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RESEARCH ARTICLE

A facile microwave enhanced synthesis of sulfur-containing 5-membered heterocycles derived from 2-mercaptobenzothiazole over $ZnCl_2$/DMF and antimicrobial activity evaluation

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An efficient and extremely fast procedure for the synthesis of 4-thiazolidinones **4a–j** by the reaction of arylidene-[(2-benzothiazolylthio)-acetamidyl] **3a–j** with thioglycolic acid in DMF in the presence of a catalytic amount of anhydrous $ZnCl_2$ under microwave irradiation is described. A considerable increase in the reaction rate has been observed with better yield in microwave technique. All the compounds have been screened for their antifungal activity against *Candida albicans (ATCC-64550), Candida krusei (ATCC-14243)* and *Candida parapsilosis (ATCC-22019)* and antibacterial activity against *Escherchia coli (Gram −ve) (ATCC-8739)*, *Staphylococcus aureus (Gram +*ve*) (ATCC-6538)* and *Bacillus substilis (Gram +ve) (ATCC-6633)*. The structures of the synthesised compounds **4a–j** have been characterized on the basis of their elemental analysis and spectral data.

Keywords: 4-Thiazolidinones; Heterocyclization; Microwave effect; Antimicrobial activity; Anhydrous $ZnCl_2$/DMF

1. Introduction

2-Mercaptobenzothiazole derivatives are known to possess various biological activities [1]. 4-Thiazolidinones are also well known for versatile pharmacological activities such as hypnotic [2], anaesthetic [3], antifungal [4], anthelmintic [5], antiviral [6], CNS [7] stimulant etc. Incorporation of the 4-oxothiazolidine moiety into a 2-mercaptobenzothiazole scaffold has been found to enhance its activity [8]. Hence, in present study the C-2″ position in 2-mercaptobenzothiazole moiety having thiol (−SH) group, was used as the target for chemical change (scheme 1). These observations promoted us to synthesise the titled compounds (**1–4**).

Condensation of 2-mercaptobenzothiazole with ethyl chloroacetate in dry acetone gave ethyl-2-(benzothiazolylthio)-acetate [9] **1**. The compound **1** on aminolysis with hydrazine

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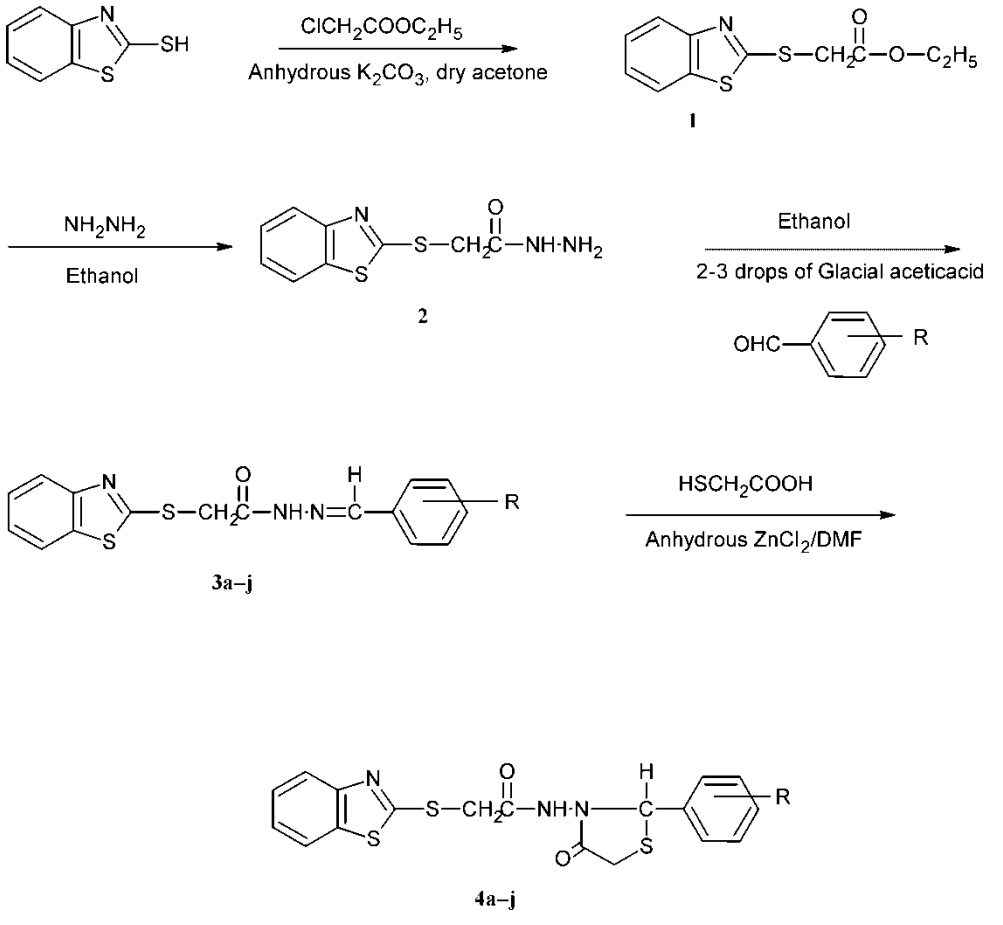


SCHEME 1

hydrate in ethanol yielded [2-(benzothiazolylthio)-acetyl]-hydrazine [9] **2**. Compound **2** underwent condensation with different carbonyls to afford the arylidene-[2-(benzothiazolylthio)-acetamidyl] [9] **3a–j**. These intermediates on reaction with thioglycollicacid yielded five membered sulfur-containing heterocyclic derivatives 2-(aryl)-3-[2-(benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines **4a–j**.

In the last few years Microwave-induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid synthesis [10] and many researchers have described accelerated organic reactions, and a large number of papers has appeared proving the synthetic utility of MORE chemistry in routine organic synthesis [11, 12]. It can be termed as e-chemistry because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry.

Under the framework of Green Chemistry [13, 14], a novel, environmentally benign approach to prepare 4-thiazolidinones is reported. Considering the above, and following earlier reported applications of MORE [15, 16] chemistry, we now report a facile anhydrous $ZnCl_2$/DMF mediated microwave synthesis of 4-thiazolidinones.

In conventional methodology the yield is sometimes lower than microwave protocols. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur. A comparative study in terms of yield and reaction period is shown

Table 1. Comparative study in terms of yield and reaction period in presence of different power watts and constant temperature for microwave and conventional techniques **4a–j**.

		[M] Microwave Irradiation Technique (MWI)					[C] Conventional method	
		Irradiation condition		[A]Yield	[B]Yield		Time	[C]Yield
Products	Substitutents R	[A,M] Power P_1 (W)/Time T_1 (min)	[B,M] Power P_2 (W)/Time T_2(min)	(%)	(%)	Constant temperature (°C)	(hr)	(%)
4a	4-NO_2	200/5.5	400/3.0	78	86	146	8.0	68
4b	3, 4, 5-$(OCH_3)_3$	300/4.5	500/2.0	80	95	150	7.0	71
4c	2-OH	350/4.0	450/2.5	83	89	148	7.5	66
4d	3-OH	350/4.0	450/2.5	83	89	148	7.5	76
4e	4-OH	300/4.5	500/2.0	80	95	150	7.0	71
4f	2-OCH_3	200/5.5	400/3.0	84	86	146	8.0	59
4g	4-OCH_3	350/4.0	450/2.5	83	89	148	7.5	62
4h	2-Cl	200/5.5	500/2.0	78	95	146	8.0	72
4i	3-Cl	250/5.0	450/2.5	79	89	144	8.5	74
4j	4-Cl	300/4.5	400/3.0	80	86	146	8.0	70

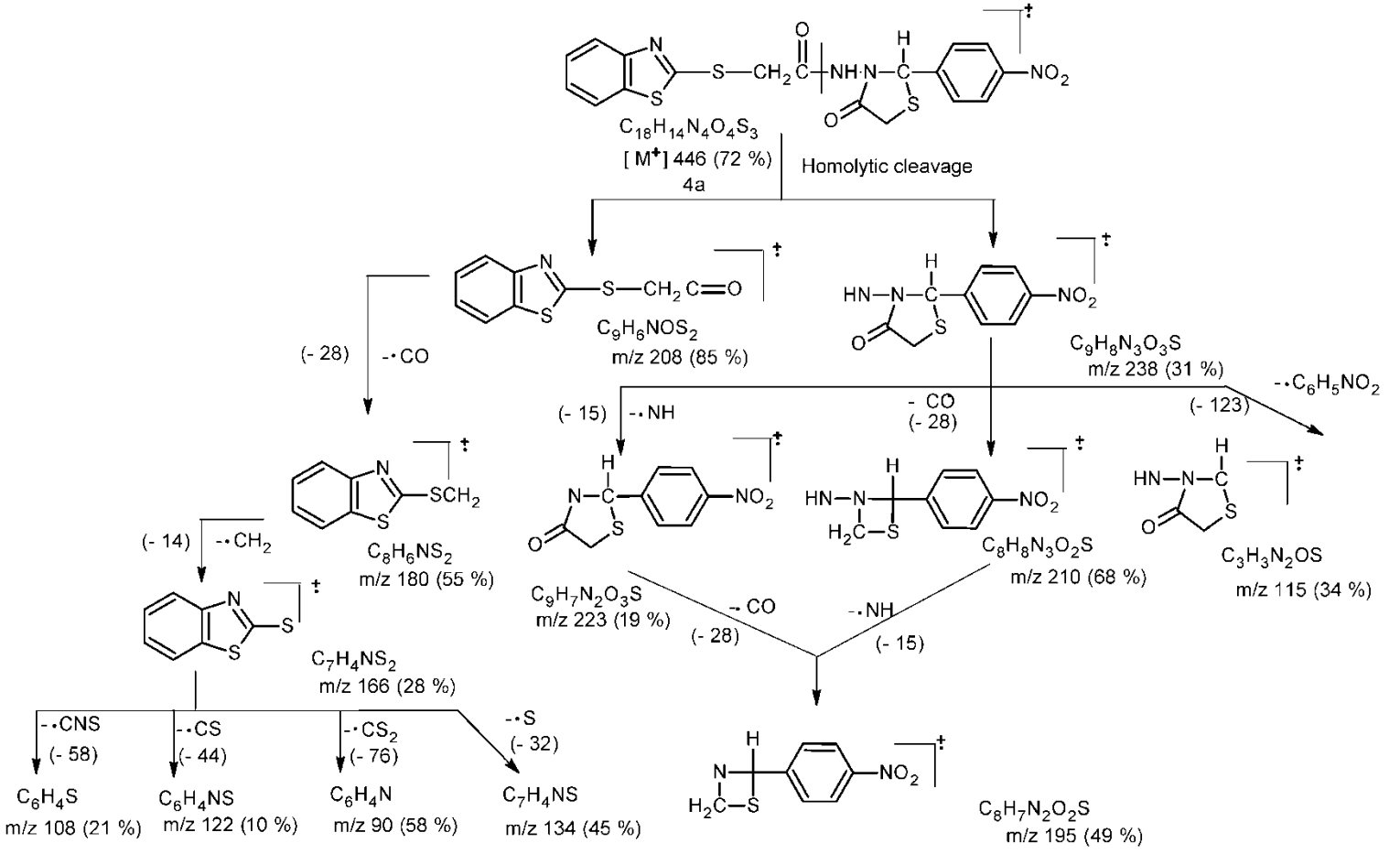
[A,M]Yield of isolated products (P_1-200-350 W, T_1-4.0-5.5 min); [B,M]Yield of isolated products (P_2-400-500 W, T_2-2.0-3.0 min); [C]Yield of isolated products.

in (table 1). All the compounds synthesised were characterized by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopies and by mass spectrometry.

2. Results and discussion

2-Mercaptobenzothiazole and ethyl chloroacetate in presence of anhydrous K_2CO_3 in dry acetone as a reaction mediator afforded compound **1**. Formation of compound **1** was evidenced by appearance of signal at δ 1.23 and 4.13 ppm due to CH_3 and CH_2 respectively in –COOCH_2CH_3 (J = 7 Hz) of compound **1** in ^{1}H NMR spectra and IR spectra bands due to 1723 cm^{-1} (>C=O of ester) and 2915, 2871, 1423, 713 cm^{-1} (CH_2 and CH_3) also confirmed the formation of compound **1**. Compound **1** and hydrazine hydrate in ethanol as a reaction afforded compound **2**. In ^{1}H NMR spectra of compound **2** the peak at δ 7.88 ppm was observed due to −CONH− and δ 4.40 ppm due to $-NH_2$ of compound **2** and in IR spectra of compound **2** the bands at 1665 cm^{-1} (>C=O of amide) and 3352, 3378 cm^{-1} ($-NHNH_2$) also confirmed the formation of compound **2**. Compound **2**, aromatic aldehyde and 2-3 drops of glacial acetic acid in ethanol as a reaction mediator afforded compound **3**. Formation of compound **3** was evidenced by appearance of signal at δ 4.40 ppm due to −N=CH− of compound **3** in ^{1}H NMR spectra, appearance of signal at δ 60 ppm due to >CH−N< of compound **3** in ^{13}C NMR spectra and IR spectra bands due to 1626 cm^{-1} (−N=CH−) also confirmed the formation of compound **3**. Compound **3**, thioglycollicacid and anhydrous $ZnCl_2$ in DMF as a reaction mediator afforded thiazolidinones **4**. In ^{1}H NMR spectra of compound **4a**, the peak at δ 3.60 ppm was observed due to CH_2 in thiazolidinones ring, in ^{13}C NMR spectra of compound **4a** the peak at δ 30 ppm was observed due to CH_2, 172.5 ppm (cyclic, >C=O) and 157.5 ppm (heteroaromatics) in thiazolidinones ring, in IR spectra of compound **4a** the bands at 1717 cm^{-1} (>C=O, cyclic) also confirmed the formation of compound **4a** and in Mass spectra of compound **4a** the molecular ion peak 446[M^+] (72%) also confirmed the formation of thiazolidinone. Fragment ion (m^+) peak was observed at 238 (31%) m/z ($C_9H_8O_3N_3S^+$), 223 (19%) m/z ($C_9H_7O_3N_2S^+$), 210 (68%) m/z ($C_8H_8O_2N_3S^+$), 208 (85%) m/z ($C_9H_6ONS_2^+$), 195 (49%) m/z ($C_8H_7N_2O_2^+$), 180 (55%) m/z ($C_8H_6NS_2^+$), 166 (28%) m/z ($C_7H_4NS_2^+$), 134 (45%) m/z ($C_7H_4NS^+$), 115 (34%) m/z ($C_3H_3N_2OS^+$), 122 (10%) m/z ($C_6H_4NS^+$), 108 (21%) m/z ($C_6H_4S^+$) and 90 (58%) m/z ($C_6H_4N^+$) by the loss of fragment radicals and neutrals • CO (-28), • NH (-15), • $C_6H_5NO_2$ (-123), • CH_2 (-14), • CNS (-58), • CS_2 (-76), • S (-32) and • CS (-44). MS spectral fragmentation pattern is presented (scheme 2) as an additional evidence for the proposed structure **4a**. The synthetic route of above mentioned compounds is shown in scheme 1.

All the reactions under microwave irradiation (MWI) were completed within 2–5 mins, whereas similar reactions under conventional heating (steam bath) at similar temperature (80–100 °C) gave poor yields with comparatively longer reaction time periods (table 1), demonstrating that the effect of microwave irradiation is not purely thermal. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state [17]. The impact of microwave irradiation and conventional heating for the synthesis of compound **4a–j** has been compared. Under microwave irradiation conditions, the yields of **4a–j** are high (95–86%). Whereas the yields are only 59–76%, when the reaction is carried out under conventional heating (steam bath). The effects of irradiation power and time on the reaction were also studied and the results summarized in tables 2 and 3. It was found the high yield compounds **4a–j** can be obtained in 500 W for 2.0 min under microwave irradiation conditions.



SCHEME 2. Mass fragmentation pattern of 2-(4-nitrophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines **4a**.

Table 2. The Effect of Microwave Irradiation Power[K].

Irradiation power (W)	250	300	350	400	450	500
Yield (%)	79	80	83	86	89	95

[K]Irradiation time is 2 min.

Table 3. The Effect of Microwave Irradiation Time[G].

Irradiation time (min)	5.0	4.5	4.0	3.0	2.5	2.0
Yield (%)	79	80	83	78	89	95

[G]Irradiation power is 500 W.

In conclusion, this new method for the synthesis of sulfur-containing-5-membered heterocycles "4-thiazolidinones" using anhydrous $ZnCl_2$ as a catalyst in DMF under microwave irradiation, offers significant improvements over existing procedures an thus helps facile entry into a variety of 4-thiazolidinones of potentially high synthetic utility. Also, this simple and reproducible technique affords various 4-thiazolidinones with short reaction times, excellent yields, and without formation of undesirable side products.

3. Antimicrobial activity

The tested microorganisms were *gram +ve* bacteria [*Bacills substilis (ATCC-6633)* and *Staphylococcus aureus (ATCC-6538)*] and *gram –ve* bacteria [*Escherchia coli (ATCC-8739)*]. In addition, some fungal pathogens [*Candida albicans (ATCC-64550)*, *Candida krusei (ATCC-14243)* and *Candida parapsilosis (ATCC-22019)*] were also tested. Sensitivity of the selected microorganisms to some synthesized compounds **4a–j** was determined *in vitro* at two concentrations (100, 400 μg/mL) in $CHCl_3$. The tests were carried out using the disk diffusion method [18] and microdilution method [18]. Results are presented in table 4.

Studies on the biological activity of compounds **4a**, **4e**, **4g**, **4h** and **4i** led to the fact that these compounds have moderate biological activity against the tested *Bacills substilis* bacteria, and only weak activity against fungi. Biological activity of compounds **4a**, **4e**, **4g** and **4h** led to the fact that these compounds have moderate biological activity against the tested *Staphylococcus aureus* bacteria, and only weak activity against fungi. Biological activity of compounds **4a** and **4g** led to the fact that these compounds have moderate biological activity against the tested *Escherchia coli* bacteria, and only weak activity against fungi. Also, that compounds **4b**, **4d** and **4f** have only a weak effect on *Bacills substilis* bacteria, compounds **4d**, **4f** and **4j** and have only a weak effect on *Staphylococcus aureus* bacteria and compound **4e** has only a weak effect on *Escherchia coli* bacteria. Compounds **4d** and **4i** showed weak antifungal activity but compounds **4a**, **4b**, **4e**, **4f**, **4g**, **4h** and **4j** showed moderate antifungal activity against *Candida albicans* species. Compounds **4b**, **4d**, **4f**, **4h** and **4j** showed weak antifungal activity but compounds **4a**, **4c**, **4e** and **4f** showed moderate antifungal activity against *Candida krusei* species. Compounds **4a**, **4e** and **4g** showed weak antifungal activity but compounds **4b**, **4d**, **4f**, **4i** and **4j** showed moderate antifungal activity against *Candida parapsilosis* species. Standard drugs Streptomycin and Griscofulvin were also screened under similar conditions for comparison. By visualizing the antimicrobial data it could be observed that some of the compounds possess significant activity. However, the activities of the tested compounds are less than that of standard antibacterial agent and antifungal agent used.

Table 4. Response of various microorganisms to some synthesized compounds **4a–j** in *in vitro* culture.

	Antibacterial in (μg/mL)			Antifungal in (μg/mL)		
	Gram +ve		*Gram −ve*			
Compounds	*B. s* [a] *(ATCC-6633)*	*S. a* [b] *(ATCC-6538)*	*E. c* [c] *(ATCC-8739)*	*C. a* [d] *(ATCC-64550)*	*C. k* [e] *(ATCC-14243)*	*C. p* [f] *(ATCC-22019)*
4a	M	M	M	M	M	W
4b	W			M	W	M
4c		M	M		M	
4d	W	W	M	W	W	M
4e	M	M	W	M	M	W
4f	W	W	M	M	W	M
4g	M	M	M	M	M	W
4h	M	M	M	M	W	
4i	M			W		M
4j		W	M	M	W	M
Zone of Inhibition of Standard Drugs (μg/mL)						
Streptomycin	S	S	S			
Griscofulvin				S	S	S

Diameter of the Zone of inhibition: W: low activity (3-6 mm) (+), M: moderate activity (7-24 mm) (++), S: standard activity (25-30 mm) (+ + +).

[a] *B. s - Bacills substilis*; [b] *S. a - Staphylococcus aureus*; [c] *E. c - Escherchia coli*; [d] *C. a - Candida albicans*; [e] *C. k - Candida krusei*; [f] *C. p - Candida parapsilosis.*

4. Experimental

All reagents, 2-mercaptobenzothiazole, solvents and catalyst are analytical grade from a commercial source and used directly. All the melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra (υ_{max} in cm^{-1}) were recorded on a shimadzu FT-IR 8300 spectrophotometer using KBr or Nujol technique; ^1H NMR spectra on a Bruker WM 400FT 400 MHz NMR instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference (chemical shifts in δ, ppm); ^{13}C NMR on a Varian AMX 400 (100 MHz) spectrometer as solutions in $CDCl_3$ and Mass spectra on a Jeol JMS D-300 spectrometer operating at 75 eV. The elemental analysis (C, H, N, S) of compounds was performed on Carlo Erba-1108 elemental analyzer. Their results were found to be in good agreement with the calculated values. The microwave assisted reactions are carried out in a "QPro-M Modified Microwave Synthesis System" manufactured by Questron Technologies Corporation, Ontario L4Z 2E9 has been used (made in Canada). In this unit, microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100 to 500 W and individual sensor for temperature control (fibre optic is used as a individual sensor for temperature control). There is an attachment for a reflux condenser with constant stirring, avoiding the risk of high pressure development and permitting synthesis on preparative scales.

In the present work, we used a new kind of QPro-M Modified Microwave Synthesis System apparatus that is well suited for stringent reaction conditions [anhydrous atmosphere, controlled temperature (fibre optic is used as a individual sensor for temperature control) and attachment of reflux condenser with constant stirring]. This high-intensity microwave generator is equipped with magnetron. The frequency can be tuned at 2450 MHz.

4.1 *Microwave mediated synthesis of ethyl-2-(benzothiazolylthio)-acetate 1*

Mercaptobenzothiazole (0.01 mole, 1.67 g) and ethyl chloroacetate (0.01 mole, 1.22 mL) in dry acetone (4 mL) in the presence of anhydrous K_2CO_3 (1 g) was taken in round bottom flask placed in a microwave oven and irradiated (300 W, 61–62 °C) for 4.5 min [19]. Upon completion of reaction (monitored by TLC), the reaction mixtures was allowed to attain room temperature and treated with cold water. The solid separated was filtered, washed with water and recrystallised from chloroform to furnish compound **1**, yield 82% as a white crystal (EtOH). mp 58 °C. Anal. Calcd for $C_{11}H_{11}NO_2S_2$: C, 52.18; H, 4.22; N, 5.40; S, 25.29. Found: C, 52.16; H, 4.23; N, 5.38; S, 25.24%; IR (KBr) υ_{max}: 3023 (aromatic ring), 1070 (aliphatic ether), 638 (C−S), 1723 (>C=O of ester), 1614 (−C=N−), 1223 and 1041 (C − O − C), 721 (C − S − C) and 2915, 2871, 1423, 713 (−CH_2 and −CH_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 1.23 (t, 3H, $J = 7$ Hz, −$COOCH_2CH_3$), 4.13 (q, 2H, $J = 7$ Hz, −$COOCH_2CH_3$), 4.46 (s, 2H, S−CH_2−), 6.73–7.87 (m, 4H, Ar-H) ppm.

4.2 *Conventional synthesis of ethyl-2-(benzothiazolylthio)-acetate 1*

Equimolar solution of 2-mercaptobenzothiazole (0.01 mole, 1.67 g) and ethyl chloroacetate (0.01 mole, 1.22 mL) in dry acetone (4 mL) in the presence of anhydrous K_2CO_3 (1 g) was refluxed on a water-bath for 16 hr. The solvent was removed by vacuum distillation and the residue was recrystallized from chloroform to furnish compound **1**, yield 66% as a white solid ($CHCl_3$). mp 58 °C. Anal. Calcd for $C_{11}H_{11}NO_2S_2$: C, 52.18; H, 4.22; N, 5.40; S, 25.29 Found: C, 52.16; H, 4.23; N, 5.38; S, 25.24%; IR (KBr) υ_{max}: 3023 (aromatic ring),

1070 (aliphatic ether), 638 (C-S), 1723 (>C=O of ester), 1614 (−C=N−), 1223 and 1041 (C-O-C), 721 (C-S-C) and 2915, 2871, 1423, 713 (−CH_2 and −CH_3) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 1.23 (t, 3H, $J = 7$ Hz, −$COOCH_2CH_3$), 4.13 (q, 2H, $J = 7$ Hz, −$COOCH_2CH_3$), 4.46 (s, 2H, S−CH_2−), 6.73–7.87 (m, 4H, Ar-H) ppm.

4.3 *Microwave mediated synthesis of [(2-benzothiazolylthio)-acetyl]-hydrazine 2*

Ethyl-(2-benzothiazolylthio)-acetate **1** (0.01 mole, 2.53 g) and hydrazine hydrate (0.01 mole, 0.9 mL) in ethanol (20 mL) was taken in round bottom flask placed in a microwave oven and irradiated (350 W, 76–78 °C) for 4 min [19]. After completion of reaction (monitored by TLC), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol to get compound **2**, yield 85% as a pinkish white powder (EtOH). mp 193 °C. Anal. Calcd for $C_9H_9N_3OS_2$: C, 45.22; H, 3.10; N, 17.60; S, 26.12. Found: C, 45.19; H, 3.07; N, 17.57; S, 26.20%; IR (KBr) υ_{max}: 3352, 3378 (−$NHNH_2$), 1665 (>C=O of amide) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 6.80–7.90 (m, 4H, Ar-H), 4.40 (s, 2H, −NH_2), 4.81 (s, 2H, S−CH_2−), 7.88 (s, 1H, −CONH−) ppm.

4.4 *Conventional synthesis of [(2-benzothiazolylthio)-acetyl]-hydrazine 2*

Ethyl-2-(benzothiazolylthio)-acetate **1** (0.01 mole, 2.53 g) and hydrazine hydrate (0.01 mole, 0.9 mL) in ethanol (20 mL) was refluxed for about 5 hr on a steam-bath. After cooling the resulting solid was filtered, dried and recrystallized from ethanol to get compound **2**, yield 61% as a pinkish white solid (EtOH). mp 193 °C. Anal. Calcd for $C_9H_9N_3OS_2$: C, 45.22; H, 3.10; N, 17.60; S, 26.12. Found: C, 45.19; H, 3.07; N, 17.57; S, 26.20%; IR (KBr) υ_{max}: 3352, 3378 (−$NHNH_2$), 1665 (>C=O of amide) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 6.80–7.90 (m, 4H, Ar-H), 4.40 (s, 2H, −NH_2), 4.81 (s, 2H, S−CH_2−), 7.88 (s, 1H, −CONH−) ppm.

4.5 *Microwave mediated synthesis of arylidene-[(2-benzothiazolylthio)-acetamidyl] 3a*

A mixture of compound **2** (0.01 mole, 2.39 g) and 4-nitrobenzaldehyde (0.01 mole, 1.51 g) and 2–3 drops glacial acetic acid in ethanol (20 mL) was taken in round bottom flask placed in a microwave oven and irradiated (400 W, 76–78 °C) for 3 min [20]. After completion of reaction (monitored by TLC). The solvent was removed and residue recrystallized from chloroform-methanol mixture to get compound **3**, yield 89% as a pale yellow crystal (MeOH-$CHCl_3$). mp 155 °C. Anal. Calcd for $C_{16}H_{12}N_4O_3S_2$: C, 51.50; H, 3.16; N, 14.91; S, 17.20. Found: C, 51.47; H, 3.15; N, 14.87; S, 17.24%; IR (KBr) υ_{max}: 3340, 1335 (−NH−), 1668 (>C=O), 1626 (−N=CH−), 1344 (Ar-NO_2) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 4.40 (s, 1H, −N=CH−), 8.13 (s, 1H, −CONH−), 6.93–7.73 (m, 4H, Ar-H) ppm.

4.6 *Conventional synthesis of arylidene-[(2-benzothiazolylthio)-acetamidyl] 3a*

A mixture of compound **2** (0.01 mole, 2.39 g) and 4-nitrobenzaldehyde (0.01 mole, 1.51 g) and 2–3 drops of glacial acetic acid in ethanol (25 mL) was refluxed on a water-bath for about 6 hr. The solvent was removed and residue was recrystallized from chloroform methanol mixture to get compound **3a**, yield 59% as a pale yellow powder (MeOH-$CHCl_3$). mp 155 °C. Anal. Calcd for $C_{16}H_{12}N_4O_3S_2$: C, 51.50; H, 3.16; N, 14.91; S, 17.20. Found: C, 51.47; H, 3.15; N, 14.87; S, 17.24%; IR (KBr) υ_{max}: 3340, 1335 (−NH−), 1668 (>C=O), 1626 (−N=CH−),

1344 (Ar-NO_2) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 4.40 (s, 1H, −N=CH−), 8.13 (s, 1H, −CONH−), 6.93–7.73 (m, 4H, Ar-H) ppm.

Likewise, other compounds **3b–j** were prepared by treating **2** with various aromatic aldehydes.

4.7 *Microwave mediated synthesis of 2-(4-nitrophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines 4a*

A mixture of **3a** (0.01 mole, 3.72 g) in DMF and $SHCH_2COOH$ (thioglycollicacid) (0.01 mole, 0.92 mL) with a pinch of $ZnCl_2$ was taken in round bottom flask placed in a microwave oven and irradiated (400 W, 146 °C) for 3 min [19]. After completion of reaction (monitored by TLC). It was then diluted with ice cold water. The solid product formed was filtered, dried and recrystallised from ethanol, yield 86% as a dark yellow solid (EtOH).

4.8 *Conventional synthesis of 2-(4-nitrophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines 4a*

A mixture of **3a** (0.01 mole, 3.72 g) in ethanol and $SHCH_2COOH$ (thioglycollicacid) (0.01 mole, 0.92 mL) with a pinch of $ZnCl_2$ was taken in a round bottom flask. It was refluxed for 8 hr on a steam-bath. After completion of reaction (monitored by TLC). The ethanol was distilled off to get product **4a**. The solid product was filtered, dried and recrystallized from ethanol, yield 68% as a yellow powder (EtOH).

Other compounds **4b–j** were prepared in the similar way using **3b–j**, respectively.

4.9 *Spectroscopic data of compounds 4a–j*

4.9.1 2-(4-Nitrophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4a). Yellow powder (EtOH), mp 168 °C; IR (KBr) υ_{max}: 3340, 1330 (−NH−), 1665 (>C=O, amidyl), 1717 (>C=O, cyclic), 1340 (Ar-NO_2) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.53 (s, 1H, −CONH−), 7.00–7.95 (m, 8H, Ar-H), 3.15 (s, 1H, >N–CH<), 4.48 (s, 2H, S-CH_2−), 3.60 (s, 2H, −CH_2-thiazolidinone) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 127 (C_1), 128.9 (C_2, C_6), 126.2 (C_3, C_5), 150 (C_4), 60 (>$C_{2'}$H-N<), 30 (−S-CH_2−), 172.5 (cyclic, >$C_{4'}$=O), 169.2 (amide, >C=O), 57 (−CH_2-thiazolidinone), 157.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 446 (72) [M^+] ($C_{18}H_{14}O_4N_4S_3^+$), 238 ($C_9H_5O_3N_3S^+$), 223 (19) ($C_9H_7O_3N_2S^+$), 210 (68) ($C_8H_8O_2N_3S^+$), 208 (85) ($C_9H_4ONS_2^+$), 195 (49) ($C_8H_7O_2N_2S^+$), 180 (55) ($C_8H_4NS_2^+$), 166 (28) ($C_7H_2NS_2^+$), 134 (45) ($C_7H_2NS^+$), 122 (10) ($C_6H_2NS^+$), 115 (34) ($C_3H_3O\,N_2S^+$), 108 (21) ($C_6H_2S^+$), 90 (58) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{14}N_4O_4S_3$: C, 48.45; H, 3.15; N, 12.58; S, 21.52. Found: C, 48.43; H, 3.13; N, 12.55; S, 21.58%.

4.9.2 2-(3,4,5-Tri–methoxyphenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4b). White powder (EtOH), mp 240 °C; IR (KBr) υ_{max}: 3335, 1335 (−NH−), 1660 (>C=O, amidyl), 1720 (>C=O, cyclic), 2825 (Ar-OCH_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.50 (s, 1H, −CONH−), 6.98–7.93 (m, 8H, Ar-H), 3.18 (s, 1H, >N–CH<), 4.46 (s, 2H, S-CH_2−), 3.63 (s, 2H, −CH_2-thiazolidinone), 3.91 (s, 3H, −OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 127.1 (C_1), 129.1 (C_2, C_6), 126.4 (C_3, C_5), 153 (C_4), 52.3 (>$C_{2'}$H-N<), 30.1 (−S-CH_2−), 172 (cyclic, >$C_{4'}$=O), 168.2 (amide, >C=O), 58 (−CH_2-thiazolidinone), 156.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics),

35.4 ($CH_3OC_6H_4-$) ppm; MS (%) (75 eV) (m/z): 491 (74) [M^+] ($C_{21}H_{20}N_3O_5S_3^+$), 283 (35) ($C_{12}H_{16}O_4N_2S^+$), 268 (48) ($C_{12}H_{15}O_4NS^+$), 255 (57) ($C_{11}H_{16}O_3N_2S^+$), 240 (39) ($C_{11}H_{16}O_3N_2S^+$), 208 (83) ($C_9H_4ONS_2^+$), 180 (58) ($C_8H_4NS_2^+$), 166 (26) ($C_7H_2NS_2^+$), 134 (47) ($C_7H_2NS^+$), 122 (12) ($C_6H_2NS^+$), 115 (31) ($C_3H_3O\,N_2S^+$), 108 (23) ($C_6H_2S^+$), 90 (57) ($C_6H_2N^+$); Anal. Calcd for $C_{21}H_{20}N_3O_5S_3$: C, 51.36; H, 4.05; N, 8.51; S, 19.55. Found: C, 51.32; H, 4.07; N, 8.55; S, 19.62%.

4.9.3 2-(2-Hydroxyphenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4c). Yellow crystalline powder (EtOH), mp 131 °C; IR (KBr) υ_{max}: 3290, 1338 (−NH−), 1670 (>C=O, amidyl), 1725 (>C=O, cyclic), 3590 (Ar-OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.49 (s, 1H, −CONH−), 7.20–7.90 (m, 8H, Ar-H), 3.17 (s, 1H, >N–CH<), 4.31 (s, 2H, S-CH_2−), 3.61 (s, 2H, −CH_2-thiazolidinone), 3.65 (s, 1H, -OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 126.9 (C_1), 128.8 (C_2, C_6), 127 (C_3, C_5), 155 (C_4), 53.3 (>$C_{2'}$H-N<), 31.5 (−S-CH_2−), 175 (cyclic, >$C_{4'}$=O), 167.2 (amide, >C=O), 59 (−CH_2-thiazolidinone), 154.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 417 (75) [M^+] ($C_{18}H_{15}N_3O_3S_3^+$), 209 (43) ($C_9H_{11}O_2N_2S^+$), 208 (89) ($C_9H_4ONS_2^+$), 194 (51) ($C_9H_{10}O_2NS^+$), 181 (35) ($C_8H_{11}ON_2S^+$), 180 (56) ($C_8H_4NS_2^+$), 166 (27) ($C_7H_2NS_2^+$), 134 (42) ($C_7H_2NS^+$), 122 (11) ($C_6H_2NS^+$), 115 (38) ($C_3H_3O\,N_2S^+$), 108 (24) ($C_6H_2S^+$), 90 (52) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{15}N_3O_3S_3$: C, 51.81; H, 3.61; N, 10.05; S, 23.02. Found: C, 51.79; H, 3.59; N, 10.07; S, 23.14%.

4.9.4 2-(3-Hydroxyphenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4d). Light yellow (EtOH), mp 143 °C; IR (KBr) υ_{max}: 3333, 1341 (−NH−), 1680 (>C=O, amidyl), 1734 (>C=O, cyclic), 3571 (Ar-OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.55 (s, 1H, −CONH−), 6.85–7.65 (m, 8H, Ar-H), 3.11 (s, 1H, >N–CH<), 4.36 (s, 2H, S-CH_2−), 3.59 (s, 2H, −CH_2-thiazolidinone), 3.64 (s, 1H, -OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 127.1 (C_1), 129.3 (C_2, C_6), 126.8 (C_3, C_5), 153.5 (C_4), 54.3 (>$C_{2'}$H-N<), 32.5 (−S-CH_2−), 175.2 (cyclic, >$C_{4'}$=O), 166.7 (amide, >C=O), 59.1 (−CH_2-thiazolidinone), 153.8 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 416 (79) [M^+] ($C_{18}H_{15}N_3O_3S_3^+$), 208 (84) ($C_9H_4ONS_2^+$), 193 (45) ($C_9H_{10}O_2NS^+$), 180 (56) ($C_8H_4NS_2^+$), 166 (23) ($C_7H_2NS_2^+$), 165 (50) ($C_8H_{10}ONS^+$), 134 (48) ($C_7H_2NS^+$), 122 (15) ($C_6H_2NS^+$), 115 (31) ($C_3H_3ON_2S^+$), 108 (24) ($C_6H_2S^+$), 90 (58) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{15}N_3O_3S_3$: C, 51.82; H, 3.63; N, 10.11; S, 23.07. Found: C, 51.80; H, 3.61; N, 10.10; S, 23.15%.

4.9.5 2-(4-Hydroxyphenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4e). Brown crystal (EtOH), mp 159 °C; IR (KBr) υ_{max}: 3390, 1337 (−NH−), 1679 (>C=O, amidyl), 1730 (>C=O, cyclic), 3583 (Ar-OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.46 (s, 1H, −CONH−), 6.88–7.90 (m, 8H, Ar-H), 3.12 (s, 1H, >N–CH<), 4.45 (s, 2H, S-CH_2−), 3.62 (s, 2H, −CH_2-thiazolidinone), 3.58 (s, 1H, −OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 126.8(C_1), 128.5 (C_2, C_6), 127.1 (C_3, C_5), 154 (C_4), 56 (>$C_{2'}$H-N<), 32 (−S-CH_2−), 176.2 (cyclic, >$C_{4'}$=O), 168.7 (amide, >C=O), 59.5 (−CH_2-thiazolidinone), 155.8 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 418 (73) [M^+] ($C_{18}H_{15}N_3O_3S_3^+$), 210 (44) ($C_9H_{11}O_2N_2S^+$), 208 (86) ($C_9H_4ONS_2^+$), 195 (45) ($C_9H_{10}O_2NS^+$), 182 (51) ($C_8H_{11}ON_2S^+$), 180 (57) ($C_8H_4NS_2^+$), 167 (36) ($C_8H_{10}ONS^+$), 166 (29) ($C_7H_2NS_2^+$), 134 (43) ($C_7H_2NS^+$), 122 (13) ($C_6H_2NS^+$), 115 (32) ($C_3H_3ON_2S^+$), 108 (23) ($C_6H_2S^+$), 90 (56) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{15}N_3O_3S_3$: C, 51.80; H, 3 .60; N, 10.03; S, 22.96. Found: C, 51.77; H, 3.57; N, 10.05; S, 23.07%.

4.9.6 2-(2-Methoxyphenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4f). Dark yellow (EtOH), mp 188 °C; IR (KBr) υ_{max}: 3375, 1337 (−NH−), 1671 (>C=O, amidyl), 1726 (>C=O, cyclic), 2828 (Ar-OCH_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.47 (s, 1H, −CONH−), 6.88–7.95 (m, 8H, Ar-H), 3.13 (s, 1H, >N–CH<), 4.49 (s, 2H, S-CH_2−), 3.64 (s, 2H, −CH_2-thiazolidinone), 3.96 (s, 3H, -OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 126.8 (C_1), 128.7 (C_2, C_6),125.9 (C_3, C_5), 153.2 (C_4), 53.1 (>$C_{2'}$H-N<), 32 (-S-CH_2−), 172.5 (cyclic, >$C_{4'}$=O), 168 (amide, >C=O), 58.2 (−CH_2-thiazolidinone), 157.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics), 35.7 ($CH_3OC_6H_4$−) ppm; MS (%) (75 eV) (m/z): 431 (78) [M^+] ($C_{19}H_{17}N_3O_3S_3^+$), 223 (42) ($C_{10}H_{13}O_2N_2S^+$), 208 (87) ($C_9H_4ONS_2^+$), 195 (46) ($C_9H_{13}ON_2S^+$), 180 (52) ($C_8H_4NS_2^+$), 166 (25) ($C_7H_2NS_2^+$), 134 (41) ($C_7H_2NS^+$), 122 (14) ($C_6H_2NS^+$), 115 (38) ($C_3H_3ON_2S^+$), 108 (23) ($C_6H_2S^+$), 90 (54) ($C_6H_2N^+$); Anal. Calcd for $C_{19}H_{17}N_3O_3S_3$: C, 52.92; H, 3.96; N, 9.10; S, 22.27. Found: C, 52.90; H, 3.94; N, 9.07; S, 22.31%.

4.9.7 2-(4-Methoxyphenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4g). Brownish yellow solid (EtOH), mp 208 °C; IR (KBr) υ_{max}: 3378, 1339 (−NH−), 1675 (>C=O, amidyl), 1721 (>C=O, cyclic), 2830 (Ar-OCH_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.53 (s, 1H, −CONH−), 6.65–7.77 (m, 8H, Ar-H), 3.16 (s, 1H, >N–CH<), 4.29 (s, 2H, S-CH_2−), 3.66 (s, 2H, −CH_2-thiazolidinone), 3.89 (s, 3H, −OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 127.8 (C_1), 129.7 (C_2, C_6),124.9 (C_3, C_5), 152.2 (C_4), 54.1 (>$C_{2'}$H-N<), 33 (−S-CH_2−), 171.5 (cyclic, >$C_{4'}$=O), 167 (amide, >C=O), 57.2 (−CH_2-thiazolidinone), 156.5 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics), 34.7 ($CH_3OC_6H_4$−) ppm; MS (%) (75 eV) (m/z): 430 (71) [M^+] ($C_{19}H_{17}N_3O_3S_3^+$), 222 (48) ($C_{10}H_{13}O_2N_2S^+$), 208 (84) ($C_9H_4ONS_2^+$), 207 (52) ($C_{10}H_{12}O_2NS^+$), 194 (39) ($C_9H_{13}ON_2S^+$), 180 (55) ($C_8H_4NS_2^+$), 179 (30) ($C_9H_{12}ONS^+$), 166 (26) ($C_7H_2NS_2^+$), 134 (43) ($C_7H_2NS^+$), 122 (15) ($C_6H_2NS^+$), 115 (38) ($C_3H_3ON_2S^+$), 108 (23) ($C_6H_2S^+$), 90 (51) ($C_6H_2N^+$); Anal. Calcd for $C_{19}H_{17}N_3O_3S_3$: C, 52.86; H, 3.90; N, 9.02; S, 22.32. Found: C, 52.88; H, 3.92; N, 9.04; S, 22.38%.

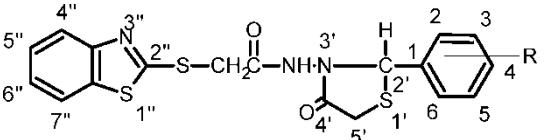
4.9.8 2-(2-Chlorophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4h). Light brown solid (EtOH), mp 211 °C; IR (KBr) υ_{max}: 3385, 1340 (−NH−), 1678 (>C=O, amidyl), 1722 (>C=O, cyclic), 835 (Ar-Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.50 (s, 1H, −CONH−), 6.72–7.82 (m, 8H, Ar-H), 3.17 (s, 1H, >N–CH<), 4.38 (s, 2H, S-CH_2−), 3.65 (s, 2H, −CH_2-thiazolidinone) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 128.8 (C_1), 128.7 (C_2, C_6), 125.9 (C_3, C_5), 151.2 (C_4), 54.3 (>$C_{2'}$H-N<), 33.2 (-S-CH_2−), 171.7 (cyclic, >$C_{4'}$=O), 167.2 (amide, >C=O), 57.4 (-CH_2-thiazolidinone), 156.7 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 435.5 (75) [M^+] ($C_{18}H_{14}N_3O_2S_3Cl^+$), 228 (44) ($C_9H_{10}ON_2SCl^+$), 213 (56) ($C_9H_9ONSCl^+$), 208 (89) ($C_9H_4ONS_2^+$), 200 (33) ($C_8H_{10}N_2SCl^+$), 185 (30) ($C_8H_9NSCl^+$), 180 (56) ($C_8H_4NS_2^+$), 166 (27) ($C_7H_2NS_2^+$), 134 (44) ($C_7H_2NS^+$), 122 (13) ($C_6H_2NS^+$), 115 (37) ($C_3H_3ON_2S^+$), 108 (22) ($C_6H_2S^+$), 90 (52) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{14}N_3O_2S_3Cl$: C, 49.61; H, 3.23; N, 9.66; S, 22.05. Found: C, 49.59; H, 3.21; N, 9.64; S, 22.20%.

4.9.9 2-(3-Chlorophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4i). Light brown powder (EtOH), mp 226 °C; IR (KBr) υ_{max}: 3380, 1341 (−NH−), 1673 (>C=O, amidyl), 1719 (>C=O, cyclic), 825 (Ar-Cl) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.48 (s, 1H, −CONH−), 7.15–7.92 (m, 8H, Ar-H), 3.18 (s, 1H, >N–CH<), 4.41 (s, 2H, S-CH_2−), 3.61 (s, 2H, −CH_2-thiazolidinone) ppm; ^{13}C NMR (100 MHz, $CDCl_3$

or DMSO-d_6) δ: 127.7 (C_1), 129.8 (C_2, C_6),124.8 (C_3, C_5), 152.3 (C_4), 53.2 (>$C_{2'}$H-N<), 34.3 (−S-CH_2−), 170.6 (cyclic, >$C_{4'}$=O), 168.3 (amide, >C=O), 58.3 (−CH_2-thiazolidinone), 157.8 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 436 (77) [M^+] ($C_{18}H_{14}N_3O_2S_3Cl^+$), 229 (47) ($C_9H_{10}ON_2SCl^+$), 214 (53) ($C_9H_9ONSCl^+$), 208 (85) ($C_9H_4ONS_2^+$), 201 (38) ($C_8H_{10}N_2SCl^+$), 186 (29) ($C_8H_9NSCl^+$), 180 (56) ($C_8H_4NS_2^+$), 166 (25) ($C_7H_2NS_2^+$), 134 (43) ($C_7H_2NS^+$), 122 (10) ($C_6H_2NS^+$), 115 (34) ($C_3H_3O\ N_2S^+$), 108 (22) ($C_6H_2S^+$), 90 (54) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{14}N_3O_2S_3Cl$: C, 49.54; H, 3.16; N, 9.60; S, 22.01. Found: C, 49.57; H, 3.18; N, 9.62; S, 22.19%.

4.9.10 2-(4-Chlorophenyl)-3-[(2-benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines (4j). Deep brown crystal (EtOH), mp 219 °C; IR (KBr) υ_{max}: 3383, 1342 (−NH−), 1668 (>C=O, amidyl), 1718 (>C=O, cyclic), 831 (Ar-Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) δ: 8.51 (s, 1H, −CONH−), 6.96–7.86 (m, 8H, Ar-H), 3.11 (s, 1H, >N–CH<), 4.40 (s, 2H, S-CH_2−), 3.58 (s, 2H, −CH_2-thiazolidinone) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ or DMSO-d_6) δ: 126.8 (C_1), 128.9 (C_2, C_6), 123.9 (C_3, C_5), 151.4 (C_4), 52.3 (>$C_{2'}$H-N<), 33.4 (−S-CH_2−), 169.7 (cyclic, >$C_{4'}$=O), 167.4 (amide, >C=O), 57.4 (−CH_2-thiazolidinone), 156.7 ($C_{1''}$, $C_{2''}$, $C_{4''}$, $C_{5''}$, $C_{6''}$, $C_{7''}$, heteroaromatics) ppm; MS (%) (75 eV) (m/z): 434 (79) [M^+] ($C_{18}H_{14}N_3O_2S_3Cl^+$), 226 (44) ($C_9H_{10}ON_2SCl^+$), 211 (53) ($C_9H_9ONSCl^+$), 208 (86) ($C_9H_4ONS_2^+$), 201 (36) ($C_8H_{10}N_2SCl^+$), 198 (49) ($C_8H_9NSCl^+$), 182 (28) ($C_8H_9NSCl^+$), 180 (53) ($C_8H_4NS_2^+$), 166 (28) ($C_7H_2NS_2^+$), 134 (41) ($C_7H_2NS^+$), 122 (17) ($C_6H_2NS^+$), 115 (32) ($C_3H_3O\ N_2S^+$), 108 (23) ($C_6H_2S^+$), 90 (56) ($C_6H_2N^+$); Anal. Calcd for $C_{18}H_{14}N_3O_2S_3Cl$: C, 49.63; H, 3.26; N, 9.68; S, 22.11. Found: C, 49.61; H, 3.23; N, 9.66; S, 22.22%.

Where,



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