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SYNTHESIS, SPECTRAL ANALYSIS AND *IN VITRO* BIOLOGICAL EVALUATION OF AZETIDINONE DERIVATIVES OF 5-NITROINDAZOLE

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Abstract:
A simple and efficient method has been developed for the synthesis of various 3-chloro-2-oxo-azetidine derivatives of 5-nitroindazole using conventional method. The series of 3-chloro-2-oxo-azetidine derivatives synthesized were structurally confirmed by analytical and spectral data and evaluated for their antimicrobial activities. Some compounds show that promising antibacterial and antifungal activities.

Keywords: Azetidinone, antibacterial, antifungal, 5-nitroindazole.

Introduction

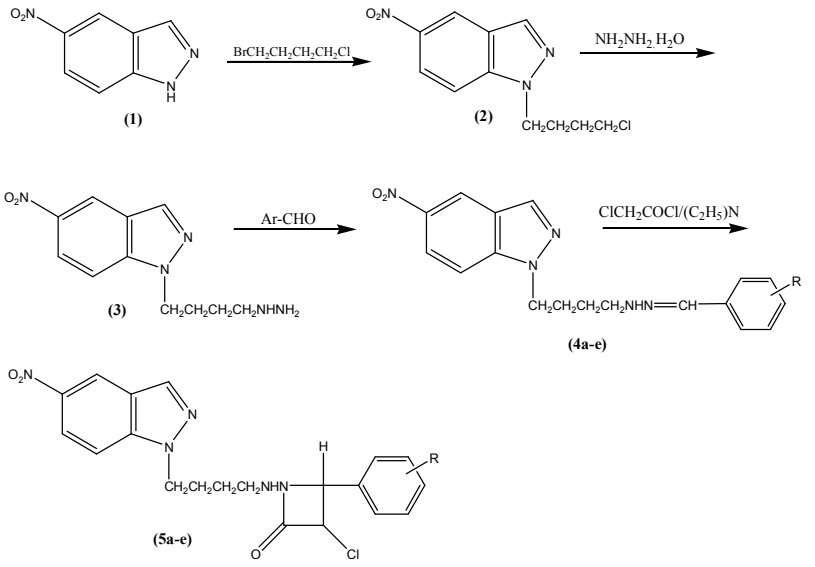
The 5-nitroindazole ring system is probably the most important heterocycle in nature. Owing to the great structural diversity of biologically active 5-nitroindazole, it is not surprising that the 5-nitroindazole ring system has become an important structural component in many pharmaceutical agents. Indazole ring possessing wide spectrum of pharmaceutical activities which include anti-inflammatory, antitumor, antiprotozoal, antimalarial, antiproliferative, analgesic, anticonvulsant, antimicrobial, antibacterial, antioxidant activity, etc [1-9]. 2-Azeti-dinones, known as β-lactams, serve as synthones for much biologically important class of organic compounds. 2-Azetidinones and its derivatives are important compounds due to their broad range of biological activities such as anti-inflammatory [10,11], antitubercular [12], antiproliferative [13], DNA cleavage [14], cholesterol absorption inhibitors [15], Antiplasmodial [16], antidepressant [17] and antimicrobial [18-20]. Based on these facts here we report the synthesis of 4-substituted aryl-3-chloro-2-oxo-azetidine derivatives of 5-nitroindazole as antimicrobial agents.

Results and Discussion

Our synthesis strategy was based on to synthesize a highly biologically active heterocyclic compound containing 5-nitroindazole and azetidinone moieties. As the results, we synthesized a series of azetidinone derivatives of 5-nitroindazole by scheme **1**.

5-nitroindazole on reaction with 1-bromo-4-chloro butane was converted into their chlorobutyl derivative (**1**), which on hydrazinolysis of with hydrazine hydrate afforded hydrazide derivative

(**2**). A new series of compounds (**3a-e)** was synthesised by treating of different aromatic aldehydes with compound (**2)** in the presence of a catalytic amount of glacial acetic acid. The target compounds **(4a-e)** furnished by treatment of chloroacetylchloride in the presence of Et_3N with compounds (**3a-e)**.



Scheme-I

All the synthesized compounds of series **(5a-e)** were tested for their antimicrobial activity, against some selected bacteria and fungi. Generally compounds possessing electronegative groups showed good antibacterial activity. Compounds possessing electron donating groups have shown good antifungal activity. Activity data are given in the table **I**. It is thus concluded that new synthesized azetidinones are good antimicrobial compounds for therapeutic uses.

Table-I: Antibacterial and Antifungal activity of Compounds 5(a-e) (MIC μg/ml)

No.	***S.aures***	***E.coli***	***S.pneumoe***	***C.albicas***	***A.fumigats***	***A.niger***
5a	20.0	10.0	10.0	5.0	20.0	20.0
5b	1.0	5.0	1.0	5.0	5.0	5.0
5c	10.0	10.	10.0	1.0	5.0	1.0
5d	1.0	5.0	5.0	5.0	1.0	5.0
5e	5.0	10.0	10.0	10.0	20.0	5.0
Norflaxacin	1.0	1.0	1.0			
Grysofulvin				1.0	1.0	1.0

Experimental Section

All the melting points were determined by open capillary method. All reagents were obtained from Sigma-Aldrich chemicals Pvt. Ltd. Solvents were commercially obtained as laboratory grade. All chemicals were used after further purification (recrystalization or distillation). TLC was carried out on silica gel G coated glass plates. The purification of the compounds was crried out by column chromatography using 100-200 mesh Silica gel. ^{1}H-NMR spectra were recorded on a Bruker DRX 300 instrument at 300 MHz in $CDCl_3$ on δ scale in ppm using TMS as a

reference. ^{13}C-NMR spectra were recorded on a Varian AMX 400 spectrophotometer at 50 MHz using $CDCl_3$. The FTIR spectra were recorded on a Perkin-elmer IR spectrophotometer using KBr disc of the sample in cm^{-1}. Mass spectra of the synthesized compounds have been recorded on a JEOL SX 102/DA-6000 spectrometer.

Evaluation of antimicrobial screening

All the synthesized compounds of series 5**(a-e)** were tested for their antimicrobial activity. For antibacterial screening a gram-positive bacterium *S. aureus* and two gram-negative becteria, *E.Coli* and *S.pneumoniae* were used. For antifungal activity *C.albicans*, *A. pumigatus* and *A.niger* was taken. Antibacterial and antifungal screenings were performed by dilution method using nutrient agar media. MIC was determined at seven concentrations (in µg/ml) ranging from 1.0 µg, 5.0 µg, 10.0 µg, 20.0 µg, 25.0 µg, 50.0 µg and 100.0 µg of each compounds. The tubes were incubated at 37ºC for 48 hrs. DMSO was used as solvent. The lowest concentration, which showed no visible growth, was taken as an end point for minimum inhibitory concentration (MIC). Norflaxacin was used as standard drug for antibacterial screening in a concentration 1.0 µg/ml/disc and grysofulvin was used as standard drug for antifungal screening in a concentration 1.0 µg/ml/disc. The MIC levels of some active compounds **(4a-e)** against these organisms are given in table I.

General Procedure of the synthesis

Synthetic Protocol for the synthesis of N-(chloro butyl)-5-nitroindazole (2)

5-Nitroindazole **(1)** (0.30 mol) was dissolved in methanol (100 ml) and 1-bromo-4-chlorobutane (0.30 mol) was added. The mixture was refluxed for about 5 hrs, filtered and the solvent was evaporated to dryness in vacuo. The crude product was readily purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (9:1 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystalized by ethanol to give compounds **2**. M.P. 192-193ºC; IR: 3048 (C-H in Ar.), 2872, 2891 (C-H in CH_2), 1569 (C=N), 1464 (C=C), 1365 (Ar-NO_2), 1325 (N-CH_2), 738 (C-Cl). ^{1}H-NMR: 6.85-7.66 (m, 3H, Ar.), 3.64 (t, 2H, J=7.00, $\underline{CH_2}CH_2CH_2CH_2$), 2.84 (t, 2H, J=7.00, $CH_2CH_2CH_2\underline{CH_2}$), 1.90 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 110.61-144.15 (Ar.), 48.44, 43.28, 32.13, 29.68. MS, m/z: 254 $(M)^+$. Anal. calcd. for $C_{11}H_{12}N_3O_2Cl$: C, 52.07; H, 4.73; N, 16.56. Found: C, 52.03; H, 4.69; N, 16.53.

Synthesis of N-(hydrazino butyl)-5-nitroindazole (3)

Compound **2** (0.149 mol) was dissolved in acetone (50 ml) and hydrazine hydrate (0.149 mol) was added. The well stirred (1 hr) mixture was refluxed for 6 hrs. After cooling and filtration the solvent was evaporated under in vacuo to obtain a solid crude product. This resulting crude product was purified by passing it through a chromatographic column packed with silica gel using acetone: methanol (9:1 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystalized by ethanol to give compounds **3**. M.P. 205-206ºC; IR: 3378 (-NH_2), 3345 (NH), 3045 (C-H in Ar.), 2874, 2892 (C-H in CH_2), 1564 (C=N), 1467 (C=C), 1361 (Ar-NO_2), 1327 (N-CH_2). ^{1}H-NMR: 7.85 (s, 1H, NH), 6.78-7.62 (m, 3H, Ar.), 3.72 (t, 2H, J=7.20, $\underline{CH_2}CH_2CH_2CH_2$), 2.88 (t, 2H, J=7.20, $CH_2CH_2CH_2\underline{CH_2}$), 1.76 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: (50 MHz, $CDCl_3$) δ: 113.63-146.21 (Ar.), 51.24, 42.49, 32.16, 30.58. MS, m/z: 249$(M)^+$. Anal. Calcd. for $C_{11}H_{15}N_5O_2$:C, 53.01; H, 6.02; N, 12.85. Found: C, 52.94; H, 5.98; N, 12.82.

Synthesis of N-[(benzylidene hydrazino)-butyl]-5-nitroindazole (4a-e)

A mixture of compound **3** (0.008 mol) and benzaldehyde (0.008 mol) in methanol (25 ml) in the presence of a catalytic amount of glacial acetic acid was refluxed for 5 hrs. The solvent was removed under reduced pressure to and the resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform : methanol (8:2 v/v) as eluant. Resulting purified product was recrystalized by chloroform to give compounds, **4a**.

N-[(benzylidene hydrazino)-butyl]-5-nitroindazole (4a). M.P. 220-221ºC: IR: 3351 (NH), 3043 (C-H in Ar.), 2872, 2888 (C-H in CH_2), 1586 (N=CH, azomethine), 1568 (C=N), 1461 (C=C), 1365 (Ar-NO_2), 1333 (N-CH_2). ^{1}H-NMR: 8.20 (s, 1H, N=CH, azomethine), 7.85 (s, 1H, NH), 6.74-7.78 (m, 9H, Ar.), 3.75 (t, 2H, J=7.20, $\underline{CH_2}CH_2CH_2CH_2$), 2.85 (t, 2H, J=7.20, $CH_2CH_2CH_2\underline{CH_2}$), 1.71 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 111.24-148.21 (Ar.), 138.84 (N=CH, azomethine), 48.56, 44.27, 31.48, 29.52. MS, m/z: 337$(M)^+$. Anal. Calcd. for $C_{18}H_{19}N_5O_2$: C, 64.09; H, 5.63; N, 20.77. Found : C, 64.04; H, 5.60; N, 20.74.

Other compounds **4b-e** were synthesized in the similar manner by treating compound **3** with selected aromatic aldehydes (**Scheme 1**).

N-[(2-chlorobenzylidene hydrazino)-butyl]-5-nitroindazole (4b).). M.P. 226-227ºC: IR: 3356 (NH), 3049 (C-H in Ar.), 2868, 2891(C-H in CH_2), 1591 (N=CH, azomethine), 1572 (C=N), 1464 (C=C), 1362 (Ar-NO_2), 1335 (N-CH_2). ^{1}H-NMR: 8.28 (s, 1H, N=CH, azomethine), 7.88 (s, 1H, NH), 6.72-7.76 (m, 8H, Ar.), 3.72 (t, 2H, J=7.25, $\underline{CH_2}CH_2CH_2CH_2$), 2.78 (t, 2H, J=7.25, $CH_2CH_2CH_2\underline{CH_2}$), 1.73 (m, 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 109.32-149.45 (Ar.), 140.42 (N=CH, azomethine), 48.74, 44.93, 32.41, 29.45. MS, m/z: 372 $(M)^+$. Anal. Calcd. for $C_{18}H_{18}N_5O_2Cl$: C, 58.14; H, 4.84; N, 18.84. Found : C, 58.11; H, 4.80; N, 18.79.

N-[(2-bromobenzylidene hydrazino)-butyl]-5-nitroindazole (4c). M.P.215-216ºC: IR: 3352 (NH), 3059 (C-H in Ar.), 2863, 2886 (C-H in CH_2), 1585 (N=CH, azomethine), 1568 (C=N), 1463 (C=C), 1364 (Ar-NO_2), 1333 (N-CH_2). ^{1}H-NMR: 8.22 (s, 1H, N=CH, azomethine), 7.82 (s, 1H, NH), 6.75-7.71 (m, 8H, Ar.), 3.73 (t, 2H, J=7.10, $\underline{CH_2}CH_2CH_2CH_2$), 2.77 (t, 2H, J=7.10, $CH_2CH_2CH_2\underline{CH_2}$), 1.69 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 110.54-150.42 (Ar.), 138.54 (N=CH, azomethine), 48.24, 44.78, 31.74, 28.76. MS, m/z: 416 $(M)^+$. Anal. Calcd. for $C_{18}H_{18}N_5O_2Br$: C, 51.92; H, 4.32; N, 16.82. Found : C, 51.89; H, 4.28; N, 16.77.

N-[(2-nitrobenzylidene hydrazino)-butyl]-5-nitroindazole (4d). M.P. 234-235ºC: IR: 3362 (NH), 3054 (C-H in Ar.), 2866, 2893 (C-H in CH_2), 1591 (N=CH, azomethine), 1575 (C=N), 1467 (C=C), 1367 (Ar-NO_2), 1339 (N-CH_2). ^{1}H-NMR: 8.30 (s, 1H, N=CH, azomethine), 7.92 (s, 1H, NH), 6.81-7.81 (m, 8H, Ar.), 3.85 (t, 2H, J=7.30, $\underline{CH_2}CH_2CH_2CH_2$), 2.88 (t, 2H, J=7.30, $CH_2CH_2CH_2\underline{CH_2}$), 1.75 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 110.55-151.58 (Ar.), 141.78 (N=CH, azomethine), 49.74, 45.92, 33.78, 30.34. MS, m/z: 382 $(M)^+$. Anal. Calcd. for $C_{18}H_{18}N_6O_2$: C, 56.54; H, 4.71; N, 21.98. Found : C, 56.50; H, 4.66; N, 21.93.

N-[(2-methoxybenzylidene hydrazino)-butyl]-5-nitroindazole (4e). M.P. 216-217ºC: IR: 3353 (NH), 3056 (C-H in Ar.), 2861, 2885 (C-H in CH_2), 1588 (N=CH, azomethine), 1564 (C=N), 1468 (C=C), 1365 (Ar-NO_2), 1331 (N-CH_2). ^{1}H-NMR: 8.28 (s, 1H, N=CH, azomethine), 7.79 (s, 1H, NH), 6.71-7.68 (m, 8H, Ar.), 3.78 (t, 2H, J=7.08, $\underline{CH_2}CH_2CH_2CH_2$), 2.78 (t, 2H, J=7.08, $CH_2CH_2CH_2\underline{CH_2}$), 1.66 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 113.86-148.36 (Ar.), 139.65 (N=CH, azomethine), 49.43, 44.28, 31.05, 29.14. MS, m/z: 367 $(M)^+$. Anal. Calcd. for $C_{19}H_{21}N_5O_3$: C, 62.12; H, 5.72; N, 19.07. Found : C, 62.08; H, 5.68; N, 19.04.

Synthesis of N-{[(2-oxo-3-chloro-4-phenyl)-azetidinimino]-butyl}-5-nitroindazole (5a).

A mixture of compound **4a** (0.003 mol) and Et_3N (0.01 mol) in methanol, $ClCH_2COCl$ (0.003 mol) was added dropwise. The well stirred (3 hrs) reaction mixture was refluxed on a steam bath

for about 6 hours. The reaction mixture was cooled and excess of solvent was evaporated under reduced pressure. The solid obtained was purified by passing it through a chromatographic column packed with Silica gel using chloroform: methanol (8:2 v/v) as eluant and recrystallised from ethanol to give compounds **5a**. M.P. 231-232 ºC: IR: 3358 (N-H), 3051 (C-H in Ar.), 2934 (CH-Cl), 2866, 2881 (C-H in CH_2), 1738 (C=O), 1564 (C=N), 1465 (C=C), 1361 (Ar-NO_2), 1338 (N-CH_2). ^{1}H-NMR: 8.12 (s, 1H, NH), 6.88-7.82 (m, 9H, Ar.), 5.52 (d,1H, J=4.25, CH-Cl), 5.38 (d, 1H, J=4.25, N-CH-Ar), 3.82 (t, 2H, J=7.15, $\underline{CH_2}CH_2CH_2CH_2$), 2.64 (t, 2H, J=7.15, $CH_2CH_2CH_2\underline{CH_2}$), 1.64 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 167 (C=O), 112.36-149.52 (Ar.), 68.36 (N-CH), 61.46 (C-Cl), 49.48, 43.84, 32.36, 29.42. MS, m/z: 414 $(M)^+$. Anal. Calcd. for $C_{20}H_{20}N_5O_3Cl_1$: C, 58.04; H, 4.83; N, 16.92. Found : C, 57.00; H, 4.81; N, 16.88.
Other compounds **5b-e** was synthesized in the similar manner by treating compound **4b-e** (Scheme 1).

N-[{4-(2-chlorophenyl)-3-chloro-2-oxoazetidinimino}-butyl]-5-nitroindazole (5b).
M.P.237-238 ºC: IR: 3362 (N-H), 3054 (C-H in Ar.), 2936 (CH-Cl), 2862, 2884 (C-H in CH_2), 1741 (C=O), 1561 (C=N), 1466 (C=C), 1368 (Ar-NO_2), 1335 (N-CH_2), 738 (Ar-Cl). ^{1}H-NMR: 8.15 (s, 1H, NH), 6.81-7.76 (m, 9H, Ar.), 5.55 (d, 1H, J=4.25, CH-Cl), 5.34 (d, 1H, J=4.25, N-CH-Ar), 3.88 (t, 2H, J=7.10, $\underline{CH_2}CH_2CH_2CH_2$), 2.62 (t, 2H, J=7.10, $CH_2CH_2CH_2\underline{CH_2}$), 1.61 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 169 (C=O), 115.32-149.64 (Ar.), 69.45 (N-CH), 60.22 (C-Cl), 50.12, 43.64, 32.85, 29.76. MS, m/z: 448 $(M)^+$. Anal. Calcd. for $C_{20}H_{19}N_5O_3Cl_2$: C, 53.57; H, 4.24; N, 15.62. Found : C, 53.52; H, 4.19; N, 15.57.

N-[{4-(2-bromophenyl)-3-chloro-2-oxoazetidinimino}-butyl]-5-nitroindazole (5c).
M.P.225-226: IR: 3358 (N-H), 3053 (C-H in Ar.), 2936 (CH-Cl), 2860, 2878 (C-H in CH_2), 1739 (C=O), 1567 (C=N), 1462 (C=C), 1371 (Ar-NO_2), 1336 (N-CH_2), 652 (Ar-Br). ^{1}H-NMR: 8.18 (s, 1H, NH), 6.71-7.72 (m, 9H, Ar.), 5.51 (d,1H, J=4.35, CH-Cl), 5.35 (d, 1H, J=4.35, N-CH-Ar), 3.87 (t, 2H, J=7.40, $\underline{CH_2}CH_2CH_2CH_2$), 2.64 (t, 2H, J=7.40, $CH_2CH_2CH_2\underline{CH_2}$), 1.58 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 165.89 (C=O), 113.32-150.32 (Ar.), 68.12 (N-CH), 60.34 (C-Cl), 48.58, 43.24, 31.62, 29.26. MS, m/z: 493 $(M)^+$. Anal. Calcd. for $C_{20}H_{19}N_5O_3Cl_1Br_1$: C, 48.73; H, 3.85; N, 14.21. Found : C, 48.69; H, 3.80; N, 14.16.

N-[{4-(2-nitrophenyl)-3-chloro-2-oxoazetidinimino}-butyl]-5-nitroindazole (5d).
M.P. 236-237ºC: IR: 3361 (N-H), 3061 (C-H in Ar.), 2941 (CH-Cl), 2867, 2891 (C-H in CH_2), 1745 (C=O), 1569 (C=N), 1463 (C=C), 1368 (Ar-NO_2), 1342 (N-CH_2). ^{1}H-NMR: 8.25 (s, 1H, NH), 6.78-7.86 (m, 9H, Ar.), 5.58 (d,1H, J=4.30, CH-Cl), 5.36 (d, 1H, J=4.30, N-CH-Ar), 3.84 (t, 2H, J=7.20, $\underline{CH_2}CH_2CH_2CH_2$), 2.69 (t, 2H, J=7.20, $CH_2CH_2CH_2\underline{CH_2}$), 1.68 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 165.62 (C=O), 113.16-152.58 (Ar.), 69.66 (N-CH), 62.12 (C-Cl), 49.12, 44.78, 33.41, 30.12. MS, m/z: 459 $(M)^+$. Anal. Calcd. for $C_{20}H_{19}N_6O_5Cl_1$: C, 52.34; H, 4.14; N, 18.32. Found : C, 52.32; H, 4.11; N, 18.27.

N-[{4-(2-methoxyphenyl)-3-chloro-2-oxoazetidinimino}-butyl]-5-nitroindazole (5e).
M.P. 231-232ºC: IR: 3355 (N-H), 3054 (C-H in Ar.), 2935 (CH-Cl), 2861, 2883 (C-H in CH_2), 1738 (C=O), 1573 (C=N), 1462 (C=C), 1365 (Ar-NO_2), 1338 (N-CH_2), 1251 (Ar-OCH_3). ^{1}H-NMR: 8.19 (s, 1H, NH), 6.81-7.83 (m, 9H, Ar.), 5.52 (d,1H, J=4.25, CH-Cl), 5.33 (d, 1H, J=4.25, N-CH-Ar), 3.88 (t, 2H, J=7.25, $\underline{CH_2}CH_2CH_2CH_2$), 2.61 (t, 2H, J=7.25, $CH_2CH_2CH_2\underline{CH_2}$), 1.57 (m 4H, $CH_2\underline{CH_2}\underline{CH_2}CH_2$). ^{13}C-NMR: 164.84 (C=O), 111.72-151.68 (Ar.), 68.38 (N-CH), 60.53 (C-Cl), 49.14, 44.43, 32.98, 29.54. MS, m/z: 444 $(M)^+$. Anal. Calcd. for $C_{21}H_{22}N_5O_4Cl_1$: C, 56.82; H, 4.96; N, 15.78. Found : C, 56.79; H, 4.92; N, 15.73.

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