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Synthesis, Characterization, Antibacterial and Urease Inhibition Studies of Some Novel Symmetrical N^3,$N^{3'}$-*bis*-(disubstituted)isophthalyl-*bis*-(thioureas)

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A series of some novel N^3,$N^{3'}$-*bis*-(disubstituted)isophthalyl-*bis*-(thioureas), with general formula $[C_6H_4\{CONHCSNR_1R_2\}_2]$, where R_1 = H (**4a-4d, 4f, 4g, 4i, 4j**), C_6H_5(**4e**), C_6H_{11}(**4h**) and R_2 = $C_5H_4N_3$(**4a**), 4-C_6H_4COOH(**4b**), 3-$NO_2C_6H_4$(**4c**), 2-$NO_2C_6H_4$(**4d**), C_6H_5(**4e**), 2,4$(CH_3)_2C_6H_3$(**4f**), C_6H_{11}(**4g, 4h**), C_5H_4N(**4i**), 3-$NH_2C_6H_4$(**4j**) have been synthesized in good to excellent yields by reaction of isophthaloyl isothiocyanate with primary and secondary amines using dry acetone as solvent. These compounds **3a-j** have been characterized by elemental analyses, infrared and ^{1}H NMR spectroscopy. These compounds were screened for their antibacterial activity against bacterial species, *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, S. sonii, Salmonella typhi* and *Pseudomonas aeroginosa*. Some compounds showed potent activity against some bacterial strains and others exhibited strong antibacterial activity. The synthesized compounds **4a-j** were also evaluated for urease inhibition and found to exhibit varying degree of urease inhibition activity. Compounds **4a-d** were found to be the most active, exhibiting IC_{50} = 26.3 ± 0.5 to 31.1 ± 0.3 μM. It was concluded that these compounds may be a potential source of active antibacterial agents and some of these compounds also exhibit promising urease inhibitory activity.

Key Words: Bisthioureas, Antibacterial activity, Synthesis, Isothiocyanate.

INTRODUCTION

Urease inhibitors are considered new targets for antiulcer drugs[1]. The activity of bacterial ureases has been proved to be important virulence factor in the development of many dangerous and harmful clinical conditions for human and animal health as well as agriculture[2]. Bacterial ureases have been reported to play a role in the formation of infectious stones[3] and development of peptic ulcers and stomach cancer[4]. Ureases also actively contribute to the development of pyelonephritis, urolithiasis, hepatic coma, hepatic encephalopathy andurinary catheter encrustation[5]. In the near past, many compounds have been proposed as urease inhibitors to reduce environmental problems and enhance the uptake of urea nitrogen by plants[6-9]. By urease inhibition, the treatment of infections caused by urease producing bacteria may also be possible.

Thiourea derivatives possess wide spread applications in the field of medicine, agriculture and analytical chemistry. These compounds exhibit a comprehensive range of biological activities such as antiviral[10,11], antibacterial[12], fungicidal[13,14], analgesic herbicidal[15,16], plant growth regulating[17], antiaggregating[18], antiarrythmic, localanesthetic[19], antihyperlipidemic[20]. Some thioureas have been recently described as potent antitumor[20,21] and non-nucleoside inhibitors of HIV reverse transcriptase[22]. Recently reported[23] some dithiourea derivatives exhibited cytotoxicity against various cancer cells and one of these indicated best inhibition activities against KB and CNE2 with IC_{50} values of 10.72 and 9.91 micrometer respectively. In the present paper we wish to report the synthesis, antibacterial and urease inhibition activities of some new N^3,$N^{3'}$-*bis*-[(disubstituted)isophthalyl-*bis*-(thioureas) compounds (**4a-j**)]. The structures of the synthesized compounds were derived by modern spectroscopic techniques and the purity of compounds was verified by elemental analysis.

EXPERIMENTAL

All chemicals used were of analytical reagent grade (AR) and of the highest purity available. They include isophthalic acid (Sigma), thionyl chloride (Sigma), potassium thiocyanate (Aldrich), adenine (Aldrich), 3-nitroaniline (Aldrich),

2-nitroaniline (Aldrich), diphenylamine (Aldrich), 2,4-dimethylaniline (BDH), cyclohexylamine (Sigma), dicyclohexylamine (Sigma), 4-aminopyridine (Aldrich), 1,3-diamino benzene (Aldrich). The organic solvents used include acetone, absolute ethyl alcohol and dimethyl formamide (DMF). These solvents were either spectroscopically pure from BDH or purified by the recommended methods and tested for their spectral purity. De-ionized water collected from all-glass equipment was used wherever required.

Elemental microanalyses of the separated solids for C, H, N and S were performed on a PE-2400 CHNS analyzer. The analyses were repeated twice to check the accuracy of data. Infrared spectra were recorded on an Alpha Centauri FT-IR spectrophotometer in wavenumber region 4000-400 cm^{-1}. The spectra were recorded as KBr pallets. The ^1H NMR were recorded using FT-80 instrument, DMSO-d_6 was used as solvent and Me_4Si as internal standard.

Synthesis of N^3,$N^{3'}$-*bis*-(disubstituted) isophthalyl-*bis*-(thioureas): A solution of isophthalyl chloride (**2**) (0.1 mol), obtained by the reaction of isophthalic acid with thionyl chloride, was prepared in dry acetone. Potassium thiocyanate (0.2 mol), previously dried at 80 ºC for 2 h, was added to this solution and stirred for 1 h at room temperature to get the isophthaloyl isothiocyanate (**3**). This solution was mixed with a solution of primary/secondary amines (0.2 mol) and stirred for 24 h at room temperature to get the target disubstituted bisthiourea derivatives (**4a-j**) in good to excellent yields (**Scheme-I**). The mixture was then poured into sufficient quantity of ice cold water and the product was settled as white to yellow precipitate which were filtered, washed with cold water and dried in vacuum desiccator. For further purification, the products were recrystallized from DMF.

N^3,$N^{3'}$-*bis*-(7H-purin-6-yl)isophthalyl-*bis*-(thiourea) (4a): White solid, m.p.: 198 ºC; IR (KBr, ν_{max}, cm^{-1}): 3346 (N-H), 1740 (C=O),1690 (C=N), 1600, 1540, 1489 (C=C) 1250, 1170 (C=S), ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 12.12 (d, J = 3.6 Hz, 2H, NH), 11.32 (s, 2H, 2NH), 10.92 (s, 1H), 10.78 (s, 1H), 8.52 -7.56 (m, 8H, Ar-H), anal. calcd. (%) for $C_{20}H_{14}N_{12}O_2S_2$: C, 46.33; H, 2.72; N, 32.41; S, 12.37. Found (%): C, 46.46; H, 2.72; N, 32.43; S, 12.35.

N^3,$N^{3'}$-*bis*-(4-carboxyphenyl)isophthalyl-*bis*-(thiourea) (4b): White solid, m.p.: 201 ºC; IR (KBr, ν_{max}, cm^{-1}): 3352, 3160 (N-H, O-H), 1660 (C=O), 1600, 1530, 1459 (C=C) 1160 (C=S), ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm):, 12.18 (s, 2H, 2NH), 9.91 (s, 2H, 2NH), 8.32-7.47 (m, 12H, Ar-H), 15.24 (s, 6H, $2CH_3$), anal. calcd. (%) for $C_{24}H_{18}N_4O_6S_2$: C, 55.16; H, 3.47; O, 10.72; S, 12.27. Found (%): C, 55.19; H, 3.45; O, 10.73; S, 12.29.

N^3,$N^{3'}$-*bis*-(3-nitrophenyl)isophthalyl-*bis*-(thiourea) (4c): Yellow solid, m.p.: 203 ºC; IR (KBr, ν_{max}, cm^{-1}); 3375 (N-H), 1670 (C=O), 1607, 1545, 1490 (C=C), 1542, 1340 (NO), 1280, 1139 (C=S), ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm):. 12.36 (s, 2H, 2NH), 9.49 (s, 2H, NH), 8.47-7.56 (m, 12H, Ar-H). Anal. calcd. (%) for $C_{22}H_{16}N_6O_6S_2$: C, 50.38; H, 3.07; O, 16.02; S, 12.23. Found (%): C, 50.40; H, 3.10; O, 16.10; S, 12.22.

N^3,$N^{3'}$-*bis*-(2-nitrophenyl)isophthalyl-*bis*-(thiourea) (4d): Yellow solid, m.p. 196 ºC; IR (KBr, ν_{max}, cm^{-1}): 3338 (NH), 1675, 1688 (C=O), 1260, 1152 (C=S), 1592, 1480, 1526 (C=C), 1540, 1332 (NO). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 11.98 (s, 2H, 2NH), 10.60 (s, 2H, 2NH), 8.30-7.40 (m, 8H, Ar-H). Anal. calcd. (%) for $C_{22}H_{16}N_6O_6S_2$: C, 50.38; H, 3.07; O, 16.02; S, 12.23. Found (%): C, 50.40; H, 3.11; O, 16.05; S, 12.23.

N^3,N^3,$N^{3'}$,$N^{3'}$-*Tetrakis*(phenyl)isophthalyl-*bis*-(thiourea) (4e): Yellow solid, m.p. 200 ºC; IR (KBr, ν_{max}, cm^{-1}); 3319 (N-H), 1676, 1680 (C=O), 1590, 1480, 1531 (C=S), 1264, 1154 (C=S). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 12.81 (s, 2H, 2NH), 8.37-7.14 (m, 24H, Ar-H). Anal. calcd. (%) for $C_{34}H_{26}N_4O_2S_2$: C, 69.60; H, 4.47; O, 9.55; S, 10.93; Found (%): C, 63.68; H, 4.50; O, 9.60; S, 10.91.

N^3,$N^{3'}$-*bis*-(2,4-dimethylphenyl)isophthalyl-*bis*-(thiourea) (4f): Yellow solid, m.p. 194 ºC; IR (KBr, ν_{max}, cm^{-1}); 3358, 3216 (N-H), 2950 (CH_3), 1660 (C=O), 1600, 1516, 1474 (C=C), 1258, 1175 (C=S). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 12.22 (s, 2H, 2NH), 9.16 (s, 2H, 2NH), 8.22-7.07 (m, 10H, Ar-H), 2.36-2.27 (m, 12H, $6CH_3$). Anal. calcd. (%) for $C_{26}H_{26}N_4O_2S_2$: C, 63.65; H, 5.34; O, 11.42; S, 13.07; Found (%): C, 63.68; H, 5.32; O, 11.45; S, 13.10.

N^3,$N^{3'}$-*bis*-(cyclohexyl)isophthalyl-*bis*-(thiourea) (4g): Yellow solid, m.p. 197 ºC; IR (KBr, ν_{max}, cm^{-1}); 3395 (N-H), 2970 (C-C), 1659 (C=O), 1600, 1509, 1445 (C=C), 1252, 1199 (C=S). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 12.11 (s, 2H, 2NH), 9.14 (s, 2H, 2NH), 8.32-7.58 (m, 4H, Ar-H), 4.57-1.36 (m, 22H cyclohexyl). Anal. calcd. (%) for $C_{22}H_{30}N_4O_2S_2$: C, 59.16; H, 6.77; O, 12.54; S, 14.36; Found (%): C, 59.20; H, 6.75; O, 12.59; S, 14.40.

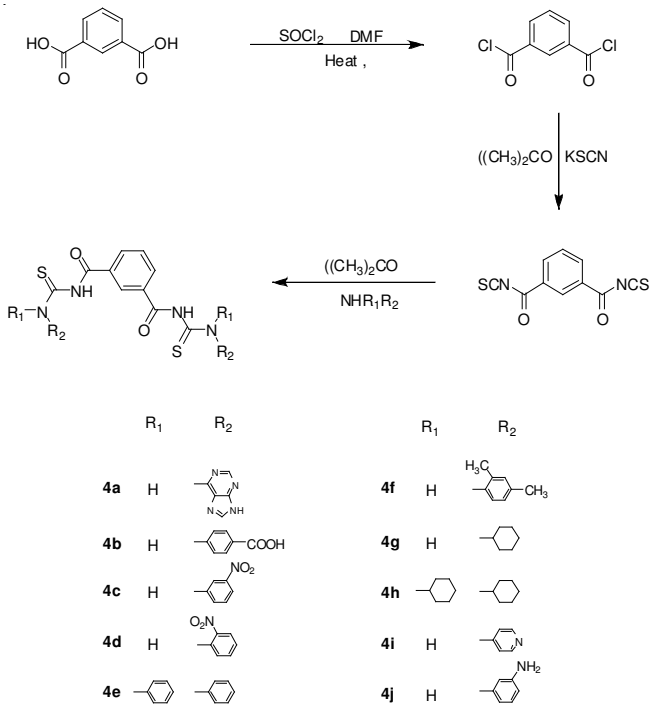
N^3,N^3,$N^{3'}$,$N^{3'}$-*Tetrakis*(cyclohexyl)isophthalyl-*bis*-(thiourea) (4h): Yellow solid, m.p. 195 ºC; IR (KBr, ν_{max}, cm^{-1}): 3442 (N-H), 1692 (C=O), 1602, 1585, 1469 (C=C), 1249, 1171 (C=S). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 11.6 (s, 2H, 2NH), 8.49-7.62 (m, 4H, Ar-H), 3.65-1.28 (44H, cyclohexyl). Anal. calcd. (%) for $C_{34}H_{50}N_4O_2S_2$: C, 66.84; H, 8.25; O, 9.17; S, 10.50; Found (%): C, 66.82; H, 8.30; O, 9.20; S, 10.55.

N^3,$N^{3'}$-*bis*-(4-pyridinyl)isophthalyl-*bis*-(thiourea) (4i): Yellow solid, m.p. 192 ºC; IR (KBr, ν_{max}, cm^{-1}); 3299 (N-H), 1690 (C=O), 1660 (C=N), 1609, 1532, 1455 (C=C), 1270, 1150 (C=S). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm):. 12.30 (s, 2H, 2NH), 9.90 (s, 2H, 2NH), 8.37 - 6.64 (m, 12H, Ar-H). Anal. calcd. (%) for $C_{20}H_{16}N_6O_2S_2$: C, 55.03; H, 3.69; O, 19.25; S, 14.69; Found (%): C, 55.09; H, 3.71; O, 19.29; S, 14.66.

N^3,$N^{3'}$-*bis*-(3-aminophenyl)isophthalyl-*bis*-(thiourea) (4j): Grey solid, m.p. 201 ºC; IR (KBr, ν_{max}, cm^{-1}): 3330, 3211 (N-H), 1685 (C=O), 1640, 1535, 1458 (C=C), 1270, 1148 (C=S). ^1H NMR (300 MHz, DMSO-d_6, Me_4Si): δ (ppm): 12.33 (s, 2H, 2NH), 9.81 (s, 2H, 2NH), 8.25-6.47 (m, 12H, Ar-H), 5.22 (s, 4H, $2NH_2$). Anal. calcd. (%) for $C_{22}H_{20}N_6O_2S_2$: C, 56.88; H, 4.34; O, 18.09; S, 13.80; Found (%); C, 56.93; H, 4.33; O, 18.16; S, 13.79.

Pharmacology

Test microorganisms: *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, S. sonii, Salmonella typhi* and *Pseudomonas aeroginosa* were used as the bacterial tested organisms. The pure bacterial strains were obtained from the Department of Veterinary Microbiology, University of Agriculture, Faisalabad, Pakistan.



Scheme-I: Synthesis of N^3,$N^{3'}$-*bis*-(discubstituted)isophthal-*bis*-(thioureas)

Antibacterial activity by disc diffusion method: Antibacterial activity of compounds **4a-j** was determined *in vitro* by using the disc diffusion method[15] against various gram-negative and gram-positive bacteria (Table-1) at a concentration of 200 µg/100 µL in DMSO solution. Ampicillin (100 µL/disc) and ciprofloxacin (100µL/disc) were used as standard drugs. 24 h old cultures, containing approximately 1.5×10^6 (CFU/mL) were spread on the surface of nutrient agar (NA) plates. The discs (6 mm diameter) were impregnated with (100 µL/disc) test samples and then placed aseptically on the inoculated agar media. Experimental plates were incubated at 37 ºC for 24 h. Antibacterial activity was evaluated by measuring the diameter of the inhibition zone (IZ) and compared with standard drugs. The inhibition zone values from 25-35 mm were taken as potent and from 20-25 mm as strong and values greater then 10mm were considered as moderate activity.

Statistical analysis: All the experiments were conducted in triplicate unless stated otherwise and statistical analysis of the data was performed by analysis of variance (One Way Anova), using STATISTICA 5.5 (Stat Soft Inc, Tulsa, Oklahoma, USA) software. A probability value of difference $p \leq 0.05$ was considered to denote a statistically significance. All data were presented as mean values ± standard deviation (SD).

Urease assay and inhibition: The reaction mixtures comprising 25 µL of Jack bean Urease solution, 55 µL of buffers and 100 mM urea were incubated with 5 µL (1 mM conc.) of the test compounds at 30 ºC for 15 min in well plates. The measurement of ammonia production (indophenol method)[26] was used to determine the urease activity. The phenol reagent (45 µ L, 1 % w/v phenol and 0.005 % w/v sodium nitroprusside) and alkali reagent (70 µL, 0.5 % w/v sodium hydroxide and 0.1 % NaOCl) were added to each well and the increasing absorbance at 630 nm was measured after 50 min, using a microplate reader (Molecular Device, USA). The change in absorbance per min was noted and the results processed using SoftMax Pro software (Molecular Device, USA). All the reactions were performed in triplicate. All the assays were performed at pH 8.2 (0.01 M $K_2HPO_4.3H_2O$, 1 mM EDTA and 0.01 M $LiCl_2$). The percentage inhibitions were calculated from the formula $100\text{-}(OD_{testwell}/OD_{control}) \times 100$. Thiourea was used as the standard inhibitor.

RESULTS AND DISCUSSION

Synthesis: The synthetic route for the newly synthesized compounds, N^3,$N^{3'}$-*bis*-(disubstituted)isophthalyl-*bis*-(thioureas) (**4a-j**), is illustrated and outlined in **Scheme-I**. Isophthaloyl chloride **2** was treated with anhydrous KSCN using dry acetone as solvent to give isophthaloyl isothiocyanate 3 in quantitative yield. The diisothiocynates 3 are useful synthetic building blocks which may be efficiently used for the synthesis of *N,N'*-disubstituted thioureas and benzenedicarbonyl bisthioureas[24]. In the present work the isothiocynate **3** was not isolated and treated directly with primary or secondary amines to give the corresponding dithiourea derivatives (**4a-j**) in good to excellent yields. Since the addition to -N=C=S system and nucleophilic substitution at carbonyl-carbon atom may compete with one another, it has been noticed that isothiocyanate **3** reacted

TABLE-1
IN VITRO ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS (**4a-j**) BY DISC DIFFUSION METHOD[a]

Compound	Gram positive bacteria		Gram negative bacteria			
	B. subtilis	*S. aureus*	*E.coli*	*S. sonii*	*S. typhi*	*P. aeroginosa*
4a	31 ± 0.81[b]	32 ± 0.81[b]	31 ± 1.41[b]	27 ± 0.0[c]	30 ± 1.82[b]	20 ± 0.61[d]
4b	-	17 ± 1.41[e]	20 ± 0.91[d]	15 ± 0.81[e]	13 ± 0.41[f]	-
4c	29 ± 0.81[c]	30 ± 2.11b[c]	24 ± 0.75[c]	21 ± 0.63[d]	31 ± 1.63[b]	28 ± 0.81[b]
4d	5 ± 0.11[f]	13 ± 0.71[f]	-	17 ± 0.0[e]	-	-
4e	-	-	-	-	-	-
4f	32 ± 1.63[b]	29 ± 1.63[c]	31 ± 1.63[b]	34 ± 1.63[b]	29 ± 0.0[b]	22 ± 0.70[c]
4g	3 ± 0.1[g]	10 ± 0.81[g]	-	11 ± 0.22[f]	13 ± 0.70[f]	1 ± 0.11[f]
4h	22 ± 1.63[d]	26 ± 1.41[d]	21 ± 0.0[d]	22 ± 0.81[d]	24 ± 0.61[c]	23 ± 1.08[c]
4i	-	-	-	-	20 ± 0.70[d]	-
4j	-	-	-	-	-	-
S1	38 ± 0.41[a]	36 ± 1.82[a]	38 ± 1.61[a]	36 ± 1.63[ab]	35 ± 1.63[a]	34 ± 1.47[a]
S2	38 ± 0.81[a]	35 ± 1.41[a]	38 ± 1.20[a]	37 ± 0.0[a]	34 ± 0.0[a]	33 ± 0.0[a]

S_1 = Ampicillin, S_2 = Ciprofloxacin, - = NIL; [a]Values are mean ± SD of three separate experiments; Letters in superscript show the significance of the results against single strain

additively with amines to give corresponding *bis*thiourea derivatives (**4a-j**), while the formation of corresponding ester was not observed in the case of **4b**. The target compounds (**4a-j**) were purified by recrystallization from DMF and characterized by IR and ^{1}H NMR data. The IR and ^{1}H NMR data for compounds (**4a-j**) has been reported. In IR spectrum, the C=S peak appeared in the range of 1139 to 1199 cm^{-1} whereas the N-H peaks appeared from 3208 to 3442 cm^{-1}. Carbonyl absorption bands were observed in the range of 1690-1657 cm^{-1}. In ^{1}H NMR spectra, the N^1-H protons appeared as singlet in the range δ 12.81to11.86 ppm whereas N^3-H protons appeared at δ 11.32 to 9.16 ppm, depending upon the nature of group attached to N^3. The appearance of N^1-H proton at higher frequency may be attributed to the presence of carbonyl and thiocarbonyl groups which exert a strong deshielding effect.

The ^{1}H NMR (DMSO) spectrum revealed signals at s 12.81-11.86 (2H, NH) in all the compounds (**4a-j**) which indicates the NH group between (C=O) and (C=S) group remains unaffected regardless group attached to terminal N atom The aromatic protons of the parent isophthloyl group appeared in the range δ 8.45 to 7.53 ppm.

Biology

Antibacterial assay: *In vitro* antibacterial activity of all the synthesized compounds (**4a-j**) was tested against six different bacterial strains according to the literature protocol[25]. The compounds **4a**, **4c** and **4f** exhibited potent activity against all tested bacteria with highest inhibition zones (Table-1). **4h** showed strong activity against *S. aureus, S. typhi, P. aeroginosa, S. sonii, B. subtilis* and *E. coli* (inhibition zone; 26, 24, 23, 22, 22, 21 mm) respectively. Moderate activity was exhibited by **4b** against *S. aureus, S. sonii* and *S. typhi*, (inhibition zone; 17, 15, 13 mm) and **4d** against *S. sonii, S. aureus* (inhibition zone; 17, 13 mm). Other compounds were also active against bacteria with low activity. The compounds **4e**, **4i** and **4j** were inactive and showed no inhibition against all bacteria. Comparative results were studied by using ampicillin and ciprofloxacin as standard antibiotics. All compounds showed less activity as compared to standard drugs. The results of the present investigation demonstrated significant ($p < 0.05$) variations in the antibacterial activity of the compounds.

Urease inhibition activity: The urease inhibition activity was carried out in accordance with the literature protocol[26] using thiourea as the standard inhibitor with an IC_{50} value of 21.0 ± 0.1 μM. The results shown by the synthesized compounds (**4a-j**) are presented in Table-2. All the scanned compounds showed moderate to good urease inhibition activity. Compounds **4b** and **4c** proved to be the most potent urease inhibitor showing an enzyme inhibition activity with an IC_{50} value of 26.3 ± 0.5 μM and 26.7 ± 0.5 μM respectively. These values are comparable to 21.0 ± 0.1 μM of the standard thiourea. The compounds **4a** and **4d** also exhibited comparatively good activity showing IC_{50} values 28.4 ± 0.3 μM and 31.1 ± 0.3 μM respectively. The leasst activity is shown by the compound **4g** showing an IC_{50} value of 720.4 ± 0.5 μM, whereas compounds **4i** and **4j** are inactive towards urease inhibition. Compounds **4e**, **4f** and **4h** showed moderate urease inhibition activity with IC_{50} values ranging between 50.1 ± 0.5-168.8 ± 0.3 μM. From these results of urease inhibition activity, it appears that there is no effect of basic skeleton of the molecule. However the groups $\mathbf{R_1}$ and $\mathbf{R_2}$ attached at the terminals of basic skeleton of molecule are seem to be responsible for variable urease inhibition activity. The results are indicating that the presence of some electron withdrawing group at the terminal positions of the molecule leads to enhance urease inhibition activity of the compound. These results of urease inhibition activity are comparable to those reported for Chiral 3-substituted-4-amino-5-thioxo-1*H*,4*H*-1,2, triazoles[27].

TABLE-2
UREASE INHIBITORY ACTIVITY OF *BIS*-THIOUREAS

S. No	Compound	IC_{50} + SEM
1	4a	28.4 ± 0.3
2	4b	26.3 ± 0.5
3	4c	26.7 ± 0.5
4	4d	31.1 ± 0.3
5	4e	50.1 ± 0.5
6	4f	83.8 ± 0.5
7	4g	720.4 ± 0.5
8	4h	168.8 ± 0.3
9	4i	NIL
10	4j	NIL
11	Thiourea	21.0 ± 0.1

Values are mean ± S.D of three separate experiments

It is therefore suggested that some structural modifications such as substitution either on central ring or on N^1 nitrogen of N^3,$N^{3'}$-*bis*-(disubstituted)isophthalyl-*bis*-(thioureas) or on both simultaneously may escort to a potent lead molecule for future research in the field of urease inhibition. Of this series the most active compounds **4b** and **4c** may act as potential molecules for structural modifications.

Conclusion

Some novel N^3,$N^{3'}$-*bis*-(disubstituted)isophthalyl-*bis*-(thioureas) have been synthesized and characterized by analytical and spectral (IR, ^{1}H NMR) techniques. Antibacterial activity of these compounds was studied against bacterial strains. Some compounds showed potent activity against some bacterial strains and others exhibited strong antibacterial activity. It was concluded that these compounds could be a potential source of active antibacterial agents. These compounds were also scanned for urease inhibition activity. Some of these these compounds exhibited promising urease inhibitory activity, which may be due to terminal $\mathbf{R_1}$ and $\mathbf{R_2}$ groups attached to basic skeleton of molecule.

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