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Original Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDY OF SOME NOVEL FLUORINE BASED 2-AMINOTHIAZOLES

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ABSTRACT

Objectives: To synthesize, characterize and evaluate antimicrobial properties of some novel fluorine based 2-aminothiazoles.

Methods: The syntheses of some novel fluorine based 2-aminothiazoles have been described by using hypervalent iodine [I(III)] mediated approach. It was observed that this is the more general and promising method for the synthesis of any thiazole, but, when other methods work, the hypervalent iodine [I(III)] mediated approach generally gives better yields. The structures of these compounds have been characterized from the rigorous analysis of their IR, ^{1}H NMR, MS and elemental analysis. These compounds were screened for their anti-microbial activity.

Results: The results revealed that compounds **7d**, **7f**, **10a**, **10b**, **10c**, **14e** and **14f** showed moderate to good antibacterial activity as compared with the standard drug Chloramphenicol.

Conclusion: The two thiazole synthetic methods described herein use readily available reagents and both of them are easily feasible, the hypervalent iodine mediated approach for the synthesis of title compounds is more significant because, in spite of the better yields, it avoids the use of highly toxic and lachrymatory α-halogenoketone, thereby being more eco-friendlier.

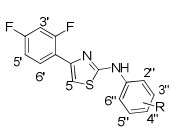
Keywords: Fluorine, 2-Aminothiazoles, Hypervalent iodine, α-Tosyloxyketones, Anti-microbial.

INTRODUCTION

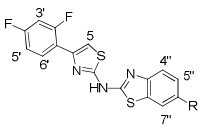
The aminothiazoles have been reported by several researchers as an excellent precursor of a large variety of biologically active compounds such as antibiotics (cephalosporins [1-3], *β*-lactams [4], sulfathiazoles [5], etc.) and bactericides [6]. The application of aminothiazole derivatives in therapy and their utilization as agents are based upon cyclooxygenase inhibition [7-10] that led us to explore a convenient method for their synthesis.

In addition to this, it has been observed that the incorporation of fluorine in many heterocyclic systems increased lipid solubility, thus enhancing the rates of absorption and transport of drug *in vivo* [11].

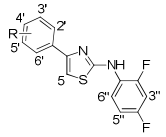
By considering the wide range of applications of aminothiazoles and in continuation of our interest in hypervalent iodine [I(III)] mediated approach, we attempted the syntheses of some novel fluorine based 2-aminothiazoles (**7a-g, 10a-c** and **14a-f**).



7a-g



10a-c



14a-f

MATERIALS AND METHODS

All the chemicals required were purchased from the local suppliers and were purified by established methods. The melting points were recorded by open capillary method and are uncorrected. The purity and homogeneity of the synthesized compounds were routinely ascertained by the thin layer chromatography, performed on plates coated with silica gel-G. All compounds were isolated and purified by thin layer chromatography and column chromatography respectively. The visualization was done using iodine vapours and U. V. light chamber. The ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument using $CDCl_3$ or DMSO-d_6 solvents and TMS (Tetra methyl silane) as internal standard. Chemical shifts (δ) are reported in ppm and coupling constants *J* are given in Hz. IR spectra were recorded using KBr disks with a Buck Scientific IR M-500 infrared spectrometer. The mass spectra was recorded on a JEOL JMS 600 mass spectrometer at an ionizing potential of 70eV (EI) electron impact ionization mode using the direct inlet system.

Experimental

Synthesis of 2-aryl/benzothiazolylamino-4-(2,4-difluorophenyl) thiazoles (7a-g, 10a-c) and 2-(2,4-difluorophenyl)amino-4-arylthiazoles (14a-f)

2,4-Difluoroacetophenone was prepared by the acetylation of 1,3-difluorobenzene [12]. [Hydroxy(tosyloxy)iodo]benzene was prepared by the method of Neiland & Karele [13] and Koser *et a.l* [14].

Synthesis of phenyl thiourea (6a-g, 13)

General Procedure: To aniline (0.1 mol) in water, concentrated HCl was added and the solution was warmed. A saturated solution of potassium thiocyanate (0.8 mol) in water was added slowly with stirring in above hydrochloride salt solution. Then the solution was heated for 4-5 hrs until the solution became turbid. The turbid solution was poured in cold water. The separated precipitate was filtered, washed with water and recrystallized from ethanol, so as to obtain pure compound phenylthiourea (Yield: 70-80%).

Synthesis of 6-Substituted 2-aminobenzthiazole (8a-c)

General procedure: The p-substituted aniline (0.1 mol) and ammonium thiocyanate (0.2 mol) in 150 ml of glacial acetic acid were cooled in an ice bath and stirred mechanically. To the solution, bromine (0.2 mol) in 25 ml of glacial acetic acid was added dropwise at such a rate to keep the temperature below 10 ^oC throughout the addition. Stirring was continued for additional thirty minutes after the bromine addition. The precipitate of the benzthiazole hydrobromide was collected, dissolved in hot water and basified with a saturated sodium carbonate solution. The free substituted benzthiazole was collected, washed with water and dried under vacuum. Recrystallization from ethanol gave 6-substituted 2-aminobenzthiazoles **8a-c** in good yield.

Synthesis of 1-(6-Substituted benzothiazol-2-yl)thiourea (9a-c)

General procedure: Benzoyl chloride (0.1 mol) was added dropwise to ammonium thiocyanate (0.1 mol) in dry acetone 50

ml with stirring. After the initial reaction had subsided, the mixture was heated for 5 min and then a hot solution of 2-amino benzthiazole (0.1 mol) in dry acetone (50 ml) was added with constant stirring. After refluxing for1 hr, the mixture was poured into water. A crystalline solid precipitated out slowly. After filtration, the solid were heated with 10% NaOH solution (300 ml) and filtered again. The filtrate was acidified with conc. HCl and then made alkaline by an addition of a little ammonia. The solid so obtained was filtered, washed with water and dried. Recrystallization from ethanol gave 1-(6-Substituted benzothiazol-2-yl)thiourea **9a-c** in good yield.

Synthesis of 2-aryl/benzothiazolylamino-4-(2,4-difluorophenyl) thiazoles (7a-g, 10a-c) and 2-(2,4-difluorophenyl)amino-4-arylthiazoles (14a-f)

Method A: Hypervalent iodine [I (III)] mediated approach

Step I: Preparation of α-tosyloxy-2,4-difluoroacetophenone

To a stirred solution of 2,4-difluoroacetophenone (0.01 mol) in acetonitrile was added HTIB (0.01 mol) and the reaction mixture was refluxed for 5 hrs. Excess of the solvent was distilled off and the residual mass was crystallized from ethanol. The product was further washed with cold ethanol and dried under vacuum, yield 75%, m. p. 110-111°C.

All other α-tosyloxyphenylketones were prepared using this standard procedure [15].

Step 2: Preparation of 2-aminothiazoles 7a-g, 10a-c and 14a-f

General procedure: An equimolar mixture of α-tosyloxyphenylketone (0.01 mol) and appropriate thiourea derivative (0.01 mol) in ethanol was refluxed for 3-4 hrs. The reaction mixture was then cooled. A crystalline solid was separated out. Filtered the solid, washed with saturated sodium bicarbonate solution and then with water. Recrystallized from ethanol gave title compounds.

Method B: Hantzsch thiazole synthesis

General procedure: An equimolar mixture of α-bromomethylketone (0.01 mol) and appropriate thiourea derivative (0.01 mol) in ethanol was refluxed for 5-6 hrs. The reaction mixture was then cooled. A crystalline solid was separated out. Filtered the solid, washed with saturated sodium bicarbonate solution and then with water. Recrystallized from ethanol gave title compounds.

7a: m. p. 210-211°C; IR (KBr): 3153 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.95-7.02 (2H, m, thiazole C_5-*H* & $C_{3'}$-*H*), 7.06-7.13 (1H, dt, *J*=8.4 & 2.4 Hz, $C_{5'}$-*H*), 7.34-7.53 (5H, m, $C_{2''}$-*H*, $C_{3''}$-*H*, $C_{4''}$-*H*, $C_{5''}$-*H* & $C_{6''}$-*H*), 8.06-8.13 (1H, td, *J*=8.4 & 6.2 Hz, $C_{6'}$-*H*), 11.60 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 288; Anal. Calcd. for $C_{15}H_{10}F_2N_2S$: C, 62.49 %; H, 3.50 %; N, 9.72 %. Found: C, 62.19 %; H, 3.24 %; N, 9.98 %.

7b: m. p. 145-146°C; IR (KBr): 3280 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.89-6.97 (1H, ddd, *J*=11.5, 8.6 & 2.7 Hz, $C_{3'}$-*H*), 6.99-7.05 (2H, m, thiazole C_5-*H* & $C_{5'}$-*H*), 7.39 (4H, s, $C_{2''}$-*H*, $C_{3''}$-*H*, $C_{5''}$-*H* & $C_{6''}$-*H*), 8.03-8.11 (1H, td, *J*=8.6 & 6.3 Hz, $C_{6'}$-*H*); MS: M^+at m/z 322; Anal. Calcd. for $C_{15}H_9ClF_2N_2S$: C, 55.82 %; H, 2.81 %; N, 8.68 %. Found: C, 55.45 %; H, 2.94 %; N, 8.98 %.

7c: m. p. 135-137°C; IR (KBr): 3292 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.38 (3H, s, $C_{4''}$-CH_3), 6.91-6.98 (2H, m, thiazole C_5-*H* & $C_{3'}$-*H*), 7.02-7.08 (1H, dt, *J*=8.6 & 2.4 Hz, $C_{5'}$-*H*), 7.23-7.26 (2H, d, *J*=8.6 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 7.27-7.30 (2H, d, *J*=8.6 Hz, $C_{3''}$-*H* & $C_{5''}$-*H*), 8.06-8.14 (1H, td, *J*=8.6 & 6.5 Hz, $C_{6'}$-*H*); MS: M^+at m/z 302; Anal. Calcd. for $C_{16}H_{12}F_2N_2S$: C, 63.56 %; H, 4.00 %; N, 9.27 %. Found: C, 63.19 %; H, 4.24 %; N, 9.38 %.

7d: m. p. 173-175°C; IR (KBr): 3204 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.85 (3H, s, $C_{4''}$-OCH_3), 6.88-6.95 (1H, ddd, *J*=12.5, 9.0 & 2.8 Hz, $C_{3'}$-*H*), 6.98-7.01 (3H, m, $C_{3''}$-*H*, $C_{5''}$-*H* & thiazole C_5-*H*), 7.04-7.11 (1H, dt, *J*=8.7 & 2.8 Hz, $C_{5'}$-*H*), 7.37-7.40 (2H, d, *J*=9.2 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 7.96-8.03 (1H, td, *J*=8.7 & 5.7 Hz, $C_{6'}$-*H*), 11.07 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 318; Anal. Calcd. for $C_{16}H_{12}F_2N_2OS$: C, 60.37 %; H, 3.80 %; N, 8.80 %. Found: C, 60.03 %; H, 3.56 %; N, 9.07 %.

7e: m. p. 242-244°C; IR (KBr): 3309 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.89-6.95 (1H, ddd, *J*=11.0, 8.9 & 2.3 Hz, $C_{3'}$-*H*), 6.97-7.02 (1H, dt, *J*=8.6 & 2.3 Hz, $C_{5'}$-*H*), 7.23 (1H, s, thiazole C_5-*H*), 7.45 (1H, brs, N-*H* exchangeable with D_2O), 7.63-7.66 (2H, d, *J*=9.0 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 8.09-8.17 (1H, td, *J*=8.6 & 6.8 Hz, $C_{6'}$-*H*), 8.26-8.29 (2H, d, *J*=9.0 Hz, $C_{3''}$-*H*, $C_{5''}$-*H*); MS: M^+at m/z 333. Anal. Calcd. for $C_{15}H_9F_2N_3O_2S$: C, 54.05 %; H, 2.72 %; N, 12.61 %. Found: C, 54.09 %; H, 2.54 %; N, 12.31 %.

7f: m. p. 150-151°C; IR (KBr): 3404 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.86-6.93 (1H, ddd, *J*=11.5, 8.8 & 2.6 Hz, $C_{3'}$-*H*), 6.94-7.00 (1H, dt, *J*=8.8 & 2.6 Hz, $C_{5'}$-*H*), 7.15 (1H, s, thiazole C_5-*H*), 7.23-7.33 (1H, dd, J=8.9 & 2.4 Hz, $C_{5''}$-*H*), 7.41-7.42 (1H, d, *J*=2.4 Hz, $C_{3''}$-*H*), 7.47 (1H, brs, N-*H* exchangeable with D_2O), 8.08-8.16 (1H, td, *J*=8.8 & 6.7 Hz, $C_{6'}$-*H*), 8.31-8.34 (1H, d, *J*=8.9 Hz, $C_{6''}$-*H*); MS: M^+at m/z 357; Anal. Calcd. for $C_{15}H_8Cl_2F_2N_2S$: C, 50.44 %; H, 2.26 %; N, 7.84 %. Found: C, 50.03 %; H, 2.24 %; N, 7.58 %.

7g: m. p. 130-132°C; IR (KBr): 3198 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.85-6.93 (4H, m, $C_{3'}$-*H*, $C_{5'}$-*H*, $C_{3''}$-*H* & $C_{5''}$-*H*), 7.09 (1H, s, thiazole C_5-*H*), 8.07-8.23 (2H, m, $C_{6'}$-*H* & $C_{6''}$-*H*); MS: M^+at m/z 324; Anal. Found: C, 55.19 %; H, 2.24 %; N, 8.98 %. Calcd. for $C_{15}H_8F_4N_2S$: C, 55.55 %; H, 2.49 %; N, 8.64 %.

10a: m. p. 258°C (decomp.); IR (KBr): 3222 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.90-6.98 (1H, ddd, *J*=11.1, 8.8 & 2.2 Hz, $C_{3'}$-*H*), 7.01-7.07 (1H, dt, *J*=8.8 & 2.2 Hz, $C_{5'}$-*H*), 7.29 (1H, s, thiazole C_5-*H*), 7.52-7.55 (1H, d, *J*=8.4 Hz, $C_{5''}$-*H*), 7.73 (1H, s, $C_{7''}$-*H*), 8.05-8.08 (1H, d, *J*=8.4 Hz, $C_{4''}$-*H*), 8.20-8.29 (1H, td, *J*=8.8 & 6.8 Hz, $C_{6'}$-*H*), 11.67 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 379; Anal. Calcd. for $C_{16}H_8ClF_2N_3S_2$: C, 50.59 %; H, 2.12 %; N, 11.06 %. Found: C, 50.19 %; H, 2.24 %; N, 10.98 %.

10b: m. p. 227-228°C; IR (KBr): 3157 cm^{-1} (N-H stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (3H, s, $C_{6''}$-CH_3), 6.90-6.97 (1H, ddd, *J*=11.3, 8.7 & 2.6 Hz, $C_{3'}$-*H*), 7.01-7.07 (1H, dt, *J*=8.3 & 2.6 Hz, $C_{5'}$-*H*), 7.16-7.19 (1H, d, *J*=8.3 Hz, $C_{5''}$-*H*), 7.27 (1H, s, thiazole C_5-*H*), 7.43-7.46 (1H, d, J=8.3 Hz, $C_{4''}$-*H*), 7.52 (1H, s, $C_{7''}$-*H*), 8.24-8.32 (1H, td, *J*=8.3 & 6.8 Hz, $C_{6'}$-*H*), 12.02 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 359. Anal. Calcd. for $C_{17}H_{11}F_2N_3S_2$: C, 56.81 %; H, 3.08 %; N, 11.69 %. Found: C, 56.69 %; H, 3.25 %; N, 11.98 %.

10c: m. p. 230-232°C; IR (KBr): 3156 cm^{-1} (N-H stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (3H, s, $C_{6''}$-OCH_3), 6.89-6.97 (2H, m, $C_{3'}$-*H* & $C_{5''}$-*H*), 7.01-7.07 (1H, dt, *J*=8.6 & 2.2 Hz, $C_{5'}$-*H*), 7.26 (1H, s, thiazole C_5-*H*), 7.49-7.52 (1H, d, *J*=8.8 Hz, $C_{4''}$-*H*), 7.54 (1H, s, $C_{7''}$-*H*), 8.23-8.31 (1H, td, *J*=8.6 & 7.0 Hz, $C_{6'}$-*H*), 12.01 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 375. Anal. Calcd. for $C_{17}H_{11}F_2N_3OS_2$: C, 54.39 %; H, 2.95 %; N, 11.19 %. Found: C, 54.69 %; H, 3.15 %; N, 11.08 %.

14a: m. p. 190-192°C; IR (KBr): 3258 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.87-6.99 (2H, m, $C_{3'}$-*H* & $C_{5'}$-*H*), 7.19 (1H, s, thiazole C_5-*H*), 8.03-8.06 (2H, d, *J*=8.8 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 8.23-8.26 (2H, d, *J*=8.8 Hz, $C_{3''}$-*H* & $C_{5''}$-*H*), 8.49-8.57 (1H, td, *J*=9.0 & 6.0 Hz, $C_{6'}$-*H*), 9.55 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 333; Anal. Calcd. for $C_{15}H_9F_2N_3O_2S$: C, 54.05 %; H, 2.72 %; N, 12.61 %. Found: C, 54.25 %; H, 2.40 %; N, 12.40 %.

14b: m. p. 238-239°C; IR (KBr): 3204 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.84-6.90 (2H, m, $C_{3'}$-*H* & $C_{5'}$-*H*), 7.45-7.49 (2H, d, *J*=8.6 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 7.51 (1H, s, thiazole C_5-*H*), 7.74-7.77 (2H, d, *J*=8.6 Hz, $C_{3''}$-*H* & $C_{5''}$-*H*), 8.23-8.32 (1H, td, *J*=8.9 & 5.9 Hz, $C_{6'}$-*H*), 9.45 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 365. Anal. Calcd. for $C_{15}H_9BrF_2N_2S$: C, 49.06 %; H, 2.47 %; N, 7.63 %. Found: C, 49.09 %; H, 2.54 %; N, 7.31 %.

14c: m. p. 172-173°C; IR (KBr): 3215 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.84-6.90 (2H, m, $C_{3'}$-*H* & $C_{5'}$-*H*), 7.31-7.34 (2H, d, *J*=8.4 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 7.53 (1H, s, thiazole C_5-*H*), 7.82-7.85 (2H, d, *J*=8.4 Hz, $C_{3''}$-*H* & $C_{5''}$-*H*), 8.25-8.33 (1H, td, *J*=8.9 & 6.0 Hz, $C_{6'}$-*H*), 9.49 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 322. Anal. Calcd. for $C_{15}H_9ClF_2N_2S$: C, 55.82 %; H, 2.81 %; N, 8.68 %. Found: C, 55.65 %; H, 2.65 %; N, 8.88 %.

14d: m. p. 188-189°C; IR (KBr): 3216 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.73 (3H, s, $C_{4''}$-*OCH_3*), 6.87-6.98 (2H, m, $C_{3'}$-*H* & $C_{5'}$-H), 7.21-7.24 (2H, d, *J*=9.0 Hz, $C_{3''}$-*H* & $C_{5''}$-H), 7.35 (1H, s, thiazole C_5-*H*), 7.67-7.70 (2H, d, *J*=9.0 Hz, $C_{2''}$-*H* & $C_{6''}$-*H*), 7.96-8.03 (1H, td, *J*=8.6 & 6.0 Hz, $C_{6'}$-*H*), 9.46 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 318; Anal. Calcd. for $C_{16}H_{12}F_2N_2OS$: C, 60.37 %; H, 3.80 %; N, 8.80 %. Found: C, 60.17 %; H, 3.76 %; N, 8.50 %.

14e: m. p. 165-167°C; IR (KBr): 3256 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.86-6.98 (2H, m, $C_{3'}$-*H* & $C_{5'}$-H), 7.21 (1H, s, thiazole C_5-*H*), 7.58-7.64 (1H, t, *J*=8.9 Hz, $C_{5''}$-H), 7.87-7.90 (1H, d, *J*=8.9 Hz, $C_{6''}$-*H*), 8.15-8.18 (1H, d, *J*=8.9 Hz, $C_{4''}$-*H*), 8.41 (1H, s, $C_{2''}$-*H*), 8.51-8.59 (1H, td, *J*=8.6 & 5.9 Hz, $C_{6'}$-*H*), 9.56 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+ at m/z 333; Anal Calcd. for $C_{15}H_9F_2N_3O_2S$: C, 54.05 %; H, 2.72 %; N, 12.61 %. Found: C, 54.35 %; H, 2.42 %; N, 12.51 %.

14f: m. p. 186-187°C; IR (KBr): 3167 cm^{-1} (N-H stretch); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.96-7.02 (2H, m, $C_{3'}$-*H* & $C_{5'}$-*H*), 7.19 (1H, s, thiazole C_5-*H*), 7.41-7.59 (5H, m, $C_{2''}$-*H*, $C_{3''}$-*H*, $C_{4''}$-*H*, $C_{5''}$-*H* & $C_{6''}$-*H*), 8.01-8.08 (1H, td, *J*=8.4 & 6.2 Hz, $C_{6'}$-*H*), 9.67 (1H, brs, N-*H* exchangeable with D_2O); MS: M^+at m/z 288; Anal. Calcd. for $C_{15}H_{10}F_2N_2S$: C, 62.49 %; H, 3.50 %; N, 9.72 %. Found: C, 62.59 %; H, 3.44 %; N, 9.58 %.

Antibacterial activity

The antibacterial activity of all the newly synthesized compounds was done by the Muller-Hinton agar-well diffusion assay technique. The stock solutions of all test compounds (100 mg/ml) were prepared by dissolving 100 mg of the test compound in DMSO (1 ml). Chloramphenicol and DMSO were used as positive and negative controls, respectively. Twenty millilitres of molten and cooled MHA and 320 ml of each test bacterial culture were mixed (separate flasks were used for each bacterial culture) and poured in sterilized and labeled petri plates. The wells of 6 mm were punched in the solidified petri plates, aseptically. Fifty micro litters from stock solutions of all compounds as well as controls was added to each well of labeled petri plates and incubated at 35°C for 24 h. The diameter of the zone of growth inhibition around each well was measured after incubation using vernier caliper. The minimum inhibitory concentration (MIC) of compounds against Gram-positive and Gram-negative test bacteria was determined in the range 100 to 40 mg/ml. All the test cultures were streaked on SCDA and incubated overnight at 37°C. Stock solution of each compound was prepared in DMSO and was appropriately diluted to get a final concentration of 100, 90, 80, 70, 60, 50 and 40 mg/ml. Standard antibiotic chloramphenicol was also diluted to get a final concentration in the same manner.

DISCUSSION

Several methods have been reported in the literature for the formation of thiazoles [16]. The most common method of thiazole synthesis involves the condensation of α-halogenoketones with thiourea (Hantzsch thiazole synthesis). However, the versatility of this reaction is somewhat limited by the difficulty in preparation, purification, toxicity and lachrymatory property of the intermediate α-halogenoketones [17].

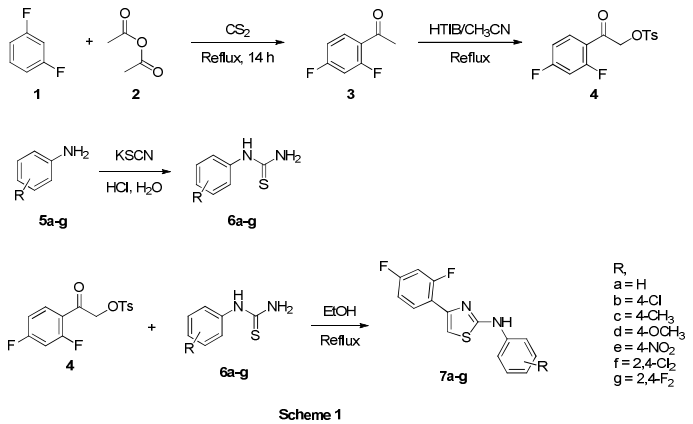
Another similar and useful synthetic method [18] involves the use of hypervalent iodine reagents [I(III)] in organic synthesis. [hydroxy(tosyloxy)iodo]benzene (HTIB or Koser's reagent) [19] is one of the hypervalent iodine reagents which has been recently used as an extremely important reagent providing new and useful synthesis of various heterocyclic compounds. One of the most important reactions of HTIB, particularly α-tosylation of carbonyl compounds, was first reported in 1982 by Koser *et al.* [20].

We first attempted to prepare the precursors α-tosyloxyketones **4** and **12a-f** required for this work which was easily obtained via synthetic route [15] starting from commercially available aryl ketones as formulated in schemes **1** and **3**.

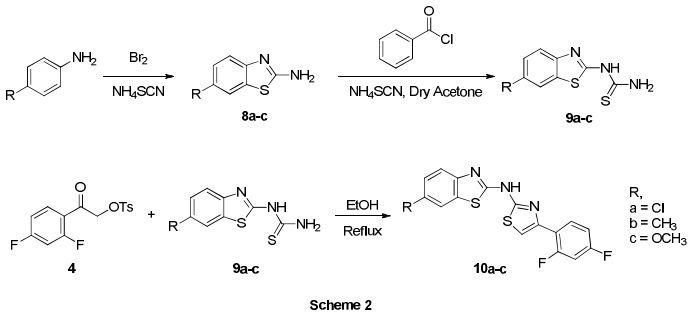
The aryl thioureas **6a-g** and **13** required for the formation of target compounds **7a-g** and **14a-f** were prepared by treating substituted aromatic amines with ammonium thiocyanate in acidic medium [21].

The various anilines on treating with bromine/ammoniumthiocyanate gave the corresponding benzothiazoles **8a-c** [22] which on treatment again with ammoniumthiocyanate/benzoyl chloride yielded benzothiazolyl urease **9a-c** [23].

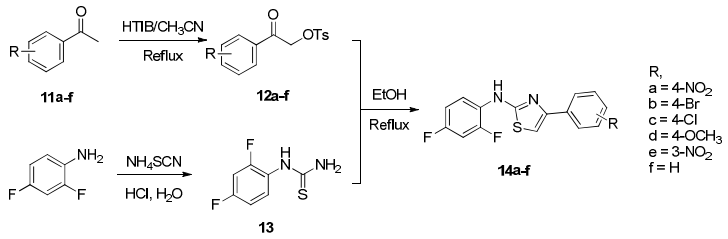
Thus, various α-tosyloxyketones were condensed with appropriate thiourea in refluxing ethanol yielded the targets compounds i. e. 2,4-disubstituted-aminothiazoles **(Scheme 1, 2** & **3)**.



Scheme 1

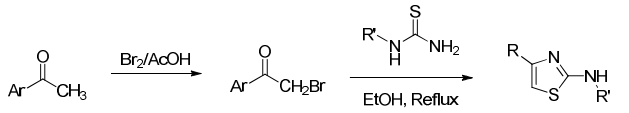


Scheme 2



Scheme 3

The structural elucidation of final targets was mainly based on IR, ^{1}H NMR, MS and elemental analyses. The IR spectra of thiazoles **7a-g, 10a-c** and **14a-f** showed an absorption band due to N-H stretching in the range of 3150-3410 cm^{-1}. The ^{1}H NMR spectrum of the recrystallized samples showed the presence of a sharp singlet due to C_5-H of the thiazole ring which confirmed the formation of the thiazole ring. It was further characterized by MS and elemental analysis.



Scheme 4

For a comparative study of yield (%), the title compounds **7a-g, 10a-c** and **14a-f** were also prepared by Hantzsch thiazole synthesis. Outline of which is shown in **Scheme 4**.

The results obtained from the respective methods are depicted in **Table 1**.

As shown in **Table 1**, the comparison of yields (%) relating to the compounds synthesized from the recently known hypervalent iodine mediated approach and those from earlier method reveals that I(III) mediated approach is superior to the conventional Hantzsch thiazole synthesis.

Evaluation of antibacterial Activity

The newly synthesized compounds **7a-g, 10a-c** and **14a-d** were tested for their antibacterial activity against *S. aureus, E. coli, B. subtilis, P. aeruginosa, S. pyogens, K. terrigena* and *K. pneumonae*. All the synthesized compounds were dissolved in DMSO and antibacterial activity studied by disc diffusion method. Compounds **7d, 7f, 10a, 10b, 10c, 14e** and **14f** showed moderate to good antibacterial activity against several species as compared with standard drug chloramphenicol.

Table 1: Comparison of yields (%) relating to the compounds synthesized by two methods

Compound	R'	Yield (%)	
		Method A[a]	Method B[b]
7a	H	98	92
7b	4-Cl	85	73
7c	4-CH_3	97	91
7d	4-OCH_3	95	83
7e	4-NO_2	76	52
7f	2,4-Cl_2	89	72
7g	2,4-F_2	83	72
10a	Cl	73	58
10b	CH_3	90	76
10c	OCH_3	93	83
14a	4-NO_2	81	70
14b	4-Br	79	51
14c	4-Cl	82	56
14d	4-OCH_3	98	86
14e	3-NO_2	91	75
14f	H	87	73

a) Hypervalent iodine [I (III)] mediated approach

b) Hantzsch thiazole synthesis

Table 2: Antibacterial activity of the compounds (7a-g, 10a-c and 14a-f) as MIC (µg/ml)

Compound	*S. aureus*	*E. coli*	*B. subtilis*	*P. aeruginosa*	*S. pyogens*	*K. terrigena*	*K. pneumonae*
7a	100	90	90	80	--	--	90
7b	90	80	90	90	--	--	100
7c	80	90	80	90	90	100	90
7d	90	70	80	70	80	90	80
7e	100	80	90	80	90	70	90
7f	70	90	100	80	70	80	100
7g	90	70	--	90	--	70	--
10a	60	60	70	60	70	80	70
10b	70	70	80	80	70	80	80
10c	70	80	80	70	80	70	70
14a	--	80	90	80	90	100	100
14b	90	70	100	90	100	90	100
14c	80	90	80	--	100	90	--
14d	100	90	100	90	80	80	90
14e	90	80	80	90	70	80	80
14f	80	70	70	80	80	90	70
Chloramphenicol	50	50	40	40	50	40	50

CONCLUSION

The two thiazole synthetic methods described herein use readily available reagents and both of them are easily feasible, the hypervalent iodine mediated approach for the synthesis of title compounds is more significant because, in spite of the better yields, it avoids the use of highly toxic and lachrymatory α-halogenoketone, thereby being more eco-friendlier. All the synthesized compounds were dissolved in DMSO and antibacterial activity studied by disc diffusion method. Compounds **7d**, **7f**, **10a**, **10b**, **10c**, **14e** and **14f** showed moderate to good antibacterial activity against several species as compared with the standard drug chloramphenicol.

CONFLICT OF INTERESTS

Declared None

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