Synthesis of 3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-aryl-1,3,5-oxadiazinane-4-thiones and 1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones

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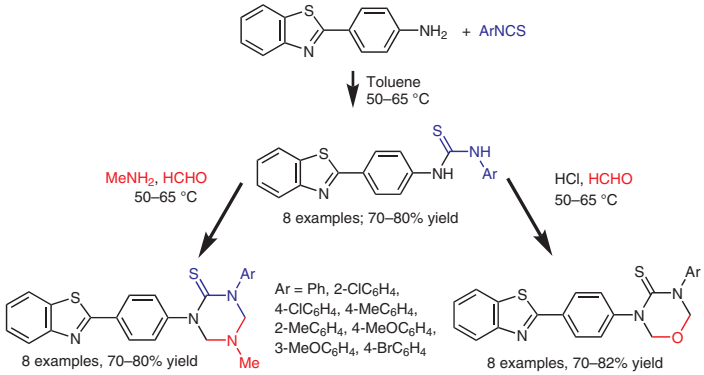


Received: 19.11.2017
Accepted after revision: 15.01.2018
Published online: 31.01.2018
DOI: 10.1055/s-0036-1591917; Art ID: so-2017-d0053-op

Abstract In this investigation 4-(benzo[d]thiazol-2-yl)benzenamine was reacted with aryl isothiocyanates to give 1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-aryl thioureas **2**, which were cyclized with acid to afford 3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-aryl-1,3,5-oxadiazinane-4-thiones **3**. On the other hand, 1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones **4** were obtained when compounds **2** were treated with amines.

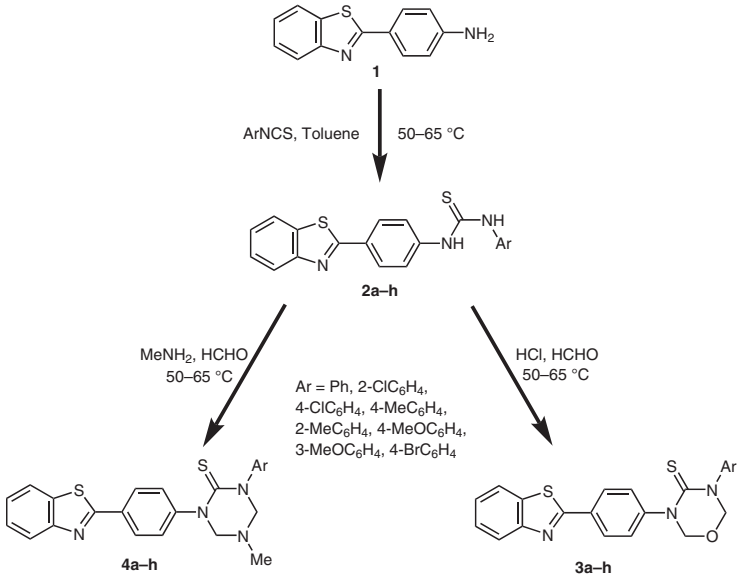
Key words benzo[*d*]thiazols, isothiocyanates, thioureas

The cyclocondensation of urea, thiourea, guanidine, or sulfamides with an aldehyde or ketone and a suitable nucleophile in accordance with the principle of 'α-ureidoalkylation' or 'vinylogous ureidoalkylation' leads to the formation of saturated or unsaturated mono- and polycyclic heterocycles. The rings may be separated or may be linked in the 1,2- or 1,3-positions. Spiro compounds can also be formed. The five-, six-, seven-, and eight-membered rings accessible in this way can contain further heteroatoms such as O, S, N, or P. Synthetic possibilities, properties, substitution reactions, and rearrangement reactions of these heterocycles have been described by Petersen.[1] These compounds have also been synthesized by Balalaie et al. in the absence of solvent under microwave irradiation.[2] Various methods have been developed for the synthesis of triazanones and oxadiazanones by Parg, Dickore, Gally et al.[3–5] Hardies has reported the synthesis of 1,3,5-tri-*N*-substituted hexahydro-2-oxo-triazones in patents.[6,7] Three-component condensation of *N*-(5-methyl-3-isoxazolyl)-*N*-arylureas with aqueous formaldehyde and primary amines under microwave irradiation in ethanol was shown to lead to 5-alkyl-1-(5-methylisoxazol-3-yl)-3-aryl[1,3,5]triazinan-2-ones in excellent yields by Rajanarender et al.[8] A series of 2,6-diphenylimino-4-(substituted)-benzylideneamino-1,3,5-thiadiazines was synthesized by Deohate and Berad.[9] Three-component condensation of *N*-(3-methyl-5-styryl-4-isoxazolyl)-*N*-arylureas, paraformaldehyde, and primary amines using montmorillonite K-10 in the absence of solvent under microwave irradiation led to isoxazolyl[1,3,5]triazinan-2-ones in high yields. Condensation of *N*-(3-methyl 5-stryryl, 4-isoxazolyl) with paraformaldehyde under similar conditions was demonstrated to provide isoxazolyl[1,3,5]oxadiazinan-4-ones in excellent yields by Rajanareder et al.[10]

1,3,5-Triazinan-2-ones are useful for the protection of amino groups,[11] as well as for the synthesis of polyamines,[12] and poly and functional aminoalcohols.[13] Water-soluble triazinan-2-ones have been used as fertilizers.[14] Several benzothiazoles exhibit antitumor activity.[15–20] Products obtained from the condensation of phenyl-substituted benzothiazoles[21–24] with pyrimido benzothiazoles and benzothiazolo quinazolines have shown efficient antiviral activity. Substituted 6-nitro- and 6-aminobenzothiazoles show antimicrobial activity.[25] Attracted by the possible enhanced activity of sturctures containing imidazopyridines, 1,3,5-triazinan-2-ones and 1,3,5-oxadiazinan-4-ones fused with benzothiazoles we have embarked on the synthesis of 1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-arylthioureas [benzothiazol phenyl aryl thioureas] **2**, 3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-aryl-1,3,5-oxadiazinane-4-thiones [benzothiazol phenyl aryl oxadiazinane thiones] **3** and 1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones [benzothiazol phenyl methyl aryl triazinane thiones] **4** with a view to exploring their biological activity.

Initially we prepared 4-(benzo[*d*]thiazol-2-yl)benzenamine (**1**) according to reported procedures[26–29] followed by the synthesis of urea derivatives from the reaction of **1** with isocyanates.[30,31] Accordingly, synthesis of 1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-arylthiourea and its substituted compounds **2** was accomplished by heating compound **1** to reflux with arylisothiocyanates in equimolar amounts. A mixture of 4-(benzo[*d*]thiazol-2-yl)benzenamine (**1**) with an equimolar quantity of arylisothiocyanate (10 mmol) in *N*,*N*-dimethylformamide (DMF) was heated to reflux for 4 h. After completion of reaction (as ascertained by TLC) the mixture was cooled and the product purified. After recrystallization from EtOH, structures of **2** were assigned on the basis of mass spectrometric and ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Compounds **2** were further added to 30% formaldehyde solution and conc. HCl and the mixture was heated to 90–95 °C for 4 h. After cooling and neutralizing the reaction mixture, compounds **3** were obtained in good yields. On the other hand, when the reaction mixture containing **2** and 30% formaldehyde solution was treated with methylamine in ethanol, compounds **4** were obtained in very good yields. The reaction times and product yields are presented in Table 1.

Table 1 Reaction Times and Yields of the Prepared Compounds



	Compound	Time (h)	Yield (%)
2a	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-(2-chlorophenyl)thiourea	4	79
2b	1-(4-(benzo[*d*]thiazol-2-yl) phenyl)-3-(4-chlorophenyl) thiourea	4	72
2c	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-(4-methylphenyl)thiourea	3	80
2d	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-(2-methylphenyl)thiourea	5	71
2e	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-(4-methoxyphenyl)thiourea	6	78
2f	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-(3-methoxyphenyl)thiourea	7	73
2g	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-(4-bromophenyl)thiourea	6	81
2h	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-phenylthiourea	5	76
3a	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(2-chlorophenyl)-1,3,5-oxadiazinane-4-thione	4	78
3b	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(4-chlorophenyl)-1,3,5-oxadiazinane-4-thione	5	71
3c	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(4-methylphenyl)-1,3,5-oxadiazinane-4-thione	4	73
3d	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(2-methylphenyl)-1,3,5-oxadiazinane-4-thione	6	80
3e	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(4-methoxyphenyl)-1,3,5-oxadiazinane-4-thione	5	76
3f	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(3-methoxyphenyl)-1,3,5-oxadiazinane-4-thione	6	73
3g	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-(4-bromoyphenyl)-1,3,5-oxadiazinane-4-thione	5	72

Table 1 (continued)

	Compound	Time (h)	Yield (%)
3h	3-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-phenyl-1,3,5-oxadiazinane-4-thione	5	70
4a	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(2-chlorophenyl)-1,3,5-triazinane-2-thione	6	77
4b	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-chlorophenyl)-1,3,5-triazinane-2-thione	5	76
4c	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-methylphenyl)-1,3,5-triazinane-2-thione	5	80
4d	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(2-methylphenyl)-1,3,5-triazinane-2-thione	6	81
4e	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-methylphenyl)-1,3,5-triazinane-2-thione	5	75
4f	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(3-methoxyphenyl)-1,3,5-triazinane-2-thione	6	73
4g	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-bromophenyl)-1,3,5-triazinane-2-thione	4	70
4h	1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-phenyl-1,3,5-triazinane-2-thione	5	71

All the synthetic protocols used for the synthesis of **2–4** are highly efficient, affording the products in 3 to 5 hours with very good yields. Reaction times for compounds containing an electron-donating group (EDG) were shorter than those with the corresponding electron-withdrawing group (EWG).

All the prepared compounds were screened for antibacterial activity and minimum inhibitory concentrations (MIC) were determined against *Staphylococcus aureus* (Sp1.; Gram positive), *Klebsiella pneumoniae* (Sp2.; Gram negative), *Salmonella paratyphi* A (Sp3.; Gram negative), *Salmonella paratyphi* B (Sp4.; Gram negative), and *Micrococcus luteus* (Sp5.; Gram negative). The results are compiled in Table 2.

The antimicrobial studies revealed that **3b** (*p*-chlorophenyl substituent) showed maximum inhibitory activity against *Staphylococcus aureus* (Sp1) which is nearest to that of the standard tetracycline. However, other compounds also exhibited considerable antimicrobial activity against *Staphylococcus aureus* including **4a** (*o*-chlorophenyl), **4d** (*o*-methylphenyl), **3a** (*o*-chlorophenyl), **3c** (*p*-methylphenyl), **4b** (*p*-chlorophenyl), **4c** (*p*-methylphenyl), and **4e** (*p*-methoxyphenyl). Against *Klebsiella pneumonia* (Sp2) considerable activity was shown by **3f** (*m*-methoxyphenyl) and **4c** (*p*-methylphenyl). Against *Salmonella paratyphi* A (Sp3) and *Salmonella paratyphi* B (Sp4) none of the compounds showed particular activity; whereas against *Micrococcus luteus* (Sp5), **3g** (*p*-bromophenyl), **3h** (phenyl), and **4h** (phenyl) exhibited good antimicrobial activity.

Chemicals were purchased from SD (Fine Chemicals, India), Aldrich (India), or Emerck. Reagent-quality solvents were obtained from Avra chemicals (India), and distilled prior to use. IR spectra were recorded on potassium bromide disks with a Perkin–Elmer 383 spectrophotometer. ^{1}H NMR spectra were obtained with a Varian 400 MHz instrument with TMS as internal standard. Chemical shifts are expressed in δ units (ppm) and the solvent used was DMSO-d_6. Mass spectra were recorded with a Hewlett Packard mass spectrometer operating at 70 eV. TLC was performed on Merck precoated silica gel plates (60F-254) with iodine as developing agent.

Table 2 Antimicrobial Studies; Minimum Inhibitory Concentrations (MIC) for **3** and **4**

Entry	Species used for activity screening				
	Sp1	Sp2	Sp3	Sp4	Sp5
3a	12	2	–	–	8
3b	19	5	2	5	9
3c	11	2	1	–	7
3d	3	1	1	1	7
3e	4	3	3	2	8
3f	10	9	1	5	6
3g	13	4	3	5	10
3h	12	2	1	1	10
4a	15	3	1	1	7
4b	10	4	3	2	8
4c	10	9	1	5	6
4d	15	3	1	1	7
4e	10	4	3	3	1
4f	3	1	1	4	3
4g	4	3	3	3	1
4h	3	1	1	1	10
tetracycline	25	18	16	10	17

Synthesis and Characterization of 1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-3-arylthioureas 2

To a solution of 4-(benzo[*d*]thiazol-2-yl)benzenamine (**1**; 10.0 mmol) in anhydrous DMF (20 mL), the requisite arylisothiocyanate (10.0 mmol) was added and the contents were heated to reflux for 4 h. The reaction was monitored by TLC. Upon completion of reaction, the mixture was cooled and the separated product was filtered and crystallized from EtOH.

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

Yield: 314 mg (79 %); pale-yellow liquid; bp 204–206 °C.

^{1}H NMR (DMSO-d_6): δ = 9.25 (brs, 2 H), 8.21 (d, 1 H), 8.01 (m, 3 H), 7.91 (m, 3 H), 7.80 (d, 1 H), 7.75 (d, 2 H), 7.40 (d, 2 H).

^{13}C NMR(100 MHz, DMSO-d_6): δ = 122.559, 125.434, 127.196, 128.656, 131.555, 132.432, 134.768, 136.077, 136.334, 139.033, 142.321, 143.777, 145.711, 146.900, 147.221, 148.365, 150.116, 153.782, 163.917, 172.742.

HRMS: *m*/*z* [M + H] = 396.0039.

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

Yield: 286 mg (72%); pale-yellow liquid; bp 201–203 °C.

^{1}H NMR (DMSO-d_6): δ = 8.27 (d, 1 H), 8.03 (m, 3 H), 7.89 (m, 3 H), 7.65 (d, 1 H), 7.46 (d, 2 H), 7.26 (d, 2 H), 2.71 (d, 3 H).

^{13}C NMR(100 MHz, DMSO-d_6): δ = 122.229, 125.334, 127.096, 128.876, 131.881, 132.224, 134.568, 136.177, 136.234, 139.133, 142.221, 143.228, 145.678, 146.332, 147.321, 148.166, 150.229, 153.729, 163.877, 172.288.

MS: *m*/*z* = 396.9 [M + H].

HRMS: *m*/*z* [M + H] = 396.0039.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-3-(4-methylphenyl)thiourea (2c)

Yield: 301 mg (80 %); off-white solid; mp 200–202 °C;

^{1}H NMR (DMSO-d_6): δ = 9.26 (brs, 2 H), 8.22 (d, 1 H), 8.03 (m, 3 H), 7.95 (m, 3 H), 7.75 (d, 1 H), 7.56 (d, 2 H), 7.26 (d, 2 H), 2.31 (d, 3 H).

^{13}C NMR(100 MHz, DMSO-d_6) 22.34, 122.526, 124.324, 127.786, 128.776, 130.899, 131.226, 132.666, 134.765, 135.424, 136.257, 140.033, 142.555, 143.776, 145.790, 146.442, 147.305, 150.122, 153.552, 163.807, 173.109 (CH_3).

MS: *m*/*z* [M + H] = 376.

HRMS: *m*/*z* [M + H] = 376.0079.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-3-(2-methylphenyl)thiourea (2d)

Yield: 267 mg (71 %); cream solid; mp 208–210 °C.

^{1}H NMR (DMSO-d_6): δ = 9.30 (brs, 2 H), 8.21 (d, 1 H), 8.04 (m, 3 H), 7.96 (m, 3 H), 7.75 (d, 1 H), 7.55 (d, 2 H), 7.25 (d, 2 H), 2.32 (s, 3 H).

MS: *m*/*z* [M + H] = 376.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-3-(4-methoxyphenyl)thiourea (2e)

Yield: 306 mg (78 %); cream solid; mp 196–197 °C.

^{1}H NMR (DMSO-d_6): δ = 9.41 (brs, 2 H), 8.41 (d, 1 H), 8.11 (m, 4 H), 7.91 (m, 2 H), 7.80 (d, 1 H), 7.70 (d, 2 H), 7.40 (d, 2 H), 3.76 (s, 3 H).

MS: *m*/*z* [M + H] = 392.

(2f)1-(4-(benzo[d]thiazol-2-yl)phenyl)-3-(3-methoxyphenyl)thiourea:

Yield: 286 mg (73%); off-white solid; mp 206–208 °C

^{1}H NMR (DMSO-d_6): δ = 9.38 (brs, 2 H), 8.40 (d, 1 H), 8.11 (m, 4 H), 7.90 (m, 2 H), 7.81 (d, 1 H), 7.71 (d, 2 H), 7.41 (d, 2 H), 3.77 (s, 3 H).

^{13}C NMR(100 MHz, DMSO-d_6): δ = 63.877, 122.513, 124.264, 127.446, 128.176, 131.221, 132.885, 134.190, 136.007, 135.111, 140.075, 142.224, 143.228, 145.611, 146.342, 147.321, 150.229, 147.405, 153.211, 163.005, 173.114.

MS: *m*/*z* [M + H] = 392.

HRMS: *m*/*z* [M + H] = 392.0021.

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

Yield: 353 mg (81%); pale-yellow liquid; bp 198–200 °C.

^{1}H NMR (DMSO-d_6): δ = 9.26 (brs, 2 H), 8.22 (d, 1 H), 8.02 (m, 4 H), 7.90 (m, 2 H), 7.81 (d, 1 H), 7.75 (d, 2 H), 7.45 (d, 2 H).

MS: *m*/*z* [M + H] = 441.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-3-phenylthiourea (2h)

Yield: 275 mg (76%); colorless liquid; bp 198–200 °C.

^{1}H NMR (DMSO-d_6): δ = 9.30 (brs, 2 H), 8.21 (d, 1 H), 8.00 (m, 3 H), 7.91 (m, 4 H), 7.80 (d, 1 H), 7.76 (d, 2 H), 7.40 (d, 2 H).

MS: *m*/*z* [M + H] = 362.

Synthesis and Characterization of 3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-aryl-1,3,5-oxadiazinane-4-thiones 3

1-(4-(Benzo[*d*]thiazol-2-yl) phenyl)-3-arylthiourea **2** (50.0 mmol), was added to 30% aqueous formaldehyde (100.0 mmol, 27.3 mL) and the mixture was then treated with conc. HCl (5 mL). After heating at 90–95 °C for 4 h, the reaction mixture was cooled and neutralized with NaOH. The precipitate formed was filtered and purified by silica gel column chromatography, eluting with 60% EtOAc/hexane.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(2-chlorophenyl)-1,3,5-oxadiazinane-4-thione (3a)

Yield: 342 mg (78%); colorless liquid; bp 216–217 °C.

^{1}H NMR (DMSO-d_6): δ = 7.92 (d, 1 H), 7.80 (d, 2 H), 7.52 (t, 2 H), 7.40 (m, 3 H), 7.24 (d, 2 H), 7.20 (m, 2 H), 5.01 (s, 4 H).

MS: *m*/*z* [M + H] = 438.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(4-chlorophenyl)-1,3,5-oxadiazinane-4-thione (3b)

Yield: 311 mg (76%); colorless liquid; bp 210–212 °C.

^{1}H NMR (DMSO-d_6): δ = 7.98 (d, 1 H), 7.84 (d, 2 H), 7.54 (t, 2 H), 7.41 (m, 3 H), 7.25 (d, 2 H), 7.21 (m, 2 H), 5.02 (s, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 89.113, 88.568, 121.564, 122.236, 125.554, 126.001, 128.776, 134.661, 136.221, 136.114, 136.441, 139.221, 142.332, 143.556, 145.113, 146.778, 148.613, 150.770, 153.229, 163.577, 166.188, 172.115.

MS: *m*/*z* [M + H] = 438.

HRMS: *m*/*z* = 438.0132.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(4-methylphenyl)-1,3,5-oxadiazinane-4-thione (3c)

Yield: 334 mg (76 %); colorless solid; mp 208–210 °C.

^{1}H NMR (DMSO-d_6): δ = 8.00 (d, 2 H), 7.86 (d, 1 H), 7.68 (t, 2 H), 7.48 (m, 3 H), 7.38 (d, 2 H), 7.28 (m, 2 H), 5.01 (s, 4 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.334, 89.243, 88.798, 121.504, 122.036, 125.550, 126.001, 128.736, 134.861, 136.421, 136.334, 136.511, 139.553, 142.330, 143.667, 145.333, 146.500, 148.683, 150.900, 153.009, 163.337, 166.198, 172.215.

MS: *m*/*z* [M + H] = 418.

HRMS: *m*/*z* = 418.0032.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(2-methylphenyl)-1,3,5-oxadiazinane-4-thione (3d)

Yield: 330 mg (76%); off-white solid; mp 218–220 °C.

^{1}H NMR (DMSO-d_6): δ = 1.60 (s, 3 H), 2.30 (s, 2 H), 2.45 (s, 2 H), 7.40–8.2 (m, aromatic protons).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.334, 79.243, 122.056, 125.750, 126.005, 128.936, 134.865, 136.451, 136.354, 136.611, 139.653, 142.770, 143.687, 145.383, 146.800, 148.653, 150.940, 153.309, 163.367, 166.348, 172.635.

MS: *m*/*z* [M + H] = 418.

HRMS: *m*/*z* = 417.0072.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(4-methoxyphenyl)-1,3,5-oxadiazinane-4-thione (3e)

Yield: 330 mg (76%); off-white solid; mp 218–220 °C.

^{1}H NMR (DMSO-d_6): δ = 8.04 (d, 2 H), 7.90 (d, 1 H), 7.65 (d, 2 H), 7.51 (m, 3 H), 7.39 (d, 2 H), 7.28 (m, 2 H), 5.01 (s, 4 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 59.113, 89.223, 88.638, 121.514, 122.226, 125.443, 126.201, 128.756, 134.331, 136.547, 136.004, 136.311, 139.543, 141.999, 143.229, 145.494, 146.009, 148.683, 150.200, 153.569, 163.357, 166.128, 172.115.

MS: *m*/*z* [M + H] = 434.

HRMS: *m*/*z* = 434.0402.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(3-methoxyphenyl)-1,3,5-oxadiazinane-4-thione (3f)

Yield: 317 mg (73%); off-white solid; mp 193–195 °C.

^{1}H NMR (DMSO-d_6): δ = 8.05 (d, 2 H), 7.90 (d, 1 H), 7.66 (d, 2 H), 7.50 (m, 3 H), 7.40 (d, 2 H), 7.29 (m, 2 H), 5.02 (s, 4 H), 3.81 (s, 3 H).

MS: *m*/*z* [M + H] = 434.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-(4-bromoyphenyl)-1,3,5-oxadiazinane-4-thione (3g)

Yield: 348 mg (73%); pale-yellow liquid; bp 215–217 °C.

^{1}H NMR (DMSO-d_6): δ = 7.98 (d, 1 H), 7.83 (d, 2 H), 7.59 (d, 2 H), 7.45 (m, 3 H), 7.34 (d, 2 H), 7.21 (m, 2 H), 5.02 (s, 4 H).

MS: *m*/*z* [M + H] = 483.

3-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-phenyl-1,3,5-oxadiazinane-4-thione (3h)

Yield: 283 mg (70%); colorless liquid; bp 194–196 °C.

^{1}H NMR (DMSO-d_6): δ = 8.01 (d, 2 H), 7.84 (d, 2 H), 7.60 (d, 2 H), 7.46 (m, 3 H), 7.32 (m, 2 H), 7.22 (m, 2 H), 5.01 (s, 4 H).

MS: *m*/*z* [M + H] = 404.

Synthesis and Characterization of 1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones 4

A mixture of 1-(4-(benzo[*d*]thiazol-2-yl)phenyl)-3-arylthiourea **2** (50.0 mmol), 30% aqueous formaldehyde (100.0 mmol, 27.3 mL) and methylamine (50 mmol) was dissolved in EtOH (20 mL) and the mixture was heated to reflux for 4–6 h, monitoring by TLC. After completion of reaction, the mixture was cooled and the separated product was filtered. The crude material was purified by silica gel column chromatography, eluting with 60 % ethyl acetate/hexane.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(2-chlorophenyl)-1,3,5-triazinane-2-thione (4a)

Yield: 347 mg (77%); colorless liquid; bp 200–202 °C.

^{1}H NMR (DMSO-d_6): δ = 8.01 (d, 2 H), 7.90 (d, 1 H), 7.71 (d, 2 H), 7.55 (m, 3 H), 7.40 (m, 2 H), 7.31 (m, 1 H), 4.85 (d, 4 H), 2.48 (s, 3 H).

MS: *m*/*z* [M + H] = 451.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-chlorophenyl)-1,3,5-triazinane-2-thione (4b)

Yield: 346 mg (76%); colorless liquid; bp 193–195 °C.

^{1}H NMR (DMSO-d_6): δ = 8.05 (d, 2 H), 7.91 (d, 1 H), 7.73 (d, 2 H), 7.54 (m, 3 H), 7.45 (m, 2 H), 7.35 (m, 1 H), 4.88 (d, 4 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.113, 89.113, 88.334, 121.655, 122.229, 125.667, 127.008, 128.990, 131.334, 132.998, 134.667, 136.111, 136. 445, 136.990, 139.003, 142.155, 143.660, 146.378, 148.066, 150.232, 153.889, 166.288, 172.288.

MS: *m*/*z* [M + H] = 438.

HRMS: *m*/*z* = 438.0002.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-methylphenyl)-1,3,5-triazinane-2-thione (4c)

Yield: 385 mg (60%); colorless solid; mp 192–194 °C.

^{1}H NMR (DMSO-d_6): δ = 8.09 (d, 2 H), 7.95 (d, 1 H), 7.75 (d, 2 H), 7.58 (m, 3 H), 7.40 (m, 2 H), 7.34 (m, 1 H), 4.89 (d, 4 H), 2.48 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.339, 39.113, 89.113, 88.334, 121.654, 122.219, 125.347, 127.058, 128.870, 131.554, 132.119, 134.457, 136.007, 136.449, 136.788, 139.113, 142.275, 143.889, 146.768, 148.998, 150.242, 153.776, 166.319, 172.588.

MS: *m*/*z* [M + H] = 481.

HRMS: *m*/*z* = 481.0152.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(2-methylphenyl)-1,3,5-triazinane-2-thione (4d)

Yield: 385 mg (81%); colorless solid; mp 207–209 °C.

^{1}H NMR (DMSO-d_6): δ = 8.10 (d, 2 H), 7.96 (d, 1 H), 7.76 (d, 2 H), 7.58 (m, 3 H), 7.38 (m, 2 H), 7.33 (m, 1 H), 4.89 (d, 4 H), 2.49 (s, 3 H), 2.32 (s, 3 H).

MS: *m*/*z* [M + H] = 481.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-methoxylphenyl)-1,3,5-triazinane-2-thione (4e)

Yield: 328 mg (75%); colorless solid; mp 211–213 °C.

^{1}H NMR (DMSO-d_6): δ = 8.01 (d, 2 H), 7.98 (d, 1 H), 7.75 (d, 2 H), 7.59 (m, 3 H), 7.40 (m, 2 H), 7.34 (m, 1 H), 4.85 (d, 4 H), 3.87 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.113, 59.113, 89.113, 88.334, 121.054, 122.209, 125.387, 127.005, 128.810, 131.564, 132.009, 134.857, 136.077, 136.449, 136.988, 139.003, 142.265, 143.819, 146.098, 148.908, 150.202, 153.726, 166.379, 172.589.

MS: *m*/*z* [M + H] = 447.

HRMS: *m*/*z* = 447.0005.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(3-methoxylphenyl)-1,3,5-triazinane-2-thione (4f)

Yield: 326 mg (73%); colorless solid; mp 206–209 °C.

^{1}H NMR (DMSO-d_6): δ = 8.02 (d, 2 H), 7.98 (d, 1 H), 7.76 (d, 2 H), 7.60 (m, 3 H), 7.38 (m, 2 H), 7.32 (m, 1 H), 4.86 (d, 4 H), 3.86 (s, 3 H), 2.48 (s, 3 H).

MS: *m*/*z* [M + H] = 447.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-(4-bromolphenyl)-1,3,5-triazinane-2-thione (4g)

Yield: 347 mg (70%); pale-yellow liquid; bp 216–218 °C.

^{1}H NMR (DMSO-d_6): δ = 8.01 (d, 2 H), 7.97 (d, 1 H), 7.80 (d, 2 H), 7.58 (m, 3 H), 7.39 (m, 2 H), 7.31 (m, 1 H), 4.87 (d, 4 H), 2.47 (s, 3 H).

MS: *m*/*z* [M + H] = 495.

1-(4-(Benzo[*d*]thiazol-2-yl)phenyl)-5-methyl-3-phenyl-1,3,5-triazinane-2-thione (4h)

Yield: 296 mg (71%); off-white liquid; bp 212–215 °C.

^{1}H NMR (DMSO-d_6): δ = 8.08 (d, 2 H), 7.95 (m, 1 H), 7.82 (m, 3 H), 7.56 (m, 3 H), 7.40 (m, 2 H), 7.31 (m, 1 H), 4.88 (d, 4 H), 2.48 (s, 3 H).

MS: *m*/*z* [M + H] = 417.

Antibacterial Screening

Antibacterial screening was performed by disk diffusion. Nutrient agar (15 mL) was plated into a Petri dish with 0.1 mL of 10 dilutions of each bacterial culture. Filter paper discs (6 mm in diameter) impregnated with various concentrations of the prepared compounds (**3a–h**, **4a–h**) were placed on test organism-seeded plates. Different dilutions of the test compounds were prepared, ranging from 1 μg mL^{-1} to 200 μg mL^{-1}. The activity was determined after 18 h of incubation at 37 °C. The diameters of zone of inhibition produced by the extract were compared with the standard antibiotic Ampicillin 0.030 mm/disc. Each assay was carried out in triplicate for the determination of antibacterial activity.

Minimum Inhibitory Concentration Measurement

The compounds (0 to 200 μg) were dissolved in DMSO (1 mL) to obtain stock solution. After preparation of test organism suspensions (1000 organism per mL), 1 drop of suspension (0.02 mL) was added to each broth dilution. After 18 h incubation at 37 °C, the tubes were then examined for growth. The MIC of each compound was taken as the lowest concentration that showed no growth. In this study, tetracycline was taken as standard reference for all measurements.

Acknowledgment

We are grateful to the Osmania University Department of Chemistry, Hyderabad for constant support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591917.

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