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

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INTRODUCTION

Bacterial and fungal infection is most common problem of the world. Some serious and life threatening 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. Benzoazolone 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 anticonvulsant1, fungicidal2. Some of the thiazole analogues are also used as antibiological, antibacterial3-5. 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 importance6. Recently found application in drug development for the treatment of antimicrobial7, anticonvulsant8, antiinflammatory9, antibacterial10,11. As part of interest in heterocycles that have been explored for developing pharmaceutically important molecules.

The biological activities of both 2-oxo-azetidine and thiazone aroused our interest in the synthesis of 2-oxo-azetidine derivatives of 2-amino-5-nitrothiazole (scheme 1).

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: CHCl3 system (2:8). 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. oxysporum 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.

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, ¹H NMR, ¹³C 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.

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, ¹H NMR, ¹³C NMR, and FAB-Mass.

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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.

Antinflammatory activity

Carageenan induced rat paw oedema method was employed for evaluating the antinflammatory 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-chloropropene (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 CHCl3 : CH3OH (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).

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), 961 (C-NO), 1348, 2887, 2912 (CH2), 3021 (CH-Ar), 3382 (NH); 1H NMR (300 MHz, CDCl3, TMS) δ 1.91-1.95 (m, 2H H-8), 3.19-3.24 (m, 2H, H-9), 3.82-3.90 (m, 2H, H-7), 7.71 (s, 1H, H-4), 7.83 (br, s, 1H, H-6); 13C NMR (75 MHz, CDCl3, TMS) δ 33.4 (C-8), 38.6 (C-9), 44.1 (C-7), 133.8 (C-4), 138.5 (C-5), 1432, 2885, 2918 (CH2), 3021 (CH-Ar), 3387 (NH), 3452 (NH2); 1H NMR (300 MHz, CDCl3, 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), 4.67 (s, 1H, H-1'), 5.97 (br s, 2H, H-3'), 7.65 (s, 1H, H-4), 7.80 (br, s, 1H, H-6); 13C NMR (75 MHz, CDCl3, TMS) δ 33.6 (C-3'), 38.6 (C-9), 44.1 (C-7), 133.8 (C-4), 138.5 (C-5), 163.6 (C-2'), 165.3 (C-2); FAB-Mass (m/z): 221 [M+] ; Anal. Calcd. for C7H11N5O3S: C 34.25, H 4.48, N 28.51; Found: C 34.25, H 4.48, N 28.51.

Synthesis of N-[3-(2-amino-5-nitrothiazolyl)-propyl]-urea, (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), 1360, 1533 (NO2), 1559 (C=C), 1662 (C=O), 1432, 2885, 2918 (CH2), 3021 (CH-Ar), 3387 (NH), 3452 (NH2); 1H NMR (300 MHz, CDCl3, 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), 4.67 (s, 1H, H-1'), 5.97 (br s, 2H, H-3'), 7.65 (s, 1H, H-4), 7.80 (br, s, 1H, H-6); 13C NMR (75 MHz, CDCl3, TMS) δ 33.6 (C-3'), 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): 221 [M+] ; Anal. Calcd. for C8H13N5O3S: C 42.55, H 4.52, N 28.55; Found: C 34.25, H 4.48, N 28.51.

Synthesis of N-[3-(1H-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 CHCl3 : CH3OH (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.

Figure 2. Structure of compound 2.

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

Synthesis of azetidinone derivatives of 2-amino-5-nitrothiazole

**Section A-Research Paper**

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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-9), 136.6 (C-5), 137.2 (C-11), 147.4 (C-10), 160.5 (C-2'), 168.8 (C-2); FAB-Mass (m/z): 412 [M$^+$]; Anal. Calcd. for C$_{14}$H$_{14}$N$_5$O$_3$SCl: 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'-[(4-chlorophenyl)methylidene]urea (3b): Yield: 62%; m.p 165-167°C; IR (cm$^{-1}$): 645 (C-Br), 871 (C-S), 965 (C-NO), 1332 (C=O), 1359, 1533 (NO$_2$), 1552 (C=C), 1560 (C=O), 1437, 2883, 2914 (CH$_3$), 3024 (CH-Ar), 3385 (NH); $^{1}$H NMR (300 MHz, CDCl$_3$, TMS) δ: 2.1-2.16 (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), 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$_5$O$_3$S: C; 50.44, H; 4.53, N; 21.00; Found: C; 50.53, H; 4.55, N; 20.95; FAB-Mass (m/z): 333 [M$^+$].
N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-N'-[(2-nitrophenyl)methylene]urea (3): Yield: 62%; m.p 162-163°C; IR (cm\(^{-1}\)): 864 (C=S), 976 (C-NO), 1341 (N-CH\(_3\)), 1369, 1541 (NO\(_2\)), 1553 (C=C), 1561 (N=CH\(_2\)), 1669 (C=O), 1438, 2890, 2924 (CH\(_2\)), 3028 (CH-\(\text{Ar}\)), 3397 (NH); \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS) \(\delta\): 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); \(^1\)C NMR (75 MHz, CDCl\(_3\), TMS) \(\delta\): 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. Caled. for C\(_{30}\)H\(_{26}\)N\(_7\)O\(_6\)S: 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\(_3\)N (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 3.00 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\(_3\)OH : CHCl\(_3\) (7 : 3 v/v) as eluant 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.

![Figure 4. Structure of compound 4a-4j.](https://example.com/figure4.png)

N-[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(phenyl)-3-chloro-2-oxo-1-azetidine-carboxamide (4a): Yield: 61%; m.p. 169-170 °C; IR (cm\(^{-1}\)): 860 (C=S), 964 (C-NO), 1335 (N-CH\(_3\)), 1360, 1556 (NO\(_2\)), 1551 (C=C), 1736 (CO cyclic), 1432, 2884, 2917 (CH\(_3\)), 2957 (CH-\(\text{Ar}\)), 3202 (CH-\(\text{Ar}\)), 3385 (NH); \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS) \(\delta\): 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); \(^1\)C NMR (75 MHz, CDCl\(_3\), TMS) \(\delta\): 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. Caled. for C\(_{48}\)H\(_{36}\)N\(_7\)O\(_6\)S: 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-(3-bromophenyl)-3-chloro-2-oxo-1-azetidine-carboxamide (4f): Yield: 68%; m.p 179-180 ºC; IR (cm−1): 572 (C-Br), 864 (C-N), 1339 (N-CH2), 1367, 1554 (NO2), 1553 (C=C), 1665 (C=O), 1746 (CO cyclic), 1440, 2891, 2918 (CH2), 2961 (CH-Cl), 3021 (CH-Ar), 3399 (NH); 1H NMR (300 MHz, CDCl3, 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); 13C NMR (CDCl3, 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 C16H15N6O6SCl: C; 42.25, H; 3.32, N; 18.47%; Found: C; 42.18, H; 3.26, N; 18.44%.

RESULTS AND DISCUSSION

N-{[3-(2-Amino-5-nitrothiazolyl)-propyl]-4-(3-nitrophenoxy)-3-chloro-2-oxo-1-azetidine-carboxamide (4i): Yield: 69%; m.p 177-178 ºC; IR (cm−1): 865 (C-S), 969 (C-NO), 1343 (N-CH2), 1365, 1544 (NO2), 1561 (C=C), 1670 (C-O), 1739 (CO cyclic), 1442, 2888, 2925 (CH2), 2958 (CH-Cl), 3028 (CH-Ar), 3392 (NH); 1H NMR (300 MHz, CDCl3, 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); 13C NMR (CDCl3, 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 C16H15N5O4SBrCl: 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-amino-5-nitrothiazole)-3-chloro-2-oxo-1-azetidine-carboxamide (4j): Yield: 62%; m.p 180-181 ºC; IR (cm−1): 869 (C-S), 971 (C-NO), 1350 (N-CH2), 1370, 1538 (NO2), 1556 (C=C), 1741 (CO cyclic), 1437, 2889, 2920 (CH2), 2959 (CH-Cl), 3023 (CH-Ar), 3387 (NH); 1H NMR (300 MHz, CDCl3, 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); 13C NMR (CDCl3, 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-14), 134.3 (C-5), 141.4 (C-10), 163.2 (C-2”), 170.7 (C-2), 171.5 (C-2”); Mass (FAB): 454M+. Anal. Calcd. for C16H15N5O4SBrCl: C; 42.25, H; 3.32, N; 18.47%; Found: C; 42.18, H; 3.29, N; 18.44%.

The $^1$H NMR spectrum of compound 2 displayed signal of (CH$_2$-N) appear at $\delta$ 3.19-3.24 ppm and its $^{13}$C NMR value of CO group appeared at $\delta$ 163.4 ppm. In the FAB-MS spectrum of compound 2 parent ion peaks found at (m/z) 611-617. The compound 2 on further reaction with selected several substituted aromatic aldehydes produced N-[3-(1H-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 spectrum found at $\delta$ 147.4-151.6 ppm. In the $^1$H NMR a broad signal of NH$_2$ has been disappeared at $\delta$ 5.96 ppm. In the FAB-Mass spectrum of 3a parent ion peak found at (m/z) 333.

The compounds 3a-3j on treatment with CICH$_2$COCl in the presence of Et$_3$N furnished final products compounds 4a-4j. In the spectra of compounds 4a-4j carbonyl group of $\beta$-lactam ring showed characteristic absorptions in the range of 1736-1746 cm$^{-1}$ and in the $^1$H NMR chemical shift at $\delta$ 8.02-8.20 ppm while in its $^{13}$C NMR signal found at $\delta$ 147.4-151.6 ppm. In the $^1$H NMR a broad signal of NH$_2$ has been disappeared at $\delta$ 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 CICH$_2$COCl in the presence of Et$_3$N furnished final products compounds 4a-4j. In the spectra of compounds 4a-4j carbonyl group of $\beta$-lactam ring showed characteristic absorptions in the range of 1736-1746 cm$^{-1}$ and in the $^1$H NMR spectrum two doublet appeared for (N=CH) and (CH-Cl) in the range of $\delta$ 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 at $\delta$ 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 1. Antibacterial and antifungal activities of compounds 4(a-j).

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<td>-</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.25</td>
<td>6.25</td>
<td>8.50</td>
<td>12.5</td>
</tr>
</tbody>
</table>

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 (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 2. Antitubercular activity of compounds 4a-j.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Concentration</th>
<th>Paw volume (cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>6.50</td>
<td>4f</td>
</tr>
<tr>
<td>4b</td>
<td>2.25</td>
<td>4g</td>
</tr>
<tr>
<td>4c</td>
<td>2.75</td>
<td>4h</td>
</tr>
<tr>
<td>4d</td>
<td>3.25</td>
<td>4i</td>
</tr>
<tr>
<td>4e</td>
<td>3.25</td>
<td>4j</td>
</tr>
</tbody>
</table>

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 (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).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Paw volume (cm$^3$)</th>
<th>Paw volume (cm$^3$)</th>
<th>Inhibition, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>0.66 ± 0.02</td>
<td>0.15 ± 0.02</td>
<td>50.00</td>
</tr>
<tr>
<td>4b</td>
<td>0.68 ± 0.02</td>
<td>0.14 ± 0.02</td>
<td>53.33</td>
</tr>
<tr>
<td>4c</td>
<td>0.65 ± 0.02</td>
<td>0.13 ± 0.01</td>
<td>56.67</td>
</tr>
<tr>
<td>4d</td>
<td>0.66 ± 0.02</td>
<td>0.13 ± 0.02</td>
<td>56.67</td>
</tr>
<tr>
<td>4e</td>
<td>0.68 ± 0.02</td>
<td>0.12 ± 0.01</td>
<td>60.00</td>
</tr>
<tr>
<td>4f</td>
<td>0.69 ± 0.03</td>
<td>0.13 ± 0.02</td>
<td>56.67</td>
</tr>
<tr>
<td>4g</td>
<td>0.65 ± 0.02</td>
<td>0.13 ± 0.01</td>
<td>56.67</td>
</tr>
<tr>
<td>4h</td>
<td>0.67 ± 0.03</td>
<td>0.12 ± 0.02</td>
<td>60.00</td>
</tr>
<tr>
<td>4i</td>
<td>0.68 ± 0.02</td>
<td>0.11 ± 0.03</td>
<td>63.33</td>
</tr>
<tr>
<td>Control</td>
<td>0.6 ± 0.03</td>
<td>0.11 ± 0.01</td>
<td>63.33</td>
</tr>
<tr>
<td>Standard</td>
<td>0.70 ± 0.03</td>
<td>0.10 ± 0.02</td>
<td>66.67</td>
</tr>
</tbody>
</table>

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

$$\text{NO}_2 > \text{Cl} > \text{Br} > \text{OH} > \text{OCH}_3 > \text{CH}_3$$

The investigation of antimicrobial (antibacterial, antifungal and antituberclular) 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.

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REFERENCES


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