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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL BENZOOXAZOLE BASED THIAZOLYL AMINES

Sunil Vodela[1], Raghu Vardhan Reddy Mekala[2]* and Hemalatha Gadegoni[3]

[1]Talla Padmavathi College of Engineering, Kazipet, Warangal-506 003, Andhra Pradesh, India.
[2]Department of Chemistry, Kakatiya University, Warangal-506 009, Andhra Pradesh, India.
[3]University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 00, Andhra Pradesh, India.

ABSTRACT

A series of various novel phenyl-(6*H*-thiazolo[4,5-*e*]benzooxazole-2-yl)-amines **(5a-f)** have been synthesized by involving 4-nitro-1*H*-benzooxazole **(1)** as starting material and 4-amino-1*H*-benzooxazole **(2)**, (1*H*-benzooxazole-4-yl)-dithiocarbamic acid methyl ester **(3)** and 1-(1*H*-benzooxazole-4-yl)-3-phenyl-thioureas **(4a-f)** as intermediates. After structural confirmation, the title compounds were screened for their antimicrobial activity.

Keywords: Benzoxazole, thiazole, antimicrobial activity.

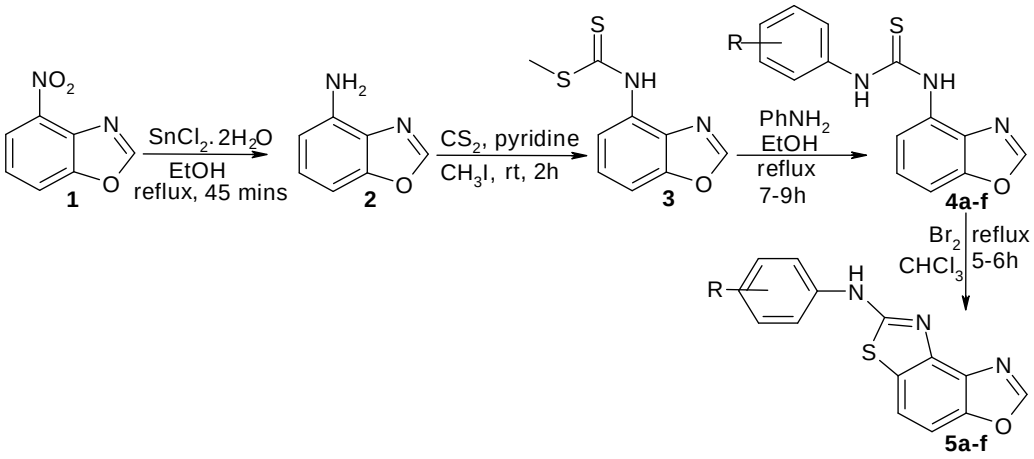
INTRODUCTION

Thiazole derivatives are an important class of heterocyclic compounds and they occupy a significant position in medicinal chemistry presenting a wide range of biological activities such as antibacterial,[1] antifungal,[2] anti-HIV,[3] hypertension,[4] anti-inflammatory,[5] anticancer[6] and anti-convulsant[7] activities.

Recent observations suggest that substituted benzoxazoles possess potential activity with lower toxicities in the chemotherapeutic approach in man.[8] Careful literature survey revealed that targets containing benzoxazole moiety have remarkable biological activities like antibacterial,[9] antihistaminic,[10] antiparasitics,[11] antiviral[12] and antifungal activity.[13]

MATERIAL AND METHODS

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a PerkinElmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H NMR and 100 MHz spectrometer ^{13}C NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.



Scheme. 1: 4/5 (a) R= H; (b) R= 3-NO_2; (c) R= 4-NO_2; (d) R= 4-Cl; (e) R= 4-Br; (f) R= 4-CH_3

Table 1: Antimicrobial activity of compounds 5a-f (zone of inhibition in mm) (activity index)*

	Antibacterial activity						Antifungal activity	
Compound	***S. aureus***	***S. albus***	***S. faecalis***	***E. coli***	***P. mirabilis***	***S. Typhi***	***C. albicans***	***A. fumigatus***
5a	16 (0.76)	18 (0.81)	23 (0.82)	15 (0.78)	15 (0.68)	09 (0.56)	20 (0.80)	22 (0.81)
5b	22 (10.4)	25 (1.13)	29 (1.03)	18 (0.94)	17 (0.85)	15 (0.93)	24 (0.96)	25 (0.92)
5c	19 (0.90)	21 (0.95)	24 (0.85)	16 (0.84)	16 (0.87)	11 (0.68)	22 (0.88)	23 (0.85)
5d	17 (0.80)	19 (0.86)	26 (0.92)	15 (0.78)	13 (0.65)	10 (0.62)	21 (0.84)	21 (0.78)
5e	19 (0.90)	20 (0.90)	23 (0.82)	17 (0.89)	14 (0.70)	12 (0.75)	23 (0.92)	24 (0.89)
5f	16 (0.76)	19 (0.86)	22 (0.78)	15 (0.78)	15 (0.68)	11 (0.68)	21 (0.84)	22 (0.81)
Amicacin	21	22	28	19	20	16	—	—
Fluconazole	—	—	—	—	—	—	25	27

*Activity index - Zone of inhibition of the sample/ Zone of inhibition of the standard

SYNTHESIS OF 4-AMINO-1*H*-BENZOOXAZOLE (2)

A solution of 4-nitro-1*H*-benzooxazole **(1)** (0.01 mol) in ethanol (20 mL) containing $SnCl_2.2H_2O$ (10 mmol) was refluxed on steam-bath for 45 min. A usual work-up, followed by crystallization of the product from dichloro methane furnished pure 4-amino-1*H*-benzooxazole **(2)**.

SYNTHESIS OF (1*H*-BENZOOXAZOLE -4-YL)-DITHIOCARBAMIC ACID METHYL ESTER (3)

A solution of 4-amino-1*H*-benzooxazole **(2)** (0.01 mol) in pyridine (2 mL) was cooled in freezing mixture 0 °C. Then CS_2 (0.03 mol) was added to it, and the solution was stirred for 2 h maintaining the temperature at room temperature. Then CH_3I (0.03 mol) was added to the reaction mixture and stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was poured into crushed ice. The solid separated was filtered, dried and purified by recrystallization with hot ethanol to give pure (1*H*-benzooxazole-4-yl)-dithiocarbamic acid methyl ester **(3)**.

SYNTHESIS OF 1-(1*H*-BENZOOXA-ZOLE-4-YL)-3-PHENYL-THIOUREAS (4a-f)

A solution of (1*H*-benzooxazole-4-yl)-dithiocarbamic acid methyl ester **(3)** (0.01 mol) and $PhNH_2$ or substituted $PhNH_2$ (0.15 mol) in ethanol (15 mL) was refluxed for 7-9 h. After completion of the reaction (monitored by TLC), the solvent was removed by distillation and the residue purified by crystallization from methanol, which yielded the corresponding 1-(1*H*-benzooxazole-4-yl)-3-(substituted-phenyl)-thiourea **(4a–f)**.

SYNTHESIS OF PHENYL-(6*H*-THIAZ-OLO[4,5-*E*] BENZOOXAZOLE-2-YL)-AMINES (5a-f)

A solution of 1-(1*H*-benzooxazole-4-yl)-3-(substituted-phenyl)-thiourea **(4)** was cyclized by bromine (0.01 mol) in $CHCl_3$ (2 mL) under constant stirring at room temperature for 5-6 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into crushed ice. The solid separated was filtered, dried and purified by recrystallization with ethanol to give pure phenyl-(6*H*-thiazolo[4,5-*e*] benzooxazole-2-yl)-amines **(5a-f)**.

4-AMINO-1*H*-BENZOXAZOLE (2)

Gray solid, yield: 70%, M.P. 111–113 °C; IR (KBr, cm^{-1}): *v* 3112 (N–H), 3024 (C–H, Ar), 1580 (C=C, Ar), 1428 (C=N), 1128 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 7.76–7.34 (m, 3H, Ar-H), 5.84 (s, 1H, CH), 3.87 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 152.3, 150.7, 139.7, 136.8, 126.7, 123.4, 117.4; MS: *m/z* 134 (M^+).

(1*H*-BENZOXAZOLE-4-YL)-DITHIOC-ARBAMIC ACID METHYL ESTER (3)

Yellow solid, yield: 75%, M.P. 121–123 °C; IR (KBr, cm^{-1}): *v* 3124 (N-H), 3032 (C–H, Ar), 1574 (C=C, Ar), 1465 (C=S), 1435 (C=N), 1225 (C–S), 1140 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 11.88 (s, 1H, NH), 7.69–7.32 (m, 3H, Ar-H), 5.80 (s, 1H, CH), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 195.7, 150.3, 151.7, 137.4, 135.8, 125.7, 122.8, 116.4, 15.6; MS: *m/z* 224 (M^+).

1-(1*H*-BENZOXAZOLE-4-YL)-3-PHENYL-THIOUREA (4a)

Pale yellow solid, yield: 72%, M.P. 130–132 °C; IR (KBr, cm^{-1}): *v* 3145 (N–H), 3028 (C–H, Ar), 1565 (C=C, Ar), 1458 (C=S), 1431 (C=N), 1232 (C–S), 1138 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 9.98 (s, 1H, NH), 9.30 (s, 1H, NH), 7.79–7.12 (m, 8H, Ar-H), 5.76 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 181.3, 153.7, 149.4, 198.3, 135.6, 134.5, 130.5 (2), 127.4 (2), 126.3, 124.2, 122.1, 118.6; MS: *m/z* 269 (M^+).

1-(1*H*-BENZOXAZOLE-4-YL)-3-(3-NITRO-PHENYL)-THIOUREA (4b)

Brown solid, yield: 71%, M.P. 148–150 °C; IR (KBr, cm^{-1}): *v* 3184 (N-H), 3025 (C–H, Ar), 1555 (C=C, Ar), 1462 (C=S), 1424 (C=N), 1235 (C–S), 1136 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 9.84 (s, 1H, NH), 9.36 (s, 1H, NH), 7.70–7.28 (m, 6H, Ar-H), 7.15 (s, 1H, Ar-H), 5.69 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 176.3, 155.4, 153.4, 149.5, 143.2, 141.8, 137.8, 132.5, 130.4, 128.4, 125.3, 122.4, 120.7, 115.8; MS: *m/z* 314 (M^+).

1-(1*H*-BENZOXAZOLE-4-YL)-3-(4-NITRO-PHENYL)-THIOUREA (4c)

White solid, yield: 72%, M.P. 155–157 °C; IR (KBr, cm^{-1}): *v* 3162 (N-H), 3024 (C–H, Ar), 1568 (C=C, Ar), 1471 (C=S), 1424 (C=N), 1228 (C–S), 1140 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 9.89 (s, 1H, NH), 9.27 (s, 1H, NH), 7.62 (d, 2H, J = 7.5 Hz, Ar-H), 7.59–7.37 (m, 3H, Ar-H), 7.25 (d, 2H, J = 7.5 Hz, Ar-H), 5.88 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 175.6, 153.4, 151.0, 146.3, 144.2, 142.5, 138.9, 127.5 (2), 124.6, 123.0 (2), 121.2, 119.8; MS: *m/z* 314 (M^+).

1-(1*H*-BENZOXAZOLE-4-YL)-3-(4-CHLORO-PHENYL)-THIOUREA (4d)

Yellow solid, yield: 74%, M.P. 169–171 °C; IR (KBr, cm^{-1}): *v* 3140 (N-H), 3028 (C–H, Ar), 1585 (C=C, Ar), 1478 (C=S), 1431 (C=N), 1230 (C–S), 1135 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 9.92 (s, 1H, NH), 9.28 (s, 1H, NH), 7.71–7.28 (m, 3H, Ar-H), 7.54 (d, 2H, J = 7.7 Hz, Ar-H), 7.29 (d, 2H, J = 7.7 Hz, Ar-H), 5.75 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 172.7, 155.7, 153.4, 139.6, 137.6, 134.3, 131.2 (2), 128.4, 127.6, 126.3, 124.3 (2), 121.4; MS: *m/z* 301 (M^+).

1-(1*H*-BENZOXAZOLE-4-YL)-3-(4-BROMO-PHENYL)-THIOUREA (4e)

White solid, yield: 78%, M.P. 148–150 °C; IR (KBr, cm^{-1}): *v* 3184 (N–H), 3012 (C–H, Ar), 1570 (C=C, Ar), 1470 (C=S), 1441 (C=N), 1234 (C–S), 1136 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 9.82 (s, 1H, NH), 9.32 (s, 1H, NH), 7.71–7.32 (m, 3H, Ar-H), 7.59 (d, 2H, J = 7.2 Hz, Ar-H), 7.32 (d, 2H, J = 7.2 Hz, Ar-H), 5.65 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 175.3, 156.3, 153.4, 142.8, 140.6, 139.7, 132.6 (2), 128.3 (2), 124.7, 121.2, 120.5, 119.7; MS: *m/z* 346 (M^+).

1-(1*H*-BENZOXAZOLE-4-YL)-3-(4-METHYL-PHENYL)-THIOUREA (4f)

Pale yellow solid, yield: 75%, M.P. 166–168 °C; IR (KBr, cm^{-1}): *v* 3162 (N–H), 3040 (C–H, Ar), 1585 (C=C, Ar), 1472 (C=S), 1444 (C=N), 1237 (C–S), 1130 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 9.89 (s, 1H, NH), 9.36 (s, 1H, NH), 7.72–7.37 (m, 3H, Ar-H), 7.68 (d, 2H, J = 7.4 Hz, Ar-H), 7.37 (d, 2H, J = 7.4 Hz, Ar-H), 5.63 (s, 1H, CH), 2.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 173.6, 153.7, 153.5, 142.7, 140.5, 139.6, 133.5, 131.5 (2), 129.7, 127.6 (2), 125.7, 121.5, 21.5; MS: *m/z* 283 (M^+).

PHENYL-(6*H*-THIAZOLO[4,5-*E*] BENZOXAZOLE-2-YL)-AMINE (5a)

Gray solid; yield: 73%, M.P. 155–157 °C; IR (KBr, cm^{-1}): *v* 3170 (N–H), 3025 (C–H, Ar), 1568 (C=C, Ar), 1445 (C=N), 1132 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.62 (s, 1H, NH), 7.56 (d, 1H, J = 7.5 Hz, Ar-H), 7.49 (d, 1H, J = 7.5 Hz, Ar-H), 7.45–7.18 (m, 5H, Ar-H), 5.68 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.6, 153.7, 151.2, 146.3, 141.7, 138.4, 132.0 (2), 128.6, 125.2, 120.0, 119.6, 116.3 (2); MS: *m/z* 267 (M^+).

(3-NITRO-PHENYL)-(6*H*-THIAZOL-O[4,5-*E*]BENZOXAZOLE-2-YL)-AMINE (5b)

Greenish yellow solid, yield: 71%, M.P. 133–135 °C; IR (KBr, cm^{-1}): *v* 3154 (N–H), 3016 (C–H, Ar), 1570 (C=C, Ar), 1436 (C=N), 1141 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.54 (s, 1H, NH), 7.48 (d, 1H, J = 7.3 Hz, Ar-H), 7.47–7.26 (m, 3H, Ar-H), 7.44 (s, 1H, Ar-H), 7.42 (d, 1H, J = 7.3 Hz, Ar-H), 5.82 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 153.7, 151.2, 148.3, 146.3, 140.8, 138.6, 131.5, 129.4, 125.3, 122.3, 120.4, 112.0, 112.3; MS: *m/z* 312 (M^+).

(4-NITRO-PHENYL)-(6*H*-THIAZOLO [4,5-*E*]BENZOXAZOLE-2-YL)-AMINE (5c)

Brown solid, yield: 70%, M.P. 140–142 °C; IR (KBr, cm^{-1}): *v* 3162 (N–H), 3028 (C–H, Ar), 1572 (C=C, Ar), 1438 (C=N), 1127 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.59 (s, 1H, NH), 7.52–7.32 (m, 3H, Ar-H), 7.49 (d, 1H, J = 7.6 Hz, Ar-H), 7.36 (d, 1H, J = 7.6 Hz, Ar-H), 7.32 (s, 1H, Ar-H), 5.84 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.3, 155.7, 152.3, 149.5, 143.8, 140.2, 139.3, 129.8, 124.2 (2), 126.4, 118.3 (2), 115.2; MS: *m/z* 312 (M^+).

(4-CHLORO-PHENYL)-(6*H*-THIAZOLO [4,5-*E*]BENZOXAZOLE-2-YL)-AMINE (5d)

Yellow solid, yield: 73%, M.P. 150–152 °C; IR (KBr, cm^{-1}): *v* 3162 (N–H), 3025 (C–H, Ar), 1568 (C=C, Ar), 1431 (C=N), 1136 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.61 (s, 1H, NH), 7.59 (d, 2H, J = 7.7 Hz, Ar-H), 7.46 (d, 1H, J = 7.2 Hz, Ar-H), 7.38 (d, 1H, J = 7.2 Hz, Ar-H), 7.35 (d, 2H, J = 7.7 Hz, Ar-H), 5.62 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 154.2, 152.3, 145.2, 138.6, 138.6, 130.2 (2), 127.3, 125.4, 123.0, 120.4, 117.2 (2); MS: *m/z* 301 (M^+).

(4-BROMO-PHENYL)-(6*H*-THIAZOLO [4,5-*E*]BENZOXAZOLE-2-YL)-AMINE (5e)

White solid, yield: 72%, M.P. 145–147 °C; IR (KBr, cm^{-1}): *v* 3154 (N–H), 3026 (C–H, Ar), 1565 (C=C, Ar), 1447 (C=N), 1138 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.65 (s, 1H, NH), 7.62 (d, 2H, J = 7.2 Hz, Ar-H), 7.59 (d, 1H, J = 7.3 Hz, Ar-H), 7.42 (d, 1H, J = 7.3 Hz, Ar-H), 7.39 (d, 2H, J = 7.2 Hz, Ar-H), 5.78 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 156.3, 153.5, 146.3, 141.0, 138.5, 132.0 (2), 129.6, 126.2, 123.1, 117.0 (2), 113.5; MS: *m/z* 346 (M^+).

(4-METHYL-PHENYL)-(6*H*-THIAZ-OLO[4,5-*E*]BENZOXAZOLE-2-YL)-AMINE (5f)

Brown solid, yield: 70%, M.P. 162–164 °C; IR (KBr, cm^{-1}): *v* 3165 (N–H), 3027 (C–H, Ar), 1563 (C=C, Ar), 1445 (C=N), 1137 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.48 (s, 1H, NH), 7.58 (d, 2H, J = 7.4 Hz, Ar-H), 7.47 (d, 1H, J = 7.6 Hz, Ar-H), 7.42 (d, 2H, J = 7.4 Hz, Ar-H), 7.37 (d, 1H, J = 7.6 Hz, Ar-H), 5.70 (s, 1H, CH), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0, 154.7, 151.0, 142.0, 137.3, 135.6, 130.5 (2), 127.5, 125.7, 122.3, 117.3 (2), 114.2, 21.5; MS: *m/z* 281 (M^+).

RESULTS AND DISCUSSION

Based on these observations, inspired by the biological profile of benzoxazoles and thiazoles, their increasing importance in pharmaceutical and biological fields and in continuation of our research on biologically active heterocycles, we have introduced thiazole moiety into the benzoxazole ring which leads to the presence of both active pharmacophores in a single molecular frame work for the intensified biological activities. Thus we have designed and synthesized a series of novel phenyl-(6*H*-thiazolo[4,5-*e*]benzooxazole-2-yl)-amines **(5a-f)** from commercially available 4-nitro-1*H*-benzooxazole **(1)**. 4-amino-1*H*-benzooxazole **(2)** has been synthesized through reduction from compound **1** with thionyl chloride in presence of ethanol solvent on constant stirring at reflux temperature for 45 mins. The key intermediate (1*H*-benzooxazole-4-yl)-dithiocarbamic acid methyl ester **(3)** was achieved from compound **2** with carbon disulfide and methyl iodide on constant stirring in presence of pyridine at room temperature for 2 h.

Compound **3** on reaction with aniline in presence of ethanol solvent under reflux for 7-9 h was turned into the final intermediate 1-(1*H*-benzooxazole-4-yl)-3-phenyl-thioureas **(4a-f)**. In subsequent ring closure reaction, the title compounds phenyl-(6*H*-thiazolo[4,5-*e*]benzooxazole-2-yl)-amines **(5a-f)** have been prepared form compound **4** on uniform stirring with bromine in $CHCl_3$ at room temperature for 5-6 h. The chemical structures of all the newly synthesized compounds were confirmed by their IR, ^{1}H & ^{13}C NMR, mass spectral data

and elemental analysis. Further, the target compounds **5a-f** were used to evaluate their antimicrobial activity.

ANTIMICROBIAL ACTIVITY

The disc-diffusion method[14] was used for the screening of anti-microbial activity. The antibacterial activity of the synthesized compounds **5a-f** was tested against gram-positive bacteria *i.e. Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus faecalis* and gram-negative bacteria *i.e.*, *Escherichia coli*, *Proteus mirabilis*, *Salmonella typhi* using a nutrient agar medium. The antifungal activity of the compounds was screened against *Candia albicans* and *Aspergillus fumigatus* using Sabouraded dextrose agar medium. The sterilized medium (autoclaved at 121°C for 15 min.) was inoculated with the suspension of the micro-organisms and poured into a Petri dish to give a depth of 3-4 mm. The paper impregnated with the synthesized compounds **5a-f** (300 µg/ml in DMF) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37° for 24 h and 48 h for antibacterial and antifungal activity, respectively. Amicacin (300 µg/ml) was used in anti-bacterial activity studies, whereas fluconazole (300 µg/ml) was used in antifungal activity studies, as reference compounds. After incubation, the relative susceptibility of the micro-organisms to the potential antimicrobial agent is demonstrated by a clear zone of growth inhibition around the disc. The inhibition zone caused by the various compounds on the micro-organisms was measured and the activity rated on the basis of the size of the inhibition zone. The observed zone of inhibition is presented in Table 1.

The synthesized compounds **5a-f** were screened "*in vitro*" for antimicrobial activity. From the data, it is clear that compound **5b** is highly active against *Staphylococcus aureus*, *Staphylococcus albus* and *Streptococcus faecalis* as compared to the standard, but shows only moderate activity against rest bacteria. Other compounds exhibit moderate to good antibacterial activity against all organisms. Similarly, **5b** and **5e** exhibit good antifungal activity against *Candida albicans* and *Aspergillus fumigatus* as compared to the standard drug. The remaining compounds are moderately active against these two micro-organisms. It can be concluded that the antimicrobial activity of such compounds may change by introduction or elimination of a specific group.

CONCLUSION

The outstanding properties of this new class of antibacterial and antifungal substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship and to optimize the effectiveness of this series of molecules.

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