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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL UREA/THIOUREA DERIVATIVES

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Abstract:
A series of novel urea/thiourea derivatives **3a-k** were synthesized by the reaction of equimolar quantities of 2-(benzo[d]thiazol-2-yl) aniline **(1)** in dry tetrahydrofuran (THF) and various isocyanates and thioisocyanates at room temperature in the presence of triethylamine (TEA) with high yields. All the title compounds were characterized by elemental; infrared (IR); ^{1}H and ^{13}C NMR; and mass spectral data analyses. Synthesized compounds were screened for their antimicrobial activity. Among the all compounds 3a, d, fe and j exhibits potential antibacterial activity. Compounds 3d and 3i shows great antifungal activity at 100µg/mL concentration.

Keywords: Urea, Thiourea, Antibacterial activity, Antifungal activity

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INTRODUCTION

The analyses of heterocycles are one of the major areas in medicinal chemistry and are privileged structures in drug discovery.[1, 2] Through high degree of binding affinity these privileged structures symbolize a class of molecules that act as ligands for various biological. Complications of multi-drug resistant microorganisms have reached on disturbing level in many countries around the world. In countries like United State and European a numbers of clinical reports explain the rising occurrence of meticillin-resistant S. aureus and other antibiotic-resistant human pathogenic microorganisms. There is a serious challenge to the medical community against the infections caused by those microorganisms and an effective therapy is necessary which has led to a search for novel antimicrobial agents. Development of these molecules must permit us to promptly find novel biologically active compounds throughout a broad range of therapeutic areas in a smaller interval scale.

The initial organic compound synthesized in the laboratory is urea, which brought a green revolution throughout the world. Later on its similar structural compound thiourea had discovered which also had significant importance in agriculture for yield improvement [3-5]. Thiourea is important sulphur and nitrogen-containing compounds that have proved to be useful substances in drug research in recent years [1–6]. Some urea derivatives possess valuable antituberculosis, antibacterial and anticonvulsant properties [7]. Most of these compounds include heterocyclic rings such as oxadiazoles, thiadiazoles, triazoles, and pyrazoles. It is well known that the 1, 2, 4-triazole-derived N-bridged heterocyclic find applications in the field of medicine, agriculture and industry [8-11]. The 1, 2, 4-triazole nucleus has also been incorporated into a wide variety of therapeutically important molecules to transform them into better drugs. Drugs such as fluconazole, itraconazole, and the new generation of triazoles posaconazole, voriconazole, and ravuconazole are the best examples of potent antifungal molecules possessing triazole nuclei [12-15]. Previous findings from our laboratory demonstrated that nucleoside and urea compounds with phosphorylation of drugs molecules shows various pharmacological properties including antimicrobial and antioxidant [16-21], anticancer [22,23], antidiabeties [24] and antialzheimers [25-31].

Urea was the initial organic compound synthesized in the laboratory, which brought a green revolution through out the world. Later on its similar structural compound thiourea had discovered which also had significant importance in agriculture for yield improvement. Later on urea and thiourea derivatives had been discovered which exhibited broad spectrum of biological activities such as herbicidal [4], inhibition of nitric oxide [5], anti-viral [6] and analgesic properties [7]. These potent biological activities of urea and thiourea derivatives have stimulated great interest in the synthesis of such compounds for extensive studies related to their biological activities. In view of these observations and applications of urea and Thiourea, we have focused on the synthesis of a series of novel urea and thiourea derivatives by reacting 2-(benzo[d]thiazol-2-yl) aniline with various isocyanates and thioisocyanates in the presence of triethylamine.

MATERIALS AND METHODS

All the chemicals were procured from Sigma-Aldrich, Merck and were used as such. Solvents used for spectroscopic and physical studies were reagent grade and were further purified by the literature methods. Melting points were determined in open capillary tubes by Guna digital melting point apparatus, expressed in (°C) and are uncorrected. Infrared spectra (υ_{max} in cm^{-1}) were recorded as KBr pellets on a Perkin - Elmer, FT-IR 100 spectrophotometer. ^{1}H and ^{13}C spectra were recorded as solutions in DMSO-d_6 on a Bruker 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C. The ^{1}H and ^{13}C chemical shifts were expressed in parts per million (ppm) with reference to tetramethylsilane (TMS) and Mass spectra were recorded in E.S.I Mode on API-3000 mass spectrometer. Elemental analysis was performed on Thermo Finnegan Instrument at University of Hyderabad, Hyderabad.

General procedure for the preparation of compounds 3a-k

1-(2-(Benzo [d]thiazol-2-yl) phenyl)-3-(4-nitrophenyl) urea (3a)

Yield: 74%, Pale yellow, mp 210-212 ºC; IR (KBr) (v_{max} cm^{-1}): 1647(C=O),1074(C-O), 3428 (NH); ^{1}H-NMR (DMSO-d_6) δ ppm: 6.80-7.30 (m, 10H, Ar-H), 7.60 (d, 2H, Ar-H) , 8.75(s,1H,NH), 8.90(s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 116.3, 119.7, 121.4, 121.6, 125.1, 124.0, 124.3, 124.6, 127.3, 128.1, 128.7, 133.6, 136.1, 143.1, 145.1, 152.7, 154.1; Anal. Calcd. For $C_{20}H_{14}N_4O_3S$: C, 61.53; H, 3.61; N, 14.35; Found: C, 61.40, H, 3.56; N, 14.30. GC-MS m/z 390 (100, $M^{+\cdot}$), 269(40), 181(60), 130(70).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-chlorophenyl)urea (3b)

Yield: 70%, Dark Brown solid, mp 180-182 ºC; IR (KBr) (v_{max} cm^{-1}): 1640(C=O),1080(C-O),

3400 (NH); ^{1}H-NMR (DMSO-d_6) δ ppm: 6.82-7.40 (m, 12H, Ar-H), 8.68(s,1H,NH), 8.78(s,1H,NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 116.2, 120.6, 121.3, 121.5, 124.0, 124.1, 125.0, 127.5, 128.1, 128.6, 129.6, 133.2, 133.5, 136.2, 137.4, 152.6, 154.3, 166.3; Anal. Calcd. For $C_{20}H_{14}ClN_3OS$: C, 63.24; H, 3.71; N, 11.06. Found: C, 63.19, H, 3.68; N, 10.90; GC-MS m/z 379 (100, $M^{+\cdot}$), 381(33, $M^{+\cdot}$+2), 269(55), 169, 143(65), 130(54).

1-(2-(Benzo[d]thiazol-2-yl) phenyl)-3-(4-bromophenyl) urea (3c)

Yield. 72%, Pale Brown solid, mp 167-169 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1633(C=O),1083(C-O), 3430 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 6.82-7.40 (m, 12H, Ar-H), 8.70(s, 1H, NH), 8.80(s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 116.2 , 121.5, 121.6, 121.7 , 122.0, 124.3, 124.6, 125.2, 127.5, 128.7, 131.7, 133.6, 136.2, 138.1, 138.4, 152.7, 154.3, 166.4; Anal. Calcd. For $C_{20}H_{14}BrN_3OS$: C, 56.61; H, 3.33; N, 9.90**;** Found: C, 56.55, H, 3.28; N, 9.80. GC-MS m/z 424 (100, $M^{+\cdot}$), 426(100, $M^{+\cdot}$+2), 269(28), 214(35).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-fluorophenyl) urea (3d)

Yield. 69%, Pale Orange Solid, mp 152-154 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1643(C=O), 1080(C-O), 3450 (NH); ^{1}H-NMR (DMSO-d_6) δ ppm: 6.81-7.50 (m, 12H, Ar-H), 8.70(s, 1H, NH), 8.92(s, 1H, NH); Anal. Calcd. For $C_{20}H_{14}FN_3OS$ C, 66.10; H, 3.88; N, 11.56. Found: C, 66.19, H, 3.78; N, 11.46; GC-MS m/z 363 (100, $M^{+\cdot}$), 269(56), 154(64).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(3-chloro-4-(trifluoromethyl)phenyl)urea(3e)

Yield 74%, Pale Orange Solid, mp 163-165 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1630(C=O), 1085(C-O), 3300 (NH); ^{1}H-NMR (DMSO-d_6) δ ppm: 6.90-7.60 (m, 12H, Ar-H), 8.50(s,1H, NH), 8.80(s, 1H, NH); Anal. Calcd. For $C_{21}H_{13}ClF_3N_3OS$: C, 56.32 H, 2.93; N, 9.38. Found: C, 56.22, H, 2.79; N, 9.20.

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-nitrophenyl)thiourea (3f)

Yield. 72%, Pale Yellow Solid, mp 215-217 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1350(C=S), 3310 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 6.70-7.30 (m, 10H, Ar-H), 7.50(d, 2H, Ar-H), 8.50(s, 1H, NH), 8.80(s,1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 120.6, 120.7, 121.4, 121.6, 124.2, 124.3, 124.6, 125.2,125.3, 127.4, 133.0, 133.6, 137.6, 143.7, 144.4, 154.2, 166.4,178.8, ; Anal. Calcd. For $C_{20}H_{14}N_4O_2S_2$**:** C, 59.10; H, 3.47; N, 13.78. Found C, 58.94; H, 3.25; N, 13.55;. GC-MS m/z 406 (100, $M^{+\cdot}$), 284(47), 196(38).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-chlorophenyl)thiourea (3g)

Yield. 68 %, White solid, mp 190-192 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1345(C=S), 3310 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 6.90-7.60 (m, 12H, Ar-H), 8.50(s, 1H, NH), 8.80(s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 120.9, 121.4, 121.6, 124.3, 124.9, 125.1, 127.6, 128.8, 129.6, 131.6, 133.0, 133.6, 136.4, 137.4, 154.2, 166.3, 179.7 ;Anal. Calcd. For $C_{20}H_{14}ClN_3S_2$: C, 60.67; H, 3.56; N, 10.61. Found C, 60.67; H, 4.00; N, 10.60 ;. GC-MS m/z 395(100, $M^{+\cdot}$), 397(33, $M^{+\cdot}$+2), 284(54), 186(33).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-bromophenyl)thiourea (3h)

Yield.78%, White Solid, mp 171-173 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1348(C=S), 3310 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 6.90-7.60 (m, 12H, Ar-H), 8.50(s, 1H, NH), 8.80(s, 1H, NH); Anal. Calcd. For $C_{20}H_{14}BrN_3S_2$; C, 54.55; H, 3.20; N, 9.54. Found C, 54.45; H, 2.98; N, 9.44 ;. GC-MS m/z **:** 440 (100, $M^{+\cdot}$), 442(100, $M^{+\cdot}$+2), 284(49), 231(29).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-fluorophenyl)thiourea (3i)

Yield. 76%, Dark Brown solid, mp 185-187 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1340(C=S), 3310 (NH); ^{1}H-NMR (DMSO-d_6) δ ppm: 6.94 - 7.80 (m, 12H, Ar-H), 8.50(s, 1H, NH), 8.80(s,1H,NH); Anal. Calcd. For $C_{20}H_{14}$ FN_3S_2: C, 63.30; H, 3.72 N, 11.07. Found C, 63.25; H, 3.76; N, 11.18 **;**. GC-MS m/z **:** 379 (100, $M^{+\cdot}$), 284(53), 169(34).

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(3-chloro-4-trifluoromethyl)phenyl)thiourea (3j)

Yield.70%, Pale Orange Solid, mp 185-187 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1350(C=S), 3310 (NH); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.00-7.80 (m, 12H, Ar-H), 8.30(s, 1H, NH), 8.70(s, 1H, NH). Anal. Calcd. For $C_{21}H_{13}ClF_3N_3S_2$: C, 54.37; H, 2.82; N, 9.06. Found C, 54.28; H, 2.76; N, 8.95.

1 -Allyl-3-(2-(benzo[d]thiazol 2byl)phenyl)thiourea (3k)

Yield 72%, Dark red solid, mp 175-177 ^{o}C; IR (KBr) (ν_{max} cm^{-1}): 1347(C=S), 3400 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 6.94 - 7.80 (m, 12H, Ar-H), 8.50(s, 1H, NH), 8.80(s, 1H, NH);Anal. Calcd. For **:** $C_{17}H_{15}N_3S_2$; C, 62.74; H, 4.65; N, 12.91. Found C, 62.70; H, 4.59; N, 12.81.

Biological activity Antibacterial activity

All the newly synthesized compounds **3a-k** were screened for their antibacterial activity against gram positive bacteria such as *Staphylococcus aureus (ATCC-29737)* and *Bacillus subtilis* (ATCC-6633) and the gram negative bacteria such as *Escherichia coli (ATCC-2343)*and *Pseudomonas aeruginosa* (MTCC-1034) using disc diffusion method [32]. The cultures were diluted with sterilized saline to bring the final inoculum size of approximately 10^5–10^6 CFU/mL. These solutions containing 10^6 cells/ mL were added to each Whatmann No.1 filter paper disc (6 mm

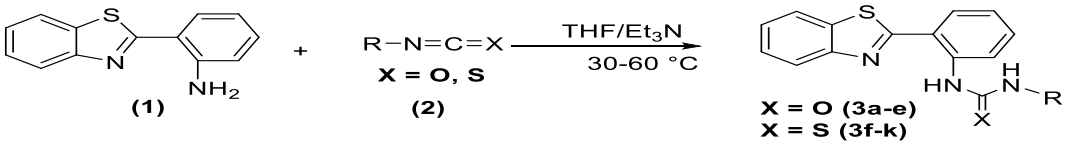
diameter) and acetone and diethyl ether was used as the control.

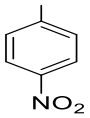
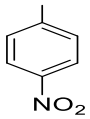
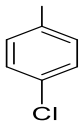
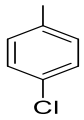
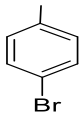
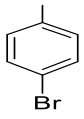
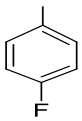
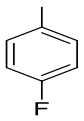
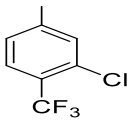
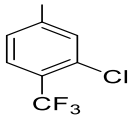
Antifungal activity

The antifungal activity of newly synthesized compounds **3a-k** was tested against three pathogenic fungi including *Aspergillus niger*, *Candica albicans* and *Fusarium oxysporium* by the poison plate technique. Test compounds were dissolved in acetone (10 mL) before mixing with Potato Dextrose Agar (PDA, 90 mL). The final concentration of the compounds in the medium was fixed at 100 *µg*/ mL. Three kinds of fungi were incubated in PDA at 25±1 °C for 5 days to get new mycelium for antifungal assay, then a mycelia disc of approximately 0.45 cm diameter cut from the culture medium was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25±1°C for 5 days. Acetone in sterilized distilled water served as control, while Amphotericin was used as positive control. For each treatment, three replicates were carried out. The radial growth of the fungal colonies was measured on the sixth day. The *in vitro* inhibiting effects of the test compounds on the fungi were calculated by the formula CV =A-B/A, where A represents the diameter of fungi growth on untreated PDA, B represents the diameter of fungi on treated PDA, and CV represents the rate of inhibition. The bacterial and fungal cultures containing discs were placed on the media and incubated at 37 °C for 24 h to 72 h for better observation. All the experiments were carried out in triplicates and the results were expressed as zone of inhibition in mm.

RESULTS AND DISCUSSION

To a stirred solution of 2-(benzo[d]thiazol-2-yl) aniline **(1)** in dry tetrahydrofuran (THF) (15 mL) and various isocyanates/thioisocyanates were added at room temperature in the presence of triethylamine (TEA). After completion of the addition, the reaction mixture was stirred for 2h at 60 ºC. The reaction progress was monitored by thin layer chromatography (TLC). After completion of the reaction, $Et_3N.HCl$ was filtered off solvent was removed in a rota-evaporator to obtain crude product. It was purified by silica gel column chromatography eluting with ethylacetate: hexane (1:2) to afford the title compounds **(3a-k).**



	R	X		R	X
3a		O	3f		S
3b		O	3g		S
3c		O	3h		S
3d		O	3i		S
3e		O	3j		S
			3k	$CH_2=CH-CH_2-$	S

Scheme.1 Synthesis of Urea and Thiourea Derivatives

The infrared spectral data of **3a-k** are given in experimental part. Characteristic IR stretching absorptions [18] were observed in the regions 3228-3428, 1630-1647 , 1341-1350 cm^{-1} for N-H, C=O and C=S, respectively. Aromatic protons of all titled compounds appeared as complex multiplets in the region 6.80-7.80 ppm. The NH protons attached to –C=O / –C=S appeared as two distinct singlet in the region 8.50-8.80 ppm. Aromatic carbons of all titled compound appeared in their expected region. The –C=O carbon of compounds **1, 3a, 3c** appeared as singlet in the region 152.6-152.7 ppm whereas the –C=S carbon of compound **3k** appeared as singlet in the region δ 178.8.

In this study we have synthesized novel derivatives of urea/Thiourea compounds were tested for their antibacterial and antifungal activities at the concentration of100 µg/mL. From the Table 1 it is demonstrated that, among the all compounds **3a, 3d, 3e** and **3j** were showed potential activity against *S. aures*, *E.coli*, *B.substilis* and *P. auroginosa.* Remaining compounds were exhibits moderate antibacterial activity when compared to positive broad spectrum antibiotic Gatifloxacin.

In addition to the antibacterial activity, we have also carried out the antifungal activity against Aspergillus niger, Candida albicans, Fusarium oxysporum. The obtained results were suggested that compounds 3d and 3i shows potential antifungal activity and other compounds elicits moderate to good antifungal activity. The obtained results were measured in terms of zone of inhibition in milli meters (Table 2).

Table 1: Antibacterial Activity of Synthesized Thiourea Derivatives

Compounds	Zone of Inhibition (m)			
	S.aureus	*B. subtilis*	*E.coli*	***P. auroginosa***
3a	11.7±0.01	14.6±0.02	14. 9±0.02	**12.8±0.02**
3b	09.7±0.02	10.4±0.03	09.1±.0.03	**09.9±.0.04**
3c	09.1±0.04	09.0±0.05	08.6±0.02	**08.7±0.03**
3d	08.5±0.02	11.0±0.03	11.4±0.04	**10.6±0.01**
3e	11.4±0.03	13.9±0.04	14.2±0.05	**12.4±0.02**
3f	11.2±.0.02	14.8±0.06	13.4±0.05	**12.0±0.06**
3g	08.4±.0.03	10.0±0.04	11.4±0.02	**10.0±0.02**
3h	08.0±.0.02	09.8±0.02	09.5±0.01	**10.5±0.03**
3i	09.0±.0.04	11.9±0.01	11.8±0.06	**11.2±0.05**
3j	10.4±.0.01	13.9±0.03	14.0±.0.04	**13.3±0.02**
3k	9.12±.0.04	10.2±.0.03	11.3±.0.04	**10.7±.0.01**
Gatifloxacin	**07.1±.0.01**	**08.8±0.02**	**07.2±.0.01**	**08.0±0.08**

Table 2: Antifungal Activity of the Title Compounds Measure in Zone Of Inhibition (mm)

Compound[a]	*A.niger*	*C.Albicans*	*F.oxysporum*
3a	07.0±0.02	07.3±0.01	08.9±0.02
3b	08.0±0.02	09.0±0.02	09.3±0.03
3c	07.4±0.04	08.2±0.03	08.4±0.03
3d	11±0.04	10.57±0.02	11±0.02
3e	09.6±0.03	09.1±0.04	08.9±0.03
3f	07.8±0.02	08.6±0.03	08.4±0.02
3g	07.3±0.05	07.6±0.02	07.1±0.03
3h	08.7±0.03	07.0±0.04	09.0±0.02
3i	11.0±0.04	11.4±0.02	10.9±0.03
3j	09.5±0.04	07.4±0.02	09.8±0.05
3k	07.0±0.02	06.9±0.02	07.0±0.04
Amphotericin[b]	13.0±0.30	12.0±0.43	11.9±0.05

Values are mean ± S.D of three replicates ($p < 0.05$). [a] 100 µg/mL, [b]100 µg/mL

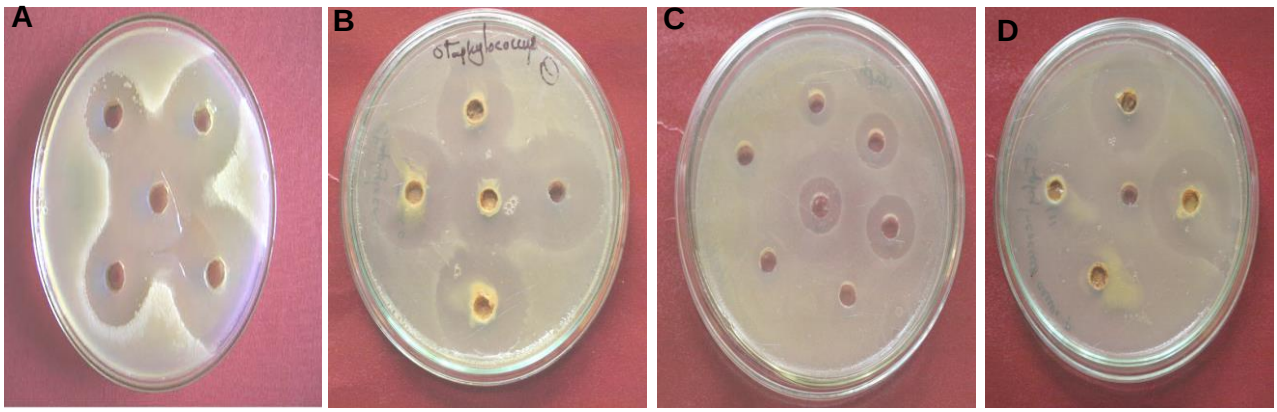


Fig 1: Schematic representation of Zone of inhibition showing anti bacterial activity of synthesized compound 3j tested against Bacillus (A), Staphylococcus (B), E.coli (C) and Pseudomonas auroginosa (D).

CONCLUSION

From the above results and aforementioned discussions it can be concluded that synthesized Thiourea derivatives (3a, 3d, 3i and 3j) have shows potential antimicrobial activities against both gram positive and negative microbes at lower concentrations. The selected compounds were needed to be tested in animal models for their better pharmacotherapy.

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