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Synthesis, Characterization, In Vitro Antibacterial Activity of Some Novel N-{(6-Substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides

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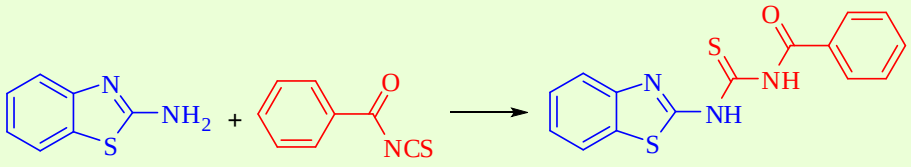
Abstract : A series of novel N-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides**5a-j**were synthesized by the reaction of 2-aminobenzothiazoles **2a-e**with appropriate benzoyl isothiocyanates **4a-f.** The structures of all newly synthesized compounds were confirmed by chemical tests, elemental (C, H, N and S) and spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) analysis.All of them were screened for their antibacterial activity against gram positive and gram negative bacteria showing promising results, and have shown moderate to potent antibacterial activity comparable to standard drug.
Keywords : Benzothiazoles, 2-Aminobenzothiazoles, Benzamides, Benzoylisothiocyanates.



2a-e 4a-f 5a-j

Introduction

The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. Among the various heterocycles, benzothiazoles have been studied prominently and found to be privileged moiety with diverse chemical reactivity and it has received overwhelming response owing to its diversified molecular design and remarkable optical and electronic properties[1,3]. They are the important nitrogen and sulphur containing heterocyclic compounds, and form the core structure of many biologically active compounds, e.g. pramipexole, riluzole, etc. Benzothiazoles have been found to possess a broad spectrum of pharmacological activities such as antibacterial[4], anticancer[5,6], antidiabetic[7], antifungal[8], anti-Inflammatory[9,10], antimicrobial[11,12], anti-proliferative[13], antimalarial[14], antitumor[15,16], antiviral[17], anthelmintics[18,19] and anticonvulsant[20] activities. N-Substituted 2-aminobenzothiazoles have also been reported to possess important biological activities[21,22].

Isothiocyanates (-N=C=S) constitute a group of heterocumulenes which is of immense importance in organic synthesis. The presence of carbonyl group, imparts unique reactivity to benzoyl isothiocyanate because

of special reactivity features which have been very well exploited in the recent past. The chemistry of benzoyl isothiocyanates is very rich and diverse, and has been employed in synthesis of a number of biologically important heterocyclic compounds[23].

Benzamides have been reported to play a crucial role in drug development[24]. Benzamides derivatives, e.g. metoclopramide and cisapride are used clinically for the treatment of different medical conditions[25].

In view of the aforesaid applications of 2-aminobenzothiazoles and benzamides, several new compounds **5a-j** containing these moieties have been synthesized. The structures of compounds are confirmed by conventional methods.

Experimental:

General.

All reactions were performed in oven-dried glassware's with magnetic stirring. All the chemicals and solvents are obtained from E-Merck, India (AR grade) and were used without further purification. Melting points of compounds were taken in an open capillary tubes by Toshniwal melting point apparatus in Celsius scale and uncorrected. The purity of the compound was verified by performing thin layer chromatography (TLC) on silica gel G (Merck) coated glass plates and spots were visualized by exposure to iodine vapors using Toluene : ethyl acetate (1:1) as a solvent system. IR spectra were recorded using KBr pellets on FTIR spectrophotometer (Perkin Elmer - Spectrum RX-IFTIR). ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT NMR Spectrometer model Advance-II (Bruker) (CIL, Chandigarh, India); ^{1}H frequency is 400 MHz Chemical shift (δ) are expressed in ppm relative to tetra methyl silane (TMS) as an internal standard. Mass spectra (FAB-MS) were recorded on Waters Micromass Q-T of Microspectrophotometer (SAIF, Chandigarh, India) and elemental analysis were carried out using Elementar Vario EL III CHN analyzer (STIC India, Cochin).

1. General procedure for the synthesis of 2-Amino-6-substituted benzothiazoles 2a-e

A saturated solution of ammonium thiocyanate (0.12 mole) 30g in 60 mL water was added slowly on to the warm mixture of 4-substituted aniline **1a-e** (0.25 mole) and conc. HCl (0.25 mole) with shaking. The solid obtained (phenyl thiourea) was filtered, washed with water, dried and crystallized from distilled water so as to get pure compound.

To the substituted Phenylthiourea (0.5 mole) sufficient amount of chloroform (20-25 mL) was added to get slurry and brominated using 5% bromine solution in chloroform till orange red colour appeared. The slurry was kept overnight. The solid hydrobromide obtained was filtered and washed several times with chloroform till the disappearance of orange red color. It was dissolved in alcohol and basified with 10% NH_4OH. The solid 2-aminobenzothiazole **2a-e**was filtered, washed with water, dried and recrystallized from ethanol.

2. Synthesis of 2/4-substituted benzoyl isothiocyanate 4a-f

Substituted benzoyl chloride (0.1 mole) was added dropwise on to a solution of ammonium thiocyanate (0.1 mole) in dry benzene (25ml) with vigorous stirring. The mixture was boiled for two hours. Cooled and filtered. The filtrate contains benzoyl isothiocyanate.

3. Synthesis of N-{(6-substituted-1,3-benzo[d]- thiazol- 2-yl)carbamothioyl}-2/4-substituted benzamides 5a-j

The mixture of 2-aminobenzothiazole (0.01mole) **2a-e** and benzoyl isothiocynate (0.01mole)

4a-f in dry benzene (25mL) and 2-propanol (5mL) was refluxed for 3 hours. The solid obtained solid was filtered, washed with benzene, dried and recrystallized from benzene. The spectral data of **5a-j** are given below.

N-(benzo[d]thiazol-2-ylcarbamothioyl)-2-methoxybenzamide**5a.**

m.p.: 176^{0}C; IR (KBr, ν_{max}, cm^{-1}): 1125.91 (C=S, stretching), 1571.59 (C=N, stretching), 1662.31 (C=O, stretching), 1651.43 (Ar C=C, stretching), 2779 (O- CH_3, stretching), 2941.85 (C–H Aliph, stretching), 3041.93 (Ar C-H, stretching), 3405.39, 3087.41 (NH, stretching);

^{1}H NMR (DMSO, δ, ppm): 7.28-8.36 (m, 8H, Ar-H), 8.19 (s, 1H, NHC=O, D_2O exchangeble), 12.74 (bs, 1H, NHC=S, D_2O exchangeable), 3.81(s, 1H, OCH_3); Mass spectra, (EI) m/z: 343 (M^+ peak).

N-(6-chlorobenzo[d]thiazol-2-ylcarbamothioyl)-2-methoxybenzamide **5b.**

m.p.: 193^{0}C; IR (KBr, ν_{max}, cm^{-1}): 698.26 (C-Cl, stretching), 1135.13 (C=S, stretching), 1455.82 (CH_3, bend), 1636.08 (Ar C=C, stretching), 1663.29 (C=N, stretching), 1697.06 (C=O, stretching), 2759.84. (O- CH_3, stretching), 2968.61 (C–H, stretching), 3059.24 (Ar C-H, stretching), 3436.54, 3204.28 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm): 7.18-8.15 (m, 8H, Ar-H), 8.91 (s, 1H, NHC=O,D_2O exchangeble), 13.16 (bs, 1H, NHC=S, D_2O exchangeable), 3.81(s, 1H, OCH_3); Mass spectra, (EI) m/z: 361 M^+ peak).

N-(6-chlorobenzo[d]thiazol-2-ylcarbamothioyl)-2-methylbenzamide **5c.**

m.p.: 221^{0}C; IR (KBr, ν_{max}, cm^{-1}): 801.23 (C-Cl, stretching), 1131.14 (C=S, stretching), 1455.84 (CH_3, bend), 1614.06 (Ar C=C, stretching), 1651.27 (C=N, stretching), 1690.23 (C=O, stretching), 2936.65 (C–H, stretching), 3052.69 (Ar C-H, stretching), 3429.34, 3171.29 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm): 7.19-8.12 (m, 8H, Ar-H), 8.93 (s, 1H, NHC=O,D_2O exchangeble), 13.23 (bs, 1H, NHC=S, D_2O exchangeable), 2.49 (s, 3H, CH_3); Mass spectra, (EI) m/z: 361 M^+ peak).

N-(6-chlorobenzo[d]thiazol-2-ylcarbamothioyl)-4-methoxybenzamide **5d.**

m.p.: 179^{0}C; IR (KBr, ν_{max}, cm^{-1}): 698.26 (C-Cl, stretching), 1089.13 (C=S, stretching), 1455.82 (CH_3, bend), 1636.08 (Ar C=C, stretching), 1663.29 (C=N, stretching), 1669.06 (C=O, stretching), 2759.84. (O- CH_3, stretching), 2968.61 (C–H, stretching), 3062.24 (Ar C-H, stretching), 3436.54, 3188.22 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm): 7.18-8.14 (m, 8H, Ar-H), 8.98 (s, 1H, NHC=O,D_2O exchangeble), 13.18 (bs, 1H, NHC=S, D_2O exchangeable), 3.81(s, 1H, OCH_3); Mass spectra, (EI) m/z: 361 M^+ peak).

N-(6-chlorobenzo[d]thiazol-2-ylcarbamothioyl)-4-methylbenzamide **5e.**

m.p.: 216^{0}C; IR (KBr, ν_{max}, cm^{-1}): 787.21 (C-Cl, stretching), 1129.13 (C=S, stretching), 1455.84 (CH_3, bend), 1614.06 (Ar C=C, stretching), 1651.27 (C=N, stretching), 1690.23 (C=O, stretching), 2931.65 (C–H, stretching), 3076.68 (Ar C-H, stretching), 3427.34, 3161.29 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm): 7.42-8.15 (m, 8H, Ar-H), 8.84 (s, 1H, NHC=O,D_2O exchangeble), 13.15 (bs, 1H, NHC=S, D_2O exchangeable), 2.84 (s, 3H, CH_3); Mass spectra, (EI) m/z: 361 M^+ peak).

N-(6-chlorobenzo[d]thiazol-2-ylcarbamothioyl)-4-nitrobenzamide **5f.**

m.p.: 262^{0}C; IR (KBr, ν_{max}, cm^{-1}): 784.71 (C-Cl, stretching), 1124.19 (C=S, stretching), 1342 (NO_2 stretching), 1603.04 (Ar C=C, stretching), 1658.39 (C=N, stretching), 1672.51 (C=O, stretching), 3037.64 (Ar C-H, stretching), 3423.14, 3159.23 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm): 7.57-8.44 (m, 8H, Ar-H), 8.86 (s, 1H, NHC=O, D_2O exchangeble), 13.05 (bs, 1H, NHC=S, D_2O exchangeable); Mass spectra, (EI) m/z: 392M^+ peak).

N-(6-bromobenzo[d]thiazol-2-ylcarbamothioyl)benzamide**5g.**

m.p.: 257^{0}C; IR (KBr, νmax, cm^{-1}): 591.87 (C-Br, stretching), 1051.29 (C=S, stretching), 1593.04 (Ar C=C, stretching), 1687.76 (C=O, stretching), 1689.57 (C=N, stretching), 3021.09 (Ar C-H, stretching), 3358, 3181.09 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm); 7.36-8.15 (m, 8H, Ar-H), 8.87(s, 1H, NHC=O, D_2O exchangeble), 13.004 (bs, 1H, NHC=S, D_2O exchangeable). Mass spectra, (EI) m/z: 392(M^+ peak).

N-(6-bromobenzo[d]thiazol-2-ylcarbamothioyl)-4-methylbenzamide **5h.**

m.p.: 218^{0}C; IR (KBr, νmax, cm^{-1}): 591.87 (C-Br, stretching), 1078.29 (C=S, stretching), 1459.84 (CH_3, bend), 1593.04 (Ar C=C, stretching), 1673.76 (C=O, stretching), 1689.57 (C=N, stretching), 2939.67 (C–H, stretching), 3038.09 (Ar C-H, stretching), 3359, 3201.09 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm); 7.42-8.74 (m, 8H, Ar-H), 8.21 (s, 1H, NHC=O, D_2O exchangeble), 13.34 (bs, 1H, NHC=S, D_2O exchangeable). Mass spectra, (EI) m/z: 406 (M^+ peak).

N-(6-methylbenzo[d]thiazol-2-ylcarbamothioyl)-4-nitrobenzamide **5i.**

m.p.: 312^{0}C; IR (KBr, νmax, cm^{-1}): 1143.07 (C=S stretch), 1143.07 (C=S stretch), 1356.07 (C-NO_2 stretch), 1449.04 CH_3 (bend), 1467.86 (Ar C=C stretch), 1658.39 (C=O stretch), 1656.01 (C=N stretch), 2851.26 (C–H Aliph), 3029.79 (Ar C-H stretch), 3446.23, 3173.61 (NH stretch);

^{1}H NMR (DMSO, δ, ppm) 7.34-8.33 (m, 8H, Ar-H), 9.89 (s, 1H, NHC=O, D_2O exchangeble), 13.16 (bs, 1H, NHC=S, D_2O exchangeable), 2.39 (s, 3H, CH_3); Mass specra (EI) m/z: 372.42 (M^+peak).

N-(6-methoxybenzo[d]thiazol-2-ylcarbamothioyl)-4-methylbenzamide **5j.**

m.p.: 219^{0}C; IR (KBr, ν_{max}, cm^{-1}): 1156.19 (C=S, stretching), 1459.82 (CH_3, bend), 1662.08 (Ar C=C, stretching), 1670.25 (C=N, stretching), 1698.09 (C=O, stretching), 2761.86 (O-CH_3, stretching), 2964.68 (C–H, stretching), 3066.28 (Ar C-H, stretching), 3440.54, 3181.36 (NH, stretching); ^{1}H NMR (DMSO, δ, ppm): 7.01-7.91 (m, 8H, Ar-H), 8.67(s, 1H, NHC=O, D_2O exchangeble), 13.26 (bs, 1H, NHC=S, D_2O exchangeable), 2.34 (s, 3H, CH_3) 3.86 (s, 1H, OCH_3); Mass spectra, (EI) m/z: 357.45 M^+ peak).

Biological activity:

The newly synthesized N-{[(6-substituted-1,3-benzo[d]thiazol-2-ylcarbamot- hioyl)-2/4-substituted benzamides**5a-j** were examined for their anti-bacterial activity by using well diffusion method. The standard cultures of *S. aureus* (Gram positive), *B. subtilis* (Gram positive), *E. coli* (Gram negative) *and P. aeruginosa* (Gram negative) were obtained from Department of Biotechnology, Dr. Ambedkar College, Nagpur. N-substituted benzoxazolyl benzamides and standard drug were dissolved in DMF to prepare stock solutions.

For the growth of bacterial colony Muller Hinton agar was used as the culture medium, that was prepared by using Beef Extract (2.00 gm), Acid Hydrolysate of Casein (17.50 gm), Starch (1.50 gm), Agar (17.00 gm), in 1000 ml of distilled Water. The pH of agar medium was adjusted to 7.3 at 25ºC. Prepared agar medium was mixed well and autoclaved at 15 lbs pressure for at least 20 minutes, to sterilize the media. In the 100ml sterile medium single loop-full of micro-organisms were inoculated and incubated for 24 h at 37°C. This media were poured in petridishes slowly and allowed to solidify. Two well were created in the agar medium with the help of a borer of 6 mm diameter. Test samples/ standards (0.05ml) was introduced into the well. All the plates were incubated at 37°C for 24 hours. The antibacterial activities of compounds were evaluated by measuring the zone of inhibition in mm. The diameter of the zone of inhibition for samples was measured and recorded **Table 2**.

Results and discussion:

Chemistry:

With the aim of obtaining more precise information about the course of reaction and some interesting pharmaceutical compounds, we have reported synthesis ofN-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides **5a-j** from 2-aminobenzothiazoles **2a-e** and benzoyl isothiocyanates **4a-f** as presented in scheme 1. 2-Aminobenzothiazoles **2a-e** were synthesized by treatment of ammonium thiocyanate on aryl amines followed by bromination and then after basification with ammonium hydroxide by a known preparation method [26].The yields of the respective 2-aminobenzothiazoles were found to be excellent. The 2-aminobenzothiazole showed characteristic peaks at 1257-1294 cm^{-1} for (C-S) , 1310-1434 cm^{-1} for (C-N), 1567-1625 cm^{-1} for (C=N), 3341 - 3410 cm^{-1} for (NH) in FTIR spectral data. The ^{1}H NMR spectra shows a broad singlet at 5.21 - 6.28 ppm due to (–NH_2)protons (D_2O exchangeable) besides those for aromatic protons in the region 6.93 - 8.24ppm.

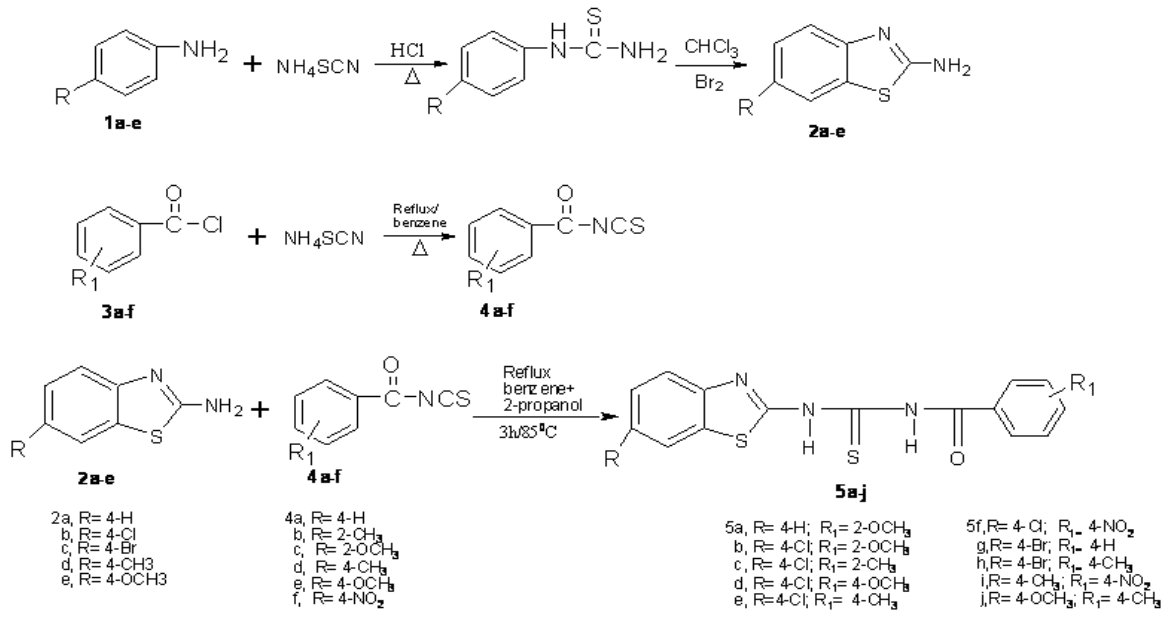
2/4-Substituted benzoylisothiocyanates **4a-f**are obtained bybenzoylation of ammonium thiocyanates[27]. The FTIR bands showed band for (C=O) at 1682-1728 cm^{-1} and (N-C-S) at 2125-2245 cm^{-1}. The ^{1}H-NMR sprectum showed multiplet at δ 7.19-8.39 for aromatic protons.

The target compounds N-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides were synthesized by modified (less time and high yield) procedure [28], the reaction was carried out in benzene – 2-propanol (5:1) mixture.Thus, interaction of 2-aminobenzothiazoles **2a-e** with benzoyl isothiocyanates **4a-f** gaveN-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides **5a-j** in excellent yield (**scheme I**).

The structural elucidation of compounds was done through chemical tests, elemental (C, H, N and S) analysis and spectroscopic tools such as, FTIR, ^{1}H NMR and mass spectroscopy. IR (KBr) spectra of the compound **5a-j** had strong absorptions at 3021 - 3106.24 (aromatic C-H) 3465.26 -3269.71 cm^{-1} for free N-H and 3204.28-3081.73 cm^{-1} for associated N-H, and displayed absorptions at 1651-1698 cm^{-1} and 1051 - 1160 cm^{-1} that were assigned to C=O and C=S functions, respectively. In the IR spectrum of the**5a-j**peaks of -C=O- stretching, -NH- bending and stretching indicated the presence of amide linkage. The ^{1}H-NMR data of **5a-j** obtained in DMSO solution are given in the experimental section and are consistent with the structural results. The aromatic protons produced well-defined signals at δ 7.01 - 8.74, ^{1}H-NMR data confirmed presence of (NHC=O) and (NHC=S) by showing singlet at 8.14 - 9.89 and broad singlet at 12.28-13.11, respectively, exchangeable with D_2O. The disappearance of the -NH_2signal from the ^{1}H NMR spectrum and the presence of singlet in the region of δ 12.28-13.34 indicate that the -NH_2group has been converted to amide linkage. The physical and chemical data for newly synthesized compounds are presented in **Table 1.**

In-Vitro Biological Activity:

The In-Vitro antimicrobial activity of the newly synthesized N-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides **5a-j** were studied against different bacterial strains such as S. aureus, *B. subtilis, E. coli* and *P. aeruginosa*. The antibacterial activities were evaluated by measuring the zone of inhibition on Muller Hilton agar plates by well disk diffusion method. The tests were repeated thrice and the results were reported as means of at least three determinations. The antibacterial activity of the compoundsis shown in **Table 2.** It can be observed that some of the newly synthesized compounds possess good to moderate antimicrobial activity as compared with standard drug ampicillin and erythromycin.



Scheme I: Synthesis of N-{(6-Substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides

Table 1:Physical properties and elemental analysis of N-{(6-substituted-1,3-benzo[d]thiazol-2-yl) carbamothioyl}-2/4-substituted benzamides 5a-j

Product Code	R	R_1	Mol. formula	Mol. weight	Yield (%	M.P.^{0}C	Found (calculated) %			
							C	H	N	S
5a	H	2-OCH	$C_{16}H_{13}N_3O_2S_2$	343.42	67	176	54.45 (55.96)	4.07 (3.82)	11.93 (12.24)	9.17 (9.32)
5b	Cl	2-OCH	$C_{16}H_{12}ClN_3O_2S_2$	377.87	83	193	51.09 (50.86)	3.56 (3.2)	10.93 (11.12)	16.37 (16.97)
5c	Cl	2-CH_3	$C_{16}H_{12}ClN_3OS_2$	361.87	74	221	52.97 (53.11)	4.26 (3.34)	12.19 (11.61)	16.94 (17.72)
5d	Cl	4-OCH	$C_{16}H_{12}ClN_3O_2S_2$	377.87	86	179	51.21 (50.86)	4.5 (3.2)	12.35 (11.12)	15.14 (16.97)
5e	Cl	4-CH_3	$C_{16}H_{12}ClN_3OS_2$	361.87	79	216	53.91 (53.11)	2.89 (3.34)	12.31 (11.61)	18.06 (17.72)
5f	Cl	4-NO_2	$C_{15}H_{10}ClN_4O_3S_2$	392.84	90	262	46.19 (45.86)	3.12 (2.31)	13.97 (14.26)	16.78 (16.32)
5g	Br	H	$C_{15}H_{10}BrN_3OS_2$	392.29	76	257	44.93 (45.92)	2.96 (2.57)	11.41 (10.71)	16.89 (16.35)
5h	Br	4-CH_3	$C_{16}H_{12}BrN_3OS_2$	406.32	81	218	48.12 (47.30)	3.05 (2.98)	11.23 (10.34)	16.05 (15.78)
5i	CH_3	4-NO_2	$C_{16}H_{12}N_4O_3S_2$	372.42	84	312	50.31 (51.60)	4.07 (3.25)	16.09 (15.04)	16.69 (17.22)
5j	OCH_3	4-CH_3	$C_{17}H_{15}N_3O_2S_2$	357.45	86	219	56.58 (57.12)	5.06 (4.23)	10.98 (11.76)	17.46 (17.94)

M.P.: Melting point

Table 2: Antibacterial activity of N-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides 5a-j

Compound		(Zone of inhibition in mm at 100 µg/mL)		
	Gram-positive		Gram-negative	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
5a	5	7	16	9
5b	3	-	15	8
5c	4	8	12	5
5d	6	13	10	4
5e	8	11	11	-
5f	7	10	9	-
5g	8	13	-	6
5h	9	4	11	7
5i	4	8	14	4
5j	-	5	8	6
Standard Drug	13	16	15	12

Conclusion:

We have efficiently synthesized series of novel N-{(6-substituted-1,3-benzo[d]thiazol-2-yl)carbamothioyl}-2/4-substituted benzamides**5a-j** from 2-aminobenzothiazole in good to excellent yields. All the compounds were characterized using spectroscopic and analytical tools. Some of final products were their

screened for their antibacterial activity and it was observed that some of the compounds are having moderate to potent anti bacterial activity which is compared with standard drug.

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