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Synthesis and Antibacterial Activity of 2-(3-Acylphenyl)amino-4-phenylthiazole[1]

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Abstract—2-(3-acylphenyl)amino-4-phenylthiazoles were synthesized from 1-(3-acetylphenyl)thiourea and 2-bromo-1-substituted phenylethanones in presence of triethylamine upon heating. The newly synthesized compounds were characterized by IR, ^{1}H NMR, MS spectrometry. All products were evaluated for their antibacterial activity against Gram positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative (*Escherichia coli*, *Klebsiella pnemoniae*) strains.

Keywords: thiazoles, 1-(3-acetylphenyl)thiourea, 2-bromo-1-phenylethanone, antibacterial activity

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INTRODUCTION

Development of antibiotic resistant bacterial and fungal strains over the recent decades resulted in substantial need of new classes of antimicrobial agents. Thiazole and its derivatives are important components of various biologically and pharmacologically active compounds such as antifungal [1], antibacterial [2], anti-inflammatory [3], antimicrobial [4–6], anti-HIV [7, 8], hypertension [9, 10], anticancer [11], anticonvulsant [12], anti-inflammatory [13], antidepressant, and antitubercular [14]. Thiazolium cycle present in vitamin B_1 serves as an electron sink and its coenzyme form is important for decarboxylation of α-keto acids [15]. Herein we report the synthesis of novel 2-(3-acylphenyl)amino-4-phenylthiazoles (Scheme 1).

Antibacterial activity. The newly synthesized thiazole derivatives were screened for their antibacterial activity against Gram positive bacteria *viz. Staphylococcus aureus* and *Bacillus subtilis* and Gram negative bacteria *viz. Escherichia coli*, *Klebsiella pnemoniae.* The products **IVe–IVg** demonstrated high activity at concentration 50 μg/mL in the disc diffusion method (Table 2).

EXPERIMENTAL

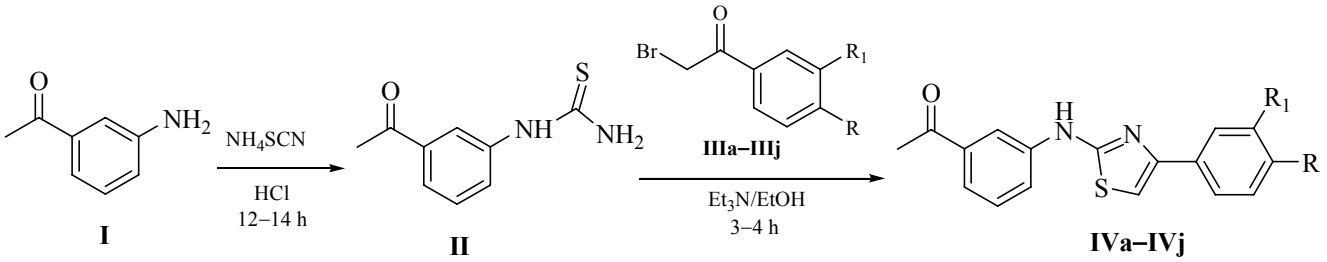
Melting points were measured by the Boetieus micro heating apparatus. Purity of compounds was tested by TLC (silica gel 60 F254, Merck). IR (KBr) spectra were recorded by Perkin-Elmer FT-IR spectrophotometer BX. ^{1}H NMR spectra were measured on Bruker AMX-400 (400 MHz) spectrometer with TMS as an internal reference. Mass spectra were measured on Quatro Lc Micromas (Waters, UK) (70 eV). Elemental analysis was carried out by a Thermo Finnigan CHNS analyzer.

Synthesis of 1-(3-Acetylphenyl)thiourea (II). A mixture of 3-aminoacetophenone (0.05 mol), ammonium thiocyanate (0.05 mol) and dilute hydrochloric acid (20 mL) was stirred at 85°C for 12 h. The reaction progress was monitored by TLC. Upon completion of the reaction the mixture was poured into ice cold water and neutralized by a base. The resulting solid was filtered off, dried and recrystallized from methanol to produce pure crystals of the compound **II**.

Synthesis of 2-(3-acylphenyl)amino-4-phenylthiazole (IVa–IVj). The mixture of 1-(3-acetylphenyl)-thiourea (**II**) (0.01 mol), aryl substituted 2-bromo-1-phenylethanone (**IIIa–IIIj**) (0.01 mol) and NEt_3 in ethanol was refluxed for 3–4 h at room temperature. The reaction progress was monitored by TLC. Upon completion of the process the reaction mixture was poured into ice cold water. The resulting solid was filtered off, dried and purified by column chromatography using EtOAc : pet ether (4 : 10) eluent to yield the compounds **IVa–IVj** (Table 1).

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 2-(3-acylphenyl)amino-4-phenylthiazole (**IVa–IVj**)



IIIa: R = H R_1 = H; **IIIb:** R = CH_3, R_1 = H; **IIIc:** R = OCH_3, R_1 = H; **IIId:** R = NO_2, R_1 = H; **IIIe:** R = F, R_1 = H; **IIIf:** R = Cl, R_1 = H; **IIIg:** R = Br, R_1 = H; **IIIh:** R = H R_1 = CH_3; **IIIi:** R = CN, R_1 = H; **IIIj:** R = H R_1 = NO_2.

Spectral data. **Compound IVa.** IR spectrum, ν, cm^{-1}: 1678 (C=O); 3445 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, $–CH_3$); 6.74 s (1H, Th-H); 7.50–7.53 m (3H, Ar-H); 7.61–7.62 m (2H, Ar-H); 7.80–7.82 d (2H, Ar-H); 7.89–7.90 d (Ar-H); 8.01 s (Ar-H). Found, %: C 69.37, H 4.80, N 9.53, S 10.90. $C_{17}H_{14}ON_2S$. Calculated, %: C 69.36, H 4.79, N 9.52, S 10.89. *M* 295 $[M + H]^+$.

Compound IVb. IR spectrum, ν, cm^{-1}: 1684 (C=O); 3600 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, $–CH_3$); 2.65 s (3H, $–CH_3$), 6.68 s (Th-H); 7.30 d (2H, Ar-H); 7.60 m (2H, Ar-H); 7.69 d (2H, Ar-H); 7.89 m (1H, Ar-H); 7.99 s (Ar-H). Found, %: C 70.13, H 5.25, N 9.11; S 10.42 $C_{18}H_{16}N_2OS$. Calculated, %: C 70.10, H 5.23, N 9.08, S 10.40. *M* 309 $[M + H]^+$.

Compound IVc. IR spectrum, ν, cm^{-1}: 1678 (C=O); 3668 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, $–CH_3$); 3.87 s (3H, $–OCH_3$); 6.61 s (Th-H); 7.02 d (2H, Ar-H); 7.48–7.49 m (2H, Ar-H); 7.76 d (2H, Ar-H); 8.07–8.09 m (2H, Ar-H). Found, %: C 66.65, H 4.98, N 9.65, S 9.89. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.64, H 4.97, N 8.64, S 9.88. *M* 325 $[M + H]^+$.

Compound IVd. IR spectrum, ν, cm^{-1}: 1660 (C=O); 3360 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, $–CH_3$); 6.94 s (Th-H); 7.52–7.58 m (3H, Ar-H); 7.71–7.74 m (2H, Ar-H); 7.83–7.85 m (2H, Ar-H); 8.41 s (Ar-H). Found, %: C 60.18, H 3.87, N 12.39, S 9.46. $C_{17}H_{13}N_3O_3S$. Calculated, %: C 60.17, H 3.86, N 12.38, S 9.45. *M* 340 $[M + H]^+$.

Compound IVe. IR spectrum (KBr), ν, cm^{-1}: 1682 (C=O); 3450 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, $–CH_3$); 6.71 s (Th-H); 7.15–7.18 m (2H, Ar-H); 7.52–7.57 m (2H, Ar-H); 7.67–7.69 m (Ar-H), 7.78–7.82 m (2H, Ar-H); 8.05 s (Ar-H). Found: C 65.39, H 4.20, F, 6.09, N 8.98, S 10.28. $C_{17}H_{13}ON_2FS$. Calculated, %: C 65.37, H 4.19, F, 6.08, N 8.97, S 10.27. *M* 313 $[M + H]^+$.

Compound IVf. IR spectrum, ν, cm^{-1}: 1672 (C=O); 3442 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.64 s (3H, $–CH_3$); 6.79 s (Th-H); 7.40–7.44 d (2H, Ar-H); 7.51–7.56 m (Ar-H); 7.66–7.69 d (Ar-H); 7.75–7.78 m (3H, Ar-H); 8.05 s (Ar-H). Found, %: C 62.12, H 3.99, N 8.53, S 9.76. $C_{17}H_{13}ON_2ClS$. Calculated, %: C 62.10, H 3.98, N 8.52, S 9.75. *M* 329 $[M + H]^+$.

Compound IVg. IR spectrum, ν, cm^{-1}: 1670 (C=O); 3448 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, $–CH_3$); 6.78 s (Th-H); 7.59–7.72 m (6H, Ar-H); 7.88–7.90 d (Ar-H); 8.02 s (Ar-H). Found, %: C 54.71, H 3.52, N 7.51, S 8.60. $C_{17}H_{13}BrN_2OS$. Calculated, %: C 54.70, H 3.51, N 7.50, S 8.59. *M* 373 $[M + H]^+$.

Compound IVh. IR spectrum, ν, cm^{-1}: 1669 (C=O); 3438 (N–H); ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H,

Table 1. Experimental data for the synthesis of 2-(3-acylphenyl)amino-4-phenylthiazole (**IVa–IVj**)

Comp. no.	mp, °C	Reaction time, h	Yield, %
IVa	158	3.0	86
IVb	231	4.0	88
IVc	183	3.0	90
IVd	162	4.0	82
IVe	177	3.0	84
IVf	170	4.0	76
IVg	214	4.0	80
IVh	242	4.5	75
IVi	203	3.5	90
IVj	178	4.0	78

Table 2. Antibacterial data of compounds **IVa–IVj**

Comp. no.	Antibacterial activity zone of inhibition, mm			
	S. aureus	*E.coli*	*B. subtilis*	*K. pnemoniae*
IVa	06	–	06	–
IVb	05	–	07	–
IVc	07	–	–	–
IVd	06	–	08	–
IVe	08	06	07	07
IVf	08	07	08	08
IVg	07	08	08	08
IVh	05	-	06	–
IVi	06	06	07	–
IVj	06	–	–	–
Gentamycine standard	10	11	09	12

–CH_3); 2.62 s (3H, –CH_3); 6.89 s (Th-H); 7.62–7.66 m (3H, Ar-H); 7.81–7.84 m (3H, Ar-H); 8.18 s (Ar-H); 8.25 s (Ar-H). Found, %: C 70.11, H 5.24, N 9.09, S 10.41. $C_{18}H_{16}N_2OS$. Calculated, %: C 70.10, H 5.23, N 9.08, S 10.40. *M* 309 $[M + H]^+$.

Compound IVi. IR spectrum, ν, cm^{-1}: 1667 (C=O); 3441 (N–H). ^1H NMR spectrum, δ, ppm: 2.60 s (3H, –CH_3); 7.09 s (Th-H); 7.46–7.50 m (3H, Ar-H); 7.65–7.86 m (3H, Ar-H); 7.89–8.02 m (2H, Ar-H). Found: C 67.71, H 4.11, N 13.17, S 10.05. $C_{18}H_{13}N_3OS$. Calculated, %: C 67.69, H 4.10, N 13.16, S 10.04. *M* 320 $[M + H]^+$.

Compound IVj. IR spectrum, ν, cm^{-1}: 1679 (C=O); 3455 (N–H). ^1H NMR spectrum, δ, ppm: 2.62 s (3H, –CH_3); 7.02 s (Th-H); 7.54–7.56 d (2H, Ar-H); 7.71–7.73 d (2H, Ar-H); 7.96–8.35 m (4H, Ar-H). Found, %: C 60.18, H 3.87, N 12.39, S 9.46. $C_{17}H_{13}N_3O_3S$. Calculated, %: C 60.17, H 3.86, N 12.38, S 9.45. *M* 340 $[M + H]^+$.

Antibacterial activity. The test organism was a two hour culture of *Escherichia coli, Klebsiella pnemoniae, Staphylococcus aureus* and *Bacillus subtilis* incubated and grown in peptone-water medium at 37°C. DMF was used as a solvent control which did not show any zones of inhibition. Muller-Hilton agar was used as a culture medium. The culture plates were incubated at 37°C for 24 h. The growth inhibition zones around the discs were measured. Each assay was repeated three times.

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