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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2- AMINOTHIAZOLE DERIVATIVES

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ABSTRACT

Novel 2- Aminothiazole derivatives were synthesized by the reaction of 2-aminothiazole (1) with chloroacetylchloride in presence of K_2CO_3 in chloroform afforded 2- chloro- N- (thiazol - 2- yl) acetamide (2). Compound (2) on condensation with substituted phenols in presence of K_2CO_3 in acetone afforded the title compound (3a-g). The chemical structures of the synthesized compounds were elucidated on the basis of IR, ^{1}H NMR data. The synthesized compounds were screened for antibacterial and antifungal activity among them the compound 3c and 3d have shown significant inhibition of bacterial and fungal growth.

INTRODUCTION: The major classes of almost all antibiotics are encountering resistance in clinical applications [1, 2]. In order to overcome this rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. Various heterocyclic nucleus acts as highly functionalized scaffold and used in biologically active molecules [3].

The heterocyclic 2- aminothiazole has attracted widespread attention due to their diverse biological activities, including antibacterial, antifungal activity [4, 5, 6]. In view of these observations, we herein report the synthesis of some novel 2- aminothiazole derivatives and evaluate their antimicrobial and antifungal activity.

EXPERIMENTAL: Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide discs on Schimadzu FTIR Spectrophotometer 8300. The ^{1}H-NMR spectra of the synthesized compounds were recorded in DMSO-d_6 using AV-300 BROKE JEOL Spectrophotometer and tetramethylsilane (TMS) as an internal standard. The signals are quoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet and are expressed in δ ppm. All reagents were of commercial quality and were used without further purification. The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized with iodine (Scheme 1).

CHEMISTRY:

Synthesis of 2- Chloro- N - (thiazole - 2- yl) acetamide (2): Equimolar amounts of 2-aminothiazole **1** (0.05 mole), chloroacetylchloride (0.05 mole) and K_2CO_3 (0.05 mole) in chloroform was refluxed for about 10 h. The mixture was filtered and solvent was washed with excess of water .The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by crystallization from ethanol to afford compound **(2)**. Yield: 48.0 %, melting point- 150-152 ^{0}C, IR (KBr) ν (cm^{-1}): 3234, 2925, 1625, 1414, 1266, 1163, 750; ^{1}H NMR (300 MHz, DMSO-d6, δ ppm): 8.48 (1H, CONH), 6.63 & 7.49 (2H, CH in thiazole), 4.36 (2H, CH_2).

General procedure for the Synthesis of 2- (substituted phenoxy) - N- (thiazol- 2 - yl) acetamide (3a- g): Equimolar amounts of substituted phenol and K_2CO_3 in dry acetone were refluxed for 2-3 h, then the compound **(2)** in dry acetone was added and reaction mixture was refluxed on water bath with continuous stirring for18-20 hr. After cooling, the reaction mixture was filtered and solvent was removed under reduced pressure. Resulting residue was washed with water and recrystallized from ethanol.

2- (Phenoxy)- N- (thiazol- 2- yl) acetamide (3a): Yield: 45.2%; melting point- 64-66 °C; IR (KBr) ν (cm^{-1}): 3233, 3003, 2925, 2856, 1628, 1489, 1397, 1262, 1153, 1079; ^{1}H NMR (DMSO-d6, δ ppm): 8.32 (1H, CONH), 6.63 & 7.49 (2H, CH in thiazole), 6.81-7.24 (5H, Ar),4.32 (2H, CH_2).

2- (4- Bromophenoxy)- N- (thiazol- 2- yl) acetamide (3b): Yield: 53%; melting point- 62-64 °C; IR (KBr) ν (cm^{-1}): 3233, 3001, 2927, 2856, 1625, 1489, 1397, 1262, 1155, 1077; ^{1}H NMR (DMSO-d6, δ ppm): 8.32 (1H, CONH), 6.62 & 7.48 (2H, CH in thiazole), 6.81-7.84 (4H, Ar),4.32 (2H, CH_2).

2- (4- Chlorophenoxy)- N- (thiazol- 2- yl) acetamide (3c): Yield: 53%; melting point- 92-94 °C; IR (KBr) ν (cm^{-1}): 3230, 3003, 2928, 2854, 1625, 1487, 1397, 1262, 1150, 1072, 771; ^{1}H NMR (DMSO-d6, δ ppm): 8.31 (1H, CONH), 6.60 & 7.49 (2H, CH in thiazole), 6.69-7.43 (4H, Ar), 4.30 (2H, CH_2).

2- (2, 4- Dichlorophenoxy)- N- (thiazol- 2- yl) acetamide (3d): Yield: 47%; melting point- 68-70 °C; IR (KBr) ν (cm^{-1}): 3235, 3002, 2926, 2850, 1628, 1484, 1395, 1262, 1153,1075,7 71; ^{1}H NMR (DMSO-d6, δ ppm): 8.30 (1H, CONH), 6.63 & 7.34 (2H, CH in thiazole), 6.99-7.94 (3H, Ar), 4.32 (2H, CH_2).

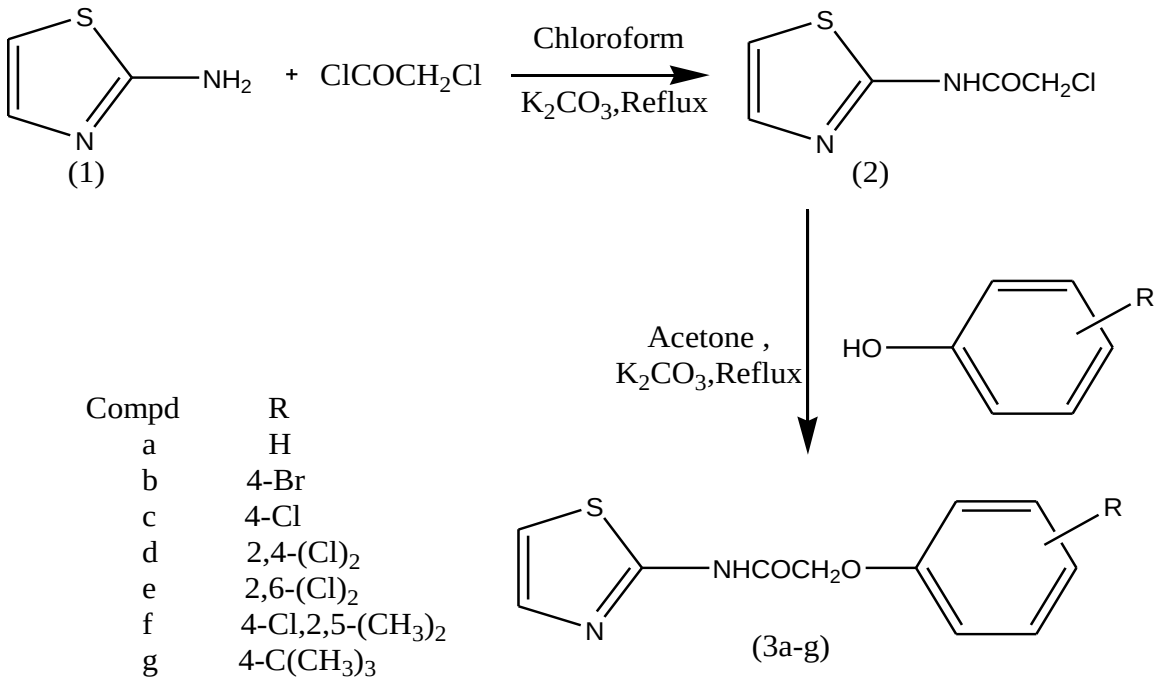
2- (2, 6- Dichlorophenoxy)- N- (thiazol- 2- yl) acetamide (3e): Yield: 51%; melting point- 78-80 °C; IR (KBr) ν (cm^{-1}): 3237, 3007, 2926, 2850, 1633, 1480, 1392, 1262, 1151, 1075, 775; ^{1}H NMR (DMSO-d6, δ ppm): 8.31(1H, CONH), 6.67 & 7.39 (2H, CH in thiazole), 6.99-7.97 (3H, Ar), 4.32 (2H, CH_2).

2- (4- Chloro- 3, 5- dimethylphenoxy)- N- (thiazol- 2- yl) acetamide (3f): Yield: 48%; melting point- 118-120 °C; IR (KBr) ν (cm^{-1}): 3233, 3003, 2923, 2857, 1628, 1484, 1390, 1260, 1151, 1072, 775; ^{1}H NMR (DMSO- d6, δ ppm): 8.31 (1H, CONH), 6.67 & 7.38 (2H, CH in thiazole), 6.94-7.97 (2H, Ar), 4.32(2H, CH_2), 2.48-2.79, (6H, CH_3).

2- (4- Tertbutylphenoxy)- N- (thiazol- 2- yl) acetamide (3g): Yield: 52%; melting point- 88-90 °C; IR (KBr) ν (cm^{-1}): 3237, 3005, 2921, 2859, 1633, 1481, 1390, 1263, 1165, 1070 ; ^{1}H NMR (DMSO-d6, δ ppm): 8.30 (1H, CONH), 6.67 & 7.38 (2H, CH in thiazole), 6.58-7.90 (4H, Ar), 4.31 (2H, CH_2), 1.53 (9H, CH_3).

Antimicrobial Activity: The cup diffusion technique was employed to study the antibacterial and antifungal activity of synthesized compounds (3a-g) against *B. subtilis* (NCIM 2439), *E. coli* (NCIM 2831), *A. niger* (NCIM 618) *and C. albican* (NCIM 3557) [7, 8]. The synthesized compounds, as 1 mg/ml solutions in dimethylformamide (DMF), were prepared. Compounds showing inhibitory zones of at least 18 mm were considered active. Ampicillin was used as a standard antibacterial agent and fluconazole was used as a standard antifungal agent.

Dimethylformamide was used as a control. Sterile nutrient agar was inoculated with the test organisms (each 100 mL of the medium received 1 mL of 24 h broth culture), and then seeded agar was poured into sterile petri dishes. Cups (8 mm in diameter) were cut in the agar, and each cup received 0.1 mL of the test compound solution. The plates were then incubated at 37 ^{o}C for 24 hr. The activities were estimated as zones of inhibition in mm diameter (Table 1).



SCHEME 1

TABLE 1: ZONE OF INHIBITION (IN MM) AGAINST THE MICROBES BY THE COMPOUNDS (3A-G)

COMPOUND	ANTIBACTERIAL ACTIVITY		ANTIFUNGAL ACTIVITY	
	B. SUBTILIS	*E. COLI*	*A. NIGER*	*C. ALBICANS*
3a	16	16	15	14
3b	15	17	17	16
3c	18	17	20	19
3d	18	19	18	17
3e	17	15	15	15
3f	14	15	14	15
3g	15	17	14	14
Ampicillin	25	25		
Fluconazole			25	25

RESULTS, DISCUSSION AND CONCLUSION: The target compounds (3a-g) were prepared as outlined in Scheme 1. The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of spectral data. The synthesized compounds were tested for activity against *B. subtilis*, *E. coli, A. niger* and *C. albicans.* The results of antimicrobial activity are shown in table 1. It is evident from the results that the compound 3c was possessed potent antifungal activity and 3d possessed potent antibacterial activity. Rest of the synthesized compounds were inactive to kill the target organisms.

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