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ORIGINAL ARTICLE

Synthesis and biological evaluation of 4-thiazolidinone derivatives as antitubercular and antimicrobial agents

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Abstract New series of *N*-[2-{2-(substitutedphenyl)-4-oxo-5-(substitutedbenzylidene)-1,3-thiazolidine}-iminoethyl]-2-amino-5-nitrothiazole, **5(a–m)** have been synthesized from 2-amino-5-nitrothiazole as a starting material by conventional as well as microwave methods. All the synthesized compounds **4(a–m)** were screened for their antibacterial and antifungal activities against some selected bacteria and fungi and antitubercular activity screened against *Mycobacterium tuberculosis*. The structure of all the synthesized compounds were confirmed by chemical and spectral analyses such as IR, ^{1}H NMR, ^{13}C NMR and FAB-Mass.

1. Introduction

4-Thiazolidine derivatives are an important class of heterocyclic compounds known for their potential pharmaceutical applications. Recently, this framework containing compounds were effective against antimicrobial (Young et al., 2004), antischistosomal activity (Taha and Soliman, 2007), antifungal (Asati et al., 2005), antiinflammatory (Jain et al., 2006), antimalarial (Kristina et al., 2009), herbicidal (Sanemitsu et al., 2006), antiviral (Eiichi et al., 2007), antidiabetic (Murugan et al., 2009), and antioxidant (Shih and Ke, 2004) activities. Thiazole derivatives are heterocyclic compounds containing nitrogen and sulfur atoms in their structure and are proved to be clinically useful agents against different kinds of disease. Thiazole derivatives have been employed in the preparation of different important drugs required for treatment of antimicrobial (Gouda et al., 2010), antibacterial (Bharti et al., 2010; Khalil et al., 2009), antifungal (Bharti et al., 2010; Joshi and Srivastava, 2001), antiinflammatory (Giri et al., 2009), and antitubercular (Shiradkar et al., 2007), some of the thiazole derivatives are used as antiprotozoal (Ricardo et al., 2003) drugs. All above biological activities of thiazole and thiazolidine derivatives aroused our attention and promoted to synthesis a new series of *N*-[2-{2-(substitutedphenyl)-4-oxo-5-(substitutedbenzylidene)-1,3-thiazolidine}-iminoethyl]-2-amino-

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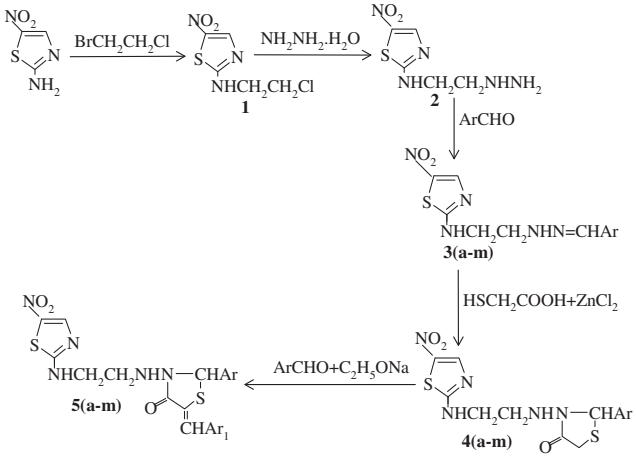

Ar = Ar_1 = substituted phenyl ring

Comp.	Ar = Ar_1	Comp.	Ar = Ar_1	Comp.	Ar = Ar_1
3a, 4a, 5a	C_6H_5	3f, 4f, 5f	3-BrC_6H_4	3k, 4k, 5k	4-$CH_3OC_6H_4$
3b, 4b, 5b	4-ClC_6H_4	3g, 4g, 5g	2-BrC_6H_4	3l, 4l, 5l	4-$CH_3C_6H_4$
3c, 4c, 5c	3-ClC_6H_4	3h, 4h, 5h	4-$NO_2C_6H_4$	3m, 4m, 5m	4-HOC_6H_4
3d, 4d, 5d	2-ClC_6H_4	3i, 4i, 5i	3-$NO_2C_6H_4$	-	-
3e, 4e, 5e	4-BrC_6H_4	3j, 4j, 5j	2-$NO_2C_6H_4$	-	-

Scheme 1

5-nitrothiazole, **5(a–m)** by conventional and microwave methods. The structure of compounds **1**, **2**, **3(a–m)**, **4(a–m)** and **5(a–m)** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, FAB-Mass and chemical analysis. All the final synthesized compounds **5(a–m)** were screened for their antimicrobial activity against some selected bacteria, fungi and antituberculosis study against *M. tuberculosis*. (Scheme 1)

2. Materials and methods

2.1. Experimental

Melting points were taken in open glass capillaries and are uncorrected. Progress of the reaction was monitored by silica gel-G coated TLC plates in MeOH:$CHCl_3$ system (1:9). The spot was visualized by exposing dry plate in iodine vapours. IR spectra were recorded in KBr disc on a Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^{1}H and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 and 75 MHz respectively using TMS as an internal standard. All chemical shifts were reported on δ scales. The FAB-Mass spectra were recorded on a Jeol SX-102 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1108 analyzer. Microwave irradiation was carried out in an open glass vessel. Modified microwave oven (800 W) was used for the synthesis of compounds. A thermocouple was used to monitor the temperature inside the vessel of the microwave. The analytical data of all the compounds were highly satisfactory. For column chromatographic purification of the products, Merck silica Gel 60 (230–400 Mesh) was used. The reagent grade chemicals were purchased from the commercial sources and further purified before use.

*2.2. General microwave method for synthesis of compound **1**, **2**, **3(a–m)**, **4(a–m)** and **5(a–m)***

A solid supported mixture of compounds (1:1 mol) was mixed thoroughly in open glass vessel and subjected to the microwave

Table 1 Data of yield and reaction time of all synthesized compounds.

Yield%			Reaction time			Yield%			Reaction time		
Comp.	Conv.	MW	Conv. (h)		MW (min)	Comp.	Conv.	MW	Conv. (h)		MW (min)
			1st stirr.	2nd reflux					1st stirr.	2nd reflux	
1	62	76	6.30	–	4.00	**4g**	66	80	2.35	3.25	3.30
2	70	85	5.00	–	3.10	**4h**	64	76	2.45	3.15	3.35
3a	60	78	3.00	2.15	3.35	**4i**	63	80	2.15	3.30	3.15
3b	64	86	3.15	2.00	3.45	**4j**	61	84	2.30	3.30	3.05
3c	67	83	3.10	2.00	3.35	**4k**	64	83	2.15	3.35	3.20
3d	65	85	3.15	1.45	4.10	**4l**	63	77	2.15	3.30	3.20
3e	67	84	2.30	2.15	3.15	**4m**	63	80	2.10	3.45	3.20
3f	65	81	3.30	2.30	3.05	**5a**	66	79	2.30	3.15	3.40
3g	63	80	3.35	2.00	2.40	**5b**	64	76	2.00	3.05	3.20
3h	64	77	3.30	2.30	3.15	**5c**	62	82	2.05	2.45	3.20
3i	62	78	3.30	1.40	3.30	**5d**	64	84	2.15	2.45	3.25
3j	61	82	3.25	2.30	2.55	**5e**	62	83	2.10	3.10	3.30
3k	62	81	3.30	2.30	3.45	**5f**	65	82	2.15	3.00	3.15
3l	61	79	3.30	2.20	4.15	**5g**	64	78	2.30	3.15	3.45
3m	62	81	3.30	2.00	3.25	**5h**	62	79	2.00	3.30	3.30
4a	65	75	2.45	3.05	3.35	**5i**	64	81	2.10	3.25	3.15
4b	65	79	2.30	3.15	3.35	**5j**	60	80	2.15	3.15	3.15
4c	67	84	2.45	2.30	3.15	**5k**	66	82	2.00	3.30	3.20
4d	66	82	2.30	2.30	3.10	**5l**	61	75	2.20	3.25	3.45
4e	60	80	2.30	3.00	3.30	**5m**	62	76	2.30	3.45	3.20
4f	63	83	2.15	3.15	3.05	–	–	–	–	–	–

irradiation at low power setting (25%, 200 W) for 2.40–4.15 min, then allowed to cool. The products were purified over a column chromatography. The products were recrystallized from ethanol at room temperature to yield compound **1**, **2**, **3(a–m)**, **4(a–m)** and **5(a–m)**. Results were given in Table 1.

*2.3. Conventional method for synthesis of the compound **1***

A mixture of 2-amino-5-nitrothiazole and 1-bromo-2-chloroethane (1:1 mol) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 6.30 h. The product was filtered and purified over a column chromatography using chloroform: methanol (8:2 v/v). The purified product was recrystallized from ethanol at room temperature to yield compound **1**.

*2.3.1. Synthesis of N-(2-chloroethyl)-2-amino-5-nitrothiazole (**1**)*

Yield: 62%, m.p. 162–166 °C; Anal. Calcd for $C_5H_6N_3O_2SCl$: C, 28.92, H, 2.91, N, 20.23%; found C, 28.90, H, 2.89, N, 20.13%; IR (cm^{-1}): 740 (C—Cl), 892 (C—S), 978 (C—NO), 1382 (N—CH_2), 1555 (NO_2), 1569 (C=C), 2880, 3074 (CH), 3382 (NH); ^{1}H NMR (δ): 4.20 (t, 2H, J = 7.60 Hz, $\underline{CH_2}$—Cl), 4.80 (t, 2H, J = 7.60 Hz, N—$\underline{CH_2}$), 7.80 (br s, 1H, NH), 7.23 (s, 1H, C_4H of thiazole); ^{13}C NMR (δ): 44.4 ($\underline{CH_2}$—Cl), 56.5 (N—$\underline{CH_2}$), 111.2 (C_5 of thiazole), 137.5 (C_4 of thiazole), 167.5 (C_2 of thiazole), Mass (FAB): 208M^+, 172, 158, 144, 129, 117, 114, 99, 83.

*2.4. Conventional method for synthesis of the compound **2***

A mixture of compound **1** and hydrazine hydrate (1:1 mol) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 5.00 h. The product was filtered and purified over a column chromatography using chloroform: methanol (7:3 v/v). The purified product was recrystallized from ethanol at room temperature to yield compound **2**.

*2.4.1. Synthesis of N-{2-(hydrazino)-ethyl}-2-amino-5-nitrothiazole (**2**)*

Yield: 70%, m.p. 142–146 °C; Anal. Calcd for $C_5H_9N_5O_2S$: C, 29.55, H, 4.46, N, 34.46%; found C, 29.50, H, 4.42, N, 34.41%; IR: 870 (C—N), 878 (C—S), 1338 (N—CH_2), 1528 (NO_2), 3376 (NH), 3370 (NH), 3480 (NH_2); ^{1}H NMR (δ): 4.27 (t, 2H, J = 7.60 Hz, $\underline{CH_2}$—NH), 4.92 (t, 2H, J = 7.60 Hz, N—$\underline{CH_2}$), 5.55 (s, 2H, NH_2), 7.70 (s, 1H, NH), 7.96 (br s, 1H, NH), 7.25 (s, 1H, C_4H of thiazole); ^{13}C NMR (δ): 47.5 ($\underline{CH_2}$—NH), 57.4 (N—$\underline{CH_2}$), 107.8 (C_5 of thiazole), 138.8 (C_4 of thiazole), 169.9 (C_2 of thiazole); Mass (FAB): 203M^+, 187, 172.

*2.5. General conventional method for synthesis of compound **3(a–m)***

A mixture of compound **2** and substituted benzaldehydes (1:1 mol) was dissolved in methanol at room temperature and allowed to react. The reaction mixture was first continuously stirred on a magnetic stirrer for about 2.30–3.35 h then kept on a steam bath for about 1.45–2.30 h. The products were cooled and filtered. The products were purified over a column chromatography using chloroform: ethanol (8:2 v/v) and recrystallized from ethanol at room temperature to yield compound **3(a–m)**.

*2.5.1. Synthesis of N-{2-(benzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3a**)*

Yield: 60%, m.p. 151–154 °C; Anal. Calcd for $C_{12}H_{13}N_5O_2S$: C, 49.47, H, 4.49, N, 24.03%; found C, 49.40, H, 4.42, N, 24.00%; IR: 1553 (N=CH), 3378 (NH); ^{1}H NMR (δ): 4.25 (t, 2H, J = 7.45 Hz, $\underline{CH_2}$—NH), 4.78 (t, 2H, J = 7.45 Hz, N—$\underline{CH_2}$), 7.60 (s, 1H, NH), 7.76 (br s, 1H, NH), 7.89 (s, 1H, N=CH), 7.21 (s, 1H, C_4H of thiazole), 6.38–7.36 (m, 5H, Ar—H); ^{13}C NMR (δ): 46.5 ($\underline{CH_2}$—N), 54.9 (N—$\underline{CH_2}$), 112.4 (C_5 of thiazole),140.9 (C_4 of thiazole), 141.6 (N=CH), 167.9 (C_2 of thiazole), 124.7, 127.8, 127.8, 129.6, 130.2, 137.9 (6C, Ar); Mass (FAB): 291M^+, 214, 187.

*2.5.2. Synthesis of N-{2-(4-chlorobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3b**)*

Yield: 64%, m.p. 162–166 °C; Anal. Calcd for $C_{12}H_{12}N_5O_2SCl$: C, 44.24, H, 3.71, N, 21.49%; found C, 44.22, H, 3.69, N, 21.45%; IR: 740 (C—Cl), 1562 (N=CH), 3372 (NH); ^{1}H NMR (δ): 4.55 (t, 2H, J = 7.40 Hz, $\underline{CH_2}$—NH), 4.90 (t, 2H, J = 7.40 Hz, N—$\underline{CH_2}$), 7.36 (s, 1H, C_4H of thiazole), 7.55 (s, 1H, NH), 7.82 (br s, 1H, NH), 8.02 (s, 1H, N=CH), 6.45–7.65 (m, 4H, Ar—H); ^{13}C NMR (δ): 49.6 ($\underline{CH_2}$—NH), 58.5 (N—$\underline{CH_2}$), 116.8 (C_5 of thiazole), 143.5 (C_4 of thiazole), 152.7 (N=CH), 174.5 (C_2 of thiazole), 126.8, 128.6, 128.9, 130.8, 135.7, 138.6 (6C, Ar); Mass (FAB): 326M^+, 290, 214, 201, 187, 180.

*2.5.3. Synthesis of N-{2-(3-chlorobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3c**)*

Yield: 67%, m.p. 167–170 °C; Anal. Calcd for $C_{12}H_{12}N_5O_2SCl$: C, 44.24, H, 3.71, N, 21.49%; found C, 44.20, H, 3.70, N, 21.40%; IR: 747 (C—Cl), 1560 (N=CH), 3384 (NH); ^{1}H NMR (δ): 4.58 (t, 2H, J = 7.45 Hz, $\underline{CH_2}$—NH), 4.95 (t, 2H, J = 7.45 Hz, N—$\underline{CH_2}$), 7.40 (s, 1H, C_4H of thiazole), 7.60 (s, 1H, NH), 7.76 (br s, 1H, NH), 8.09 (s, 1H, N=CH), 6.40–7.69 (m, 4H, Ar—H); ^{13}C NMR (δ): 45.5 ($\underline{CH_2}$—NH), 48.3 (N—$\underline{CH_2}$), 114.3 (C_5 of thiazole), 143.4 (C_4 of thiazole), 153.8 (N=CH), 173.8 (C_2 of thiazole), 126.8, 128.7, 129.8, 130.5, 135.5, 139.2A (6C, Ar); Mass (FAB): 326M^+.

*2.5.4. Synthesis of N-{2-(2-chlorobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3d**)*

Yield: 65%, m.p. 162–165 °C; Anal. Calcd for $C_{12}H_{12}N_5O_2SCl$: C, 44.24, H, 3.71, N, 21.49%; found C, 44.18, H, 3.68, N, 21.42%; IR: 741 (C—Cl), 1560 (N=CH), 3372 (NH); ^{1}H NMR (δ): 4.56 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$—NH), 4.98 (t, 2H, J = 7.50 Hz, N—$\underline{CH_2}$), 7.36 (s, 1H, C_4H of thiazole), 7.53 (s, 1H, NH), 7.80 (br s, 1H, NH), 8.12 (s, 1H, N=CH), 6.35–7.71 (m, 4H, Ar—H); ^{13}C NMR (δ): 48.4 ($\underline{CH_2}$—NH), 58.6 (N—$\underline{CH_2}$), 112.4 (C_5 of thiazole), 142.7 (C_4 of thiazole), 155.9 (N=CH), 173.8 (C_2 of thiazole), 127.6, 128.9, 130.8, 131.7, 135.8, 139.8 (6C, Ar); Mass (FAB): 326M^+.

*2.5.5. Synthesis of N-{2-(4-bromobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3e**)*

Yield: 67%, m.p. 172–175 °C; Anal. Calcd for $C_{12}H_{12}N_5O_2SBr$: C, 38.93, H, 3.26, N, 18.91%; found C, 38.90, H, 3.22, N, 18.89%; IR: 632 (C—Br), 1609 (N=CH),

3372 (NH); ^{1}H NMR (δ): 4.50 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$—NH), 5.10 (t, 2H, J = 7.50 Hz, N—$\underline{CH_2}$), 7.27 (s, 1H, C_4H of thiazole), 7.64 (s, 1H, NH), 7.90 (br s, 1H, NH), 8.02 (s, 1H, N=CH), 6.53–7.90 (m, 4H, Ar—H); ^{13}C NMR (δ): 48.7 ($\underline{CH_2}$—NH), 56.2 (N—$\underline{CH_2}$), 112.7 (C_5 of thiazole), 142.8 (C_4 of thiazole), 152.5 (N=CH), 167.5 (C_2 of thiazole), 125.9, 127.2, 128.6, 129.4, 135.7, 137.9 (6C, Ar); Mass (FAB): 370M$^+$, 290, 214.

*2.5.6. Synthesis of N-{2-(3-bromobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3f**)*

Yield: 65%, m.p. 177–180 °C; Anal. Calcd for $C_{12}H_{12}N_5O_2SBr$: C, 38.93, H, 3.26, N, 18.91%; found C, 38.90, H, 3.20, N, 18.89%; IR: 640 (C—Br), 1570 (N=CH), 3370 (NH); ^{1}H NMR (δ): 4.54 (t, 2H, J = 7.45 Hz, $\underline{CH_2}$ – NH), 4.95 (t, 2H, J = 7.45 Hz, N—$\underline{CH_2}$), 7.28 (s, 1H, C_4H of thiazole), 7.61 (s, 1H, NH), 7.88 (br s, 1H, NH), 8.06 (s, 1H, N=CH), 6.54–7.92 (m, 4H, Ar—H); ^{13}C NMR (δ): 48.4 ($\underline{CH_2}$—N), 57.5 (N—$\underline{CH_2}$), 113.8 (C_5 of thiazole), 145.2 (C_4 of thiazole),155.4 (N=CH), 167.4 (C_2 of thiazole), 126.3, 127.8, 128.7, 130.8, 135.9, 138.5 (6C, Ar); Mass (FAB): 370M$^+$.

*2.5.7. Synthesis of N-{2-(2-bromobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3g**)*

Yield: 63%, m.p. 173–176 °C; Anal. Calcd for $C_{12}H_{12}N_5O_2SBr$: C, 38.93, H, 3.26, N, 18.91%; found C, 38.88, H, 3.20, N, 18.83%; IR: 647 (C—Br), 1570 (N=CH), 3370 (NH); ^{1}H NMR (δ): 4.58 (t, 2H, J = 7.40 Hz, $\underline{CH_2}$—NH), 5.10 (t, 2H, J = 7.40 Hz, N—$\underline{CH_2}$), 7.28 (s, 1H, C_4H of thiazole), 7.54 (s, 1H, NH), 7.85 (br s, 1H, NH), 8.11 (s, 1H, N=CH), 6.62–7.92 (m, 4H, Ar—H); ^{13}C NMR (δ): 49.6 ($\underline{CH_2}$—NH), 58.4 (N—$\underline{CH_2}$), 113.3 (C_5 of thiazole), 142.5 (C_4 of thiazole), 156.2 (N=CH), 169.6 (C_2 of thiazole), 126.6, 127.8, 129.8, 130.6, 136.7, 138.8 (6C, Ar); Mass (FAB): 370M$^+$.

*2.5.8. Synthesis of N-{2-(4-nitrobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3h**)*

Yield: 64%, m.p. 169–172 °C; Anal. Calcd for $C_{12}H_{12}N_6O_4S$: C, 42.85, H, 3.59, N, 24.98%; found C, 42.80, H, 3.52, N, 24.93%; IR: 848 (C—N), 1549 (N=O), 1576 (N=CH), 3370 (NH); ^{1}H NMR (δ): 4.60 (t, 2H, J = 7.35 Hz, $\underline{CH_2}$—NH), 5.05 (t, 2H, J = 7.35 Hz, N—$\underline{CH_2}$), 7.36 (s, 1H, C_4H of thiazole), 7.45 (s, 1H, NH), 7.99 (br s, 1H, NH), 8.17 (s, 1H, N=CH), 7.04–8.05 (m, 4H, Ar—H); ^{13}C NMR (δ): 49.7 ($\underline{CH_2}$—N), 59.3 (N—$\underline{CH_2}$), 113.9 (C_5 of thiazole), 143.7 (C_4 of thiazole), 154.8 (N=CH), 170.8 (C_2 of thiazole), 127.6, 128.8, 129.7, 131.9, 136.7, 143.9 (6C, Ar); Mass (FAB): 336M$^+$, 306, 290, 214.

*2.5.9. Synthesis of N-{2-(3-nitrobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3i**)*

Yield: 62%, m.p. 166–169 °C; Anal. Calcd for $C_{12}H_{12}N_6O_4S$: C, 42.85, H, 3.59, N, 24.98%; found C, 42.82, H, 3.55, N, 24.94%; IR: 842 (C—N), 1536 (N=O), 1572 (N=CH), 3370 (NH); ^{1}H NMR (δ): 4.50 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$—NH), 4.94 (t, 2H, J = 7.50 Hz, N—$\underline{CH_2}$), 7.50 (s, 1H, NH), 7.90 (br s, 1H, NH), 7.45 (s, 1H, C_4H of thiazole), 8.13 (s, 1H, N=CH), 7.10–8.20 (m, 4H, Ar—H); ^{13}C NMR (δ): 47.9 ($\underline{CH_2}$—NH), 57.6 (N—$\underline{CH_2}$), 114.6 (C_5 of thiazole), 143.8 (C_4 of thiazole), 154.7 (N=CH), 170.8 (C_2 of thiazole), 125.7, 129.8, 130.9, 131.6, 137.8, 144.6 (6C, Ar); Mass (FAB): 336M$^+$.

*2.5.10. Synthesis of N-{2-(2-nitrobenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3j**)*

Yield: 61%, m.p. 163–165 °C; Anal. Calcd for $C_{12}H_{12}N_6O_4S$: C, 42.85, H, 3.59, N, 24.98%; found C, 42.83, H, 3.55, N, 24.90%; IR: 845 (C—N), 1542 (N=O), 1570 (N=CH), 3344 (NH); ^{1}H NMR (δ): 4.42 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$—NH), 4.69 (t, 2H, J = 7.50 Hz, N—$\underline{CH_2}$), 7.45 (s, 1H, NH), 7.95 (br s, 1H, NH), 7.34 (s, 1H, C_4H of thiazole), 8.09 (s, 1H, N=CH), 6.95–8.10 (m, 4H, Ar—H); ^{13}C NMR (δ): 49.4 ($\underline{CH_2}$—NH), 59.8 (N—$\underline{CH_2}$), 116.9 (C_5 of thiazole), 144.8 (C_4 of thiazole), 156.6 (N=CH), 171.8 (C_2 of thiazole), 126.4, 129.7, 131.3, 131.6, 138.5, 145.8 (6C, Ar); Mass (FAB): 336M$^+$.

*2.5.11. Synthesis of N-{2-(4-methoxybenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3k**)*

Yield: 62%, m.p. 139–142 °C; Anal. Calcd for $C_{13}H_{15}N_5O_3S$: C, 48.58, H, 4.70, N, 21.79%; found C, 48.555, H, 4.62, N, 21.72%; IR: 1569 (N=CH), 2948 (OCH_3), 3368 (NH); ^{1}H NMR (δ): 4.49 (t, 2H, J = 7.45 Hz, $\underline{CH_2}$—NH), 4.66 (s, 3H, OCH_3), 4.98 (t, 2H, J = 7.45 Hz, N—$\underline{CH_2}$), 7.32 (s, 1H, C_4H of thiazole), 7.46 (s, 1H, NH), 7.73 (br s, 1H, NH), 7.91 (s, 1H, N=CH), 6.66–7.59 (m, 4H, Ar—H); ^{13}C NMR (δ): 48.7 ($\underline{CH_2}$—NH), 52.5 (OCH_3), 57.7 (N—$\underline{CH_2}$), 154.8 (N=CH), 171.4 (C_2 of thiazole), 114.8 (C_5 of thiazole), 138.7 (C_4 of thiazole), 113.7, 117.6, 123.8, 127.5, 136.9, 161.8 (6C, Ar); Mass (FAB): 321M$^+$, 306, 278, 214.

*2.5.12. Synthesis of N-{2-(4-methylbenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3l**)*

Yield: 61%, m.p. 135–138 °C; Anal. Calcd for $C_{13}H_{15}N_5O_2S$: C, 51.13, H, 4.95, N, 22.93%; found C, 51.10, H, 4.90, N, 22.91%; IR: 1549 (N=CH), 2927 (CH_3), 3360 (NH); ^{1}H NMR (δ): 2.61 (s, 3H, CH_3), 4.38 (t, 2H, J = 7.40 Hz, $\underline{CH_2}$—NH), 4.92 (t, 2H, J = 7.40 Hz, N—$\underline{CH_2}$), 7.16 (s, 1H, C_4H of thiazole), 7.32 (s, 1H, NH), 7.60 (br s, 1H, NH), 7.86 (s, 1H, N=CH), 6.65–7.45 (m, 4H, Ar—H); ^{13}C NMR (δ): 26.6 (CH_3), 47.4 ($\underline{CH_2}$—NH), 56.5 (N—$\underline{CH_2}$), 111.4 (C_5 of thiazole), 137.9 (C_4 of thiazole), 152.8 (N=CH), 171.5 (C_2 of thiazole), 124.4, 127.7, 128.6, 129.6, 134.5, 137.6 (6C, Ar); Mass (FAB): 305M$^+$, 279, 214.

*2.5.13. Synthesis of N-{2-(4-hydroxybenzylidenimino)-ethyl}-2-amino-5-nitrothiazole (**3m**)*

Yield: 62%, m.p. 131–134 °C; Anal. Calcd for $C_{12}H_{13}N_5O_3S$: C, 46.89, H, 4.26, N, 22.78%; found C, 46.85, H, 4.22, N, 22.73%; IR: 1559 (N=CH), 3388 (NH), 3477 (OH); ^{1}H NMR (δ): 4.53 (t, 2H, J = 7.35 Hz, $\underline{CH_2}$—NH), 4.29 (s, 1H, OH), 5.09 (t, 2H, J = 7.35 Hz, N—$\underline{CH_2}$), 7.30 (s, 1H, C_4H of thiazole), 7.57 (s, 1H, NH), 7.78 (br s, 1H, NH), 7.90 (s, 1H, N=CH), 6.50–7.49 (m, 4H, Ar—H); ^{13}C NMR (δ): 49.5 ($\underline{CH_2}$—NH), 59.7 (N—$\underline{CH_2}$), 112.8 (C_5 of thiazole), 140.6 (C_4 of thiazole), 153.4 (N=CH), 170.6 (C_2 of thiazole), 111.7, 116.4, 123.8, 128.9, 137.5, 154.8 (6C, Ar); Mass (FAB)1: 307M$^+$, 290, 216, 181.

*2.6. General conventional methods for synthesis of compound **4(a–m)***

A mixture of compound **3(a–m)** and thioglycolic acid (1:1 mol) dissolved in methanol was allow to react in the presence of a catalytic amount of $ZnCl_2$. The reaction mixture was first continuously stirred on a magnetic stirrer for about

2.10–2.30 h then kept on steam bath for about 1.45–4.15 h at 80–90 °C. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography using chloroform: ethanol (7:3 v/v) and recrystallized from ethanol at room temperature to yield compound **4(a–m)**.

2.6.1. Synthesis of N-2-[-{-(2-phenyl-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4a)

Yield: 65%, m.p. 161–164 °C; Anal. Calcd for $C_{14}H_{15}N_5O_3S_2$: C, 46.01, H, 4.13, N, 19.16%; found C, 45.96, H, 4.10, N, 19.10%; IR: 678 (C—S—C), 748 (C—Cl), 1329 (C—N), 1738 (CO cyclic), 2912 (S—CH_2); ^{1}H NMR 3.10 (s, 2H, S—CH_2), 4.96 (d, 1H, N—CH), 7.26 (s, 1H, C_4H of thiazole), 6.45–7.45 (m, 4H, Ar—H); ^{13}C NMR (δ): 35.5 (CH_2—S), 56.2 (N—CH), 111.8 (C_5 of thiazole), 137.8 (C_4 of thiazole), 168.7 (CO cyclic), 170.6 (C_2 of thiazole), 124.7, 126.7, 127.5, 128.8, 131.9, 137.7 (6C, Ar); Mass (FAB): 365M$^+$, 337, 260, 187, 178. 150.

2.6.2. Synthesis of N-2-[-{2-(4-chlorophenyl)-4-oxo-1-3-thiazolidine-imino}-ethyl-2-amino-5-nitrothiazole (4b)

Yield: 65%, m.p. 178–181 °C; Anal. Calcd for $C_{14}H_{14}N_5O_3S_2Cl$: C, 42.05, H, 3.52, N, 17.51%; found C, 42.00, H, 3.49, N, 17.47%; IR: 689 (C—S—C), 738 (C—Cl), 1345 (C—N), 1749 (CO cyclic), 2946 (S—CH_2); ^{1}H NMR: 3.30 (s, 2H, S—CH_2), 4.98 (d, 1H, N—CH), 7.31 (s, 1H, C_4H of thiazole), 6.64–7.78 (m, 4H, Ar—H—H); ^{13}C NMR (δ): 34.4 (CH_2—S), 58.2 (N—CH), 116.7 (C_5 of thiazole), 140.4 (C_4 of thiazole), 177.9 (CO cyclic), 171.8 (C_2 of thiazole), 124.7, 126.8, 127.7, 128.5, 129.8, 138.5 (6C, Ar); Mass (FAB): 400M$^+$, 372, 365, 185, 178.

2.6.3. Synthesis of N-2-[-{2-(3-chlorophenyl)-4-oxo-1-3-thiazolidine-imino}-ethyl-2-amino-5-nitrothiazole (4c)

Yield: 67%, m.p. 176–178 °C; Anal. Calcd for $C_{14}H_{14}N_5O_3S_2Cl$: C, 42.05, H, 3.52, N, 17.51%; found C, 42.01, H, 3.46, N, 17.45%; IR: 672 (C—S—C), 749 (C—Cl), 1338 (C—N), 1744 (CO cyclic), 2930 (S—CH_2); ^{1}H NMR: 3.40 (s, 2H, S—CH_2), 4.90 (d, 1H, N—CH), 7.40 (s, 1H, C_4H of thiazole), 6.72–7.74 (m, 4H, Ar—H); ^{13}C NMR (δ): 39.5 (CH_2—S), 53.4 (N—CH), 109.7 (C_5 of thiazole), 139.5 (C_4 of thiazole), 176.9 (CO cyclic), 171.6 (C_2 of thiazole), 125.9, 127.8, 128.6, 128.6, 130.5, 136.9 (6C, Ar); Mass (FAB): 400M$^+$.

2.6.4. Synthesis of N-2-[-{2-(2-chlorophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4d)

Yield: 66%, m.p. 174–177 °C; Anal. Calcd for $C_{14}H_{14}N_5O_3S_2Cl$: C, 42.05, H, 3.52, N, 17.51%; found C, 42.03, H, 3.49, N, 17.45%; IR: 678 (C—S—C), 758 (C—Cl), 1339 (C—N), 1748 (CO cyclic), 2938 (S—CH_2); ^{1}H NMR: 3.40 (s, 2H, S—CH_2), 4.93 (d, 1H, N—CH), 7.36 (s, 1H, C_4H of thiazole), 6.67–7.76 (m, 4H, Ar—H); ^{13}C NMR (δ): 39.6 (CH_2—S), 60.7 (N—CH), 112.5 (C_5 of thiazole), 138.9 (C_4 of thiazole), 174.9 (CO cyclic), 172.5 (C_2 of thiazole), 125.7, 127.6, 127.9, 128.4, 129.6, 137.9 (6C, Ar); Mass (FAB): 400M$^+$.

2.6.5. Synthesis of N-2-[-{2-(4-bromophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4e)

Yield: 60%, m.p. 187–190 °C; Anal. Calcd for $C_{14}H_{14}N_5O_3S_2Br$: C, 37.84, H, 3.17, N, 15.76%; found C, 37.80, H, 3.12, N, 15.76%; IR: 688 (C—S—C), 758 (C—Br), 1345 (C—N), 1748 (CO cyclic), 2946 (S—CH_2); ^{1}H NMR: 3.42 (s, 2H, S—CH_2), 4.89 (d, 1H, N—CH), 7.39 (s, 1H, C_4H of thiazole), 6.46–7.91 (m, 4H, Ar—H); ^{13}C NMR (δ): 40.5 (CH_2—S), 61.6 (N—CH), 112.8 (C_5 of thiazole), 139.8 (C_4 of thiazole), 173.9 (CO cyclic), 172.2 (C_2 of thiazole), 125.8, 126.9, 127.6, 128.8, 129.8, 137.5 (6C, Ar); Mass (FAB): 444M$^+$, 416, 364, 257, 229, 187, 177, 149.

2.6.6. Synthesis of N-2-[-{2-(3-bromophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4f)

Yield: 63%, m.p. 185–187 °C; Anal. Calcd for $C_{14}H_{14}N_5O_3S_2Br$: C, 37.84, H, 3.17, N, 15.76%; found C, 37.81, H, 3.10, N, 15.74%; IR: 670 (C—S—C), 748 (C—Br), 1339 (C—N), 1738 (CO cyclic), 2936 (S—CH_2); ^{1}H NMR: 3.44 (s, 2H, S—CH_2), 4.85 (d, 1H, N—CH), 7.30 (s, 1H, C_4H of thiazole), 6.61–7.98 (m, 4H, Ar—H); ^{13}C NMR (δ): 38.4 (CH_2—S), 54.3 (N—CH), 110.2 (C_5 of thiazole), 137.6 (C_4 of thiazole), 175.4 (CO cyclic), 171.2 (C_2 of thiazole), 126.7, 127.8, 128.8, 129.6, 130.4, 137.3 (6C, Ar); Mass (FAB): 444.

2.6.7. Synthesis of N-2-[-{2-(2-bromophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4g)

Yield: 66%, m.p. 180–183 °C; Anal. Calcd for $C_{14}H_{14}N_5O_3S_2Br$: C, 37.84, H, 3.17, N, 15.76%; found C, 37.78, H, 3.11, N, 15.69%; IR: 675 (C—S—C), 742 (C—Br), 1332 (C—N), 1738 (CO cyclic), 2920 (S—CH_2); ^{1}H NMR: 3.46 (s, 2H, S—CH_2), 4.88 (d, 1H, N—CH), 7.32 (s, 1H, C_4H of thiazole), 6.85–7.96 (m, 4H, Ar—H); ^{13}C NMR (δ): 34.6 (CH_2—S), 51.6 (N—CH), 113.4 (C_5 of thiazole), 138.8 (C_4 of thiazole), 171.5 (CO cyclic), 167.6 (C_2 of thiazole), 126.5, 127.6, 128.8, 129.4, 130.8, 137.3 (6C, Ar); Mass (FAB): 444M$^+$.

2.6.8. Synthesis of N-2-[-{2-(4-nitrophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4h)

Yield: 64%, m.p. 187–189 °C; Anal. Calcd for $C_{14}H_{14}N_6O_5S_2$: C, 40.96, H, 3.43, N, 20.47%; found C, 40.93, H, 3.40, N, 20.40%; IR: 687 (C—S—C), 1020 (NO), 1329 (C—N), 1548 (NO_2), 1748 (CO cyclic), 2936 (S—CH_2); ^{1}H NMR: 3.40 (s, 2H, S—CH_2), 4.85 (d, 1H, N—CH), 7.32 (s, 1H, C_4H of thiazole), 6.98–7.97 (m, 4H, Ar—H); ^{13}C NMR (δ): 38.7 (CH_2—S), 57.4 (N—CH), 113.4 (C_5 of thiazole), 138.4 (C_4 of thiazole), 174.6 (CO cyclic), 169.2 (C_2 of thiazole), 126.7, 127.7, 128.6, 129.8, 129.9, 136.6 (6C, Ar); Mass (FAB): 410M$^+$, 380, 364, 336, 280, 223, 195, 149, 117.

2.6.9. Synthesis of N-2-[-{2-(3-nitrophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4i)

Yield: 63%, m.p. 182–186 °C; Anal. Calcd for $C_{14}H_{14}N_6O_5S_2$: C, 40.96, H, 3.43, N, 20.47%; found C, 40.90, H, 3.39, N, 20.41%; IR: 674 (C—S—C), 745 (C—Cl), 1020 (NO), 1326 (C—N), 1547 (NO_2), 1746 (CO cyclic), 2986 (S—CH_2); ^{1}H NMR: 3.37 (s, 2H, S—CH_2), 4.94 (d, 1H, N—CH), 7.39 (s, 1H, C_4H of thiazole), 6.90–8.13 (m, 4H, Ar—H); ^{13}C NMR (δ): 42.8 (CH_2—S), 61.7 (N—CH), 111.7 (C_5 of thiazole), 139.6 (C_4 of thiazole), 173.9 (CO cyclic), 172.1 (C_2 of thiazole), 126.8, 127.8, 128.8, 129.9, 131.9, 135.7 (6C, Ar); Mass (FAB): 410M$^+$.

2.6.10. Synthesis of N-2-[-{2-(2-nitrophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4j)

Yield: 61%, m.p. 179–181 °C; Anal. Calcd for $C_{14}H_{14}N_6O_5S_2$: C, 40.96, H, 3.43, N, 20.47%; found C, 40.92, H, 3.38, N,

20.42%; IR: 670 (C—S—C), 743 (C—Cl), 1012 (NO), 1325 (C—N), 1539 (NO_2), 1736 (CO cyclic), 2988 (S—CH_2); ^{1}H NMR: 3.31 (s, 2H, S—CH_2), 4.97 (d, 1H, N—CH), 7.39 (s, 1H, C_4H of thiazole), 7.02–8.11 (m, 4H, Ar—H); ^{13}C NMR (δ): 45.8 (CH_2—S), 60.6 (N—CH), 114.4 (C_5 of thiazole), 141.5 (C_4 of thiazole), 172.2 (C_2 of thiazole), 174.6 (CO cyclic), 126.3, 127.8, 128.7, 129.6, 130.5, 138.9 (6C, Ar); Mass (FAB): 410M$^+$.

2.6.11. Synthesis of N-2-[-{2-(4-methoxyphenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4k)

Yield: 64%, m.p. 165–167 °C; Anal. Calcd for $C_{15}H_{17}N_5O_4S_2$: C, 45.55, H, 4.33, N, 17.70%; found C, 45.52, H, 4.30, N, 17.65%; IR: 670 (C—S—C), 1334 (C—N), 1742 (CO cyclic), 2935 (S—CH_2), 3024 (OCH_3); ^{1}H NMR: 3.25 (s, 2H, S—CH_2), 3.58 (s, 3H, OCH_3), 4.89 (d, 1H, N—CH), 7.29 (s, 1H, C_4H of thiazole), 6.66–7.69 (m, 4H, Ar—H); ^{13}C NMR (δ): 41.6 (CH_2—S), 57.9 (N—CH), 53.8 (OCH_3), 111.8 (C_5 of thiazole), 138.8 (C_4 of thiazole), 171.8 (CO cyclic), 172.6 (C_2 of thiazole), 125.6, 127.8, 128.4, 129.6, 133.4, 139.4 (6C, Ar); Mass (FAB): 395M$^+$, 380, 367, 364, 352, 336, 208, 193, 187, 180, 177.

2.6.12. Synthesis of N-2-[-{2-(4-methylphenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4l)

Yield: 63%, m.p. 163–165 °C; Anal. Calcd for $C_{15}H_{17}N_5O_3S_2$: C, 47.47, H, 4.51, N, 18.45%; found C, 47.43, H, 4.47, N, 18.40%; IR: 670 (C—S—C), 743 (C—Cl), 1327 (C—N), 1740 (CO cyclic), 2933 (S—CH_2), 2932 (CH_3); ^{1}H NMR: 2.77 (s, 3H, CH_3), 3.29 (s, 2H, S—CH_2), 4.74 (d, 1H, N—CH), 7.32 (s, 1H, C_4H of thiazole), 6.49–7.74 (m, 4H, Ar—H); ^{13}C NMR (δ): 27.4 (CH_3), 46.6 (CH_2—S), 60.6 (N—CH), 109.5 (C_5 of thiazole), 137.8 (C_4 of thiazole), 172.4 (CO cyclic), 167.2 (C_2 of thiazole), 126.9, 127.7, 128.3, 132.7, 136.9 (6C, Ar); Mass (FAB): 379M$^+$, 353, 325, 261.

2.6.13. Synthesis of N-2-[-{2-(4-hydroxyphenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (4m)

Yield: 63%, m.p. 160–162 °C; Anal. Calcd for $C_{14}H_{15}N_5O_4S_2$: C, 44.08, H, 3.96, N, 18.36%; found C, 44.02, H, 3.93, N, 18.32%; IR: 679 (C—S—C), 1336 (C—N), 1743 (CO cyclic), 2938 (S—CH_2), 3449 (OH); ^{1}H NMR: 3.40 (s, 2H, S—CH_2), 4.46 (s, 1H, OH), 4.81 (d, 1H, N—CH), 7.31 (s, 1H, C_4H of thiazole), 6.54–7.45 (m, 4H, Ar—H); ^{13}C NMR (δ): 50.7 (CH_2—S), 61.5 (N—CH), 111.7 (C_5 of thiazole), 138.8 (C_4 of thiazole), 174.6 (CO cyclic), 168.6 (C_2 of thiazole), 126.74, 127.6, 128.6, 129.8, 132.5, 137.5 (6C, Ar); Mass (FAB): 381M$^+$, 364, 325, 194, 166.

*2.7. General conventional method for synthesis of compound **5(a–m)***

A mixture of compound **4(a–m)** and substituted benzaldehydes (1:1 mol) was dissolved in methanol in the presence of alkali metal alkoxide (C_2H_5ONa) and allow to react. The reaction mixture was first continuously stirred on a magnetic stirrer for about 2.00–2.30 h then kept on steam bath for about 2.45–3.45 h at 80–90 °C. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography using chloroform: methanol (7:3 v/v) and recrystallized from acetone at room temperature to yield final products compound **5(a–m)**.

2.7.1. Synthesis of N-2-[-{2-phenyl-4-oxo-5-benylidene-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5a)

Yield: 66%, m.p. 161–163 °C; Anal. Calcd for $C_{21}H_{19}N_5O_3S_2$: C, 55.61, H, 4.22, N, 15.44%; found C, 55.56, H, 4.20, N, 15.41%; IR: 1508 (C═CH), 2978 (C═CH); ^{1}H NMR: 6.25 (s, 1H, C═CH), 7.22 (s, 1H, C_4H of thiazole), 6.42–7.42 (m, 10H, Ar—H); ^{13}C NMR (δ): 110.6 (C_5 of thiazole), 139.6 (C_4 of thiazole), 143.6 (C═CH), 146.8 (C═CH), 170 (C_2 of thiazole), 170.7 (CO cyclic), 124.5, 125.6, 125.9, 126.8, 126.9, 127.8, 127.9, 128.9, 128.9, 129.7, 137.8, 138.9 (12C, Ar); Mass (FAB): 454M$^+$, 426, 377, 349.

2.7.2. Synthesis of N-2-[-{2-(4-chlorophenyl)-4-oxo-5-(4-chlorobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5b)

Yield: 64%, m.p. 166–169 °C; Anal. Calcd for $C_{21}H_{17}N_5O_3S_2Cl_2$: C, 48.27, H, 3.27, N, 13.40%; found C, 48.20, H, 3.22, N, 13.36%; IR: 1520 (C═CH), 2946 (C═CH); ^{1}H NMR: 6.47 (s, 1H, C═CH), 7.32 (s, 1H, C_4H of thiazole), 6.47–7.69 (m, 8H, Ar—H); ^{13}C NMR (δ): 112.7 (C_5 of thiazole), 141.5 (C_4 of thiazole), 144.8 (C═CH), 147.8 (C═CH), 172.1 (C_2 of thiazole), 175.7 (CO cyclic), 126.7, 127.6, 128.5, 128.9, 129.4, 129.8, 130.7, 131.6, 132.8, 133.8, 134.7, 138.9 (12C, Ar); Mass (FAB): 522M$^+$, 494, 487, 411, 383, 307.

2.7.3. Synthesis of N-2-[-{-5-(3-chlorobenzylidene)-2-(3-chlorophenyl)-4-oxo-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5c)

Yield: 62%, m.p. 164–166 °C; Anal. Calcd for $C_{21}H_{17}N_5O_3S_2Cl_2$: C, 48.27, H, 3.27, N, 13.40%; found C, 48.23, H, 3.21, N, 13.35%; IR: 1526 (C═CH), 2952 (C═CH); ^{1}H NMR: 6.45 (s, 1H, C═CH), 7.42 (s, 1H, C_4H of thiazole), 6.58–7.60 (m, 8H, Ar—H); ^{13}C NMR (δ): 111.6 (C_5 of thiazole), 140.8 (C_4 of thiazole), 143.5 (C═CH), 146.8 (C═CH), 171.5 (C_2 of thiazole), 173.3 (CO cyclic), 126.2, 126.7, 127.4, 127.8, 128.3, 128.7, 129.5, 131.6, 132.8, 133.4, 134.2, 137.8 (12C, Ar); Mass (FAB): 522M$^+$.

2.7.4. Synthesis of N-2-[-{2-(2-chlorophenyl)-4-oxo-5-(2-chlorobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5d)

Yield: 64%, m.p. 162–164 °C; Anal. Calcd for $C_{21}H_{17}N_5O_3S_2Cl_2$: C, 48.27, H, 3.27, N, 13.40%; found C, 48.25, H, 3.22, N, 13.33%; IR: 1525 (C═CH), 2938 (C═CH); ^{1}H NMR: 6.48 (s, 1H, C═CH), 7.46 (s, 1H, C_4H of thiazole), 6.50–7.65 (m, 8H, Ar—H); ^{13}C NMR (δ): 110.8 (C_5 of thiazole), 139.9 (C_4 of thiazole), 144.6 (C═CH), 146.9 (C═CH), 171.8 (C_2 of thiazole), 173.4 (CO cyclic), 126.9, 126.9, 127.4, 127.8, 128.5, 129.8, 130.6, 132.8, 133.7, 134.4, 135.7, 138.8 (12C, Ar); Mass (FAB): 522M$^+$.

2.7.5. Synthesis of N-2-[-{2-(4-bromophenyl)-4-oxo-5-(4-bromobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5e)

Yield: 62%, m.p. 168–172 °C; Anal. Calcd for $C_{21}H_{17}N_5O_3S_2Br_2$: C, 41.25, H, 2.80, N, 11.45%; found C, 41.19, H, 2.77, N, 11.43%; IR: 1517 (C═CH), 2945 (C═CH); ^{1}H NMR: 6.40 (s, 1H, C═CH), 7.42 (s, 1H, C_4H of thiazole), 6.55–7.95 (m, 8H, Ar—H); ^{13}C NMR (δ): 112.2 (C_5 of thiazole), 140.8 (C_4 of thiazole), 144.6 (C═CH), 147.8 (C═CH), 171.2 (C_2 of thiazole), 173.9 (CO cyclic), 119.8, 123.4, 125.4,

126.1, 126.8, 127.8, 128.7, 129.6, 130.4, 131.6, 140.7, 141.9 (12C, Ar); Mass (FAB): $611M^+$, 583, 531, 427, 424, 401, 396, 240, 214.

2.7.6. Synthesis of N-2-[-{2-(3-bromophenyl)-4-oxo-5-(3-bromobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5f)

Yield: 65%, m.p. 175–177 °C; Anal. Calcd for $C_{21}H_{17}N_5O_3S_2Br_2$: C, 41.25, H, 2.80, N, 11.45%; found C, 41. 20, H, 2.75, N, 11.40%; IR: 1521 (C═CH), 2962 (C═CH); ^{1}H NMR: 6.24 (s, 1H, C═CH), 6.58 (s, 1H, C_4H of thiazole), 6.58–7.97 (m, 8H, Ar—H); ^{13}C NMR (δ): 112.9 (C_5 of thiazole), 139.9 (C_4 of thiazole), 144.8 (C═CH), 148.9 (C═CH), 172.3 (C_2 of thiazole), 174.7 (CO cyclic), 123.5, 124.7, 126.8, 127.5, 127.9, 128.5, 129.6, 129.8, 130.8, 132.8, 141.7, 142.6 (12C, Ar); Mass (FAB): $611M^+$.

2.7.7. Synthesis of N-2-[-{2-(2-bromophenyl)-4-oxo-5-(2-bromobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5g)

Yield: 64%, m.p. 176–178 °C; Anal. Calcd for $C_{21}H_{17}N_5O_3S_2Br_2$: C, 41.25, H, 2.80, N, 11.45%; found C, 41.22, H, 2.79, N, 11.42%; IR: 1526 (C═CH), 2933 (C═CH); ^{1}H NMR: 6.52 (s, 1H, C═CH), 7.32 (s, 1H, C_4H of thiazole), 6.45–8.02 (m, 8H, Ar—H); ^{13}C NMR (δ): 113.4 (C_5 of thiazole), 141.4 (C_4 of thiazole), 145.1 (C═CH), 148.5 (C═CH), 171.2 (C_2 of thiazole), 176.7 (CO cyclic), 119.8, 120.8, 124.9, 125.4, 126.8, 127.6, 128.8, 128.9, 129.9, 130.7, 140.8, 142.6 (12C, Ar); Mass (FAB): $611M^+$.

2.7.8. Synthesis of N-2-[-{2-(4-nitrophenyl)-4-oxo-5-(4-nitrobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5h)

Yield: 62%, m.p. 171–174 °C; Anal. Calcd for $C_{21}H_{17}N_7O_7S_2$: C, 46.40, H, 3.15, N, 18.03%; found C, 46.33, H, 3.11, N, 17.93%; IR: 1530 (C═CH), 2991 (C═CH); ^{1}H NMR: 6.41 (s, 1H, C═CH), 7.38 (s, 1H, C_4H of thiazole), 6.85–8.22 (m, 8H, Ar—H); ^{13}C NMR (δ): 112.2 (C_5 of thiazole), 139.4 (C_4 of thiazole), 143.6 (C═CH), 146.5 (C═CH), 174.7 (CO cyclic), 170.2 (C_2 of thiazole), 126.4, 127.6, 128.8, 128.6, 129.5, 138.8 (12C, Ar); Mass (FAB): $544M^+$, 540, 470, 444, 357, 327.

2.7.9. Synthesis of N-2-[-{2-(3-nitrophenyl)-4-oxo-5-(3-nitrobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5i)

Yield: 64%, m.p. 176–179 °C; Anal. Calcd for $C_{21}H_{17}N_7O_7S_2$: C, 46.40, H, 3.15, N, 18.03%; found C, 46.37, H, 3.13, N, 17.98%; IR: 1522 (C═CH), 2946 (C═CH); ^{1}H NMR: 6.48 (s, 1H, C═CH), 7.44 (s, 1H, C_4H of thiazole), 6.90–8.28 (m, 8H, Ar—H); ^{13}C NMR (δ): 110.2 (C_5 of thiazole), 138.4 (C_4 of thiazole), 141.8 (C═CH), 144.9 (C═CH), 175.7 (CO cyclic), 169.8 (C_2 of thiazole), 118.7, 120.7, 124.9, 125.6, 126.7, 127.5, 128.6, 129.6, 130.4, 132.8, 146.8, 148.6 (12C, Ar); Mass (FAB): $544M^+$.

2.7.10. Synthesis of N-2-[-{2-(2-nitrophenyl)-4-oxo-5-(2-nitrobenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5j)

Yield: 60%, m.p. 177–180 °C; Anal. Calcd for $C_{21}H_{17}N_7O_7S_2$: C, 46.40, H, 3.15, N, 18.03%; found C, 46.35, H, 3.08, N, 18.00%; IR: 1532 (C═CH), 2948 (C═CH); ^{1}H NMR: 6.32 (s, 1H, C═CH), 7.44 (s, 1H, C_4H of thiazole), 6.82–8.20 (m, 8H, Ar—H); ^{13}C NMR (δ): 111.2 (C_5 of thiazole), 140.4 (C_4 of thiazole), 143.7 (C═CH), 146.6 (C═CH), 168.8 (C_2 of thiazole), 175.7 (CO cyclic), 116.8, 121.6, 123.8, 125.7, 126.8, 127.6, 128.8, 129.6, 130.6 132.7, 145.6, 146.8 (12C, Ar); Mass (FAB): $544M^+$.

2.7.11. Synthesis of N-2-[-{2-(4-methoxyphenyl)-4-oxo-5-(4-methoxybenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5k)

Yield: 66%, m.p. 155–158 °C; Anal. Calcd for $C_{23}H_{23}N_5O_5S_2$: C, 53.78, H, 4.51, N, 13.63%; found C, 53.72, H, 4.45, N, 13.56%; IR: 1518 (C═CH), 2941 (C═CH), 2978 (OCH_3); ^{1}H NMR: 3.63 (s, 3H, OCH_3), 6.34 (s, 1H, C═CH), 7.37 (s, 1H, C_4H of thiazole), 6.45–7.77 (m, 8H, Ar—H); ^{13}C NMR (δ): 63.5 (OCH_3), 108.7 (C_5 of thiazole), 138.8 (C_4 of thiazole), 144.8 (C═CH), 148.5 (C═CH), 170.5 (C_2 of thiazole), 171.7 (CO cyclic), 114.7, 115.7, 120.8, 121.9, 124.6, 125.7, 127.8, 128.8, 128.9, 129.6, 155.6, 156.9 (12C, Ar); Mass (FAB): $514M^+$, 499, 486, 471, 443.

2.7.12. Synthesis of N-2-[-{2-(4-methylphenyl)-4-oxo-5-(4-methylbenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5l)

Yield: 61%, m.p. 152–154 °C; Anal. Calcd for $C_{23}H_{23}N_5O_3S_2$: C, 57.36, H, 4.81, N, 14.54%; found C, 57.30, H, 4.78, N, 14.50%; IR: 1512 (C═CH), 2938 (C═CH), 2970 (CH_3); ^{1}H NMR: 2.80 (s, 3H, CH_3), 6.35 (s, 1H, C═CH), 7.38 (s, 1H, C_4H of thiazole), 6.30–7.90 (m, 8H, Ar—H); ^{13}C NMR (δ): 26.9 (CH_3), 107.2 (C_5 of thiazole), 136.4 (C_4 of thiazole), 141.1 (C═CH), 146.9 (C═CH), 170.3 (CO cyclic), 169.7 (C_2 of thiazole), 123.7, 124.5, 125.6, 126.8, 126.8, 127.7, 127.9, 128.6, 129.7, 130.8, 138.6, 139.8 (12C, Ar); Mass (FAB): $482M^+$, 467, 454, 439, 363, 337.

2.7.13. Synthesis of N-2-[-{2-(4-hydroxyphenyl)-4-oxo-5-(4-hydroxybenzylidene)-1-3-thiazolidine}-imino]-ethyl-2-amino-5-nitrothiazole (5m)

Yield: 62%, m.p. 150–153 °C; Anal. Calcd for $C_{21}H_{19}N_5O_5S_2$: C, 51.94, H, 3.94, N, 14.42%; found C, 51.80, H, 3.82, N, 14.39%; IR: 1501 (C═CH), 2951 (C═CH), 3478 (OH); ^{1}H NMR: 4.94 (s, 1H, OH), 6.46 (s, 1H, C═CH), 7.39 (s, 1H, C_4H of thiazole), 6.48–7.58 (m, 8H, Ar—H); ^{13}C NMR (δ): 113.5 (C_5 of thiazole), 143.3 (C_4 of thiazole), 146.1 (C═CH), 148.5 (C═CH), 171.2 (C_2 of thiazole), 173.7 (CO cyclic), 120.9, 124.8, 125.7, 126.6, 127.8, 128.8, 128.9, 129.8, 131.3, 137.5, 138.6, 152.8 (12C, Ar); Mass (FAB): $486M^+$, 458, 469, 384, 368, 308.

3. Results and discussion

The reaction of 1-bromo-2-chloro-ethane with 2-amino-5-nitrothiazole was carried out in methanol to afford a product compound **1** The spectroscopic analyses of compound **1** showed absorption peaks for N—CH and C—Cl at 1382 and 740 cm^{-1} in the IR spectrum. In the IR spectrum confirms the formation of compound **1**. This fact was also supported by the disappearance of NH absorption of the 2-amino-5-nitrothiazole. The compound **1** on the reaction with hydrazine hydrate with continuous stirring at room temperature yielded compound **2**. In the spectroscopic analyses of compound **2** we found two absorption peaks in IR spectrum for NH and NH_2 at 3370 and 3480 cm^{-1} respectively while

absorption of C—Cl has disappeared. This is clearly indicated that compound **1** gives the substitution reaction with hydrazine hydrate. This fact was also supported by ^{1}H and ^{13}C NMR spectra because two signals appeared in the ^{1}H NMR spectrum for NH and NH_2 at δ 7.70 and δ 5.55 ppm respectively. All the facts together were strong evidence for the synthesis of compound **2**. The compound **2** gave the condensation reaction with substituted benzaldehydes resulting in the production of Schiff bases N=CH, compound **3(a–m)** which was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra of compound **3(a–m)**. In the IR spectra an absorption was found in the range of 1549–1609 cm^{-1} while a strong signal appeared in the range of δ 7.82–8.17 and δ 141.6–156.6 ppm in the ^{1}H NMR and ^{13}C NMR spectra for N=CH of compound **3(a–m)** respectively. The facts have also supported by the disappearance of the signal of NH_2 in the ^{1}H NMR spectra. The compound **3(a–m)** on reaction with equimolar amount of thioglycolic acid in the presence of $ZnCl_2$ (act as a catalyst) in the trace amount gives the cycloaddition reaction and produced a five membered thiazolidinone ring, compound **4(a–m)**. The compound **4(a–m)** showed a characteristic absorption for the cyclic carbonyl group in the range of 1738–1749 cm^{-1} in the IR spectra. The ^{1}H NMR spectra aroused our attention and clearly indicate the presence of the two active methylene protons in the thiazolidine ring in the range of δ 3.10–3.46 ppm. The ^{13}C NMR spectra of compound **4(a–m)** also supported the fact that cyclic carbonyl group present and a signal appeared in the range of δ 168.7–177.9 ppm. All these facts were also supported by the two evidences that are (a) disappearance of N=CH proton and (b) appearance of N—CH proton in the range of δ 4.74–4.98 ppm in the ^{1}H NMR spectra of compound **4(a–m)**. The compound **4(a–m)** underwent the Knoevenagel condensation reaction with substituted benzaldehydes in the presence of alkali metal alkoxide (C_2H_5ONa) to afford the compound **5(a–m)**. In the ^{1}H NMR spectra of the compound **5(a–m)**, we found the disappearance of two methylene protons of compound **5(a–m)** and an appearance of a new signal for C=CH in the range of δ 6.24–6.52 ppm in the ^{1}H NMR and two new signals for C=CH and C=CH appeared in the range of δ 141.1–146.1 and δ 144.9–148.9 ppm in the ^{13}C NMR spectra of the compound **5(a–m)**. These all above facts clearly confirmed the synthesis of all final products. All above compounds **1**, **2**, **3(a–m), 4(a–m) and 5(a–m)** were also synthesized by microwave method. Characterization data were given in Table 1. All these above facts clearly confirmed the synthesis of all final products. Antimicrobial and antitubercular data (as shown in Tables 2 and 3) revealed that all the synthesized compound **5(a–m)** have a structure activity relationship (SAR) because activity of compounds varies with substitution. Nitro group containing compounds (**5h**, **5i** and **5j**) showed higher activity than chloro (**5c**, **5d**), or bromo group containing compounds (**5e**, **5f**). Chloro and bromo derivatives also have higher activity than other rested compounds. On the basis of SAR, it was concluded that the activity of compounds depends on the electron withdrawing nature of the substituted groups. The sequence of the activity is following

$$NO_2 > Cl > Br > OCH_3 < OH > CH_3$$

Table 2 Antibacterial activity of compounds **5(a–m)**.

Compound	*B. subtilis*		*E. coli*		*S. aureus*		Compound	*A. niger*		*A. flavus*		*C. albicans*	
	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm		50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm
5a	17	21	17	22	15	23	**5a**	09	15	17	20	17	20
5b	23	29	20	30	22	28	**5b**	12	22	15	20	14	24
5c	24	34	22	32	24	30	**5c**	16	30	12	24	14	30
5d	25	33	20	32	23	31	**5d**	18	29	10	34	13	31
5e	22	30	22	31	25	33	**5e**	15	28	12	28	15	31
5f	21	30	21	32	24	30	**5f**	16	29	11	27	14	30
5g	20	28	20	29	20	27	**5g**	14	28	10	31	10	28
5h	22	36	19	33	22	34	**5h**	12	31	09	32	12	35
5i	20	37	20	32	22	33	**5i**	12	29	10	31	12	33
5j	24	32	21	34	20	35	**5j**	13	30	11	34	10	32
5k	18	25	19	24	18	24	**5k**	11	19	10	24	11	23
5l	14	18	14	20	16	22	**5l**	10	16	10	20	10	20
5m	12	27	23	27	17	28	**5m**	14	24	13	25	12	27
Streptomycin	28	37	26	34	27	35	Griseofulvin	22	32	20	35	24	36

Table 3 Antitubercular activity of compounds **5(a–m)**.

Compound	% Activity		Compound	% Activity		Compound	% Activity		Compound	% Activity	
	25 ppm	50 ppm		25 ppm	50 ppm		25 ppm	50 ppm		25 ppm	50 ppm
5a	32	59	**5e**	50	78	**5i**	57	83	**5m**	54	76
5b	52	82	**5f**	60	79	**5j**	58	81	–	–	–
5c	53	80	**5g**	59	76	**5k**	58	60	–	–	–
5d	62	80	**5h**	62	82	**5l**	42	55	–	–	–
Standards	100	100	Standards	100	100	Standards	100	100	Standards	100	100

Isoniazid and rifampicin were taken as standards, showed 100% activity at 25 and 50 ppm concentrations.

4. Biological study

Series of newly synthesized compounds were highly active against selected microorganisms. The minimal inhibition values were determined using the filter paper disc diffusion method (Asati et al., 2005) and the concentrations have been used in ppm. All the final synthesized compounds **5(a–m)** have dissolved in methanol and screened *in vitro* for their antibacterial activity against *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans*. Standards for antibacterial and antifungal activity streptomycin and griseofulvin were used respectively. Standards also screened under the similar conditions for comparison. The antitubercular activity screened against the *M. tuberculosis*. For the antitubercular activity isoniazid and rifampicin were used as standard and also screened under the similar conditions.

4.1. Antibacterial activity

The above synthesized compounds were screened against some selected bacteria and examined for the inhibition of growth of the organism. The concentrations of the compounds were given in ppm. The diameter of the inhibition zones in (mm) were given in Table 2.

4.2. Antifungal activity

The above synthesized compounds were screened against selected fungi and their minimal inhibition zones in (mm) were presented in Table 2 and concentrations of the compounds were given in ppm.

4.3. Antitubercular activity

The above synthesized compounds were screened against *M. tuberculosis* (H37Rv strain) using L.J. medium (conventional) method at 25 and 50 ppm concentrations. The results were showing in Table 3. The standard antitubercular drugs isoniazid and rifampicin were taken as standards, showed 100% activity at both the above concentrations.

5. Conclusion

Compound **1, 2, 3(a–m), 4**(**a**–**m**) and **5(a–m**) were synthesized by conventional and microwave methods, reaction time and yields of the synthesized compound displayed that the microwave method is more efficient than the conventional method. Compound **5**(**a**–**m**) were screened for their antibacterial, antifungal and antitubercular activity against selected microorganisms. The investigation of antimicrobial data revealed that the compounds (**5c**), (**5d**), (**5e**), (**5f**), (**5h**), (**5i**) and (**5j**) displayed highly active in the series, compounds (**5b**), (**5g**) and (**5m**) showed moderate activity and rest compounds showed less activity against all the strains compared with standard drugs.

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