Artigo

SYNTHESIS OF 2-AZETIDINONE DERIVATIVES OF 6-NITRO-1*H*-INDAZOLE AND THEIR BIOLOGICAL IMPORTANCE

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A new series of 3-chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(substituted phenyl)-2-azetidinones (**4a-j**) was synthesized in four steps from 6-nitro-1*H*-indazole and characterized by IR, ^{1}H NMR, ^{13}C NMR, FAB-mass spectrometry and chemical methods. Compounds **4**(**a-j**) were screened *in vitro* for their antibacterial, antifungal and antitubercular activities against some selected microorganism and for their antiinflammatory activity (*in vivo*) against albino rats (either sex). All above activities of compounds **4**(**a-j**) showed acceptable results.

Keywords: synthesis; azetidinone; biosignificance.

INTRODUCTION

Indazole nucleus represents a very attractive scaffold to obtain new molecules endowed with antiprotozoal activity.[1] In the present study our research group has reported the synthesis of new indazole derivatives owing to their interesting antimicrobial, antitubercular and antiinflammatory activities. Indazoles have been found to possess promising medicinal activities such as antibacterial, antiinflammatory, inhibitors of human cytosolic phospholipase, nitric oxide synthases and antiproliferative activities.[2-7]

The azetidin-2-one skeleton has been recognized as a useful building block in synthesis of biologically important compounds. This is mainly the strain energy associated with the four membered azetidin-2-one ring, makes it susceptible for nucleophilic ring cleavage. This factor is also responsible for their application as synthons for various stereoselective syntheses of biological active heterocyclic compounds. β-Lactam derivatives display interesting biological activities such as CXCR2 receptor potent antagonists, antimicrobial, antitubercular and anti-HCMV activities.[8-13] As a consequence, the interest of organic chemists in the synthesis of new β-lactam derivatives remains high.[14] These activities aroused our attention and prompted us to synthesize some β-lactam derivatives. In the present study, we are reporting the synthesis of some new 2-azetidinone derivatives of 6-nitro-1*H*-indazole. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, FAB-Mass and chemical methods. Compounds **4(a-j)** have been screened *in vitro* for their antibacterial, antifungal and antitubercular activities against some selected microorganism and the antiinflammatory activity (*in vivo*) screened against albino rats (either sex). All above activities of compounds **4(a-j)** showed acceptable results.

RESULTS AND DISCUSSION

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4--(substitutedphenyl)-2-azetidinone, compounds **4(a-j)** were synthesized in four different steps (Scheme 1).[14] 6-Nitro-*1H*-indazole on reaction with $Cl(CH_2)_2Br$ at room temperature afforded 1-(2-chloroethyl)-6-nitro-1*H*-indazole, compound **1**. IR spectrum of compound **1** displayed absorption at 1326 and 768 cm^{-1} for (N-CH_2) and (C-Cl), respectively. This clearly indicated the disappearance of –NH absorption (3442 cm^{-1}). The compound **1** on reaction with hydrazine hydrate at room temperature yielded 1-(2-hydrazinoethyl)-6-nitro-1*H*-indazole, compound **2**. IR spectrum of compound **2** showed absorption peak for NH at 3342 cm^{-1} while absorption of (C-Cl) has disappeared. The ^{1}H NMR spectra of compound **2** displayed signal for (CH_2-NH) at δ 3.30-3.34 ppm. The compound **2** on further reaction with several substituted aromatic aldehydes produced (*E*/*Z*)-substituted benzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl]hydrazones, compounds **3(a-j)**. For the compounds **3(a-j)** characteristic absorption peak for Schiff base (N=CH) in IR spectra appeared in the range of 1553-1583 cm^{-1}, the ^{1}H NMR chemical shift in the range of δ 7.89-7.98 ppm and its ^{13}C NMR signal was found in the range of δ 150.6-155.7 ppm. In the ^{1}H NMR a broad signal of NH_2 at δ 5.92 ppm disappeared. Compounds **3(a-j)** on treatment with $ClCH_2COCl$ in the presence of Et_3N furnished the final products, compounds **4(a-j)**. The spectra of compounds **4(a-j)** carbonyl group of β-lactam ring showed characteristic absorption peak in the range of 1729-1741 cm^{-1} and ^{1}H NMR spectra two doublet appeared for (N-CH) and (CH-Cl) in the range of δ 5.22-5.37 and 4.22-4.68 ppm respectively. In the ^{13}C NMR spectra three signals appeared for (N-CH), (CH-Cl) and (CO cyclic) in the range of (δ) 61.4-65.7, 50.1-53.5 and 168.1-172.7 ppm, respectively. The IR absorption and ^{1}H NMR signal for N=CH have been disappeared. All above facts strongly indicate the synthesis of all above compounds.

Pharmacological results and discussion

A new series of 3-chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl] amino}-4-(substitutedphenyl)-2-azetidinone, compounds **4(a-j)** were synthesized and screened for their antibacterial and antifungal activities against some selected bacteria and fungi respectively and antitubercular activity was screened against *M. tuberculosis* (H37Rv strain). Results of antimicrobial, antitubercular and antinflammatory activities are given in Tables 1 and 2. Results of given activities revealed that the synthesized compounds **4(a-j)** have a structure activity relationship (SAR) because the activity of them varies with substitution. Nitro group containing compounds **(4h, 4i** and **4j)** showed higher activity than chloro **(4c, 4d)** or bromo containing compounds **(4e, 4f)**. Chloro or bromo derivatives also have higher activity than other tested compounds.

On the basis of SAR, we concluded that the activity of compounds

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Table 1. Antibacterial, antifungal and antitubercular activities of compounds **4(a-j)** with MIC value (μg/mL)

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	12.5	>6.25	12.5	6.25	>25	>25	>25	>25	>12.5
4b	>3.25	6.25	3.25	>3.25	>25	>12.5	>25	>25	>2.5
4c	6.25	>3.25	6.25	3.25	>12.5	25	>12.5	>12.5	>2.5
4d	>3.25	6.25	3.25	6.25	>12.5	>25	>12.5	>12.5	2.5
4e	6.25	>3.25	3.25	>3.25	>12.5	25	25	>25	>2.5
4f	6.25	3.25	6.25	>3.25	>12.5	>12.5	>12.5	>12.5	>2.5
4g	>3.25	6.25	>3.25	6.25	25	>12.5	>12.5	25	6.25
4h	3.25	>3.25	3.25	3.25	25	>12.5	>12.5	>25	2.5
4i	3.25	3.25	>3.25	3.25	>12.5	>12.5	>12.5	>12.5	2.5
4j	3.25	>3.25	3.25	3.25	>12.5	>12.5	>12.5	>12.5	>2.5

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 in the range of 1.25-2.50 μg/mL for *M. tuberculosis*.

Table 2. Antiinflammatory activity of compounds **4(a-j)**

Compound code	Before carageenan administration (mean ± SEM)	Total increase in paw volume after 5 h (mean ± SEM)	Percent inhibition
4a	0.60 ± 0.02	0.16 ± 0.02	50.00
4b	0.64 ± 0.02	0.14 ± 0.02	56.25
4c	0.66 ± 0.02	0.13 ± 0.01	59.38
4d	0.68 ± 0.02	0.13 ± 0.02	59.38
4e	0.66 ± 0.03	0.14 ± 0.02	56.25
4f	0.65 ± 0.02	0.12 ± 0.01	62.50
4g	0.67 ± 0.02	0.13 ± 0.01	59.38
4h	0.64 ± 0.03	0.12 ± 0.01	62.50
4i	0.65 ± 0.02	0.10 ± 0.03	68.75
4j	0.67 ± 0.03	0.11 ± 0.02	65.63
Control	0.66 ± 0.02	0.32 ± 0.01	-
Standard; phenylbutazone	0.68 ± 0.03	0.08 ± 0.02	75.00

depends on electron withdrawing nature of the substituent groups. The sequence of the activity is following.

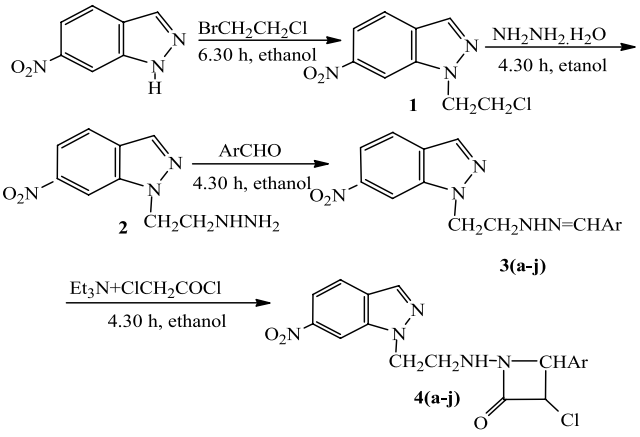
$$NO_2 > Cl > Br > H$$

CONCLUSION

A new series of compounds **4(a-j)** has been synthesized successfully by a simple route and investigated for their antimicrobial, antitubercular and antiinflammatory activities. Data of all activities revealed that the compounds **(4b)**, **(4d)**, **(4f)**, **(4g)**, **(4h)**, **(4i)** and **(4j)** displayed higher activities than the other compounds of the series.

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 (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. 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.



Ar = substituted phenyl ring

Comp.	Ar	Comp.	Ar
3a, 4a	C_6H_5	**3f, 4f**	3-BrC_6H_4
3b, 4b	4-ClC_6H_4	**3g, 4g**	2-BrC_6H_4
3c, 4c	3-ClC_6H_4	**3h, 4h**	4-$NO_2C_6H_4$
3d, 4d	2-ClC_6H_4	**3i, 4i**	3-$NO_2C_6H_4$
3e, 4e	4-BrC_6H_4	**3j, 4j**	2-$NO_2C_6H_4$

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

Procedure for the synthesis of compound 1

6-Nitro-*1H*-indazole (0.308 mole) and 1-bromo-2-chloroethane (0.308 mole) in ethanol (100 mL) were stirred on a magnetic stirrer for about 6.30 h 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 (150 mL). The purified product was dried under vacuo and recrystallized from acetone at room temperature to yield compound **1** (Figure 1).

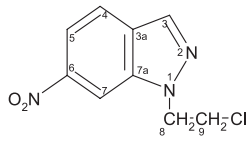


Figure 1. *Structure of compound* ***1***

1-(2-chloroethyl)-6-nitro-1*H*-indazole 1

Yield: 61%, m.p. 154-155 ºC; IR (cm^{-1}): 768 (C-Cl), 899 (C-N), 1326 (N-CH_2), 1532 (NO_2), 1572 (C=C), 1448, 2842, 2889, (CH_2), 3020 (CH-Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.41 (t, 2H, *J* = 7.45 H-9), 4.26 (t, 2H, *J* = 7.45 Hz, H-8), 7.86-8.35 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.8 (C-9), 47.1 (C-8), 118.7 (C-4), 120.4 (C-7), 122.2 (C-5), 126.1 (C-3a), 135.7 (C-7a), 136.2 (C-6), 137.0 (C-3); Anal. calcd for $C_9H_8N_3O_2Cl$: C,47.90, H,3.57, N,18.62; Found: C,47.85, H,3.52, N,18.56%; Mass (FAB): 225M$^+$.

Procedure for the synthesis of compound 2

Compound **1** (0.208 mole) and hydrazine hydrate (0.208 mole) in ethanol (100 mL) were stirred on a magnetic stirrer for about 4.30 h 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 acetone at room temperature to yield compound **2** (Figure 2).

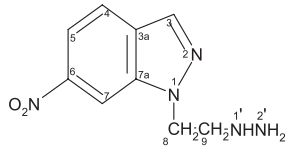


Figure 2. *Structure of compound* ***2***

1-(2-hydrazinoethyl)-6-nitro-1*H*-indazole 2

Yield: 72%, m.p. 136-138 ºC; IR (cm^{-1}): 752 (C-Cl), 872 (C-N), 1328 (N-CH_2), 1523 (NO_2), 1556 (C=C), 1648 (CO), 1435, 2839, 2910 (CH_2), 3027 (CH-Ar), 3342 (NH), 3456 (NH_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.30-3.34 (m, 2H, H-9), 4.18 (t, 2H, *J* = 7.45 Hz, H-8), 5.72 (s, 1H, H-1'), 5.92 (s, 2H, H-2'), 7.34-7.96 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.4 (C-9), 46.7 (C-8), 117.6 (C-4), 119.3 (C-7), 121.4 (C-5), 125.8 (C-3a), 134.5 (C-6), 136.7 (C-3), 139.2 (C-7a); Anal. calcd for $C_9H_{11}N_5O_2$: C,48.86, H,5.01, N,31.65; Found: C,48.82, H,5.00, N,31.61%; Mass (FAB): 221M$^+$.

General procedure for the synthesis of compounds 3(a-j)

The compound **2** (0.026 mole) and benzaldehyde (0.026 mole) in ethanol (100 mL) in the presence of 2-4 drops of glacial acetic acid were first stirred on a magnetic stirrer for about 2.00 h followed by reflux on a steam bath for about 2.30 h. 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 (80 mL). The purified product was dried under vacuo and recrystallized from acetone at room temperature to furnish compound **3a** (Figure 3).

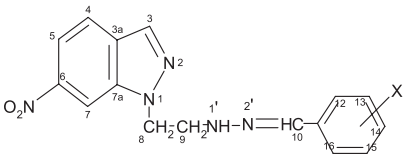


Figure 3. *Structure of compound* ***3(a-j)***

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

(*E*)-Benzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl]hydrazone 3[a]

Yield: 60%, m.p. 155-156 ºC; IR (cm^{-1}): 742 (C-Cl), 871 (C-N), 1328 (N-CH_2), 1523 (NO_2), 1534 (C=C), 1555 (N=CH), 1650 (C=O), 1442, 2839, 2897 (CH_2), 3027 (CH-Ar), 3356 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.24-3.27 (m, 2H, H-9), 4.14 (t, 2H, *J* = 7.45 Hz, H-8), 5.89 (s, 1H, H-1'), 7.98 (s, 1H, H-10), 7.22-7.97 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 38.4 (C-9), 45.3 (C-8), 115.7 (C-4), 119.4 (C-7), 120.5 (C-5), 121.5 (C-3a), 121.8 (C-12 and C-16), 122.4 (C-13 and C-15), 126.5 (C-14), 128.4 (C-11), 131.3 (C-6), 132.5 (C-3), 139.2 (C-7a), 150.6 (C-10); Anal. calcd for $C_{16}H_{15}N_5O_2$: C,62.12, H,4.88, N,22.64; Found: C,62.06, H,4.82, N,22.61%; Mass (FAB): 309M$^+$.

(*E*)-4-Chlorobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3b

Yield: 64%, m.p. 160-162 ºC; IR (cm^{-1}): 745 (C-Cl), 909 (C-N), 1347 (N-CH_2), 1537 (NO_2), 1574 (C=C), 1583 (N=CH), 1638 (C=O), 1444, 2846, 2919 (CH_2), 3012 (CH-Ar), 3346 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.43-3.48 (m, 2H, H-9), 4.24 (t, 2H, *J* = 7.45 Hz, H-8), 5.69 (s, 1H, H-1') 7.92 (s, 1H, H-10), 7.73-8.19 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.4 (C-9), 45.3 (C-8), 119.3 (C-4), 121.8 (C-7), 122.3 (C-5), 123.6 (C-3a), 124.9 (C-12 and C-16), 125.2 (C-13 and C-15), 128.3 (C-14), 129.8 (C-11), 131.3 (C-6), 135.7 (C-3), 140.5 (C-7a), 152.5 (C-10); Anal. calcd for $C_{16}H_{14}N_5O_2Cl$: C,55.90, H,4.10, N,20.37; Found: C,55.87, H,4.03, N,20.31%; Mass (FAB): 344M$^+$.

(*E*)-3-Chlorobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3c

Yield: 64%, m.p. 158-160 ºC; IR (cm^{-1}): 753 (C-Cl), 879 (C-N), 1338 (N-CH_2), 1534 (NO_2), 1545 (C=C), 1553 (N=CH), 1655 (C=O), 1434, 2843, 2897 (CH_2), 3035 (CH-Ar), 3364 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.38-3.44 (m, 2H, H-9), 4.28 (t, 2H, *J* = 7.45 Hz, H-8), 5.67 (s, 1H, H-1'), 7.92 (s, 1H, H-10), 7.75-8.27 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.4 (C-9), 45.4 (C-8), 117.4 (C-4), 121.2 (C-7), 121.7 (C-5), 122.7 (C-3a), 123.5 (C-12), 124.5 (C-16), 125.7 (C-13), 126.5 (C-15), 129.3 (C-14), 131.8 (C-11), 133.4 (C-6), 134.8 (C-3), 141.5 (C-7a), 154.6 (C-10); Anal. calcd for $C_{16}H_{14}N_5O_2Cl$: C,55.90, H,4.10, N,20.37; Found: C,55.85, H,4.07, N,20.33%; Mass (FAB): 344M$^+$.

(*E*)-2-Chlorobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3d

Yield: 65%, m.p. 155-157 ºC; IR (cm^{-1}): 746 (C-Cl), 878 (C-N), 1344 (N-CH_2), 1529 (NO_2), 1537 (C=C), 1566 (N=CH), 1661 (C=O), 1453, 2852, 2892 (CH_2), 3034 (CH-Ar), 3360 (NH); ^{1}H NMR ($CDCl_3$,

300 MHz) δ: 3.44-3.51 (m, 2H, H-9), 4.21 (t, 2H, *J* = 7.40 Hz, H-8), 5.64 (s, 1H, H-1'), 7.94 (s, 1H, H-10), 7.69-8.30 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.6 (C-9), 48.3 (C-8), 117.6 (C-4), 119.0 (C-7), 122.2 (C-5), 123.6 (C-3a), 124.5 (C-12), 124.9 (C-16), 125.6 (C-13), 126.8 (C-15), 127.6 (C-14), 130.2 (C-11), 133.8 (C-6), 134.5 (C-3), 140.1 (C-7a), 152.7 (C-10); Anal. calcd for $C_{16}H_{14}N_5O_2Cl$: C,55.90, H,4.10, N,20.37; Found: C,55.83, H,4.05, N,20.35%; Mass(FAB): 344M$^+$.

(*E*)-4-Bromobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3e

Yield: 66%, m.p. 153-155 ºC; IR (cm^{-1}): 884 (C-N), 1342 (N-CH_2), 1527 (NO_2), 1534 (C=C), 1568 (N=CH), 1654 (C=O), 1459, 2843, 2905 (CH_2), 3035 (CH-Ar), 3369 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.41-3.50 (m, 2H, H-9), 4.33 (t, 2H, *J* = 7.50 Hz, H-8), 5.65 (s, 1H, H-1'), 7.93 (s, 1H, H-10), 7.74-8.26 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.3 (C-9), 47.5 (C-8), 116.7 (C-4), 119.4 (C-7), 120.8 (C-57), 123.5 (C-12 and C-16), 125.4 (C-3a), 126.4 (C-13 and C-15), 130.8 (C-14), 131.1 (C-11), 133.2 (C-6), 135.3 (C-3), 144.6 (C-7a), 154.3 (C-10); Anal. calcd for $C_{16}H_{14}N_5O_2Br$: C,49.50, H,3.63, N18.03; Found: C,49.45, H,3.60, N,18.00%; Mass (FAB): 388M$^+$.

(*E*)-3-Bromobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3f

Yield: 63%, m.p. 149-151 ºC; IR (cm^{-1}): 877 (C-N), 1331 (N-CH_2), 1538 (NO_2), 1543 (C=C), 1575 (N=CH), 1667 (C=O), 1449, 2843, 2895 (CH_2), 3043 (CH-Ar), 3368 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.46-3.52 (m, 2H, H-9), 4.34 (t, 2H, *J* = 7.45 Hz, H-8), 5.62 (s, 1H, H-1'), 7.89 (s, 1H, H-10), 7.64-8.36 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 34.3 (C-9), 44.6 (C-8), 115.4 (C-4), 119.6 (C-7), 120.5 (C-5), 121.3 (C-3a), 122.8 (C-12), 124.5 (C-16), 125.3 (C-13), 126.3 (C-15), 128.6 (C-14), 131.7 (C-11), 132.8 (C-6), 133.9 (C-3), 143.2 (C-7a), 155.7 (C-10); Anal. Calcd for $C_{16}H_{14}N_5O_2Br$: C,49.50, H,3.63, N18.03; Found: C,49.44, H,3.53, N17.97%; Mass (FAB): 488M$^{+\cdot}$

(*E*)-2-Bromobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3g

Yield: 62%, m.p. 146-148 ºC; IR (cm^{-1}): 873 (C-N), 1338 (N-CH_2), 1534 (NO_2), 1547 (C=C), 1566 (N=CH), 1652 (C=O), 1443, 2856, 2895 (CH_2), 3036 (CH-Ar), 3372 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.47-3.52 (m, 2H, H-9), 4.24 (t, 2H, *J* = 7.50 Hz, H-8), 5.63 (s, 1H, H-1'), 7.95 (s, 1H, H-10), 7.80-8.22 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 33.6 (C-9), 42.4 (C-8), 115.8 (C-4), 118.3 (C-7), 119.3 (C-5), 120.7 (C-3a), 122.6 (C-12), 123.3 (C-16), 125.2 (C-13), 126.7 (C-15), 130.5 (C-14), 132.7 (C-11), 135.3 (C-6), 137.8 (C-3), 141.4 (C-7a), 152.3 (C-10); Anal. calcd for $C_{16}H_{14}N_5O_2Br$: C,49.50, H,3.63, N18.03; Found: C,49.42, H,3.56, N,17.93%; Mass (FAB): 388M$^+$.

(*E*)-4-Nitrobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3h

Yield: 63%, m.p. 168-170 ºC; IR (cm^{-1}): 753 (C-Cl), 878 (C-N), 1340 (N-CH_2), 1528 (NO_2), 1537 (C=C), 1562 (N=CH), 1665 (C=O), 1456, 2847, 2899 (CH_2), 3039 (CH-Ar), 3359 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.43-3.52 (m, 2H, H-9), 4.32 (t, 2H, *J* = 7.40 Hz, H-8), 5.56 (s, 1H, H-1'), 7.92 (s, 1H, H-10), 7.81-8.19 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 43.1 (C-9), 45.4 (C-8), 113.6 (C-4), 120.9 (C-7), 121.2 (C-5), 122.5 (C-3a), 123.1 (C-12 and C-16), 124.4 (C-13 and C-15), 129.8 (C-14), 131.3 (C-11), 132.9 (C-6), 133.6 (C-3), 140.3 (C-7a), 155.7 (C-10); Anal. calcd for $C_{16}H_{14}N_6O_4$: C,54.23, H,3.98, N,23.71; Found: C,54.20, H,3.95, N,23.67%; Mass (FAB): 354M$^+$.

(*E*)-3-Nitrobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3i

Yield: 62%, m.p. 164-166 ºC; IR (cm^{-1}): 747 (C-Cl), 880 (C-N), 1335 (N-CH_2), 1533 (NO_2), 1539 (C=C), 1562 (N=CH), 1656 (C=O), 1455, 2848, 2895 (CH_2), 3041 (CH-Ar), 3356 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.48-3.52 (m, 2H, H-9), 4.34 (t, 2H, *J* = 7.40 Hz, H-8), 5.62 (s, 1H, H-1'), 7.94 (s, 1H, H-10), 7.70-8.22 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.1 (C-9), 46.3 (C-8), 117.5 (C-4), 120.1 (C-7), 120.6 (C-5), 121.2 (C-3a), 122.4 (C-12), 123.5 (C-16), 124.3 (C-13), 125.8 (C-15), 126.3 (C-14), 127.4 (C-11), 131.5 (C-6), 134.2 (C-3), 139.1 (C-7a), 153.2 (C-10); Anal. calcd for $C_{16}H_{14}N_6O_4$: C,54.23, H,3.98, N,23.71; Found: C,54.20, H,3.94, N,23.65%; Mass (FAB): 354M$^+$.

(*E*)-2-Nitrobenzaldehyde [2-(6-nitro-1*H*-indazol-1-yl)ethyl] hydrazone 3j

Yield: 63%, m.p. 165-167 ºC; IR (cm^{-1}): 752 (C-Cl), 877 (C-N), 1336 (N-CH_2), 1524 (NO_2), 1540 (C=C), 1555 (N=CH), 1658 (C=O), 1446, 2850, 2899 (CH_2), 3034 (CH-Ar), 3367 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.40-3.46 (m, 2H, H-9), 4.21 (t, 2H, *J* = 7.50 Hz, H-8), 5.54 (s, 1H, H-1'), 7.89 (s, 1H, H-10), 7.73-8.26 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.1 (C-9), 46.3 (C-8), 115.1 (C-4), 119.4 (C-7), 120.5 (C-5), 121.7 (C-12), 122.1 (C-3a), 122.8 (C-16), 123.2 (C-13), 123.7 (C-15), 126.6 (C-14), 127.2 (C-11), 130.4 (C-6), 131.7 (C-3), 138.7 (C-7a), 153.4 (C-10); Anal. calcd for $C_{16}H_{14}N_6O_4$: C,54.23, H,3.98, N,23.71; Found: C,54.19, H,3.92, N,23.62%; Mass (FAB): 354M$^+$.

General procedure for the synthesis of compounds 4(a-j)

The compound **3a** (0.008 mole) and chloroacetyl chloride (0.008 mole) were dissolved in ethanol (100 mL) in the presence of Et_3N (0.008 mole) were allowed to react at room temperature. The reaction mixture was first stirred on a magnetic stirrer for about 2.00 h followed by reflux on a steam bath for about 2.30 h. 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 (80 mL). The purified product was dried under vacuo and recrystallized from acetone at room temperature to furnish compound **4a** (Figure 4).

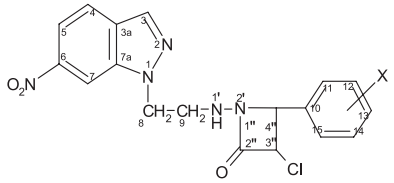


Figure 4. *Structure of compound* ***4(a-j)***

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

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-phenyl-2-azetidinone 4a

Yield: 66%, m.p. 157-159 ºC; IR (cm^{-1}): 747 (C-Cl), 875 (C-N), 1335 (N-CH_2), 1529 (NO_2), 1542 (C=C), 1659 (C=O), 1729 (CO cyclic), 1448, 2844, 2892 (CH_2), 2930 (CH-Cl), 3025, (CH-Ar), 3360

(NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.31-3.35 (m, 2H, H-9), 4.24 (t, 2H, *J* = 7.45 Hz, H-8), 4.35 (d, 1H, *J* = 4.75 Hz, H-3"), 5.22 (d, 1H, *J* = 4.75 Hz, H-4"), 5.86 (s, 1H, H-1'), 7.10-7.74 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 38.9 (C-9), 46.2 (C-8), 50.1 (C-3"), 61.4 (C-4"), 116.2 (C-4), 121.7 (C-7), 122.3 (C-5), 126.6 (C-11 and C-15), 127.1 (C-3a), 128.2 (C-13), 129.1 (C-12 and C-14), 132.5 (C-6), 134.8 (C-3), 135.2 (C-10), 140.4 (C-7a), 168.1 (C-2"); Anal. calcd for $C_{18}H_{16}N_5O_3Cl$: C,56.03, H,4.18, N,18.15; Found: C,56.00, H,4.12, N,18.10%; Mass (FAB): 386M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(4-chlorophenyl)-2-azetidinone 4b

Yield: 65%, m.p. 161-162 ºC; IR (cm^{-1}): 759 (C-Cl), 885 (C-N), 1337 (N-CH_2), 1531 (NO_2), 1545 (C=C), 1662 (C=O), 1735 (CO cyclic), 1450, 2849, 2895 (CH_2), 2932 (CH-Cl), 3032, (CH-Ar), 3365 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.31-3.36 (m, 2H, H-9), 4.22 (t, 2H, *J* = 7.35 Hz, H-8), 4.62 (d, 1H, *J* = 4.80 Hz, H-3"), 5.36 (d, 1H, *J* = 4.80 Hz, H-4"), 5.77 (s, 1H, H-1'), 7.16-7.82 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.6 (C-9), 49.4 (C-8), 52.7 (C-3"), 65.4 (C-4"), 120.1 (C-4), 122.6 (C-7), 123.2 (C-5), 128.6 (C-11 and C-15), 129.4 (C-3a), 130.7 (C-13), 132.5 (C-12 and C-14), 135.0 (C-6), 135.6 (C-10), 136.7 (C-3), 142.6 (C-7a), 170.5 (C-2"); Anal. calcd for $C_{18}H_{15}N_5O_3Cl_2$: C,51.44, H,3.59, N,16.66; Found: C,51.42, H,3.54, N,16.61%; Mass(FAB): 420M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(3-chlorophenyl)-2-azetidinone 4c

Yield: 62%, m.p. 160-162 ºC; IR (cm^{-1}): 755 (C-Cl), 876 (C-N), 1340 (N-CH_2), 1533 (NO_2), 1547 (C=C), 1665 (C=O), 1740 (CO cyclic), 1454, 2852, 2901 (CH_2), 2935 (CH-Cl), 3028, (CH-Ar), 3362 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.31-3.38 (m, 2H, H-9), 4.20 (t, 2H, *J* = 7.35 Hz, H-8), 4.68 (d, 1H, *J* = 5.00 Hz, H-3"), 5.36 (d, 1H, *J* = 5.00 Hz, H-4"), 5.74 (s, 1H, H-1'), 6.79-7.94 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.7 (C-9), 50.9 (C-8), 52.6 (C-3"), 65.7 (C-4"), 116.9 (C-4), 121.1 (C-7), 122.5 (C-5), 129.5 (C-11), 129.8 (C-15), 130.4 (C-3a), 131.6 (C-13), 132.2 (C-12), 133.7 (C-14), 136.9 (C-6), 137.1 (C-3), 138.2 (C-10), 141.7 (C-7a), 169.7 (C-2"); Anal. calcd for $C_{18}H_{15}N_5O_3Cl_2$: C,51.44, H,3.59, N,16.66; Found: C,51.40, H,3.55, N,16.61%; Mass (FAB): 420M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(2-chlorophenyl)-2-azetidinone 4d

Yield: 66%, m.p. 161-163 ºC; IR (cm^{-1}): 751 (C-Cl), 880 (C-N), 1348 (N-CH_2), 1534 (NO_2), 1546 (C=C), 1665 (C=O), 1738 (CO cyclic), 1448, 2853, 2903 (CH_2), 2940 (CH-Cl), 3027 (CH-Ar), 3370 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.30-3.36 (m, 2H, H-9), 4.23 (t, 2H, *J* = 7.35 Hz, H-8), 4.53 (d, 1H, *J* = 4.90 Hz, H-3"), 5.30 (d, 1H, *J* = 4.90 Hz, H-4"), 5.72 (s, 1H, H-1'), 6.81-7.82 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.6 (C-9), 48.8 (C-8), 53.5 (C-3"), 62.6 (C-4"), 119.7 (C-4), 123.5 (C-7), 124.3 (C-5), 126.9 (C-11), 127.0 (C-15), 127.4 (C-3a), 128.6 (C-13), 129.7 (C-12), 130.2 (C-14), 133.5 (C-6), 134.3 (C-3), 137.5 (C-10), 142.3 (C-7a), 171.8 (C-2"); Anal. calcd for $C_{18}H_{15}N_5O_3Cl_2$: C,51.44, H,3.59, N,16.66; Found: C,51.42, H,3.55, N,16.61%; Mass (FAB): 420M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(4-bromophenyl)-2-azetidinone 4e

Yield: 62%, m.p. 159-161 C; IR (cm^{-1}): 578 (C-Br), 886 (C-N), 1342 (N-CH_2), 1540 (NO_2), 1548 (C=C), 1662 (C=O), 1736 (CO cyclic), 1456, 2854, 2897 (CH_2), 2942 (CH-Cl), 3032, (CH-Ar), 3368 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.39-3.45 (m, 2H, H-9), 4.28 (t, 2H, *J* = 7.35 Hz, H-8), 4.62 (d, 1H, *J* = 5.00 Hz, H-3"), 5.32 (d, 1H, *J* = 5.00 Hz, H-4"), 5.79 (s, 1H, H-1'), 7.25-7.95 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.9 (C-9), 47.6 (C-8), 51.5 (C-3"), 64.4 (C-4"), 117.3 (C-4), 120.7 (C-7), 121.6 (C-5), 128.7 (C-11 and C-15), 129.6 (C-3a), 130.5 (C-13), 131.7 (C-12 and C-14), 134.3 (C-6), 135.7 (C-3), 138.5 (C-10), 141.6 (C-7a), 172.5 (C-2"); Anal. calcd for $C_{18}H_{15}N_5O_3BrCl$: C,46.52, H,3.25, N,15.07; Found: C,46.45, H,3.20, N,15.01%; Mass (FAB): 465M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(3-bromophenyl)-2-azetidinone 4f

Yield: 63%, m.p. 155-157 ºC; IR (cm^{-1}): 571 (C-Br), 877 (C-N), 1343 (N-CH_2), 1536 (NO_2), 1550 (C=C), 1663 (C=O), 1737 (CO cyclic), 1456, 2851, 2896 (CH_2), 2943 (CH-Cl), 3035, (CH-Ar), 3364 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.34-3.38 (m, 2H, H-9), 4.26 (t, 2H, *J* = 7.35 Hz, H-8), 4.45 (d, 1H, *J* = 4.90 Hz, H-3"), 5.37 (d, 1H, *J* = 4.90 Hz, H-4"), 5.77 (s, 1H, H-1'), 7.21-7.92 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.8 (C-9), 49.3 (C-8), 51.4 (C-3"), 63.3 (C-4"), 119.6 (C-4), 122.6 (C-7), 123.8 (C-5), 129.7 (C-11), 130.1 (C-15), 130.8 (C-3a), 131.5 (C-13), 132.3 (C-12), 133.7 (C-14), 135.8 (C-6), 136.6 (C-10), 137.5 (C-3), 142.3 (C-7a), 172.7 (C-2"); Anal. calcd for $C_{18}H_{15}N_5O_3BrCl$: C, 46.52, H,3.25, N,15.07; Found: C,46.47, H,3.21, N,15.22%; Mass (FAB): 465M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(2-bromophenyl)-2-azetidinone 4g

Yield: 62%, m.p. 156-158 ºC; IR (cm^{-1}): 565 (C-Br), 758 (C-Cl), 883 (C-N), 1346 (N-CH_2), 1535 (NO_2), 1546 (C=C), 1664 (C=O), 1738 (CO cyclic), 1452, 2846, 2900 (CH_2), 2941 (CH-Cl), 3028, (CH-Ar), 3361 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.31-3.39 (m, 2H, H-9), 4.25 (t, 2H, *J* = 7.35 Hz, H-8), 4.44 (d, 1H, *J* = 5.10 Hz, H-3"), 5.35 (d, 1H, *J* = 5.10 Hz, H-4"), 5.72 (s, 1H, H-1'), 7.27-7.84 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.2 (C-9), 50.5 (C-8), 53.2 (C-3"), 61.8 (C-4"), 118.4 (C-4), 124.7 (C-7), 125.4 (C-5), 127.6 (C-11), 128.2 (C-15), 128.5 (C-3a), 129.2 (C-13), 130.6 (C-12), 131.2 (C-14), 133.7 (C-6), 134.6 (C-3), 138.1 (C-10), 139.2 (C-7a), 169.3 (C-2"); Anal. calcd for $C_{18}H_{15}N_5O_3BrCl$: C,46.52, H,3.25, N,15.07; Found: C,46.42, H,3.20, N,15.01%; Mass (FAB): 465M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(4-nitrophenyl)-2-azetidinone 4h

Yield: 65%, m.p. 169-171 ºC; IR (cm^{-1}): 869 (C-NO), 756 (C-Cl), 879 (C-N), 1349 (N-CH_2), 1541 (NO_2), 1546 (C=C), 1666 (C=O), 1740 (CO cyclic), 1454, 2845, 2904 (CH_2), 2940 (CH-Cl), 3024, (CH-Ar), 3363 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.34-3.38 (m, 2H, H-9), 4.29 (t, 2H, *J* = 7.35 Hz, H-8), 4.38 (d, 1H, *J* = 4.80 Hz, H-3"), 5.27 (d, 1H, *J* = 4.80 Hz, H-4"), 5.75 (s, 1H, H-1'), 7.10-7.71 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 42.1 (C-9), 46.6 (C-8), 52.3 (C-3"), 64.4 (C-4"), 120.7 (C-4), 123.5 (C-7), 124.3 (C-5), 126.7 (C-11 and C-15), 127.8 (C-3a), 128.2 (C-13), 129.4 (C-12 and C-14), 132.6 (C-6), 134.6 (C-3), 139.4 (C-10), 141.2 (C-7a), 170.7 (C-2"); Anal. calcd for $C_{18}H_{15}N_6O_5Cl$: C,50.18, H,3.50, N,19.50; Found: C,50.12, H,3.45, N,19.52%; Mass (FAB): 431M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(3-nitrophenyl)-2-azetidinone 4i

Yield: 64%, m.p. 167-169 ºC; IR (cm^{-1}): 750 (C-Cl), 862 (C-NO),

1350 (N-CH_2), 1538 (NO_2), 1545 (C=C), 1665 (C=O), 1739 (CO cyclic), 1455, 2849, 2899 (CH_2), 2946 (CH-Cl), 3027, (CH-Ar), 3366 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.30-3.35 (m, 2H, H-9), 4.19 (t, 2H, *J* = 7.35 Hz, H-8), 4.24 (d, 1H, *J* = 4.80 Hz, H-3"), 5.32 (d, 1H, *J* = 4.80 Hz, H-4"), 5.78 (s, 1H, H-1'), 6.90-7.74 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 40.4 (C-9), 47.8 (C-8), 50.2 (C-3"), 63.3 (C-4"), 117.7 (C-4), 122.5 (C-5), 123.6 (C-7), 129.6 (C-11), 130.1 (C-15), 130.6 (C-3a), 131.5 (C-13), 132.7 (C-12), 132.9 (C-14), 135.5 (C-6), 136.1 (C-3), 137.9 (C-10), 140.6 (C-7a), 171.2 (C-2"); Anal. calcd for $C_{18}H_{15}N_6O_5Cl$: C,50.18, H,3.50, N,19.50; Found: C,50.15, H,3.40, N,19.46%; Mass (FAB): 431M$^+$.

3-Chloro-1-{[2-(6-nitro-1*H*-indazol-1-yl)ethyl]amino}-4-(2-nitrophenyl)-2-azetidinone 4j

Yield: 62%, m.p. 164-165 ºC; IR (cm^{-1}): 757 (C-Cl), 869 (C-NO), 1347 (N-CH_2), 1534 (NO_2), 1547 (C=C), 1663 (C=O), 1741 (CO cyclic), 1460, 2850, 2896 (CH_2), 2945 (CH-Cl), 3030, (CH-Ar), 3367 (NH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.34-3.39 (m, 2H, H-9), 4.29 (t, 2H, *J* = 7.35 Hz, H-8), 4.41 (d, 1H, *J* = 4.80 Hz, H-3"), 5.34 (d, 1H, *J* = 4.80 Hz, H-4"), 5.74 (s, 1H, H-1'), 7.05-7.71 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 41.6 (C-9), 48.7 (C-8), 50.3 (C-3"), 62.6 (C-4"), 118.8 (C-4), 124.5 (C-7), 125.8 (C-5), 127.6 (C-11), 127.9 (C-15), 128.3 (C-3a), 129.2 (C-13), 130.7 (C-12), 132.1 (C-14), 134.1 (C-6), 135.5 (C-3), 139.4 (C-10), 140.4 (C-7a), 168.9 (C-2"); Anal. calcd for $C_{18}H_{15}N_6O_5Cl$: C,50.18, H,3.50, N,19.50; Found: C,50.11, H,3.42, N,19.44%; Mass (FAB): 431M$^+$.

Biological study

Antibacterial, antifungal and antitubercular activities

The antibacterial, antifungal and antitubercular activities of compounds **4(a-j)** have been assayed *in vitro* against selected bacteria, *Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae,* fungi, *Aspergillus niger, Aspergillus flavus, Candida albicans Fusarium oxisporium* and *Mycobacterium tuberculosis* H37Rv strain respectively. MIC value of compounds **4(a-j)** were determined using filter paper disc diffusion method (antibacterial and antifungal activities) and L. J. medium (Conventional) method (antitubercular activity). Streptomycin and Griseofulvin used as standard for antibacterial and antifungal activities showed MIC range for all bacterial strain 1.25-3.25 µg/mL and for all fungal strain 6.25-12.5 µg/mL respectively and for antitubercular activity, Isoniazid and Rifampicin taken as standards (MIC range 1.25-2.50 µg/mL). All standards also screened under the similar condition for comparison. All concentrations used in µg/mL. Results of all given activities of above compounds were given in Table 1.

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 rate paw oedema was produced by the method of Winter *et al*..[15] The percentage inhibition of inflammation was calculated by applying Newbould formula. Results of the compounds **4(a-j)** were given in Table 2.

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