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Synthesis and Biological Significance of Some 2-Azetidinone Derivatives

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Abstract

A new series of *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(substitutedphenyl)-3-chloro-2-oxo-1-iminoazetidine, compounds **4(a-j)** were synthesized. The structures of all the synthesized compounds were confirmed by chemical and spectral analyses such as IR, ^{1}H NMR, ^{13}C NMR and FAB-Mass. The compounds **4(a-j)** were screened for their antibacterial, antifungal and antitubercular activities and gave acceptable results.

Keywords: Synthesis; 1,2,3-Benzotriazole; Azetidinone; Antimicrobial; Antitubercular

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. Also, 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. In addition, in 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.

It has been reported that benzotriazole derivatives possess a wide variety of biological activities such as antimicrobial [1,2], antibacterial [3], antifungal [4], antitubercular [5], antioxidant [6], antiviral [7], anti-inflammatory [8], antitumor [9] and anticonvulsant [10]. Similarly 2-azetidinone derivatives are also emerging chemotherapeutic agents possess several biological activity some of them are antimicrobial [11], antibacterial [12], antimalarial [13], anticancer [14], antiviral [15], antitubercular [16], antioxidant [17]. These activities of both aroused our attention to synthesize some new compounds which contains benzotriazole and azetidine in single frame work. In the present study our research group reporting synthesis of new series of *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(substitutedphenyl)-3-chloro-2-oxo-1-iminoazetidine, compounds **4(a-j)** from 1,2,3-benzotriazole. The structures of all synthesized compounds were confirmed by chemical and spectral analyses such as IR, ^{1}H NMR, ^{13}C NMR and FAB-Mass.

Materials and Methods

Melting points were taken in open glass capillaries and are uncorrected. Progress of reaction was monitored

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

Comp.	Antibacterial activity			Antifungal activity			Antitubercular activity
	B. subtilis	*E. coli*	*S. aureus*	*A. niger*	*A. flavus*	*C. albicans*	*M. tuberculosis*
4a	9.25	7.25	6.50	15.5	15.5	17.50	6.25
4b	3.75	6.25	3.25	8.5	10.25	12.75	2.75
4c	3.25	2.25	3.25	6.50	8.75	12.75	1.50
4d	3.50	2.25	2.25	7.25	9.25	13.25	2.25
4e	3.25	2.00	2.50	7.50	9.75	12.75	2.50
4f	3.50	2.25	2.50	8.50	8.75	12.50	1.25
4g	3.50	6.25	3.75	9.25	14.5	14.50	4.25
4h	3.25	1.75	2.25	6.50	8.50	12.25	1.50
4i	3.25	2.00	2.50	6.25	8.75	12.75	1.75
4j	3.25	1.75	2.25	6.50	9.25	12.50	2.25
Streptomycin	3.25	1.75	2.25	-	-	-	-
Griseofulvin	-	-	-	6.25	8.75	12.50	-

the mic values of standard streptomycin for all bacteria strain and griseofulvin for all fungi strain were in the range of 1.25-3.25 and 6.25-12.5 µg/ml respectively.
isoniazid and rifampicin were used as standards, mic values were 1.25 and 2.50 µg/ml respectively.

by silica gel-G coated TLC plates using MeOH: $CHCl_3$ system (1:9). 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 ^1H NMR and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 and 75 MHz respectively using TMS as an internal standard respectively. All chemical shifts were reported on δ scale. 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 compounds were highly satisfactory. For the 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.

Antibacterial, Antifungal and Antitubercular Activities

The antibacterial, antifungal and antitubercular activity of compound **4(a-j)** has been assayed in vitro against selected bacteria, *B. subtilis*, *E. coli*, *S. aureus*, and fungi *A. niger*, *A. flavus*, *C. albicans* and *M. tuberculosis* H37Rv strain respectively. The MIC of compounds **4(a-j)** were determined using filter paper disc diffusion method[18] (antibacterial and antifungal activities) and L.J. medium (Conventional) method (antitubercular activity). Streptomycin and Griseofulvin used as standard for antibacterial and antifungal activities respectively and for antitubercular activity, Isoniazid and Rifampicin taken as standards. Concentration of the compounds was given in µg/mL. Results of activities of compounds **4(a-j)** were given in Table 1.

Procedure for the Synthesis of the Compound (1)

1,2,3-Benzotriazole (0.420 mole) and 1-bromo-2-chloroethane (0.420 mole) in methanol (100 ml) were stirred on a magnetic stirrer for about 6.00 hours at room temperature. The completion of the reaction was monitored by silica gel-G coated TLC plates. 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 (150 ml). The purified product was dried under vacuo and recrystallized from ethanol to yield compound **1** (Fig. 1).

*1-(2-chloroethyl)-1*H*-1,2,3-benzotriazole (1)*

Yield: 61 %, m. p. 73-75 °C; Anal. Calcd for $C_8H_8N_3Cl$: C,52.90, H,4.43, N,23.13 %; found C,52.85, H,4.40, N,23.10 %; IR (cm^{-1}): 748 (C-Cl), 1321 (N-C), 1465 (C=C), 1540 (N=N), 1431, 2834, 2896 (CH_2), 3023 (CH-Ar); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.45 (t, 2H, *J* = 7.45 Hz, H-9), 4.11 (t, 2H, *J* = 7.45 Hz, H-8), 7.24-7.91 (m, 4H ArH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 39.2 (C-9), 43.5 (C-8), 116.1 (C-6), 119.4 (C-4), 127.8 (C-7), 129.3 (C-5), 143.4 (C-3a),

148.7 (C-7a); Mass (FAB): $181M^+$.

Procedure for the Synthesis of Compound (2)

The compound **1** (0.273 mole) and hydrazine hydrate (0.273 mole) were stirred on a magnetic stirrer for about 4.00 hours. 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 chloroform : methanol (8 : 2 v/v) as eluant (150 ml). The purified product was recrystallized from ethanol to yield compound **2** (Fig. 2).

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-hydrazine (2)*

Yield: 73 %, m. p. 58-60 °C; Anal. Calcd for $C_8H_{11}N_5$: C,54.22, H,6.25, N,39.52 %; found C,54.20, H,6.22, N,39.50 %; IR (cm^{-1}): 1332 (N-C), 1466 (C=C), 1545 (N=N), 1663 (CO), 1433, 2837, 2898 (CH_2), 3020 (CH-Ar), 3363 (NH), 3417 (NH_2); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.32-3.39 (m, 2H, H-9), 4.14 (t, 2H, *J* = 7.40 Hz, H-8), 5.62 (s, 1H, H-1'), 5.90 (s, 2H, H-2'), 7.29-7.88 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 40.7 (C-9), 46.3 (C-8), 118.5 (C-4), 120.7 (C-7), 126.9 (C-5), 127.4 (C-6), 143.6 (C-3a), 147.2 (C-7a); Mass (FAB): $177M^+$.

General Conventional Procedure for the Synthesis of the Compound 3(a-j)

The compound **2** (0.036 mole) and benzaldehyde (0.036 mole) in methanol (100 ml) in the presence of 2-4 drops glacial acetic acid were first stirred on a magnetic stirrer for about 2.00 hours at room temperature 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, cooled and purified over a silica gel packed column chromatography using CH_3OH: $CHCl_3$ (7:3 v/v) system as eluant (80 ml). The purified product was dried under vacuo and recrystallized from ethanol at room temperature to furnish compound **3a** (Fig. 3).

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

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(phenyl)methylidene]-hydrazine (3a)*

Yield: 56 %, m. p. 68-70 °C; Anal. Calcd for $C_{15}H_{15}N_5$: C,67.90, H,5.69, N,26.39 %; found C,67.85, H,5.64, N,26.35 %; IR (cm^{-1}): 1303 (N-C), 1465 (C=C), 1543 (N=N), 1552 (N=CH), 1666 (CO), 1427, 2838, 2893 (CH_2), 3021 (CH-Ar), 3362 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.23-3.31 (m, 2H, H-9), 4.16 (t, 2H, *J* = 7.35 Hz, H-8), 5.70 (s, 1H, H-1'), 7.89 (s, 1H, H-10), 7.12-7.87 (m, 9H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 41.0 (C-9), 48.7 (C-8), 114.2 (C-4), 120.5 (C-7), 124.8 (C-5), 125.7 (C-12 and C-16), 126.8 (C-13 and C-15), 127.3 (C-6), 128.5 (C-14), 130.4 (C-11), 135.3 (C-3a), 144.6 (C-10), 147.7 (C-7a); Mass (FAB): $265M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(4-chlorophenyl)methylidene]-hydrazine (3b)*

Yield: 65 %, m. p. 75-76 °C; Anal. Calcd for $C_{15}H_{14}N_5Cl$: C,60.10, H,4.70, N,23.36 %; found C,60.04, H,4.67, N,23.30 %; IR (cm^{-1}): 743 (C-Cl), 1309 (N-C), 1465 (C=C), 1543 (N=N), 1566 (N=CH), 1668 (CO), 1430, 2835, 2900 (CH_2), 3034 (CH-Ar), 3366 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.31-3.37 (m, 2H, H-9), 4.18 (t, 2H, *J* = 7.35 Hz, H-8), 5.76 (s, 1H, H-1'), 7.93 (s, 1H, H-10), 6.75-7.88 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 41.7 (C-9), 45.8 (C-8), 113.7 (C-4), 120.7 (C-7), 124.6 (C-5), 126.3 (C-12 and C-16), 127.4 (C-6), 128.7 (C-13 and C-15), 130.5 (C-3a), 134.8 (C-14), 136.7 (C-11), 143.6 (C-7a), 151.4 (C-10); Mass (FAB): $300M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(3-chlorophenyl)methylidene]-hydrazine (3c)*

Yield: 67 %, m. p. 66-67 °C; Anal. Calcd for $C_{15}H_{14}N_5Cl$: C,60.10, H,4.70, N,23.36 %; found C,60.02, H,4.64, N,23.32 %; IR (cm^{-1}): 749 (C-Cl), 1321 (N-C), 1468 (C=C), 1555 (N=N), 1561 (N=CH), 1669 (CO), 1436, 2837, 2908 (CH_2), 3031 (CH-Ar), 3366 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.37-3.41 (m, 2H, H-9), 4.20 (t, 2H, *J* = 7.40 Hz, H-8), 5.72 (s, 1H, H-1'), 7.93 (s, 1H, H-10), 7.06-7.91 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.5 (C-9), 49.6 (C-8), 112.6 (C-4), 121.0 (C-7), 125.7 (C-5), 126.6 (C-12), 127.1 (C-16), 127.9 (C-6), 129.0 (C-14), 130.6 (C-15), 133.7 (C-3a), 136.6 (C-13), 138.4 (C-11), 145.7 (C-7a), 151.3 (C-10); Mass (FAB): $300M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(2-chlorophenyl)methylidene]- hydrazine (3d)*

Yield: 65 %, m. p. 65-67 °C; Anal. Calcd for $C_{15}H_{14}N_5Cl$: C,60.10, H,4.70, N,23.36 %; found C,60.03, H,4.64, N,23.31 %; IR (cm^{-1}): 750 (C-Cl), 1324 (N-C), 1464 (C=C), 1544 (N=N), 1553 (N=CH), 1664 (CO), 1432, 2837, 2895 (CH_2), 3023 (CH-Ar),

3364 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.28-3.34 (m, 2H, H-9), 4.16 (t, 2H, *J* = 7.55 Hz, H-8), 5.78 (s, 1H, H-1'), 7.88 (s, 1H, H-10), 7.34-7.52 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.6 (C-9), 47.2 (C-8), 111.3 (C-4), 114.5 (C-13 and C-15), 119.6 (C-7), 122.9 (C-5), 128.2 (C-12 and C-16), 130.0 (C-6), 131.1 (C-11), 132.8 (C-3a), 148.6 (C-7a), 154.2 (C-10), 159.6 (C-15); Mass(FAB): $300M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(4-bromophenyl)methylidene]*-hydrazine (3e)

Yield: 66 %, m. p. 70-71 °C; Anal. Calcd for $C_{15}H_{14}N_5Br$: C,52.34, H,4.09, N,20.34 %; found C,52.31, H,4.03, N,20.30 %; IR (cm^{-1}): 643 (C-Br), 1322 (N-C), 1472 (C=C), 1546 (N=N), 1563 (N=CH), 1673 (CO), 1436, 2842, 2905 (CH_2), 3026 (CH-Ar), 3370 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.32-3.37 (m, 2H, H-9), 4.30 (t, 2H, *J* = 7.60 Hz, H-8), 5.73 (s, 1H, H-1'), 7.98 (s, 1H, H-10) 7.23-7.90 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.7 (C-9), 47.4 (C-8), 114.2 (C-4), 119.6 (C-7), 123.8 (C-13), 125.5 (C-5), 126.8 (C-16), 128.4 (C-6), 129.5 (C-12), 131.6 (C-15), 132.4 (C-14), 134.6 (C-3a), 139.1 (C-11), 146.3 (C-7a), 152.6 (C-10); Mass (FAB): $344M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(3-bromophenyl)methylidene]*-hydrazine (3f)

Yield: 64 %, m. p. 71-73 °C; Anal. Calcd for $C_{15}H_{14}N_5Br$: C,52.34, H,4.09, N,20.34 %; found C,52.29, H,4.01, N,20.30 %; IR (cm^{-1}): 638 (C-Br), 1314 (N-C), 1470 (C=C), 1545 (N=N), 1557 (N=CH), 1668 (CO), 1442, 2838, 2901 (CH_2), 3024 (CH-Ar), 3373 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.32-3.36 (m, 2H, H-9), 4.22 (t, 2H, = 7.55 Hz, H-8), 5.72 (s, 1H, H-1'), 8.02 (s, 1H, H-10), 7.01-7.93 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 44.5 (C-9), 51.4 (C-8), 114.0 (C-4), 121.5 (C-7), 121.7 (C-12), 124.2 (C-5), 128.3 (C-15), 129.4 (C-6), 130.5 (C-16), 131.4 (C-14), 133.9 (C-13), 134.2 (C-3a), 142.3 (C-11), 149.7 (C-7a), 152.4 (C-10); Mass (FAB): $344M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(2-bromophenyl)methylidene]*-hydrazine (3g)

Yield: 62 %, m. p. 68-70 °C; Anal. Calcd for $C_{15}H_{14}N_5Br$: C,52.34, H,4.09, N,20.34 %; found C,52.26, H,4.00, N,20.24 %; IR (cm^{-1}): 636 (C-Br), 1315 (N-C), 1471 (C=C), 1547 (N=N), 1562 (N=CH), 1671 (CO), 1439, 2841, 2901 (CH_2), 3029 (CH-Ar), 3369 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.30-3.35 (m, 2H, H-9), 4.29 (t, 2H, *J* = 7.50 Hz, H-8), 5.77 (s, 1H, H-1'), 7.97 (s, 1H, H-10), 7.11-7.99 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 41.3 (C-9), 47.3 (C-8), 114.1 (C-4), 121.3 (C-7), 123.2 (C-14), 125.1 (C-5), 128.4 (C-12 and C-16), 129.3 (C-6), 132.4 (C-13 and C-15), 134.5 (C-3a), 136.9 (C-11), 148.2 (C-7a), 152.7 (C-10); Mass (FAB): $344M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(4-nitrophenyl)methylidene]*-hydrazine (3h)

Yield: 66 %, m. p. 78-80 °C; Anal. Calcd for $C_{15}H_{14}N_6O_2$: C,58.05, H,4.54, N,27.08 %; found C,58.01, H,4.50, N,27.01 %; IR (cm^{-1}): 1330 (N-C), 1533 (N=O), 1468 (C=C), 1548 (N=N), 1560 (N=CH), 1666 (CO), 1433, 2844, 2898 (CH_2), 3028 (CH-Ar), 3374 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.33-3.37 (m, 2H, H-9), 4.18 (t, 2H, *J* = 7.60 Hz, H-8), 5.87 (s, 1H, H-1'), 8.12 (s, 1H, H-10), 7.26-7.99 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 45.1 (C-9), 48.9 (C-8), 110.6 (C-4), 120.5 (C-7), 123.6 (C-13), 125.2 (C-5), 127.3 (C-16), 129.1 (C-6), 130.4 (C-14), 132.9 (C-3a), 134.2 (C-11), 135.6 (C-15), 145.3 (C-7a), 146.2 (C-12), 155.4 (C-10); Mass (FAB): $310M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(3-nitrophenyl)methylidene]*-hydrazine (3i)

Yield: 64 %, m. p. 75-77 °C; Anal. Calcd for $C_{15}H_{14}N_6O_2$: C,58.05, H,4.54, N,27.08 %; found C,58.00, H,4.49, N,27.02 %; IR (cm^{-1}): 1317 (C-N), 1530 (N=O), 1467 (C=C), 1547 (N=N), 1556 (N=CH), 1670 (CO), 1438, 2840, 2899 (CH_2), 3033 (CH-Ar), 3372 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.28-3.33 (m, 2H, H-9), 4.24 (t, 2H, *J* = 7.60 Hz, H-8), 5.81 (s, 1H, H-1'), 8.10 (s, 1H, H-10), 7.32-7.91 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 45.7 (C-9), 50.8 (C-8), 110.2 (C-4), 120.4 (C-7), 123.4 (C-13 and C-15), 125.2 (C-5), 128.4 (C-6), 130.3 (C-12 and C-16), 133.6 (C-3a), 138.2 (C-11), 144.3 (C-7a), 149.5 (C-14), 155.9 (C-10); Mass(FAB): $310M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]*-N'-*[(2-nitrophenyl)methylidene]*-hydrazine (3j)

Yield: 60 %, m. p. 64-66 °C; Anal. Calcd for $C_{15}H_{14}N_6O_2$: C,58.05, H,4.54, N,27.08 %; found C,57.95, H,4.50, N,27.01 %; IR (cm^{-1}): 1327 (N-C), 1528 (N=O), 1469 (C=C), 1546 (N=N), 1554 (N=CH), 1669 (CO), 1435, 2838, 2896 (CH_2), 3031 (CH-Ar), 3371 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.30-3.34 (m, 2H, H-9), 4.22 (t, 2H, *J* = 7.60 Hz, H-8), 5.83 (s, 1H, H-1'), 8.07 (s, 1H, H-10), 7.21-7.86 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 44.2 (C-9),

49.4 (C-8), 111.2 (C-4), 119.5 (C-7), 121.5 (C-12), 124.2 (C-14), 125.4 (C-5), 129.3 (C-6), 129.9 (C-15), 133.5 (C-3a), 133.9 (C-16), 139.8 (C-11), 146.9 (C-7a), 149.6 (C-13), 154.3 (C-10); Mass (FAB): 310M^+.

General Method for the Synthesis of the Compound 4(a-j)

The compound **3a** (0.009 mole), Et_3N (0.009 mole) and chloroacetyl chloride (0.009 mole) in methanol (100 ml) were first stirred on a magnetic stirrer for about 2.00 hours at room temperature followed by reflux on a steam bath for about 4.00 hours. The completion of the reaction was monitored by silica gel-G coated TLC plates. The product was filtered, cooled and purified over a silica gel packed column chromatography using CH_3OH: $CHCl_3$ (7:3 v/v) system as eluant (75 ml). The purified product was dried under vacuo and recrystallized from ethanol at room temperature to furnish compound **4a** (Fig. 4).

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

N-*[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(phenyl)-3-chloro-2-oxo-1-iminoazetidine (4a)*

Yield: 64 %, m. p. 78-80 °C; Anal. Calcd for $C_{17}H_{16}N_5OCl$: C, 59.73, H, 4.71, N, 20.48 %; found C, 59.70, H, 4.67, N, 20.44 %; IR (cm^{-1}): 1326 (N-C), 1330 (C-NH), 1468 (C=C), 1547 (N=N), 1666 (CO), 1727 (CO cyclic), 1435, 2840, 2898 (CH_2), 2902 (CH-Cl), 3024 (CH-Ar), 3366 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.24-3.28 (m, 2H, H-9), 4.11 (t, 2H, *J* = 7.50 Hz, H-8), 4.48 (d, 1H, *J* = 5.00 Hz, H-3"), 5.17 (d, 1H, *J* = 5.00 Hz, H-4"), 5.60 (s, 1H, H-1'), 6.85-7.72 (m, 9H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 40.8 (C-9), 46.9 (C-8), 54.2 (C-3"), 62.4 (C-4"), 112.1 (C-4), 118.6 (C-7), 121.2 (C-5), 126.4 (C-11 and C-15), 127.6 (C-6), 128.6 (C-13), 130.8 (C-12 and C-14), 134.9 (C-3a), 138.6 (C-10), 144.9 (C-7a), 169.8 (C-2"); Mass (FAB): 341M^+.

N-*[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(4-chlorophenyl)-3-chloro-2-oxo-1-iminoazetidine (4b)*

Yield: 65 %, m. p. 73-75 °C; Anal. Calcd for $C_{17}H_{15}N_5OCl_2$: C, 54.26, H, 4.01, N, 23.36 %; found C, 54.22, H, 3.97, N, 23.31 %; IR (cm^{-1}): 765 (C-Cl), 1327 (N-C), 1340 (C-NH), 1478 (C=C), 1557 (N=N), 1675 (CO), 1739 (CO cyclic), 1446, 2845, 2909 (CH_2), 2917 (CH-Cl), 3035 (CH-Ar), 3377 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.30-3.35 (m, 2H, H-9), 4.12 (t, 2H, *J* = 7.55 Hz, H-8), 4.65 (d, 1H, *J* = 5.10 Hz, H-3"), 5.39 (d, 1H, *J* = 5.10 Hz, H-4"), 5.64 (s, 1H, H-1'), 6.86-7.75 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.5 (C-9), 49.3 (C-8), 53.7 (C-3"), 63.6 (C-4"), 116.2 (C-4), 120.9 (C-7), 123.7 (C-5), 127.7 (C-11 and C-15), 128.6 (C-6), 129.4 (C-12 and C-14), 132.8 (C-3a), 135.5 (C-13), 136.7 (C-10), 146.9 (C-7a), 174.5 (C-2"); Mass (FAB): 376M^+.

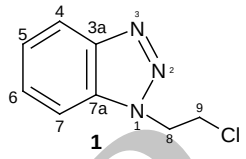


Figure 1. Structure of compound **1**.

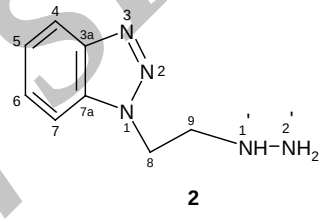


Figure 2. Structure of compound **2**.

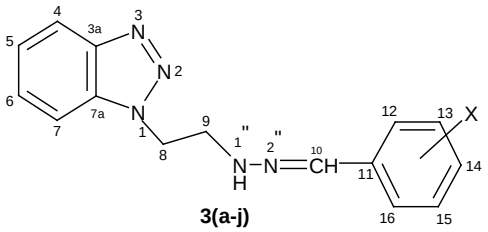


Figure 3. Structure of compounds **3(a-j)**.

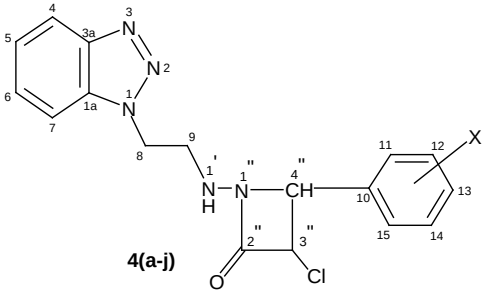


Figure 4. Structure of compounds **4(a-j)**.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(3-chlorophenyl)-3-chloro-2-oxo-1-iminoazetidine (4c)*

Yield: 66 %, m. p. 74-76 °C; Anal. Calcd for $C_{17}H_{15}N_5OCl_2$: C, 54.26, H, 4.01, N, 23.36 %; found C, 54.21, H, 3.97, N, 23.31 %; IR (cm^{-1}): 776 (C-Cl), 1334 (C-N), 1473 (C=C), 1551 (N=N), 1672 (CO), 1733 (CO cyclic), 1440, 2845, 2903 (CH_2), 2910 (CH-Cl), 3029 (CH-Ar), 3371 (NH), ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.30-3.35 (m, 2H, H-9), 4.15 (t, 2H, *J* = 7.50 Hz, H-8), 4.63 (d, 1H, *J* = 5.10 Hz, H-3"), 5.34 (d, 1H, *J* = 5.10 Hz, H-4"), 5.64 (s, 1H, H-1'), 6.79-7.64 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.9 (C-9), 49.3 (C-8), 55.8 (C-3"), 65.7 (C-4"), 114.2 (C-4), 118.4 (C-7), 124.3 (C-5), 126.7 (C-11), 128.3 (C-15), 129.1 (C-6), 129.9 (C-13), 131.4 (C-14), 134.4 (C-3a), 135.3 (C-12), 138.1 (C-10), 147.9 (C-7a), 171.2 (C-2"); Mass (FAB): $376M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(2-chlorophenyl)-3-chloro-2-oxo-1-iminoazetidine (4d)*

Yield: 61 %, m. p. 80-81 °C; Anal. Calcd for $C_{17}H_{15}N_5OCl_2$: C, 54.26, H, 4.01, N, 23.36 %; found C, 54.20, H, 3.99, N, 23.33 %; IR (cm^{-1}): 773 (C-Cl), 1339 (C-N), 1477 (C=C), 1556 (N=N), 1674 (CO), 1738 (CO cyclic), 1445, 2844, 2908 (CH_2), 2916 (CH-Cl), 3034 (CH-Ar), 3376 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.25-3.31 (m, 2H, H-9), 4.14 (t, 2H, *J* = 7.60 Hz, H-8), 4.62 (d, 1H, *J* = 5.10 Hz, H-3"), 5.33 (d, 1H, *J* = 5.10 Hz, H-4"), 5.68 (s, 1H, H-1'), 6.81-7.62 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 43.1 (C-9), 48.7 (C-8), 55.2 (C-3"), 64.6 (C-4"), 114.5 (C-4), 119.9 (C-7), 124.7 (C-5), 127.6 (C-14), 128.9 (C-6), 129.4 (C-12), 130.4 (C-13), 132.2 (C-15), 133.3 (C-3a), 135.1 (C-11), 137.9 (C-10), 147.4 (C-7a), 173.7 (C-2"); Mass (FAB): $376M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(4-bromophenyl)-3-chloro-2-oxo-1-iminoazetidine (4e)*

Yield: 66 %, m. p. 77-78 °C; Anal. Calcd for $C_{17}H_{15}N_5OBrCl$: C, 48.53, H, 3.59, N, 16.64 %; found C, 48.50, H, 3.54, N, 16.61 %; IR (cm^{-1}): 578 (C-Br), 1336 (C-N), 1474 (C=C), 1553 (N=N), 1674 (CO), 1735 (CO cyclic), 1442, 2841, 2905 (CH_2), 2913 (CH-Cl), 3031 (CH-Ar), 3373 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.22-3.28 (m, 2H, H-9), 4.20 (t, 2H, *J* = 7.55 Hz, H-8), 4.63 (d, 1H, *J* = 5.15 Hz, H-3"), 5.44 (d, 1H, *J* = 5.15 Hz, H-4"), 5.70 (s, 1H, H-1'), 7.37-7.95 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 43.2 (C-9), 49.6 (C-8), 47.3 (C-3"), 59.7 (C-4"), 112.4 (C-4), 119.4 (C-7), 123.9 (C-13), 124.5 (C-5), 128.6 (C-6), 130.8 (C-11 and C-15), 131.4 (C-12 and C-14), 132.6 (C-3a), 136.5 (C-10), 147.9 (C-7a), 172.3 (C-2"); Mass (FAB): $421M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(3-bromophenyl)-3-chloro-2-oxo-1-iminoazetidine (4f)*

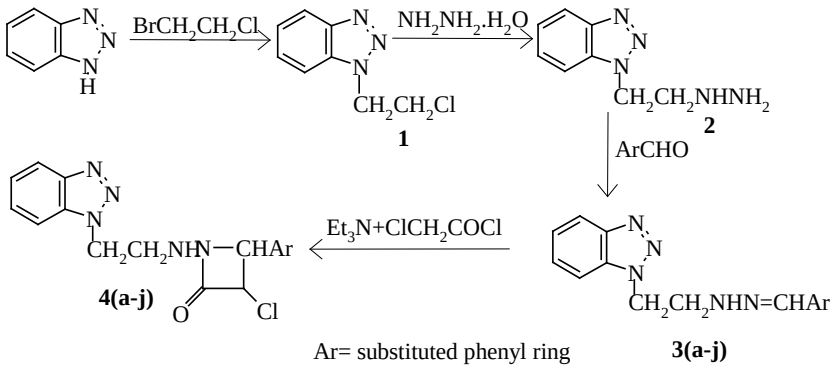
Yield: 63 %, m. p. 79-80 °C; Anal. Calcd for $C_{17}H_{15}N_5OBrCl$: C, 48.53, H, 3.59, N, 16.64 %; found C, 48.49, H, 3.52, N, 16.61 %; IR (cm^{-1}): 572 (C-Br), 1338 (C-N), 1476 (C=C), 1555 (N=N), 1673 (CO), 1737 (CO cyclic), 1444, 2843, 2907 (CH_2), 2915 (CH-Cl), 3033 (CH-Ar), 3375 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.32-3.37 (m, 2H, H-9), 4.21 (t, 2H, *J* = 7.65 Hz, H-8), 5.38 (d, 1H, *J* = 5.15 Hz, H-4"), 5.57 (d, 1H, *J* = 5.15 Hz, H-3"), 5.72 (s, 1H, H-1'), 7.31-7.92 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.8 (C-9), 48.6 (C-3"), 49.2 (C-8), 59.9 (C-4"), 109.2 (C-4), 118.9 (C-7), 123.7 (C-12), 124.7 (C-5), 125.6 (C-15), 128.4 (C-6), 129.8 (C-11), 132.5 (C-14), 133.4 (C-13), 134.5 (C-3a), 140.3 (C-10), 145.6 (C-7a), 172.6 (C-2"); Mass (FAB): $421M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(2-bromophenyl)-3-chloro-2-oxo-1-iminoazetidine (4g)*

Yield: 61 %, m. p. 84-86 °C; Anal. Calcd for $C_{17}H_{15}N_5OBrCl$: C, 48.53, H, 3.59, N, 16.64 %; found C, 48.50, H, 3.54, N, 16.60 %; IR (cm^{-1}): 566 (C-Br), 1333 (C-N), 1472 (C=C), 1550 (N=N), 1671 (CO), 1732 (CO cyclic), 1439, 2844, 2902 (CH_2), 2907 (CH-Cl), 3028 (CH-Ar), 3370 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.36-3.40 (m, 2H, H-9), 4.16 (t, 2H, *J* = 7.60 Hz, H-8), 4.66 (d, 1H, *J* = 5.15 Hz, H-3"), 5.15 (d, 1H, *J* = 5.15 Hz, H-4"), 5.69 (s, 1H, H-1'), 7.27-7.84 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 43.0 (C-9), 48.5 (C-8), 49.8 (C-3"), 58.8 (C-4"), 111.1 (C-4), 119.5 (C-7), 120.3 (C-11), 125.7 (C-5), 127.2 (C-14), 128.4 (C-6), 130.1 (C-15), 131.5 (C-13), 132.2 (C-3a), 133.2 (C-12), 142.6 (C-10), 147.9 (C-7a), 172.5 (C-2"); Mass (FAB): $421M^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(4-nitrophenyl)-3-chloro-2-oxo-1-iminoazetidine (4h)*

Yield: 64 %, m. p. 80-81 °C; Anal. Calcd for $C_{17}H_{15}N_6O_3Cl$: C, 52.78, H, 3.90, N, 21.72 %; found C, 52.72, H, 3.82, N, 21.70 %; IR (cm^{-1}): 868 (C-NO), 1540 (NO_2), 1335 (C-N), 1473 (C=C), 1552 (N=N), 1673 (CO), 1734 (CO cyclic), 1441, 2846, 2904 (CH_2), 2912 (CH-Cl), 3030 (CH-Ar), 3372 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.32-3.38 (m, 2H, H-9), 4.20 (t, 2H, *J* = 7.65 Hz, H-8), 5.44 (d, 1H, *J* = 5.25 Hz,



Scheme 1. Synthesis of compounds **1, 2, 3(a-j)** and **4(a-j)**.

H-4"), 4.59 (d, 1H, *J* = 5.25 Hz, H-3"), 5.72 (s, 1H, H-1'), 7.1-7.71 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 42.7 (C-9), 48.2 (C-8), 50.0 (C-3"), 63.8 (C-4"), 112.2 (C-4), 118.5 (C-7), 122.6 (C-12 and C-14), 124.8 (C-5), 127.9 (C-11 and C-15), 128.3 (C-6), 132.4 (C-3a), 139.8 (C-10), 145.9 (C-7a), 147.9 (C-13), 173.6 (C-2"); Mass (FAB): 387M$^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(3-nitrophenyl)-3-chloro-2-oxo-1-iminoazetidine (4i)*

Yield: 62 %, m. p. 82-83 °C; Anal. Calcd for $C_{17}H_{15}N_6O_3Cl$: C, 52.78, H, 3.90, N, 21.72 %; found C, 52.74, H, 3.87, N, 21.68 %; IR (cm^{-1}): 864 (C-NO), 1338 (C-N), 1542 (NO_2), 1239 (N-C), 1332 (C-NH), 1471 (C=C), 1549 (N=N), 1670 (CO), 1731 (CO cyclic), 1438, 2843, 2901 (CH_2), 2906 (CH-Cl), 3027 (CH-Ar), 3369 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.34-3.39 (m, 2H, H-9), 4.19 (t, 2H, *J* = 7.60 Hz, H-8), 4.47 (d, 1H, *J* = 5.20 Hz, H-3"), 5.45 (d, 1H, *J* = 5.20 Hz, H-4"), 5.74 (s, 1H, H-1'), 7.16-7.79 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 43.6 (C-9), 49.9 (C-8), 51.3 (C-3"), 63.2 (C-4"), 113.3 (C-4), 118.9 (C-7), 122.7 (C-11), 124.8 (C-13), 125.9 (C-5), 128.8 (C-6), 129.4 (C-14), 132.6 (C-3a), 132.9 (C-15), 139.7 (C-10), 146.9 (C-7a), 147.9 (C-12), 175.6 (C-2"); Mass (FAB): 487M$^+$.

N-*[2-(1H-1,2,3-benzotriazol-1-yl)ethyl]-4-(2-nitrophenyl)-3-chloro-2-oxo-1-iminoazetidine (4j)*

Yield: 61 %, m. p. 79-80 °C; Anal. Calcd for $C_{17}H_{15}N_6O_3Cl$: C, 52.78, H, 3.90, N, 21.72 %; found C, 52.75, H, 3.84, N, 21.67 %; IR (cm^{-1}): 869 (C-NO), 1325 (C-N), 1542 (NO_2), 1475 (C=C), 1554 (N=N), 1672 (CO), 1736 (CO cyclic), 1443, 2842, 2906 (CH_2), 2914 (CH-Cl), 3032 (CH-Ar), 3374 (NH); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ: 3.25-3.30 (m, 2H, H-9), 4.12 (t, 2H, *J* = 7.50 Hz, H-8), 4.45 (d, 1H, *J* = 5.25 Hz, H-3"), 5.54 (d, 1H, *J* = 5.25 Hz, H-4"), 5.64 (s, 1H, H-1'), 7.05-7.71 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ: 43.5 (C-9), 49.2 (C-8), 54.6 (C-3"), 64.8 (C-4"), 112.4 (C-4), 117.4 (C-7), 122.5 (C-12), 123.8 (C-5), 127.6 (C-15), 128.6 (C-6), 130.8 (C-13), 132.9 (C-3a), 133.5 (C-10), 135.3 (C-14), 145.7 (C-7a), 146.5 (C-11), 174.5 (C-2"); Mass (FAB): 387M$^+$.

Results and Discusion

Synthesis

N-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-4-(substitutedphenyl)-3-chloro-2-oxo-1-imino azetidine, compounds **4(a-j)** were synthesized in four steps. Reaction of 1,2,3-benzotriazole with $Cl(CH_2)_2Br$ at room temperature afforded N^1-(2-chloroethyl)-1,2,3-benzotriazole**. (1)** IR spectrum of compound **1** displayed absorption at 1321 and 748 for (C-N) and (C-Cl) respectively, this clearly indicated the disappearance of NH absorption (3445) of 1,2,3 benzotriazole. The compound **1** on reaction with hydrazine hydrate at room temperature yielded *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-hydrazine, **(2)**. IR spectrum of compound **2** showed absorption for NH and NH_2 at 3363 and 3417 cm^{-1} respectively, while absorption for (C-Cl) has been disappeared in IR spectrum of compound **1**. The ^{1}H NMR spectrum of **2** displayed a signal at δ 5.62 and 5.90 ppm for NH and NH_2 respectively. The compound **2** on further reaction with selected substituted aromatic aldehydes produced *N*-[2-(1*H*-1,2,3-benzotriazol-1-yl)ethyl]-*N*'-[(substitutedphenyl)methylidene]-hydrazine **3(a-j)**. The characteristic absorption for Schiff base in IR spectra of compounds **3(a-j)** appeared in the range of 1549-1566 cm^{-1} and in the ^{1}H and ^{13}C NMR spectra, signal appeared at δ 7.88-

8.12 and δ 144.6-155.9 ppm respectively. In the ^{1}H NMR spectrum of compound **2** a broad signal of NH_2 has been disappeared. The compounds **3(a-j)** on treatment with $ClCH_2COCl$ in the presence of Et_3N furnished final products **4(a-j)**. In the IR spectra of compounds **4(a-j)** carbonyl group of β-lactam ring showed characteristic absorption in the range of 1726-1739 cm^{-1} and ^{1}H NMR spectra of compounds **4(a-j)** showed two doublet for (N-CH) and (CH-Cl) in the range δ 5.15-5.54 and 4.45-4.66 ppm respectively. In ^{13}C NMR spectra of compounds **4(a-j)** three characteristic signals appeared for (N-CH), (CH-Cl) and (CO cyclic) in the range of (δ) 59.7-65.7, 47.6-55.8 and 166.8-175.6 ppm respectively. The IR absorption, ^{1}H and ^{13}C NMR signals of N=CH have been disappeared. These all fact collectively suggested for the synthesis of all above compounds.

Biological Activity

The results of the all described activities (antibacterial, antifungal, and antitubercular) were summarized in Table 1. The results of the antimicrobial screening data revealed that all the compounds **4(a-j)** showed considerable and varied activity against the selected microorganism.

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 compound **4a** showed less activity against all the strains compared with standard drugs.

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