

# Antitubercular Activity of Some Substituted Phenothiazine Derivatives

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Received: 12 Nov. 2017, Revised: 23 Dec. 2017, Accepted: 27 Dec. 2017.

Published online: 1 May 2018.

**Abstract:** In search of newer and potent antitubercular agents, a series of phenothiazine derivatives were evaluated for antitubercular activity. This study may prove to be helpful in development and optimization of existing antitubercular activity of this class of compounds. Quaternized chlorpromazine, triflupromazine, and promethazine derivatives were tested as antitubercular agents against both actively growing and non-replicating *Mycobacterium tuberculosis* H37Rv. A slight variation in the substitution pattern on the phenothiazine nucleus often causes a marked difference in activities and therefore phenothiazines with various substituents are being synthesized and tested for activities in search of better medicinal agents.

**Keywords:** Phenothiazines, antitubercular, *M. tuberculosis*, Promethazine; Chlorpromazine.

## 1 Introduction

The chemistry of nitrogen-sulfur heteroatom containing aromatic compounds is becoming more popular as an area of research. From medicinal chemistry perspective, phenothiazines are an important group of condensed three-ring heterocycles (Gupta and Kumar, 1988). Phenothiazine derivatives and their analogues containing 1,4-thiazine structural fragment show diverse biological activities including as tranquilizers (El-Said, 1981), anti-inflammatory (Sharma et al., 2005; Tilak, et al., 1998), antimalarial (Dominguez, et al., 1997), antipsychotropic (Lin, et al., 1991), antimicrobial (Raval, and Desai 2005; Kaatz et al., 2003), antitubercular (Viveros and Amaral, 2001; Amaral and Kristiansen, 2000) antitumour (Motohashi et al., 2000; Motohasho, et al., 1999; Kurihara, et al., 1996; Kurihara, et al., 1999) and stimulation of the penetration of anticancer agents via the blood-brain barrier (BBB). However, solid cancers of the brain and stomach are generally resistant to chemotherapeutic agents (Ghosh and Chattopadhyay, 1993). Phenothiazines are inexpensive and widely available, and therefore have been examined as antitubercular drugs. It has been reported (Floyd, et al., 1993) that some phenothiazines inhibit intracellular replication of viruses including human immunodeficiency viruses (HIV). Furthermore, some of these derivatives have been reported to exhibit significant anti-TB activities (Viveros and Amaral, 2001; Amaral and Kristiansen, 2000) and great interest has arisen in the design and synthesis of

new phenothiazines to explore their antitubercular activities. Phenothiazine derivatives that contain aminoalkyl substituents at the thiazine nitrogen atom are used as antipsychotropic and antihistamine drugs (Isaacson, 1998). Extensive search has been conducted regarding new methods of synthesizing potentially useful phenothiazine analogs having pharmacological activities (Zifba et al., 2010).

Tuberculosis (TB), the disease caused by *Mycobacterium tuberculosis* (Mtb), infects about two billion people. The WHO estimates that about two million people die each year from TB due to the lack of inability to afford proper health care (Cande, et al., 2009; Maher, and Raviglionem, 1999). Overcrowding and ill-nourishment of poor people living in large cities leads to a high incidence of the disease due to the ease at which the infection can be transferred (Lowell, 1999). This situation contributes to the accelerated speed at which TB spreads in underdeveloped countries. TB has become a serious worldwide problem, infecting in synergy with human immunodeficiency virus (HIV) infection (Upadhyaya, et al., 2009). There is also an alarming increase in cases of TB caused by multidrug-resistant tuberculosis (MDR-TB), due in part to inadequate drug therapy as a result of incorrectly selected medications or suboptimal drug dosing (Savini, et al., 2002; Bearing, et al., 1999). WHO declared TB as a global health emergency and aimed at saving 14 million lives between 2006 and 2015 (Eswaran, et al., 2010). TB is difficult to treat due to

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residence of bacteria within the macrophages and its unusual cell wall barrier. Moreover, MDR-TB and extensively drug resistant (XDR) TB have emerged recently (Bairwa, et al., 2010). One of the most important issues in current medical practice is antibiotic-resistant bacterial infections (Chambers. 1997; Livermore. 2000; CDC. 2002). Their pervasiveness justifies the search for innovative antimicrobial agents featuring novel chemical structures and mechanisms of action, helpful in combating infections (Fung et al., 2001; Wright and Sutherland. 2007; Girdhar et al., 2010; Zilba et al., 2010). In this article, describe some phenothiazine derivatives as antitubercular agent (Zieba et al., 2012).

Thus, there is a need for new drugs targeting enzymes essential to mycobacterial survival. One such target is type II NADH-menaquinone dehydrogenase (ndh-2). By inhibiting ndh-2, the electron transport chain in Mtb becomes blocked and shuts down (Weinstein, et al., 2005). Ndh-2 is also found in a number of other bacteria such as *Staphylococcus aureus* and *Enterococcus faecalis* but is not expressed in humans (Melo, et al., 2004). Humans rely only on type I NADH dehydrogenase (ndh-1) and thus minimal toxicity in humans is predicted with ndh-2 inhibitors. The Mtb is an obligate aerobe that is capable of long-term persistence under conditions of low oxygen tension. Analysis of the Mtb genome predicts the existence of a branched aerobic respiratory chain terminating in a cytochrome *bds* system and a cytochrome *aa3* system. Both chains can be initiated with type II NADH: Menaquinone oxidoreductase. A biochemical characterization of the aerobic respiratory chains from Mtb and show that phenothiazine analogs specifically inhibit NADH: Menaquinone oxidoreductase activity. Type-II NADH-Menaquinone oxidoreductase (NDH-2) is an essential respiratory enzyme of the pathogenic bacterium Mtb that plays a vital role in its growth (Miesel, et al., 1998; Yano, et al., 2006; Melo, et al., 2004; Amaral, et al., 2007; Agarwal et al., 2013).

In the 1950s and 1960s psychiatrists noticed a more pronounced inhibition of Mtb occurring in TB-infected, schizophrenic patients taking higher doses of an antipsychotic drug, chlorpromazine, as opposed to patients who were taking lower doses of this drug (Kardos, et al., 1964). The N-(benzyl)-chlorpromazine inhibited Mtb in vitro at an even lower concentration than chlorpromazine itself. This was the first quaternized promazine derivative (QPD) discovered to be an antibacterial agent against Mtb. Chlorpromazine and its QPD were both found to selectively inhibit ndh-2; there was no inhibition of ndh-1 (Yano, et al., 2006). Other phenothiazines were also described to have anti-TB activity (Ratnakar, et al., 1995; Gadre, and Talwar. 1999).

**Biological activities of Phenothiazine derivatives:** Phenothiazine is also a bioactive heterocyclic compound of pharmaceutical importance and possesses different biological activities viz. antibacterial (Rawat and Srivastava

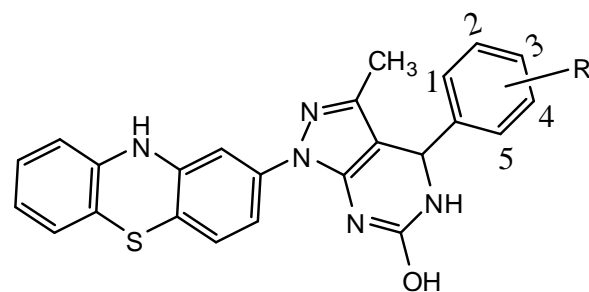
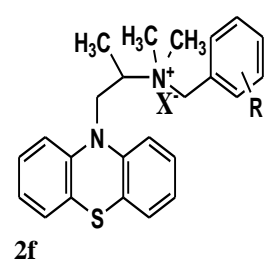
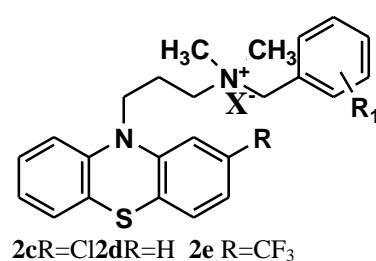
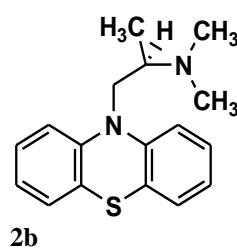
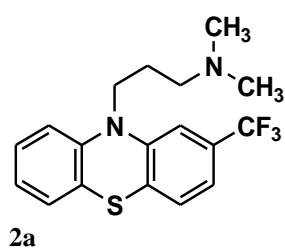
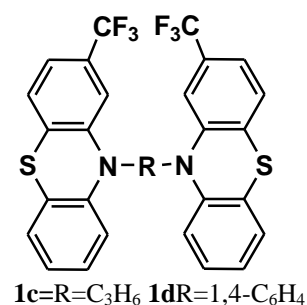
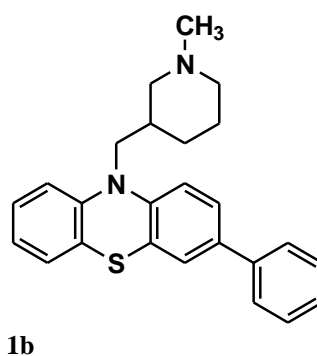
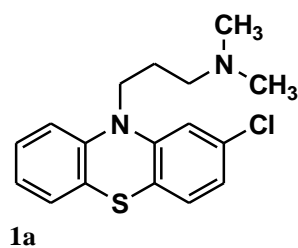
1998; Trivedi et al., 2008), antifungal (Weng and Tan. 2003), antitubercular (Rajasekaran and Tripathi. 2003), and anti-inflammatory (Kasmi-Mir, et al., 2006) etc.

**Antituber activities of Phenothiazine derivatives:** Phenothiazines have been reported for their antitubercular (anti-TB) activity for many years, and the phenothiazine drug chlorpromazine (CPZ) (1a) is reported to have been successfully used to treat a TB patient. In this concern, a series of psychotropic phenothiazines were tested as anti-TB agents against *M. tuberculosis* (Mtb) H37Rv. Among all, three compounds (1b-d) exhibited promising activity with a mean MIC of 2.13 µg/mL (Madrid et al., 2007). Whereas quaternized CPZ, triflupromazine (2a) and promethazine (2b) derivatives inhibited non-replicating Mtb at concentrations equal to or double their MICs against the actively growing strain. All the active compounds (2c-f) were non-toxic toward Vero cells (IC<sub>50</sub> > 128 µM). The benzyl or substituted benzyl groups, an electron withdrawing substituent on the phenothiazine ring improved the potency. The optimum anti-TB structures possessed N-(4- or 3-chlorobenzyl) substitution on triflupromazine (Bate et al., 2007).

Some 2-heterocycle-substituted phenothiazines having a pyrazolo[3,4-d]pyrimidines were tested for their anti-TB activity against Mtb H37 Rv (Trivedi et al., 2008). Several pyrimidine derivatives containing a phenothiazine ring, 3-methyl-1-(10H-phenothiazin-2-yl)-4-phenyl-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidines (3a-h) 3-Methyl-1-(10H-phenothiazin-2-yl)-4-phenyl-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d] pyrimidine (3a), 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(2-hydroxyphenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3b), 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(4-hydroxyphenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3c), 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(2-chlorophenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3d), 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(4-chlorophenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3e), 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(2-nitrophenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3f), 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(3-nitrophenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3g) and 3-Methyl-1-(10H-phenothiazin-2-yl)-4-(4-methoxyphenyl)-6-hydroxy-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (3h) were tested at > 6.25 µg/ml against Mtb H37Rv in BECTEC 12B medium. The anti-TB activities in Table 1.

The anti-TB activity, all the compounds showed mild to moderate activity. Compounds 3c, 3d and 3e were found to be predominantly active against Mtb H37Rv strain (Trivedi et al., 2008).

Several phenothiazine analogs inhibited non-replicating Mtb at concentrations equal to or double their MICs against the actively growing strain. All active compounds were non-toxic toward Vero cells (IC<sub>50</sub> > 128 IM).



### Compounds **3a-h**

SNo.	R	1	2	3	4	5
3a	H	H	H	H	H	H
3b	2-OH	OH	H	H	H	H
3c	4-OH	H	H	OH	H	H
3d	2-Cl	Cl	H	H	H	H
3e	4-Cl	H	H	Cl	H	H
3f	2-NO <sub>2</sub>	NO <sub>2</sub>	H	H	H	H
3g	3-NO <sub>2</sub>	H	NO <sub>2</sub>	H	H	H
3h	4-OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	H

**Table 1.**Antitubercular activity of **3a-h**

SNo.	R	MIC	% Inh	Activity	SNo.	R	MIC	% Inh	Activity
<b>3a</b>	H	>6.25	79	-	<b>3e</b>	4-Cl	<6.25	94	+
<b>3b</b>	2-OH	>6.25	75	-	<b>3f</b>	2-NO <sub>2</sub>	>6.25	74	-
<b>3c</b>	4-OH	<6.25	94	+	<b>3g</b>	3-NO <sub>2</sub>	>6.25	77	-
<b>3d</b>	2-Cl	<6.25	92	+	<b>3h</b>	4-OCH <sub>3</sub>	>6.25	63	-

N-Allylchlorpromazinium bromide was only weakly anti-TB, but replacing allyl with benzyl or substituted benzyl improved potency. An electron-withdrawing substituent on the phenothiazine ring was also essential. Branching at the carbon chain decreased anti-TB activity. The optimum anti-TB structures possessed N-(4- or 3-chlorobenzyl) substitution on triflupromazine (Bate et al., 2007).

The quaternized derivatives of promazine, chlorpromazine, and triflupromazine, and to measure their MICs against both actively growing and non-replicating Mtb.

The minimum inhibitory concentration (MIC) of QPDs against actively growing Mtb H37Rv was determined using the microplate alamar blue assay (MABA) (Collins and Franzblau, 1997; Falzari, et al., 2005). The activities of three compounds (4c, 6c, and 7c) were confirmed for both MABA and LORA using a colony-forming unit determination by subculturing from the microplate onto drug-free 7H11 agar. MICs for actively growing Mtb were 1.9-, 2.1-, and 2.9-fold higher than the MABA MICs, and 1.7-, 1.9-, and 2.1-fold higher than the corresponding LORA MICs. The in vitro cytotoxicity for VERO cells was determined for all compounds with a MABA MIC of less than 10  $\mu$ M using a dye reduction assay following 3 days exposure to test compounds as previously described. The IC<sub>50</sub> of all compounds was >128  $\mu$ M (except for 3b which was >64  $\mu$ M, the highest concentration tested).

From the MICs in Table 2, N-benzyl substitution in QPDs is a requirement for significant anti-TB activity (1a vs. 2). Alkyl chain branching (8a, 8f-h) decreases potency, three of the QPDs having MICs both <4  $\mu$ M against actively growing Mtb and <8  $\mu$ M against non-replicating Mtb possess N-(4- or 3-chlorobenzyl) groups and electron-withdrawing substituents on the phenothiazine ring (4c, 7b-c). Based on this MIC data and the lack of in vitro mammalian cell toxicity, we will attempt to improve these leads by studying the anti-TB potency of other electron-withdrawing substituents on the phenothiazine ring and various halogen

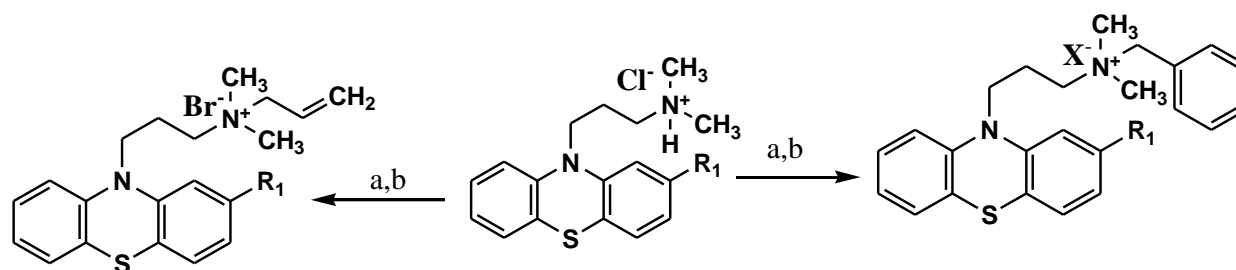
substitutions on the benzyl group. If these improved leads also lack mammalian cell toxicity, animal studies will be warranted (Bate et al., 2007).

A series of 10-(3-chloropropyl)-10H-phenothiazine 9, N-[3-(10H-phenothiazin-10-yl)propyl]urea 10, N-[3-(10H-phenothiazin-10-yl)propyl]-N'-[(substituted phenyl)methylidene]urea, 11a-s, N-[3-(10H-phenothiazin-10-yl)propyl]-2-(substituted phenyl)-4-oxo-3-thiazolidinecarboxamide 13a-s and N-[3-(10H-phenothiazin-10-yl)propyl]-2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)-3-thiazolidinecarboxamide, 13a-s were tested for their anti-TB activity against the Mtb (Sharma et al., 2012). All the compounds were exhibited anti-TB activity against Mtb.

The anti-TB activities of compounds 9, 10, 11a-s, 12a-s and 13a-s were assayed in vitro against Mtb H37Rv strain (Sharma, et al., 2011) at 25 and 50  $\mu$ g mL<sup>-1</sup> and lower concentrations. For the anti-TB activity, isoniazid and rifampicin were taken as standards. The compounds 13c, 13d, 13e, 13f, 13h, 13i and 13j displayed high activity, compounds 12h, 12j, 13b, 13g and 13q showed moderate activity and the other compounds showed less activity against all the strains compared with standard drugs. The activity of compounds varies with substitution. The nitro group-containing compounds 13h, 13i and 13j showed higher activity than the chloro group- (5c and 13d) or the bromo group-containing compounds (13e and 13f). The chloro- and bromo-derivatives also had a higher activity than the other tested compounds.

It could be concluded that the activity of compounds depended on the electron withdrawing nature of the substituent groups (Sharma et al., 2012). The sequence of the activity is following: NO<sub>2</sub> > Cl > Br > OCH<sub>3</sub> < OH > CH<sub>3</sub>. Standards drugs, isoniazid and rifampicin, showed 100 % activity at both tested concentrations.

The compounds 9, 10, 11a-s, 12a-s and 13a-s some compounds displayed good biological activities while the others showed lower anti-TB activities.



**5** Chlorpromazine.HCl R<sub>1</sub>=Cl  
Promazine.HCl R<sub>1</sub>=H  
Triflupromazine.HCl R<sub>1</sub>=CF<sub>3</sub>  
(a) potassium carbonate, water, ethyl acetate;  
(b) benzyl or allyl halide, acetone.

**4:** R<sub>1</sub>=Cl; **6:** R<sub>1</sub>=H; **7:** R<sub>1</sub>=CF<sub>3</sub>  
**a**=R<sub>2</sub>=H X=Br; **b**=R<sub>2</sub>=4-Cl X=Cl  
**c**=R<sub>2</sub>=3-Cl X=Cl; **d**=R<sub>2</sub>=2-Cl X=Cl  
**e**=R<sub>2</sub>=4-F X=Cl; **f**=R<sub>2</sub>=4-CH<sub>3</sub> X=Cl  
**g**=R<sub>2</sub>=4-OCH<sub>3</sub> X=Cl; **h**=R<sub>2</sub>=4-NO<sub>2</sub> X=Cl

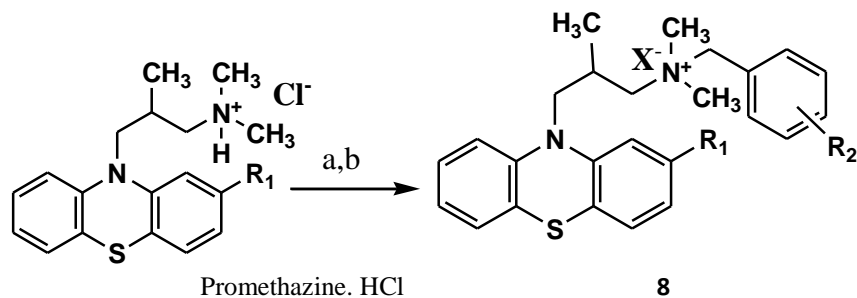
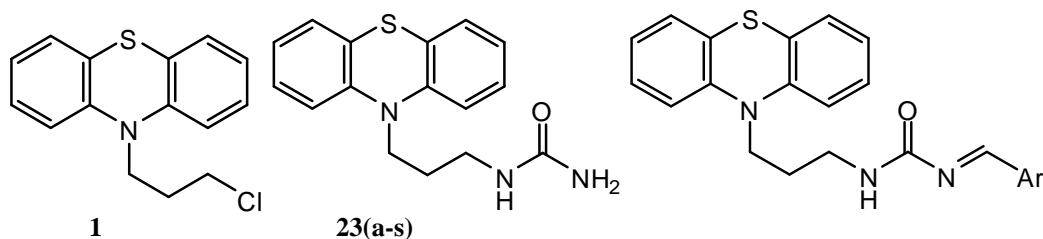
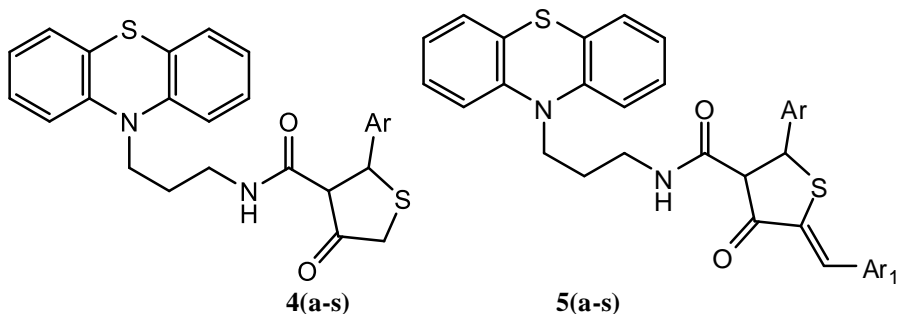


Table 2. QPD antitubercular activity

Compound (R <sub>2</sub> )	MIC (SD) in IM versus <i>M. tuberculosis</i> that is		Compound (R <sub>2</sub> )	MIC (SD) in IM versus <i>M. tuberculosis</i> that is	
	Actively growing	Non-replicating		Actively growing	Non-replicating
<b>4a</b> (H)	7.33(0.4)	11.1(2.4)	<b>6e</b> (4-F)	14.6	32.9
<b>4b</b> (4-Cl)	6.06(1.9)	6.7(0.9)	<b>6f</b> (4-CH <sub>3</sub> )	9.9(2.0)	15.0(0.2)
<b>4c</b> (3-Cl)	4.5(1.3)	6.7(0.4)	<b>7b</b> (4-Cl)	3.81(0.1)	6.1(0.4)
<b>4d</b> (2-Cl)	5.6(1.8)	7.6(0.3)	<b>7c</b> (3-Cl)	3.8(0.1)	5.8(0.9)
<b>4e</b> (4-F)	7.6(0.2)	13.7(0.9)	<b>7d</b> (2-Cl)	7.3(0.3)	7.5(0.2)
<b>4f</b> (4-CH <sub>3</sub> )	4.7(1.0)	7.5(0.3)	<b>7e</b> (4-F)	6.4(2.2)	10.0(1.5)
<b>4g</b> (4-OCH <sub>3</sub> )	8.5(1.3)	11.9(1.2)	<b>7f</b> (4-CH <sub>3</sub> )	6.8(0.2)	6.9(0.6)
<b>4h</b> (4-NO <sub>2</sub> )	12.3(4.0)	27.5(1.6)	<b>8a</b> (H)	31.6	99.7
<b>5</b>	30.6	105.9	<b>8f</b> (4-CH <sub>3</sub> )	12.1	34.7
<b>6b</b> (4-Cl)	9.31(2.2)	15.4(3.2)	<b>8g</b> (4-OCH <sub>3</sub> )	14.4	105.2
<b>6c</b> (3-Cl)	7.5(0.3)	13.0(0.6)	<b>8h</b> (4-NO <sub>2</sub> )	20.7	>128.0
<b>6d</b> (2-Cl)	14.3	24.6			



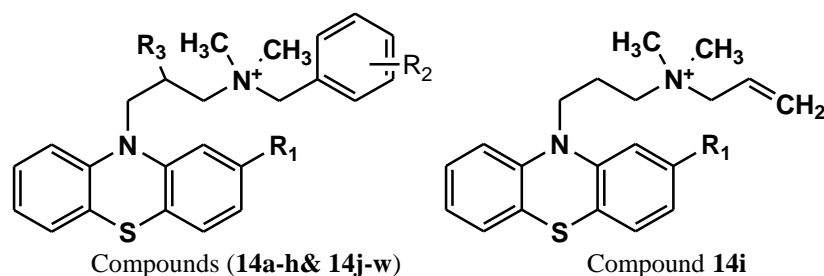


Compound	Ar = Ar <sub>1</sub>	Compound	Ar = Ar <sub>1</sub>	Compound	Ar = Ar <sub>1</sub>
11a, 12a, 13a	C <sub>6</sub> H <sub>5</sub>	11h, 12h, 13h	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	11o, 12o, 13o	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
11b, 12b, 13b	4-ClC <sub>6</sub> H <sub>4</sub>	11i, 12i, 13i	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	11p, 12p, 13p	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
11c, 12c, 13c	3-ClC <sub>6</sub> H <sub>4</sub>	11j, 12j, 13j	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	11q, 12q, 13q	4-HOC <sub>6</sub> H <sub>4</sub>
11d, 12d, 13d	2-ClC <sub>6</sub> H <sub>4</sub>	11k, 12k, 13k	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	11r, 12r, 13r	3-HOC <sub>6</sub> H <sub>4</sub>
11e, 12e, 13e	4-BrC <sub>6</sub> H <sub>4</sub>	11l, 12l, 13l	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	11s, 12s, 13s	2-HOC <sub>6</sub> H <sub>4</sub>
11f, 12f, 13f	3-BrC <sub>6</sub> H <sub>4</sub>	11m, 12m, 13m	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>		
11g, 12g, 13g	2-BrC <sub>6</sub> H <sub>4</sub>	11n, 12n, 13n	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>		

**Table3.** Antitubercular activity of compounds **1**, **2**, **3a-s**, **4a-s** and **5a-s**

Compd	Anti-TB activity, %		Compd	Anti-TB activity, %		Compd	Anti-TB activity, %	
	<i>Mtb</i> H37Rv strain			<i>Mtb</i> H37Rv strain			<i>Mtb</i> H37Rv strain	
	<i>c</i> /μg mL-1			<i>c</i> /μg mL-1			<i>c</i> /μg mL-1	
<b>9</b>	13	20	<b>10</b>	10	18	<b>13a</b>	22	45
<b>11a</b>	18	22	<b>12a</b>	20	35	<b>13b</b>	32	74
<b>11b</b>	25	32	<b>12b</b>	25	55	<b>13c</b>	36	80
<b>11c</b>	27	34	<b>12c</b>	30	60	<b>13d</b>	32	80
<b>11d</b>	30	35	<b>12d</b>	30	60	<b>13e</b>	30	78
<b>11e</b>	28	40	<b>12e</b>	30	68	<b>13f</b>	30	79
<b>11f</b>	27	50	<b>12f</b>	32	70	<b>13g</b>	29	76
<b>11g</b>	25	52	<b>12g</b>	30	75	<b>13h</b>	32	82
<b>11h</b>	32	65	<b>12h</b>	30	70	<b>13i</b>	27	83
<b>11i</b>	35	68	<b>12i</b>	32	68	<b>13j</b>	28	81
<b>11j</b>	38	66	<b>12j</b>	35	70	<b>13k</b>	28	60
<b>11k</b>	25	40	<b>12k</b>	30	50	<b>13l</b>	30	63
<b>11l</b>	28	42	<b>12l</b>	32	53	<b>13m</b>	31	65
<b>11m</b>	23	43	<b>12m</b>	30	50	<b>13n</b>	22	45
<b>11n</b>	20	38	<b>12n</b>	29	41	<b>13o</b>	18	49
<b>11o</b>	24	35	<b>12o</b>	28	42	<b>13p</b>	20	47
<b>11p</b>	25	38	<b>12p</b>	30	45	<b>13q</b>	24	76
<b>11q</b>	28	50	<b>12q</b>	33	70	<b>13r</b>	27	70
<b>11r</b>	30	52	<b>12r</b>	34	70	13s	25	65
<b>11s</b>	32	55	<b>12s</b>	33	65			



**Table 4.** Structure and Antitubercular activity data of compounds (Agarwal et al., 2013).

S No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	MIC	S No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	MIC
14a	Cl	H	H	7.33	14m	H	p-F	H	14.6
14b	Cl	p-Cl	H	6.06	14n	H	p-CH <sub>3</sub>	H	9.9
14c	Cl	m-Cl	H	4.5	14o	CF <sub>3</sub>	p-Cl	H	3.81
14d	Cl	o-Cl	H	5.6	14p	CF <sub>3</sub>	m-Cl	H	3.8
14e	Cl	p-F	H	7.6	14q	H	p-Cl	H	7.3
14f	Cl	p-CH <sub>3</sub>	H	4.7	14r	CF <sub>3</sub>	p-F	H	6.4
14g	Cl	p-OCH <sub>3</sub>	H	8.5	14s	CF <sub>3</sub>	p-CH <sub>3</sub>	H	6.8
14h	Cl	p-NO <sub>2</sub>	H	12.3	14t	H	H	CH <sub>3</sub>	31.6
14i				30.6	14u	H	p-CH <sub>3</sub>	CH <sub>3</sub>	12.1
14j	H	p-Cl	H	9.3	14v	H	p-OCH <sub>3</sub>	CH <sub>3</sub>	14.4
14k	H	m-Cl	H	7.5	14w	H	p-NO <sub>2</sub>	CH <sub>3</sub>	20.7
14l	H	o-Cl	H	14.3					

## 4 Conclusions

This study may prove to be helpful in development and optimization of existing anti-TB activity of phenothiazine compounds. Development of new chemotherapeutic drugs is the need of the hour to improve TB control. In the last forty years no new compound has been brought to the market for the treatment of TB. However, in recent years there is an enhanced activity in the research and development of new drugs for TB. Some compounds are presently in clinical development, while others are being investigated pre-clinically in an attempt to explore new molecules for the target based treatment of TB. Simultaneously some new targets are being identified and validated for their practical usefulness. The review provides an overview of the drugs that are being used and the compounds that are in clinical or preclinical studies and also attempted to highlight the efforts that are being made in the development of new molecules. Various phenothiazine analogs were developed. Other compounds of this group are presently under investigation. The phenothiazines nucleus, which has a useful structure for further molecular exploration for the development of new derivatives with different biological activities, has received much attention in recent years.

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