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Research Article

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Synthesis and Biological Activity of Indoles with Azetidinone Moiety.

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Abstract: Phenylhydrazine was reacted with ethyl-3-oxobutanoate and furnished compound 1. Compound 2 was obtained by reaction of compound 1 with hydrazine. Compound 2 was converted in to compound 3-5 by reaction with substituted aromatic aldehydes. Compounds 6-8 were obtained by reaction with triethylamine in presence of dioxane respectively. All the newly synthesized compounds were characterized by their spectral and elemental analysis data. Screening avaluation of these compounds was checked by cup plate method and result was recorded in zone of inhibition and compared with standard drug.

Keywords: Indole, azetidinone, antifungal activity, fluconazole.

INTRODUCTION

The synthesis of heterocyclic compounds has drawn the chemist from long time due ti their important biological activities. Indole derivatives play an important role in heterocyclic compound history and possess a wide range of biological activity like antifungal[1-4], antioxidant[5], antimicrobial[6-9] activities. Azetidinone is very well-known compound for the biological field. The derivative of azetidinone nucleus has been founded to possess different pharmacological properties like, antimicrobial[10-18], antifungal[19-20] anticancer[21] activity. The aim of this approach was to further evaluate the antifungal activity of indole derivatives with azetidinone moiety by making some structure modification and focus to improve the biological activity.

MATERIAL AND METHOD

In this work different kinds of reagent and glassware were used and dissolved in appropriate solvents. The melting points were noted down by melting point apparatus using ordinary glass capillary tube and purity of reaction was recorded by TLC plate method on silica gel. Perkin Erlmer 2400 was used to confirm various portion of elemental part. Beckman and Brucker spectrometer were used to check different value of IR and ^{1}HNMR respectively.

EXPERIMENTAL

Synthesis of Ethyl 2-methyl-1H-indole-3-carboxylate (1)

Compound 1 was synthesized according to the method of Kumar. Phenyl hydrazine (0.01mol) was reacted with ethyl 3-oxobutanoate (0.01mol) and glacial acetic acid then reflux for 8 h. The reaction mixture was poured onto ice. The product was filtered, washed, dried and recrystallized with ethanol to give compound 1.

Yield: 74%. m.p 82^{0}C. IR (KBr) ν_{max} in cm^{-1} 1609 C=C, 1640 C=O, 1655 C-N, 3043 C-H, 3485 N-H. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 2.80 (m, 2H, CH_2), 3.24 (s, 3H, indole-CH_3), 3.81 (t, 3H, CH_3), 6.24 (d, 1H, C-NH), 7.10-7.83 (m, 4x1H, C-H indole), $C_{12}H_{13}NO_2$; Calcd ; C: 70.92.; H: 6.45; N : 6.89%; Found C: 70.94; H: 6.49; N: 6.48%.

Preparation of 2-methyl-1H-indole-3-carbohydrazide (2)

Methanolic solution of compound 1 (0.01 mol) was refluxed for 6 h with hydrated hydrazine (0.01 mol). The product was filtered off, washed with methanol and crystallized from appropriate solvent to give compound 2.

Yield: 69%. m.p 95^{0}C. IR (KBr) ν_{max} in cm^{-1} 1613 C=C, 1642 C=O, 1650 C-N, 3047 C-H, 3488 N-H. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.43 (d, 2H, NH_2), 3.86 (s, 3H, CH_3), 5.97 (t, 1H, CO-NH), 6.25 (d, 1H, C-NH), 7.11-7.85 (m, 4x1H, C-H indole); $C_{10}H_{11}N_3O$; Cald ; C: 63.48.; H: 5.86; N : 22.21%; Found C: 63.44; H: 5.89; N: 22.24%.

Preparation of N'-benzylidene-2-methyl-1H-indole-3-carbohydrazide (3)

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A reaction mixture of compound 2 (0.01 mol) and deferent substituted aromatic aldehydes (0.01 mol) in 20 ml of DMF with few drops of acetic acid was added and refluxed for 6h. The reaction mixture was allowed to cool. The product was filtered and crystallized from ethanol to obtained compounds 3.
Yield: 60%. m.p 120^{0}C. IR (KBr) ν_{max} in cm^{-1} 1556 CH=N, 1614 C=C, 1649 C=O, 1658 C-N, 3040 C-H, 3482 N-H. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.87 (s, 3H, CH_3), 6.20 (s, 2x1H, C-NH), 7.13-7.74 (m, 4x1H, C-H indole); 7.87-8.12 (m, 5x1H, CH-Ar), 8.42 (d, 1H, CH=N), $C_{17}H_{15}N_3O$,: Cald ; C: 73.63.; H: 5.45; N : 15.15%; Found C: 73.65; H: 5.49; N: 15.18%.

The compounds 4 and 5 were prepared using a similar method of compound 3. Elemental and spectral analyses of compounds 4 and 5 have given below.
N'-(4-hydroxybenzylidene)-2-methyl-1H-indole-3-carbohydrazide (4)
Yield: 54%. m.p 135^{0}C. IR (KBr) ν_{max} in cm^{-1} 1552 CH=N, 1613 C=C, 1641 C=O, 1660 C-N, 3044 C-H, 3481 N-H, 3490 OH. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.84 (s, 3H, CH_3), 6.28 (s, 2x1H, C-NH), 7.10-7.75 (m, 4x1H, C-H indole); 7.83-8.15 (m, 4x1H, CH-Ar), 8.54 (d, 1H, CH=N), 12.14 (s, 1H, OH), $C_{17}H_{15}N_3O_2$; Cald ; C: 69.61.; H: 5.15; N : 14.33%; Found C: 69.65; H: 5.18; N: 14.68%.
N'-(4-chlorobenzylidene)-2-methyl-1H-indole-3-carbohydrazide (5)
Yield: 50%. m.p 145^{0}C. IR (KBr) ν_{max} in cm^{-1} 745 C-Cl, 1551 CH=N, 1611 C=C, 1647 C=O, 1668 C-N, 3041 C-H, 3485 N-H. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.86 (s, 3H, CH_3), 6.30 (s, 2x1H, C-NH), 7.12-7.81 (m, 4x1H, C-H indole); 7.89-8.14 (m, 4x1H, CH-Ar), 8.48 (d, 1H, CH=N), $C_{17}H_{14}ClN_3O$; Cald ; C: 65.49.; H: 4.53; N : 13.48%; Found C: 65.45; H: 4.50; N: 13.45%.
N-(3-chloro-2-oxo-4-phenyl-azetidin-1-yl)-2-methyl-1H-indole-3-carboxamide (6)

Compound 3 (0.01 mol) in dry dioxane (10 ml) and triethyamine (0.005 mol) was take in round bottom flask. The reaction mixture was stirred on an ice bath and when temperature dropped below 0-5^0 C, then chloroacetylchloride (0.01mol) was added drop wise with stirring. The reaction mixture was then kept a side for 46 h and cool with ice water. The product was dried and recrystallized from appropriate solvent to give compound 6.
Yield: 45%. m.p 161^{0}C. IR (KBr) ν_{max} in cm^{-1} 1559 CH=N, 1617 C=C, 1643 C=O, 1664 C-N, 3048 C-H, 3489 N-H. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.69 (d, 1H, CH-Cl), 3.87 (s, 3H, CH_3), 6.26 (s, 2x1H, C-NH), 7.13-7.80 (m, 4x1H, C-H indole); 7.87-8.11 (m, 5x1H, CH-Ar), 8.55 (s, 1H, CH-N), $C_{19}H_{16}ClN_3O_2$, 353.80; : Cald ; C: 64.50.; H: 4.56; N : 11.88%; Found C: 64.47; H: 4.53; N: 11.86%.

The compounds 7 and 8 were prepared using a similar method of compound 6. Elemental and spectral analyses of compounds 7 and 8 have given below.
N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-methyl-1H-indole-3-carboxamide (7)
Yield: 39%. m.p184^{0}C. IR (KBr) ν_{max} in cm^{-1} 1556 CH=N, 1618 C=C, 1650 C=O, 1670 C-N, 3044 C-H, 3470 N-H, 3499 OH; . ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.63 (d, 1H, CH-Cl), 3.83 (s, 3H, CH_3), 6.28 (s, 2x1H, C-NH), 7.14-7.86 (m, 4x1H, C-H indole); 7.85-8.10 (m, 4x1H, CH-Ar), 8.53 (s, 1H, CH-N), 12.40 (s, 1H, OH-Ar), $C_{19}H_{16}ClN_3O_3$, 369.80; : Cald ; C: 61.71.; H: 4.36; N : 11.36%; Found C: 61.74; H: 4.39; N: 11.38%.

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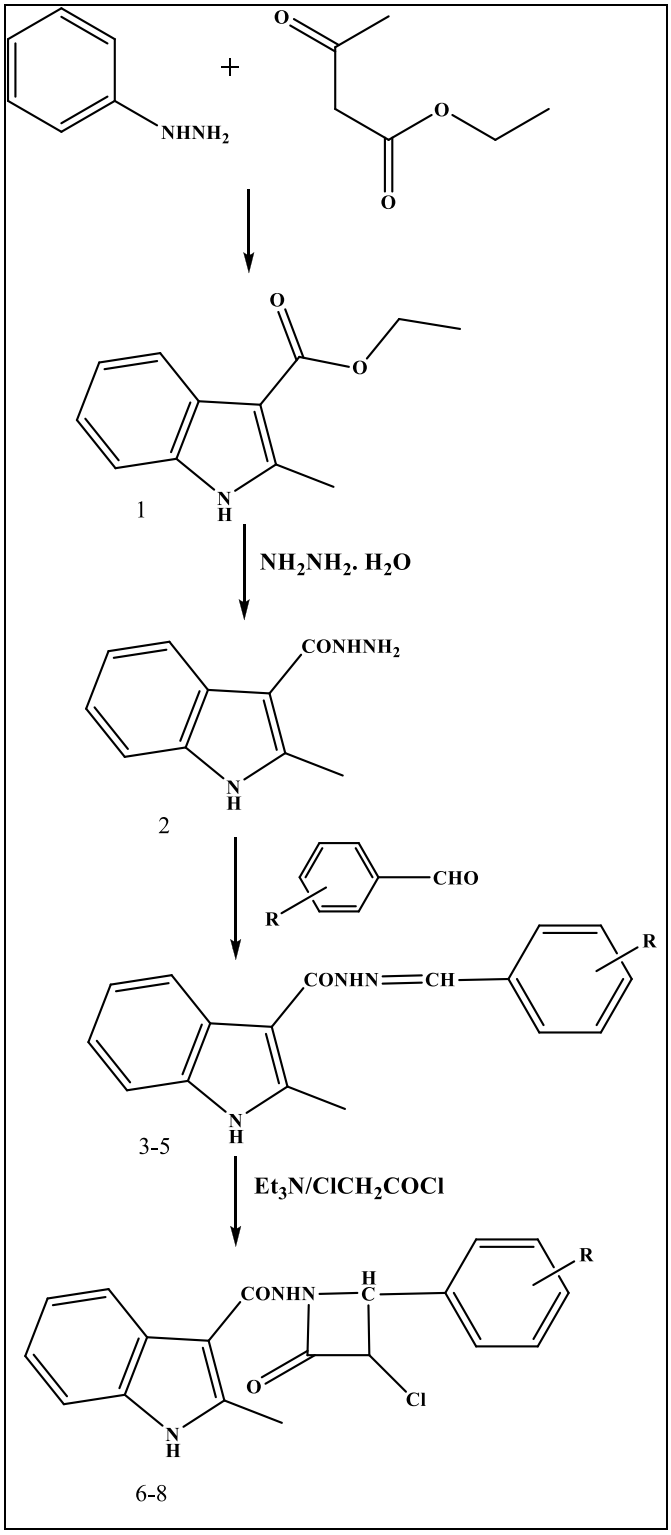

R = H, 4-OH, 4-Cl

Scheme 1

N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-2-methyl-1H-indole-3-carboxamide (8)
Yield: 67%. m.p 206^{0}C. IR (KBr) ν_{max} in cm^{-1} 763 C-Cl, 1555 CH=N, 1618 C=C, 1647 C=O, 1651 C-N, 3045 C-H, 3485 N-H. ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 3.65 (d, 1H, CH-Cl), 3.86 (s, 3H, CH_3), 6.30 (s, 2x1H, C-NH), 7.10-7.82 (m, 4x1H, C-H indole); 7.87-8.18 (m, 4x1H, CH-Ar), 8.59 (s, 1H, CH-N), $C_{19}H_{15}Cl_2N_3O_2$, 388.25; : Cald ; C: 58.78.; H: 3.89; N : 10.82%; Found C: 58.75; H: 3.86; N: 10.85%.

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Table 1: Antifungal activity of compounds 1-8

Compounds	R group	Fungal Inhibition Zone /mm		
		C. albicans	C. albicans ATCC	C. krudei
1	-	-	5	-
2	-	8	7	6
3	H	10	9	7
4	4-OH	15	12	10
5	4-Cl	20	16	12
6	H	23	19	14
7	4-OH	25	21	16
8	4-Cl	28	25	20
Fluconazole		29	25	19

BIOLOGICAL STUDY

All the synthesized derivatives of indole with azetidinone moiety were screened for their in vitro antifungal activity against various fungal strains like c. albicans, c. albicans ATCC and c. krusei by disc diffusion method[22]. Standard drug, fluconazole was used for comparision against fungal strain. Zone of inhibition of different fungal strain was recorded in diameter in mm. Compounds 2, 3 have shown mild, and compounds 4 and 5 have shown moderate antifungal activity against all these fungal strains. Incorporating azetidinone moiety in indole derivatives, compounds 6, 7 and 8 increase antifungal activities against fungal strains. Compound 8 showed good antifungal activity against c. albicans, c. albicans ATCC and c. krusei as compared standard drug fluconazole.

CONCLUSION

A new series of indole derivatives incorporating with azetidinone moiety were synthesized and characterized by elemental and spectral (IR and ^{1}HNMR) analysis. The newly synthesized compounds were evaluated for their in vitro antifungal activity. Some of the compounds of this series exhibited good antifungal activity. These compounds were compared with standard drug fluconazole.

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