Synthesis and Evaluation of Some Novel 2-Amino-4-Aryl Thiazoles for Antitubercular Activity

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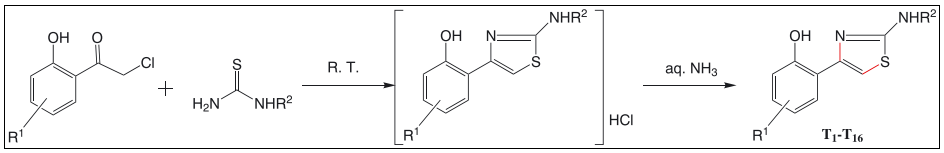

A series of novel 2-amino-4-aryl thiazoles were synthesized from α-chloroacetophenone and thiourea at room temperature using acetone as solvent. The structures of synthesized compounds were confirmed by spectral data. All the compounds were evaluated for antitubercular activity by macro broth dilution method against *Mycobacterium Tuberculosis H37Rv* as standard strain. The synthesized compound displays notable antitubercular activity.

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INTRODUCTION

In recent years, the interest in synthesis of biologically active heterocyclic compounds is greatly increased. The heterocycles containing nitrogen and sulfur atom has acquired more importance in medicinal chemistry. The thiazole ring is a part of many potent biologically active molecules such as Sulfathiazole (Antimicrobial drug), Tiazofurin (Antineoplastics drug), and Ritonavir (Antiretroviral drug). This class of compounds has various medicinal applications like antibiotics [1], photo sensitizers [2], antibacterial [3], antitubercular [4,5], antifungal [6], anti-HIV [7], and anti-inflammatory [8]. Some thiazole derivatives have found applications in drug development for the treatment of allergies [9], hypertension [10], and schizophrenia [11]. Amino thiazoles are also used as ligands of estrogen receptors [12].

Several methods for the synthesis of thiazole and its derivatives were developed by Hantzsch, Tchernic, Cook Helborn, Gabriel, and other groups [13,14]. Other methods developed by different workers, from α-haloketone and thioamide using β-cyclodextrin as catalyst [15], by the reaction of acetophenone with thiourea using Br_2/I_2 as catalyst [16], from α-bromoketone, primary amine and phenylisothiocynate in presence of catalytic amount of triethylamine [17], 2-aminothiazole derivatives were synthesized from α-bromoketone, thiourea catalytic amount of ammonium chloride [18], ring expansion of 1-arylmethyl-2-(thiocynatomethyl)aziridine with an acyl chloride in presence of $TiCl_4$ [19].

Tuberculosis (TB) is a highly contagious infectious disease. According to World Health Organization, one-third of world's population is currently infected with TB [20]. In 2015, there is an estimated 10.4 million of new (incident) TB cases worldwide and an estimated 1.4 million TB deaths, additional 0.4 million deaths resulting from TB disease among people living with HIV [21]. Currently, TB is treated with the combination of first line antitubercular drugs like rifampicin, isoniazid, ethambutal, and Pyrazinamide for 6 to 8 months. The organism *Mycobacterium Tuberculosis* shows resistance to isoniazid and rifampicin. Totally, drug resistant TB and possibility of infection with HIV is a serious problem. The earlier mentioned drugs have side effects like hepatotoxicity, breathlessness, pruritus, hyper pigmentation nausea, vomiting, and diarrhea.

The first line antitubercular agent Pyrazinamide is a nicotinamide analog. Pyrazinamide kill the dormant nongrowing tubercle bacilli of low metabolism activity when administered with isoniazid or rifampicin. This is never used alone, because of these side effects of current drugs and the serious threats of TB, the search of new effective anti-TB drug against the resistant strains having fever or no side effects has gaining more importance.

It was found that the biological activity of thiazole increases with increase in lipophilic character of the molecule, it is an important parameter related to membrane permeation in biological system [22]. The halogen substituted aromatic substituents at fourth position increases lipophilic nature. In addition, the amino group at second position of thiazole would be essential element for hydrogen bonding [23]. Therefore, the present study was designed to synthesize such scaffold and to evaluate their antitubercular activity.

RESULT AND DISCUSSION

The reaction of α-chloroacetophenone and thiourea in acetone at room temperature gives 2-amino-4-arylthizole.

Scheme 1. Synthesis of 2-amino-4-arylthiazoles (T_1–T_{16}). [Color figure can be viewed at wileyonlinelibrary.com]

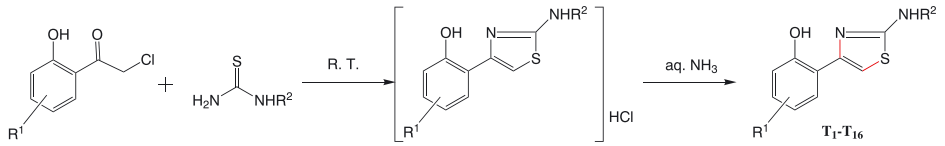


Table 1

Antitubercular activity of 2-amino-4-arylthiazoles.

Sr. No	Entry	Interpretation
01	Pyrazinamide	−Ve
02	T_1	−Ve
03	T_2	−Ve
04	T_3	−Ve
05	T_4	−Ve
06	T_5	−Ve
07	T_6	−Ve
08	T_7	−Ve
09	T_8	−Ve
10	T_9	−Ve
11	T_{10}	−Ve
12	T_{11}	−Ve
13	T_{12}	−Ve
14	T_{13}	−Ve
15	T_{14}	−Ve
16	T_{15}	−Ve
17	T_{16}	−Ve
18	Growth control	+Ve

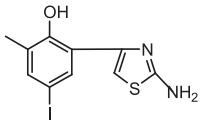
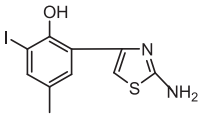
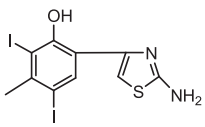
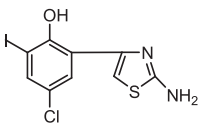
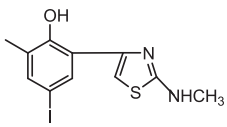
Legends: +Ve = growth seen, −Ve = no growth.

The reaction was completed within 15–34 min. After completion of reaction, the solid so obtained was filtered, washed with diethyl ether, neutralization of its aqueous solution afforded 2-amino-4-arylthiazole. (Scheme 1) All the products were confirmed by spectral analysis. IR spectra shows absorption band at 3320–3370 cm^{-1} for ─NH stretching; 3110–3150 cm^{-1} for ─OH stretching; 2350–2370 cm^{-1} for C═N stretching; 1580–1610 cm^{-1} for C─N stretching; 1050–1070 cm^{-1} for C─S stretching; 732–750 cm^{-1} for C─S─C bending. In ^{1}HNMR, spectra singlet δ 6.6–7.0 for C─H proton indicates formation of thiazole ring. Mass spectra shows clear and distinct molecular ion peak corresponding to the expected molecular weight of compounds.

Antitubercular activities of synthesized compounds were studied by macrobroth dilution method using Pyrazinamide (1000 μg/mL) as positive control and *M. tuberculosis H37Rv* as standard strain. The results (Table 1) show that all the compounds exhibited

Table 2

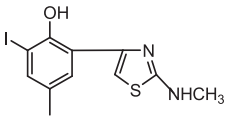
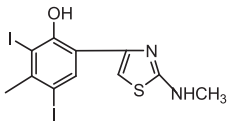
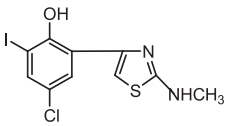
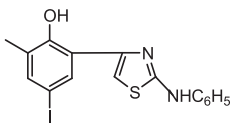
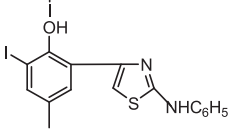
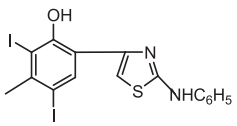
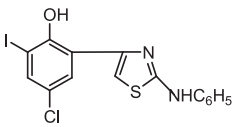
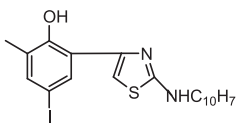
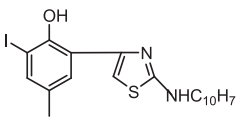
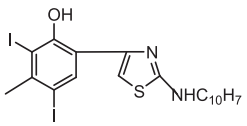
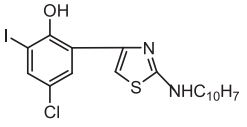
Characterization data of 2-amino-4-arylthiazoles (T_1–T_{16}).

Entry	Compound	Yield (%)[a]	MP (°C)[b]	Reaction time (min)
T_1		80	160	15
T_2		77	142	20
T_3		75	150	22
T_4		77	175	27
T_5		81	132	17

(*Continues*)

Table 2

(*Continued*)

Entry	Compound	Yield (%)[a]	MP (°C)[b]	Reaction time (min)
T_6		76	122	24
T_7		74	118	25
T_8		77	129	32
T_9		82	112	16
T_{10}		77	135	21
T_{11}		73	130	24
T_{12}		72	121	29
T_{13}		79	116	20
T_{14}		75	167	26
T_{15}		71	157	31
T_{16}		68	145	34

[a]Yields were isolated and unoptimized.
[b]±1 °C.

good activity against said strain of microorganism at 1500 μg/mL. The results can be correlated with the antitubercular activity of reported derivatives of thiazole, for example, 4-methyl-*N*-(4–0 × 0–2-phenylthiazolidin-3-yl)-2-(pyrazine-2-yl)thaizol-5-carboxamide (MIC 30 μg/mL) [24], 2-aminothazol-4-yl)methylester (MIC 1–10 μg/mL) [23], Thiazole based on t-3-alkyl-r-2,C-6-diarylpiperidin-4-one (MIC 265 μg/mL) [25], Substituted phenyl thiazole derivatives (MIC 100 μg/mL) [26], S-derivatives of clubbed triazolyl thiazole (MIC 332 μg/mL) [5], and *N*-3-(4- (chlorophenylthiazol-2-yl)-2-(amino)methyl)-quinazoline-4-(3*H*)-one (MIC 100 μg/mL) [27].

CONCLUSION

A series of novel 2-amino-4-aryl thiazoles were synthesized from α-chloroacetophenone and thiourea under mild and catalyst free condition. The structures of compounds were confirmed by spectral analysis. These compounds were screened for antitubercular activity by Macro Broth dilution method using Pyrazinamide as positive control and *M. tuberculosis H37Rv* as standard strain. All the synthesized compounds inhibit growth at 1500 μg/mL concentration.

EXPERIMENTAL

All the chemicals were of analytical grade. The melting points were determined by open capillary methods and are uncorrected. Synthesized compounds were purified by simple crystallization. The purity of compound was checked by thin-layer chromatography. The IR spectra were recorded on "Shimadzu" IR spectrophotometer using KBr pallet. ^{1}HNMR spectra were recorded on "Avance-300" spectrometer using $CDCl_3$ as solvent and tetramethylslane as internal standard. Mass spectra were recorded in electron impact mode.

General procedure for the synthesis of 2-amino-4-arylthiazole. Corresponding α-chloroacetophenone (1 mmol.) and thiourea (1 mmol.) were dissolved separately in acetone. Both the solutions were mixed and kept at room temperature for 15–34 min. The resulting white product was filtered and washed with diethyl ether. Neutralization of its aqueous solution with dilute ammonia afforded 2-amino-4-arylthiazole and recrystallization from absolute ethanol gave analytically pure products. (Table 2).

Synthesis of 2-(2-aminothiazol-4-yl)-4-iodo-6-methylphenol (T_1). White solid, IR (KBr.) cm^{-1} 3313–3370 (─NH_2), 3116 (─OH), 2360 (C═N), 1604 (C─N), 1049 (C─S), 752 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 11.79 (s, 1H), 7.65 (d, 1H), 7.34 (d, 1H), 6.71 (s, 1H), 5.05 (s, 2H), 2.34 (s, 3H); M.S.–*m/z* −332 M^+, *Anal*. % Calcd for $C_{10}H_9IN_2OS$: C, 36.16; H, 2.73; N, 8.43. Found: C, 36.11; H, 2.70; N, 8.58.

Synthesis of 2-(2-aminothiazol-4-yl)-6-iodo-4-methylphenol (T_2). White solid, IR (KBr.) cm^{-1} 3320–3370 (─NH_2), 3120 (─OH), 2356 (C═N), 1608 (C─N), 1051 (C─S), 749 (C─S─C Bending);^{1}HNMR ($CDCl_3$) δ ppm = 12.12 (s, 1H), 7.31 (d, 1H), 7.14 (d, 1H), 6.61 (s, 1H), 4.12 (s, 2H), 2.35 (s, 3H); M.S.–*m/z* −332 M^+, *Anal*. % Calcd for $C_{10}H_9IN_2OS$: C, 36.16; H, 2.73; N, 8.43. Found: C, 36.10; H, 2.70; N, 8.57.

Synthesis of 6-(2-aminothiazol-4-yl)-2,4-diiodo-3-methylphenol (T_3). White solid, IR (KBr.) cm^{-1} 3315–3350 (─NH_2), 3130 (─OH), 2350 (C═N), 1600 (C─N), 1048 (C─S), 749 (C─S─C Bending);^{1}HNMR ($CDCl_3$) δ ppm = 12.11 (s, 1H), 7.51 (s, 1H), 6.58 (s, 1H), 4.13 (s, 2H), 2.31 (s, 3H); M.S.–*m/z* −457 M^+, *Anal*. % Calcd for $C_{10}H_8I_2N_2OS$: C, 26.22; H, 1.76; N, 6.12. Found: C, 26.25; H, 1.75; N, 6.10.

Synthesis of 2-(2-aminothiazol-4-yl)-4-chloro-6-iodophenol (T_4). White solid, IR (KBr.) cm^{-1} 3310–3350 (─NH_2), 3120 (─OH), 2355 (C═N), 1610 (C─N), 1055 (C─S), 745 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.10 (s, 1H), 7.44 (d, 1H), 7.32 (d, 1H), 6.88 (s, 1H), 4.12 (s, 2H); M.S.–*m/z* −351 M^+, *Anal*. % Calcd for $C_9H_6ClIN_2OS$: C, 30.66; H, 1.72; N, 7.95. Found: C, 30.60; H, 1.70; N, 7.87.

Synthesis of 4-iodo-2-methyl-6-(2-(methylamino)thiazol-4-yl) phenol (T_5). White solid, IR (KBr.) cm^{-1} 3312 (─NH), 3116 (─OH), 2360 (C═N), 1604 (C─N), 1049 (C─S), 732 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.17 (s, 1H), 7.66 (d, 1H), 7.33 (d, 1H), 6.67 (s, 1H), 5.15 (q, 2H), 3.04 (d, 3H), 2.22 (s, 3H); M.S.–*m/z* −346 M^+, *Anal*. % Calcd for $C_{11}H_{11}IN_2OS$: C, 38.16; H, 3.20; N, 8.09. Found: C, 37.99; H, 3.18; N, 8.01.

Synthesis of 2-iodo-4-methyl-6-(2-(methylamino)thiazol-4-yl) phenol (T_6). White solid, IR (KBr.) cm^{-1} 3315 (─NH), 3110 (─OH), 2320 (C═N), 1600 (C─N), 1045 (C─S), 750 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.09 (s, 1H), 7.51 (d, 1H), 7.32 (d, 1H), 6.71 (s, 1H), 4.13 (q, 2H), 2.41 (d, 3H), 2.29 (s, 3H); M.S.–*m/z* −346 M^+, *Anal*. % Calcd for $C_{11}H_{11}IN_2OS$: C, 38.16; H, 3.20; N, 8.09. Found: C, 37.98; H, 3.14; N, 8.01.

Synthesis of 2,4-diiodo-3-methyl-6-(2-(methylamino)thiazol-4-yl)phenol (T_7). White solid, IR (KBr.) cm^{-1} 3318 (─NH), 3100 (─OH), 2330 (C═N), 1610 (C─N), 1059 (C─S), 745 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.13 (s, 1H), 7.45 (s, 1H), 6.69 (s, 1H), 4.14 (q, 2H), 2.40 (d, 3H), 2.28 (s, 3H); M.S.–*m/z* −472 M^+, *Anal*. % Calcd for $C_{11}H_{10}I_2N_2OS$: C, 27.99; H, 2.14; N, 5.93. Found: C, 27.80; H, 2.10; N, 5.90.

Synthesis of 4-chloro-2-iodo-6-(2-(methylamino)thiazol-4-yl) phenol (T_8). White solid, IR (KBr.) cm^{-1} 3312 (─NH), 3150 (─OH), 2360 (C═N), 1605 (C─N), 1055 (C─S), 755 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.10 (s, 1H), 7.51 (d, 1H), 7.32 (d, 1H), 6.71

(s, 1H), 4.20 (q, 2H), 2.45 (d, 3H); M.S.– *m/z* −365 M^+, *Anal*. % Calcd for $C_{10}H_8ClIN_2OS$: C, 32.76; H, 2.20; N, 7.64. Found: C, 32.70; H, 2.18; N, 7.63.

Synthesis of 4-iodo-2-methyl-6-(2-(phenylamino)thiazol-4-yl) phenol (T_9). White solid, IR (KBr.) cm^{-1} 3363 (─NH), 3124 (─OH), 2360 (C═N), 1593 (C─N), 1060 (C─S), 752 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.26 (s, 1H), 7.54 (d, 1H), 7.17 (q, 1H), 6.82 (s, 1H), 1.58 (s, 1H), 7.40 (t, 2H) 7.31 (q, 3H), 2.26 (s 3H); M.S.– *m/z* −408 M^+, *Anal*. % Calcd for $C_{16}H_{13}IN_2OS$: C, 47.07; H, 3.21; N, 6.86. Found: C, 47.10; H, 3.20; N, 6.85.

Synthesis of 2-iodo-4-methyl-6-(2-(phenylamino)thiazol-4-yl) phenol (T_{10}). White solid, IR (KBr.) cm^{-1} 3380 (─NH), 3140 (─OH), 2365 (C═N), 1600 (C─N), 1055 (C─S), 745 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.2 (s, 1H), 7.5 (d, 1H), 7.17 (d, 1H), 6.81 (s, 1H), 1.58 (s, 1H), 7.41 (t, 2H) 7.33 (q, 3H), 2.28 (s, 3H); M.S.– *m/z* −408 M^+, *Anal*. % Calcd for $C_{16}H_{13}IN_2OS$: C, 47.07; H, 3.21; N, 6.86. Found: C, 47.10; H, 3.22; N, 6.84.

Synthesis of 2,4-diiodo-3-methyl-6-(2-(phenylamino)thiazol-4-yl)phenol (T_{11}). White solid, IR (KBr.) cm^{-1} 3370 (─NH), 3170 (─OH), 2360 (C═N), 1608 (C─N), 1057 (C─S), 755 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.02 (s, 1H), 7.17 (s, 1H), 6.89 (s, 1H), 1.55 (s, 1H), 7.48 (t, 2H) 7.34 (q, 3H), 2.27 (s, 3H); M.S.– *m/z* −533 M^+, *Anal*. % Calcd for $C_{16}H_{12}I_2N_2OS$: C, 35.98; H, 2.26; N, 5.24. Found: C, 36.00; H, 2.25; N, 5.25.

Synthesis of 4-chloro-2-iodo-6-(2-(phenylamino)thiazol-4-yl) phenol (T_{12}). White solid, IR (KBr.) cm^{-1} 3360 (─NH), 3160 (─OH), 2372 (C═N), 1610 (C─N), 1049 (C─S), 749 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.0 (s, 1H), 7.52 (d, 1H), 7.32 (d, 1H), 6.9 (s, 1H), 1.9 (s, 1H), 7.48 (t, 2H) 7.30 (q, 3H); M.S.– *m/z* −428 M^+, *Anal*. % Calcd for $C_{15}H_{10}ClIN_2OS$: C, 42.03; H, 2.35; N, 6.53. Found: C, 42.00; H, 2.36; N, 6.53.

Synthesis of 4-iodo-2-methyl-6-(2-(naphthalen-3-ylamino) thiazol-4-yl)phenol (T_{13}). White solid, IR (KBr.) cm^{-1} 3392 (─NH), 3120ss (─OH), 2365 (C═N), 1615 (C─N), 1075 (C─S), 759 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.03 (s, 1H), 7.57 (d, 1H), 7.12 (d, 1H), 6.81 (s, 1H), 1.59 (s, 1H), 6.7–7.4 (m, 7H), 2.23 (s 3H); M.S.– *m/z* −458 M^+, *Anal*. % Calcd for $C_{20}H_{15}IN_2OS$: C, 52.41; H, 3.30; N, 6.11. Found: C, 52.42; H, 3.28; N, 6.10.

Synthesis of 2-iodo-4-methyl-6-(2-(naphthalen-3-ylamino) thiazol-4-yl)phenol (T_{14}). White solid, IR (KBr.) cm^{-1} 3395 (─NH), 3170 (─OH), 2372 (C═N), 1625 (C─N), 1065 (C─S), 757 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.13 (s 1H), 7.58 (d 1H), 7.19 (d 1H), 6.91 (s 1H), 2.01 (s 1H), 6.7–7.4 (m 7H), 2.21 (s 3H); M.S.– *m/z* −458 M^+, *Anal*. % Calcd for $C_{20}H_{15}IN_2OS$: C, 52.41; H, 3.30; N, 6.11. Found: C, 52.40; H, 3.31; N, 6.12.

Synthesis of 2,4-diiodo-3-methyl-6-(2-(naphthalen-3-ylamino) thiazol-4-yl)phenol (T_{15}). White solid, IR (KBr.) cm^{-1} 3372 (─NH), 3115 (─OH), 2371 (C═N), 1617 (C─N), 1088 (C─S), 769 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.21 (s, 1H), 7.27 (s, 1H), 6.78 (s, 1H), 1.99 (s, 1H), 6.7–7.4 (m,7H), 2.21 (s, 3H); M.S.– *m/z* −484 M^+, *Anal*. % Calcd for $C_{20}H_{14}I_2N_2OS$: C, 41.12; H, 2.42; N, 4.80. Found: C, 41.11; H, 2.44; N, 4.81.

Synthesis of 4-chloro-2-iodo-6-(2-(naphthalen-3-ylamino) thiazol-4-yl)phenol (T_{16}). White solid, IR (KBr.) cm^{-1} 3382 (─NH), 3119 (─OH), 2375 (C═N), 1605 (C─N), 1055 (C─S), 755 (C─S─C Bending); ^{1}HNMR ($CDCl_3$) δ ppm = 12.3 (s, 1H), 7.57 (d, 1H), 7.12 (d, 1H), 6.81 (s, 1H), 2.29 (s, 1H), 6.7–7.4 (m, 7H); M.S.– *m/z* −478 M^+, *Anal*. % Calcd for $C_{19}H_{12}ClIN_2OS$: C, 47.67; H, 2.53; N, 5.85. Found: C, 47.65; H, 2.55; N, 5.82.

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