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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME SUBSTITUTED 2-((1H-INDOL-4-YL)OXY)-N'-BENZYLIDENEACETOHYDRAZIDE

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ABSTRACT

Reaction of 4- hydroxy indole with ethyl chloroacetate to form ethyl 2-((1H-indol-4-yl)oxy)acetate (1). Compound 1 react with hydrazine hydrate in ethanol yield 2-((1H-indol-4-yl)oxy)acetohydrazide (2). The condensation of (2) with various aldehydes yield the corresponding substituted 2-((1H-indol-4-yl)oxy)-N'-benzylideneacetohydrazide (3a-j). The compounds obtained were identified by spectral data and have been screened for antimicrobial activity.

KEYWORDS: Indole, schiff's base, antimicrobial activity.

INTRODUCTION

Schiff bases are the important compound owing to their wide range of biological activities and industrial application. They have been found to posses the pharmacological activities such as antimalarial[1], anticancer[2], antibacterial[3], antifungal[4], antitubercular[5], anti-inflammatory, antimicrobial[6], and antiviral[7], etc. They also serve as a back bone for the synthesis of various heterocyclic compounds.

The indole framework is widely distributed in compounds with significant biological and pharmacological relevance. The development of synthetic methodologies leading to indole derivatives has attracted much attention among organic chemists. The carbon-carbon bond formation at the C-3 of indole takes advantage of the electron rich nature of this position which can be viewed as possessing enamine like character. Furthermore 3-substituted indoles are components of many drugs and are commonly found in molecules of Pharmaceutical interest in a variety of therapeutic areas.

This initiated the synthesis of compounds containing both the Indole moiety coupling schiff base systems in the same matrix to serve as a new scaffold for the synthesis of antimicrobial agents. The present work deals with the reaction of 2-(quinolin-8-yloxy) acetohydrazide (2) with different aromatic aldehydes to form schiff's bases (3a-j). Finally, the structures of all the various synthesized compounds were assigned on the basis of IR and 1H NMR spectral data and these compounds were screened for their antimicrobial activity.

MATERIALS AND METHODS

All the chemicals used to synthesize the title compounds were of laboratory grade and purchased from S.D. Fine Chemicals and Sigma Aldrich. All the reactions were carried out under prescribed laboratory conditions. Melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK, 60F) using chloroform: methanol (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on Josco FTIR model 8400 spectrophotometer, 1H NMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard.

Synthesis of ethyl 2-((1H-indol-4-yl)oxy)acetate (1)

An equimolar mixture of 4- hydroxy indole (0.01 mol, 1.43gm), ethyl chloroacetate (0.01mol, 138gm) and anhydrous potassium carbonate (0.02mol, 3.76gm) in dry acetone (60 ml) was refluxed on a water bath for 24 hr. The inorganic solid was filtered and the excess solvent was removed on a rota vapour, dried and recrystalized from ethanol. The compound was separated as reddish brown crystals.

Synthesis of 2-((1H-indol-4-yl)oxy)acetohydrazide (2)

To a suspension of (1) (0.01 mol) in absolute ethanol (50 ml), hydrazine hydrate (99%, 0.015 mol) was added and the reaction mixture was refluxed for 15hrs. The solution was concentrated and allowed to cool overnight. The resulting solid obtained was filtered, washed with cold ethanol, dried and recrystalized from ethanol. The compound was separated as brown crystals.

Synthesis of 2-((1H-indol-4-yl)oxy)-N'-benzylideneacetohydrazide (3a- j)

Equimolar quqntity of the hydrazide compound (2, 0.01mol**)** and various aromatic aldehydes (3a-j, 0.01mol) in ethanol (50 ml) were heated on a water bath for 4-8 hrs. The resulting Schiffs bases (3a-j) were cooled and poured into crushed ice. The precipitate thus obtained

was filtered washed with cold water and purified by recrystallized from ethanol. The detailed scheme of synthesis is given in the Figure-1. The physicochemical data of the compounds (3a-j) is described in Tables 1.

SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

2-((1H-indol-4-yl)oxy)-N'-benzylideneacetohydrazide(3a): IR(KBr in cm^{-1}): 3432 (NH), 3111,3108,2977,2813,1641(C=O),1581(N=CH),1568,1502,1473,1381,1252,1153,1071,924 817,771.^{1}H NMR (DMSO, δ ppm):11.51(s, 1H, CONH),9.89s, 1H, N=CH),8.77 6.55(m, 11H, Ar),5.02(s, 2H, O-CH_2- O).

2-((1H-indol-4-yl)oxy)-N'-(4-chlorobenzylidene)acetohydrazide(3b):IR(KBr in cm^{-1}): 3352(NH),3099,3010,2978,2811,1645(C=O),1581(N=CH),1562,1508,1478,381,1256,1161 1067,928,821,775 ^{1}H NMR(DMSO, δ ppm):11.71(s, 1H, CONH), 9.92(s, 1H, N=CH),8.72-6.62(m, 10H, Ar),5.01(s, 2H, -OCH_2).

2-((1H-indol-4-yl)oxy)-N'-(4-bromobenzylidene)acetohydrazide(3c):IR(KBr in cm^{-1}): 3351NH),3101,3043,2967,2812,1641C=O),1581(N=CH),1557,1510,1481,1371,1251,1151, 1067,928,816,771.^{1}H NMR (DMSO, δ ppm):11.71(s, 1H, CONH), 9.91(s, 1H, N=CH), 8.72-6.62(m, 10H, Ar),5.03(s, 2H, -OCH_2).

2-((1H-indol-4-yl)oxy)-N'-(4-nitrobenzylidene)acetohydrazide(3d):IR(KBr in cm^{-1}): 3346(NH),3122,3021,2962,2857,1647C=O),1583(N=CH),1381,1351,1561,1519,1479,1387, 1354,1251,1149,1061,931,812,779,^{1}H NMR(DMSO, δ ppm):11.51(s, 1H, CONH),9.91(s, 1H, N=CH), 8.76- 6.56(m, 11H, Ar),5.01(s, 2H, O-CH_2- O).

2-((1H-indol-4-yl)oxy)-N'-(4-hydroxybenzylidene)acetohydrazide(3e):IR(KBr in cm^{-1}): 3346(NH),3111,3017,2968,2823,1641C=O),1581(N=CH),1563,1504,1481,1379,1254,1157, 1067,931,821,774 ^{1}H NMR (DMSO, δ ppm):11.27(s, 1H, CONH), 9.91(s, 1H, N=CH), 8.76-6.71(m, 10H, Ar),5.03(s, 2H, OCH_2), 3.41(b, s, 1H, OH).

2-((1H-indol-4-yl)oxy)-N'-(4-methylbenzylidene)acetohydrazide(3f):IR(KBr in cm^{-1}): 3349(NH),3122,3016,2959,2816,1637C=O),1587(N=CH),1553,1511,1477,1378,1251,1151, 1067,931,816,773,^{1}H NMR (DMSO, δ ppm):11.19(s, 1H, CONH), 9.91(s, 1H, N=CH), 8. 88-6.61(m, 10H, Ar),5.02(s, 2H, OCH_2), 2.50(s, 3H, CH_3).

2-((1H-indol-4-yl)oxy)-N'-(4-methoxybenzylidene)acetohydrazide(3g): IR (KBr in cm^{-1}): 3340(NH),3111,3026,2972,2861,1645(C=O),1580(N=CH),1377,1360,1559,1514,1481,1378, 1351,1257,1159,1057,928,811,778.^{1}H NMR (DMSO, δ ppm):11.31(s, 1H, CONH), 9.87(s, 1H, N=CH), 8.66- 6.55(m, 10H, Ar),5.03(s, 2H, OCH_2),3.77(b, s, 1H, OH).

2-((1H-indol-4-yl)oxy)-N'-(4-(dimethylamino)benzylidene)acetohydrazide(3h):IR(KBr in cm^{-1}):3348(NH),3122,3027,2977,2858,1646(C=O),1578(N=CH),1374,1361,1553,1521,1477, 1382,1346,1265,1151,1050,931,811,773 ^{1}H NMR (DMSO, δ ppm):11.20(s, 1H, CONH), 9.51(s, 1H, N=CH), 8. 86 -6.71(m, 10 H, Ar), 5.01 (s, 2H, OCH_2), 2.21 (s, 6H, -N($CH_3)_2$).

2-((1H-indol-4-yl)oxy)-N'-(3-hydroxy-4-methoxybenzylidene)acetohydrazide(3i):IR(KBr incm^{-1}):3447(NH),3121,3128,2981,2846,645(C=O),1577(N=CH),1556,1512,1482,1377,1253 ,1155,1067,924,816,771.^{1}H NMR (DMSO, δ ppm):11. 30(s, 1H, NH), 9.8 0 (s, 1H, N=CH), 8. 78 -6.65(m, 9 H, Ar),5.03(s, 2H, OCH_2), 4.51(b, s, 1H, -3-OH of phenyl), 3.55(s, 3H, 4-OCH_3 of phenyl).

2-((1H-indol-4-yl)oxy)-N'-(3,4-dimethoxybenzylidene)acetohydrazide(3j): IR (KBr in cm^{-1}):3441(NH),3122,3022,2980,2861,1648(C=O),1582(N=CH),1560,1361,1564,1521,1477, 1381,1361,1265,1160,1060,931,816,770 ^{1}H NMR (DMSO, δ ppm):11.11s,1H,NH),9.76(s, 1H, N=CH), 8.87(m, 9 H, Ar), 5.02(s, 2H, OCH_2), 3.30(s, 6H, -$(OCH_3)_2$).

ANTIMICROBIAL EVALUATION

In Vitro Evaluation of Antibacterial Activity of Compounds 3a-j

Broth microdilution method using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of synthesized compounds *3a-j* against Gram-positive (*S. aureus and B. Subtilis*) and Gram-negative (*S. typhi and E. coli*) bacteria. The antibacterial activity of the test compounds was compared with Ofloxacin. Solutions of the test compounds and reference drugs were prepared in Muller-Hinton agar. Test compounds, standard drug Ofloxacin were dissolved in dimethylsulfoxide (DMSO, 1 ml) and the solution was diluted with distilled water (9 ml) to get the concentration level of 200µg/ml. The petri dishes were inoculated with 1-5 x 10^4 colonies forming units (cfu/ml) and incubated at 37 ˚C for 18 h. And finally the zone of inhibition is measured. The results of the study are described in Table 2.

In Vitro Evaluation of Antifungal Studies of Compounds 3a-j

Antifungal activities of all the synthesized compounds were preliminarily screened for the in vitro growth inhibitory activity against *A. Niger* and *C. Albicans* by using the disc diffusion method. The fungi were cultured in potato dextrose agar medium. Potato dextrose agar medium (prepared from potato 150 g; dextrose 5 g and agar 2 g in 200 ml of distilled water) was poured in the sterilized Petri plates and allowed to solidify. The plates were inoculated with a spore suspension of *A. Niger* and *C. Albicans* (106 spores/ml of medium). The compounds to be tested were dissolved in acetone to a final concentration of 200µg/ml and soaked in filter paper discs (Whatmann no. 4, 5 mm diameter). These discs were placed on the already seeded plates and incubated at 28 ± 2 ºC for four days. To avoid the activity of the solvent that is used in the test solutions, a solvent only treated plate was maintained, which showed a 1 mm diameter zone of inhibition. Finally, after four days, the zone of inhibition was measured the results are tabulated in table 2. Fluconazole was used as standard.

RESULTS AND DISCUSSION

All the synthesized compounds were purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FTIR and 1HNMR spectral data.

In accordance with the data obtained from antimicrobial activity, all the synthesized compounds have shown good activity against the tested microbes. Among these, compounds bearing Chlorine and nitro substitution has shown good activity against all the tested bacteria and fungi.

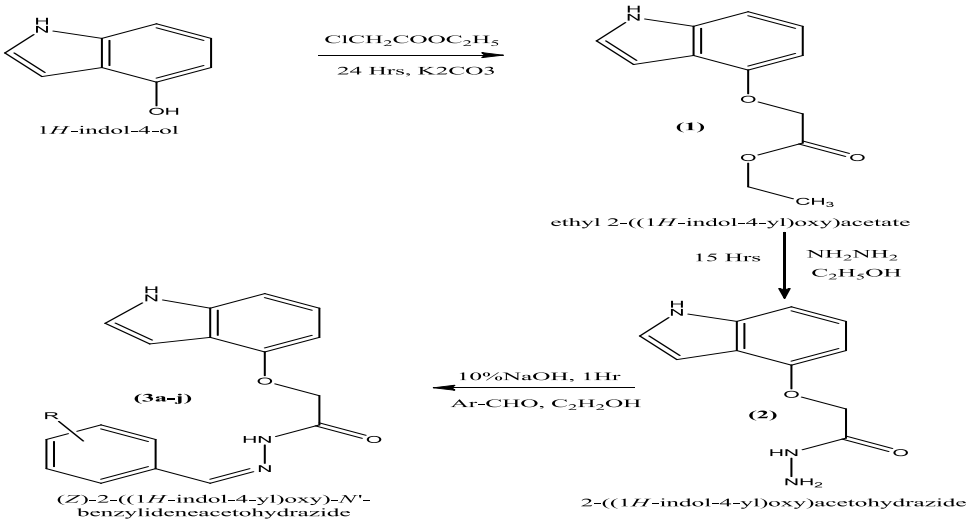
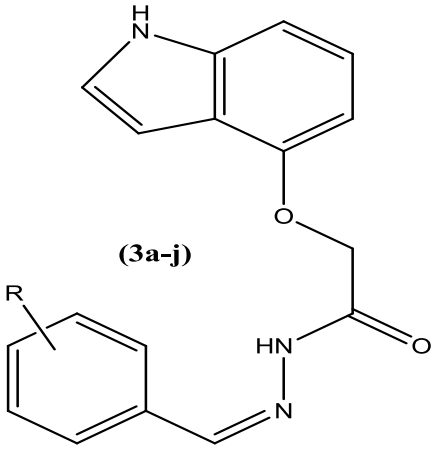


Figure 1: scheme of synthesis.

Where R: H, 4-Cl, 4-Br, 4-NO_2, 4-OH, 4-CH_3, 4-OCH_3, 4-N $(CH_3)_2$, 3-OH, 4-OCH_3, 3, 4-$(OCH_3)_2$.

Table 1: Physicochemical Characterization of 2-((1H-indol-4-yl)oxy)-N'-benzylidene acetohydrazide (3a-j).



Sl. No.	R	Physical State	Mol. Formula	% yield	M.P. (^oC)
3a	H	white crystals	$C_{17}H_{14}N_3O_2$	70	121-23
3b	4-Cl	yellow crystals	$C_{17}H_{13}N_3O_2Cl$	82	137-39
3c	4-Br	brown crystals	$C_{17}H_{13}N_3O_2Br$	67	124-26
3d	4-NO_2	cream crystals	$C_{17}H_{13}N_4O_4$	79	91-93
3e	4-OH	orange crystals	$C_{17}H_{14}N_3O_3$	71	107-09
3f	4-Me	colorless crystals	$C_{18}H_{16}N_3O_2$	84	144-46
3g	4-OMe	cream crystals	$C_{18}H_{16}N_3O_2$	81	81-83
3h	4-$N(CH_3)_2$	yellow crystals	$C_{19}H_{19}N_4O_2$	76	138-40
3i	3-OH, 4-OMe	colorless crystals	$C_{18}H_{16}N_3O_4$	82	122-25
3j	3,4-$(OMe)_2$	white crystals	$C_{19}H_{18}N_3O_4$	73	173-75

Table 2: Zone of inhibition (mm) data of synthesized compounds.

Sl. no.	Comp.	R	Zone of inhibition (mm)					
			S. aureus	***B. Subtilis***	***S. typhi***	***E. coli***	***A. Niger***	***C. Albicans***
1	**3a**	H	6.7	7.1	6.2	6.3	8.6	8.8
2	**3b**	4-Cl	10.1	10.3	9.9	9.8	9.5	9.8
3	**3c**	4-Br	8.8	8.8	8.3	8.1	10	10.3
4	**3d**	4-NO_2	11.6	11.8	10.7	10.9	15.1	15.4
5	**3e**	4-OH	10.1	9.9	9.3	9.2	12.1	12.3
6	**3f**	4-Me	8.4	8.2	8.1	8.4	10.2	10.3
7	**3g**	4-OMe	11.7	11.8	11.2	11.0	14.3	14.6
8	**3h**	4-$N(CH_3)_2$	12.7	12.8	11.4	11.2	14.4	14.1
9	**3i**	3-OH, 4-OMe	8.1	8.3	7.7	7.9	9.9	9.8
10	**3j**	3,4-$(OMe)_2$	12.4	12.2	11.6	11.8	15.2	15.5
11	**Ofloxacin**		20.5	19	19.5	20	--	--
12	**Fluconazole**		--	--	--		24.5	25

CONCLUSION

Antibacterial and antifungal activity of the synthesized derivatives was done in comparison with Ofloxacin and Fluconazole as standard to reveal the potency of synthesized derivatives. All the selected strains of bacteria and fungi namely S. Aureus, B. Subtilis, S. Typhi, E. Coli, C. Albicans and A. Niger showed sensitivity to all derivatives at concentration of 200µg/ml. Among these, compound bearing p-chloro, p-nitro, p-dimethylamino, p-methoxy and 3, 4-dimetoxy substitution has shown good activity against all the tested bacteria and fungi.

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