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ARTICLE

Synthesis and Antimicrobial Activity of 1,2,3-Triazole Linked Benzo[*d*]oxazole-2-thiol/ oxazolo[4,5-*b*]pyridine-2-thiol Derivatives

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ABSTRACT

A new series of 1,2,3-triazole linked mercaptobenzoxazole/oxazolo-[4,5-*b*] pyridine-2-thiol derivatives (**6a-j**) were synthesized starting from 2-aminophenol/2-aminopyridin-3-ol in three steps *via* cyclization, alkylation followed by reaction with various aromatic azides using click chemistry approach. All the synthesized compounds were evaluated for their antimicrobial activity *viz. E. coli, P. aeruginosa, S. aureus* and *S. pyogenus* and three pathogenic fungi *viz. C. albicans, A. niger* and *A. clavatus* and promising compounds were identified.

KEYWORDS

Mercaptobenzoxazole, Oxazolo[4,5-*b*]pyridine-2-thiol, Sharpless condition, Antibacterial activity, Antifungal activity.

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INTRODUCTION

Recently, fused heterocyclic compounds attract the attention of scientists working not only in the area of natural product but also in synthetic organic chemistry due to its important contribution in the field of medicinal chemistry and serves as key template for the development of various drugs. In particular, benzoxazoles and its derivatives [1-5] exhibit great attention in pharmaceutical chemistry due their important biological activity such as melatonin receptor agonists [6], COX inhibitor [7], anticancer agents [8], 55-HT_3 receptor antagonists [9] and HIV-1 reverse transcriptase inhibitors [10,11].

2-Mercaptobenzoxazole is a thiol derivative of benzoxazole moiety which exists in tautomeric forms of thiol and thione (Fig. 1) [12]. The remarkable therapeutic activity of 2-mercapto-benzoxazole render them target compounds in organic synthesis and drug discovery [13]. In medicinal chemistry, the findings focused on synthesis of oxazolopyridine-2-thiol derivatives as this nucleus contain pyridine fragment and might offer some advantages over 2-mercaptobenzoxazole moiety. Water solubility, site for protonation and salt formation are the key benefit of pyridine fragment, which might enhance the interaction with targeted protein *via* hydrogen bonding and may help in modulating the physical and biological property of the molecule.

Triazoles serve as an important pharmcophore in medicinal chemistry for developing numerous therapeutic agents such as antiviral [14-16], anticancer [17], antibiotic agent [18], anti-

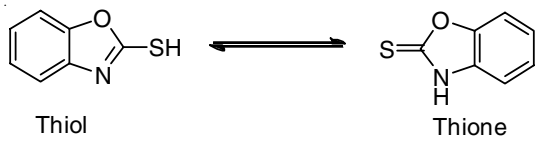


Fig. 1. Tautomeric forms of 2-mercaptobenzoxazole

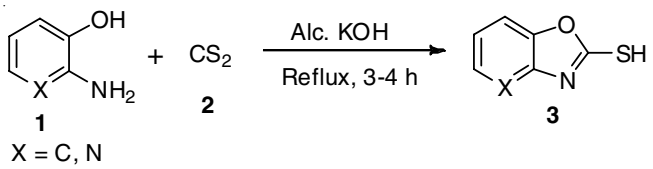
microbial [19], anti-inflammatory [20], local anaesthetic [21,22], antineoplastic [23] and anticonvulsant [24]. Moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* condition are favourable properties of 1,2,3-triazole, which may responsible for their enhancement of biol-ogical profile of the molecule. Various attempts were made for modifying the triazole moiety to improve the biological activity and resulted in large number of compounds with modified triazole ring having diverse pharmacological activities.

In this article, an attempt is made to synthesize and characterize some new derivatives of 1,2,3-triazole linked benzo[*d*]oxazole-2-thiol/oxazolo[4,5-*b*]pyridine-2-thiol derivatives were and also evaluated for their antimicrobial properties.

EXPERIMENTAL

All chemicals and reagents were purchased from commercially available source and used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 G F_{254} and visualization on TLC was achieved by UV light or iodine indicator. With Merck 60-120 mesh silica gel, column chromatography was employed. ^{13}C & ^{1}H spectra were recorded using the Bruker UXNMR/XWIN-NMR (300 MHz) instrument. Chemical shifts (δ) were obtained downfield from the internal TMS standard in ppm. ESI+ software with an electrospray ionization (ESI)-mode positive ion trap detector and a capillary voltage of 3.98 kV was used to record the ESI spectra on Micro mass, Quattro LC. Melting points were uncorrected and determined using the open capillary tube melting point apparatus.

Synthesis of benzoxazole/pyridine oxazole (3): 2-Aminophenol/3-hydroxy-2-aminopyridine (**1**) (4.5 mmol), carbon disulphide (**2**) (4 mL) and KOH (5.35 mmol) were placed in a 100 mL round bottom flask and refluxed in 10 mL of 95% ethanol for 7-8 h. The reaction mixture was cooled to room temperature and concentrated. Then 1 M aqueous HCl solution was added to this concentrated reaction mixture. The obtained product was washed and filtered using water (2 × 10 mL) and then was air dried. This dried product was recrystallized using ethanol (**Scheme-I**).



Scheme-I: Synthesis of benzoxazole/pyridinoxazole

Synthesis of 2-(prop-2-ynylthio)benzo[*d*]oxazole/2-(prop-2-ynylthio)oxazolo[4,5-*b*] pyridine (5): Benzo[*d*]-oxazole-2-thiol/oxazolo[4,5-*b*]pyridine-2-thiol (**3**) (3 mmol) was dissolved in dry DMF (10 mL). Potassium carbonate (6 mmol) was added to the resulting mixture and the reaction mixture was stirred for 25 min at room temperature. In this reaction mixture, propargyl bromide (**4**) (3.6 mmol) was slowly added dropwise over a period of 25 min and stirring was continued for 4 h. After reaction completion was confirmed through TLC, the reaction was terminated using water, and the product was extracted by employing EtOAc (3 × 20 mL). The acquired extract was washed using brine (20 mL) and water (3 × 25 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Purification through silica gel chromatography (10% ethyl acetate in hexane) led to the formation of the desired product (**Scheme-II**).

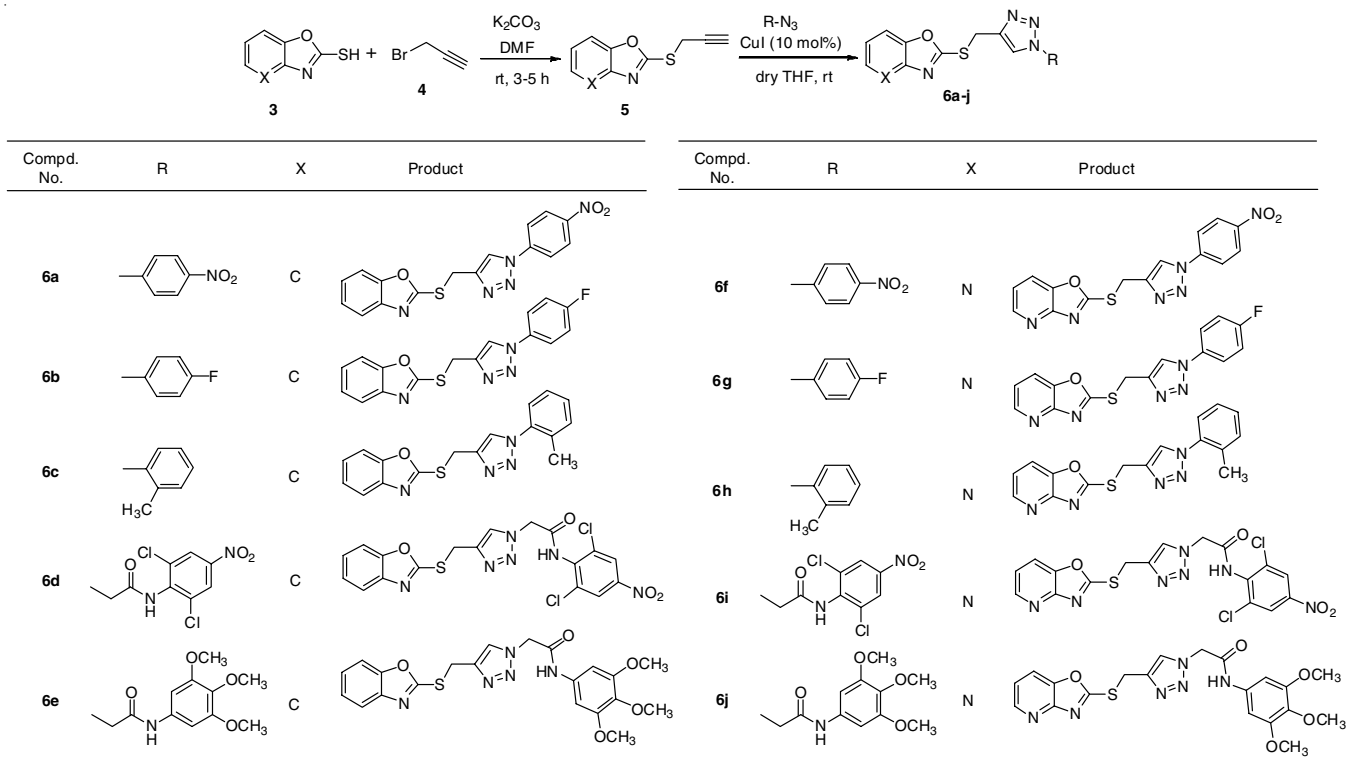
Synthesis of 1,2,3-triazole linked 2-mercaptobenzoxazole/oxazole pyridine-2-thiol derivatives (6a-j): In dry THF (5 mL), 0.27 mmol of propargylated benzo[*d*]oxazole-2-thiol/oxazolo[4,5-*b*]pyridine-2-thiol (**5**) was dissolved. A catalytic amount of CuI was added and subsequently, at room temperature to dry THF, azide (0.27 mmol) was slowly added in nitrogen atmosphere and stirred at 24 h. Reaction completion was confirmed through TLC. Under reduced pressure, the solvent was removed. The residue was diluted and extracted using distilled water and EtOAc (3 × 15 mL), respectively. Over anhydrous Na_2SO_4, the combined organic layer was dried, and this layer was concentrated to obtain the product. The purification of the crude product through column chromatography provided the desired product (**Scheme-II**).

2-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)benzo[*d*]oxazole (6a) [26]**:** Yield 80%; m.p. 203-205 ºC; IR (KBr, λ_{max}, cm^{-1}): 3158, 2941, 1603, 1535, 1328, 851; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ 4.86 (s, 2H), 7.32-7.40 (m, 2H), 7.63-7.69 (m, 2H), 8.14-8.21 (m, 2H), 8.45-8.51 (d, 2H, *J* = 8.6 Hz), 8.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): δ 28.84, 110.18, 119.34, 120.67, 121.60, 124.09, 124.79, 125.79, 141.16, 144.46, 148.92, 149.88, 163.51; MS (ESI): *m/z* 353 $[M+H]^+$.

2-((1-(4-Fluorohenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)benzo[*d*]oxazole (6b) [26]**:** Yield 88%; m.p. 192-194 ºC; IR (KBr, λ_{max}, cm^{-1}): 3077, 2933, 1604, 1534, 1460, 1324, 1127; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ 4.98 (s, 2H), 7.29-7.36 (m, 2H), 7.45-7.54 (m, 2H), 7.63-7.74 (m, 2H), 7.77-7.90 (m, 2H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): δ 26.78, 109.93, 116.47, 118.48, 120.90, 121.61, 122.40, 123.15, 124.22, 124.35, 141.80, 144.40, 152.44, 163.55; MS (ESI): *m/z* 327 $[M+H]^+$.

2-((1-*o*-Tolyl-1*H*-1,2,3-triazol-4-yl)methylthio)benzo[*d*]oxazole (6c) [26]**:** Yield 81%; m.p. 190-192 ºC; IR (KBr, λ_{max}, cm^{-1}): 3147, 2958, 1559, 1460, 1372, 1041; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H), 4.80 (s, 2H), 7.27-7.33 (m, 2H), 7.34-7.40 (m, 2H), 7.44-7.52 (m, 2H), 7.61-7.72 (m, 2H), 8.47 (s, 1H); ^{13}C NMR (75 MHz, DMSO): δ 17.91, 27.99, 110.08, 118.44, 124.28, 125.27, 125.96, 126.34, 129.85, 131.59, 133.56, 136.38, 141.62, 143.57, 151.81, 164.94; MS (ESI): *m/z* 323 $[M+H]^+$.

2-(4-Benzo[*d*]oxazole-2-ylthio)methyl-1*H*-1,2,3-triazol-1-yl)-*N*-(2,6-dichloro-4-nitrophenyl)acetamide (6d): Yield 70%; m.p.: 130-132 ºC; IR (KBr, λ_{max}, cm^{-1}): 3440, 3151, 2925, 1684, 1509, 1222, 1139, 836; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ 4.81 (s, 2H), 5.01 (s, 2H), 7.04-7.12 (m, 1H), 7.16-7.27 (m, 1H), 7.32-7.42 (m, 1H), 7.60-7.69 (m, 1H), 8.50 (s, 1H), 8.72 (s, 2H), 10.12 s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$



Scheme-II: Synthesis of 1,2,3-triazoles linked 2-mercaptobenzoxazole/oxazolopridine-2-thiol

+ DMSO): δ 29.09, 50.56, 111.86, 117.17, 117.94, 122.68, 123.38, 124.38, 131.24, 132.93, 139.76, 148.48, 166.40, 171.62; MS (ESI): *m/z* 480 $[M+H]^+$.

2-(4-Benzo[*d*]oxazole-2-ylthio)methyl-1*H*-1,2,3-triazol-1-yl)-*N*-(3,4,5-trimethoxyphenyl)acetamide (6e): Yield 70%; m.p. 136-138 ºC; IR (KBr, λ_{max}, cm^{-1}): 3423, 3149, 2931, 1604, 1538, 1461, 1130, 842; ^{1}H NMR (300 MHz, DMSO): δ 3.69-4.04 (m, 9H), 4.82 (s, 2H), 5.26 (s, 2H), 7.01-7.13 (m, 1H), 7.20 (s, 2H), 7.34-7.40 (m, 1H), 7.27 (d, 1H, *J* = 8.87 Hz), 7.65 (d, 1H, *J* = 8.49 Hz), 8.48 (s, 1H), 11.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO): δ 29.80, 50.63, 55.96, 59.94, 101.14, 108.38, 116.89, 117.85, 121.08, 123.40, 132.80, 139.08, 145.54, 153.15, 166.85; MS (ESI): *m/z* 456 $[M+H]^+$.

((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)-oxazole [4,5-*b*]pyridine (6f): Yield 81%; m.p. 136-140 ºC; IR (KBr, λ_{max}, cm^{-1}): 3263, 2931, 1606, 1536, 849; ^{1}H NMR (300 MHz, DMSO): δ 4.32 (s, 2H), 6.48 (t, 1H, *J* = 7.62 Hz), 6.98 (d, 1H, *J* = 7.62 Hz), 7.83 (d, 1H, *J* = 5.31 Hz), 8.08 (s, 1H), 8.11(d, 2H, *J* = 8.18 Hz), 8.43 (d, 2H, *J* = 8.18 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ δ29.70, 113.36, 119.41, 125.63, 126.38, 144.60, 146.60, 146.90, 152.59; MS (ESI): *m/z* 455 $[M+H]^+$.

2-((1-(4-Fluorohenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)oxazole[4,5-*b*]pyridine (6g): Yield 78%; m.p. 143-146 ºC; IR (KBr, λ_{max}, cm^{-1}): 3210, 2930, 1604, 1511, 1457, 1259, 1050; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.84 (s, 2H), 7.25-7.32 (m, 1H), 7.46-7.56 (m, 2H), 7.70-7.79 (m, 1H), 7.88-7.99 (m, 2H), 8.49 (m, 1H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): δ 29.67, 113.30, 119.05, 119.56, 126.23, 127.39, 145.75, 150.26, 152.99, 168.81; MS (ESI): *m/z* 328 $[M+H]^+$.

2-((1-*o*-Tolyl-1*H*-1,2,3-triazol-4-yl)methylthio)-oxazole[4,5-*b*]pyridine (6h): Yield 72%; m.p. 209-212 ºC; IR (KBr, λ_{max}, cm^{-1}): 3157, 2924, 1611, 1575, 1496, 1370, 1177, 1025; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ 2.11 (s, 3H), 4.80 (s, 2H), 7.23-7.33 (m, 1H), 7.42-7.50 (m, 1H), 7.52-7.62 (m, 2H), 7.64-7.74 (m, 1H), 7.77-7.84 (m, 1H), 8.03-8.11 (m, 1H), 8.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): δ 18.12, 30.06, 113.27, 119.34, 124.09, 124.79, 125.79, 134.33, 145.13, 147.05, 153.09, 163.51; MS (ESI): *m/z* 324 $[M+H]^+$.

2-(4-Oxazole[4,5-*b*]pyridine-2-ylthio)methyl-1*H*-1,2,3-triazol-1-yl)-*N*-(2,6-dichloro-4-nitrophenyl)acetamide (6i): Yield 70%; m.p. 189-192 ºC; IR (KBr, λ_{max}, cm^{-1}): 3334, 3126, 2927, 1682, 1547, 1331, 1117; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ 4.83 (s, 2H), 5.10 (s, 2H), 7.25-7.34 (m, 1H), 7.50-7.54 (m, 1H), 8.54 (s, 1H), 8.60-8.64 (m, 1H), 8.80 (s, 2H), 11.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): δ 30.31, 51.75, 117.87, 118.14, 119.26, 119.36, 120.19, 129.39, 131.62, 140.65, 147.71, 154.66, 166.97; MS (ESI): *m/z* 481 $[M+H]^+$.

2-(4-Oxazole[4,5-*b*]pyridine-2-ylthio)methyl-1*H*-1,2,3-triazol-1-yl)-*N*-(3,4,5-trimethoxyphenyl)acetamide (6j): Yield 72%; m.p. 215-217 ºC; IR (KBr, λ_{max}, cm^{-1}): 3423, 3125, 2932, 1585, 1494, 1447, 1369, 1127, 841; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.72-4.10 (m, 9H), 4.85 (s, 2H), 5.28 (s, 2H), 7.10-7.20 (m, 1H), 7.30 (s, 2H), 7.55-7.62 (m, 1H), 8.56 (s, 1H), 8.80-8.85 (m, 1H), 11.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.11, 51.36, 56.20, 60.83, 100.19, 116.77, 117.81, 120.52, 120.94, 123.15, 133.94, 139.42, 148.83, 153.39, 162.21, 169.89; MS (ESI): *m/z* 457 $[M+H]^+$.

Biological activity

Antimicrobial activity: Their antibacterial activity of the synthesized compounds **6a-j** against *P. aeruginosa*, *E. coli*, *S. pyogenus* and *S. aureus* and their antifungal activity against *A. niger*, *C. albicans* and *A. clavatus* were screened using the broth dilution method by employing DMSO as a solvent at different

concentrations. In primary and secondary screening, serial dilutions were prepared. In primary screening and 250, 500 and 1000 µg/mL of the synthesized compounds were used. The synthesized compounds active in primary screening were further analyzed against all microorganisms in a second set of dilution. Similarly, the synthesized compounds that were active during primary screening were diluted for secondary screening to acquire 6.250, 12.5, 25, 50, 100 and 200 µg/mL. Before inoculation, a control tube with no antibiotic was immediately sub cultured by evenly spreading a loopful on a quarter of a medium suitable plate to grow the test organism. This tube was incubated overnight at 37 ºC. The minimum inhibitory concentration (MIC) of control organisms was read to determine the drug concentration accuracy. The lowest concentration that led to the inhibition of organism growth was recorded as MIC. The of growth inhibition zone was measured. The measured activity was compared with the activity of standard drugs. For comparison, the commercial antibacterials ampicillin, chloramphenicol, gentamycin, norfloxacin and ciprofloxacin and antifungals griseofulvin and nystatin were also analyzed under the similar conditions.

Antibacterial activity: The MIC of synthesized compounds **6a-j** was examined against two representative Gram-positive microorganisms *viz*. *Streptococcus pyogenes* (MTCC442) and *Staphylococcus aureus* (MTCC96); and against Gram-negative organism *e.g*. *P. aeruginosa* (MTCC441) and *E. coli* (MTCC443). Broth dilution techniques were used for assays. Moreover, for comparison, standard antibacterial agents including ampicillin, gentamycin, ciprofloxacin, chloramphenicol and norfloxacin were examined under similar conditions.

RESULTS AND DISCUSSION

All 1,2,3-triazoles were synthesized from the appropriate aromatic azides as outline in **Schemes I** and **II**. First, compound benzo[*d*]oxazole-2-thiol/oxazolo-[4,5-*b*]pyridine-2-thiol (**3**) was synthesized by treating CS_2 with 2-aminophenol/2-aminopyridin-3-ol (**1**) by using alcoholic KOH under reflux conditions in water, affording a good yield of the respective product (**Scheme-I**) [25,26]. The structure of compound **3** was verified using mass spectrometry. The results showed the *m/z* value at 152 and 153 $[M+H]^+$ for benzoxazole-2-thiol and oxazolopyridine-2-thiol, respectively.

The reaction of propargyl bromide with compound **3** conducted using two equivalents of an inorganic base, K_2CO_3, at ambient temperature in DMF led to the formation of 2-(prop-2-ynylthio)oxazolo[4,5-*b*]pyridine/2-(prop-2-ynylthio)benzo-[*d*]oxazole (**5**) (**Scheme-II**). The formation of propargylated oxazolo pyridine-2-thiol and benzoxazole-2-thiol compounds was confirmed using ^{1}H NMR, which showed signals at 4.17 and 4.09 ppm for the two CH_2 protons.

Furthermore, the 1,3-dipolar cycloaddition of 2-(prop-2-ynylthio)oxazolo[4,5-*b*]pyridine/2-(prop-2-ynylthio)benzo-[*d*]oxazole (**5**) with different aromatic azides catalyzed through Cu(I) in THF by using the click chemistry method under sharpless conditions led to the exclusive formation of 1,4-disubstituted 1,2,3-triazole-linked 2-mercaptobenzoxazole/oxazole pyridinethiol derivatives (**6a-j**) [27,28]. The ^{13}C NMR revealed the triazollyl proton and C-atom at 8.04-8.80 and 117.81-119.56 ppm, respectively, for different derivatives.

Biological activity

Antimicrobial activity: The *in vitro* antifungal activity of the novel synthesized compounds **6a-j** was investigated against fungal strains, *Aspergillus niger* (MTCC282), *Candida albicans* (MTCC 227) and *Aspergillus clavatus* (MTCC 1323), by employing greseofulvin and nystatin as standard antifungal drugs. According to the antifungal activity data of compounds **6a-j**, against *C. albicans* strain, compounds **6j** and **6g** exhibited a higher antifungal activity than greseofulvin did as a standard drug. Compounds **6b** and **6h** exhibited an activity which was equipotent with that of greseofulvin standard drug against *C. albicans* strain. Against *A. niger* strain, compounds **6a** and **6j** exhibited moderate activity, while rest of the synthesized compounds showed a relatively lower activity. Compounds **6a** and **6j** exhibited reasonable

TABLE-1
THE ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES DATA OF SYNTHESIZED COMPOUNDS (**6a-j**)

Compound	Minimum inhibitory concentration (µg/mL)						
	Antibacterial activity				Antifungal activity		
	E. coli MTCC 443	*P. aeruginosa* MTCC 441	*S. aureus* MTCC 96	*S. pyogenus* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
6a	62.5	200	200	250	1000	250	250
6b	100	200	100	100	500	1000	1000
6c	200	100	100	125	1000	500	500
6d	200	100	125	200	1000	500	500
6e	62.5	100	250	200	1000	500	500
6f	125	200	200	250	1000	1000	1000
6g	62.5	100	250	100	250	> 1000	> 1000
6h	125	62.5	200	200	500	500	500
6i	200	200	250	250	1000	500	500
6j	200	200	125	200	100	250	250
Gentamycin	0.05	1	0.25	0.5	–	–	–
Ampicillin	100	--	250	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	25	25	50	50	–	–	–
Norfloxacin	10	10	10	10	–	–	–
Nystatin	–	–	–	–	100	100	100
Greseofulvin	–	–	–	–	500	100	100

activity against *A. clavatus* strain compared with the standard greseofulvin drug, while compounds **6b**, **6c**, **6d**, **6e**, **6f**, **6g**, **6h** and **6i** exihibted low activity. The results indicated that *C. albicans* strain was more sensitive than other fungal strains towards the fabricated compounds. Compounds **6g** and **6j** were the most potential antifungal agents (Table-1).

Antibacterial activity: The *in vitro* antibacterial activity of all the synthesized compounds **6a-j** was evaluated. The results indicated that compounds **6a-j** exhibit a considerable activity against ampicillin with a high degree of variation. Compounds **6e** and **6g** exhibited substantial activity against the Gram-negative bacterial strains. The activity of compounds **6b**, **6f** and **6h** against *E. coli* (MTCC443) was moderate and that of compounds **6c**, **6d** and **6h** against *P. aeruginosa* (MTCC441) was reasonable. Against Gram-positive *S. aureus* (MTCC96), compounds **6b**, **6c**, **6d** and **6j** exhibited sensibility. Compared with the MIC of the standard drugs and tested compounds, the sensitivity of Gram-negative bacterial strains was higher than that of Gram-positive bacterial strains (Table-1).

Conclusion

A series of 1,2,3-triazole linked of 2-mercaptobenzoxazole/ oxazole pyridine-2-thiaol derivatives (**6a-j**) have been synthesized through a facile strategy and screened for antimicrobial activity. The results of antibacterial screening revealed that compounds **6a**, **6e** and **6g** showed good inhibition toward *E. coli* bacteria strain with ampiciline drug and compounds **6g** and **6j** exhibited higher inhibition towards *C. albican* fungi strain against greseofulvin drug.

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