Synthesis and Biological Study of Some 4-oxo-Thiazolidine Derivatives of 2-Aminothiazole

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Conventional and microwave assisted synthesis of new series of *N*-[2-{2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole **5a—5m** have been developed. The cycloaddition reaction of thioglycolic acid with *N*-{2-(substituted benzylidenehydrazino)-ethyl}-2-aminothiazole **3a—3m** in the presence of anhydrous $ZnCl_2$ afforded new heterocyclic compounds *N*-[2-{2-(substituted phenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole **4a—4m**. The later product on treatment with several selected substituted aromatic aldehydes in the presence of C_2H_5ONa undergoes Knoevenagel reaction to yield **5a—5m**. The structures of compounds **1**, **2**, **3a—3m**, **4a—4m** and **5a—5m** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, FAB-Mass and chemical analysis. All above compounds were screened for their antimicrobial activities against some selected bacteria and fungi and antituberculosis study against *M. tuberculosis*.

Keywords conventional, microwave, synthesis, 2-aminothiazole, 4-oxo-thiazolidine, antimicrobial, antitubercular

Introduction

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities. They have recently found application in drug development for the treatment of anti-inflammatory,[1,2] antituberculosis,[3] antiprotozoal,[4] anticancer,[5] anticonvulsants,[6] antifungal,[7] anti-HIV[8] and antibacterial.[7,9] Some thiazole derivatives are used in clinical practice as antipsychotic,[10] and anticoccidial agents.[11] 4-thiazolidine derivatives constitution is an important class of heterocyclic compounds for their potential pharmaceutical applications. Consequently, a large number of synthetic protocols leading to the compounds have been reported in this literature. Heterocycles containing thiazolidine moity are of interest because they show some pharmacological and biological activities. Thiazolidines derivatives were reported to possess antifungal,[12,13] antibacterial, antiinflammatory,[14,15] herbicidal,[16] antibiotic agents,[17] antidiabetic[18] and analgesic[19] activities *etc*. All above biological activities of thiazole and thiazolidine derivatives aroused our attention and promoted us to synthesize a new series of *N*-[2-{2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole, **5a—5m** by conventional and microwave methods. The structures of compounds **1**, **2**, **3a—3m**, **4a—4m** and **5a—5m** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, FAB-Mass and chemical analysis. All the final synthesized compounds **5a—5m** were screened for their antimicrobial activities against some selected bacteria and fungi and antituberculosis study against *M. tuberculosis*.

Experimental

Melting points were taken in open capillaries and uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates in MeOH/$CHCl_3$ system (1∶9, volume ratio). The spot was visualized by exposing dry plate in iodine vapours chamber. 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 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.

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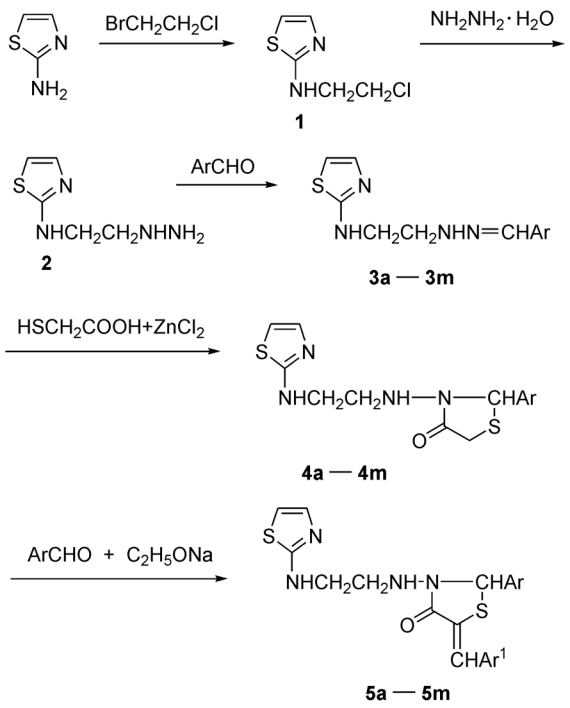
Received September 29, 2010; revised October 29, 2010; accepted December 3, 2010.
Project supported by the

Scheme 1



Comp.	Ar=Ar^1	Comp.	Ar=Ar^1
3a—5a	C_6H_5	**3h—5h**	4-$NO_2C_6H_4$
3b—5b	4-ClC_6H_4	**3i—5i**	3-$NO_2C_6H_4$
3c—5c	3-ClC_6H_4	**3j—5j**	2-$NO_2C_6H_4$
3d—5d	2-ClC_6H_4	**3k—5k**	4-$CH_3OC_6H_4$
3e—5e	4-BrC_6H_4	**3l—5l**	4-$CH_3C_6H_4$
3f—5f	3-BrC_6H_4	**3m—5m**	4-HOC_6H_4
3g—5g	2-BrC_6H_4		

General method for the synthesis of compounds 1, 2, 3a—3m and 4a—4m by microwave method

A solid supported mixture of compounds (1∶1, molar ratio) was mixed thoroughly in open glass vessel and subjected to the microwave 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 and recrystallized from ethanol at room temperature to yield compounds **1**, **2**, **3a—3m** and **4a—4m**.

Synthesis of the compound 1 by conventional method

A mixture of 2-aminothiazole and 1-bromo-2-chloroethane (1∶1, molar ratio) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 6.15 h. The product was filtered and purified over a column chromatography. The purified product was recrystallized from ethanol at room temperature to yield compound **1**.

Synthesis of *N*-(2-chloroethyl)-2-aminothiazole (1) Yield 62%, m.p. 67—69 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.36 (t, J=7.60 Hz, 2H, CH_2Cl), 3.76—3.83 (m, 2H, NCH_2), 7.22 (d, J=4.68 Hz, 1H, C^{4}H of thiazole), 7.72 (d, J=4.68 Hz, 1H, C^{5}H of thiazole), 7.90 (t, J=4.30 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 45.8 (CH_2Cl), 52.6 (NCH_2), 109.8 (C^5 of thiazole), 139.2 (C^4 of thiazole), 169.2 (C^2 of thiazole); IR (KBr) v: 758 (C—Cl), 882 (C—S), 1349 (N—CH_2), 1562 (C=C), 2887, 3046 (CH), 3480 (NH) cm^{-1}; Mass (FAB) m/z: 163 (M^+). Anal. calcd for $C_5H_7N_2SCl$: C 36.92, H 4.33, N 17.22; found C 36.90, H 4.31, N 17.19.

Synthesis of compound 2 by conventional method A mixture of compound **1** and hydrazine hydrate (1∶1, molar ratio) 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. The purified product was recrystallized from ethanol at room temperature to yield compound **2**.

Synthesis of *N*-{2-(hydrazino)-ethyl}-2-aminothiazole (2) Yield 70%, m.p. 51—53 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.26—3.33 (m, 2H, CH_2NH), 3.75—3.83 (m, 2H, NCH_2), 5.56 (s, 2H, NH_2), 6.86 (d, J=4.90 Hz, 1H, C^{5}H of thiazole), 7.28 (d, J=4.90 Hz, 1H, C^{4}H of thiazole), 7.73 (t, J=4.70 Hz, 1H, NH), 7.86 (t, J=4.35 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 49.6 (CH_2NH), 54.8 (NCH_2), 114.5 (C^5 of thiazole), 142.6 (C^4 of thiazole), 173.1 (C^2 of thiazole); IR (KBr) v: 870 (C—S), 1228 (C—N), 3372 (NH), 3434 (NH_2) cm^{-1}; Mass (FAB) m/z: 158 (M^+). Anal. calcd for $C_5H_{10}N_4S$: C 37.95, H 6.37, N 20.26; found C 37.92, H 6.34, N 20.25.

General procedure for the synthesis of compounds 3a—3m by conventional method

A mixture of compound **2** and substituted benzaldehydes (1∶1, molar ratio) 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—3.30 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 and recrystallized from ethanol at room temperature to yield compounds **3a—3m**.

Synthesis of *N*-{2-(benzylidenehydrazino)-ethyl}-2-aminothiazole (3a) Yield 60%, m.p. 60—63 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.22—3.34 (m, 2H, CH_2NH), 3.72—3.80 (m, 2H, NCH_2), 6.62 (d, J=4.90 Hz, 1H, C^{5}H of thiazole), 7.24 (d, J=4.90 Hz, 1H, C^{4}H of thiazole), 7.68 (t, J=4.75 Hz, 1H, NH), 7.88 (t, J=4.35 Hz, 1H, NH), 7.96 (s, 1H, N=CH), 6.30—7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 47.7 (CH_2NH), 52.6 (NCH_2), 113.9 (C^5 of thiazole), 139.5 (C^4 of thiazole), 151.5 (N=CH), 169.8 (C$_2$ of thiazole), 124.7, 125.8, 127.8, 129.7, 131.8, 137.9 (6C, Ar); IR (KBr) v: 1552 (N=CH), 3360 (NH) cm^{-1}; Mass (FAB) m/z: 246 (M^+). Anal. calcd for $C_{12}H_{14}N_4S$: C 58.51, H

5.72, N 22.74; found C 58.45, H 5.67, N 22.70.

Synthesis of *N*-{2-(4-chlorobenzylidenehydrazino)-ethyl}-2-aminothiazole (3b) Yield 64%, m.p. 80—83 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.25—3.32 (m, 2H, CH_2NH), 3.83—3.89 (m, 2H, NCH_2), 7.32 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.44 (d, J=4.95 Hz, 1H, C^4H of thiazole), 7.77 (t, J=4.70 Hz, 1H, NH), 7.95 (t, J=4.38 Hz, 1H, NH), 8.05 (s, 1H, N=CH), 6.40—7.88 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 48.5 (CH_2NH), 57.5 (NCH_2), 116.5 (C^5 of thiazole), 144.5 (C^4 of thiazole), 158 (N=CH), 172.0 (C^2 of thiazole), 125.4, 128.8, 129.5, 130.9, 134.8, 140.2 (6C, Ar); IR (KBr) v: 3371 (NH), 1575 (N=CH), 749 (C—Cl) cm^{-1}; Mass (FAB) m/z: 281 (M^+). Anal. calcd for $C_{12}H_{13}N_4SCl$: C 51.33, H 4.66, N 19.95; found C 51.30, H 4.61, N 19.93.

Synthesis of *N*-{2-(3-chlorobenzylidenehydrazino)-ethyl}-2-aminothiazole (3c) Yield 67%, m.p. 80—81 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.30—3.36 (m, 2H, CH_2NH), 3.79—3.85 (m, 2H, NCH_2), 7.18 (d, J=4.94 Hz, 1H, C^5H of thiazole), 7.27 (d, J=4.94 Hz, 1H, C^4H of thiazole), 7.82 (t, J=4.77 Hz, 1H, NH), 7.94 (t, J=4.35 Hz, 1H, NH), 7.99 (s, 1H, N=CH), 6.43—7.65 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 48.5 (CH_2NH), 57.5 (NCH_2), 113.6 (C^5 of thiazole), 141.6 (C^4 of thiazole), 157.5 (N=CH), 172.2 (C^2 of thiazole), 126.3, 128.9, 130.8, 132.8 136.9, 137.8 (6C, Ar); IR (KBr) v: 755 (C—Cl), 1568 (N=CH), 3371 (NH) cm^{-1}; Mass (FAB) m/z: 281 (M^+). Anal. calcd for $C_{12}H_{13}N_4SCl$: C 51.33, H 4.66, N 19.95; found C 51.32, H 4.60, N 19.90.

Synthesis of *N*-{2-(2-chlorobenzylidenehydrazino)-ethyl}-2-aminothiazole (3d) Yield 65%, m.p. 82—84 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.35—3.42 (m, 2H, CH_2NH), 3.80—3.88 (m, 2H, NCH_2), 7.22 (d, J=5.05 Hz, 1H, C^5H of thiazole), 7.38 (d, J=5.05 Hz, 1H, C^4H of thiazole), 7.78 (t, J=4.78 Hz, 1H, NH), 7.87 (t, J=4.36 Hz, 1H, NH), 7.95 (s, 1H, N=CH), 6.68—7.38 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 49.5 (CH_2NH), 57.8 (NCH_2), 112.5 (C^5 of thiazole), 141.8 (C^4 of thiazole), 159.5 (N=CH), 171.3 (C^2 of thiazole), 126.6, 128.7, 129.5, 130.5, 132.8, 139.9 (6C, Ar); IR (KBr) v: 748 (C—Cl), 1571 (N=CH), 3386 (NH) cm^{-1}; Mass (FAB) m/z: 281 (M^+). Anal. calcd for $C_{12}H_{13}N_4SCl$: C 51.33, H 4.66, N 19.95; found C 51.27, H 4.63, N 19.92.

Synthesis of *N*-{2-(4-bromobenzylidenehydrazino)ethyl}-2-aminothiazole (3e) Yield 66%, m.p. 78—80 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.32—3.40 (m, 2H, CH_2NH), 3.82—3.91 (m, 2H, NCH_2), 7.14 (d, J=5.15 Hz, 1H, C^5H of thiazole), 7.29 (d, J=5.15 Hz, 1H, C^4H of thiazole), 7.69 (t, J=4.70 Hz, 1H, NH), 7.88 (t, J=4.36 Hz, 1H, NH), 7.98 (s, 1H, N=CH), 6.49—7.99 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 48.7 (CH_2NH), 56.8 (NCH_2), 114.7 (C^5 of thiazole), 142.9 (C^4 of thiazole), 155.6 (N=CH), 171.5 (C^2 of thiazole), 123.8, 127.5, 129.8, 132.8, 133.9, 137.7 (6C, Ar); IR (KBr) v: 630 (C—Br), 1545 (N=CH), 3382 (NH) cm^{-1}; Mass (FAB) m/z: 325 (M^+). Anal. calcd for $C_{12}H_{13}N_4SBr$: C 44.31, H 4.02, N 17.22; found C 44.27, H 3.95, N 17.15.

Synthesis of *N*-{2-(3-bromobenzylidenehydrazino)-ethyl}-2-aminothiazole (3f) Yield 65%, m.p. 76—78 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.34—3.40 (m, 2H, CH_2NH), 3.80—3.88 (m, 2H, NCH_2), 7.17 (d, J=5.20 Hz, 1H, C^5H of thiazole), 7.32 (d, J=5.20 Hz, 1H, C^4H of thiazole), 7.55 (t, J=4.82 Hz, 1H, NH), 7.83 (t, J=4.35 Hz, 1H, NH), 7.95 (s, 1H, N=CH), 6.53—7.97 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 49.8 (CH_2NH), 57.4 (NCH_2), 112.9 (C^5 of thiazole), 141.9 (C^4 of thiazole), 157.6 (N=CH), 172.6 (C^2 of thiazole), 124.5, 126.9, 129.8, 131.8, 137.7, 141.7 (6C, Ar); IR (KBr) v: 652 (C—Br), 1573 (N=CH), 3376 (NH) cm^{-1}; Mass (FAB) m/z: 325 (M^+). Anal. calcd for $C_{12}H_{13}N_4SBr$: C 44.31, H 4.02, N 17.22; found C 44.25, H 4.00, N 17.18.

Synthesis of *N*-{2-(2-bromobenzylidenehydrazino)-ethyl}-2-aminothiazole (3g) Yield 63%, m.p. 79—81 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.33—3.41 (m, 2H, CH_2NH), 3.90—3.97 (m, 2H, NCH_2), 7.16 (d, J=5.10 Hz, 1H, C^5H of thiazole), 7.38 (d, J=5.10 Hz, 1H, C^4H of thiazole), 6.69 (t, J=4.83 Hz, 1H, NH), 7.80 (t, J=4.32 Hz, 1H, NH), 8.02 (s, 1H, N=CH), 6.62—7.93 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 48.1 (CH_2NH), 59.4 (NCH_2), 111.7 (C^5 of thiazole), 140.9 (C^4 of thiazole), 159 (N=CH), 171.2 (C^2 of thiazole), 126.8, 128.5, 129.5, 131.7, 133.9, 145.8 (6C, Ar) cm^{-1}; IR (KBr) v: 642 (C—Br), 1564 (N=CH), 3379 (NH); Mass (FAB) m/z: 325 (M^+). Anal. calcd for $C_{12}H_{13}N_4SBr$: C 44.31, H 4.02, N 17.22; found C 44.27, H 3.92, N 17.18.

Synthesis of *N*-{2-(4-nitrobenzylidenehydrazino)-ethyl}-2-aminothiazole (3h) Yield 64%, m.p. 85—87 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.41—3.47 (m, 2H, CH_2NH), 3.76—3.84 (m, 2H, NCH_2), 7.24 (d, J=5.16 Hz, 1H, C^5H of thiazole), 7.40 (d, J=5.16 Hz, 1H, C^4H of thiazole), 7.61 (t, J=4.85 Hz, 1H, NH), 7.70 (t, J=4.32 Hz, 1H, NH), 8.05 (s, 1H, N=CH), 7.02—8.21 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 48.3 (CH_2NH), 56.3 (NCH_2), 114.9 (C^5 of thiazole), 142.6 (C^4 of thiazole), 157.4 (N=CH), 172.9 (C^2 of thiazole), 122.6, 124.9, 128.8, 129.8, 138.8, 147.9 (6C, Ar); IR (KBr) v: 842 (C—N), 1552 (N=O), 1588 (N=CH), 3388 (NH) cm^{-1}; Mass (FAB) m/z: 291 (M^+). Anal. calcd for $C_{12}H_{13}N_5SO_2$: C 49.47, H 4.49, N 24.03; found C 49.42, H 4.44, N 24.00.

Synthesis of *N*-{2-(3-nitrobenzylidenehydrazino)-ethyl}-2-aminothiazole (3i) Yield 62%, m.p. 82—83 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.36—3.42 (m, 2H, CH_2NH), 3.82—3.92 (m, 2H, NCH_2), 7.24 (d, J=5.05 Hz, 1H, C^5H of thiazole), 7.36 (d, J=5.05 Hz, 1H, C^4H of thiazole), 6.68 (t, J=4.80 Hz, 1H, NH), 7.77 (t, J=4.35 Hz, 1H, NH), 7.98 (s, 1H, N=CH), 7.09—8.16 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 45.9 (CH_2NH), 51.6 (NCH_2), 113.6 (C^5 of thiazole), 141.2 (C^4 of thiazole), 156.7 (N=CH), 171.8 (C^2 of thiazole),

122.8, 125.6, 128.9, 133.7, 137.5, 151.5 (6C, Ar); IR (KBr) *v*: 3381 (NH), 1538 (N=O), 1578 (N=CH), 854 (C—N) cm^{-1}; Mass (FAB) *m/z*: 291 (M^+). Anal. calcd for $C_{12}H_{13}N_5SO_2$: C 49.47, H 4.49, N 24.03; found C 49.40, H 4.42, N 23.96.

Synthesis of *N*-{2-(2-nitrobenzylidenehydrazino)-ethyl}-2-aminothiazole (3j) Yield 61%, m.p. 86—88 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.35—3.41 (m, 2H, CH_2N), 3.89—3.94 (m, 2H, NCH_2), 7.26 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.35 (d, J=4.95 Hz, 1H, C^4H of thiazole), 7.64 (t, J=4.72 Hz, 1H, NH), 7.72 (t, J=4.30 Hz, 1H, NH), 8.07 (s, 1H, N=CH), 7.16—8.29 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 47.3 (CH_2N), 55.3 (NCH_2), 113.7 (C^5 of thiazole), 141.8 (C^4 of thiazole), 155.9 (N=CH), 171.5 (C^2 of thiazole), 122.8, 125.6, 127.8, 133.7, 137.9, 149.6 (6C, Ar); IR (KBr) *v*: 842 (C—N), 1548 (N=O), 1579 (N=CH), 3352 (NH) cm^{-1}; Mass (FAB) *m/z*: 291 (M^+). Anal. calcd for $C_{12}H_{13}N_5SO_2$: C 49.47, H 4.49, N 24.03; found C 49.43, H 4.49, N 23.93.

Synthesis of *N*-{2-(4-methoxybenzylidenehydrazino)-ethyl}-2-aminothiazole (3k) Yield 60%, m.p. 71—73 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.28—3.36 (m, 2H, CH_2NH), 3.59 (s, 3H, OCH_3), 3.78—3.86 (m, 2H, NCH_2), 7.19 (d, J=5.16 Hz, 1H, C^5H of thiazole), 7.30 (d, J=5.16 Hz, 1H, C^4H of thiazole), 7.78 (t, J=4.68 Hz, 1H, NH), 7.88 (t, J=4.37 Hz, 1H, NH), 7.92 (s, 1H, N=CH), 6.64—7.78 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 47.6 (CH_2NH), 53.7 (OCH_3), 55.6 (NCH_2), 110.2 (C^5 of thiazole), 138.8 (C^4 of thiazole), 155.8 (N=CH), 169.8 (C^2 of thiazole), 114.7, 117.9, 126.8, 128.9, 131.6, 159.9 (6C, Ar); IR (KBr) *v*: 1574 (N=CH), 2952 (OCH_3), 3369 (NH) cm^{-1}; Mass (FAB) *m/z*: 276 (M^+). Anal. calcd for $C_{13}H_{16}N_4SO$: C 56.49, H 5.83, N 20.27; found C 56.42, H 5.80, N 20.22.

Synthesis of *N*-{2-(4-methylbenzylidenehydrazino)-ethyl}-2-aminothiazole (3l) Yield 61%, m.p. 66—68 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.50 (s, 3H, CH_3), 3.24—3.30 (m, 2H, CH_2NH), 3.72—3.81 (m, 2H, NCH_2), 7.04 (d, J=5.20 Hz, 1H, C^5H of thiazole), 7.19 (d, J=5.20 Hz, 1H, C^4H of thiazole), 7.68 (t, J=4.70 Hz, 1H, NH), 7.74 (t, J=4.30 Hz, 1H, NH), 7.80 (s, 1H, N=CH), 6.49—7.59 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.9 (CH_3), 45.3 (CH_2NH), 54.7 (NCH_2), 108.5 (C^5 of thiazole), 139.2 (C^4 of thiazole), 154.7 (N=CH), 170.2 (C^2 of thiazole), 125.8, 127.8, 129.8, 131.7, 134.9, 139.8 (6C, Ar); IR (KBr) *v*: 1562 (N=CH), 2937 (CH_3), 3352 (NH) cm^{-1}; Mass (FAB) *m/z*: 206 (M^+). Anal. calcd for $C_{13}H_{16}N_4S$: C 59.97, H 6.19, N 21.51; found C 59.92, H 6.14, N 21.50.

Synthesis of *N*-{2-(4-hydroxybenzylidenehydrazino)-ethyl}-2-aminothiazole (3m) Yield 62%, m.p. 75—78 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.12 (s, 1H, OH), 3.37—3.44 (m, 2H, CH_2NH), 3.91—3.99 (m, 2H, NCH_2), 7.16 (d, J=5.15 Hz, 1H, C^5H of thiazole), 7.36 (d, J=5.15 Hz, 1H, C^4H of thiazole), 7.72 (t, J=4.78 Hz, 1H, NH), 7.84 (t, J=4.32 Hz, 1H, NH), 8.01 (s, 1H, N=CH), 6.52—7.69 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 48.8 (CH_2NH), 59.1 (NCH_2), 113.7 (C^5 of thiazole), 140.6 (C^4 of thiazole), 158.7 (N=CH), 172.1 (C^2 of thiazole), 116.7, 118.9, 126.9, 129.8, 131.7, 154.8 (6C, Ar); IR (KBr) *v*: 1569 (N=CH), 3380 (NH), 3478 (OH) cm^{-1}; Mass (FAB) *m/z*: 262 (M^+). Anal. calcd for $C_{12}H_{14}N_4SO$: C 54.94, H 5.37, N 21.35; found C 54.90, H 5.32, N 21.31.

General conventional methods for the synthesis of compounds 4a—4m

A mixture of compounds **3a**—**3m** and thioglycolic acid (1∶1, molar ratio) dissolved in methanol was allowed to react in the presence of catalytic amount of $ZnCl_2$. The reaction mixture was first continuous stirred on a magnetic stirrer for about 2.00—2.45 h, then kept on steam bath for about 2.30—3.45 h at 80—90 ℃. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography and recrystallized from ethanol at room temperature to yield compounds **4a**—**4m**.

Synthesis of *N*-[2-{-2-(phenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4a) Yield 64%, m.p. 70—73 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.29 (s, 2H, SCH_2), 4.52 (s, 1H, NCH), 6.96 (d, J=5.15 Hz, 1H, C^5H of thiazole), 7.25 (d, J=5.15 Hz, 1H, C^4H of thiazole), 6.34—7.49 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 35.6 (CH_2S), 60.5 (NCH), 108.8 (C^5 of thiazole), 138.1 (C^4 of thiazole), 170.6 (C^2 of thiazole), 172.6 (CO, cyclic), 125.8, 126.6, 127.5, 128.7, 130.6, 137.5 (6C, Ar); IR (KBr) *v*: 672 (C—S—C), 1320 (C—N), 1732 (CO cyclic), 2928 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 320 (M^+). Anal. calcd for $C_{14}H_{16}N_4S_2O$: C 52.47, H 5.03, N 17.48; found C 52.40, H 5.00, N 17.43.

Synthesis of *N*-[2-{2-(4-chlorophenyl)-4-oxo-1,3-thiazolidine-imino}-ethyl-2-aminothiazole (4b) Yield 65%, m.p. 88—90 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.58 (s, 2H, SCH_2), 4.86 (s, 1H, NCH), 6.90 (d, J=5.10 Hz, 1H, C^5H of thiazole), 7.38 (d, J=5.10 Hz, 1H, C^4H of thiazole), 6.37—7.74 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.5 (CH_2S), 64.8 (NCH), 113.8 (C^5 of thiazole), 141.7 (C^4 of thiazole), 172.5 (C^2 of thiazole), 174.5 (CO cyclic), 126.7, 127.8, 128.6, 129.7, 130.8, 138.9 (6C, Ar); IR (KBr) *v*: 676 (C—S—C), 753 (C—Cl), 1328 (C—N), 1746 (CO cyclic), 2930 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 355 (M^+). Anal. calcd for $C_{14}H_{15}N_4S_2OCl$: C 47.38, H 4.26, N 15.78; found C 47.33, H 4.24, N 15.75.

Synthesis of *N*-[2-{2-(3-chlorophenyl)-4-oxo-1,3-thiazolidine-imino}-ethyl-2-aminothiazole (4c) Yield 65%, m.p. 91—93 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.61 (s, 2H, SCH_2), 4.82 (s, 1H, NCH), 6.92 (d, J=5.05 Hz, 1H, C^5H of thiazole), 7.36 (d, J=5.05 Hz, 1H, C^4H of thiazole), 6.38—7.72 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 38.6 (CH_2S), 64.2 (NCH), 113.6 (C^5 of thiazole), 142.4 (C^4 of thiazole), 171.6 (C^2 of thiazole), 175.8 (CO cyclic), 125.8, 126.6, 127.7, 128.8, 129.8, 137.9 (6C, Ar); IR (KBr) *v*: 672 (C—S—C), 743 (C—Cl), 1325 (C—N), 1748 (CO cyclic), 2936

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(S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 355 (M^+). Anal. calcd for $C_{14}H_{15}N_4S_2OCl$: C 47.38, H 4.26, N 15.78; found C 47.34, H 4.24, N 15.72.

Synthesis of *N*-[2-{2-(2-chlorophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4d) Yield 66%, m.p. 85—87 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.65 (s, 2H, SCH_2), 4.89 (s, 1H, NCH), 6.95 (d, J=5.05 Hz, 1H, C^5H of thiazole), 7.42 (d, J=5.05 Hz, 1H, C^4H of thiazole), 6.32—7.66 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.2 (CH_2S), 64.2 (NCH), 113.8 (C^5 of thiazole), 142.4 (C^4 of thiazole), 172.8 (C^2 of thiazole), 176.6 (CO cyclic), 126.6, 127.8, 128.7, 129.8, 130.9, 139.6 (6C, Ar); IR (KBr) *v*: 672 (C—S—C), 744 (C—Cl), 1327 (C—N), 1755 (CO cyclic), 2938 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 355 (M^+). Anal. calcd for $C_{14}H_{15}N_4S_2OCl$: C 47.38, H 4.26, N 15.78; found C 47.33, H 4.20, N 15.71.

Synthesis of *N*-[2-{2-(4-bromophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4e) Yield 60%, m.p. 84—86 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.49 (s, 2H, SCH_2), 4.81 (s, 1H, NCH), 6.82 (d, J=5.00 Hz, 1H, C^5H of thiazole), 7.39 (d, J=5.00 Hz, 1H, C^4H of thiazole), 6.41—7.99 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.4 (CH_2S), 62.1 (NCH), 113.8 (C^5 of thiazole), 141.2 (C^4 of thiazole), 172.8 (C^2 of thiazole), 176.6 (CO cyclic), 126.7, 127.9, 128.8, 129.7, 130.9, 139.8 (6C, Ar); IR (KBr) *v*: 678 (C—S—C), 744 (C—Br), 1327 (C—N), 1752 (CO cyclic), 2938 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 399 (M^+). Anal. calcd for $C_{14}H_{15}N_4S_2OBr$: C 42.10, H 3.78, N 14.03; found C 42.05, H 3.72, N 14.00.

Synthesis of *N*-[2-{2-(3-bromophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4f) Yield 64%, m.p. 85—87 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.47 (s, 2H, SCH_2), 4.85 (s, 1H, NCH), 6.88 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.43 (d, J=4.95 Hz, 1H, C^4H of thiazole), 6.45—8.09 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.7 (CH_2S), 63.6 (NCH), 114.4 (C^5 of thiazole), 141.3 (C^4 of thiazole), 171.5 (C^2 of thiazole), 174.4 (CO cyclic), 126.8, 127.8, 128.5, 128.7, 129.8, 138.7 (6C, Ar); IR (KBr) *v*: 672 (C—S—C), 752 (C—Br), 1337 (C—N), 1748 (CO cyclic), 2987 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 399 (M^+). Anal. calcd for $C_{14}H_{15}N_4S_2OBr$: C 42.10, H 3.78, N 14.03; found C 42.07, H 3.74, N 14.01.

Synthesis of *N*-[2-{2-(2-bromophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4g) Yield 66%, m.p. 82—83 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.44 (s, 2H, SCH_2), 4.81 (s, 1H, NCH), 6.84 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.38 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.47—7.98 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.5 (CH_2S), 62.3 (NCH), 110.6 (C^5 of thiazole), 138.9 (C^4 of thiazole), 171.6 (C^2 of thiazole), 174.2 (CO cyclic), 126.6, 127.8, 128.7, 129.7, 129.9, 137.9 (6C, Ar); IR (KBr) *v*: 672 (C—S—C), 744 (C—Br), 1320 (C—N), 1742 (CO cyclic), 2935 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 399 (M^+). Anal. calcd for $C_{14}H_{15}N_4S_2OBr$: C 42.10, H 3.78, N 14.03; found C 42.01, H 3.70, N 13.9.

Synthesis of *N*-[2-{2-(4-nitrophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4h) Yield 64%, m.p. 83—85 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.48 (s, 2H, SCH_2), 4.78 (s, 1H, NCH), 6.82 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.40 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.98—8.34 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.7 (CH_2S), 62.5 (NCH), 113.5 (C^5 of thiazole), 139.9 (C^4 of thiazole), 169.8 (C^2 of thiazole), 173.7 (CO cyclic), 125.7, 126.6, 127.7, 128.7, 129.9, 138.4 (6C, Ar); IR (KBr) *v*: 666 (C—S—C), 840 (C—NO), 1334 (C—N), 1518 (NO_2), 1746 (CO cyclic), 2938 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 365 (M^+). Anal. calcd for $C_{14}H_{15}N_5S_2O_3$: C 46.01, H 4.13, N 19.16; found C 45.91, H 4.10, N 19.12.

Synthesis of *N*-[2-{2-(3-nitrophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4i) Yield 63%, m.p. 80—82 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.47 (s, 2H, SCH_2), 4.86 (s, 1H, NCH), 6.88 (d, J=5.00 Hz, 1H, C^5H of thiazole), 7.37 (d, J=5.00 Hz, 1H, C^4H of thiazole), 7.08—8.27 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.9 (CH_2S), 62.5 (NCH), 111.7 (C^5 of thiazole), 140.8 (C^4 of thiazole), 169.5 (C^2 of thiazole), 172.8 (CO cyclic), 126.8, 127.8, 128.7, 129.6, 131.5, 139.9 (6C, Ar); IR (KBr) *v*: 670 (C—S—C), 864 (C—NO), 1322 (C—N), 1531 (NO_2), 1742 (CO cyclic), 2937 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 365 (M^+). Anal. calcd for $C_{14}H_{15}N_5S_2O_3$: C 46.01, H 4.13, N 19.16; found C 45.94, H 4.08, N 19.12.

Synthesis of *N*-[2-{2-(2-nitrophenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4j) Yield 61%, m.p. 78—81 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.48 (s, 2H, SCH_2), 4.81 (s, 1H, NCH), 6.87 (d, J=5.05 Hz, 1H, C^5H of thiazole), 7.38 (d, J=5.05 Hz, 1H, C^4H of thiazole), 7.12—8.38 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 38.4 (CH_2S), 62.8 (NCH), 111.7 (C^5 of thiazole), 139.5 (C^4 of thiazole), 170.8 (C^2 of thiazole), 171.7 (CO cyclic), 126.8, 127.9, 128.7, 128.8, 129.5, 138.8 (6C, Ar); IR (KBr) *v*: 678 (C—S—C), 845 (C—NO), 1332 (C—N), 1537 (NO_2), 1745 (CO cyclic), 2921 (S—CH_2) cm^{-1}; Mass (FAB) *m/z*: 365 (M^+). Anal. calcd for $C_{14}H_{15}N_5S_2O_3$: C 46.01, H 4.13, N 19.16; found C 45.95, H 4.08, N 19.11.

Synthesis of *N*-[2-{2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4k) Yield 64%, m.p. 76—78 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.40 (s, 2H, SCH_2), 3.65 (s, 3H, OCH_3), 4.78 (s, 1H, NCH), 6.82 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.38 (d, J=4.95 Hz, 1H, C^4H of thiazole), 6.59—7.47 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.4 (CH_2S), 60.6 (NCH), 111.7 (C^5 of thiazole), 137.9 (C^4 of thiazole), 170.2 (C^2 of thiazole), 172.7 (CO cyclic), 126.6, 127.8, 128.6, 129.8, 130.6, 138.9 (6C, Ar); IR (KBr) *v*: 677 (C—S—C), 1329 (C—N), 1739 (CO cyclic), 2922 (S—CH_2), 2966 (OCH_3) cm^{-1}; Mass (FAB) *m/z*: 350 (M^+). Anal. calcd for $C_{15}H_{18}N_4S_2O_2$: C 51.40, H 5.17, N 15.98; found C 51.30, H 5.14, N 15.95.

Synthesis of *N*-[2-{2-(4-methylphenyl)-4-oxo-

1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4l) Yield 63%, m.p. 70—72 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.65 (s, 3H, CH_3), 3.38 (s, 2H, SCH_2), 4.78 (s, 1H, NCH), 6.87 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.31 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.49—7.51 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.6 (CH_3), 33.2 (CH_2S), 63.6 (NCH), 111.7 (C^5 of thiazole), 138.1 (C^4 of thiazole), 167.4 (C^2 of thiazole), 169.2 (CO cyclic), 124.3, 125.7, 127.4, 129.8, 130.7, 131.9, 137.8 (6C, Ar); IR (KBr) ν: 670 (C—S—C), 1332 (C—N), 1741 (CO cyclic), 2975 (S—CH_2), 2970 (CH_3) cm^{-1}; Mass (FAB) m/z: 334 (M^+). Anal. calcd for $C_{15}H_{18}N_4S_2O$: C 53.86, H 5.42, N 16.75; found C 53.82, H 5.36, N 16.72.

Synthesis of *N*-[2-{2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (4m) Yield 63%, m.p. 80—81 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.55 (s, 2H, SCH_2), 4.20 (s, 1H, OH), 4.87 (s, 1H, NCH), 6.85 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.38 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.47—7.61 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 43.2 (CH_2S), 63.8 (NCH), 114.5 (C^5 of thiazole), 140.4 (C^4 of thiazole), 171.6 (C^2 of thiazole), 174.7 (CO, cyclic), 124.7, 125.8, 127.7, 128.9, 129.8, 138.8 (6C, Ar); IR (KBr) ν: 665 (C—S—C), 1329 (C—N), 1742 (CO cyclic), 2928 (S—CH_2), 3480 (OH) cm^{-1}; Mass (FAB) m/z: 336 (M^+). Anal. calcd for $C_{14}H_{16}N_4S_2O_2$: C 49.98, H 4.79, N 16.65; found C 49.92, H 4.74, N 16.60.

General conventional methods for the synthesis of compounds 5a—5m

A mixture of compounds **4a**—**4m** and substituted benzaldehydes (1∶1 molar, ratio) was dissolved in methanol in the presence of alkali metal alkoxide (C_2H_5ONa) and allowed 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—3.30 h at 80—90 ℃. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography and recrystallized from ethanol at room temperature to yield final products compounds **5a**—**5m**.

Synthesis of *N*-[2-{2-(phenyl)-4-oxo-5-(benzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5a) Yield 66%, m.p. 69—71 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.32 (s, 1H, C=CH), 6.90 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.35 (d, J=4.95 Hz, 1H, C^4H of thiazole), 6.71—7.92 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 110.8 (C^5 of thiazole), 139.4 (C^4 of thiazole), 143.8 (C=CH), 146.9 (C=CH), 169.8 (C^2 of thiazole), 124.8, 125.8, 126.4, 126.8, 127.8, 127.7, 128.8, 128.7, 129.6, 130.7, 137.8, 138.8 (12C, Ar); IR (KBr) ν: 1612 (C=CH), 2962 (C=CH) cm^{-1}; Mass (FAB) m/z: 408 (M^+). Anal. calcd for $C_{21}H_{20}N_4S_2O$: C 61.73, H 4.93, N 13.71; found C 61.70, H 4.92, N 13.69.

Synthesis of *N*-[2-{2-(4-chlorophenyl)-4-oxo-5-(4-chlorobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5b) Yield 63%, m.p. 85—87 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.48 (s, 1H, C=CH), 6.90 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.39 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.85—7.72 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 114.2 (C^5 of thiazole), 141.6 (C^4 of thiazole), 145.7 (C=CH), 149.5 (C=CH), 170.3 (C^2 of thiazole), 125.6, 126.8, 126.7, 127.8, 128.8, 129, 129.9, 130.1, 130.8, 131.7, 138.4, 139.2 (12C, Ar); IR (KBr) ν: 774 (C—Cl), 1625 (C=CH), 2980 (C=CH) cm^{-1}; Mass (FAB) m/z: 477 (M^+). Anal. calcd for $C_{21}H_{18}N_4S_2OCl_2$: C 52.83, H 3.80, N 11.73; found C 52.80, H 3.78, N 11.70.

Synthesis of *N*-[2-{-2-(3-chlorophenyl)-4-oxo-5-(3-chlorobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5c) Yield 62%, m.p. 86—88 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.44 (s, 1H, C=CH), 7.00 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.37 (d, J=4.95 Hz, 1H, C^4H of thiazole), 6.71—7.63 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 111.7 (C^5 of thiazole), 140.7 (C^4 of thiazole), 148.6 (C=CH), 154.3 (C=CH), 172.6 (C^2 of thiazole), 123.5, 124.8, 125.9, 125.8, 126.2, 126.8, 127.8, 128.9, 129.5, 129.8, 138.7, 140.9 (12C, Ar); IR (KBr) ν: 772 (C—Cl), 1623 (C=CH), 2980 (C=CH) cm^{-1}; Mass (FAB) m/z: 477 (M^+). Anal. calcd for $C_{21}H_{18}N_4S_2OCl_2$: C 52.83, H 3.80, N 11.73; found C 52.81, H 3.74, N 11.67.

Synthesis of *N*-[2-{2-(2-chlorophenyl)-4-oxo-5-(2-chlorobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5d) Yield 64%, m.p. 81—83 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.45 (s, 1H, C=CH), 6.94 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.38 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.71—7.63 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 112.9 (C^5 of thiazole), 140.2 (C^4 of thiazole), 147.6 (C=CH), 153.2 (C=CH), 172.9 (C^2 of thiazole), 124.5, 125.8, 126.7, 127.3, 127.8, 128.8, 129.6, 130.8, 131.8, 132.5, 138.6, 141.1 (12C, Ar); IR (KBr) ν: 762 (C—Cl), 1628 (C=CH), 2987 (C=CH) cm^{-1}; Mass (FAB) m/z: 477 (M^+). Anal. calcd for $C_{21}H_{18}N_4S_2OCl_2$: C 52.83, H 3.80, N 11.73; found C 52.78, H 3.74, N 11.67.

Synthesis of *N*-[2-{2-(4-bromophenyl)-4-oxo-5-(4-bromobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5e) Yield 63%, m.p. 80—82 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.40 (s, 1H, C=CH), 6.92 (d, J=5.00 Hz, 1H, C^5H of thiazole), 7.36 (d, J=5.00 Hz, 1H, C^4H of thiazole), 6.80—7.77 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 116.9 (C^5 of thiazole), 138.7 (C^4 of thiazole), 144.8 (C=CH), 146.8 (C=CH), 170.5 (C^2 of thiazole), 120.8, 121.8, 124.5, 125.7, 126.8, 127.5, 127.9, 128.8, 130.4, 131.5, 137.8, 139.9 (12C, Ar) cm^{-1}; IR (KBr) ν: 645 (C—Br), 1629 (C=CH), 2980 (C=CH); Mass (FAB) m/z: 566 (M^+). Anal. calcd for $C_{21}H_{18}N_4S_2OBr_2$: C 44.53, H 3.20, N 9.89; found C 44.50, H 3.18, N 9.87.

Synthesis of *N*-[2-{2-(3-bromophenyl)-4-oxo-5-(3-bromobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5f) Yield 65%, m.p. 78—80 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.44 (s, 1H, C=CH), 6.92 (d, J=5.15 Hz, 1H, C^5H of thiazole), 7.35 (d, J=5.15

Hz, 1H, C^4H of thiazole), 6.78—7.79 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 113.5 (C^5 of thiazole), 140.5 (C^4 of thiazole), 144.8 (C=CH), 150.2 (C=CH), 172.5 (C^2 of thiazole), 121.7, 123.8, 125.6, 126.8, 127.7, 128.5, 128.9, 129.7, 131.6, 132.8, 138.6, 140.8 (12C, Ar); IR (KBr) ν: 645 (C—Br), 1628 (C=CH), 2980 (C=CH) cm^{-1}; Mass (FAB) *m/z*: 566 (M^+). Anal. calcd for $C_{21}H_{18}N_4S_2OBr_2$: C 44.53, H 3.20, N 9.791; found C 44.45, H 3.12, N 9.81.

Synthesis of *N*-[2-{2-(2-bromophenyl)-4-oxo-5-(2-bromobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5g) Yield 64%, m.p. 80—82 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.51 (s, 1H, C=CH), 6.92 (d, J=5.10 Hz, 1H, C^5H of thiazole), 7.35 (d, J=5.10 Hz, 1H, C^4H of thiazole), 6.79—7.75 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 113.1 (C^5 of thiazole), 142.5 (C^4 of thiazole), 144.4 (C=CH), 148.3 (C=CH), 172.3 (C^2 of thiazole), 122.5, 124.8, 125.7, 126.7, 127.8, 128.7, 129.8, 130.6, 131.7, 132.8, 137.9, 138.7 (12C, Ar); IR (KBr) ν: 642 (C—Br), 1624 (C=CH), 2980 (C=CH) cm^{-1}; Mass (FAB) *m/z*: 566 (M^+). Anal. calcd for $C_{21}H_{18}N_4S_2OBr_2$: C 44.53, H 3.20, N 9.791; found C 44.51, H 3.10, N 9.79.

Synthesis of *N*-[2-{2-(4-nitrophenyl)-4-oxo-5-(4-nitrobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5h) Yield 62%, m.p. 77—79 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.58 (s, 1H, C=CH), 7.09 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.38 (d, J=4.95 Hz, 1H, C^4H of thiazole), 6.89—7.81 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.4 (CH_2S), 63.2 (NCH), 112.6 (C^5 of thiazole), 141.2 (C^4 of thiazole), 145.8 (C=CH), 149.3 (C=CH), 171.5 (C^2 of thiazole), 122.7, 123.8, 125.7, 126.2, 126.8, 127.4, 127.9, 128.5, 129.7, 130.9, 137.7, 138.9 (12C, Ar); IR (KBr) ν: 858 (C—NO), 1532 (NO_2), 1628 (C=CH), 2980 (C=CH) cm^{-1}; Mass (FAB) *m/z*: 498 (M^+). Anal. calcd for $C_{21}H_{18}N_6S_2O_5$: C 50.59, H 3.63, N 16.85; found C 50.52, H 3.61, N 16.81.

Synthesis of *N*-[2-{2-(3-nitrophenyl)-4-oxo-5-(3-nitrobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5i) Yield 63%, m.p. 81—83 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.54 (s, 1H, C=CH), 7.01 (d, J=4.95 Hz, 1H, C^5H of thiazole), 7.40 (d, J=4.95 Hz, 1H, C^4H of thiazole), 6.87—7.86 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 112.2 (C^5 of thiazole), 140.4 (C^4 of thiazole), 144.6 (C=CH), 149.8 (C=CH), 172.7 (C^2 of thiazole), 120.7, 122.8, 123.8, 125.7, 126.9, 127.8, 128.9, 129.7, 131.8, 132.7, 135.6, 136.8 (12C, Ar); IR (KBr) ν: 852 (C—NO), 1515 (NO_2), 1622 (C=CH), 2980 (C=CH) cm^{-1}; Mass (FAB) *m/z*: 498 (M^+). Anal. calcd for $C_{21}H_{18}N_6S_2O_5$: C 50.59, H 3.63, N 16.85; found C 50.54, H 3.56, N 16.80.

Synthesis of *N*-[2-{2-(2-nitrophenyl)-4-oxo-5-(2-nitrobenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5j) Yield 60%, m.p. 86—88 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.44 (s, 1H, C=CH), 6.92 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.36 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.88—7.81 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 112.8 (C^5 of thiazole), 140.2 (C^4 of thiazole), 144.5 (C=CH), 148.9 (C=CH), 171.4 (C^2 of thiazole), 123.6, 124.6, 125.7, 126.2, 126.8, 127.8, 128.8, 129.7, 130.4, 132.5, 137.5, 139.9 (12C, Ar); IR (KBr) ν: 860 (C—NO), 1528 (NO_2), 1635 (C=CH), 2978 (C=CH) cm^{-1}; Mass (FAB) *m/z*: 498 (M^+). Anal. calcd for $C_{21}H_{18}N_6S_2O_5$: C 50.59, H 3.63, N 16.85; found C 50.52, H 3.62, N 16.81.

Synthesis of *N*-[2-{2-(4-methoxyphenyl)-4-oxo-5-(4-methoxybenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5k) Yield 66%, m.p. 78—79 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.68 (s, 3H, OCH_3), 6.40 (s, 1H, C=CH), 6.92 (d, J=4.85 Hz, 1H, C^5H of thiazole), 7.42 (d, J=4.85 Hz, 1H, C^4H of thiazole), 6.82—7.78 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 109.4 (C^5 of thiazole), 138.7 (C^4 of thiazole), 142.1 (C=CH), 145.5 (C=CH), 170.3 (C^2 of thiazole), 111.7, 112.7, 113.8, 114.2, 124.8, 126.9, 127.5, 128.8, 129.7, 138.6, 154.8, 157.8 (12C, Ar); IR (KBr) ν: 1593 (C=CH), 2982 (C=CH), 2974 (OCH_3) cm^{-1}; Mass (FAB) *m/z*: 468 (M^+). Anal. calcd for $C_{23}H_{24}N_4S_2O_3$: C 58.95, H 5.16, N 11.95; found C 58.92, H 5.12, N 11.91.

Synthesis of *N*-[2-{2-(4-methylphenyl)-4-oxo-5-(4-methylbenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5l) Yield 60%, m.p. 74—76 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.61 (s, 3H, CH_3) 6.45 (s, 1H, C=CH), 6.92 (d, J=4.85 Hz, 1H, C^5H of thiazole), 7.32 (d, J=4.85 Hz, 1H, C^4H of thiazole), 6.79—7.67 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 107.7 (C^5 of thiazole), 138.7 (C^4 of thiazole), 140.7 (C=CH), 144.7 (C=CH), 170.2 (C^2 of thiazole), 122.9, 124.8, 125.9, 126.8, 127.9, 128.7, 129.9, 130.5, 133.8, 134.6, 135.9, 137.8 (12C, Ar); IR (KBr) ν: 1580 (C=CH), 2972 (C=CH) 1347 (CH_3) cm^{-1}; Mass (FAB) *m/z*: 436 (M^+). Anal. calcd for $C_{23}H_{24}N_4S_2O$: C 63.27, H 5.54, N 12.83; found C 63.25, H 5.51, N 12.80.

Synthesis of *N*-[2-{2-(4-hydroxyphenyl)-4-oxo-5-(4-hydroxybenzylidene)-1,3-thiazolidine}-iminoethyl]-2-aminothiazole (5m) Yield 60%, m.p. 86—87 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.22 (s, 1H, OH), 6.38 (s, 1H, C=CH), 6.80 (d, J=4.90 Hz, 1H, C^5H of thiazole), 7.35 (d, J=4.90 Hz, 1H, C^4H of thiazole), 6.71—7.62 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 112.6 (C^5 of thiazole), 141.2 (C^4 of thiazole), 143.6 (C=CH), 149.6 (C=CH), 169.6 (C^2 of thiazole), 116.8, 120.9, 122.8, 123.7, 124.8, 126.8, 127.9, 128.7, 130.7, 137.6, 155.6, 157.8 (12C, Ar); IR (KBr) ν: 1628 (C=CH), 2980 (C=CH), 3618 (OH) cm^{-1}; Mass (FAB) *m/z*: 440 (M^+). Anal. calcd for $C_{21}H_{20}N_4S_2O_3$: C 57.25, H 4.57, N 12.71; found C 57.21, H 4.53, N 12.67.

Results and discussion

The reaction of 1-bromo-2-chloroethane with 2-aminothiazole 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 1349 and 758 cm^{-1} in the IR spectrum. The IR

spectrum confirms the formation of compound **1**. 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 3372 and 3434 cm^{-1} respectively, while absorption of C—Cl has disappeared. This clearly indicate that compound **1** gives the substitution reaction with hydrazine hydrate. This fact was also supported by ^1H and ^{13}C NMR spectra because two signals appeared in the ^1H NMR spectrum for NH and NH_2 at δ 6.73 and 5.56 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 compounds **3a**—**3m**, which were confirmed by IR, ^1H NMR and ^{13}C NMR spectra. In the IR spectra an absorption was found in the range of 1545—1588 cm^{-1} while a strong signal appeared in the range of δ 7.80—8.07 and δ 151.5—159.5 in the ^1H NMR and ^{13}C NMR spectra for N=CH of compounds **3a**—**3m**, respectively. The facts were also supported by the disappearance of the signal of NH_2 in the ^1H NMR spectra. The compounds **3a**—**3m** on reaction with equimolar amount of thioglycolic acid in the presence of $ZnCl_2$ (acted as a catalyst) in the trace amount gave the cycloaddition reaction and produced a five membered thiazolidinone ring, compounds **4a**—**4m**. The compounds **4a**—**4m** showed a characteristic absorption for the cyclic carbonyl group in the range of 1732—1755 cm^{-1} in the IR spectra. The ^1H 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 3.29—3.65. The ^{13}C NMR spectra of compounds **4a**—**4m** also supported the fact that cyclic carbonyl group was present and a signal appeared in the range of δ 176.6—169.2. 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 4.52—4.89 in the ^1H NMR spectra of compounds **4a**—**4m**. The compounds **4a**—**4m** underwent the Knoevenagel condensation reaction with substituted benzaldehydes in the presence of alkali metal alkoxide (C_2H_5ONa) to afford the compounds **5a**—**5m**. In the ^1H NMR spectra of the compounds **5a**—**5m**, we found the disappearance of two methylene protons of compounds **5a**—**5m** and an appearance of a new signal for C=CH in the range of δ 6.32—6.58 in the ^1H NMR and two new signals for C=CH and C=CH appearing in the range of δ 140.7—148.6 and δ 144.7—154.3 in the ^{13}C NMR spectra of the compounds **5a**—**5m**. These above facts clearly confirmed the synthesis of all final products. All above compounds **1**, **2**, **3a**—**3m, 4a**—**4m** and **5a**—**5m** were also synthesized by microwave method. Yield and reaction time data were given in Table 1.

Pharmacology

Series of newly synthesized compounds were highly active against selected microorganisms. The minimal inhibition values were determined using the filter paper disc diffusion method and the concentrations have been used in μg/mL. All the final synthesized compounds **5a**—**5m** have been screened *in vitro* for their antibacterial activities against *B. subtilis*, *E. coli* and *S. aureus* and antifungal activities against *A. niger*, *A. flavus* and *C. albicans*. Standards for antibacterial and antifungal activities Streptomycin and Griseofulvin were used respectively. Standards were also screened under the similar conditions for comparison. The antitubercular activity was screened against the *M. tuberculosis.* For the antitubercular activity Isoniazid and Rifampicin were used as standards and also screened under the similar conditions.

We have investigated that compounds have a structure-activity relationship because activity of compounds varies with substitution. Nitro group containing compounds (**5h**, **5i** and **5j**) showed higher activity than chloro (**5c**, **5d**), or bromo (**5e**, **5f**) group containing compounds. Chloro and bromo derivatives also have higher activity than other rested compounds. On the basis of SAR, it could be concluded that the activity of compounds depends on electron withdrawing nature of the substituted groups. The sequence of the activity is as follows:

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

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 μg/mL. The diameters of the inhibition zones in mm are given in Table 2.

Antifungal activity

The above synthesized compounds were screened against selected fungi, and their determined minimal inhibition zones in mm and were presented in Table 2. Concentrations of compounds were given in μg/mL.

Antitubercular activity

The above synthesized compounds were screened against *M. tuberculosis* (H37Rv strain) using L. J. medium (Conventional) method at 25, 50 μg/mL and lower concentrations. The results are shown in Table 3. Antitubercular drugs Isoniazid and Rifampicin (MIC range 0.2—4.5 μg/mL) were taken as standards.

Conclusion

Compound **5a**—**5m** were synthesized by an efficient route and screened for their antibacterial, antifungal and antitubercular activity against selected micro-

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

Comp.	Yield/%		Reaction time			Comp.	Yield/%		Reaction time		
	Conv.	MW	Conv./h		MW/min		Conv.	MW	Conv./h		MW/min
			1st stirring	2nd refluxing					1st stirring	2nd refluxing	
1	62	77	6.15	—	4.00	**4g**	66	80	2.30	3.30	3.30
2	70	86	5.00	—	3.10	**4h**	64	77	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	3.40	**4j**	61	84	2.30	3.30	3.10
3c	67	84	3.15	2.00	3.35	**4k**	64	83	2.15	3.30	3.20
3d	65	85	3.15	1.45	4.10	**4l**	63	76	2.15	3.30	3.25
3e	66	84	2.30	2.15	3.15	**4m**	63	80	2.00	3.45	3.20
3f	65	83	3.30	2.30	3.10	**5a**	66	79	2.30	3.15	3.35
3g	63	80	3.30	2.00	2.40	**5b**	63	78	2.00	3.00	3.20
3h	64	77	3.30	2.30	3.15	**5c**	62	82	2.00	2.45	3.20
3i	62	78	3.30	1.45	3.30	**5d**	64	82	2.15	2.45	3.15
3j	61	80	3.30	2.30	2.55	**5e**	63	83	2.15	3.15	3.30
3k	60	81	3.30	2.30	3.50	**5f**	65	82	2.15	3.00	3.10
3l	61	79	3.30	2.15	4.15	**5g**	64	78	2.30	3.15	3.45
3m	62	80	3.30	2.00	3.25	**5h**	62	78	2.00	3.30	3.30
4a	64	76	2.45	3.00	3.30	**5i**	63	81	2.00	3.30	3.15
4b	65	79	2.30	3.15	3.35	**5j**	60	80	2.15	3.15	3.10
4c	65	85	2.45	2.30	3.15	**5k**	66	81	2.00	3.30	3.20
4d	66	82	2.30	2.30	3.10	**5l**	60	75	2.15	3.15	3.45
4e	60	81	2.30	3.00	3.30	**5m**	60	75	2.15	3.15	3.45
4f	64	83	2.15	3.15	3.00	—	—	—	—	—	—

Table 2 Antibacterial and antifungal activities of compounds **5a**—**5m**[a]

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

[a] Concentrations given in μg/mL.

Table 3 Antitubercular activities of compounds **5a**—**5m**[a]

Comp.	Activity/%		Comp.	Activity/%		Comp.	Activity/%	
	25	50		25	50		25	50
5a	32	55	**5f**	60	79	**5k**	38	60
5b	62	82	**5g**	49	76	**5l**	42	55
5c	63	80	**5h**	62	82	**5m**	45	66
5d	52	80	**5i**	57	83	—	—	—
5e	50	78	**5j**	58	81	—	—	—
Standard	100	100	Standard	100	100	Standard	100	100

[a] Concentrations given in μg/mL.

organisms. The investigation of antimicrobial data revealed that the compounds **5c**, **5d**, **5e**, **5f**, **5h**, **5i** and **5j** displayed high activies in the series, compounds **5b**, **5g** and **5m** showed moderate activity and the rest compounds showed less activity against all the strains compared with standard drugs.

Acknowledgement

The authors are thankful to SAIF, Central Drugs Research Institute Lucknow (India) for providing spectral and analytical data of the compounds. We are thankful to Head, Department of Biotechnology, Dr. H. S. Gour, University (A Central University), Sagar (India) for antimicrobial (antibacterial and antifungal) and Microcare laboratory and Tuberculosis Research Center Surat, Gujrat (India) for antituberculosis activity. We are also thankful to Head, Department of Chemistry Dr. H. S. Gour, University (A Central University), Sagar (India) for giving the facilities to carry out the work.

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(E1009299 Cheng, F.; Fan, Y.)

