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Original article

SYNTHESIS AND ANTIMICROBIAL PROFILE OF SOME NEWER 2-AMINO-THIAZOLE DERIVATIVES

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Abstract

Various substituted acetophenones (1-4) on treatment with iodine and thiourea yielded 2-amino-4-(substituted-phenyl)-thiazole (1a-4a), which on further treatment with acetic anhydride generated N-(4-(substitutedphenyl)thiazol-2-yl)acetamide (1b-4b). In another scheme, 3-(2-Aminothiazol-4-yl)phenol (1a) reacted with various substituted aldehydes to get N-(substitutedbenzylidene)-4-(substitutedphenyl)thiazol-2-amine (1c-4c). All the synthesized compounds were characterized by their respective FTIR, ^{1}H NMR, Mass data and Elemental Analysis. Synthesized compounds (1b-4b, and 1c-4c) were 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. In Scheme-1, compound 4b was found to be most effective with the largest zone of inhibition while in Scheme-2, compound 3c was found to be most effective against Staphylococcus aureus, Escherichia coli, Asperigillus flavus and Asperigillus fumigates. Compound 1c was found to be most effective against Pseudomonas aeruginosa while Compounds 1c and 3c both were found to be equally most effective against Candida albicans.

Key words: *Thiazole, Acetophenones, Antibacterial, Antifungal, Substituted aldehydes, Zone of inhibition.*

Bazı Yeni 2-amino-tiazol Türevlerinin Sentezi ve Mikrobiyal Profilleri

Çeşitli substitüte asetofenonlar (1-4) iyot ve tiyoüre ile muamele edildiğinde 2-amino-4-(substituted-phenyl)-thiazole (1a-4a) ve sonrasında acetik anhidrid ile muamele edildiklerinde N-(4-(substitutedphenyl)thiazole-2-yl)acetamide (1b-4b) oluşmaktadır. Başka bir şemada, 3-(2-Aminothiazol-4-yl)phenol (1a) çeşitli sübstitüe aldehitlerle reaksiyona girmekte ve N-(substitutedbenzylidene)-4-(substitutedphenyl)thiazol-2-amine (1c-4c) bileşiğini vermektedir. Tüm sentezlenen bileşikler FTIR, 1H NMR, kütle verileri ve elementel analiz ile karakterize edilmiştir. Sentezlenen bileşiklerin (1b-4b, and 1c-4c) antimikrobiyal aktiviteleri, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Asperigillus flavus and Asperigillus fumigates üzerinde antibakteriyal ve antifungal etkileri disk difüzyon yöntemi ile araştırılmıştır. Birinci şemada, 4b bileşiği en geniş inhibisyon alanı ile en etkili, İkinci şemada ise 3c bileşiği Staphylococcus aureus, Escherichia coli, Asperigillus flavus ve Asperigillus fumigates'e karşı en etkili bileşik olarak tespit edilmiştir. 1c bileşiği Pseudomonas aeruginosa üzerinde en etkili bileşik iken 1c ve 3c nin her ikiside Candida albicans üzerinde eşit derecede en yüksek etkili bileşikler olarak tespit edilmiştir.

Anahtar kelimeler: *Tiazol, Asetofenonlar, Antibakteriyal, Antifungal, Sübstitüe aldehitler, İnhibisyon alanı*

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INTRODUCTION

Thiazole derivatives have attracted a great deal of interest owing to their anticancer (1-3), antibacterial (4,5), antifungal (4,5), anti-inflammatory (4), antitubercular (6), cardiotonic (7) and antidegenerative activity on cartilage (8) etc. Thiazoles are known to be allosteric enhancer of A_1 adenosine receptors (9) whereas other analogs are known to be inhibitors of protein phosphatases (10). Azoles are particularly desirable structures for screening and are prevalent in drugs that have reached the market place. Azoles have prominent antimicrobial activities (11-13).

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 antimicrobial activities when properly substituted at 2-position. In view of these observations and in continuation to develop better and potent antimicrobial agents, some newer thiazole derivatives were synthesized.

EXPERIMENTAL

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. All the necessary solvents and chemicals used in the present research work were procured from the Qualigens Ltd., Merck India Pvt. Ltd (India), Loba Chemicals Ltd, Sigma-Aldrich and S d fine chem Limited.

General method for the synthesis of (1a-4a)

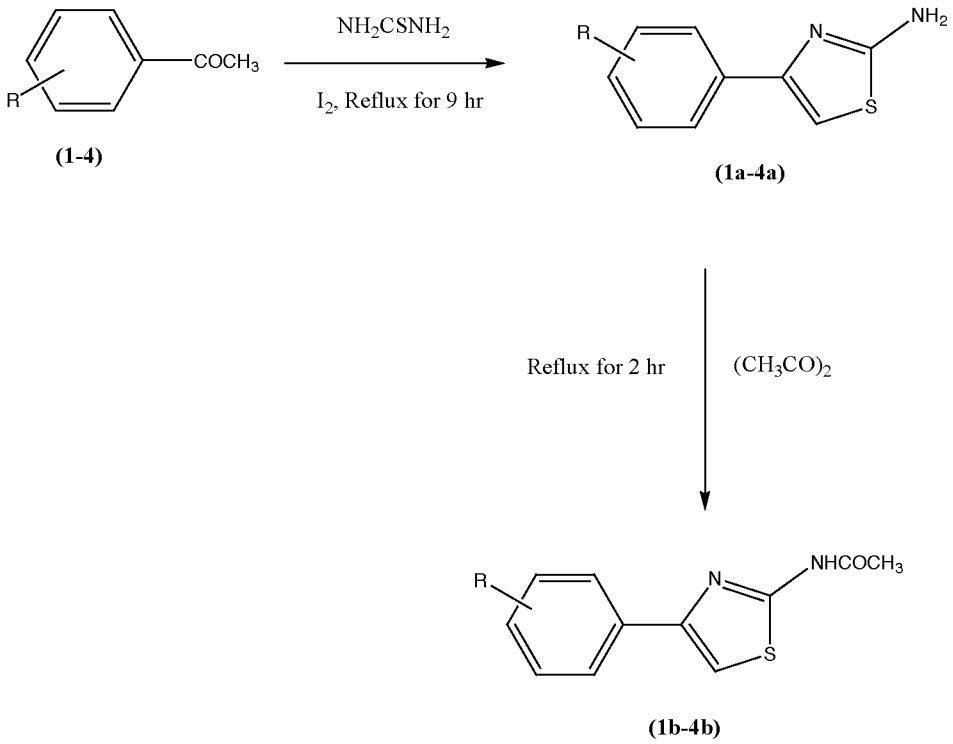
Various substituted acetophenones (1-4) (0.01mol) were refluxed with iodine (0.01mol) and thiourea (0.02mol) for 9 hrs to get 2-amino-4-(substituted-phenyl)thiazole **(1a-4a)**. The solid obtained was washed with diethyl ether, after which it was washed with sodium thiosulfate. Finally, it was washed with water and the residue was filtered, dried and recrystallized from distilled water.

General method for the synthesis of (1b-4b)

Then, 2-amino-4-(substituted-phenyl)thiazole **(1a-4a)** (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 **(1b-4b)**. 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 (1b-4b)

Compound	R	Molecular formula	Molecular weight	Yield (%)	m.p. (°C)
1b	*m*-hydroxy	$C_{11}H_{10}N_2O_2S$	234.27	68.58	133-134
2b	*m*-chloro	$C_{11}H_9ClN_2OS$	252.72	62.24	212-213
3b	*o*-chloro	$C_{11}H_9ClN_2OS$	252.72	61.27	214-215
4b	*m*-bromo	$C_{11}H_9BrN_2OS$	297.17	67.56	218-219



Scheme 1. Where R = *m*-hydroxy, *m*-chloro, *o*-chloro and *m*-bromo group

N-(4-(3-hydroxyphenyl)thiazol-2-yl)acetamide (1b): FTIR (KBr): 3576.55 (O-H stretching), 3344.12 (N-H stretching), 3039.42 (aromatic C-H stretching), 2918.17 (C-H stretching of methyl), 1618.32 (C=O stretching), 1577.32 (C=N stretching), 1479.13 (aromatic C-C stretching), 1321.42 (C-O stretching), 1271.28 (C-N stretching), 681.2 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 2.48 (s, 3H, CH_3), 4.69 (s, 1H, OH), 6.85 (s, 1H, =C-H of thiazole), 7.24-7.66 (m, 4H, Ar-H), 8.39 ppm (s, 1H, NH). ESI-MS: m/z (%) 234 $[M]^+$, 219, 191 (base peak), 150, 149. Elemental Analysis: % C, H, N (Cal.) Found: C (56.39) 56.38; H (4.30) 4.34; N (11.96) 11.94.

N-(4-(3-chlorophenyl)thiazol-2-yl)acetamide (2b): FTIR (KBr): 3391.41 (N-H stretching), 2988.53 (aromatic C-H stretching), 2952.28 (C-H stretching of methyl), 1634.91 (C=O stretching), 1574.98 (C=N stretching), 1482.83 (aromatic C-C stretching), 1315.85 (C-N stretching), 740.43 (C-Cl stretching), 650.43 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 2.46 (s, 3H, CH_3), 6.54 (s, 1H, =C-H of thiazole), 7.11-7.62 (m, 4H, Ar-H), 9.15 ppm (s,

1H, NH). ESI-MS: m/z (%) 254 $[M+2]^+$, 252 $[M]^+$, 237, 209 (base peak), 168, 167, 41. Elemental Analysis: % C, H, N (Cal.) Found: C (52.28) 52.25; H (3.59) 3.57; N (11.08) 11.06.

N-(4-(2-chlorophenyl)thiazol-2-yl)acetamide (3b): FTIR (KBr): 3393.34 (N-H stretching), 2981.23 (aromatic C-H stretching), 2962.29 (C-H stretching of methyl), 1638.91 (C=O stretching), 1579.18 (C=N stretching), 1477.67 (aromatic C-C stretching), 1313.26 (C-N stretching), 741.43 (C-Cl stretching), 652.67 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 2.45 (s, 3H, CH_3), 6.55 (s, 1H, =C-H of thiazole), 7.12-7.64 (m, 4H, Ar-H), 9.16 ppm (s, 1H, NH). ESI-MS: m/z (%)254 $[M+2]^+$, 252 $[M]^+$, 237, 209 (base peak), 168, 167, 41. Elemental Analysis: % C, H, N (Cal.) Found: C (52.28) 52.24; H (3.59) 3.57; N (11.08) 11.07.

N-(4-(3-bromophenyl)thiazol-2-yl)acetamide (4b): FTIR (KBr): 3419.63 (N-H stretching), 3021.73 (aromatic C-H stretching), 2991.76 (C-H stretching of methyl), 1674.56 (C=O stretching), 1599.18 (C=N stretching), 1481.91 (aromatic C-C stretching), 1321.91 (C-N stretching), 692.26 (C-S stretching of thiazole), 578.34 cm^{-1} (C-Br stretching). ^{1}HNMR (DMSO-d_6) δ: 2.76 (s, 3H, CH_3), 6.95 (s, 1H, =C-H of thiazole), 7.37-7.82 (m, 4H, Ar-H), 8.71 ppm (s, 1H, NH). ESI-MS: m/z (%) 299 $[M+2]^+$, 297 $[M]^+$, 282, 254 (base peak), 213, 212. Elemental Analysis: % C, H, N (Cal.) Found: C (44.46) 44.44; H (3.05) 3.04; N (9.43) 9.41.

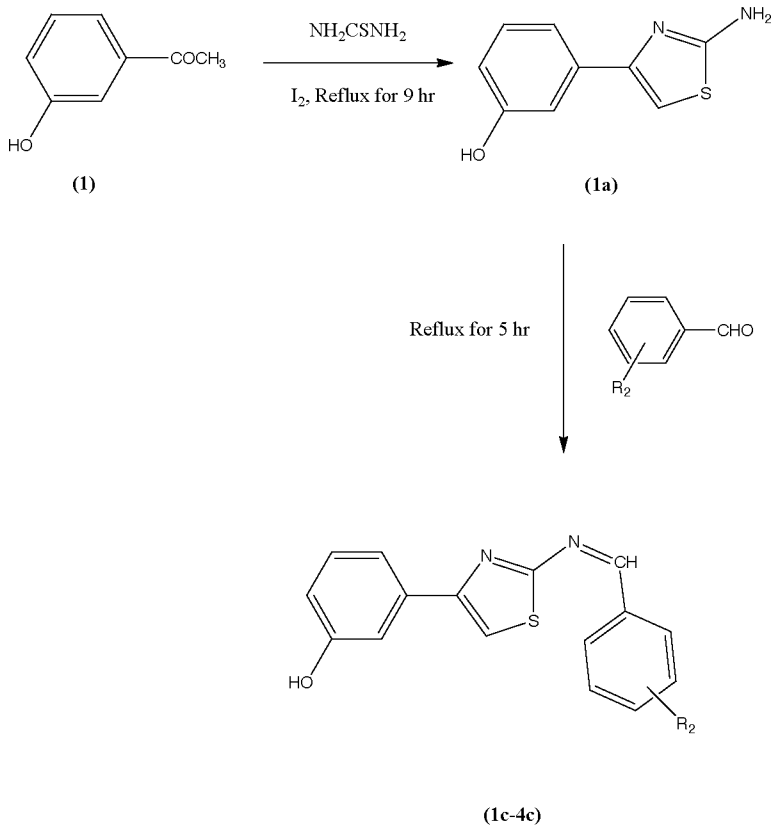
General method for the synthesis of (1c-4c)

3-(2-Aminothiazol-4-yl)phenol **(1a)** (0.01mol) was refluxed with various substituted aromatic aldehydes **(5-8)** (0.01mol) in ethanol along with glacial acetic acid (2-3 drops) for 5 hrs to get N-(substituted-benzylidene)-4-(substituted-phenyl)thiazol-2-amine (**1c-4c**). The final products were purified by recrystallization from water : DMF (1 : 1). Physical data of compounds synthesized are summarized in Table-2.

Table 2. Physical data of compounds (1c-4c)

Compound	R_2	Molecular formula	Molecular weight	Yield (%)	m.p. (°C)
1c	*o*-chloro	$C_{16}H_{11}ClN_2OS$	314.79	61.34	145-146
2c	*m*-hydroxy	$C_{16}H_{12}N_2O_2S$	296.34	65.38	118-119
3c	*m*-chloro	$C_{16}H_{11}ClN_2OS$	314.79	71.48	144-145
4c	*p*-hydroxy	$C_{16}H_{12}N_2O_2S$	296.34	63.75	133-134

3-(-2-(2-chlorobenzylideneamino)thiazol-4-yl)phenol (1c): FTIR (KBr): 3650.25 (O-H stretching), 3048.54 (aromatic C-H stretching), 2970.43 (C-H stretching of N=C-H), 1644.35 (C=N stretching), 1574.67 (aromatic C-C stretching), 1339.87 (C-O stretching), 1278.26 (C-N stretching), 838.24 (C-Cl stretching), 677.28 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 4.48 (s, 1H, OH), 6.10 (s, 1H, =C-H of thiazole), 6.32-7.72 (m, 8H, Ar-H), 8.45 ppm (s, 1H, N=C-H). ESI-MS: m/z (%) 316 $[M+2]^+$, 314 $[M]^+$, 203 (base peak), 150, 149, 138, 112, 77. Elemental Analysis: % C, H, N (Cal.) Found: C (61.05) 61.01; H (3.52) 3.55; N (8.90) 8.86.



Scheme 2. Where R_2 = *o*-chloro, *m*-hydroxy, *m*-chloro and *p*-hydroxy group.

3-(-2-(3-hydroxybenzylideneamino)thiazol-4-yl)phenol (2c): FTIR (KBr): 3666.65 (O-H stretching), 3055.46 (aromatic C-H stretching), 2968.33 (C-H stretching of N=C-H), 1642.12 (C=N stretching), 1576.24 (aromatic C-C stretching), 1338.88 (C-O stretching), 1264.18 (C-N stretching), 676.26 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 4.85 (s, 2H, OH), 6.10 (s, 1H, =C-H of thiazole), 6.36-7.85 (m, 8H, Ar-H), 8.30 ppm (s, 1H, N=C-H). ESI-MS: m/z (%) 296 $[M]^+$, 203 (base peak), 150, 149, 120, 106, 65. Elemental Analysis: % C, H, N (Cal.) Found: C (64.85) 64.87; H (4.08) 4.13; N (9.45) 9.42.

3-(-2-(3-chlorobenzylideneamino)thiazol-4-yl)phenol (3c): FTIR (KBr): 3661.66 (O-H stretching), 3062.43 (aromatic C-H stretching), 2958.48 (C-H stretching of N=C-H), 1632.28 (C=N stretching), 1572.58 (aromatic C-C stretching), 1330.21 (C-O stretching), 1286.24 (C-N stretching), 835.88 (C-Cl stretching), 673.24 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 4.48 (s, 1H, OH), 6.16 (s, 1H, =C-H of thiazole), 6.36-7.72 (m, 8H, Ar-H), 8.46 ppm (s, 1H, N=C-H). ESI-MS: m/z (%) 316 $[M+2]^+$, 314 $[M]^+$, 203 (base peak), 150, 149, 138, 112, 77. Elemental Analysis: % C, H, N (Cal.) Found: C (61.05) 61.03; H (3.52) 3.58; N (8.90) 8.84.

3-(2-(4-Hydroxybenzylideneamino)thiazol-4-yl)phenol (4c): FTIR (KBr): 3637.55 (O-H stretching), 3047.32 (aromatic C-H stretching), 2918.1 (C-H stretching of N=C-H), 1612.38 (C=N stretching), 1579.59 (aromatic C-C stretching), 1323.08 (C-O stretching), 1276.79 (C-N stretching), 680.19 cm^{-1} (C-S stretching of thiazole). ^{1}HNMR (DMSO-d_6) δ: 4.85 (s, 2H, OH), 6.14 (s, 1H, =C-H of thiazole), 6.36-7.85 (m, 8H, Ar-H), 8.34 ppm (s, 1H, N=C-H). ESI-MS: m/z (%) 296 $[M]^+$, 203 (base peak), 150, 149, 120, 106, 65. Elemental Analysis: % C, H, N (Cal.) Found: C (64.85) 64.87; H (4.08) 4.11; N (9.45) 9.47.

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. All the test strains were freshly cultured. The results were recorded in duplicate using Ciprofloxacin and Fluconazole as standards and are given in Table 3-6.

Table 3. Antibacterial Activity of compounds (1b-4b)

Compounds	Zone of Inhibition (mm)		
	S. aureus	***E. coli***	***P. aeruginosa***
1b.	13.3 ± 0.33	13.4 ± 0.00	12.5 ± 0.00
2b.	20.3 ± 0.33	19.3 ± 0.00	19 ± 0.00
3b.	19.3 ± 0.33	20 ± 0.00	18 ± 0.00
4b.	21 ± 0.00	20.2 ± 0.00	21.3 ± 0.33
Ciprofloxacin	27 ± 0.00	28 ± 0.00	27 ± 0.00
DMF	-	-	-

All the values are expressed as mean ± SEM of triplicates

Table 4. Antifungal Activity of compounds (1b-4b)

Compounds	Zone of Inhibition (mm)		
	C. albicans	***A. flavus***	***A. fumigatus***
1b.	9.3 ± 0.33	8.4 ± 0.00	7.5 ± 0.00
2b.	11.3 ± 0.33	12.3 ± 0.00	11 ± 0.00
3b.	11.3 ± 0.33	10.3 ± 0.00	10 ± 0.00
4b.	13.2 ± 0.00	13.2 ± 0.00	11.3 ± 0.33
Fluconazole	17 ± 0.00	16 ± 0.00	17 ± 0.00
DMF	-	-	-

All the values are expressed as mean ± SEM of triplicates

Table 5. Antibacterial Activity of compounds (1c-4c)

Compounds	Zone of Inhibition (mm)		
	S. aureus	***E. coli***	***P. aeruginosa***
1c.	20.3 ± 0.33	20 ± 0.00	21.2 ± 0.00
2c.	16.7 ± 0.33	17.3 ± 0.33	17.4 ± 0.00
3c.	21.5 ± 0.33	20.5 ± 0.00	19.3 ± 0.00
4c.	19.5 ± 0.00	19.5 ± 0.00	18.3 ± 0.00
Ciprofloxacin	27 ± 0.00	28 ± 0.00	27 ± 0.00
DMF	-	-	-

All the values are expressed as mean ± SEM of triplicates

Table 6. Antifungal Activity of compounds (1c-4c)

Compounds	Zone of Inhibition (mm)		
	C. albicans	*A. flavus*	*A. fumigatus*
1c.	12 ± 0.00	13 ± 0.00	12.3 ± 0.00
2c.	10.4 ± 0.00	11 ± 0.00	9.7 ± 0.67
3c.	12 ± 0.00	13.2 ± 0.00	13.5 ± 0.00
4c.	11.3 ± 0.33	12.7 ± 0.67	11.2 ± 0.00
Fluconazole	17 ± 0.00	16 ± 0.00	17 ± 0.00
DMF	-	-	-

All the values are expressed as mean ± SEM of triplicates

RESULTS AND DISCUSSION

Various substituted acetophenones **(1-4)** reacted with iodine and thiourea to get 2-Amino-4-(substituted-phenyl)-thiazole (14) **(1a-4a)**. Next, the 2-amino group of 2-Amino-4-(substituted-phenyl)-thiazole **(1a-4a)** was acetylated with acetic anhydride, which led to the formation of *N*-(4-(substitutedphenyl)thiazol-2-yl)acetamide **(1b-4b)** in moderate to good yields (Scheme-1). In scheme-2, 2-Amino-4-phenyl-thiazole **(1a)** reacted with various substituted aldehydes to get N-(substitutedbenzylidene)-4-(substitutedphenyl)thiazol-2-amine **(1c-4c)**. The FTIR spectra of compounds **1b-4b** exhibited bands in the region of 3344.12-3419.63 cm^{-1} due to N-H stretching and in the region 1618.32-1674.56 cm^{-1} due to C=O stretching of amide. In ^1H NMR spectra of compounds **1b-4b**, one proton singlet appeared between δ 8.396-9.162 ppm was assigned to N-H proton which disappeared on D_2O exchange. The FTIR spectra of compounds **1c-4c** exhibited bands in the region of 2918.10-2970.43 cm^{-1} due to C-H stretching of N=C-H. In ^1H NMR spectra of compounds **1b-4b**, one proton singlet appeared between δ 8.300-8.464 ppm was assigned to N=C-H proton.

The synthesized compounds were screened for antibacterial and antifungal activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Asperigillus flavus and Asperigillus fumigatus* by disk diffusion method. In Scheme-1, compound **4b** was found to be most effective with the largest zone of inhibition while Compounds **2b** and **3b** were found to be very effective against all the test strains. Compound **1b** was found to be least effective against all the test strains. Scheme-2, compound **3c** was found to be most effective against *Staphylococcus aureus, Escherichia coli, Asperigillus flavus and Asperigillus fumigates.* Compound **1c** was found to be most effective against *Pseudomonas aeruginosa* while Compounds **1c** and **3c** both were found to be equally most effective against *Candida albicans.* Compound **2c** was found to be least effective against all the test strains while compound **4c** was found to possess moderate activity against all the test strains.

CONCLUSION

The structures of the synthesized compounds were assigned on the basis of elemental analysis, ^1H NMR, FTIR and Mass spectral data and physical data. Both analytical and spectral data (IR, 1H-NMR, MS) of all the synthesized compounds were in full agreement with the proposed structure. After comparing the antimicrobial results of all the compounds, it was

concluded that in Scheme-1, compound **4b** was found to be most effective with the largest zone of inhibition while in Scheme-2, compound **3c** was found to be most effective against *Staphylococcus aureus, Escherichia coli, Asperigillus flavus and Asperigillus fumigates.* Compound **1c** was found to be most effective against *Pseudomonas aeruginosa* while Compounds **1c** and **3c** both were found to be equally most effective against *Candida albicans.*

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