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Synthesis and biological evaluation of some new 3,4-dihydropyrimidin-4-ones

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Abstract

Condensation of 5-cyano-2-hydrazino-3-*N*-methyl-6-phenyl/*p*-chlorophenyl-3,4-dihydropyrimidin-4-one (**3a** and **3b**) with 2,4-bisalkyl/arylamino-6-chloro-*s*-triazine (**4**) gave the corresponding 2,4-bisalkyl/arylamino-6-[5′-cyano-3′-*N*-methyl]-6′-phenyl/*p*-chlorophenyl-3′,4′-dihydropyrimidin-4′-one-2′-yl-hydrazino-*s*-triazines (**5a**–**n** and **6a**–**n**). The compounds **4** have been prepared by the condensation of cyanuric chloride and different alkyl/aryl amines. The reaction between 5-cyano-3-*N*-methyl-2-methylthio-6-phenyl/*p*-chlorophenyl-3,4-dihydropyrimidin-4-one (**2a** and **2b**) with hydrazine hydrate furnished **3a** and **3b**, respectively. The condensation of 6-phenyl/*p*-chlorophenyl/5-cyano-2-mercapto-3,4-dihydropyrimidin-4-one (**1a** and **1b**) with methyl iodide yielded **2a** and **2b**, respectively. All the products have been evaluated in vitro for their antimicrobial activity against several microbes and antitubercular activity against *Mycobacterium tuberculosis H37 Rv*.

Keywords: Dihydropyrimidine; *s*-Triazine; Antitubercular activity; Antimicrobial activity

1. Introduction

The 3,4 dihydropyrimidine derivatives have been investigated for their medicinal interest related to the traditional antithyroid activity of the 5-fluoro-2-thiouracil [1]. The 3,4-dihydropyrimidine derivatives ethirimol and methirimol were some of the earliest fungicides. Furthermore dihydropyrimidine derivatives also show the different pharmacological activities like antitumor [2], analgesic [3], antineoplastic [4], cardiovascular [5], antiallergic [6], etc. Substituted *s*-triazines have become attractive targets in organic synthesis because of their reactivity and significance in biological activities such as antitumor [7], antiviral [8], fungicidal [9], antimalarial [10], CNS depressant [11], herbicidal [12], etc.

Although several potent antibiotics usable in the therapy are available, research on new substances possessing an antimicrobial activity is still of considerable interest owing to the continuous increase in bacterial resistance. On the basis of the above considerations and in order to contribute to the definition of antimicrobial properties of compounds and structurally related analogs, some new 3,4-dihydro pyrimidine derivatives have been investigated.

The target compounds **5a**–**n** and **6a**–**n** have been synthesized by the condensation of 5-cyano-2-hydrazino-3-*N*-methyl-6-phenyl/*p*-chlorophenyl-3,4-dihydropyrimidin-4-one (**3**) and 2,4-bisalkyl/arylamino-6-chloro-*s*-triazine (**4**) (Scheme 1). The condensation of cyanuric chloride and different alkyl/arylamines gave **4**. The reaction between **2** and hydrazine hydrate furnished **3**.

The constitution of these products have been supported by elemental analyses, IR, ^{1}H NMR and mass spectral studies. All the products have been screened for their in vitro antimicrobial activity against different strain of bacteria and fungi, and antitubercular activity against *Mycobacterium tuberculosis H37 Rv*. The compounds demonstrating at least $>90\%$ inhibition in the primary screen have been retested at lower concentration to determine the actual minimum inhibition concentration (MIC) in the BACTEC 460.

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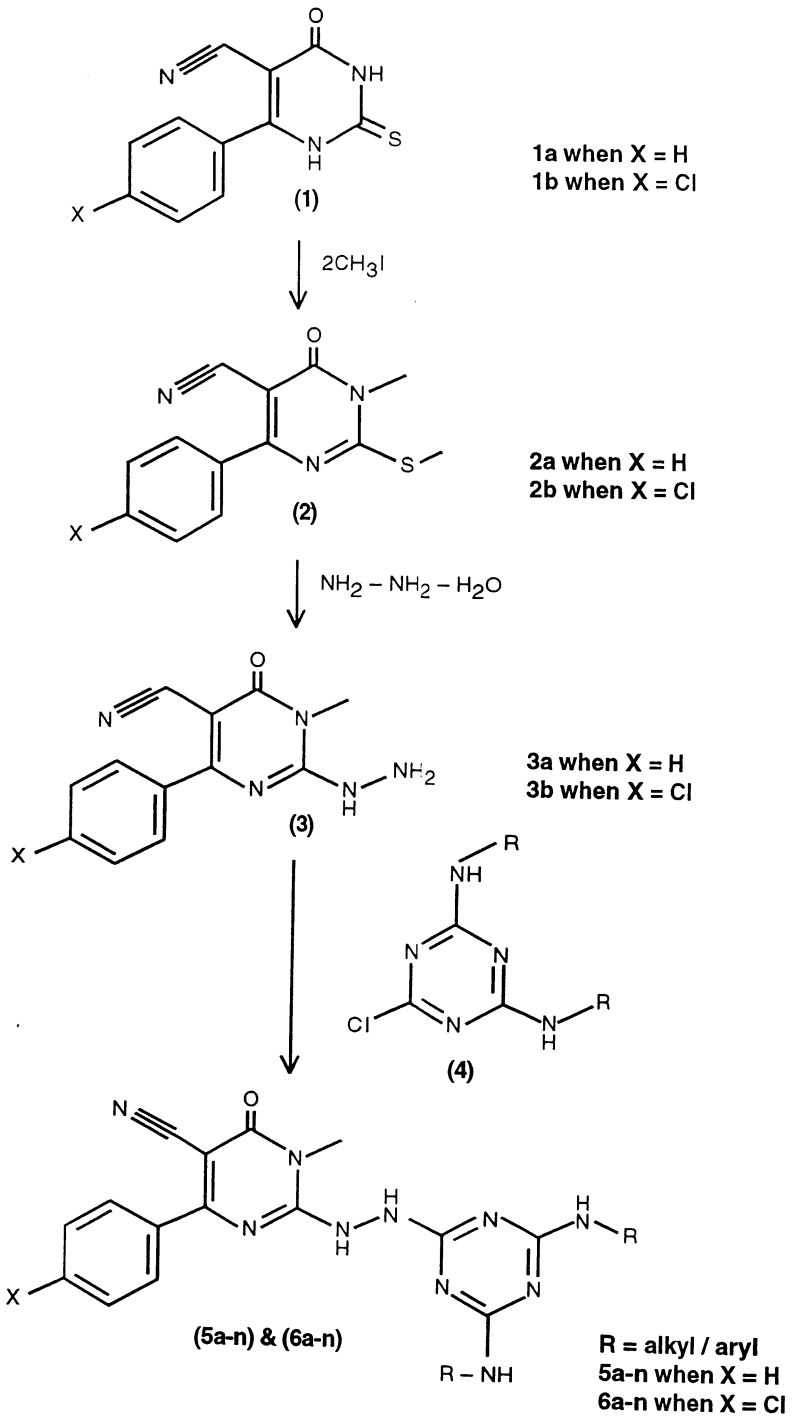
2. Results and discussion

Tables 2 and 3, respectively, describe the in vitro antimicrobial activity against strains of *S. albus*, *B. mega*, *S. typhosa*, *E. coli*, *A. niger* and antitubercular activity against *Mycobacterium tuberculosis H37 Rv* with MIC data of the synthesized compounds **5a**–**n** and **6a**–**n**.

Looking at the structure–activity relationship, it can be concluded that the presence of halogen at 3 and/or 4 position, i.e. **5f**–**5h**, **6d**–**6g** in 1H aryl ring of the arylamino substituted *s*-triazinyl group showed maximum activity towards *B. megaterium* and *S. typhosa*. Presence of halogen (Cl) at 3, 4 or 5 position in the aryl ring, i.e. **5f**–**5h**, **6f** and also methoxy at 4 position in **5l**, **6l** has been found to enhance the antibacterial activity



Scheme 1.

towards *E. coli*. The diethyl chain in the triazinyl nucleus **5a** showed the highest activity towards *B. megaterium* and *S. typhosa* but diminished in the presence of chlorine when present with the pyrimidine structure **6a**.

A perusal of the data in Table 2 indicates that compounds having halogen at 3 and/or 4 position (**5d**, **5f**, **6e**, **6f**) showed maximum antitubercular activity up to 92% inhibition. MIC data of these compounds showed **5i** to be highly potent with a MIC value of 6.25 μg. The rest of the compounds displayed their activity in the range of 12.5 μg. However, none of the compounds could match the activity of the rifampicin.

3. Chemical experimental section

Melting points were determined in open capillaries and are uncorrected, purity of the compounds was checked by TLC. IR (KBr) spectra were recorded on a Nicolet-Magna-IR 550 Series-II spectrophotometer and ^{1}H-NMR spectra were recorded on a BRUKER spectrometer 300 MHz using TMS as an internal standard.

3.1. Synthesis of 5-cyano-3-N-methyl-2-methylthio-6-phenyl-3,4-dihydropyrimidin-4-one: ***2a*** *and* ***2b***

To a solution of 5-cyano-2-mercapto-6-phenyl-3,4-dihydropyrimidin-4-one (2.63 g, 0.01 mol) in DMF (20 ml), potassium carbonate (2.76 g, 0.02 mol) and methyl iodide (2.84 g, 0.02 mol) were added and the mixture was stirred for 3 h. The contents were poured into water and crystallized from DMF. Yield 60%, m.p. 174 °C.

6-*p*-Chlorophenyl-5-cyano-3-*N*-methyl-2-methylthio-3,4-dihydropyrimidin-4-one (**2b**) was prepared similarly. Yield 73%, m.p. 211 °C.

3.2. Synthesis of 5-cyano-2-hydrazino-3-N-methyl-6-phenyl-3,4-dihydropyrimidin-4-one: ***3a*** *and* ***3b***

A mixture of 5-cyano-3-*N*-methyl-2-methylthio-6-phenyl-3,4-dihydropyrimidin-4-one (2.57 g, 0.01 mol) and hydrazine hydrate (2.5 g, 0.05 mol) in absolute alcohol was refluxed for 12 h in an oil bath and poured onto crushed ice, filtered and crystallized from absolute alcohol. Yield 65%, m.p. 275 °C.

6-*p*-Chlorophenyl-5-cyano-2-hydrazino-3-*N*-methyl-3,4-dihydropyrimidin-4-one (**3b**) was prepared similarly. Yield 55%, m.p. 230 °C.

3.3. Synthesis of 2,4-bisethylamino-6-chloro-s-triazine ***(4)***

To a solution of cyanuric chloride (3.65 g, 0.02 mol) in acetone (20 ml), ethylamine (2.56 ml, 0.04 mol) was added dropwise at 0 °C and followed by increasing temperature but keeping the pH of the solution just about 7 by occasional addition of saturated solution of sodium bicarbonate. After completion of the addition, the reaction mixture was stirred at room temperature (r.t.) for 4 h maintaining the pH at 7. The content was then poured onto ice, filtered and crystallized from ethanol. Yield 70%.

Other 2,4-bisalkyl/arylamino-6-chloro-*s*-triazines were prepared similarly.

3.4. Synthesis of 2,4-bisethylamino-6-(5′-cyano-3′-N-methyl-6′-phenyl-3′,4′-dihydropyrimidin-4′-one-2′-yl-hydrazino)-s-triazine: ***(5a–n)***

A mixture of 5-cyano-2-hydrazino-3-*N*-methyl-6-phenyl-3,4-dihydropyrimidin-4-one (2.41 g, 0.01 mol) and 2,4-bisethylamino-6-chloro-*s*-triazine (2.01 g, 0.01 mol) in dioxane (25 ml) was refluxed for 3 h during which solution of sodium bicarbonate (0.84 g, 0.01 mol) was added in fractions. The content was then poured onto crushed ice, product isolated was crystallized from absolute alcohol. Yield 63%, m.p. 225 °C.

Anal. Calc. for $C_{19}H_{22}N_{10}O$: C, 56.15; H, 5.41; N, 34.48. Found: C, 56.11; H, 5.38; N, 34.32%. IR (cm^{-1}, KBr): ν_{max}(N–H str.) 3262, ν_{max}(C–H str.) 2975, 2930, ν_{max}(C≡N str.) 2191, ν_{max}(C=O str.) 1635, ν_{max}(C=N + C=C str.) 1564, ν_{max}(N–C str.) 1111. ^{1}H NMR (TFA, δ ppm): 1.17 (t, 6H, 2 × CH_2–CH_3), 3.16 (q, 4H, 2 × CH_2–CH_3), 3.37 (s, 3H, N–CH_3), 7.42–7.46 (m, 3H, Ar-H), 7.85–7.87 (d, 2H, Ar-H).

Other *s*-triazine derivatives have been prepared similarly. The physical constants are recorded in Table 1.

3.5. Synthesis of 2,4-bis (4″-chlorophenylamino)-6-(6′-p-chlorophenyl-5′-cyano-3′-N-methyl-3′,4′-dihydropyrimidin-4′-one-2′-yl-hydrazino)-s-triazine: ***(6a–n)***

A mixture of 5-cyano-2-hydrazino-3-*N*-methyl-6-*p*-chlorophenyl-3,4-dihydropyrimidin-4-one (2.41 g, 0.01 mol) and 2,4-bischlorophenylamino-6-chloro-*s*-triazine (2.66 g, 0.01 mol) in dioxane (25 ml) was refluxed for 3 h during which solution of sodium bicarbonate (0.84 g, 0.01 mol) was added in fractions. The content was then poured onto crushed ice, product isolated was crystallized from absolute alcohol. Yield 42%, m.p. 260 °C.

Anal. Calc. for $C_{27}H_{19}N_{10}OCl_3$: C, 53.50; H, 3.13; N, 23.12. Found: C, 53.44; H, 3.09; N, 22.92%. IR (cm^{-1}, KBr): ν_{max}(N–H str.) 3391, ν_{max}(C–H str.) 2950, ν_{max}(C≡N str.) 2222, ν_{max}(C=O str.) 1664, ν_{max}(C=N + C=C str.) 1544, ν_{max}(N–C str.) 1101, ν_{max}(C–Cl str.) 764. ^{1}H NMR (TFA, δ ppm): 3.88 (s, 3H, N–CH_3), 6.89–7.36 (m, 12H, Ar-H), 8.30 (s, 2H, 2 × N–H), 9.37 (s, 1H, N–H), 9.83 (s, 1H, N–H).

Other *s*-triazine derivatives have been prepared similarly. The physical constants are recorded in Table 1.

Table 1
Physical constants of the compounds **5a–n** and **6a–n**

Comp.	R	Yield (%)	Melting point (°C)	Molecular formula	Analysis					
					N (%)		C (%)		H (%)	
					Calc.	Found	Calc.	Found	Calc.	Found
5a	C_2H_5–	63	225	$C_{19}H_{22}N_{10}O$	34.48	34.32	56.15	56.11	5.41	5.38
5b	C_6H_5–CH_2–	51	277	$C_{29}H_{26}N_{10}O$	26.41	26.33	65.66	65.62	4.90	4.87
5c	C_4H_3O–CH_2–	47	170	$C_{25}H_{22}N_{10}O_3$	27.45	27.33	58.82	58.78	4.31	4.26
5d	3-Cl–C_6H_4–	63	>300	$C_{27}H_{20}N_{10}OCl_2$	24.51	24.40	56.74	56.79	3.50	3.44
5e	4-Cl–C_6H_4–	59	290	$C_{27}H_{20}N_{10}OCl_2$	24.51	24.38	56.74	56.69	3.50	3.45
5f	3-Cl-4-F–C_6H_3–	48	80	$C_{27}H_{18}N_{10}OCl_2F_2$	23.06	22.92	53.37	53.32	2.96	2.92
5g	2,4-Cl_2–C_6H_4–	46	125	$C_{27}H_{18}N_{10}OCl_4$	21.87	21.69	50.62	50.57	2.81	2.76
5h	3,5-Cl_2–C_6H_3–	47	160	$C_{27}H_{18}N_{10}OCl_4$	21.87	21.69	50.62	50.57	2.81	2.75
5i	2,4-$(CH_3)_2$–C_6H_3–	42	130	$C_{31}H_{30}N_{10}O$	25.08	24.91	66.66	66.62	5.37	5.32
5j	2-OCH_3–C_6H_4–	51	240	$C_{29}H_{26}N_{10}O_3$	24.91	24.82	61.92	61.87	4.62	4.57
5k	3-OCH_3–C_6H_4–	48	85	$C_{29}H_{26}N_{10}O_3$	24.91	24.82	61.92	61.86	4.62	4.56
5l	4-OCH_3–C_6H_4–	54	180	$C_{29}H_{26}N_{10}O_3$	24.91	24.82	61.92	61.88	4.62	4.58
5m	3-NO_2–C_6H_4–	50	80	$C_{27}H_{20}N_{12}O_5$	28.37	28.30	54.72	54.67	3.37	3.32
5n	2-C_5H_4N–	48	>300	$C_{28}H_{18}N_{14}O$	38.73	38.61	48.72	48.66	2.58	2.51
6a	C_2H_5–	65	207	$C_{19}H_{21}N_{10}OCl$	31.78	31.66	51.75	51.70	4.76	4.71
6b	C_6H_5–CH_2–	48	192	$C_{29}H_{25}N_{10}OCl$	24.80	24.67	61.64	61.58	4.42	4.37
6c	C_4H_3O–CH_2–	49	160	$C_{25}H_{21}N_{10}O_3Cl$	25.71	25.60	55.09	55.04	3.85	3.80
6d	3-Cl–C_6H_4–	48	280	$C_{27}H_{19}N_{10}OCl_3$	23.12	22.92	53.50	53.44	3.13	3.09
6e	4-Cl–C_6H_4–	42	260	$C_{27}H_{19}N_{10}OCl_3$	23.12	22.98	53.50	53.46	3.13	3.08
6f	3-Cl-4-F–C_6H_3–	49	227	$C_{27}H_{17}N_{10}OCl_3F_2$	21.82	21.72	50.50	50.45	2.65	2.60
6g	2,4-Cl_2–C_6H_4	51	164	$C_{27}H_{17}N_{10}OCl_5$	20.75	20.64	48.03	48.00	2.52	2.46
6h	3,5-Cl_2–C_6H_3–	53	126	$C_{27}H_{17}N_{10}OCl_5$	20.75	20.67	48.03	47.98	2.52	2.47
6i	2,4-$(CH_3)_2$–C_6H_3–	47	160	$C_{31}H_{29}N_{10}OCl$	23.62	23.55	62.78	62.73	4.89	4.83
6j	2-OCH_3–C_6H_4–	53	135	$C_{29}H_{23}N_{10}O_3Cl$	23.47	23.33	58.53	58.48	3.86	3.82
6k	3-OCH_3–C_6H_4–	41	185	$C_{29}H_{23}N_{10}O_3Cl$	23.47	23.42	58.53	58.49	3.86	3.81
6l	4-OCH_3–C_6H_4–	45	>300	$C_{29}H_{23}N_{10}O_3Cl$	23.47	23.38	58.53	58.47	3.86	3.80
6m	3-NO_2–C_6H_4–	52	120	$C_{27}H_{19}N_{12}O_5Cl$	26.81	26.67	51.71	51.66	3.03	3.00
6n	2-C_5H_4N–	50	270	$C_{23}H_{17}N_{14}OCl$	36.29	36.21	51.06	51.01	3.14	3.09

4. Biological experimental section

4.1. Antimicrobial activity

Antimicrobial activity experiments were carried out by the cup–plate method [13] towards different strains of bacteria and fungi which are described below.

4.1.1. Antibacterial activity

The purified products were screened for their antibacterial activity towards strains of *S. albus*, *B. megaterium*, *S. typhosa* and *E. coli*. The nutrient agar broth was prepared by the usual method. Fifteen milliliters of N-agar were spread in a Petri dish (13 cm in diameter) and allowed to set for 30 min. About 5 ml of N-agar was inoculated aseptically in a test-tube with 0.2 ml of 24 h old bacterial subculture at 40–50 °C, mixed well by gentle shaking and spread over the previously settled layer of N-agar in the Petri dish. The cups (8 mm in diameter) were formed with the help of borer and filled with 0.05 ml (40 μg) solution of sample in DMF. Along with the test solutions in each Petri dish one cup was filled with solvent which acts as the control. The plates were incubated at 37 °C for 24 h and the resultant zones of inhibition of bacterial growth were measured in mm and are recorded in Table 2.

4.1.2. Antifungal activity

A. niger was employed for testing antifungal activity using the cup–plate method. The culture was maintained on Sabouraud's agar slants. Fifteen milliliters of sterilized Sabouraud's agar medium was spread in a Petri dish (13 cm in diameter) and allowed to set for 30 min. Five milliliters of sterilized Sabouraud's agar medium was inoculated with 72 h old 0.2 ml suspension of fungal spores in a test-tube and spread over the previously settled layer of Sabouraud's agar medium in the Petri dish. The cups (8 mm in diameter) were punched in the Petri dish and filled with 0.05 ml (40 μg) of a solution of the sample in DMF. The plates were incubated at 30 °C for 48 h. After the completion of the incubation period, the zones of inhibition of growth in millimeter were measured. Along with the test solutions in each Petri dish one cup was filled up with solvent, which acts as the control. The zones of inhibition are recorded in Table 2.

Table 2
Biological activities of the compounds **5a–n** and **6a–n**

Comp.	R	Antimicrobial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	Antitubercular activity (% of inhibition)
		S. albus	*B. mega*	*S. typhosa*	*E. coli*	*A. niger*	*Mycobacterium tuberculosis H37 Rv*
5a	C_2H_5–	11	20	18	11	20	46
5b	C_6H_5–CH_2–	11	14	12	20	17	82
5c	C_4H_3O–CH_2–	12	14	15	12	08	47
5d	3-Cl–C_6H_4–	10	12	16	12	25	92
5e	4-Cl–C_6H_4–	14	14	14	18	10	
5f	4-Cl-4-F–C_6H_3–	13	17	14	20	10	98
5g	2,4-$(Cl)_2$–C_6H_3–	12	17	15	18	18	14
5h	3,5-$(Cl)_2$–C_6H_3–	12	19	15	18	14	98
5i	2,4-$(CH_3)_2$–C_6H_3–	11	12	13	14	14	95
5j	2-OCH_3–C_6H_4–	12	11	12	16	20	63
5k	3-OCH_3–C_6H_4–	11	12	11	12	27	92
5l	4-OCH_3–C_6H_4–	11	12	12	20	20	71
5m	3-NO_2–C_6H_4–	10	11	13	15	20	58
5n	2-C_5H_4N–	12	13	14	12	20	
6a	C_2H_5–	14	14	12	14	20	69
6b	C_6H_5–CH_2–	13	10	10	14	10	84
6c	C_4H_3O–CH_2–	11	10	11	13	13	17
6d	3-Cl–C_6H_4–	12	15	11	15	22	
6e	4-Cl–C_6H_4–	13	15	13	17	10	94
6f	3-Cl-4-F–C_6H_3–	14	18	14	18	13	98
6g	2,4-Cl_2–C_6H_3–	10	18	11	15	21	
6h	3,5-Cl_2–C_6H_3–	11	10	15	14	25	66
6i	2,4-$(CH_3)_2$–C_6H_3–	17	11	15	17	22	56
6j	2-OCH_3–C_6H_4–	12	12	11	14	13	12
6k	3-OCH_3–C_6H_4–	12	12	12	14	10	21
6l	4-OCH_3–C_6H_4–	10	11	10	18	09	52
6m	3-NO_2–C_6H_4–	10	12		18	15	98
6n	2-C_5H_4N–	12	12		11		
	Benzylpenicillin	23	17				
	Chloramphenicol			19	19		
	Griseofulvin					20	
	Rifampicin						98

Table 3
MIC of the compounds which demonstrated >90% inhibition in primary screen against *M. tuberculosis H37 Rv*

Comp.	MIC versus H37 Rv (μg/ml)	IC 50 VERO cely (μg/ml)	SI (IC_{50}/MIC)	Comment
5d	12.5	27	2	MIC RMP = 0.25 μg/ml IC_{50} (INH ⇒ 1000; RMP = 61; DMSO = 1.08%)
5f	12.5			MIC RMP = 0.25 μg/ml insoluble, fell out in tissue culture medium at 5 μg/ml unable to test IC_{50}
5h	>12.5	13	<1	MIC RMP = 0.25 μg/ml IC_{50} (INH ⇒ 1000; RMP = 80; DMSO = 1.30%)
5i	6.25	8	1.3	MIC RMP = 0.25 μg/ml IC_{50} (INH ⇒ 1000; RMP = 80; DMSO = 1.30%)
5k	>12.5	32	<2.6	MIC RMP = 0.25 μg/ml IC_{50} (INH ⇒ 1000; RMP = 61; DMSO = 1.08%)
6e	12.5			MIC RMP = 0.25 μg/ml insoluble, in DMSI 5 μg/ml unable to test IC_{50}
6f	>12.5	41	<3	MIC RMP = 0.25 μg/ml IC_{50} (INH ⇒ 1000; RMP = 80; DMSO = 1.30%)
6m	>12.5	9	<0.7	MIC RMP = 0.25 μg/ml IC_{50} (INH ⇒ 1000; RMP = 80; DMSO = 1.30%)

4.2. Antitubercular activity

The antitubercular evaluation of the compounds was carried out at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), USA. Primary screening of the compounds for antitubercular activity have been conducted at 12.5 μg/ml towards *Mycobacterium tuberculosis H37 Rv* in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demonstrating at least >90% inhibi-

tion (Table 3) in the primary screen have been retested at lower concentration towards *Mycobacterium tuberculosis H37 Rv* to determine the actual minimum inhibitory concentration (MIC) in the BACTEC 460.

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