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SYNTHESIS AND ANTIMICROBIAL PROFILE OF SOME NEWER HETEROCYCLES BEARING THIAZOLE MOIETY

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ABSTRACT

Various substituted acetophenones on treatment with iodine and thiourea yielded 2-amino-4-(substituted-phenyl)-thiazole, which on further treatment with acetic anhydride generated *N*-(4-(substitutedphenyl)thiazol-2-yl)acetamide (1-5). All the synthesized compounds were characterized by their respective FTIR, ^{1}H NMR and mass data. Synthesized compounds (1, 2, 3, 4, 5) when subjected to investigation for their antimicrobial activities i.e. antibacterial and antifungal studies against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Asperigillus flavus and Asperigillus fumigatus* by disk diffusion method, revealed that compound 2 deemed to be most potent with largest zone of inhibition.

KEYWORDS: Thiazole, Acetophenones, Antimicrobial, Substituted Aldehydes.

RESUMO

Tratamento de acetofenonas substituídas com iodo e tiouréia levou a formação de vários 2-amino tiazóis -4- (fenilsubstituidos) . O tratamento destes com anihidrido acético gerou N-(4-fenilsubstituido)tiazol-2-il) acetamidas (1-5). Todos os compostos sintetizados foram caracterizados com técnicas de infravermelho com transformadas de Fourier, RMN de ^{1}H e espectrometria de massa. .As propriedades frmacêuticas dos compostos 1,2,3,4 e 5 foram avaliadas com *Staphylococcus aureus, Eschericia coli, Pseudomonas aeruginosa, Cândida albicans. Aspergillus flavus e Aspergillus fumigatus.* O composto 2 foi o mais potente.

PALAVRAS CHAVE: Tiazol, Acetofenonas, Aldeídos Substituídos, Atividade Antimicrobiana.

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INTRODUCTION

Thiazole derivatives have attracted a great deal of interest owing to their anticancer activity[1-3], antibacterial activity[4], antifungal activity[4], anti-inflammatory activity[4], antitubercular activity[5], cardiotonic activity[6], antidegenerative activity on cartilage[7] etc. Thiazoles are known to be allosteric enhancer of A_1 adenosine receptors[8] whereas other analogs are known to be inhibitors of protein phosphatases[9]. Heterocycle-bearing substrates are particularly desirable structures for screening and are prevalent in drugs that have reached the market place.

The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic chemistry. Therefore to meet the facile results of these tough challenges thiazole nucleus was being considered. Among the wide variety of heterocycles that have been explored for developing pharmaceutically molecules, thiazole derivatives have played a vital role in the medicinal chemistry. There are large numbers of synthetic compounds with thiazole nucleus used for anticancer activities when properly substituted at 2-position. In view of these observations and in continuation to develop better and potent anticancer agents, some newer thiazole derivatives were synthesized.

MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. IR spectrum of compounds in KBr pellets were recorded on a FTIR-8400S spectrophotometer (SHIMADZU). ^{1}HNMR spectra of the compounds were recorded on Bruker DRX 300 NMR spectrophotometer in DMSO-d_6 using TMS as internal standard. Mass spectra of the compounds were recorded on MSN-9629 mass spectrometer. Elemental analysis was carried out on Elemental Vario EL III Carlo Erba 1108. The purity of compounds was monitored by thin layer chromatography. Thin layer chromatographic analysis of the compounds were performed on silica gel G coated glass plates using Chloroform: Methanol: Pet.Ether (9:1:0.5) as mobile phase. The spots were visualized by exposure to iodine vapours.

General method for the synthesis of 2-amino-4-(substituted-phenyl)-thiazole

Various substituted acetophenones (0.01mol) were refluxed with iodine (0.01mol) and thiourea (0.02mol) for 9 hrs to get 2-amino-4-(substituted-phenyl)thiazole. The solid obtained was washed with diethyl ether, after which it was washed with sodium thiosulfate. Finally, it was washed with water and the residue was filtered, dried and recrystallized from distilled water.

General method for the synthesis of (1-5)

Then, 2-amino-4-(substituted-phenyl)thiazole (0.01mol) was refluxed with acetic anhydride (0.01mol) for 2hrs. This led to the formation of N-(4-(substituted-phenyl)thiazol-2-yl)acetamide (1-5). The final products were purified by recrystallization from ethanol. Physical data of compounds synthesized are summarized in Table-1.

Table-1. Physical data of compounds (1-5)

Compound	R	Molecular Formula	Mol. Wt.	Yield (%)	m.p. (°C)
1	H	$C_{11}H_{10}N_2OS$	218.27	61	98-99
2	*p*-chloro	$C_{11}H_9ClN_2OS$	252.72	69	209-210
3	*p*-bromo	$C_{11}H_9BrN_2OS$	297.17	65	202-203
4	*p*-hydroxy	$C_{11}H_{10}N_2O_2S$	234.27	65	141-142
5	*o*-hydroxy	$C_{11}H_{10}N_2O_2S$	234.27	70	115-116

***N*-(4-phenylthiazol-2-yl)acetamide (1):** UV λ_{max} (Methanol): 232 nm. FTIR (KBr): 3392.55 (N-H stretching), 2977.89 (aromatic C-H stretching), 2931.6 (C-H stretching of methyl), 1622.02 (C=O stretching), 1569.95 (C=N stretching), 1498.59 (aromatic C-C stretching), 690.47 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 2.142 (s, 3H, CH_3), 7.117 (s, 1H, =C-H of thiazole), 7.273-7.854 (m, 5H, Ar-H), 8.854 ppm (s, 1H, NH, D_2O exchangeable). ESI-MS: m/z (%) 219 (8) $[M+1]^+$, 218 (43) $[M]^+$, 203 (40), 175 (100), 134 (43), 133 (23). Elemental Analysis: Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.50; H, 4.63; N, 12.81; S, 14.68 %.

***N*-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (2):** UV λ_{max} (Methanol): 224 nm. FTIR (KBr): 3394.48 (N-H stretching), 2981.74 (aromatic C-H stretching), 2947.03 (C-H stretching of methyl), 1623.95 (C=O stretching), 1564.16 (C=N stretching), 1492.8 (aromatic C-C stretching), 746.4 (C-Cl stretching), 651.03 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ : 2.466 (s, 3H, CH_3), 6.545 (s, 1H, =C-H of thiazole), 7.116-7.625 (m, 4H, Ar-H), 9.154 ppm (s, 1H, NH, D_2O exchangeable). ESI-MS: m/z (%) 254 (17) $[M+2]^+$, 253 (6) $[M+1]^+$, 252 (46) $[M]^+$, 237 (32), 209 (100), 168 (42), 167 (22). Elemental Analysis: Calcd for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; Cl, 14.03; N, 11.08; S, 12.69. Found: C, 52.27; H, 3.57; Cl, 14.02; N, 11.06; S, 12.71 %.

***N*-(4-(4-bromophenyl)thiazol-2-yl)acetamide (3):** UV λ_{max} (Methanol): 225 nm. FTIR (KBr): 3417.63 (N-H stretching), 3029.33 (aromatic C-H stretching), 2993.32 (C-H stretching of methyl), 1672.17 (C=O stretching), 1598.88 (C=N stretching), 1488.94 (aromatic C-C stretching), 693.26 (C-S stretching of thiazole), 570.89 cm^{-1} (C-Br stretching). ^{1}HNMR (DMSO-d_6) δ : 2.763 (s, 3H, CH_3), 6.967 (s, 1H, =C-H of thiazole), 7.317-7.825 (m, 4H, Ar-H), 8.778 ppm (s, 1H, NH, D_2O exchangeable). ESI-MS: m/z (%) 299 (43) $[M+2]^+$, 298 (8) $[M+1]^+$, 297 (42) $[M]^+$, 282 (40), 254 (100), 213 (32), 212 (27). Elemental Analysis: Calcd for $C_{11}H_9BrN_2OS$: C, 44.46; H, 3.05; Br, 26.89; N, 9.43; S, 10.79. Found: C, 44.45; H, 3.01; Br, 26.87; N, 9.46; S, 10.80 %.

***N*-(4-(4-hydroxyphenyl)thiazol-2-yl)acetamide (4):** UV λ_{max} (Methanol): 242 nm. FTIR (KBr): 3558.42 (O-H stretching), 3406.05 (N-H stretching), 3048.29 (aromatic C-H stretching), 2923.88 (C-H stretching of methyl), 1631.67 (C=O stretching), 1554.52 (C=N

stretching), 1526.93 (aromatic C-C stretching), 675.04 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 2.228 (s, 3H, CH_3), 4.955 (s, 1H, OH, D_2O exchangeable), 6.369 (s, 1H, =C-H of thiazole), 7.296-7.658 (m, 4H, Ar-H), 8.564 ppm (s, 1H, NH, D_2O exchangeable). ESI-MS: m/z (%) 235 (6) $[M+1]^+$, 234 (28) $[M]^+$, 219 (22), 191 (100), 150 (20), 149 (14). Elemental Analysis: Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.40; H, 4.33; N, 11.98; S, 13.65 %.

***N*-(4-(2-hydroxyphenyl)thiazol-2-yl)acetamide (5):** UV λ_{max} (Methanol): 267 nm. FTIR (KBr): 3555.6 (O-H stretching), 3408.42 (N-H stretching), 3046.05 (aromatic C-H stretching), 2926.05 (C-H stretching of methyl), 1633.88 (C=O stretching), 1554.07 (C=N stretching), 1523.96 (aromatic C-C stretching), 1291.67 (C-O stretching), 673.68 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 2.156 (s, 3H, CH_3), 4.702 (s, 1H, OH, D_2O exchangeable), 6.911 (s, 1H, =C-H of thiazole), 7.316-7.625 (m, 4H, Ar-H), 8.778 ppm (s, 1H, NH, D_2O exchangeable). ESI-MS: m/z (%) 235 (6) $[M+1]^+$, 234 (28) $[M]^+$, 219 (22), 191 (100), 150 (20), 149 (14). Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.37; H, 4.33; N, 11.98; S, 13.67 %.

Antimicrobial activity

The synthesized compounds 1-5 were screened for antibacterial (*S. aureus, E. coli, P. aeruginosa*) and antifungal (*C. albicans, A. flavus, A. fumigatus*) activities by disk diffusion method at a concentration of 2 mg/mL using DMF as a solvent. The results were recorded in duplicate using Ciprofloxacin and Fluconazole as standards and are given in Table 2 & 3.

Table-2: Antibacterial Activity of compounds (1-5)

Compounds	Zone of Inhibition (mm)		
	S. aureus	*E. coli*	*P. aeruginosa*
1.	15.5 ± 0.00	17 ± 0.33	16 ± 0.00
2.	21.5 ± 0.33	20.5 ± 0.00	19.3 ± 0.00
3.	19.7 ± 0.67	20.3 ± 0.33	20.3 ± 0.33
4.	16.4 ± 0.00	15 ± 0.00	15.5 ± 0.00
5.	17.3 ± 0.00	17 ± 0.33	17 ± 0.67
Ciprofloxacin	27 ± 0.00	28 ± 0.00	27 ± 0.00
DMF	-	-	-

Table 3. Antifungal Activity of Compounds (1-5)

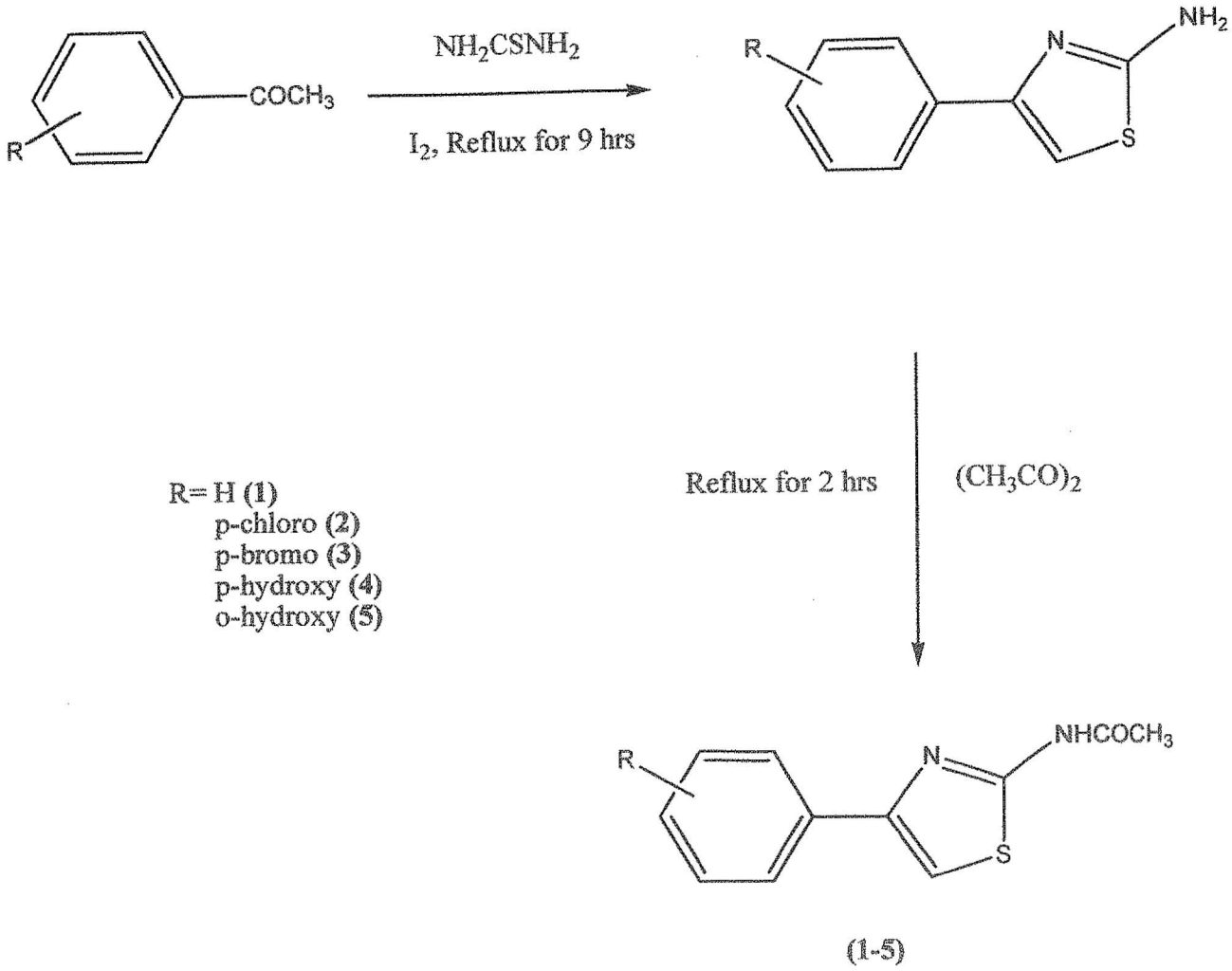
Compounds	Zone of Inhibition (mm)		
	C. albicans	*A. flavus*	*A. fumigatus*
1.	5.4 ± 0.00	5.0 ± 0.00	6.5 ± 0.00
2.	11.3 ± 0.33	12.5 ± 0.00	11 ± 0.00
3.	10.7 ± 0.67	9.3 ± 0.33	8.3 ± 0.33
4.	8.2 ± 0.00	7.4 ± 0.00	8.0 ± 0.00
5.	8.3 ± 0.00	7.8 ± 0.00	8.7 ± 0.67
Fluconazole	17 ± 0.00	16 ± 0.00	17 ± 0.00
DMF	-	-	-

RESULTS AND DISCUSSION

Various substituted acetophenones reacted with iodine and thiourea to get 2-Amino-4-(substituted-phenyl)-thiazole[10]. Nextly, the 2-amino group of 2-Amino-4-(substituted-phenyl)-thiazole was acetylated with acetic anhydride, which led to the formation of *N*-(4-(substitutedphenyl)thiazol-2-yl)acetamide (**1-5**) in moderate to good yields (Scheme-1). The FTIR spectra of compounds **1-5** exhibited bands in the region of 3344.12-3417.23 cm^{-1} due to N-H stretching and in the region 1622.02-1672.46 cm^{-1} due to C=O stretching of amide. In ^1H NMR spectra of compounds **1-5**, one proton singlet appeared between δ 8.85-9.15 ppm was assigned to N-H proton which disappeared on D_2O exchange.

The structures of the synthesized compounds were assigned on the basis of elemental analysis, ^1H NMR, FTIR and mass spectral data and physical data. The synthesized compounds 1-5 were screened for antibacterial (*S. aureus, E. coli, P. aeruginosa*) and antifungal (*C. albicans, A. flavus, A. fumigatus*) activities by disk diffusion method at a concentration of 2 mg/mL using DMF as a solvent. This revealed that compound **2** deemed to be most potent with the largest zone of inhibition for both i.e. antibacterial activity and antifungal Activity.

SCHEME 1:



(1-5)

Where R = H, *p*-chloro, *p*-bromo, *p*-hydroxy and *o*-hydroxy- group

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