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Synthesis and biological activity of N-[-3-{-(4-substitutedaryl-3-chloro-2-oxo-azetidine)-carbamyl}propyl]-2-aminothiazole by conventional and microwave irradiation

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ABSTRACT

*A new series of N-[3-{-(4-subtitutedaryl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole **4(a-s)** have been synthesized from 2-aminothiazole as a starting material by conventional as well as microwave methods. All the synthesized compound 4**(a-s)** were screened for their antibacterial and antifungal activities against some selected bacteria and fungi with their MIC values and antitubercular activity screened against M. 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.*

Keywords: Synthesis, 2-aminothiazole, azetidinone, antimicrobial, antitubercular.

INTRODUCTION

Thiazole derivatives are five membered heterocyclic compounds containing nitrogen and sulpher atoms in their structure and are proved to be clinically useful agents against different kinds of diseases. It has been shown to possess a broad spectrum of biological activity. Antimicrobial [1], Antiinflammatory [2] observed in some Thiazole derivatives. Some synthetic Thiazole derivatives have exhibited a range of biological activities such as antitubercular [3], antitumor [4], antiprotozoal [5], antibacterial [6], and antifungal [6,7] etc. β-lactam ring containing heterocycles are still the most prescribed used in medicine. They are considered as an important contribution of science to humanity. The long term of β-lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organism. Azetidinone which are part of the antibiotic structure, are known to exhibits interesting biological activities such as antimicrobial [8], antibacterial [9], anticancer [10], Brain Cholinergic Activity [11], mutagenic properties [12] etc. A new series of N-[3-{-(4-subtitutedaryl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole **4(a-s)** have been synthesized by conventional as well as microwave methods. All the synthesized compound 4**(a-s)** were screened for their antibacterial and antifungal activities against some selected bacteria and fungi with their MIC values and

antitubercular activity screened against M. *tuberculosis* (H37Rv strain). 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.

MATERIAL AND METHODS

Melting points were taken in open capillaries and are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates using MeOH: $CHCl_3$ system (2:8). The spot was visualized by exposing dry plate at 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 NMR and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 and 75 MHz using TMS as an internal standard respectively. 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. 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.

General procedure for the synthesis of compound 1, **2**, **3(a-s)** and **4(a-s) by microwave method**

A solid supported mixture of compounds (1:1 mole) was mixed thoroughly in open glass vessel and subjected to the microwave irradiation at low power setting (25%, 200W) for about 3.00-4.25 mins., The completion of reaction was monitored by silica gel- G coated TLC plate and visualized in the iodine vapors chamber. After the completion of the reaction, reaction mixture was allowed to cool on an ice bath, filtered the products and purified over column chromatography. The products were recrystallized from ethanol at room temperature to yield compound **1**, **2, 3(a-s)** and **4(a-s)**.

General procedure for the synthesis of compound 1 by conventional method

A mixture of 2-aminothiazole and 1-bromo-3-chloropropane (1:1 mole) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 7.45 hrs. 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-(3-chloropropyl)-2-aminothiazole (1)

Yield: 58%, m.p. 75-77 ºC; Anal. Calcd for $C_6H_9N_2SCl$: C,40.79, H,5.13, N,15.85%; found C,40.72, H,5.10, N,15.81%; IR (cm^{-1}): 736 (C-Cl), 884 (C-S), 1332 (N-CH_2), 1560 (C=C), 2885-3086 (CH), 3382 (NH); ^{1}H NMR (δ): 2.35 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.42 (t, 2H, J = 7.30 Hz, $CH_2CH_2\underline{CH_2}$-Cl), 4.24 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 6.78 (d, 1H, J = 4.40 Hz, C_5H of thiazole), 7.16 (d, 1H, J = 4.40 Hz, C_4H of thiazole) 7.89 (t, 1H, J = 4.30 Hz, NH); ^{13}C NMR (δ): 32.4 ($CH_2\underline{CH_2}CH_2$), 40.8 ($CH_2CH_2\underline{CH_2}$-Cl), 46.1 (N-$CH_2CH_2CH_2$), 109.3 (C_5 of thiazole), 139.2 (C_4 of thiazole), 169 (C_2 of thiazole), Mass (FAB): $176M^{+}$.

General procedure for the synthesis of compound 2

A mixture of compound **1** and urea (1:1 mole) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 6.30 hrs. The product filtered and purified over a column chromatography. The purified product was recrystallized from ethanol at room temperature to yield compounds **2.**

Synthesis of N-{3-(aminocarbamyl)-propyl}-2-aminothiazole (2)
Yield: 72%, m.p. 57-59 ºC; Anal. Calcd for $C_7H_{12}N_4OS$: C,41.98, H,6.03, N,27.97 %; found C,41.87, H,5.98, N,27.89 %; IR: 874 (C-S), 1238 (C-N), 1662 (C=O), 3371 (NH), 3423 (NH_2); ^{1}H NMR (δ): 2.41 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.42 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 4.20 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.63 (t, 1H, J = 4.75 Hz, NHCO), 5.83 (br s, 2H, $CONH_2$), 6.78 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.16 (d, 1H, J = 4.75 Hz, C_4H of thiazole), 7.95 (t, 1H, J = 4.35 Hz, NH); ^{13}C NMR (δ): 32.7 ($CH_2\underline{CH_2}CH_2$), 39.1 ($CH_2CH_2\underline{CH_2}$NH), 44.7 (N-CH_2CH_2 CH_2), 109.7 (C_5 of thiazole), 138.1 (C_4 of thiazole), 163.4 (CO), 168.9 (C_2 of thiazole); Mass(FAB): 200M^+.

General procedure for the synthesis of compound 3(a-s) by conventional method
A mixture of compound 2 and several substitutedbenzaldehydes (1:1 mole) were dissolved in methanol at room temperature respectively and allow to reaction. The reaction mixture was first continuously stirred on a magnetic stirrer for about 3.30-3.45 hrs. then kept on a steam bath for about 1.30-2.30 hrs. The products were cooled and filtered at room temperature. The filtered products were purified over a column chromatography and recrystallized from ethanol at room temperature to yield compound **3(a-s).**

Synthesis of N-{3-(benzylidencarbamyl)-propyl}-2-aminothiazole (3a)
Yield: 60%, m.p. 65-67 ºC; Anal. Calcd for $C_{14}H_{16}N_4OS$: C,58.31, H,5.59, N,19.42%; found C,58.25, H,5.50, N,19.35%; IR: 3368 (NH), 1660 (C=O), 1551 (N=CH); ^{1}H NMR (δ): 2.28 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.41 (m, 2H, $CH_2CH_2\underline{CH_2}$-N), 4.16 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.56 (t, 1H, J = 4.80 Hz, NHCO), 7.28 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 6.60 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.84 (s, 1H, N=CH), 7.98 (t, 1H, J = 4.32 Hz, NH), 6.40-7.11 (m, 5H, Ar-H); ^{13}C NMR (δ): 32.2 ($CH_2\underline{CH_2}CH_2$), 39.2 ($CH_2CH_2\underline{CH_2}$-N), 45.4 (N-$CH_2CH_2CH_2$), 113.2 (C_5 of thiazole), 140 (C_4 of thiazole), 144.2 (N=CH), 161.7 (CO), 169.9 (C_2 of thiazole), 124.2, 125.6, 127.8, 129.4, 131.7, 137.8 (6C, Ar); Mass (FAB): 288M^+.

Synthesis of N-{3-(4-chlorobenzylidencarbamyl)-propyl}-2-aminothiazole (3b)
Yield: 62%, m.p. 80-82 ºC; Anal. Calcd for $C_{14}H_{15}N_4OSCl$: C,52.09, H,4.68, N,17.35%; found C,52.03, H,4.62, N,17.32%; IR: 3374 (NH), 1676 (C=O), 1566 (N=CH), 740 (C-Cl); ^{1}H NMR (δ): 2.36 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.53 (m, 2H, $CH_2CH_2\underline{CH_2}$-N), 4.34 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.55 (t, 1H, J = 4.85 Hz, NHCO), 7.38 (d,1H, J = 4.85 Hz, C_4H of thiazole), 7.18 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.96 (s, 1H, N=CH), 8.02 (t, 1H, J = 4.34 Hz, NH), 6.68-7.81 (m, 4H, Ar-H); ^{13}C NMR (δ): 34.9 ($CH_2\underline{CH_2}CH_2$), 41.4 ($CH_2CH_2\underline{CH_2}$-NH), 47.8 (N-$CH_2CH_2CH_2$), 115.3 (C_5 of thiazole), 143.7 (C_4 of thiazole), 152 (N=CH), 166.2 (CO), 172.9 (C_2 of thiazole), 125.2, 128.1, 129.4, 130.2, 134.5, 140.6 (6C, Ar); Mass (FAB): 322M^+.

Synthesis of N-{3-(3-chlorobenzylidencarbamyl)-propyl}-2-aminothiazole (3c)
Yield: 63%, m.p.84-85 ºC; Anal. Calcd for $C_{14}H_{15}N_4OSCl$: C,52.09, H,4.68, N,17.35%; found C,52.01, H,4.60, N,1.24%; IR: 743 (C-Cl), 1561 (N=CH), 1675 (C=O), 3374(NH); ^{1}H NMR (δ): 2.45 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.51 (m, 2H, $CH_2CH_2\underline{CH_2}$-N), 3.86 m, 2H, N-$\underline{CH_2}CH_2$ CH_2), 5.65 (t, 1H, J = 4.78 Hz, NHCO), 7.14 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.29 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.92 (s, 1H, N=CH), 8.05 (t, 1H, J = 4.35 Hz, NH), 7.1-7.8 (m, 4H, Ar-H); ^{13}C NMR (δ): 33.4 ($CH_2\underline{CH_2}CH_2$), 43.4 ($CH_2CH_2\underline{CH_2}$-N), 47.5 (N-$CH_2CH_2CH_2$), 114 (C_5 of thiazole), 142.1 (C_4 of thiazole), 147.4 (N=CH), 165 (CO), 171 (C2 of thiazole), 126.4, 128.7, 130.2, 132.4, 136.5, 137.2 (6C, Ar); Mass (FAB): 322M^+.

Synthesis of N-{3-(2-chlorobenzylidencarbamyl)-propyl}-2-aminothiazole (3d)
Yield: 63%, m.p. 78-80 ºC; Anal. Calcd for $C_{14}H_{15}N_4OSCl$: C,52.09, H,4.68, N,17.35%; found C,52.0, H,4.61, N,17.31%; IR: 740 (C-Cl), 1564 (N=CH), 1673 (C=O), 3378 (NH); ^{1}H NMR (δ):

2.42 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.48 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.80 (m, 2H, N-$\underline{CH_2}CH_2$ CH_2), 5.53 (t, 1H, J = 4.80 Hz, NHCO), 7.15 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 7.34 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.87 (s, 1H, N=CH), 8.10 (t, 1H, J = 4.37 Hz, NH), 7.2-7.9 (m, 4H, Ar-H); ^{13}C NMR (δ): 33.7 ($CH_2\underline{CH_2}CH_2$), 44.2 ($CH_2CH_2\underline{CH_2}$-N), 48.2 (N-$CH_2CH_2CH_2$), 111.9 (C_5 of thiazole), 141.9 (C_4 of thiazole), 150.6 (N=CH), 164.5 (CO), 170.1 (C_2 of thiazole), 126.4, 128.5, 128.9, 129.3, 132.5, 139.4 (6C, Ar); Mass (FAB): 322M^+.

Synthesis of N-{3-(4-bromobenzylidencarbamyl)-propyl}-2-aminothiazole (3e)

Yield: 65%, m.p. 75-77 ºC; Anal. Calcd for $C_{14}H_{15}N_4OSBr$: C,45.78, H,4.11, N,15.25%; found C,45.72, H,4.04, N,15.17%; IR: 636 (C-Br), 1558 (N=CH), 1666 (C=O), 3368 (NH); ^{1}H NMR(δ): 2.36 (m, 2H, CH2CH2CH2), 3.49 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.76 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.59 (t, 1H, J = 4.85 Hz, NHCO), 7.02 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.91 (s, 1H, N=CH), 8.05 (t, 1H, J = 4.38 Hz, NH), 7.39-7.68 (m, 4H, Ar-H); ^{13}C NMR (δ): 33.1 ($CH_2\underline{CH_2}CH_2$), 43.2 ($CH_2CH_2\underline{CH_2}$-NH), 46.5 (N-$CH_2CH_2CH_2$), 111.7 (C_5 of thiazole), 140.4 (C_4 of thiazole), 150 (N=CH), 161.1 (CO), 169.1 (C_2 of thiazole), 123.3, 126.7, 129.8, 132.2, 133.4, 137.6 (6C, Ar); Mass (FAB): 367M^+.

Synthesis of N-{3-(3-bromobenzylidencarbamyl)-propyl}-2-aminothiazole (3f)

Yield: 64%, m.p. 72-73 ºC; Anal. Calcd for $C_{14}H_{15}N_4OSBr$: C,45.78, H,4.11, N,15.25%; found C,45.72, H,4.04, N,15.22%; IR: 642 (C-Br), 1563 (N=CH), 1669 (C=O), 3366 (NH); ^{1}H NMR (δ): 2.39 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.50 (m, 2H, $CH_2CH_2\underline{CH_2}$ –NH), 3.78 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.55 (t, 1H, J = 4.77 Hz, NHCO), 7.07 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.29 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.88 (s, 1H, N=CH), 8.13 (t, 1H, J = 4.35 Hz, NH), 7.23-7.90 (m, 4H, Ar-H); ^{13}C NMR (δ): 41.3 ($CH_2\underline{CH_2}CH_2$), 49.4 ($CH_2CH_2\underline{CH_2}$-N), 47.1 (N-$\underline{CH_2}CH_2CH_2$), 112.6 (C_5 of thiazole), 141.5 (C_4 of thiazole), 151.6 (N=CH), 163.9 (CO), 172.4 (C_2 of thiazole), 124.1, 126.7, 129.2, 131.5, 137.7, 141.2 (6C, Ar); Mass (FAB): 367M^+.

Synthesis of N-{3-(2-bromobenzylidencarbamyl)-propyl}-2-aminothiazole (3g)

Yield: 66%, m.p. 74-76 ºC; Anal. Calcd for $C_{14}H_{15}N_4OSBr$: C,45.78, H,4.11, N,15.25%; found C,45.71, H,4.03, N,15.11%; IR: 628 (C-Br), 1558 (N=CH), 1672 (C=O), 3367 (NH); ^{1}H NMR (δ): 2.35 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.31 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.77 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.49 (t, 1H, J = 4.78 Hz, NHCO), 7.02 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.26 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 8.02 (s, 1H, N=CH), 8.15 (t, 1H, J = 4.31 Hz, NH), 7.31-7.63 (m, 4H, Ar-H); ^{13}C NMR(δ): 45.5 ($CH_2\underline{CH_2}CH_2$), 51.1 ($CH_2CH_2\underline{CH_2}$-NH), 51.4 (N-$CH_2CH_2CH_2$), 109.7 (C_5 of thiazole), 139.9 (C_4 of thiazole), 152 (N=CH), 154.1 (CO), 171.6 (C_2 of thiazole), 126.4, 128.5, 129.3, 131.1, 133.5, 141.4 (6C, Ar); Mass (FAB): 367M^+.

Synthesis of N-{3-(4-nitrobenzylidencarbamyl)-propyl}-2-aminothiazole (3h)

Yield: 64%, m.p. 75-77 ºC; Anal. Calcd for $C_{14}H_{15}N_5O_3S$: C,50.44, H,4.53, N,21%; found C,50.41, H,4.50, N,20.93%; IR: 847 (C-N), 1538 (N=O), 1568 (N=CH), 1678 (C=O), 3368 (NH); ^{1}H NMR (δ): 2.39 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.59 (m, 2H, $CH_2CH_2\underline{CH_2}$-N), 3.84 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.41 (t, 1H, J = 4.75 Hz, NHCO), 7.18 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.42 (d, 1H, J = 4.75 Hz, C_4H of thiazole), 8.07 (s, 1H, N=CH), 8.12 (t, 1H, J = 4.28 Hz, NH), 7.32-7.91 (m, 4H, Ar-H); ^{13}C NMR (δ): 40.7 ($CH_2\underline{CH_2}CH_2$), 48.3 ($CH_2CH_2\underline{CH_2}$-N), 48.3 (N-$CH_2CH_2CH_2$), 112.7 (C_5 of thiazole), 140.6 (C_4 of thiazole), 155.9 (N=CH), 162.4 (CO), 171.9 (C_2 of thiazole), 121.4, 124.6, 128.6, 129.1, 138.7, 147.5 (6C, Ar); Mass (FAB): 333M^+.

Synthesis of N-{3-(3-nitrobenzylidencarbamyl)-propyl}-2-aminothiazole (3i)

Yield: 63%, m.p. 71-73 ºC; Anal. Calcd for $C_{14}H_{15}N_5O_3S$: C,50.44, H,4.53, N,21%; found C,50.35, H,4.49, N,20.90%; IR: 3351 (NH), 1635 (C=O), 1524 (N=O), 1572 (N=CH), 848 (C-

N); ^{1}H NMR (δ): 3.72 (t, 2H, N-$\underline{CH_2}CH_2CH_2$), 2.35 (m, 2H, J = 7.45 Hz, $CH_2\underline{CH_2}CH_2$), 3.16 (m, 2H, CH_2 $CH_2\underline{CH_2}$-NH), 5.72 (t, 1H, J = 4.80 Hz, NHCO), 7.38 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.14 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 8.01 (s, 1H, N=CH), 8.08 (t, 1H, J = 4.35 Hz, NH), 7.21-7.86 (m, 4H, Ar-H); ^{13}C NMR (δ): 43.1 (N-$CH_2CH_2CH_2$), 41.7 ($CH_2\underline{CH_2}CH_2$), 47.2 ($CH_2CH_2\underline{CH_2}$-NH), 171.2 (CO), 154.7 (N=CH), 171.3 (C_2 of thiazole), 112.6 (C5 of thiazole), 140 (C4 of thiazole), 122.3, 125.2, 128.4, 133.4, 137.5, 150.5 (6C, Ar); Mass (FAB): 333M^+.

Synthesis of N-{3-(2-nitrobenzylidencarbamyl)-propyl}-2-aminothiazole (3j)

Yield: 60%, m.p. 70-72 ºC; Anal. Calcd for $C_{14}H_{15}N_5O_3S$: C,50.44, H,4.53, N,21%; found C,50.39, H,4.45, N,20.97%; IR: 842 (C-N), 1531 (N=O), 1575 (N=CH), 1644 (C=O), 3351 (NH); ^{1}H NMR (δ): 2.31 (m, 2H, $CH_2CH_2CH_2$), 3.35 (m, 2H, $CH_2CH_2\underline{CH_2}$-N), 3.72 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.53 (t, 1H, J = 4.85 Hz, NHCO), 7.12 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.32 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 8.07 (s, 1H, N=CH), 8.12 (t, 1H, J = 4.37 Hz, NH), 7.26-7.99 (m, 4H, Ar-H); ^{13}C NMR (δ): 40 ($CH_2\underline{CH_2}CH_2$), 47.1 ($CH_2CH_2\underline{CH_2}$-N), 47.3 (N-$CH_2CH_2CH_2$), 110.7 (C_5 of thiazole), 139.1 (C_4 of thiazole), 155.1 (N=CH), 158 (CO), 171.5 (C_2 of thiazole), 122.3, 125.2, 127.6, 133.4, 137.5, 149.2 (6C, Ar); Mass (FAB): 333M^+.

Synthesis of N-{3-(4-methoxybenzylidencarbamyl)-propyl}-2-aminothiazole (3k)

Yield: 61%, m.p. 65-67 ºC; Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C,56.58, H,5.69, N,17.59%; found C,56.52, H,5.66, N, 17.54%; IR: 1561 (N=CH), 2945 (OCH_3), 3351 (NH); ^{1}H NMR (δ): 2.16 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.28 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.57 (s, 3H, OCH_3), 3.63 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.31 (t, 1H, J = 4.78 Hz, NHCO), 7.12 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.34 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.85 (s, 1H, N=CH), 7.98 (t, 1H, J = 4.25 Hz, NH), 7.34-7.52 (m, 4H, Ar-H); ^{13}C NMR (δ): 45.2 ($CH_2\underline{CH_2}CH_2$), 47.6 ($CH_2CH_2\underline{CH_2}$-NH), 47 (N-$CH_2CH_2CH_2$), 51.7 (OCH_3), 109.1 (C_5 of thiazole), 138 (C_4 of thiazole), 154.2 (N=CH), 160.5 (CO), 169.2 (C_2 of thiazole), 114.5, 117.6, 126.2, 128.1, 130.4, 159.6 (6C, Ar); Mass (FAB): 318M^+.

Synthesis of N-{3-(3-methoxybenzylidencarbamyl)-propyl}-2-aminothiazole (3l)

Yield: 63%, m.p. 64-66 ºC; Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C,56.58, H,5.69, N,17.59%; found C,56.50, H,5.62, N,17.53%; IR: 1557 (N=CH), 2943 (OCH_3), 3358 (NH); ^{1}H NMR (δ): 2.11 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.46 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.61 (s, 3H, OCH_3), 3.78 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.39 (t, 1H, J = 4.75 Hz, NHCO), 7.01 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 7.26 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.91 (s, 1H, N=CH), 7.97 (t, 1H, J = 4.23 Hz, NH), 7.41-7.82 (m, 4H, Ar-H); ^{13}C NMR (δ): 41.2 ($CH_2\underline{CH_2}CH_2$), 49.6 ($CH_2CH_2\underline{CH_2}$-NH), 47.7 (N-$CH_2CH_2CH_2$), 54.7 (OCH_3), 109.2 (C_5 of thiazole), 137.6 (C_4 of thiazole), 153.7 (N=CH), 161.9 (CO), 169 (C_2 of thiazole), 112.4, 117.5, 121.6, 129.4, 138.6, 160.4 (6C, Ar); Mass (FAB): 318M^+.

Synthesis of N-{3-(2-methoxybenzylidencarbamyl)-propyl}-2-aminothiazole (3m)

Yield: 64%, m.p. 62-65 ºC; Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C,56.58, H,5.69, N,17.59%; found C,56.51, H,5.67, N,17.51%; IR: 3361 (NH), 2947 (OCH_3), 1559 (N=CH);^{1}H NMR (δ): 3.74 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 2.14 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.47 (m, 2H, CH_2 $CH_2\underline{CH_2}$-NH), 3.67 (s, 3H, OCH_3), 5.54 (t, 1H, J = 4.70 Hz, NHCO), 7.32 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 6.82 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.76 (s, 1H, N=CH), 7.96 (t, 1H, J = 4.28 Hz, NH), 7.22-7.72 (m, 4H, Ar-H); ^{13}C NMR (δ): 48.1 (N-$CH_2CH_2CH_2$), 42 ($CH_2\underline{CH_2}CH_2$), 49 ($CH_2CH_2\underline{CH_2}$-NH), 53.7 (OCH_3), 158.1 (CO), 151 (N=CH), 170 (C_2 of thiazole), 108.4 (C5 of thiazole), 137.3 (C4 of thiazole), 111.3, 116.3, 122.3, 128.4, 137.5, 159.3 (6C, Ar); Mass (FAB): 318 M^+.

Synthesis of N-{3-(4-methylbenzylidencarbamyl)-propyl}-2-aminothiazole (3n)
Yield: 65%, m.p. 58-59 ºC; Anal. Calcd for $C_{15}H_{18}N_4OS$: C,59.58, H,5.99, N,18.52%; found C,59.52, H,5.90, N,18.43%; IR: 1549 (N=CH), 2917 (CH_3), 3340 (NH); ^{1}H NMR (δ): 2.06 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.29 (s, 3H, CH_3), 3.32 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.72 (m, 2H, $N\underline{CH_2}CH_2CH_2$), 5.38 (t, 1H, J = 4.72 Hz, NHCO), 6.81 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 7.19 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.89 (s, 1H, N=CH), 7.90 (t, 1H, J = 4.25 Hz, NH), 7.39-7.79 (m, 4H, Ar-H); ^{13}C NMR (δ): 24.9 (CH_3), 39.6 ($CH_2\underline{CH_2}CH_2$), 50.3 ($CH_2CH_2\underline{CH_2}$-NH), 46.7 (N-$CH_2CH_2CH_2$), 151.2 (N=CH), 160.8 (CO), 171.2 (C_2 of thiazole), 109.5 (C_5 of thiazole), 139.4 (C_4 of thiazole), 125.1, 127.7, 129.2, 130.2, 134.4, 139.4 (6C, Ar); Mass (FAB): 302M^+, 287, 275, 211, 184.

Synthesis of N-{3-(3-methybenzylidencarbamyl)-propyl}-2-aminothiazole (3o)
Yield: 61%, m.p. 61-62 ºC; Anal. Calcd for $C_{15}H_{18}N_4OS$: C,59.58, H,5.99, N,18.52%; found C,59.55, H,5.89, N,18.47%; IR: 1544 (N=CH), 2921 (CH_3), 3345 (NH); ^{1}H NMR (δ): 2.09 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.25 (s, 3H, CH_3), 3.43 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.75 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.39 (t, 1H, J = 4.72 Hz, NHCO), 6.90 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 7.22 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.81 (s, 1H, N=CH), 7.91 (t, 1H, J = 4.27 Hz, NH), 7.31-7.83 (m, 4H, Ar-H); ^{13}C NMR (δ): 22.9 (CH_3), 40.1 ($CH_2\underline{CH_2}CH_2$), 52.1 ($CH_2CH_2\underline{CH_2}$-NH), 45.7 (N-$CH_2CH_2CH_2$), 109.8 (C_5 of thiazole), 139.1 (C_4 of thiazole), 152 (N=CH), 159.8 (CO), 170 (C_2 of thiazole), 126.2, 128.6, 128.7, 129.5, 135.3, 138.4 (6C, Ar); Mass(FAB): 302M^+.

Synthesis of N-{3-(2-methylbenzylidencarbamyl)-propyl}-2-aminothiazole (3p)
Yield: 63%, m.p. 57-60 ºC; Anal. Calcd for $C_{15}H_{18}N_4OS$: C,59.58, H,5.99, N,18.52%; found C,59.51, H,5.95, N,18.43%; IR: 1551 (N=CH), 2908 (CH_3), 3341 (NH); ^{1}H NMR (δ): 2.03 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.30 (s, 3H, CH_3), 3.39 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.68 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 5.52 (t, 1H, J = 4.73 Hz, NHCO), 6.84 (d, 1H, J = 4.70 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 7.78 (s, 1H, N=CH), 7.94 (t, 1H, J = 4.30 Hz, NH), 7.34-7.76 (m, 10H, Ar-H);^{13}C NMR (δ): 21.9 (CH_3), 38.2 ($CH_2\underline{CH_2}CH_2$), 53.3 (CH_2 $CH_2\underline{CH_2}$-NH), 45.7 (N-$CH_2CH_2CH_2$), 108.2 (C_5 of thiazole), 138.4 (C_4 of thiazole), 154 (N=CH), 151.2 (CO), 169.5 (C_2 of thiazole), 125.3, 126.4, 128.7, 130.2, 134.7, 137.8 (6C, Ar); Mass (FAB): 302M^+.

Synthesis of N-{3-(4-hydroxybenzylidencarbamyl)-propyl}-2-aminothiazole (3q)
Yield: 64%, m.p. 78-79 ºC; Anal. Calcd for $C_{14}H_{15}N_4O_2S$: C,55.24, H,4.96, N,18.40%; found C,55.17, H,4.92, N,18.33%; IR: 1557 (N=CH), 3385 (NH), 3472 (OH); ^{1}H NMR (δ): 2.24 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.57 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.79 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 4.15 (s, 1H, OH), 5.42 (t, 1H, J = 4.75 Hz, NHCO), 7.10 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.32 (d, 1H, J = 4.75 Hz, C_4H of thiazole), 8.07 (s, 1H, N=CH), 8.11 (t, 1H, J = 4.30 Hz, NH),7.32-7.79 (m, 4H, Ar-H); ^{13}C NMR (δ): 39.9 ($CH_2\underline{CH_2}CH_2$), 51.1 ($CH_2CH_2\underline{CH_2}$-NH), 47.1 (N-$CH_2CH_2CH_2$), 108.7 (C_5 of thiazole), 138.6 (C_4 of thiazole), 153.3 (N=CH), 148.7 (CO), 169.1 (C_2 of thiazole), 115.7, 117.9, 126.3, 129.5, 130.2, 154.2 (6C, Ar); Mass (FAB): 304M^+.

Synthesis of N-{3-(3-hydroxybenzylidencarbamyl)-propyl}-2-aminothiazole (3r)
Yield: 63%. m.p. 72-73 ºC; Anal. Calcd for $C_{14}H_{15}N_4O_2S$: C,55.24, H,4.96, N,18.40%; found C,55.17, H,4.85, N,18.38%; IR: 1561 (N=CH), 3379 (NH), 3464 (OH); ^{1}H NMR (δ): 2.28 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.49 (m, 2H, $CH_2CH_2\underline{CH_2}$-N), 3.81 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 4.26 (s, 1H, OH), 5.56 (t, 1H, J = 4.75 Hz, NHCO), 7.12 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.30 (d, 1H, J = 4.75 Hz, C_4H of thiazole), 8.10 (s, 1H, N=CH), 8.15 (t, 1H, J = 4.30 Hz, NH), 7.36-7.74 (m, 4H, Ar-H); ^{13}C NMR (δ): 42 ($CH_2\underline{CH_2}CH_2$), 52.7 (CH_2 $CH_2\underline{CH_2}$-N), 46 (N-$CH_2CH_2CH_2$), 109.2 (C_5 of thiazole), 139.6 (C_4 of thiazole), 151 (N=CH), 146.7 (CO), 168.2 (C_2 of thiazole), 112.4, 115.5, 119.3, 129.6, 138.4, 155.2 (6C, Ar); Mass (FAB): 304M^+.

Synthesis of N-{3-(2-hydroxybenzylidencarbamyl)-propyl}-2-aminothiazole (3s)
Yield: 62%, m.p. 68-70 ºC; Anal. Calcd for $C_{14}H_{15}N_4O_2S$: C,55.24, H,4.96, N,18.40%; found C,55.20, H,4.88, N,18.35%; IR: 1567 (N=CH), 3381 (NH), 3468 (OH); ^{1}H NMR (δ): 2.21 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.44 (m, 2H, $CH_2CH_2\underline{CH_2}$-NH), 3.76 (m, 2H, N-$\underline{CH_2}CH_2CH_2$), 4.36 (s, 1H, OH), 5.33 (t, 1H, J = 4.80 Hz, NHCO), 6.92 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.32 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 8.07 (s, 1H, N=CH), 8.13 (t, 1H, J = 4.32 Hz, NH),7.25-7.69 (m, 4H, Ar-H); ^{13}C NMR (δ): 38.4 ($CH_2\underline{CH_2}CH_2$), 52.3 ($CH_2CH_2\underline{CH_2}$-NH), 42.1 (N-$CH_2CH_2CH_2$), 109.6 (C_5 of thiazole), 138.2 (C_4 of thiazole), 151.3 (N=CH), 148.1 (CO), 168.3 (C_2 of thiazole), 111.7, 121.4, 124.3, 127.7, 130.5, 154.2 (6C, Ar); Mass (FAB): 304M$^+$.

General procedure for the synthesis of compound 4(a-s) by conventional method
A mixture of compound **3(a-s)** and chloroacetyl chloride in the presence of Et_3N (1:1:1 mole) was dissolved in methanol at room temperature and allow to react. The reaction mixture was first continuously stirred on a magnetic stirrer for about 2.25-2.40 hrs. then kept on a steam bath for about 3.30-3.45 hrs. The products were filtered and cooled at room temperature. The filtered products were purified over a column chromatography and recrystallized from ethanol at room temperature to yield compound **4(a-s).**

Synthesis of N-[3-{(4-phenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4a)
Yield: 65% m.p. 70-71 ºC; Anal. Calcd for $C_{16}H_{17}N_4O_2SCl$: C,52.67, H,4.69, N,15.35%; found C,52.61, H,4.62, N,15.33%; IR: 1327 (C-N), 2907 (CH-Cl), 1739 (CO cyclic); ^{1}H NMR (δ): 4.46 (d, 1H, CH-Cl), 5.22 (d, 1H, N-CH), 5.42 (t, 1H, J = 4.85 Hz, NHCO), 8.01 (t, 1H, J = 4.35 Hz, NH), 6.85-7.72 (m, 11H, Ar-H); ^{13}C NMR (δ): 54.2 (CH-Cl), 62.4 (N-CH), 110.7 (C_5 of thiazole), 139.8 (C_4 of thiazole), 163.7 (CO cyclic), 170.5 (C_2 of thiazole), 124.5, 126.2, 128.5, 130.2, 132.6, 137.6 (6C, Ar); Mass (FAB): 364M$^+$.

Synthesis of N-[3-{4-(4-chlorophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4b)
Yield: 64%, m.p. 87-89 ºC; Anal. Calcd for $C_{16}H_{16}N_4O_2SCl_2$: C,48.12, H,4.0, N,14.03%; found C,48.08, H,3.92, N,14.00%; IR: 762 (C-Cl), 1337 (C-N), 1750 (CO cyclic), 2911 (CH-Cl); ^{1}H NMR (δ): 4.62 (d, 1H, J = 4.90 Hz, CH-Cl), 5.36 (d, 1H, J = 4.90 Hz, N-CH), 7.15 (s, 1H, NH), 7.24 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.09 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 6.86-7.72 (m, 4H, Ar-H); ^{13}C NMR (δ): 53.8 (CH-Cl), 63.4 (N-CH), 113.2 (C_5 of thiazole), 142.1 (C_4 of thiazole), 166.2 (CO cyclic), 172.5 (C_2 of thiazole), 127.2, 128.6, 130.3, 132.4, 136.1, 140.5 (6C, Ar); Mass (FAB): 399M$^+$.

Synthesis of N-[3-{4-(3-chlorophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4c)
Yield: 65% m.p. 84-85 ºC; Anal. Calcd for $C_{16}H_{16}N_4O_2SCl_2$: C,48.12, H,4.00, N,14.03%; found C,48.02, H,3.95, N,13.96%; IR: 774 (C-Cl), 1335 (C-N), 1752 (CO cyclic), 2913 (CH-Cl); ^{1}H NMR (δ): 4.68 (d, 1H, J = 4.95 Hz, CH-Cl), 5.36 (d, 1H, J = 4.95 Hz, N-CH), 7.12 (s, 1H, NH), 7.21 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.05 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 6.79-7.64 (m, 4H, Ar-H); ^{13}C NMR (δ): 55.8 (CH-Cl), 65.1 (N-CH), 112.6 (C_5 of thiazole), 141.4 (C_4 of thiazole), 165.5 (CO cyclic), 171.6 (C_2 of thiazole), 126.1, 128.4, 129.7, 132.1, 135.1, 139.6 (6C, Ar); Mass(FAB): 399M$^+$.

Synthesis of N-[3-{4-(2-chlorophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4d)

Yield: 64% m.p. 80-81 ºC; Anal. Calcd for $C_{16}H_{16}N_4O_2SCl_2$: C,48.12, H,4.00, N,14.03%; found C,48.08, H,3.92, N,13.97%; IR: 771 (C-Cl), 1333 (C-N), 1757 (CO cyclic), 2918 (CH-Cl); ^{1}H NMR (δ): 4.53 (d, 1H, J = 4.90 Hz, CH-Cl), 5.26 (d, 1H, J = 4.90 Hz, N-CH), 7.09 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 6.81-7.62 (m, 4H, Ar-H); ^{13}C NMR (δ): 55.8 (CH-Cl), 61.4 (N-CH), 112.4 (C_5 of thiazole), 141.1 (C_4 of thiazole), 165.2 (CO cyclic), 172 (C_2 of thiazole), 126.1, 128.4, 129.5, 130.1, 133.5, 137.2 (6C, Ar); Mass (FAB): 399M$^+$.

Synthesis of N-[3-{4-(4-bromophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4e)

Yield: 62% m.p. 77-79 ºC; Anal. Calcd for $C_{16}H_{16}N_4O_2SBrCl$: C,43.29, H,3.60, N,12.62%; found C,43.20, H,3.54, N,12.55%; IR: 578 (C-Br), 1315 (C-N), 1741 (CO cyclic), 2892 (CH-Cl); ^{1}H NMR (δ): 4.62 (d, 1H, J = 5.00 Hz, CH-Cl), 5.42 (d, 1H, J = 5.00 Hz, N-CH), 6.95 (s, 1H, NH), 7.05 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.35-7.95 (m, 4H, Ar-H); ^{13}C NMR (δ): 171 (C_2 of thiazole), 112.1 (C_5 of thiazole), 140.9 (C_4 of thiazole), 47.1 (CH-Cl), 59.1 (N-CH), 161.3 (CO cyclic), 122.5, 128.5, 129.4, 131.5, 134.2, 137.7 (6C, Ar); Mass (FAB): 444M$^+$.

Synthesis of N-[3-{4-(3-bromophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4f)

Yield: 64% m.p. 76-77 ºC; Anal. Calcd for $C_{16}H_{16}N_4O_2SBrCl$: C,43.29, H,3.60, N,12.62%; found C,43.22, H,3.49, N,12.53%; IR: 571 (C-Br), 1318 (C-N), 1748 (CO cyclic), 2896 (CH-Cl); ^{1}H NMR (δ): 5.45 (d, 1H, J = 4.95 Hz, CH-Cl), 5.37 (d, 1H, J = 4.95 Hz, N-CH), 6.95 (s, 1H, NH), 7.01 (d, 1H, J = 4.80 Hz, C5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C4H of thiazole), 7.31-7.92 (m, 4H, Ar-H); ^{13}C NMR (δ): 170.9 (C_2 of thiazole), 112 (C_5 of thiazole), 140.7 (C_4 of thiazole), 59.9 (N-CH), 48.7 (CH-Cl), 165.3 (CO cyclic), 123.3, 125.2, 129.4, 130.7, 132.1, 139 (6C, Ar); Mass (FAB): 444M$^+$.

Synthesis of N-[3-{4-(2-bromophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4g)

Yield: 66% m.p. 74-75 ºC; Anal. Calcd for $C_{16}H_{16}N_4O_2SBrCl$: C,43.29, H,3.60, N,12.62%; found C,43.21, H,3.53, N,12.58%; IR: 565 (C-Br), 1324 (C-N), 1755 (CO cyclic), 2884 (CH-Cl); ^{1}H NMR (δ): 5.64 (d, 1H, J = 5.00 Hz, CH-Cl), 5.15 (d, 1H, J = 5.00 Hz, N-CH), 6.97 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 7.27-7.84 (m, 4H, Ar-H); ^{13}C NMR (δ): 170.1 (C_2 of thiazole), 111.6 (C_5 of thiazole), 140.4 (C_4 of thiazole), 47.7 (CH-Cl), 58.1 (N-CH), 162.5 (CO cyclic), 120.4, 125.5, 127.9, 130.3, 133.1, 141.6 (6C, Ar); Mass (FAB): 444M$^+$.

Synthesis of N-[3-{4-(4-nitrophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4h)

Yield: 63% m.p. 82-83 ºC; Anal. Calcd for $C_{16}H_{16}N_5O_4SCl$: C,46.88, H,3.90, N,17.09%; found C,46.84, H,3.84, N,17.01%; IR: 868 (C-NO), 1538 (NO_2), 1741 (CO cyclic), 2921 (CH-Cl); ^{1}H NMR (δ): 4.38 (d, 1H, J = 5.05 Hz, CH-Cl), 5.43 (d, 1H, J = 5.05 Hz,N-CH), 6.95 (s, 1H, NH), 6.81 (d, 1H, J = 4.90 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.90 Hz, C_4H of thiazole), 7.13-7.71 (m, 4H, Ar-H); ^{13}C NMR (δ): 170.4 (C_2 of thiazole), 111.8 (C_5 of thiazole), 140 (C_4 of thiazole), 161 (CO cyclic), 68.8 (N-CH), 51 (CH-Cl), 122.3, 125.2, 127.6, 129.5, 137.5, 147.2 (6C, Ar); Mass (FAB): 409M$^+$.

Synthesis of N-[3-{4-(3-nitrophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4i)

Yield: 64% m.p. 82-84 ºC; Anal. Calcd for $C_{16}H_{16}N_5O_4SCl$: C,46.88, H,3.90, N,17.09%; found C,46.84, H,3.84, N,16.98%; IR: 862 (C-NO), 1542 (NO_2), 1749 (CO cyclic), 2914 (CH-Cl); ^{1}H NMR (δ): 4.39 (d, 1H, J = 4.95 Hz, CH-Cl), 5.42 (d, 1H, J = 4.95 Hz, N-CH), 6.95 (s, 1H, NH), 6.90 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.16-7.79 (m, 4H, Ar-H); ^{13}C NMR (δ): 54 (CH-Cl), 63.8 (N-CH), 111.6 (C_5 of thiazole), 140.2 (C_4 of thiazole), 167 (CO cyclic), 171.3 (C_2 of thiazole), 120.1, 123.4, 128.6, 132.4, 139.5, 149.1 (12C, Ar); Mass (FAB): 409M^+.

Synthesis of N-[3-{4-(2-nitrophenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4j)

Yield: 63% m.p. 80-81 ºC; Anal. Calcd for $C_{16}H_{16}N_5O_4SCl$: C,46.88, H,3.90, N,17.09%; found C,46.78, H,3.87, N,16.91%; IR: 869 (C-NO), 1542 (NO_2), 1745 (CO cyclic), 2918 (CH-Cl); ^{1}H NMR (δ): 4.31 (d, 1H, J = 5.10 Hz, CH-Cl), 5.54 (d, 1H, J = 5.10 Hz, N-CH), 6.95 (s, 1H, NH), 6.94 (d, 1H, J = 4.95 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.95 Hz, C_4H of thiazole), 7.05-7.71 (m, 4H, Ar-H); ^{13}C NMR (δ): 54.6 (CH-Cl), 64.8 (N-CH), 111.3 (C_5 of thiazole), 140.1 (C_4 of thiazole), 163 (CO cyclic), 170.8 (C_2 of thiazole), 123.4, 127.5, 129.6, 132.4, 135.5, 145.7 (6C, Ar); Mass (FAB): 409M^+.

Synthesis of N-[3-{4-(4-methoxyphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4k)

Yield: 65% m.p. 72-74 ºC; Anal. Calcd for $C_{17}H_{19}N_4O_3SCl$: C,51.71, H,4.81, N,14.19%; found C,51.64, H,4.78, N,14.13%; IR: 1163 (C-O), 1326 (N-C), 1736 (CO cyclic), 2891 (CH-Cl); ^{1}H NMR (δ): 3.64 (s, 3H, OCH_3), 4.41 (d, 1H, J = 4.90 Hz, CH-Cl), 5.39 (d, 1H, J = 4.90 Hz, N-CH), 6.95 (s, 1H, NH), 6.89 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.75 Hz, C_4H of thiazole), 7.26-7.92 (m, 4H, Ar-H); ^{13}C NMR (δ): 49.1 (CH-Cl), 54 (OCH_3), 64.4 (N-CH), 110.6 (C_5 of thiazole), 139.8 (C_4 of thiazole), 162.5 (CO cyclic), 170.7 (C_2 of thiazole), 113.4, 116.1, 125, 127.4, 130.2, 159.2 (6C, Ar); Mass (FAB): 394M^+.

Synthesis of N-[3-{4-(3-methoxyphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4l)

Yield: 62% m.p. 75-76 ºC; Anal. Calcd for $C_{17}H_{19}N_4O_3SCl$: C,51.71, H,4.81, N,14.19%; found C,51.68, H,4.72, N,14.11%; IR: 1728 (CO cyclic), 2895 (CH-Cl); ^{1}H NMR (δ): 3.59 (s, 3H, OCH_3), 4.49 (d, 1H, J = 5.10 Hz, CH-Cl), 5.29 (d, 1H, J = 5.10 Hz, N-CH), 6.95 (s, 1H, NH), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 6.82 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.36-8.02 (m, 4H, Ar-H); ^{13}C NMR (δ): 169.1 (C_2 of thiazole), 108.2 (C_5 of thiazole), 137.4 (C_4 of thiazole), 164.5 (CO cyclic), 62.4 (N-CH), 49.8 (CH-Cl), 54.8 (OCH_3), 111.3, 115, 119.5, 129.3, 138.4, 161 (6C, Ar); Mass (FAB): 394M^+.

Synthesis of N-[3-{4-(2-methoxyphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4m)

Yield: 61% m.p. 69-71 ºC; Anal. Calcd for $C_{17}H_{19}N_4O_3SCl$: C,51.71, H,4.81, N,14.19%; found C,51.67, H,4.72, N,14.08%; IR: 1738 (CO cyclic), 2885 (CH-Cl); ^{1}H NMR (δ): 3.52 (s, 3H, OCH_3), 4.45 (d, 1H, J = 5.00 Hz, CH-Cl), 5.39 (d, 1H, J = 5.00 Hz, N-CH), 6.95 (s, 1H, NH), 6.92 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.75 Hz, C_4H of thiazole), 7.04-7.87 (m, 4H, Ar-H); ^{13}C NMR (δ): 47.4 (CH-Cl), 54.1 (OCH_3), 63.1 (N-CH), 108.4 (C_5 of thiazole), 138.1 (C_4 of thiazole), 163.2 (CO cyclic), 168.3 (C_2 of thiazole), 114.3, 121.2, 123.6, 128.4, 130.2, 158.4 (6C, Ar); Mass (FAB): 394M^+.

Synthesis of N-[3-{4-(4-methylphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4n)

Yield: 63% m.p. 68-69 ºC; Anal. Calcd for $C_{17}H_{19}N_4O_2SCl$: C,53.89, H,5.0, N, 14.79%; found C,53.81, H,4.92, N,14.73%; IR: 1740 (CO cyclic), 2889 (CH-Cl), 2924 (CH_3); ^{1}H NMR (δ): 2.38 (s, 3H, CH_3), 4.53 (d, 1H, J = 5.05 Hz, CH-Cl), 5.42 (d, 1H, J = 5.05 Hz, N-CH), 6.95 (s, 1H, NH), 6.87 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 7.28-7.98 (m, 4H, Ar-H); ^{13}C NMR (δ): 24.7 (CH_3), 51.7 (CH-Cl), 62.8 (N-CH), 111.3 (C_5 of thiazole), 138.2 (C_4 of thiazole), 164.8 (CO cyclic), 170.5 (C_2 of thiazole), 126.2, 118.4, 129.5, 131.2, 134.5, 137.8 (6C, Ar); Mass (FAB): 379M^+.

Synthesis of N-[3-{4-(3-methylphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4o)

Yield: 63% m.p. 65-66 ºC; Anal. Calcd for $C_{17}H_{19}N_4O_2SCl$: C,53.89, H,5.00, N, 14.79% found C,53.86, H,4.95, N,14.68%; IR: 1746 (CO cyclic), 2894 (CH-Cl), 2927 (CH_3); ^{1}H NMR (δ): 2.32 (s, 3H, CH_3), 4.57 (d, 1H, J = 4.95 Hz, CH-Cl), 5.34 (d, 1H, J = 4.95 Hz, N-CH), 6.95 (s, 1H, NH), 6.84 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 7.18-7.84 (m, 4H, Ar-H); ^{13}C NMR (δ): 23.5 (CH_3), 51 (CH-Cl), 63.8 (N-CH), 111 (C_5 of thiazole), 139.9 (C_4 of thiazole), 163.8 (CO cyclic), 169.5 (C_2 of thiazole), 122.7, 125.2, 127.3, 129.7, 136, 139.4 (6C, Ar); Mass (FAB): 379M^+.

Synthesis of N-[3-{4-(2-methylphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4p)

Yield: 64% m.p. 63-64 ºC; Anal. Calcd for $C_{17}H_{19}N_4O_2SCl$: C,53.89, H,5.00, N, 14.79%; found C,53.84, H,4.90, N,14.69%; IR: 1746 (CO cyclic), 2876 (CH-Cl), 2913 (CH_3); ^{1}H NMR (δ): 2.36 (s, 3H, CH_3), 4.48 (d, 1H, J = 5.00 Hz, CH-Cl), 5.45 (d, 1H, J = 5.00 Hz, N-CH), 6.95 (s, 1H, NH), 6.93 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 7.21-8.09 (m, 4H, Ar-H); ^{13}C NMR (δ): 23.4 (CH_3), 50.9 (CH-Cl), 62.2 (N-CH), 161.2 (CO cyclic), 170.4 (C_2 of thiazole), 109.8 (C_5 of thiazole), 138.4 (C_4 of thiazole), 125, 126.3, 127.9 129.4, 135.4, 138.3 (6C, Ar); Mass (FAB): 379M^+.

Synthesis of N-[3-{4-(4-hydroxyphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4q)

Yield: 60% m.p. 93-97 ºC; Anal. Calcd for $C_{16}H_{17}N_4O_3SCl$: C,50.45, H,4.46, N,14.71%; found C,50.41, H,4.42, N,14.63%; IR: 1758 (CO cyclic), 2917 (CH-Cl), 3467 (OH); ^{1}H NMR (δ): 4.20 (s,1H, OH), 4.59 (d, 1H, J = 5.10 Hz, CH-Cl), 5.38 (d, 1H, J = 5.10 Hz, N-CH), 6.95 (s, 1H, NH), 7.24 (d,1H, J=4.75 Hz, C_4H of thiazole), 6.88 (d, 1H, J = 4.75 Hz, C_5H of thiazole), 7.09-8.12 (m, 4H, Ar-H); ^{13}C NMR (δ): 53.2 (CH-Cl), 63.7 (N-CH), 110.6 (C_5 of thiazole), 139.8 (C_4 of thiazole), 166.4 (CO cyclic), 169.6 (C_2 of thiazole), 113.6, 118.4, 122.7, 129.5, 138, 153.4 (6C, Ar); Mass (FAB): 381M^+.

Synthesis of N-[3-{4-(3-hydroxyphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4r)

Yield: 62% m.p. 90-92 ºC; Anal. Calcd for $C_{16}H_{17}N_4O_3SCl$: C,50.45, H,4.46, N,14.71%; found C,50.39, H,4.40, N,14.65%; IR: 1762 (CO cyclic), 2923 (CH-Cl), 3469 (OH); ^{1}H NMR (δ): 4.22 (s, 1H, OH), 4.57 (d, 1H, J = 5.15 Hz, CH-Cl), 5.41 (d, 1H, J = 5.15 Hz, N-CH), 6.95 (s, 1H, NH), 6.91 (d, 1H, J = 4.85 Hz, C_5H of thiazole), 7.24 (d, 1H, J = 4.85 Hz, C_4H of thiazole), 7.12-8.13 (m, 4H, Ar-H); ^{13}C NMR (δ): 51.2 (CH-Cl), 64.7 (N-CH), 109.1 (C_5 of thiazole), 139 (C_4 of thiazole), 162.7 (CO cyclic), 169 (C_2 of thiazole), 112.4, 117.2, 121, 127.5, 136.3, 155.7 (6C, Ar); Mass (FAB): 381M^+.

Synthesis of N-[3-{4-(2-hydroxyphenyl-3-chloro-2-oxo-azetidine)-carbamyl}-propyl]-2-aminothiazole (4s)

Yield: 61% m.p. 87-89 ºC; Anal. Calcd for $C_{16}H_{17}N_4O_3SCl$: C,50.45, H,4.46, N,14.71%; found C,50.38, H,4.39, N,14.63%; IR: 1762 (CO cyclic), 2919 (CH-Cl), 3459 (OH); ^{1}H NMR (δ): 4.25 (s, 1H, OH), 4.57 (d, 1H, J = 5.00 Hz, CH-Cl), 5.39 (d, 1H, J = 5.00 Hz, N-CH), 6.95 (s, 1H, NH), 7.24 (d, 1H, J = 4.80 Hz, C_4H of thiazole), 6.99 (d, 1H, J = 4.80 Hz, C_5H of thiazole), 7.19-8.21 (m, 4H, Ar-H); ^{13}C NMR (δ): 54 (CH-Cl), 63.2 (N-CH), 109.5 (C_5 of thiazole), 137.1 (C_4 of thiazole), 161.9 (CO cyclic), 169.4 (C_2 of thiazole), 111.3, 116.3, 122.3, 128.4, 137.5, 154.6 (6C, Ar); Mass (FAB): 381M$^+$.

RESULTS AND DISCUSSION

The appearance of an absorption band in the IR spectrum of the compound **1** for (N-CH_2) and (C-Cl) at 1332 and 736 cm^{-1} respectively which is strong evidence for the substitution at (N-H) proton of 2-aminothiazole (N-H band appeared at 3382cm^{-1}). The appearance of absorption band in IR spectrum of **2** appears for (CO), (NH) and (NH_2) at 1662, 3371 and 3423 cm^{-1} respectively. Appearance of absorption band in the spectra of compound **3(a-s)** for (N=C) in range of 1544-1575 cm^{-1} is a strong evidence for condensation. In the IR spectra of compound **4(a-s)** appearances of absorptions for (CO cyclic) in range 1728-1762 cm^{-1} suggesting the cyclization. This fact also supported by the disappearance of the peak of (N=CH) in the compound **3(a-s)**. In the ^{1}H spectrum of the compound **1** a new signal appeared for N-CH_2 at (δ) 4.24 ppm. In the ^{1}H spectrum of the compound **2** showed two signals for NH and NH_2 at (δ) 6.72 and 5.83 ppm respectively. Presence of signals of NH and NH_2 confirm the structure **2**. In the compound **3(a-s),** the ^{1}H spectra showed a singlet for N=CH in the range of (δ) 7.76-8.17 ppm which provide a strong evidence for benzylidene type proton and also supported by disappearance of NH_2 proton. In the ^{1}H NMR spectra of compound **4(a-s)** showed a strong signal of (CH-Cl) and (N-CH) of azetidine ring in the range of (δ) 4.31-4.68 and (δ) 5.15-5.54 ppm respectively and fact also supported by disappearance of N=CH signal in the compound **3(a-s).** ^{13}C NMR spectra of the compound **1** showed a strong signal of N-CH_2 at (δ) 46.1 ppm while in compound **2** characteristic signal of CO group appeared at (δ) 163.4 ppm. The signal for N=CH appeared in the range of (δ) 144.2-155.9 ppm in the compounds **3(a-s)** which confirm the presence of carbon on with doubly bonded to nitrogen. In the spectra of compound **4(a-s)** three new characteristic signals were found for (CH-Cl), (N-CH) and cyclic CO in the range of (δ) 47.1-55.8, 50.1-68.8 and 161-167 ppm respectively. It is strong evidence of the cyclization and also supported by disappearance of N=CH signal. FAB-Mass spectrum of compound **1** showed a parent peak at m/z 176 corresponding to the molecular formula $C_6H_9N_2SCl$ In the FAB-Mass spectrum of compound **2** showed a parent peak at 200 m/z for molecular formula $C_7H_{12}N_4SO$. In the FAB-Mass spectra of compound **3a** showed a parent peak at m/z 288 for molecular formula $C_{14}H_{16}N_4OS$. In the FAB-Mass spectrum of compound **4a** showed a parent peak at m/z 364 for molecular formula $C_{16}H_{17}N_4O_2SCl$. The data of yield and reaction time of all synthesized compounds were given in table 1.

Pharmacology

The antibacterial, antifungal and antitubercular activity of compound **4(a-s)** has been assayed in vitro against selected bacteria, B. *subtilis*, E. *coli*, S. *aureus*, K. *pneumoniae*, fungi, A. *niger*, A. *flavus*, C. *albicans*, F. *oxisporium* and M. *tuberculosis* H37Rv strain respectively. MIC values of compound **4(a-s)** were determined using filter paper disc diffusion method (antibacterial and antifungal activitry) and L. J. medium (Conventional) method (antitubercular activity) at 100 µg/mL and lower concentrations. Streptomycin and Griseofulvin used as standard for antibacterial and antifungal activity showed MIC range for all bacterial strain 6.25-12.5 µg/mL and for all fungal strain 12.5-25 µg/mL respectively and for antitubercular activity, Isoniazid and

Rifampicin taken as standards (MIC range 1.25-6.25 µg/mL). All standards also screened under the similar condition for comparison. Results of all given activities of above compounds were given in Table 2 and 3.

Table 1: Comparative data of yield and reaction time of all synthesized compounds

Comp.	Yield %		Reaction time			Comp.	Yield %		Reaction time		
	Conv.	MW	Conv. (hrs.)		MW (mins.)		Conv.	MW	Conv. (hrs.)		MW (mins.)
			1st stirrer.	2nd reflux.					1st stirrer.	2nd reflux.	
1	58	77	7.45	-	4.00	3s	62	77	3.45	2.30	3.30
2	72	85	6.30	-	3.10	4a	65	79	2.30	3.30	3.45
3a	60	76	3.45	2.00	3.35	4b	64	79	2.30	3.30	3.30
3b	62	80	3.45	1.45	3.45	4c	65	83	2.25	3.45	3.30
3c	63	82	3.45	1.45	3.35	4d	64	82	2.30	3.45	3.45
3d	63	81	3.30	1.30	4.15	4e	62	82	2.30	3.45	3.30
3e	65	83	3.45	2.30	3.20	4f	64	81	2.25	3.30	3.50
3f	64	83	3.30	2.30	3.15	4g	66	78	2.30	3.45	3.45
3g	66	79	3.30	1.45	3.40	4h	63	78	2.30	3.30	3.30
3h	64	79	3.45	2.30	3.30	4i	64	81	2.35	3.45	3.45
3i	63	78	3.30	1.30	3.25	4j	63	82	2.30	3.45	3.25
3j	60	83	3.30	2.15	3.00	4k	65	81	2.30	3.30	3.45
3k	61	78	3.30	2.15	3.40	4l	62	78	2.35	3.30	3.35
3l	63	83	3.45	2.10	3.30	4m	61	79	2.40	3.45	3.45
3m	64	82	3.30	2.30	4.15	4n	63	77	2.30	3.45	3.45
3n	65	78	3.45	2.15	4.15	4o	63	76	2.35	3.30	3.50
3o	61	75	3.30	2.30	4.25	4p	64	78	2.30	3.45	3.30
3p	63	79	3.30	2.15	4.00	4q	60	75	2.25	3.45	3.30
3q	64	78	3.30	2.15	3.20	4r	62	81	2.30	4.00	3.45
3r	63	77	3.45	2.25	3.35	4s	61	82	2.30	4.15	3.30

Conv. = conventional method, MW = microwave method.

Table 2. Antibacterial, antifungal and antitubercular activity of compound 4(a-s)

Comp.	Antibacterial activity				Antifungal activity				Antitubercular activity
	B. *subtilis*	E. *coli*	S. *aureus*	K. *pneumoniae*	A. *niger*	A. *flavus*	F. *oxisporium*	C. *albicans*	M. *tuberculosis*
4a	>25	>25	>25	>25	>50	100	100	>100	>25
4b	12.5	>12.5	>12.5	>12.5	>25	50	>50	>50	>12.5
4c	12.5	12.5	>6.25	12.5	>25	>25	>25	>25	>6.25
4d	>12.5	12.5	12.5	12.5	>25	25	>50	>25	12.5
4e	12.5	12.5	12.5	12.5	>25	>25	>25	>50	>6.25
4f	12.5	>12.5	>12.5	>12.5	>50	>25	>50	>25	>12.5
4g	12.5	>12.5	>12.5	>12.5	>25	>25	>50	50	>12.5
4h	>12.5	>6.25	12.5	>6.25	25	>25	>25	>25	>6.25
4i	>12.5	>6.25	>12.5	>6.25	>25	>25	>25	>25	>6.25
4j	>6.25	>12.5	>6.25	>12.5	>25	>25	>25	>25	>6.25
4k	25	25	>25	>25	>100	>50	>50	100	>12.5
4l	>25	>25	25	>25	>50	>50	>100	>100	25
4m	25	>25	25	>25	100	>50	>50	100	>25
4n	>25	25	>25	>25	>100	>50	>100	>100	>25
4o	>25	>25	>25	>25	100	>100	100	>100	>50
4p	>25	>25	>25	>25	>50	100	>100	>100	50
4q	>25	>12.5	25	>12.5	>25	>50	>50	>50	25
4r	>12.5	25	>12.5	>25	>50	>50	>25	>50	>12.5
4s	>12.5	>12.5	25	>12.5	>25	25	>50	50	>12.5

streptomycin and gresiofulvin were used as standarads for antibacterial and antifungal activity respectively, mic in rhe range of 6.25-12.5 and 12.5-25 µg/ml respectively.; isoniazid and rifampicin taken as standards (mic range 1.25-6.25 µg/ml) for antitubercular activity.

all above concentration used in µg/ml.

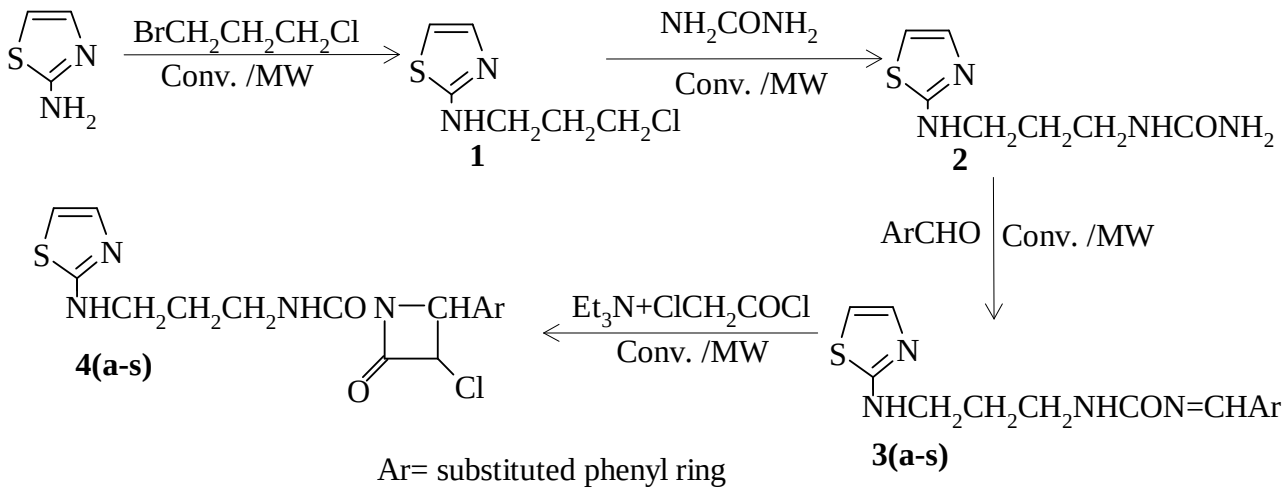

Figure: 1. Scheme for the synthesis of compounds 1, 2, 3(a-s), 4(a-s).

Comp.	Ar	Comp.	Ar	Comp.	Ar
3a, 4a	C_6H_5	3h, 4h	4-$NO_2C_6H_4$	3o, 4o	3-$CH_3C_6H_4$
3b, 4b	4-ClC_6H_4	3i, 4i	3-$NO_2C_6H_4$	3p, 4p	2-$CH_3C_6H_4$
3c, 4c	3-ClC_6H_4	3j, 4j	2-$NO_2C_6H_4$	3q, 4q	4-HOC_6H_4
3d, 4d	2-ClC_6H_4	3k, 4k	4-$CH_3OC_6H_4$	3r, 4r	3-HOC_6H_4
3e, 4e	4-BrC_6H_4	3l, 4l	3-$CH_3OC_6H_4$	3s, 4s	2-HOC_6H_4
3f, 4f	3-BrC_6H_4	3m, 4m	2-$CH_3OC_6H_4$	-	-
3g, 4g	2-BrC_6H_4	3n, 4n	4-$CH_3C_6H_4$	-	-

CONCLUSION

Concluded that antimicrobial and antitubercular data shown in Table 2 and 3 revealed that the compounds **(4c), (4d), (4e), (4f), (4h), (4i)** and **(4j)** displayed highly active compounds of the series, compounds **(4b), (4g)** and **(4s)** showed moderate activity and rest compounds showed less activity against all the strains compared with standard drugs.

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