SYNTHESIS OF AZETIDINONE DERIVATIVES OF 2-AMINO-5-NITROTHIAZOLE AND THEIR MEDICINAL IMPORTANCE

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Keywords: Synthesis, 2-amino-5-nitrothiazole, azetidinone, antimicrobial, antitubercular, antiinflammatory.

New series of *N*-[3-(2-amino-5-nitrothiazolyl)-propyl]-4-(substitutedphenyl)-3-chloro-2-oxo-1-azetidine-carboxamide, compounds **4a-4j** have been synthesized and characterized by chemical and spectral analyses such as IR, ^{1}H NMR, ^{13}C NMR and FAB-Mass. All the synthesized compounds **4a-4j** 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.* Anti-inflammatory activity was *in vivo* screened against albino rats. Some compounds of the series showed good activities.

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INTRODUCTION

Bacterial and fungal infection is most common problem of the world. Some serious and life threating diseases also caused by bacterial or fungal infection. Tuberculosis is one of the most common infectious diseases. According to World Health Organization (WHO), 196 countries reported 2.6 million new smear positive TB cases in 2008, of which 1.78 million people died from it. Another hand inflammation is also major problem of all over the world because many people die every year cause of inflammation. In case of accident and organ transplantation or surgery microbial infection is also common problem. From the last decade, researchers made a continuous effort to fight these diseases.

Several new classes of chemotherapeutic agents have been introduced in the last decade. Several azole or azetidine constitute containing drugs displayed promising results. Benzotriazole derivatives are also member of significant class of chemistry because of their wide use in organic synthesis and pharmaceutical chemistry. Thiazole is one of the most intensively investigated class of aromatic five membered heterocyclic system has been employed as a anticonvulsant[1], fungicidal[2]. Some of the thiazole analogues are also used as antibiological[3], antibacterial[4,5]. All these facts were driving force to develop novel thiazole derivatives with wide structure variations.

2-Azetidinone derivatives play a vital role owing to their wide range biological activity and industrial importance[6]. Recently found application in drug development for the treatment of antimicrobial[7], anticonvulsant[8], antiinflammatory[9], antibacterial[10,11]. As part of interest in heterocycles that have been explored for developing pharmaceutically important molecules.

The biological activities of both 2-oxo-azetidine and thiazole aroused our interest in the synthesis of 2-oxo-azetidine derivatives of 2-amino-5-nitrothiazole (scheme **1)**. All synthesized compounds were screened against some selected bacteria and fungi for their antimicrobial activity and antitubercular activity screened against *M. tuberculosis* using H37Rv strain. Anti-inflammatory activity was *in vivo* screened against albino rats. The structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and FAB-Mass.

EXPERIMENTAL

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.

Biological importance

Antimicrobial activity

The MIC values of compounds **4a-4j** have been determined using the filter paper disc diffusion method and the concentrations have been used in μg/mL. All the final synthesized compounds **4a-4j** have been screened for their antibacterial activity against *B. subtilis*, E. *coli, S. aureus* and *K. pneumoniae* and screened for their antifungal activity against *A. niger, A. flavus, F. oxisporium* and *C. albicans*. The MIC values of standard Streptomycin and Griseofulvin for all bacteria and fungi were in the range of 1.25-3.25 and 6.25-12.5 μg/mL respectively. The MIC values of the compounds **4a-4j** were presented in Table 1.

Antitubercular activity

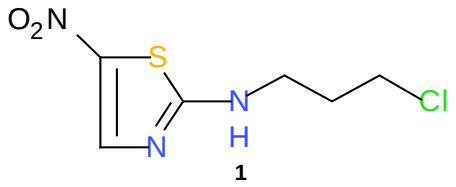
The synthesized compounds **4a-4j** were screened against *M. tuberculosis* (H37Rv strain) using L. J. medium (Conventional) method at 50 µg/mL and lower concentrations. The standard antitubercular drugs Isoniazid and Rifampicin (MIC range 2-4 µg/mL) were taken as standards. The results were showing in Table 2.

Antiinflammatory activity

Carageenan induced rat paw oedema method was employed for evaluating the antiinflammatory activity of compounds at a dose 50 mg/ kg bw in albino rats (weighing 80-110 gm, each group contain 5 animal) using phenylbutazone as a standard drug for comparison at a dose 30 mg/ kg bw. The percentage inhibition of inflammation was calculated by applying Newbould formula. Results of some active compounds were given in Table 3.

Synthesis of 1-(3-chloropropyl)-2-amino-5-nitrothiazole, (1)

2-Amino-5-nitrothiazole (0.345 mole) and 1-bromo-3-chloropropane (0.345 mole) in methanol (100 ml) were stirred on a magnetic stirrer for about 6.30 hours at room temperature. The completion of the reaction was monitored by silica gel-G coated TLC plates. After the completion of the reaction the product was filtered and purified over a silica gel packed column chromatography using $CHCl_3$: CH_3OH (8 : 2 v/v) system as eluant (120 ml). The purified product was dried under vacuo and recrystallized from ethanol at room temperature to yield compound **1** (Figure 1).



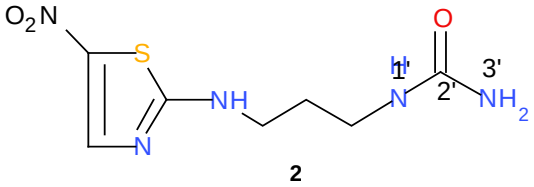
1

Figure 1. Structure of compound **1**.

1-(3-Chloropropyl)-2-amino-5-nitrothiazole (**1**): Yield: 62%; m.p. 173-175 ºC; IR (cm-1): 727 (C-Cl), 881 (C-S), 968 (C-NO), 1313 (N-CH2), 1362, 1532 (NO2), 1559 (C=C), 1436, 2832, 2897 (CH2), 3009 (CH-Ar), 3388 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 1.91-1.95 (m, 2H H-8), 3.27 (t, 2H, J = 7.35 Hz, H-9), 3.85-3.89 (m, 2H, H-7), 7.71 (s, 1H, H-4), 7.83 (br, s, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 34.4 (C-8), 41.7 (C-9), 45.9 (C-7), 134.2 (C-4), 137.8 (C-5), 166.5 (C-2); FAB-Mass (m/z): 221 [M+]; Anal. Calcd. for $C_6H_8N_3O_2SCl$: C; 32.51, H; 3.63, N; 18.95; Found: C; 32.49, H; 3.59, N; 18.87.

Synthesis of *N*-[3-(2-amino-5-nitrothiazolyl)-propyl]-urea, (2)

Compound **1** (0.2256 mol) and urea (0.2256 mol) in methanol (100 ml) were stirred on a magnetic stirrer for about 6.30 hours at room temperature. The completion of the reaction was monitored by silica gel-G coated TLC plates. After the completion of the reaction the product was filtered and purified over a silica gel packed column chromatography using $CHCl_3$: CH_3OH (8 : 2 v/v) system as eluant (120 ml). The purified product was dried under vacuo and recrystallized from ethanol at room temperature to yield compound **2** (Figure 2).



2

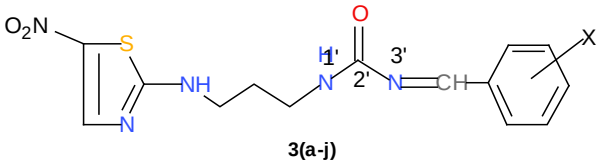
Figure 2. Structure of compound **2**.

N-[3-(2-Amino-5-nitrothiazolyl)propyl]urea (**2**): Yield: 70%; m.p. 153-155 ºC; IR (cm^{-1}): 879 (C-S), 966 (C-NO), 1324 (N-CH_2), 1360, 1533 (NO_2), 1559 (C=C), 1662 (C=O), 1432, 2885, 2918 (CH_2), 3021 (CH-Ar), 3387 (NH), 3452 (NH_2); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.08-2.12 (m, 2H, H-8), 3.19-3.24 (m, 2H, H-9), 3.82-3.90 (m, 2H, H-7), 5.67 (s, 1H, H-1'), 5.97 (br s, 2H, H-3'), 7.65 (s, 1H, H-4), 7.80 (br, s, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 33.4 (C-8), 38.6 (C-9), 44.1 (C-7), 133.8 (C-4), 138.5 (C-5), 163.4 (C-2'), 165.3 (C-2); FAB-Mass *(m/z)*: 245 [M^+]; Anal. Calcd. for $C_7H_{11}N_5O_3S$: C; 34.28, H; 4.52, N; 28.55; Found: C; 34.25, H; 4.48, N; 28.51.

Synthesis of *N*-[3-(1*H*-2-amino-5-nitrothiazolyl)propyl]-*N'*-[phenylmethylidene]urea, compound 3a:

The compound **2** (0.0330 mole) and benzaldehyde (0.0330 mole) in methanol (100 ml) in the presence of 2-4 drops of glacial acetic acid were first stirred on a magnetic stirrer for about 2.00 hours followed by reflux on a steam bath for about 3.30 hours. The completion of the reaction was monitored by silica gel-G coated TLC plates. The product was filtered and cooled at room temperature. The filtered product was purified over a silica gel packed column chromatography using CH_3OH : $CHCl_3$ (7 : 3 v/v) as eluant (75 ml). The purified product was dried under vacuo and recrystallized from ethanol at room temperature to furnish compound **3a** (Figure 3).

Compounds **3b-3j** have also been synthesized by using similar method as above.



3(a-j)

Figure 3. Structure of compound **3a-3j**.

*N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(phenyl)methylidene]urea (**3a**):* Yield: 62%; m.p. 148-149ºC; IR (cm^{-1}): 856 (C-S), 961 (C-NO), 1329 (N-CH_2), 1356, 1531 (NO_2), 1547 (C=C), 1565 (N=CH), 1661 (C=O), 1427, 2878, 2912 (CH_2), 3016 (CH-Ar), 3382 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.02-2.07 (m, 2H, H-8), 3.20-3.25 (m, 2H, H-9), 3.80-3.85 (m, 2H, H-7), 5.60 (s, 1H, H-1'), 7.24 (s, 1H, H-4),

7.89 (s, 1H, H-6), 8.02 (s, 1H, H-10), 6.75-7.84 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 28.2 (C-8), 36.5 (C-9), 42.4 (C-7), 126.7 (C-12 and C-16), 128.4 (C-14), 129.3 (C-13 and C-15), 130.7 (C-4), 136.6 (C-5), 137.2 (C-11), 147.4 (C-10), 160.5 (C-2'), 168.8 (C-2); Anal. Calcd. for $C_{14}H_{15}N_5O_3S$: C; 50.44, H; 4.53, N; 21.00; Found: C; 50.35, H; 4.55, N; 20.95; FAB-Mass *(m/z)*: 333 [M^+].

N-[3-(2-Amino-5-nitrothiazolyl)propyl]-N'-[(4-chlorophenyl)methylidene]urea (**3b**): Yield: 62%; m.p 178-179ºC; IR (cm^{-1}): IR: 744 (C-Cl), 870 (C-S), 968 (C-NO), 1342 (N-CH_2), 1365, 1541 (NO_2), 1556 (C=C), 1568 (N=CH), 1670 (C=O), 1430, 2884, 2917 (CH_2), 3022 (CH-Ar), 3390 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.11-2.15 (m, 2H, H-8), 3.22-3.27 (m, 2H, H-9), 3.83-3.88 (m, 2H, H-7), 5.64 (s, 1H, H-1'), 7.89 (s, 1H, H-4), 7.98 (s, 1H, H-6), 8.13 (s, 1H, H-10), 6.94-7.65 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 28.6 (C-8), 40.1 (C-9), 43.2 (C-7), 126.6 (C-12 and C-16), 128.9 (C-14), 129.6 (C-13 and C-15), 130.9 (C-4), 135.2 (C-5), 141.4 (C-11), 147.7 (C-10), 160.2 (C-2'), 168.4 (C-2); FAB-Mass *(m/z)*: 367 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_5O_3SCl$: C; 45.71, H; 3.83, N; 19.04; Found: C; 45.60, H; 3.81, N; 19.01.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(3-chlorophenyl)methylidene]urea (**3c**): Yield: 62%; m.p 174-175ºC; IR (cm^{-1}): 745 (C-Cl), 866 (C-S), 977 (C-NO), 1336 (N-CH_2), 1360, 1536 (NO_2), 1550 (C=C), 1558 (N=CH), 1667 (C=O),1434, 2892, 2930 (CH_2), 3026 (CH-Ar), 3386 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.11-2.15 (m, 2H, H-8), 3.28-3.32 (m, 2H, H-9), 3.84-3.89 (m, 2H, H-7), 5.72 (s, 1H, H-1'), 7.30 (s, 1H, H-4), 7.95 (s, 1H, H-6), 8.14 (s, 1H, H-10), 6.82-7.93 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 30.3 (C-8), 39.6 (C-9), 43.5 (C-7), 127.7 (C-12), 128.4 (C-16), 129.4 (C-14), 130.3 (C-13), 131.7 (C-15), 133.4 (C-4), 137.1 (C-5), 141.9 (C-11), 151.2 (C-10), 161.3 (C-2'), 169.8 (C-2); FAB-Mass *(m/z)*: 367 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_5O_3SCl$: C; 45.71, H; 3.83, N; 19.04; Found: C; 45.67, H; 3.77, N; 18.98.

N-[3-(2-Amino-5-nitrothiazolyl)propyl]-N'-[(2-chlorophenyl)methylidene]urea (**3d**): Yield: 62%; m.p 172-173ºC; IR (cm^{-1}): 747 (C-Cl), 860 (C-S), 962 (C-NO), 1330 (N-CH_2), 1358, 1534 (NO_2), 1549 (C=C), 1566 (N=CH), 1663 (C=O), 1428, 2880, 2913 (CH_2), 3017 (CH-Ar), 3384 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.08-2.12 (m, 2H, H-8), 3.30-3.35 (m, 2H, H-9), 3.82-3.86 (m, 2H, H-7), 5.70 (s, 1H, H-1'), 7.31 (s, 1H, H-4), 7.91 (s, 1H, H-6), 8.18 (s, 1H, H-10), 6.86-7.84 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 31.2 (C-8), 38.8 (C-9), 44.7 (C-7), 127.3 (C-12), 128.6 (C-16), 129.7 (C-14), 130.4 (C-13), 132.5 (C-15), 134.5 (C-4), 138.2 (C-11), 138.9 (C-5), 151.6 (C-10), 162.4 (C-2'), 169.3 (C-2), (Ar); FAB-Mass *(m/z)*: 367 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_5O_3SCl$: C; 45.71, H; 3.83, N; 19.04; Found: C; 45.65, H; 3.75, N; 19.02.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(4-bromophenyl)methylidene]urea (**3e**): Yield: 62%; m.p 170-171ºC; IR (cm^{-1}): 638 (C-Br), 858 (C-S), 970 (C-NO), 1335 (N-CH_2), 1370, 1537 (NO_2), 1551 (C=C), 1575 (N=CH), 1674 (C=O), 1440, 2886, 2921 (CH_2), 3019 (CH-Ar), 3387 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.07-2.12 (m, 2H, H-8), 3.29-3.34 (m, 2H, H-9), 3.81-3.85 (m, 2H, H-7), 5.73 (s, 1H, H-1'), 7.28 (s, 1H, H-4), 7.91 (s, 1H, H-6), 8.20 (s, 1H, H-10), 6.70-7.85 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 29.3 (C-8), 36.8 (C-9), 42.6 (C-7), 128.6 (C-12 and C-16), 130.5 (C-14), 131.2 (C-13 and C-15), 132.2 (C-4), 136.3 (C-5), 138.8 (C-11), 150.7 (C-10), 162.1 (C-2'), 170.4 (C-2); FAB-Mass *(m/z)*: 412 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_5O_3SBr$: C; 40.78, H; 3.42, N; 16.98; Found: C; 45.75, H; 3.39, N; 6.92.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(3-bromophenyl)methylidene]urea (**3f**): Yield: 62%; m.p 169-170ºC; IR (cm^{-1}): 643 (C-Br), 860 (C-S), 963 (C-NO), 1337 (N-CH_2), 1374, 1540 (NO_2), 1554 (C=C), 1571 (N=CH), 1671 (C=O), 1432, 2888, 2922 (CH_2), 3025 (CH-Ar), 3388 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.10-2.17 (m, 2H, H-8), 3.30-3.36 (m, 2H, H-9), 3.87-3.92 (m, 2H, H-7), 5.67 (s, 1H, H-1'), 7.39 (s, 1H, H-4), 7.99 (s, 1H, H-6), 8.16 (s, 1H, H-10), 6.69-7.81 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 31.8 (C-8), 37.2 (C-9), 45.4 (C-7), 128.3 (C-12), 128.7 (C-16), 130.8 (C-14), 131.6 (C-13), 132.7 (C-4), 133.8 (C-15), 136.4 (C-5), 139.4 (C-11), 148.6 (C-10), 161.9 (C-2'), 170.7 (C-2); FAB-Mass *(m/z)*: 412 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_5O_3BrS$: C; 40.78, H; 3.42, N; 16.98; Found: C; 40.73, H; 3.37, N; 16.94.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(2-bromophenyl)methylidene]urea (**3g**): Yield: 62%; m.p 165-167ºC; IR (cm^{-1}): 645 (C-Br), 871 (C-S), 965 (C-NO), 1332 (N-CH_2), 1359, 1533 (NO_2), 1552 (C=C), 1560 (N=CH), 1664 (C=O), 1437, 2883, 2914 (CH_2), 3024 (CH-Ar), 3385 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.11-2.16 (m, 2H, H-8), 3.25-3.29 (m, 2H, H-9), 3.88-3.93 (m, 2H, H-7), 5.71 (s, 1H, H-1'), 7.40 (s, 1H, H-4), 7.94 (s, 1H, H-6), 8.14 (s, 1H, H-10), 6.71-7.89 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 31.5 (C-8), 37.6 (C-9), 45.8 (C-7), 129.4 (C-12), 130.6 (C-16), 131.3 (C-14), 132.1 (C-13), 133.7 (C-15), 133.9 (C-4), 137.5 (C-5), 140.6 (C-11), 148.9 (C-10), 163.6 (C-2'), 171.4 (C-2); FAB-Mass *(m/z)*: 412 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_5O_3BrS$: C; 40.78, H; 3.42, N; 16.98; Found: C; 40.70, H; 3.36, N; 16.93.

N-[3-(2-amino-5-nitrothiazolyl)-propyl]-N'-[(4-nitrophenyl)-methylidene]urea (**3h**): Yield: 62%; m.p 167-168ºC; IR (cm^{-1}): 865 (C-S), 974 (C-NO), 1340 (N-CH_2), 1367, 1532 (NO_2), 1560 (C=C), 1573 (N=CH), 1673 (C=O), 1435, 2891, 2925 (CH_2), 3021 (CH-Ar), 3393 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.12-2.15 (m, 2H, H-8), 3.24-3.30 (m, 2H, H-9), 3.91-3.96 (m, 2H, H-7), 5.65 (s, 1H, H-1'), 7.32 (s, 1H, H-4), 7.99 (s, 1H, H-6), 8.17 (s, 1H, H-10), 6.74-7.95 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 29.8 (C-8), 40.4 (C-9), 44.5 (C-7), 129.8 (C-12 and C-16), 131.2 (C-14), 132.7 (C-13 and C-15), 134.8 (C-4), 138.6 (C-5), 140.3 (C-11), 150.7 (C-10), 160.4 (C-2'), 171.3 (C-2); FAB-Mass *(m/z)*: 378 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_6O_5S$: C; 44.44, H; 3.72, N; 22.21; Found: C; 44.40, H; 3.69, N; 22.19.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(3-nitrophenyl)methylidene]urea (**3i**): Yield: 62%; m.p 165-166ºC; IR (cm^{-1}): 859 (C-S), 972 (C-NO), 1338 (N-CH_2), 1371, 1545 (NO_2), 1557 (C=C), 1563 (N=CH), 1665 (C=O), 1431, 2894, 2927 (CH_2), 3030 (CH-Ar), 3394 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.11-2.15 (m, 2H, H-8), 3.29-3.33 (m, 2H, H-9), 3.85-3.89 (m, 2H, H-7), 5.66 (s, 1H, H-1'), 7.33 (s, 1H, H-4), 7.92 (s, 1H, H-6), 8.15 (s, 1H, H-10), 6.78-7.86 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 30.7 (C-8), 38.3 (C-9), 45.8 (C-7), 131.4 (C-4), 130.1 (C-12), 130.9 (C-16), 132.6 (C-14), 133.4 (C-13), 134.1 (C-15), 136.9 (C-5), 137.5 (C-11), 149.2 (C-10), 163.6 (C-2'), 172.7

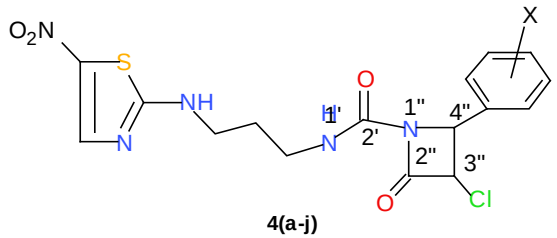
(C-2); FAB-Mass *(m/z)*: 378 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_6O_5S$: C; 44.44, H; 3.72, N; 22.21; Found: C; 44.38, H; 3.66, N; 22.17.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(2-nitro-phenyl)methylidene]urea (**3j**): Yield: 62%; m.p 162-163ºC; IR (cm^{-1}): 864 (C-S), 976 (C-NO), 1341 (N-CH_2), 1369, 1541 (NO_2), 1553 (C=C), 1561 (N=CH), 1669 (C=O), 1438, 2890, 2924 (CH_2), 3028 (CH-Ar), 3397 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.15-2.19 (m, 2H, H-8), 3.20-3.26 (m, 2H, H-9), 3.87-3.93 (m, 2H, H-7), 5.68 (s, 1H, H-1'), 7.36 (s, 1H, H-4), 7.96 (s, 1H, H-6), 8.10 (s, 1H, H-10), 6.80-7.90 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 30.7 (C-8), 39.7 (C-9), 44.5 (C-7), 131.8 (C-4), 130.5 (C-12), 131.6 (C-16), 132.4 (C-14), 133.6 (C-13), 134.5 (C-15), 137.3 (C-5), 139.7 (C-11), 149.9 (C-10), 163.2 (C-2'), 172.1 (C-2); FAB-Mass *(m/z)*: 378 [M^+]; Anal. Calcd. for $C_{14}H_{14}N_6O_5S$: C; 44.44, H; 3.72, N; 22.21; Found: C; 44.35, H; 3.70, N; 22.18.

Synthesis of *N*-[3-(2-amino-5-nitrothiazolyl)-propyl]-4-phenyl-3-chloro-2-oxo-1-azetidine-carboxamide (4a):

The compound **3a** (0.009 mole) and chloroacetyl chloride (0.009 mole) in methanol (100 ml) in the presence of Et_3N (0.009 mole) were allowed to react at room temperature. The reaction mixture was first stirred on a magnetic stirrer for about 2.00 hours followed by reflux on a steam bath for about 3.30 hours. The completion of the reaction was monitored by silica gel-G coated TLC plates. The product was filtered and cooled at room temperature. The filtered product was purified over a silica gel packed column chromatography using CH_3OH : $CHCl_3$ (7 : 3 v/v) as eluant (90 ml). The purified product was dried under vacuo and recrystallized from acetone at room temperature to furnish compound **4a** (Figure 4).

Compounds **4b-4j** have also been synthesized by using similar method as above.



4(a-j)

Figure 4. Structure of compound **4a-4j**.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4a**): Yield: 61%; m.p. 169-170 ºC; IR (cm^{-1}): 860 (C-S), 964 (C-NO), 1335 (N-CH_2), 1360, 1536 (NO_2), 1551 (C=C), 1666 (C=O), 1736 (CO cyclic), 1432, 2884, 2917 (CH_2), 2957 (CH-Cl), 3021 (CH-Ar), 3385 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.07-2.11 (m, 2H, H-8), 3.22-3.29 (m, 2H, H-9), 3.88-3.94 (m, 2H, H-7), 4.36 (d, 1H, *J* = 4.80 Hz, H-3"), 5.12 (d, 1H, *J* = 4.80Hz, H-4"), 5.65 (s, 1H, H-1'), 7.81 (s, 1H, H-4), 7.94 (s, 1H, H-6), 6.72-7.96 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 29.1 (C-8), 37.5 (C-9), 44.9 (C-7), 50.2 (C-3"), 59.4 (C-4"), 128.1 (C-11 and C-16), 128.5 (C-15), 129.7 (C-12 and C-14), 132.7 (C-4), 136.6 (C-5), 138.5 (C-10), 161.5 (C-2'), 169.2 (C-2), 170.2 (C-2"); Mass (FAB): 409M^+; Anal. Calcd. for $C_{16}H_{16}N_5O_4SCl$: C; 46.88, H; 3.93, N; 17.08%; Found: C; 46.82, H; 3.91, N; 17.02%;

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(4-chloro-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4b**): Yield: 64%; m.p 178-179 ºC; IR (cm^{-1}): 758 (C-Cl), 863 (C-S), 966 (C-NO), 1345 (N-CH_2), 1362, 1540 (NO_2), 1560 (C=C), 1667 (C=O), 1742 (CO cyclic), 1436, 2887, 2921 (CH_2), 2960 (CH-Cl), 3026 (CH-Ar), 3391 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.12-2.16 (m, 2H, H-8), 3.25-3.31 (m, 2H, H-9), 3.88-3.90 (m, 2H, H-7), 4.38 (d, 1H, *J* = 4.80Hz, H-3"), 5.15 (d, 1H, *J* = 4.80Hz, H-4"), 5.66 (s, 1H, H-1'), 7.92 (s, 1H, H-4), 7.95 (s, 1H, H-6), 6.83-7.97 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 29.6 (C-8), 38.3 (C-9), 45.1 (C-7), 52.6 (C-3"), 60.2 (C-4"), 128.6 (C-11 and C-16), 129.1 (C-15), 129.9 (C-12 and C-14), 135.2 (C-4), 138.8 (C-10), 139.5 (C-5), 163.5 (C-2'), 179.2 (C-2), 170.6 (C-2"); Mass (FAB): 444M^+. Anal. Calcd. for $C_{16}H_{15}N_5O_4SCl_2$: C; 43.25, H; 3.40, N; 15.76%; Found: C; 43.23, H; 3.34, N; 15.68%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(3-chloro-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4c**): Yield: 65%; m.p 182-183 ºC; IR (cm^{-1}): 763 (C-Cl), 866 (C-S), 973 (C-NO), 1336 (N-CH_2), 1363, 1541 (NO_2), 1557 (C=C), 1674 (C=O), 1740 (CO cyclic), 1434, 2890, 2919 (CH_2), 2968 (CH-Cl), 3025 (CH-Ar), 3395 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.15-2.18 (m, 2H, H-8), 3.31-3.36 (m, 2H, H-9), 3.89-3.92 (m, 2H, H-7), 4.40 (d, 1H, *J* = 4.80Hz, H-3"), 5.16 (d, 1H, *J* = 4.80Hz, H-4"), 5.68 (s, 1H, H-1'), 7.95 (s, 1H, H-4), 7.97 (s, 1H, H-6), 6.74-7.80 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 30.4 (C-8), 38.7 (C-9), 46.2 (C-7), 54.2 (C-3"), 61.3 (C-4"), 127.9 (C-11), 128.5 (C-16), 129.4 (C-15), 130.8 (C-12), 131.3 (C-14), 133.6 (C-4), 138.4 (C-5), 142.2 (C-10), 163.7 (C-2'), 171.4 (C-2), 172.5 (C-2"); Mass (FAB): 444M^+. Anal. Calcd. for $C_{16}H_{15}N_5O_4SCl_2$: C; 43.25, H; 3.40, N; 15.76%; Found: C; 43.19, H; 3.35, N; 15.71%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(2-chloro-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4d**): Yield: 67%; m.p 188-189 ºC; IR (cm^{-1}): 765 (C-Cl), 867 (C-S), 974 (C-NO), 1337 (N-CH_2), 1368, 1537 (NO_2), 1554 (C=C), 1668 (C=O), 1743 (CO cyclic), 1441, 2893, 2927 (CH_2), 2966 (CH-Cl), 3022 (CH-Ar), 3389 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.19-2.20 (m, 2H, H-8), 3.30-3.34 (m, 2H, H-9), 3.92-3.97 (m, 2H, H-7), 4.45 (d, 1H, *J* = 4.75Hz, H-3"), 5.19 (d, 1H, *J* = 4.75Hz, H-4"), 5.72 (s, 1H, H-1'), 7.86 (s, 1H, H-4), 7.98 (s, 1H, H-6), 6.65-7.98 (m, 4H, Ar-H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 30.8 (C-8), 39.3 (C-9), 46.8 (C-7), 51.3 (C-3"), 61.8 (C-4"), 128.6 (C-11), 129.8 (C-16), 130.2 (C-15), 130.8 (C-12), 131.7 (C-14), 134.0 (C-4), 137.6 (C-5), 139.1 (C-10), 164.2 (C-2'), 171.9 (C-2), 172.8 (C-2"); Mass (FAB): 444M^+. Anal. Calcd. for $C_{16}H_{15}N_5O_4SCl_2$: C; 43.25, H; 3.40, N; 15.76%; Found: C; 43.21, H; 3.38, N; 15.73%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(4-bromo-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4e**): Yield: 66%; m.p 186-187 ºC; IR (cm^{-1}): 567 (C-Br), 871 (C-S), 965 (C-NO), 1342 (N-CH_2), 1364, 1546 (NO_2), 1563 (C=C), 1672 (C=O), 1737 (CO cyclic), 1439, 2894, 2926 (CH_2), 2963 (CH-Cl), 3024 (CH-Ar), 3396 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.15-2.20 (m, 2H, H-8), 3.32-3.38 (m, 2H, H-9), 3.94-3.98 (m, 2H, H-7), 4.42 (d, 1H, *J* =

4.80Hz, H-3"), 5.30 (d, 1H, *J* = 4.80Hz, H-4"), 5.69 (s, 1H, H-1'), 7.88 (s, 1H, H-4), 8.01 (s, 1H, H-6), 6.6-7.73 (m, 4H, Ar-H); ^{13}C NMR (CDCl3, 75 MHz) δ: 31.5 (C-8), 37.9 (C-9), 44.8 (C-7), 54.7 (C-3"), 62.1 (C-4"), 129.3 (C-11 and C-16), 130.6 (C-15), 131.2 (C-12 and C-14), 134.4 (C-4), 139.5 (C-10), 140.7 (C-5), 164.8 (C-2'), 170.5 (C-2), 171.1 (C-2"); Mass (FAB): 489M$^+$. Anal. Calcd. for $C_{16}H_{15}N_5O_4SBrCl$: C; 39.31, H; 3.09, N; 14.32%; Found: C; 39.26, H; 3.06, N; 14.24%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(3-bromo-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4f**): Yield: 68%; m.p 184-185 ºC; IR (cm^{-1}): 565 (C-Br), 871 (C-S), 967 (C-NO), 1340 (N-CH_2), 1366, 1539 (NO_2), 1553 (C=C), 1650 (C=O), 1736 (CO cyclic), 1441, 2829 (CH_2), 2910 (CH_2), 2964 (CH-Cl), 3043 (CH-Ar), 3352 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.12-2.16 (m, 2H, H-8), 3.34-3.39 (m, 2H, H-9), 3.96-3.99 (m, 2H, H-7), 4.43 (d, 1H, *J* = 4.75Hz, H-3"), 5.22 (d, 1H, *J* = 4.75Hz, H-4"), 5.70 (s, 1H, H-1'), 7.95 (s, 1H, H-4), 8.04 (s, 1H, H-6), 6.72-7.01 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 31.7 (C-8), 41.8 (C-9), 48.2 (C-7), 52.4 (C-3"), 62.5 (C-4"), 130.7 (C-11), 131.5 (C-16), 132.1 (C-4), 132.7 (C-15), 133.4 (C-12), 134.9 (C-14), 137.5 (C-5), 142.0 (C-10), 162.6 (C-2'), 169.8 (C-2), 170.9 (C-2") (6C, Ar); Mass (FAB): 444M$^+$. Anal. Calcd. for $C_{16}H_{15}N_5O_4SBrCl$: C; 39.31, H; 3.09, N; 14.32%; Found: C; 39.27, H; 3.01, N; 14.29%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(2-bromo-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4g**): Yield: 67%; m.p 179-180 ºC; IR (cm^{-1}): 572 (C-Br), 864 (C-S), 980 (C-NO), 1346 (N-CH_2), 1369, 1542 (NO_2), 1553 (C=C), 1663 (C=O), 1741 (CO cyclic), 1438, 2892 (CH_2), 2924, 2965 (CH-Cl), 3029 (CH-Ar), 3394 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.07-2.10 (m, 2H, H-8), 3.31-3.35 (m, 2H, H-9), 3.89-3.93 (m, 2H, H-7), 4.39 (d, 1H, *J* = 4.70Hz, H-3"), 5.23 (d, 1H, *J* = 4.70Hz, H-4"), 5.72 (s, 1H, H-1'), 7.89 (s, 1H, H-4), 8.05 (s, 1H, H-6), 6.75-7.76 (m, 4H, Ar-H); ^{13}C NMR (CDCl3, 75 MHz) δ: 32.3 (C-8), 41.4 (C-9), 45.7 (C-7), 50.6 (C-3"), 63.8 (C-4"), 129.7 (C-11), 130.5 (C-16), 131.4 (C-15), 131.7 (C-4), 132.4 (C-12), 133.7 (C-14), 138.6 (C-5), 140.2 (C-10), 162.9 (C-2'), 171.7 (C-2), 172.3 (C-2") (6C, Ar); Mass (FAB): 444M$^+$. Anal. Calcd. for $C_{16}H_{15}N_5O_4SBrCl$: C; 39.31, H; 3.09, N; 14.32%; Found: C; 39.28, H; 3.05, N; 14.28%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(4-nitro-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4h**): Yield: 65%; m.p 178-179 ºC; IR (cm^{-1}): 870 (C-S), 975 (C-NO), 1339 (N-CH_2), 1367, 1543 (NO_2), 1554 (C=C), 1665 (C=O), 1746 (CO cyclic), 1440, 2891, 2918 (CH_2), 2961 (CH-Cl), 3021 (CH-Ar), 3399 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.16-2.18 (m, 2H, H-8), 3.32-3.36 (m, 2H, H-9), 3.90-3.94 (m, 2H, H-7), 4.47 (d, 1H, *J* = 4.70Hz, H-3"), 5.25 (d, 1H, *J* = 4.70Hz, H-4"), 5.76 (s, 1H, H-1'), 7.90 (s, 1H, H-4), 8.07 (s, 1H, H-6), 6.78-7.80 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 33.4 (C-8), 41.9 (C-9), 46.8 (C-7), 52.3 (C-3"), 63.7 (C-4"), 126.9 (C-11 and C-16), 128.2 (C-15), 130.5 (C-12 and C-14), 137.9 (C-4), 139.6 (C-5), 143.7 (C-10), 161.8 (C-2'), 170.9 (C-2), 171.2 (C-2"); Mass (FAB): 454M$^+$. Anal. Calcd. for $C_{16}H_{15}N_6O_6SCl$: C; 42.25, H; 3.32, N; 18.47%; Found: C; 42.14, H; 3.22, N; 18.41%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(3-nitro-phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4i**): Yield: 69%; m.p 177-178 ºC; IR (cm^{-1}): 865 (C-S), 969 (C-NO), 1343 (N-CH_2), 1365, 1544 (NO_2), 1561 (C=C), 1670 (C=O), 1739 (CO cyclic), 1442, 2888, 2925 (CH_2), 2958 (CH-Cl), 3028 (CH-Ar), 3392 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.09-2.12 (m, 2H, H-8), 3.31-3.37 (m, 2H, H-9), 3.90-3.97 (m, 2H, H-7), 4.48 (d, 1H, *J* = 4.80Hz, H-3"), 5.26 (d, 1H, *J* = 4.80Hz, H-4"), 5.76 (s, 1H, H-1'), 7.92 (s, 1H, H-4), 8.10 (s, 1H, H-6), 6.77-7.83 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 33.2 (C-8), 39.8 (C-9), 47.7 (C-7), 53.4 (C-3"), 64.7 (C-4"), 130.4 (C-11), 131.7 (C-16), 132.5 (C-15), 132.9 (C-12), 133.6 (C-14), 136.8 (C-4), 139.4 (C-5), 140.8 (C-10), 162.2 (C-2'), 172.8 (C-2), 173.6 (C-2"); Mass (FAB): 454M$^+$. Anal. Calcd. for $C_{16}H_{15}N_6O_6SCl$: C; 42.25, H; 3.32, N; 18.47%; Found: C; 42.15, H; 3.26, N; 18.43%.

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(2-nitrophe-nyl)-3-chloro-2-oxo-1-azetidinecarboxamide (**4j**): Yield: 62%; m.p 180-181 ºC; IR (cm^{-1}): 869 (C-S), 971 (C-NO), 1350 (N-CH_2), 1370, 1538 (NO_2), 1556 (C=C), 1671 (C=O), 1741 (CO cyclic), 1437, 2889, 2920 (CH_2), 2959 (CH-Cl), 3023 (CH-Ar), 3387 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 2.11-2.15 (m, 2H, H-8), 3.30-3.34 (m, 2H, H-9), 3.94-3.98 (m, 2H, H-7), 4.49 (d, 1H, *J* = 4.75Hz, H-3"), 5.28 (d, 1H, *J* = 4.75Hz, H-4"), 5.78 (s, 1H, H-1'), 7.94 (s, 1H, H-4), 8.12 (s, 1H, H-6), 6.90-7.84 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 33.5 (C-8), 40.7 (C-9), 48.6 (C-7), 51.5 (C-3"), 64.1 (C-4"), 131.1 (C-11), 132.2 (C-16), 132.7 (C-15), 133.4 (C-12), 133.9 (C-4), 134.3 (C-14), 136.3 (C-5), 141.4 (C-10), 163.2 (C-2'), 170.7 (C-2), 171.5 (C-2"); Mass (FAB): 454M$^+$. Anal. Calcd. for $C_{16}H_{15}N_6O_6SCl$: C; 42.25, H; 3.32, N; 18.47%; Found: C; 42.18, H; 3.29, N; 18.44%.

RESULTS AND DISCUSSION

N-[3-(2-amino-5-nitrothiazolyl)-propyl]-4-(substituted phenyl)-3-chloro-2-oxo-1-azetidine-carboxamide, compounds **4a-4j** were synthesized in four different steps: 2-amino-5-nitrothiazole on reaction with $Cl(CH_2)_3Br$ at room temperature to afford 1-(3-chloropropyl)-2-amino-5-nitrothiazole, compound **1**. IR spectrum of compound **1** displayed absorption at 1313 and 727 cm^{-1} for (N-CH_2) and (C-Cl) respectively. In the FAB-Mass spectrum of compound **1** parent ion peak found at 221 M$^+$. The compound **1** on reaction with urea at room temperature yielded *N*-[3-(2-amino-5-nitrothiazolyl)-propyl]-urea, compound **2**. IR spectrum of compound **2** showed absorption for NH at 3387 and for CO at 1662 cm^{-1} while absorption of (C-Cl) has been disappeared.

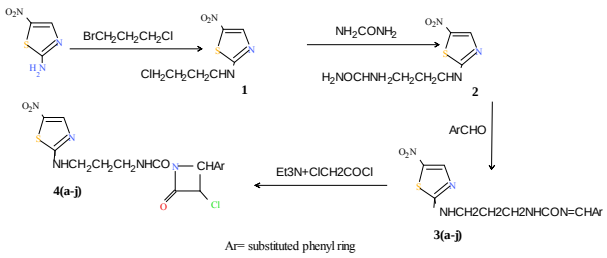


Table 1. Antibacterial and antifungal activities of compounds **4(a-j).**

Compd.	*B. subtilis*	*E. coli*	*S. aureus*	*K. pneumoniae*	*A. niger*	*A. flavus*	*F. oxisporium*	*C. albicans*
4a	10.25	13.5	7.25	13.5	>25	>25	13.5	>25
4b	15.5	7.25	7.25	9.25	13.5	>25	13.5	>25
4c	5.25	6.25	4.25	7.25	7.5	7.5	10.5	13.5
4d	6.25	7.50	7.25	7.25	8.25	10.5	10.25	12.75
4e	8.25	4.25	7.25	7.25	10.5	9.5	8.5	12.5
4f	4.25	7.25	6.25	6.25	9.5	8.75	10.25	13.25
4g	7.25	13.5	7.25	7.25	13.5	12.5	13.5	13.5
4h	4.25	4.25	7.25	4.25	7.50	8.5	8.5	12.75
4i	4.25	4.25	4.25	6.25	8.25	6.75	8.75	12.5
4j	4.25	6.25	4.25	4.25	7.50	7.25	8.5	12.5
Streptomycin	1.25	2.25	3.25	2.75	-	-	-	-
Griseofulvin	-	-	-	-	7.25	6.25	8.50	12.5

The ^{1}H NMR spectrum of compound 2 displayed signal of (CH_2-N) appear at δ 3.19-3.24 ppm and its ^{13}C NMR value of CO group appeared at δ 163.4 ppm. In the FAB-MS spectrum of compound **2** parent ion peaks found at (m/z) 245. The compound **2** on further reaction with selected several substituted aromatic aldehydes produced *N*-[3-(1*H*-2-amino-5-nitrothiazolyl)-propyl]-*N*'-[(substituted phenyl)-methylidene]urea, compounds **3a-3j**. For the compounds **3a-3j** characteristic absorption for Schiff base (N=CH) in IR spectra appeared in the range of 1558-1575cm^{-1} and in the ^{1}H NMR chemical shift at δ 8.02-8.20 ppm while in its ^{13}C NMR signal found at δ 147.4-151.6 ppm. In the ^{1}H NMR a broad signal of NH_2 has been disappeared at δ 5.96 ppm. In the FAB-Mass spectrum of 3a parent ion peak found at (m/z) 333.

The compounds **3a-j** on treatment with $ClCH_2COCl$ in the presence of Et_3N furnished final products compounds **4a-4j**. In the spectra of compounds 4a-4j carbonyl group of β-lactam ring showed characteristic absorptions in the range of 1736-1746 cm^{-1} and ^{1}H NMR spectrum two doublet appeared for (N-CH) and (CH-Cl) in the range of δ 5.12-5.30 and 4.36-4.49 ppm respectively with coupling constant J 5.00 Hz but in the ^{13}C NMR spectra three signals appeared for (N-CH), (CH-Cl) and (CO cyclic) at (δ) 59.4-64.7, 50.2-54.7 and 170.2-173.6 ppm respectively. The IR absorption ^{1}H and ^{13}C NMR signal of (N=CH) have been disappeared. The results of the all described activities (antibacterial, antifungal, antitubercular and antiinflammatory) were summarized in Tables 1, 2 and 3.

Table 2. Antitubercular activity of compounds **4a-j.**

Compound	Concentration	Compound	Concentration
4a	6.50	**4f**	2.75
4b	2.25	**4g**	3.50
4c	2.75	**4h**	2.25
4d	3.25	**4i**	2.25
4e	3.25	**4j**	2.50

The results of the antimicrobial screening data revealed that all the compounds **4a-4j** showed considerable and varied activity against the selected microorganism. A new series of *N*-[3-(2-amino-5-nitrothiazolyl)-propyl]-4-(substituted phenyl)-3-chloro-2-oxo-1-azetidine-carboxamide, compounds **4a-4j** were prepared and screened for their antimicrobial, antitubercular and anti-inflammatory activities data (as shown in Table 1 and 2) revealed that all the synthesized compounds **4a-4j** have a structure activity relationship (SAR) because activities of compounds varies with substitution. Nitro group containing compounds (**4h, 4i** and **4j**) showed higher activity than chloro (**4c, 4d**), or bromo group containing compounds (**4e, 4f**).

Table 3. Anti-inflammatory activity of compounds **4(a-j)**.

Compound	Paw volume (cm^3)[a]	Paw volume (cm^3)[b]	Inhibition,%
4a	0.66 ± 0.02	0.15 ± 0.02	50.00
4b	0.68 ± 0.02	0.14 ± 0.02	53.33
4c	0.65 ± 0.02	0.13 ± 0.01	56.67
4d	0.66 ± 0.02	0.13 ± 0.02	56.67
4e	0.68 ± 0.02	0.12 ± 0.01	60.00
4f	0.69 ± 0.03	0.13 ± 0.02	56.67
4g	0.65 ± 0.02	0.13 ± 0.01	56.67
4h	0.67 ± 0.03	0.12 ± 0.02	60.00
4i	0.68 ± 0.02	0.11 ± 0.03	63.33
4j	0.6 ± 0.03	0.11 ± 0.01	63.33
Control	0.69 ± 0.02	0.30 ± 0.01	-
Standard[c]	0.70 ± 0.03	0.10 ± 0.02	66.67

a) Before carageenan administration; (mean ± SEM) b) Total increase in paw volume after 5 hours (mean ± SEM); c) phenylbutazone standard

Chloro and bromo derivatives also have higher activity than other rested compounds. On the basis of SAR, concluded that the activity of compounds depends on electron withdrawing nature of the substituted groups. The sequence of the activity is following

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

The investigation of antimicrobial (antibacterial, antifungal and antitubercular) data revealed that the compounds **4c, 4d, 4e, 4f, 4h, 4i** and **4j** displayed high activity in the series, the compounds **4b** and **4g** showed moderate activity and rest compounds showed less activity against all the strains compared with standard drugs. In the anti-inflammatory activity (Table 3) compounds **4c, 4d, 4e, 4f, 4h, 4i** and **4j** showed high activity while rested compounds displayed moderate to less activity.

CONCLUSION

Concluded that all compounds have been synthesized successfully and screened for antimicrobial, antitubercular and anti-inflammatory activities data of compounds (shown in Table 1, 2 and 3) revealed that the compounds shows moderate to good activities 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 also thankful to Head, Department of Chemistry Dr. H. S. Gour, University, Sagar (India) for giving the facilities to carryout the work.

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Received: 01.03.2013.
Accepted: 18.04.2013.