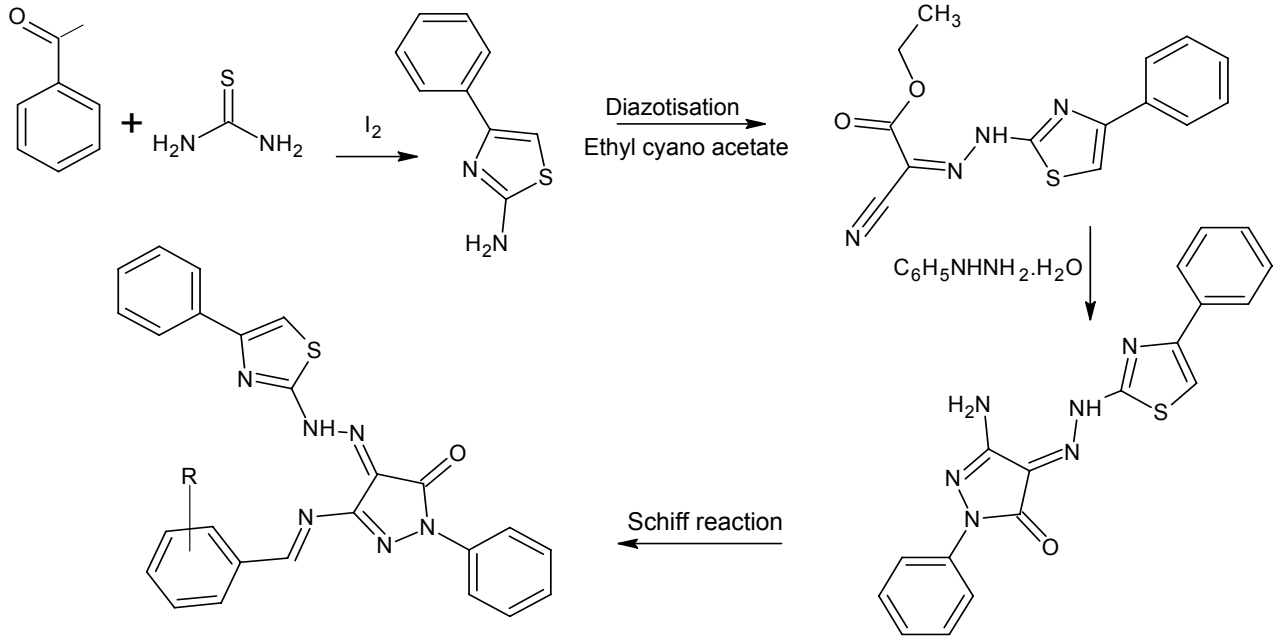
Table 6

List of compounds with various substitutions of R_1 and R_2

Compound code	R_1	R_2	Compound code	R_1	R_2
1.	--	--	24.	H	*t*-CH=$CHCH_3$
2.	--	--	25	H	*t*-CH=$CHCH_2CH_2CH_3$
3.	H	2-$(OCH_2C_6H_5)C_6H_4$	26.	H	*t*-CH=$CH(CH_2)_3CH_3$
4.	$(CH_2)_4$ CH_3	C_6H_5	27.	H	C=$CCH_3CH_2CH_2CH=CH_2$
5.	H	4-BrC_6H_4	28.	H	$CH_2CHCH_3CH_2CH_2CH=C(CH_3)_2$
6.	H	2-ClC_6H_4	29.	CH_3	CH_3
7.	H	3,4-$F_2C_6H_3$	30.	CH_2ph	$CH_2CO_2CH_2CH_3$
8.	H	4-IC_6H_4	31.	Both R_1R2= $CCH_2CH(CH_3)CH_2C(CH_3)_2CH_3$	

Table 6 (continued)

9.	H	3-I-4,5-$(OCH_3)_2C_6H_2$	32.	H	$CH{=}C(C_6H_5)_2$
10.	H	3-I-4-OH-5-$OCH_3C_6H_2$	33.	H	*t*-CH=CH-4-$OCH_3C_6H_4$
11.	H	4-ClC_6H_5	34.	H	*t*-CH=CH-2-$NO_2C_6H_4$
12.	H	3,4-$Cl_2C_6H_3$	35.	H	C(n-C_3H_7)=$CH(CH_2)_3CH_3$
13.	H	2,6-$F_2C_6H_3$	36.	H	C(i-C_3H_7)=$CHCH_2CH(CH_3)_2$
14.	H	2,3-$Cl_2C_6H_3$	37.	H	*t*-CH=CH-2-$OCH_3C_6H_4$
15.	H	2,6-$Cl_2C_6H_3$	38.	H	*t*-CCH_3=CHC_6H_5
16.	H	2-$NO_2C_6H_4$	39.	H	CH=$NNHCOC_5H_4N$
17.	H	4-Cl-3-$NO_2C_6H_3$	40.	CH_2CH_2 CH_3	$CH_2CO_2CH_2CH_3$
18.	CH_3	C_6H_5	41.	CH_3	$CH_2CO_2CH_2CH_3$
19.	H	4-$CH_3(CH_2)_5OC_6H_4$	42.	H	4-(CH=$NNHCOC_5H_4N$)C_6H_4
20.	H	3-$NO_2C_6H_4$	43.	CH_2CH_2 C_6H_5	$CO_2CH_2CH_3$
21.	H	C_6H_5	44.	H	$CH_3(CH_2)_{11}CH_2$
22.	H	4-$CH_3(CH_2)_3OC_6H_4$	45.	H	$CH_3(CH_2)_{10}CH_2$
23.	H	*t*-CH=$CHCH_2CH_3$	46.	Both $R_1R2{=}C(CH_2CH_2)_2CH_2$	



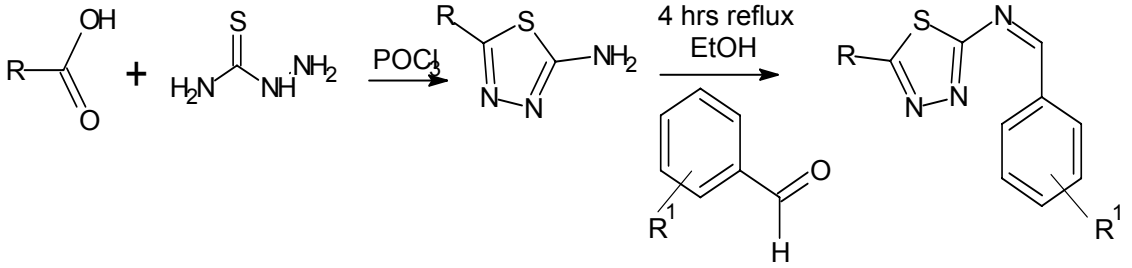
Scheme 8

Table 7

List of compounds with various substitutions of R

Compound code	R	Compound code	R	Compound code	R	Compound code	R
TZP4a	H	TZP4g	2,4-OH	TZP4d	4-Cl	TZP4j	3-OCH_3,4-OH
TZP4b	2-Cl	TZP4h	3,4-OH	TZP4e	3-F	TZP4k	4-$N(CH_3)_2$
TZP4c	3-Cl	TZP4i	3-OCH_3	TZP4f	4-OH	TZP4l	4-NO_2

Karigar and coworkers have reported synthesis, docking and antitubercular activity of some newer Schiff bases. Initially 2-amino-5-substituted acid-1,3,4-thiadiazoles are prepared by the reaction of thiosemicarbazide with substituted acids. The 5-pyridin-3-yl-1,3,4-thiadiazol-2-amines were dissolved in ethanol and reacted with corresponding aromatic aldehydes to yield Schiff bases. Schiff bases were characterized by the elemental analysis, IR, NMR and mass spectral studies. Compounds are subjected to antitubercular activity. The compounds Vk, Vl, Vm, Vn showed good antitubercular inhibitory activity compared to other compounds with MIC value of 6.25μg/mL.[34][Scheme 9, Table: 8]

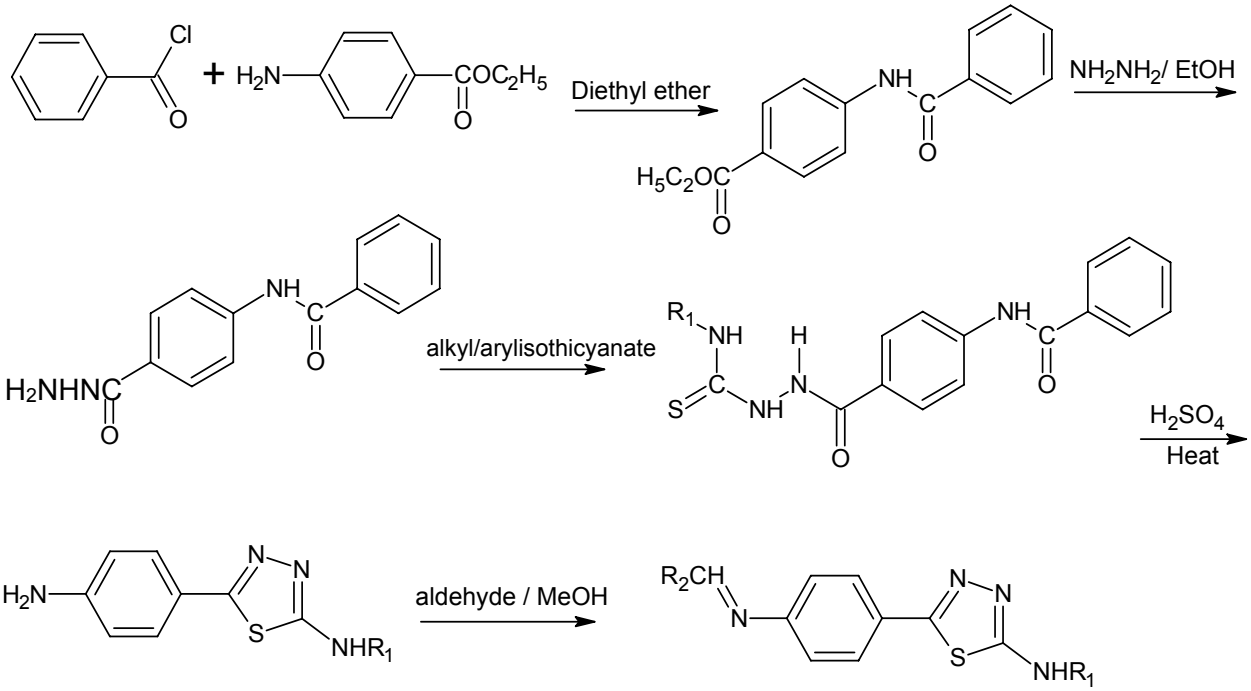


Scheme 9

Table 8

List of compounds with various substitutions of R andR^1

Compound	R	R^1	Compound	R	R^1
Va	Nicotinic acid	H	Vh	Isonicotinic acid	H
Vb	Nicotinic acid	2-Cl	Vi	Isonicotinic acid	2-Cl
Vc	Nicotinic acid	4-Cl	Vj	Isonicotinic acid	4-Cl
Vd	Nicotinic acid	2-OCH_3	Vk	Isonicotinic acid	2-OCH_3
Ve	Nicotinic acid	4-OCH_3	Vl	Isonicotinic acid	4-OCH_3
Vf	Nicotinic acid	2-OH	Vm	Isonicotinic acid	2-OH
Vg	Nicotinic acid	4-OH	Vn	Isonicotinic acid	4-OH

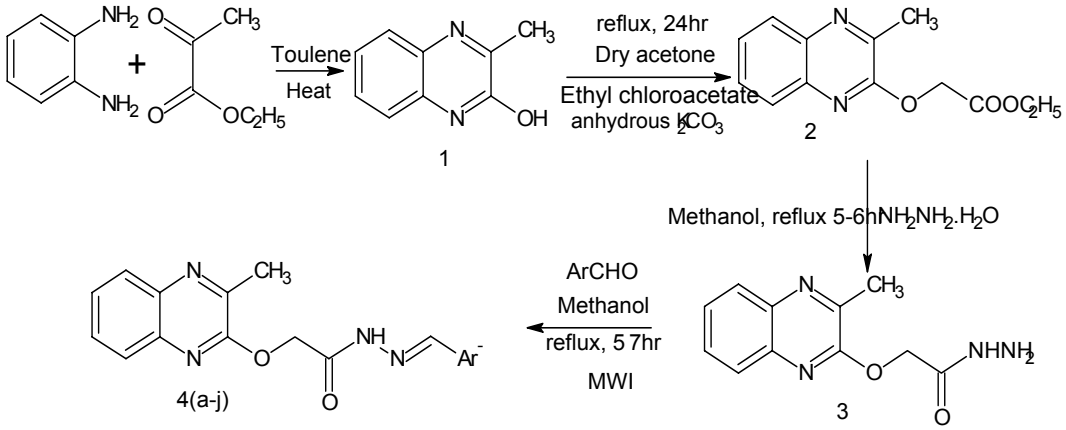


Scheme 10

Table 9

List of compounds with various substitutions of R_1 and R_2

Compound	R_1	R_2	Compound	R_1	R_2
5a	Phenyl	2-hydroxyphenyl	7c	4-methyl Phenyl	3-nitrophenyl
5c	Phenyl	3-nitrophenyl	8a	ethyl	2-hydroxyphenyl
6a	benzyl	2-hydroxyphenyl	8b	ethyl	5-nitrofurfuryl
6b	benzyl	5-nitrofurfuryl	8c	ethyl	3-nitrophenyl
6c	benzyl	3-nitrophenyl	9a	methyl	2-hydroxyphenyl
6d	benzyl	3-hydrophenyl	9b	methyl	5-nitrofurfuryl
7a	4-methyl Phenyl	2-hydroxyphenyl			
7b	4-methyl Phenyl	5-nitrofurfuryl	9c	methyl	3-nitrophenyl



Scheme 11

Table 10

List of compounds with various substitutions

Compound code	Ar	Compound code	Ar
4a	C_6H_5	4f	4-$(OCH_3)C_6H_4$
4b	4-ClC_6H_4	4g	4-$N(CH_3)_2C_6H_4$
4c	3-$NO_2C_6H_4$	4h	3-indolyl
4d	4-OHC_6H_4	4i	2-furyl
4e	3,4-$(OCH_3)C_6H_3$	4j	5-(-4-nitrophenyl)-2-furfuryl

Nilufer and coworkers have reported the synthesis and antituberculosis activity of 2-(aryl/alkylamino)-5-(4- aminophenyl)-1,3,4-thiadiazoles and their Schiff bases. Initially ethyl 4-(benzoylamino) benzoate was synthesized by treating benzoate and benzocain with benzoyl chloride in ether. Then hydrazine hydrate was added, refluxed and aryl/alkylisothiocyanate was added in ethanol to give 1-(4-benzoylamino)benzoyl-4-alky/arylthiosemicarbazide. To this sulfuric acid was added, refluxed and neutralized with sodium hydroxide to obtain 2-(aryl / alkylamino)-5-(4-aminophenyl)-1,3,4-thiadiazole as the product. Schiff bases were obtained by treating the thiadiazole derivative with aldehyde in methanol. The spectral characterization was done for the synthesized compounds by elemental analysis, IR, NMR and mass spectral studies. The screening of antitubercular activity against *Mycobacterium tuberculosis* H37Rv revealed that compound 5a showed significant inhibitory activity with MIC value of 6.25μg/mL. Other compounds 7a and 7c showed moderate activity. [35][Scheme 10, Table: 9]

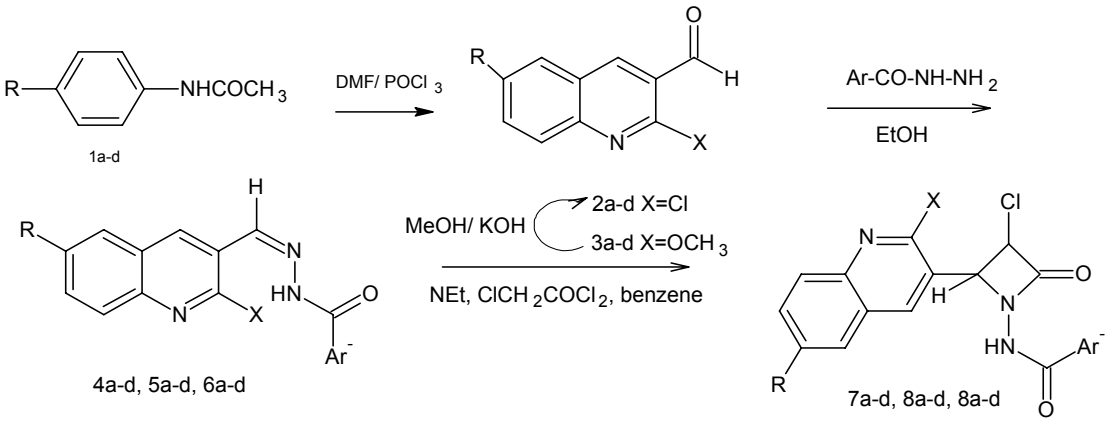
Achutha *et al*. have reported microwave-assisted synthesis of some quinoxaline-incorporated Schiff bases and their biological evaluation. The Schiff bases were synthesized by microwave irradiation method in which 2-[(3-methylquinoxalin- 2-yl)oxy] acetohydrazide was reacted with heterocyclic/aromatic aldehyde in glacial acetic acid and characterized by FTIR, ^{1}HNMR and mass spectrometry. All the newly synthesized compounds were evaluated for their possible in vitro antitubercular activity. Compounds 4c, 4d, 4i, and 4j exhibited substantial antitubercular activity, particularly at MIC 6.25 μg/mL and emerged as the most active compound in this series.[36] [Scheme 11, Table: 10]

Shrinivas and coworkers have reported design, synthesis of quinolinyl Schiff bases and azetidinones as enoyl ACP-reductase inhibitors. Initially 6-substituted-2-chloroquinoline-3-carbaldehydes was chosen as starting material to design Schiff bases. Various 4-substituted acetanilides were treated with Vilsmeier-Haack reagent to obtain 6-substituted-2-chloroquinoline-3-carbaldehydes which was then treated with methanol in the presence of potassium hydroxide furnished 6-substituted-2-methoxyquinoline-3-carbaldehydes. The Schiff bases were prepared by reacting 6-substituted-2-methoxyquinoline-3-carbaldehydes with isoniazid and 4-(1H-pyrrol-1-yl)benzohydrazide in the presence of glacial acetic acid. The 6-substituted-2-chloroquinoline-3-carbaldehydes was reacted with isoniazid in the presence of glacial acetic acid to get N-[(6-substituted-2-chloroquinolin-3-yl) methylene] isonicotinohydrazides. All the synthesized compounds are characterized by FTIR, ^{1}H NMR and mass spectrometry. The antitubercular screening against *Mycobacterium tuberculosis* H37Rv of the synthesized compounds showed that compound 5c and 5d had very significant inhibitory activity with MIC value of 1.6μg/mL. Other compounds 4a, 4c,

4d, 5a and 5b showed moderate activity. [37][Scheme 12, Table: 11]

Joshi *et al*. have reported synthesis of new 4-(2,5-dimethylpyrrol-1-yl)/4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: a novel class of potential antibacterial, antifungal and antitubercular agents. At first by Paal–Knorr condensation reaction between ethyl 4-aminobenzoate and acetonyl acetone in glacial acetic acid furnished ethyl 4-(2,5-dimethylpyrrol-1- yl)benzoate. Reaction of hydrazine hydrate with the ester of 4-(2,5-dimethylpyrrol-1- yl)benzoate in ethanolic medium produced 4-(2,5- dimethylpyrrol-1-yl)benzoic acid hydrazide, which was then treated with acetone acetophenone, benzophenone and 4-aminoacetophenone resulted in the formation of the corresponding hydrazone derivatives. The reaction of 4-(2,5- dimethylpyrrol-1-yl)benzoic acid hydrazide with different aldehydes in alcohol gave different Schiff bases. All the compounds are subjected to antitubercular activity. The synthesized hydrazone derivatives 3a-h showed inhibitory activity with MIC value of 31.25µg/mL and Schiff bases 7b, 7c, 7d showed MIC value of 16 µg/mL. [38] [Scheme 13, Table: 12]

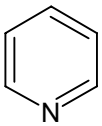
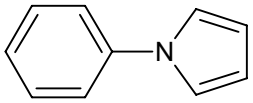
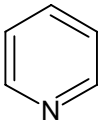
Murali and coworkers have reported synthesis, antibacterial, and antitubercular studies of some novel isatin derivatives. The synthesis of N-benzyl isatin was done by reacting isatin with benzyl chloride, which upon reaction with p-phenylenediamine gives N-benzyl imesatin. The compound was subjected to react with various substituted aromatic aldehydes in ethanol to form Schiff bases. IR, 1H NMR, 13C NMR, mass spectral and elemental analysis data was in agreement with the proposed structures of the synthesized compounds. The synthesized compounds were tested for their antimycobacterial activity. Results showed that compound A2 exhibited promising antimycobacterial activity compared to other synthesized compounds with an MIC value of 4.26µg/mL. The halogen-substituted, particularly bromine substituted compound A2 showed better inhibition than the other substitutions.[39] [Scheme 14, Table: 13]

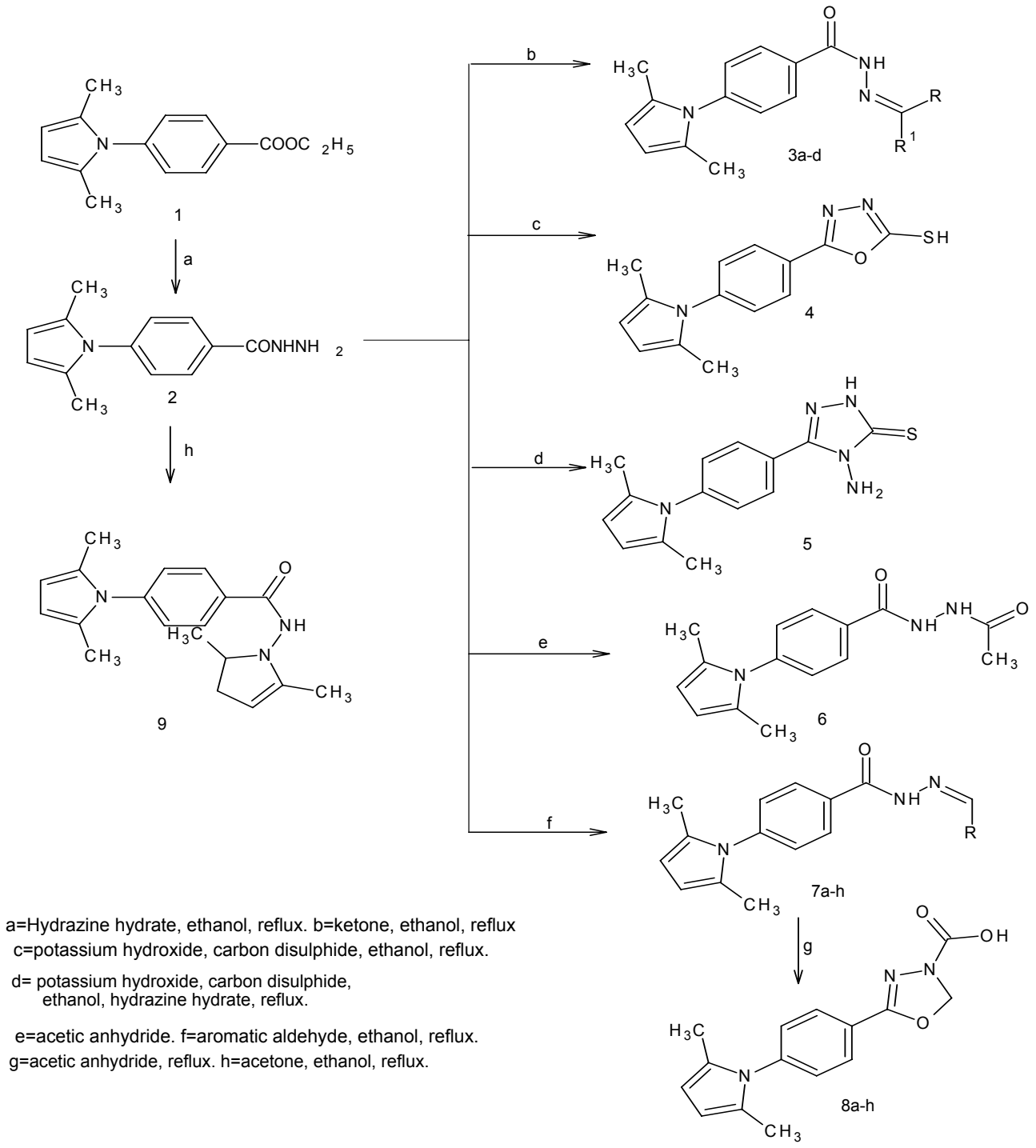


Scheme 12

Table 11

List of compounds with various substitutions of R and Ar

Compound code	R	Compound code	Ar
A	H	4a-d, 7a-d, X=OCH_3	
B	Cl	5Aa-d, 8a-d X=OCH_3	
c	Br	6a-d, 9a-d X=Cl	
d	CH_3		

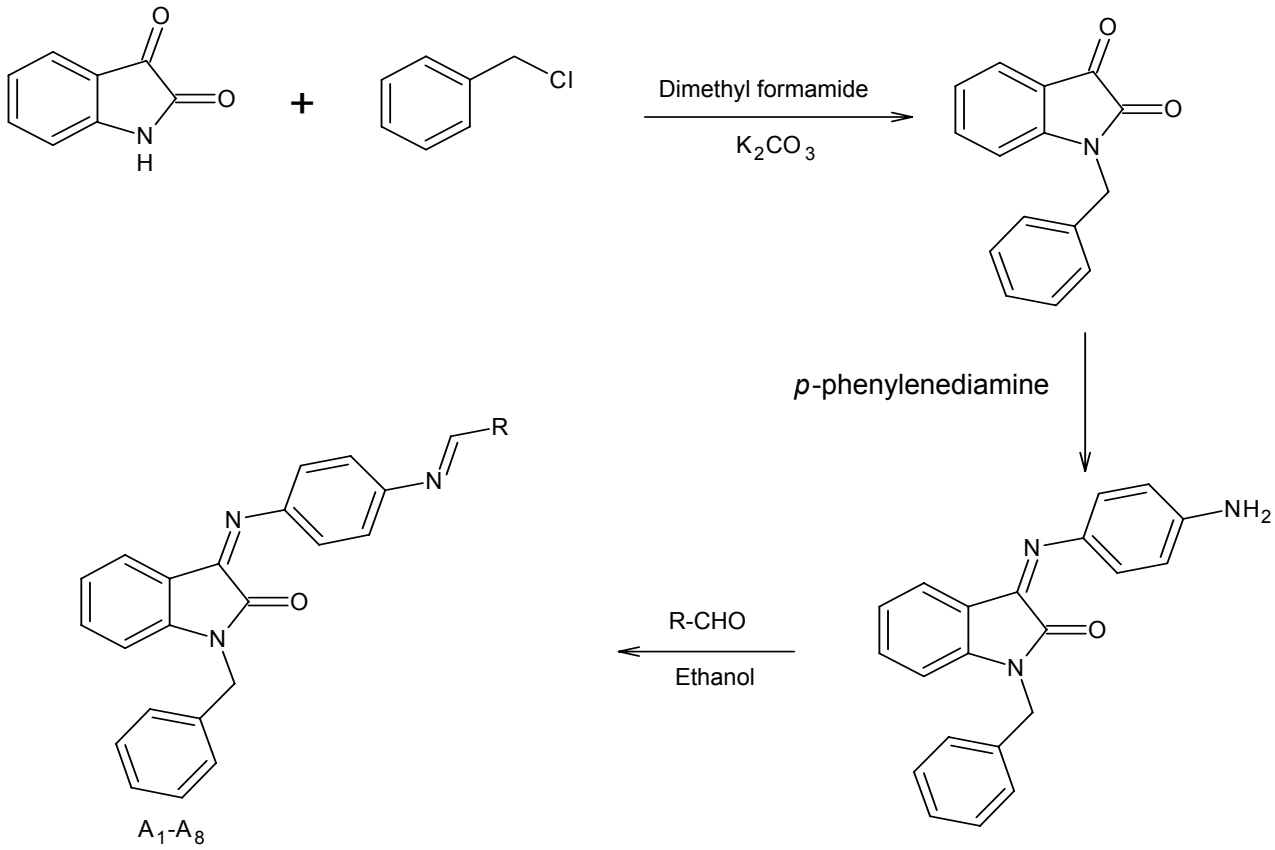


Scheme 13

Table 12

List of compounds with various substitutions of R and R^1

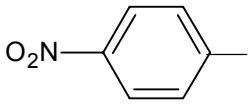
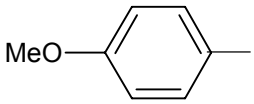
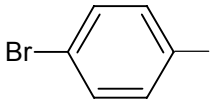
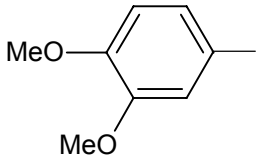
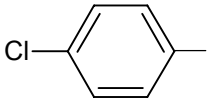
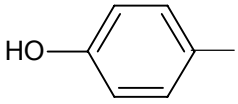
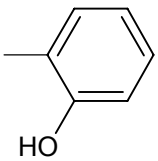
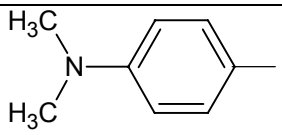
3a-d			8a-h			
Compound code	**R**	**R^1**	**Compound code**	**R**	**Compound code**	**R**
3a	CH_3	CH_3	a	C_6H_5	e	3-$NO_2C_6H_4$
3b	CH_3	C_6H_5	b	2-Cl C_6H_4	f	2-$NO_2C_6H_4$
3c	C_6H_5	C_6H_5	c	4-Br C_6H_4	g	4-OHC_6H_4
3d	CH_3	4-$NH_2C_6H_4$	d	2,6-Cl_2 C_6H_3	h	4-$N(CH_3)C_6H_4$

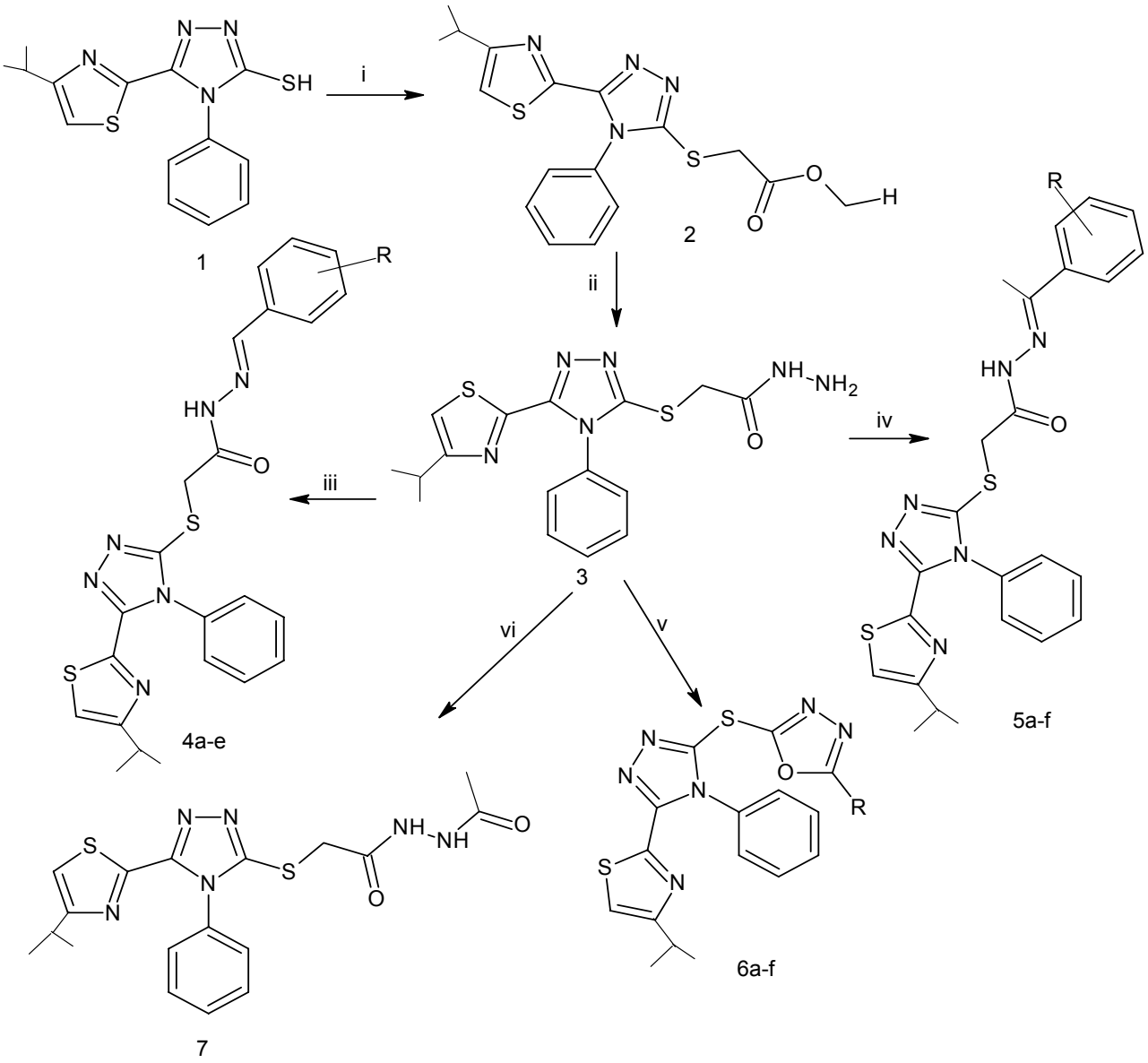


Scheme 14

Table 13

List of compounds with various substitutions of R

Compound code	R	Compound code	R
A1		A5	
A2		A6	
A3		A7	
A4		A8	



i= ethyl bromoacetate, NaOH, ethanol, reflux. ii=hydazine hydrate, etanol, reflux
aryl aldehyde, ethanol, glacial acetic acid, reflux iv= actophenone, ethanol, glacial acetic acid, reflux
v=aromatic acid, $POCl_3$, reflux

Scheme 15

Table 14

List of compounds with various substitutions of R

Compound code	R	Compound code	R
4a	3,4-OCH_3	5e	4-Br
4b	4-Cl	5f	4-Cl
4c	4-OH	6a	C_6H_5
4d	3-OCH_3, 4-Cl	6b	CH_2Cl
4e	3-NO_2	6c	C_6H_4Cl
5a	4-NO_2	6d	$C_6H_4NO_2$
5b	4-OCH_3	6e	$C_6H_4CH_3$
5c	4-OH	6f	C_6H_4OH
5d	4-CH_3		

Suresh Kumar *et al.* have reported synthesis and pharmacological evaluation of novel 4-isopropylthiazole-4-phenyl-1,2,4-triazole derivatives as potential antimicrobial and antitubercular agents. The acetylation of 5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol with ethyl bromoacetate in the presence of sodium hydroxide and absolute ethanol yielded 5-(4-isopropylthiazol-2-yl)-ethyl-2-(4-phenyl-4H-1,2,4-triazol-3-ylthio)acetate, which was then treated with hydrazine hydrate in the presence of absolute ethanol. The product 5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazol-3-ylthio) acetohydrazide formed was treated with substituted aromatic aldehydes and also with acetophenones to yield Schiff bases and acetohydrazides, respectively. Synthesized compounds were characterized by IR, 1H NMR, 13C NMR, mass spectral and elemental analysis. On antitubercular screening all the compounds were found to be active, in particular compounds 4c and 6c exhibited excellent activity with MIC value 8 and 4µg/mL respectively. [40][Scheme 15, Table: 14]

CONCLUSION

Currently the focus on the chemistry of Schiff bases in the research and development of new drug entities is of much importance due to its wide variety of pharmacological activities. In the field of drug design, Schiff bases have a persuasive role as ligand due to its ease of synthesis through simple condensation process. This review was focused on the importance of Schiff bases as potent scaffold for antitubercular activity. We have discussed various synthetic routes of Schiff bases which may be useful in future research to select a potent derivative of Schiff base for antitubercular activity. Selecting such derivative of Schiff base which has already shown antitubercular activity and increasing its potency, by considering their structural activity relationship may result in designing of a very potent antitubercular drug which is of very urgent need in the treatment of tuberculosis. The review helps in the challenge of selecting and developing Schiff bases as most persuasive antitubercular agents and also as an important tool for the development of better novel pharmacologically active compounds in terms of efficacy and safety. Also the review had shown that the synthesis of Schiff base is easier since many methods with different precursors are used which are feasible in laboratory. We conclude that incorporating various biologically active pharmacophores in Schiff bases may lead to a highly potent antitubercular drug in future.

Expansions:
MDR – Multi drug resistance
XDR – Extreme drug resistance

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