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Synthesis and Antimicrobial Activity of Novel Urea/Thiourea Derivatives

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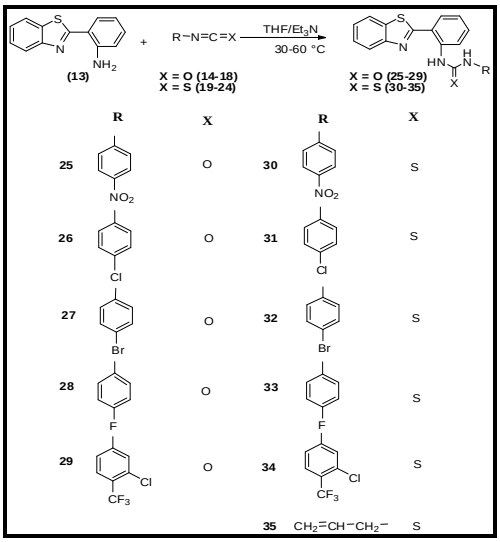
ABSTRACT

Synthesis of novel urea and thiourea derivatives has been accomplished by reacting 2-(benzo [d]thiazol-2-yl) aniline with various isocyanates and thio isocyanates. Structures of all the newly synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR, mass and elemental analysis. Their structures were established by analytical and spectral data. All the newly synthesized compounds 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 aeruginogsa (MTCC-1034) using cup plate agar diffusion method. Synthesized compounds exhibited high antibacterial activity against both gram positive and gram- negative strains. Compounds 28, 33 exhibited good antifungal activity, remaining title compounds exhibited moderate antibacterial and antifungal activities. All the newly synthesized compounds exhibited promising antimicrobial activity.

Graphical Abstract

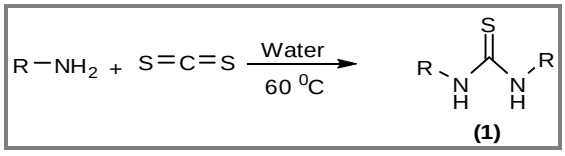


Synthesis of urea and thiourea derivatives

Keywords: Urea, Thiourea, Antibacterial activity, Antifungal activity.

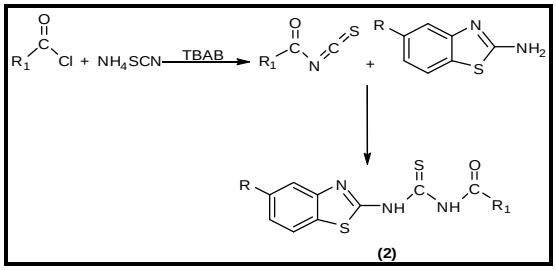
INTRODUCTION

Urea was the first organic compound synthesized in the laboratory, which brought a green revolution through out the World. Later on its similar structural compound thiourea had invented, which also had significant importance in agriculture for yield improvement [1-3]. 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]. Urea and thiourea are used in synthesis of some Schiff bases as ligands [8]. Amiri *et al* [9] reported an operationally simple and entirely green protocol for the synthesis of thiourea derivatives by the reaction of carbon disulfide with primary amines in pure water. This protocol is a highly atom-economic process for production of highly pure, hindered thioureas without any catalyst and tedious work-up.



(1)

A mild and efficient protocol for the preparation of thiourea (**2**) was reported by Saeed *et al* [10] from benzothiazole moiety as potent antimicrobial and anticancer agents.



(2)

Ettari *et al.,* [11] synthesized a new series of phenyl ethyl thiourea (PET) derivatives, with the aim to extend the SAR studies of the well known PET molecules endowed with anti-HIV activity.

Azam *et al.,* [12] were designed and synthesized a few urea and thiourea derivatives of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidine and studied their antagonistic effects on haloperidol-induced catalepsy and oxidative stress in mice. A majority of the compounds exhibited significant anti Parkinson activity.

An efficient procedure was developed for the synthesis of thiourea derivatives from 2-(4-chlorophenoxymethyl) benzoic acid by Chifiriuc [13] and evaluated their antimicrobial activity. Bhandari *et al.,* [14] synthesized a series of urea and thiourea analogues of fluoxetine and evaluated their anorexigenic and antidepressant activities. Liav *et al.,* [15] synthesized N-D-aldopentofuranosyl-N'-[p-(isoamyloxy)phenyl] -thiourea derivatives and their potential anti-TB therapeutic activities was evaluated. Santos *et al.,* [16] synthesized a series of novel new 1-phenyl-3-{4-[(2E)-3-phenylprop-2-enoyl] phenyl}-thiourea and urea derivatives and evaluated their anti-nociceptive activity. Echevarria *et al.,* [17] synthesized a series of new N-3,3-diphenylpropyl-N-(p-X-benzyl)-N'-phenylureas and thioureas by the reaction of secondary amines and phenyl isocyanate or isothiocyanate. Their cytotoxic effects were evaluated and exhibited promising antiproliferative action. Shao-Yong Ke *et al.,* [18] synthesized a series of *N*-(5-aryl-2-furoyl) thiourea derivatives containing substituted pyrimidine ring under phase transfer catalysis PEG-400 using ultrasound irradiation.

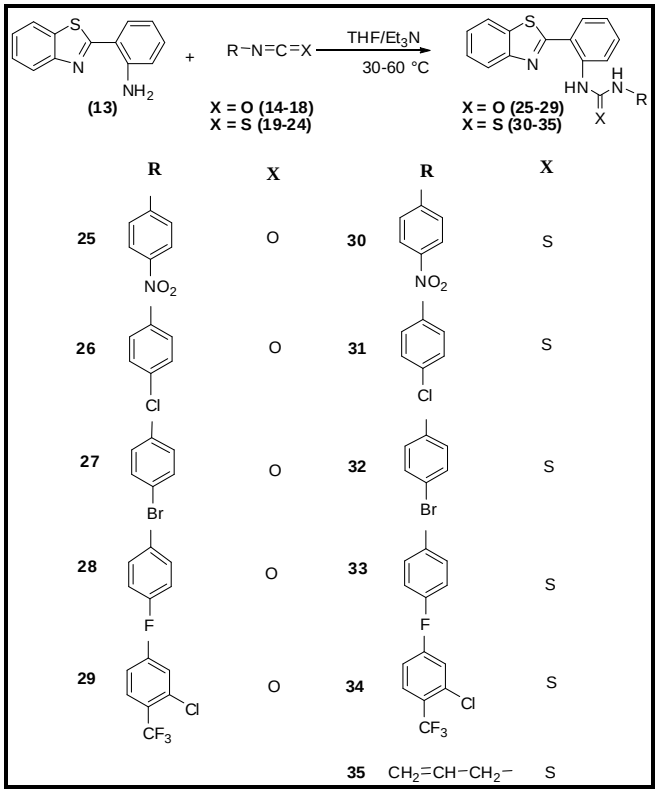
These potent biological activities of urea and thiourea derivatives have stimulated great interest in the synthesis of such compounds for extensive studies related to their biological activities. In view of

these observations and applications of urea and thiourea, the author has 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 thio isocyanates in the presence of triethylamine.

MATERIALS AND METHODS

All 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 [19-22]. Melting points were determined in open capillary tubes by Guan 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}HNMR and ^{13}CNMR 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}HNMR and ^{13}CNMR 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 Finnig an Instrument at University of Hyderabad, Hyderabad.

Synthesis of novel urea and thiourea derivatives was accomplished by reacting 2-(benzo[d]thiazol-2-yl) aniline with various substituted isocyanates and thio isocyanates: To a stirred solution of 2-(benzo[d]thiazol-2-yl) aniline in dry tetrahydrofuran (THF) (15 mL), various isocyanates and thio isocyanates were added at room temperature in the presence of triethylamine (TEA). After completion of the addition, the reaction mixture was stirred for 2 h at 60°C. 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 (**25-35**) (Scheme 1).



Scheme.1 Synthesis of urea and thiourea derivatives.

RESULTS AND DISCUSSION

The prepared compounds spectral data was given below-

1-(2-(Benzo[d]thiazol-2-yl)phenyl)-3-(4-nitrophenyl)urea (25): Yield 74%, Pale yellow, mp 210-212 ^{o}C; 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 (26): Yield 70%, Dark brown solid, mp 180-182 ^{o}C; 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 (27): Yield 72%, Pale brown solid, mp 167-169 ^{o}C; IR (KBr) (v_{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 (28): Yield 69%, Pale orange Solid, mp 152-154 ^{o}C; IR (KBr) (v_{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 (29): Yield 74%, Pale orange solid, mp 163-165 ^{o}C; IR (KBr) (v_{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 (30): Yield 72%, Pale yellow solid, mp 215-217 ^{o}C; IR (KBr) (v_{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 (31): Yield 68 %, White solid, mp 190-192 ^{o}C; IR (KBr) (v_{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 (32): Yield 78%, White Solid, mp 171-173 ^{o}C; IR (KBr) (v_{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 (33): 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 (34): 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-2-yl) phenyl) thiourea (35): 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.

Infrared absorption spectra: 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. The IR spectral data confirm the functional groups present in the compound **26** (Figure 1).

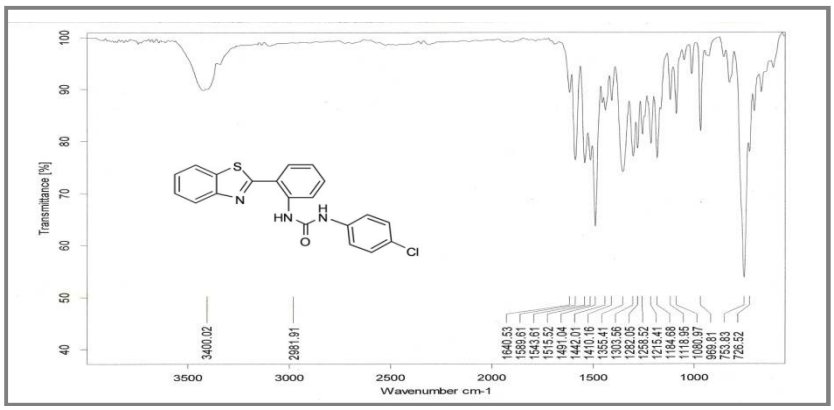


Figure 1. IR Spectrum of 1-(2-(benzo[d]thiazol-2-yl) phenyl)-3-(4-chlorophenyl) urea (**26**).

Proton NMR spectra: 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 singlets in the region 8.50-8.80 ppm (Figure 2 and 3).

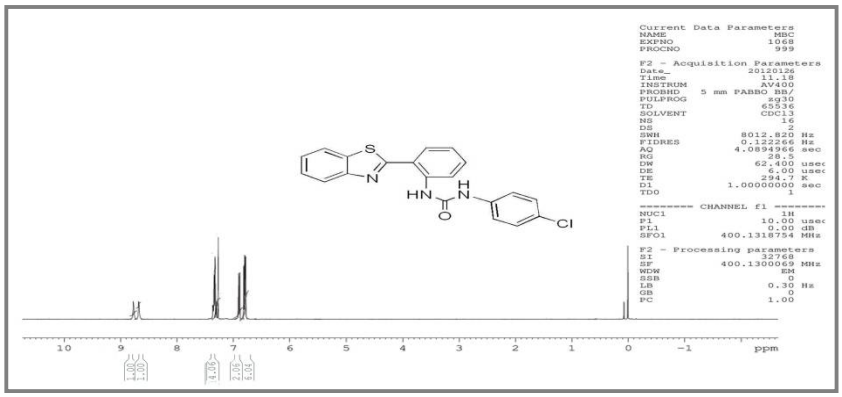


Figure 2. ^{1}H NMR Spectrum of 1-(2-(benzo[d]thiazol-2-yl)phenyl)-3-(4-chlorophenyl) urea **(26).**

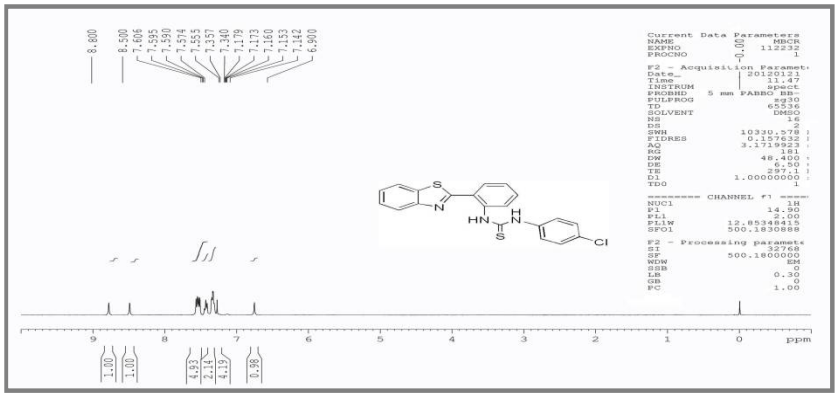


Figure 3. [1]H NMR Spectrum of 1-(2-(benzo[d]thiazol-2-yl)phenyl)-3-(4-chlorophenyl)thiourea **(31).**

[13]CNMR spectra: Aromatic carbons of all titled compound appeared in their expected region. The –C=O carbon of compounds **25, 26, 27** appeared as singlet in the region 152.6 -152.7 ppm whereas the –C=S carbon of compound **30** appeared as singlet in the region δ 178.8 (Figure 4 and 5).

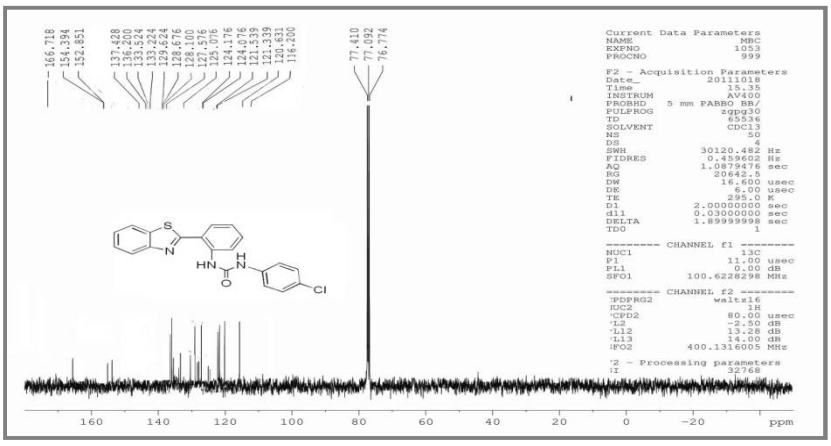


Figure 4. [13]C Spectrum of 1-(2-(benzo[d]thiazol-2-yl) phenyl)-3-(4-chlorophenyl) urea **(26)**.

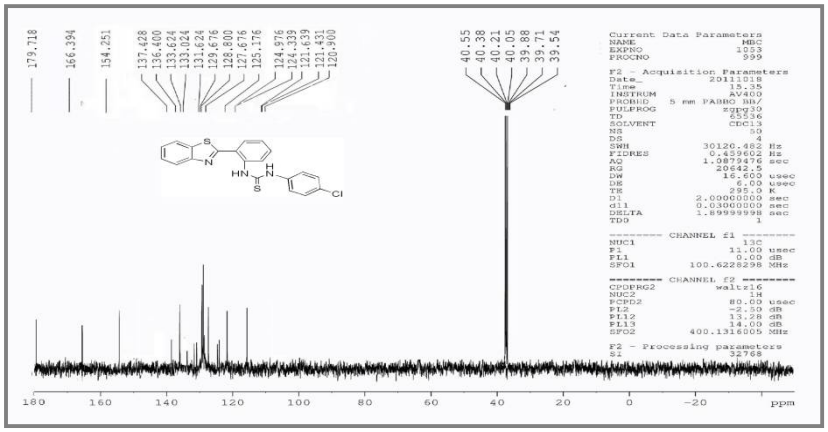


Figure 5. [13]C NMR Spectrum of 1-(2-(benzo[d]thiazol-2-yl) phenyl)-3-(4-chlorophenyl) thiourea **(31)**.

APPLICATION

Antibacterial assay: All the newly synthesized compounds **25-35** 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 cup plate agar diffusion method [**19**]. The cultures were diluted with sterilized saline to bring the final inoculum size of approximately 10^5–10^6 CFU mL^{-1}. These solutions containing 10^6 cells mL^{-1} were added to each Whatman No.1 filter paper disc (6 mm diameter) and acetone and diethyl ether was used as the control. The results were presented in table 1 and compared with Gatifloxacin (100 µg mL^{-1}). Among the synthesized compounds **25, 29, 30** and **34** exhibited high antibacterial activity against both gram positive and gram- negative strains. Remaining title compounds exhibited moderate antibacterial activities.

Table 1. Antibacterial activity of the title compounds

Compounds[a]	Zone of Inhibition (mm)			
	S.aureus (ATCC-29737)	*B. subtilis (ATCC-6633)*	*E.coli (ATCC-2343)*	*P. aeruginosa (MTCC-1034)*
25	11.7±0.01	14.6±0.02	14. 9±0.02	12.8±0.02
26	09.7±0.02	10.4±0.03	09.1±.0.03	09.9±.0.04
27	09.1±0.04	09.0±0.05	08.6±0.02	08.7±0.03
28	08.5±0.02	11.0±0.03	11.4±0.04	10.6±0.01
29	11.4±0.03	13.9±0.04	14.8±0.05	11.9±0.02
30	11.2±.0.02	14.8±0.06	13.4±0.05	12.0±0.06
31	08.4±.0.03	10.0±0.04	11.4±0.02	10.0±0.02
32	08.0±.0.02	09.8±0.02	09.5±0.01	10.5±0.03
33	09.0±.0.04	11.9±0.01	11.8±0.06	11.2±0.05
34	10.4±.0.01	13.9±0.03	14.0±.0.04	13.3±0.02
35	07.1±.0.01	08.8±0.02	07.2±.0.01	08.0±0.08
Gatifloxacin[b]	12.3±0.50	15.0±0.30	15.3±0.72	13.7±0.42

Values are mean ± S.D of three replicates ($p< 0.05$) , [a] 100 µg mL^{-1} , [b] 100 µg mL^{-1}

Antifungal assay: The antifungal activity of newly synthesized compounds **25-35** was tested against three pathogenic fungi, namely *Aspergillus niger, Candica albicans* and *Fusarium oxysporium* by the poison plate technique [**20**]. 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^{-1}. 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.

The results were presented in table 2 and compared with Amphotericin (100 µg mL^{-1}). Compounds **28, 33** exhibited good antifungal activity. Remaining title compounds exhibited moderate antifungal activities.

All the newly synthesized compounds exhibited high to moderate activity, among the synthesized compounds 25, 29 30 and 34 exhibited high antibacterial activity towards both gram positive and gram-negative strains. Compounds 28, 33 exhibited good antifungal activity, remaining title compounds exhibited moderate antibacterial and antifungal activities.

Table 2. Antifungal activity of the title compounds
Zone of inhibition (mm)

Compound[a]	*A.niger*	*C.Albicans*	*F.oxysporum*
25	07.0±0.02	07.3±0.01	08.9±0.02
26	08.0±0.02	09.0±0.02	09.3±0.03
27	07.4±0.04	08.2±0.03	08.4±0.03
28	10.5±0.04	09.8±0.02	09.3±0.02
29	09.6±0.03	09.1±0.04	08.9±0.03
30	07.8±0.02	08.6±0.03	08.4±0.02
31	07.3±0.05	07.6±0.02	07.1±0.03
32	08.7±0.03	07.0±0.04	09.0±0.02
33	10.0±0.04	11.4±0.02	09.9±0.03
34	09.5±0.04	07.4±0.02	09.8±0.05
35	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^{-1}, [b]100 µg mL^{-1}

Statistical analysis: Data of antimicrobial activity were expressed as means ± S.D of three replicates. On the basis of the calculated value by using ANOVA method it has been observed that the difference below 0.05 level ($P<0.05$) were considered as statistically significant.

CONCLUSION

Synthesis of novel urea and thiourea derivatives has been accomplished by reacting 2-(benzo[d]thiazol-2-yl) aniline with various isocyanates and thio isocyanates. Their structures were established by analytical and spectral data. They were screened for their antimicrobial activity. All the newly synthesized compounds exhibited promising antimicrobial activity.

REFERENCES

[1]. M. P. Sahu, D.Singh, Role of thiourea in improving productivity of wheat (*Triticumaestivum* L.), *J. Plant Growth Regul*., **1995**, 4, 169.
[2]. M. P. Sahu, N.S Solanki, L.N. Dashora, Effects of Thiourea, Thiamine and Ascorbic Acid on Growth and Yield of Maize (*Zea mays* L.), *J. Agron Crop Sci*., **1993**, 171, 65.
[3]. M. P .Sahu, N. S. Solanki, Role of Sulphydryl Compounds in Improving Dry Matter Partitioning and Grain Production of Maize (*Zea mays* L.), *J. Argon Crop Sci*., **1991**,167, 356.
[4]. P. A. Yonova , G. M. Stoilkova, Synthesis and biological activity of urea and thiourea derivatives from 2-aminoheterocyclic compounds, *J. Plant Growth Regul.*, **2004**, 23, 280.
[5]. Y. J. Kim, J. H Ryu,. Y. J Cheon, H. J. Lim, R. Jeon, Design and synthesis of urea and thiourea derivatives and their inhibitory activities on lipopolysaccharide-induced NO production, *Bioorg. Medicinal Chem Lett.*, **2007**, 17, 3317.
[6]. J. D. Bloom, R. G. Dushin, K. J. Curran, F. Donahue,. E. B. Norton, E. Terefenko, T. R.Jonas, A. A. Ross, B. Feld, S.A. Lang, M. J. D. Grandi, Thiourea inhibitors of herpes viruses. Part 2: *N*-Benzyl-*N′*-arylthiourea inhibitors of CMV, *Bioorg. Medicinal Chem*., **2004**, 14, 3401.
[7]. J. Rojas, M. Paya, J. N. Domínguez, L. Ferrandiz, The synthesis and effect of fluorinated chalcone derivatives on nitric oxide production, *Bioorg. Medicinal Chem. Lett.*, **2002**, 12(15), 1951.
[8]. Omar H. Al-Obaidi, Synthesis, Characterization and Theoretical Treatment Of Sandwich Schiff Base Complexes Derived from Urea and Thiourea with some Transition Metals and Study of its Biological Activity, *J. Applicable Chem.*, **2012**, 1 (3), 352-359.
[9]. N. Azizi , A. K. Amiri, H. Ghafuri, M. Bolourtchian, Toward a practical and waste-free synthesis of thioureas in water, *Mol. Divers*, **2011**, 15, 157.

[10]. S. Saeed, N. Rashid, P. G. Jones, M. Ali, R. Hussain, Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents, *Eur. J. Med. Chem.*, **2010**, 45, 1323.
[11]. R. Ettari, A. Pinto, N. Micale, Synthesis and anti-HIV activity evaluation of new phenyl ethyl thiourea (PET) derivatives, *Arkivoc*, xiv, **2009**, 227.
[12]. F. Azam, I. A. Alkskas, M. A. Ahmed, Synthesis of some urea and thiourea derivatives of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidine and their antagonistic effects on haloperidol-induced catalepsy and oxidative stress in mice, *Eur. J. Med. Chem.*, **2009**, 44, 3889.
[13]. C. Limban, M. C. B. Chifiriuc , A. V. Missir, I. C. Chiriţa , C. Bleotu, Antimicrobial Activity of Some New Thioureides Derived from 2-(4-Chlorophenoxymethyl)benzoic Acid, *Molecules*, 2008, 13, 567.
[14]. K. Bhandari, N Srinivas, L, Sharma, S, Srivastava, A. Nath, C. Nath, Substituted urea/thiourea derived from fluoxetine as potent appetite suppressants, *Med. Chem. Res.*, **2008**, 17, 103.
[15]. A. Liav, S. K. Angala, P. J. Brennan and M. Jackson, *N*-D-Aldopentofuranosyl-*N′*-[*p*-(isoamyl oxy)phenyl]-thiourea derivatives: Potential anti-TB therapeutic agents, *Bioorg. edicinal Chem. Lett.*, **2008**, 18, 2649.
[16]. L. D. Santos, L. A Lima, V.C. Filho, R. Corrêa, F. D C. Buzzi, R. J. Nunes, Synthesis of new 1-phenyl-3-{4-[(2*E*)-3-phenylprop-2-enoyl]phenyl}-thiourea and urea derivatives with anti-nociceptive activity *Bioorg. Medicinal Chem.*, **2008**, 16, 8526.
[17]. A. E. Souza, K. Pissinate, M. D. G. Nascimento, N. F. Gynberg, Synthesis of new 1-phenyl-3-{4-[(2*E*)-3-phenylprop-2-enoyl]phenyl}-thiourea and urea derivatives with anti-nociceptive activity, *Bioorg. Medicinal Chem. Lett.*, **2006**, 14, 492.
[18]. S. J. Xuea, S.Y. Kea, T. B. Weib, Ultrasonic Irradiated Synthesis of N-(5-aryl-2-furoyl) thiourea Derivatives Containing Substituted Pyrimidine Ring under Phase Transfer Catalysis, *J. Chin. Chem. Soc.*, **2004**, 51, 1013.
[19]. Jag Mohan, Organic Spectroscopy P Ultrasonic Irradiated Synthesis of N-(5-aryl-2-furoyl) thiourea Derivatives Containing Substituted Pyrimidine Ring under Phase Transfer Catalysis principles and Applications, *Narosa Publications*, Second Edition, India, **2010**.
[20]. A. L. Barry, The Antimicrobial Susceptibility Test: Principle and Practices; Edited by Illus lea and Febiger, Philadelphia, PA, USA, **1976**, 180, [Biol. Abstr. 1977, 64, 25183].
[21]. S. Q. Song, L. G. Zhou, D. Li, D. Tang, J. Q. Li, W. B. Jiang, Antifungal activity of five plants from xinjiang. *Nat.Prod. Res. Dev.*, **2004**, 16, 157.
[22]. W. L. F.Armarego, D. D .Perrin, Purification of Laboratory Chemicals, 4thed., Butterworth, Heinemann, Oxford, OX2, 8DP, **1997**.