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Synthesis and Antimicrobial Activity of Novel 2,4-Disubstituted Thiazoles

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A novel series of 2,4-disubtituted thiazole derivatives were synthesized. The structures of the compounds were established by IR, ^{1}H, ^{13}C NMR and mass spectroscopy. They were screened for antibacterial and antifungal activity against *Bacillus megaterium*, *Bacillus cereus*, *Escherichia coli* and *Saccharomyces cerevisiae*, *Candida albicans*, respectively.

Key Words: 2,4-Disubstitued thiazoles, α-Bromo ketones, Antimicrobial activity.

INTRODUCTION

Heterocycles containing nitrogen and sulfur have been under investigation for a long time because of their significant medicinal properties. Among the wide range of heterocycles explored to develop pharmaceutically important molecules, thiazoles and their derivatives have attracted organic and medicinal chemists because of their diverse biological activities[1-6]. Thiazoles are important subunits in many complex natural compounds and drugs such as vitamine B1, epothilones, nizatidine, ritonavir, sulfathiazole, abafungin, bleomycine and tiazofurin. It has been observed over the years that thiazole derivatives have numerous biological activities such as antibacterial activity, antihypertensive activity, antiinflammatory activity, antischizophrenia activity, anti HIV activity, antiallergic activity, analgesic activity, fibrinogen receptor antagonist activity with antithrombotic activity, as bacterial DNA gyrase B inhibitor activity, antitumor activity[7-18].

In view of the importance of thiazoles derivatives and as part of our continued interest in developing new biologically important molecules, we have synthesized some novel thiazole derivatives and antimicrobial activity of these compounds were studied and reported.

EXPERIMENTAL

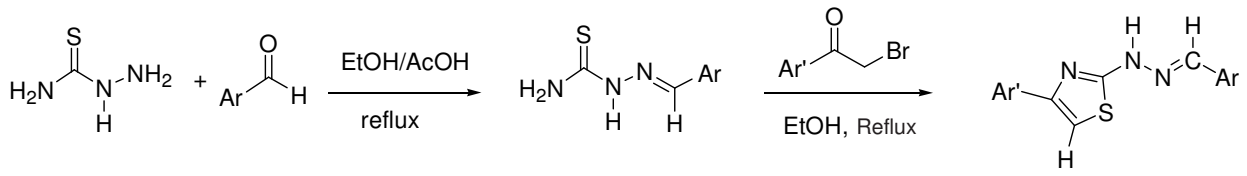
All reagents were obtained from Aldrich Chemical Company and used as supplied. Mueller Hinton Agar and Potato Dextrose Agar were obtained from Becton, Dickinson and Company, USA. Melting points were determined in open capillaries using Electrothermal (IA 9100) digital melting point apparatus and are uncorrected. IR spectra were recorded on Bruker (Tensor 37) FT-IR spectrometer using KBr pellets. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker AM500 FT-NMR spectrometer. Mass spectra (ESI) were recorded on an AGILENT 1200 LC-MSD Trap spectrometer.

General procedure for the synthesis of compounds 1a-e (Scheme-I): A mixture of equimolar quantities of aldehyde (2 mmol) and thiosemicarbazide (2 mmol) in 10 mL of ethanol and catalytic amount of acetic acid was refluxed on an oil bath for 3-6 h. The progress of reaction was monitored by TLC. After completion of reaction, the product that separated out on cooling was filtered and washed with water. The solid was then dried and recrystallized from EtOH.

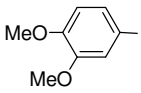
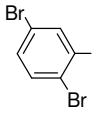
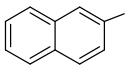
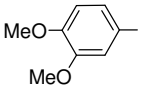
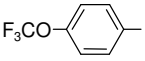
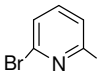
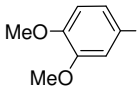
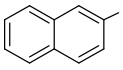
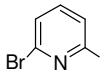
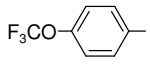
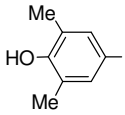
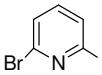
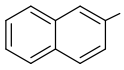
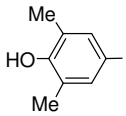
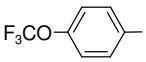
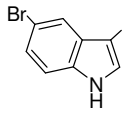
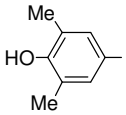
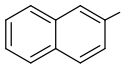
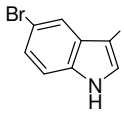
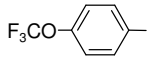
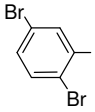
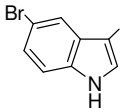
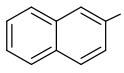
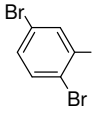
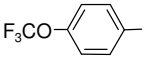
2-(3,4-Dimethoxybenzylidene)hydrazinecarbothioamide (1a): Yield 85 %, m.p. 256-257 ºC; IR (KBr, ν_{max}, cm^{-1}): 3352, 3263, 2960, 1653, 1540, 855; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.76 (s, 3H), 3.81 (s, 3H), 6.93 (d, J = 8.5 Hz, 1H), 7.13 (dd, J = 8.5, 2.0 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.98 (s, 1H), 8.02 (s, 1H), 8.16 (s, 1H), 11.32 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.5, 55.7, 108.6, 111.3, 122.2, 126.9, 142.7, 149.2, 150.7, 177.6.

2-(4-Hydroxy-3,5-dimethylbenzylidene)hydrazinecarbothioamide (1b): Yield 94 %, m.p. 249-250 ºC; IR (KBr, ν_{max}, cm^{-1}): 3352, 3269, 2987, 1653, 1541, 868; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 6H), 7.36 (s, 2H), 7.82 (s,1H), 7.89 (s, 1H), 8.05 (s, 1H), 8.69 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.5, 124.4, 125.0, 127.7, 143.0, 155.2, 177.4.

2-(2,5-Dibromobenzylidene)hydrazinecarbothioamide (1c): Yield 84 %, m.p. 246-247 ºC; IR (KBr, ν_{max}, cm^{-1}): 3489, 3400, 1655, 816; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.47 (dd, J = 8.8, 2.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 8.35 (s, 1H),



1a-e **2a-o**

Comp	Ar	Ar'	Comp	Ar	Ar'
2a			**2i**		
2b			**2j**		
2c			**2k**		
2d			**2l**		
2e			**2m**		
2f			**2n**		
2g			**2o**		
2h					

Scheme-I: Synthesis of 2,4 disubstituted thiazoles

8.36 (s, 2H), 8.52 (d, *J* = 2.5 Hz, 1H), 11.68 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 121.5, 122.3, 129.8, 133.7, 134.7, 135.0, 139.2, 178.4.

2-[(6-Bromopyridin-2-yl)methylene]hydrazine-carbothioamide (1d): Yield 80 %, m.p. 226-227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3397, 3263, 1654, 1532, 894; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.97 (s, 1H), 8.23 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.41 (s, 1H), 11.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 119.4, 128.0, 139.7, 140.5, 140.7, 154.6, 178.5.

2-[(5-Bromo-1*H*-indol-3-yl)methylene]hydrazine-carbothioamide (1e): Yield 82%, m.p. 241-242 ºC; IR (KBr,

ν_{max}, cm^{-1}): 3397, 3263, 1654, 1583, 884; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.31 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.52 (s, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 8.01 (s, 1H), 8.28 (s, 1H), 8.31 (s, 1H), 11.17 (s, 1H), 11.78 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 110.8, 113.4, 113.8, 123.8, 125.3, 125.6, 132.2, 135.8, 140.5, 176.7.

General procedure for the synthesis of compounds 2a-o (Scheme-I): A mixture of equimolar quantities of thiosemicarbazone (2 mmol) and α-bromo ketone (2 mmol) in 10 mL of absolute ethanol was refluxed on an oil bath for 2-3 h. The progress of reaction was monitored by TLC. After completion of reaction, the solution was cooled, solid that separated was filtered and dried. Finally, the product was recrystallized from ethanol.

2-[2-(3,4-Dimethoxybenzylidene)hydrazinyl]-4-phenylthiazole (2a): Yield 83 %, m.p. 250-251 ºC; IR (KBr, ν_{max}, cm^{-1}): 3426, 3010, 1621, 1512, 743; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.79 (s, 3H), 3.81 (s, 3H), 7.01 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.29-7.32 (m, 2H), 7.41(t, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 8.01 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.4, 55.6, 103.5, 108.5, 111.8, 120.4, 125.6, 127.1, 127.6, 128.6, 134.2, 142.2, 149.0, 149.6, 150.2, 168.3; MS (ESI): *m/z* 340.2 (M + 1).

2-[2-(3,4-Dimethoxybenzylidene)hydrazinyl]-4-[4-(trifluoromethoxy)phenyl]thiazole (2b): Yield 70 %, m.p. 270-271 ºC; IR (KBr, ν_{max}, cm^{-1}): 3448, 3050, 1627, 1265, 1513, 1265, 761; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.79 (s, 3H), 3.81 (s, 3H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.37-7.39 (m, 3H), 7.95-7.97 (m, 3H), 12.10 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.4, 55.5, 104.4, 108.5, 111.7, 119.1, 120.2, 121.1, 127.2, 134.0, 141.6, 147.5, 149.0, 150.1, 168.5; MS (ESI): *m/z* 423.0 (M^+).

2-[2-(3,4-Dimethoxybenzylidene)hydrazinyl]-4-(naphthalen-2-yl)thiazole (2c): Yield 91 %, m.p. 261-262 ºC; IR (KBr, ν_{max}, cm^{-1}): 3421, 3010, 1621, 1512, 1273, 754; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.80 (s, 3H), 3.82 (s, 3H), 7.02 (d, *J* = 8.5 Hz, 1H), 7.19 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.46 (s, 1H), 7.49-7.53 (m, 2H), 7.90-7.95 (m, 3H), 7.99-8.02 (m, 2H), 8.38 (s, 1H), 12.09 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.4, 55.6, 104.2, 108.5, 111.8, 120.2, 123.9, 124.0, 125.9, 126.4, 127.2, 127.5, 128.0, 128.1, 132.4, 133.1, 141.5, 149.0, 150.1, 150.5, 168.4; MS (ESI): *m/z* 390.3 (M + 1).

2,6-Dimethyl-4-[(2-(4-phenylthiazol-2-yl)hydrazono)-methyl]phenol (2d): Yield 80 %, m.p. 214-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3424, 3312, 2921, 1637, 1560, 700; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, 6H), 7.23 (s, 2H), 7.26 (s, 1H), 7.27-7.30 (m, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.90 (s, 1H), 8.66 (s, 1H), 11.88 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.6, 103.1, 124.6, 125.4, 125.5, 126.6, 127.4, 128.6, 134.8, 142.1, 154.8, 168.4; MS (ESI): *m/z* 323.0 (M^+).

2,6-Dimethyl-4-[(2-(4-(4-(trifluoromethoxy)phenyl)-thiazol-2-yl)hydrazono)methyl]phenol (2e): Yield 68 %, m.p. 171-172 ºC; IR (KBr, ν_{max}, cm^{-1}): 3447, 3274, 2921, 1637, 1563; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.19 (s, 6H), 7.22 (s, 2H), 7.35 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.89 (s, 1H), 7.95-7.96 (m, 2H), 8.66 (s, 1H), 11.92 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.6, 104.2, 121.1, 124.6, 125.3, 126.6, 127.2, 134.1, 142.3, 147.5, 154.8, 168.6; MS (ESI): *m/z* 407.1 (M^+).

2,6-Dimethyl-4-[(2-(4-(naphthalen-2-yl)thiazol-2-yl)hydrazono)methyl]phenol (2f): Yield 73 %, m.p. 271-272 ºC; IR (KBr, ν_{max}, cm^{-1}): 3436, 3057, 1623, 1492, 749; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.26 (s, 6H), 7.32 (s, 2H), 7.50-7.59 (m, 4H), 7.96-8.06 (m, 5H), 8.41 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.4, 105.0, 124.7, 125.1, 125.5, 127.3, 127.7, 128.3, 128.9, 130.7, 131.2, 133.3, 144.6, 149.2, 155.9, 169.3; MS (ESI): *m/z* 374.2 (M + 1).

2-[2-(2,5-Dibromobenzylidene)hydrazinyl]-4-phenylthiazole (2g): Yield 74 %, m.p. 177-178 ºC; IR (KBr, ν_{max}, cm^{-1}): 3423, 3060, 1637, 1563, 1434, 1025, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.29-7.32 (m, 1H), 7.38 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.49 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.85-7.87 (m, 2H), 7.96 (d, *J* = 2.5 Hz, 1H), 8.28 (s, 1H), 12.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 104.3, 121.1, 121.3, 125.5, 127.6, 128.4, 128.6, 133.1, 134.4, 135.1, 135.2, 137.7, 167.6; MS (ESI): *m/z* 437.9 (M^+).

2-[2-(2,5-Dibromobenzylidene)hydrazinyl]-4-[4-(trifluoromethoxy)phenyl]thiazole (2h): Yield 81 %, m.p. 203-204 ºC; IR (KBr, ν_{max}, cm^{-1}): 3438, 2922, 1638, 1591, 1489, 1273, 700; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.46 (s, 1H), 7.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.95-7.96 (m, 2H), 7.98 (s, 1H), 8.28 (s, 1H), 12.59 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 105.4, 119.1, 121.1, 121.3, 127.3, 128.4, 133.1, 133.7, 135.1, 137.9, 147.6, 167.8; MS (ESI): *m/z* 522.0 (M + 1).

2-[2-(2,5-Dibromobenzylidene)hydrazinyl]-4-(naphthalen-2-yl)thiazole (2i): Yield 80 %, m.p. 141-142 ºC; IR (KBr, ν_{max}, cm^{-1}): 3424, 3056, 1624, 1562, 1024, 749; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.47-7.53 (m, 4H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.90-8.02 (m, 5H), 8.30 (s, 1H), 8.38 (s, 1H), 12.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 105.1, 121.1, 121.3, 123.9, 124.1, 126.0, 126.4, 127.5, 128.0, 128.1, 128.4, 131.9, 132.4, 133.0, 133.1, 135.0, 135.1, 137.7, 167.7; MS (ESI): *m/z* 487.9 (M^+).

2-[2-((6-Bromopyridin-2-yl)methylene)hydrazinyl]-4-phenylthiazole (2j): Yield 74 %, m.p. 170-171 ºC; IR (KBr, ν_{max}, cm^{-1}): 3316, 3060, 1625, 1549, 1160, 707; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.29-7.32 (m, 1H), 7.40-7.43 (m, 3H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 3H), 7.97 (s, 1H), 12.59 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 104.5, 118.4, 124.8, 125.5, 125.6, 127.5, 127.6, 128.6, 139.4, 140.0, 141.0, 154.5, 167.4; MS (ESI): *m/z* 359.0 (M^+).

2-[2-((6-Bromopyridin-2-yl)methylene)hydrazinyl]-4-[4-(trifluoromethoxy)phenyl]thiazole (2k): Yield 65 %, m.p. 210-211 ºC; IR (KBr, ν_{max}, cm^{-1}): 3426, 3078, 1640, 1563, 1162; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.48 (s, 1H), 7.60 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.86 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.95-7.98 (m, 3H), 12.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 105.6, 118.4, 119.0, 121.1, 121.2, 127.3, 127.4, 127.5, 133.7, 139.6, 140.0, 140.9, 147.6, 154.4, 167.7; MS (ESI): *m/z* 443.0 (M^+).

2-[2-((6-Bromopyridin-2-yl)methylene)hydrazinyl]-4-(naphthalen-2-yl)thiazole (2l): Yield 73 %, m.p. 230-231 ºC; IR (KBr, ν_{max}, cm^{-1}): 3422, 3054, 1626, 1560, 751; ^{1}H NMR

TABLE-1
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **2a-o**

Compound	Zone of inhibition/mm[a]								
	B. megaterium			*B. cereus*			*E. coli*		
	50 ppm	25 ppm	10 ppm	50 ppm	25 ppm	10 ppm	50 ppm	25 ppm	10 ppm
2a	15	14	13	10	10	9	10	10	8
2b	10	10	9	11	10	10	–	–	–
2c	–	–	–	–	–	–	–	–	–
2d	–	–	–	–	–	–	–	–	–
2e	12	12	8	–	–	–	12	11	10
2f	–	–	–	10	10	8	10	10	8
2g	10	8	8	10	8	8	13	12	10
2h	–	–	–	–	–	–	18	15	12
2i	15	12	10	13	10	9	15	12	10
2j	12	12	10	10	9	9	15	13	10
2k	–	–	–	–	–	–	–	–	–
2l	12	10	10	12	10	10	13	12	11
2m	–	–	–	–	–	–	–	–	–
2n	15	15	8	–	–	–	–	–	–
2o	15	13	10	–	–	–	15	12	11
Penicillin	20	–	–	14	–	–	20	–	–

[a]– indicates no activity.

(500 MHz, DMSO-d_6): δ 7.50-7.55 (m, 3H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 8 Hz, 2H), 8.00-8.02 (m, 2H), 8.38 (s, 1H), 12.64 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 105.3, 118.4, 123.8, 124.0, 124.1, 124.2, 126.0, 126.4, 127.5, 128.1, 131.9, 132.4, 133.1, 139.5, 140.0, 140.9, 141.0, 150.6, 154.4, 167.5; MS (ESI): *m/z* 409.0 (M^+).

2-[2-((5-Bromo-1*H*-indol-3-yl)methylene)hydrazinyl]-4-phenylthiazole (2m): Yield 81 %, m.p. 241-242 ºC; IR (KBr, ν_{max}, cm^{-1}): 3406, 3246, 3056, 1625, 1236, 737; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.28-7.35 (m, 3H), 7.39-7.44 (m, 3H), 7.83 (d, *J* = 2.5 Hz, 1H), 7.86 (d, *J* = 7.0 Hz, 2H), 8.24 (s, 1H), 8.43 (s, 1H), 11.69 (s, 1H), 11.87 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 102.8, 111.3, 113.0, 113.9, 124.0, 125.0, 125.5, 125.7, 127.4, 128.5, 130.5, 134.9, 135.7, 138.5, 168.6; MS (ESI): *m/z* 397.0 (M^+).

2-[2-((5-Bromo-1*H*-indol-3-yl)methylene)hydrazinyl]-4-[4-(trifluoromethoxy)phenyl]thiazole (2n): Yield 76 %, m.p. 286-287 ºC; IR (KBr, ν_{max}, cm^{-1}): 3410, 3246, 3124, 1629, 1265; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.34 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.40-7.44 (m, 4H), 7.83 (d, *J* = 3.0 Hz, 1H), 7.95-7.97 (m, 2H), 8.24 (s, 1H), 8.4 (d, *J* = 1.5 Hz, 1H), 11.70 (s, 1H), ^{13}C NMR (125 MHz, DMSO-d_6): δ 103.9, 111.3, 113.1, 113.9, 121.2, 124.0, 125.1, 125.8, 127.3, 130.7, 134.1, 135.8, 138.9, 147.5, 168.8; MS (ESI): *m/z* 481.1 (M^+).

2-[2-((5-Bromo-1*H*-indol-3-yl)methylene)hydrazinyl]-4-(naphthalen-1-yl)thiazole (2o): Yield 69 %, m.p. 193-194 ºC; IR (KBr, ν_{max}, cm^{-1}): 3432, 3212, 3055, 1641, 1581, 1276, 749; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.36 (d, *J* = 8.5 Hz, 1H), 7.43-7.54 (m, 4H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.90-7.94 (m, 3H), 8.02 (d, *J* = 8.5 Hz, 1H), 8.27 (s, 1H), 8.39 (s, 1H), 8.46 (s, 1H), 11.69 (s, 1H), 11.91 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 103.6, 111.3, 113.1, 113.9, 123.9, 124.0, 125.0, 125.8, 125.9, 126.4, 127.6, 128.0, 128.1, 130.6, 132.3, 132.4, 133.2, 135.8, 138.7, 168.6; MS (ESI): *m/z* 447.1 (M^+).

Antimicrobial assay: The antimicrobial activity of compounds **2a-o** was performed by well diffusion method. Penicillin was used as standard drug and Dimethyl sulfoxide was used as a control. The microbial test organisms were grown in nutrient broth for 24 h at 37 ºC. Each strain was swabbed uniformly into the individual plates using sterile cotton swabs. Wells of 5 mm diameter were made on Muller-Hinton agar (bacteria) and potato dextrose agar (fungi) plates using gel puncture. Into these wells different concentrations of 30 µL of synthesized compounds were introduced. After incubation at 37 ºC for 24 h the different levels of zone of inhibition were measured using the meter scale.

RESULTS AND DISCUSSION

A novel series of 2,4-disubstituted 1,3-thiazoles (**2a-o**) were synthesized in a two step synthetic process. In the first step thiosemicarbazones (**1a-e**) were synthesized by the condensation of varies aldehydes with thiosemicarbazide in ethanol in the presence of catalytic amount of acetic acid. In the second step these thiosemicarbazones (**1a-e**) which are obtained in the first step reacted with α-bromo ketones in refuxing ethanol to yield the corresponding 2,4-disubstituted 1,3-thiazoles (**2a-o**). The chemical structures of all the synthesized compounds were charecterised by IR, ^{1}H, ^{13}C NMR and mass spectrometry. FT-IR spectra of compounds **2a-o** showed absorption bands at 3448-3212 and 1641-1621 cm^{-1} for NH and C=N (azomethine) groups, respectively. The absence of the absorption band corresponding to carbonyl stretching frequency of the α-bromo ketones clearly confirmed the formation of thiazole ring.

The ^{1}H NMR spectra of compounds **2a-o** showed singlets in the regions of 12.64-11.87 ppm indicating the presence of NH. The compounds **2d-f** showed singlet in the region of 8.66-8.41 ppm for phenolic proton. The compounds **2m-o** exhibited sharp singlet in the region of 11.70-11.67 ppm corresponding to the NH protan of the indole. ^{13}C NMR spectra showed the signals in the range of 169.3-167.4 and 105.6-102.8 ppm corresponding to carbon atom of thiazole-C-2 and thiazole-C-5, respectively. The mass spectral data of compounds **2a-o** are provided in the experimental section.

Antibacterial activity: All the compounds **2a-o** were tested for their antibacterial activity against *Bacillus megaterium* (*B. megaterium*), *Bacillus cereus (B. cereus) and Escherichia coli* (*E.coli*) by the well diffusion method at different concentrations. Results are summarized in Table-1. Compounds **2a**, **2i**, **2n** and **2o** showed moderate acitivity against *B. megaterium.* Other compounds showed negligible or no activity against *B. megaterium.* Compound **2i** showed excellent activity against *B. cereus* and other compounds showed moderate/no activity. Compound **2h** only exhibited excellent activity and other compounds showed negligible or no activity against *E.coli*.

Antifungal activity: All the compounds **2a-o** were also tested for their antifungal activity against *Saccharomyces cerevisiae (S.cerevisiae) and Candida albicans (C.albicans)* by the well-diffusion method at different concentrations. Results are summarized in Table-2. Compounds **2a**-**c**, **2e** and **2n** showed excellent activity against *S.cerevisiae.* Other compounds showed moderate/negligible activity. Compounds **2b** and **2k** exhibited good activity against *C.albicans* and other compounds showed moderate or negligible activity.

TABLE-2
ANTIFUNGAL ACTIVITY OF COMPOUNDS **2a-o**

Compound	Zone of inhibition (mm[a])					
	S. cerevisiae			*C. albicans*		
	50 ppm	25 ppm	10 ppm	50 ppm	25 ppm	10 ppm
2a	24	20	18	8	8	7
2b	23	23	22	24	24	23
2c	25	24	23	22	20	20
2d	17	15	11	18	17	17
2e	25	21	21	23	20	20
2f	22	18	14	21	20	20
2g	14	13	13	–	–	–
2h	18	18	17	21	20	20
2i	18	17	17	13	13	12
2j	12	12	10	12	12	10
2k	18	17	16	24	23	23
2l	15	15	15	18	18	17
2m	–	–	–	8	8	7
2n	24	20	23	20	20	18
2o	20	18	17	18	18	17
Penicillin	26	–	–	28	–	–

[a]– indicates no activity.

Conclusion

We have synthesized a new series of 2,4-disubtituted thiazole derivatives and their antibacterial and antifungal activity was evaluated. Among the all compounds, compound **2i** against *B. cereus* and compound **2h** against *E.coli* showed excellent antibacterial activity. Compounds **2a-c**, **2e** and **2n** showed excellent antifungal activity against *S. cerevisiae.* Compounds **2b** and **2k** exhibited good activity against *C. albicans.*

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