Synthesis and Antimicrobial Activity of 6*H*–Indolo[2,3-B]Quinoxalines N-Mannich Base Derivatives

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Abstract

A new series of fused quinoxalines as indoloquinoxalines were synthesized by condensing the appropriate isatin and o-phenylenediamine. N-mannich bases were synthesized by reacting diethoxymethane and various secondary amines with indoloquinoxalines. These reaction produced good reaction and impurity formation also very less and comparively good reagent.Allcompounds produced good antibacterial and anti inflammatory activities. Their chemical structures were confirmed by UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS data.

Keywords: Indoloquinoxalines, Antimicrobial activity, Anti-fungal activity, Schiff bases, Mannich base

Introduction

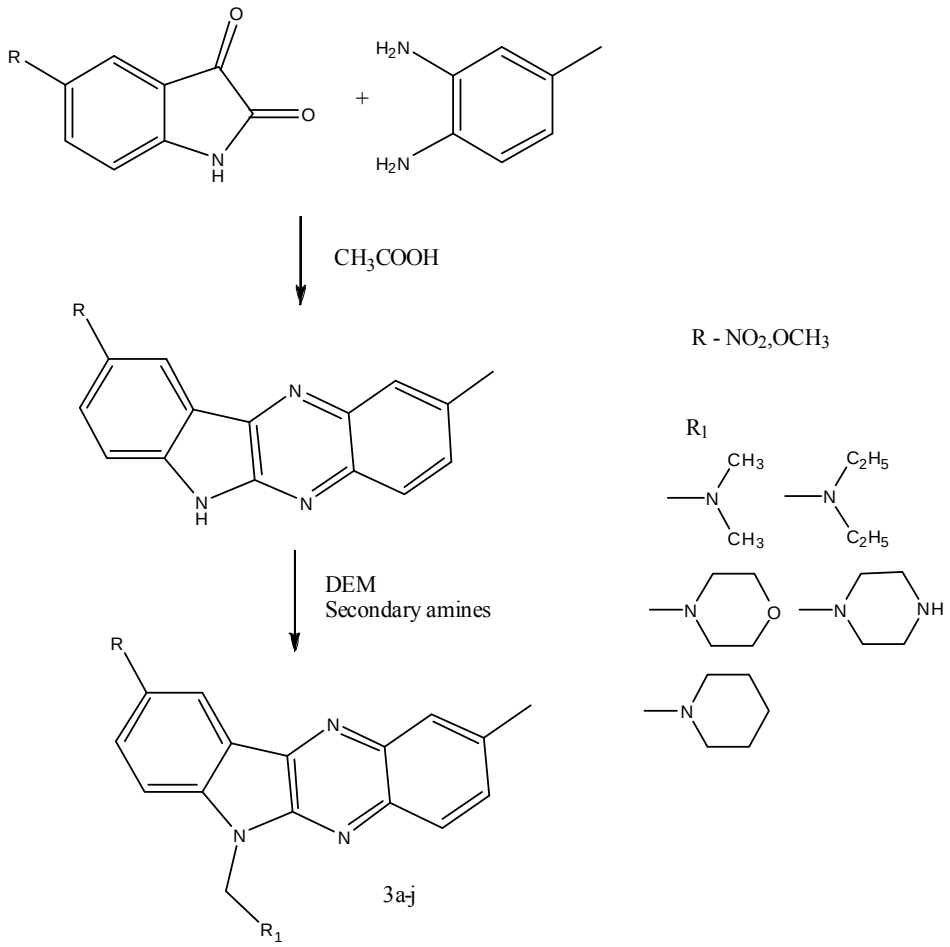
Among the various classes of nitrogen-containing heterocyclic compounds, quinoxalines display a broad spectrum of biological activity. It known to possess antibacterial, antifungal, and cyto-toxic activities. Quinoxalines play an important role as a basic skeleton for the design of a number of antibiotics such as Echinomycin, Levomycin and Actinoleucin. The quinoxaline ring is also a constituents of many pharmacologically and biologically active compounds such as insecticides, fungicides, herbicides and anthelmintics.[1]Quinoxaline derivatives[2-4] have been found application in dyes. In view of the literature regarding antimicrobial potency of quinoxaline and its mode of action that prevent DNA-directed RNA synthesis by virtue of binding to cpG site on DNA.

The amino alkylation of aromatic substrates by the Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds. It also provides a convenient access to many useful synthetic building blocks because the amino group can be easily converted into a variety of other functionalities. It has been generally known that the reaction pathways of the Mannich reaction depend on the nucleophilicity of substrate and the pH of reaction medium

Experimental

The following experimental methods were used for the characterization of the synthesized compounds. The melting points (m.p.) were determined using Gallenkamp melting point apparatus. The IR spectra were recorded in KBr discs on a Perkin Elmer 1000 FT-IR spectrophotometer (υmax in cm-1). The 1H NMR and 13C NMR spectra were collected in DMSO-d6 or ($CDCl_3$) using a JEOLECP-400[9]. The chemical shifts were reported as parts per million (d ppm) and the coupling constants (J) are given in Hz, tetra methyl silane (TMS) was used as an internal standard. The mass spectra (m/z, %) were obtained

on electron impact using an AEI MS902 mass spectrometer. The purity of all compounds was checked by TLC using glass plates coated with silica gel and dichloromethane/methanol (9:1) as a solvent system. Spectral data (IR, NMR, and mass spectra) confirmed the structures of the synthesized compounds.



SCHEME - I

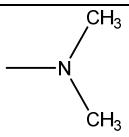
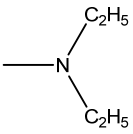
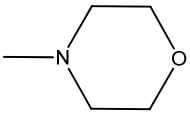
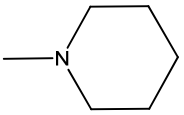
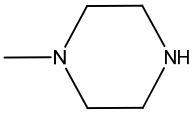
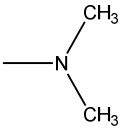
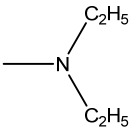
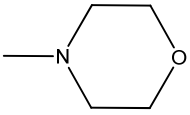
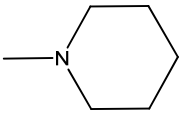
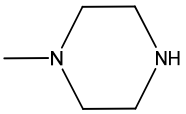
I. Synthesis of 2-methyl-9-nitro-6H-indolo[2,3-b]quinoxaline

Indolo[2,3-b]quinoxaline and its derivatives were easily prepared by condensation of isatin and the appropriate 1,2-phenylenediamine in glacial acetic acid according to Schunck's and Marchlewski's method.

II. Synthesis of imminium ions using diethoxymethane in place of formaldehyde.

Synthesis of Mannich bases: N-Mannich bases (3a-j) were prepared by condensing equimolar proportions of the appropriate substituted 7-nitro/methoxy 10H-indoloquinoxaline in 10 ml of dimethylformamide was added in to a mixture of sec-amined and diethoxy methane with continue stirring for 1.0 h at 60°C.Then the reaction mixture was cooled to room temparature,the product was filtered and washed with acetone.(**Scheme - I**). Structures of the synthesized compounds were established on the basis of physicochemical, elemental analysis are shown in Table -1.

Table-1 ;Physico chemical analysis

S.No	Compounds	M.W	R	R_1	m.p(°C)	yield
3a	$C_{18}H_{17}N_5O_2$	335.14	NO_2		237	65
3b	$C_{20}H_{21}N_5O_2$	363.17	NO_2		285	70
3c	$C_{20}H_{19}N_5O_3$	377.40	NO_2		245	55
3d	$C_{21}H_{21}N_5O_2$	375.42	NO_2		263	65
3e	$C_{20}H_{20}N_6O_2$	376.41	NO_2		255	80
3f	$C_{19}H_{20}N_4O$	320.39	OCH_3		240	75
3g	$C_{21}H_{24}N_4O$	348.44	OCH_3		215	65
3h	$C_{21}H_{22}N_4O_2$	362.42	OCH_3		238	70
3i	$C_{22}H_{24}N_4O$	360.45	OCH_3		245	55
3j	$C_{21}H_{23}N_5O$	361.44	OCH_3		235	75

Synthesis of N-Mannich Base Reaction

N,N-dimethyl-1-(2-methyl-9-nitro-6H-indolo[2,3-b]quinoxalin-6-yl)methanamine(3a)

[1] H-NMR ($CDCl_3$) δ 7.95-7.26 aromatic protons, 4.93(s,2H,C-CH_2-N), 2.26 (s, 6H, NCH_3), 2.34 (s, 3H, Ar-CH_3); [13]C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9,CH_3- 44.7,CH_3-44.7,CH_3 - 21.3; MS (m/z): 335.138[M_+].

N-ethyl-N-((2-methyl-9-nitro-6H-indolo[2,3-b]quinoxalin-6-yl)methyl)ethanamine(3b)
^{1}H-NMR (CDCl3) *δ 7.26*-7.35 aromatic protons, 4.93(s,2H,C-CH_2-N), 3.36 (s, 2H, CCH_2 N), 2.58 (q, 4H, NCH_2CH_3), 1.08 (t, 6H, CH_2CH_3); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,88.9-CH_2,44.7N-CH_2,44.7N- CH_2,21.3-CH_3, 10.3 - CH_3;
MS (m/z):363.170[M_+].

4-((2-methyl-9-nitro-6H-indolo[2,3-b]quinoxalin-6-yl)methyl)morpholine (3c)
^{1}H-NMR (DMSO) δ 7.26-7.35 aromatic protons,4.93(s,2H,C-CH_2-N), 3.67(s, 4H, CH_2OCH_2), 3.23(s, 2H, CCH_2 N),2.47(t,4H,CH_2NCH_2);^{13}C-NMR ($CDCl_3$)δ 144.8 –129.8 quinoxaline,135.5-111.6-indole,CH_2-88.9,75.2(NCH_2N),66.4(CH_2OCH_2), 53.3(CCH_2N), 53.2(CH_2NCH_2),21.3-CH_3; MS (m/z): 377.149[M_+].

2-methyl-9-nitro-6-(piperidin-1-ylmethyl)-6H-indolo[2,3-b]quinoxaline (3d)
^{1}H-NMR (DMSO-d6) *δ* 7.2-7.8 aromatic protons, 4.03(s,2H,C-CH_2-N), 8.48(s,1H,N=CH-C), 3.24 (s, 2H, CC*H*$_2$ N),2,46 (t, 4H, CH_2NCH_2), 1.62-1.44 (m, 6H, $CH_2CH_2CH_2CH_2CH_2$);
^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9, 75.2(NCH_2N),, 53.8 (CH_2NCH_2), 53.2 (CCH_2 N), 25.6 ($CH_2CH_2CH_2$) 25.3 ($CH_2CH_2CH_2$); ,-CH_3 - 21.3 ; MS (m/z): 375.37 [M_+].

2-methyl-9-nitro-6-(piperazin-1-ylmethyl)-6H-indolo[2,3-b]quinoxaline (3e)
^{1}H-NMR (DMSO-d6) *δ* 7.2-7.8 aromatic protons, 4.02 (s, 2H, CC*H*$_2$ N), 3.67 (t, 2H, CH_2CH_2NH), 3.55 (t, 2H, CH_2CH_2NH), 2.93 (s, 1H, NH), 2.96 (t, 2H, $NHCH_2CH_2$), 2.76 (t, 2H, $NHCH_2CH_2$); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9, 54.3 (CCH_2N), 52.4 ($CH_2NC\ H_2$), 51.3 ($CH_2NHC\ H_2$); MS (m/z): 376.16[M_+].

1-(9-methoxy-2-methyl-6H-indolo[2,3-b]quinoxalin-6-yl)-N,N-dimethylmethanamine(3f)
^{1}H-NMR (CDCl3) *δ* 4.00(s,1H,C-NH-C),7.2-7.8 aromatic protons, 4.03(s,2H,C-CH_2-N), 8.48(s,1H,N=CH-C), 3.01 (s, 2H, CCH_2 N),2.08 (s, 6H, NCH_3); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9,55.3-OCH_3,CH_3- 44.7,CH_3- 44.7,CH_3 - 21.3; MS (m/z): 320.164[M_+].

N-ethyl-N-((9-methoxy-2-methyl-6H-indolo[2,3-b]quinoxalin-6-yl)methyl)ethanamine (3g)
^{1}H-NMR (CDCl3) *δ* 4.00(s,1H,C-NH-C),7.2-7.8 aromatic protons, 4.03(s,2H,C-CH_2-N), 8.48(s,1H,N=CH-C), 3.36 (s, 2H, CCH_2 N), 2.58 (q, 4H,J =3.2 Hz, NCH_2CH_3), 1.08 (t, 6H, J =3.2 Hz, CH_2CH_3); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9,55.3- OCH_3,N-CH_2- 44.7,N- CH_2- 44.7,-CH_3 - 21.3, 10.3 - CH_3;MS (m/z):348.195[M_+].

4-((9-methoxy-2-methyl-6H-indolo[2,3-b]quinoxalin-6-yl)methyl)morpholine(3h)
^{1}H-NMR (DMSO) δ 4.00(s,1H,C-NH-C),7.2-7.8 aromatic protons, 4.03(s,2H,C-CH_2-N), 8.48(s,1H,N=CH-C), 3.67 (t, 4H, CH_2OCH_2), 3.23 (s, 2H, CCH_2 N), 2.47 (t, 4H, CH_2NCH_2); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9, 75.2(NCH_2N), 55.3 - OCH_3,53.8-(CH_2NCH_2), 53.2 (CCH_2 N), 25.6 ($CH_2CH_2CH_2$) 25.3 ($CH_2CH_2CH_2$); ,-CH_3 - 21.3; MS (m/z): 362.174[M_+].

9-methoxy-2-methyl-6-(piperidin-1-ylmethyl)-6H-indolo[2,3-b]quinoxaline (3i)

^{1}H-NMR (DMSO-d6) δ 7.2-7.8 aromatic protons, 4.03(s,2H,C-CH_2-N), 3.24 (s, 2H, CCH_2 N),2.46 (t, 4H, CH_2NCH_2), 1.62-1.44 (m, 6H, $CH_2CH_2CH_2CH_2CH_2$); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9, 75.2(NCH_2N),55.3 - OCH_3, 53.8 (CH_2NCH_2), 53.2 (CCH_2 N), 25.6 ($CH_2CH_2CH_2$) 25.3 ($CH_2CH_2CH_2$); ,-CH_3 - 21.3;MS (m/z): 360.195[M_+].

9-methoxy-2-methyl-6-(piperazin-1-ylmethyl)-6H-indolo[2,3-b]quinoxaline (3j)

^{1}H-NMR (DMSO-d6) δ 7.2-7.8 aromatic protons, 4.03(s,2H,C-CH_2-N), 8.48(s,1H,N=CH-C), 4.02 (s, 2H, CC*H*$_2$ N), 3.67 (t, 2H, CH_2CH_2NH), 3.55 (t, 2H, CH_2CH_2NH), 2.93 (s, 1H, NH), 2.96 (t, 2H, $NHCH_2CH_2$), 2.76 (t, 2H, $NHCH_2CH_2$); ^{13}C-NMR ($CDCl_3$) δ 144.8 –129.8 quinoxaline,135.5-111.6 indole,CH_2- 88.9, 55.3 – OCH_3,54.3 (CCH_2N), 52.4 (CH_2NC H_2), 51.3 (CH_2NHC H_2);MS (m/z): 361.190[M_+].

Results and Discussion

In the present investigation, we have synthesized a derivative of novel Series of Indolo[2,3-b]quinoxalinewere easily prepared by condensation of isatin and the appropriate 1,2-phenylenediamine. 2-methyl-9-nitro-6HIndolo[2,3-b]quinoxaline converted by the addition of diethoxy methane and dimethyl amine converted into N,N-dimethyl-1-(2-methyl-9-nitro-6H-indolo[2,3-b]quinoxalin-6-yl)methanamine.as shown in [Scheme- I]. The compounds are evaluated in vivo for their anti-inflammatory activity, and anti microbial activity

Evaluation of *In- Vitro* Anti Microbial activity

Bacteria are the most abundant prokaryotic organism that is vital to life of living things. Bacteria are ubiquitous, place a major positive role to the life of living things but some of them cause harmful diseases to the living things (humans. animals, plants, etc.). In nature bacteria can adopt any kind of living conditions than any other groups of organisms. Fungi are eukaryotic organism that is subdivided in to yeasts and moulds. [10] Yeasts are unicellular eukaryotic organisms which have size of large bacteria. The yeast mainly used in the fermentation of wine and beer, and in production of bread. Moulds are long chain cells often seen as fuzzy masses on bread and other acidic food products. Bacteria and fungi are the primary decomposers of organic matters in the world. As like bacteria some of the fungi cause harmful human diseases such as athlete's foot and thrush.

Preparation of Test Inoculums

(a) Subculture (preparation of seeded broth)

The strains of fungi were inoculated into test tubes containing 10 mL of Sabouraud dextrose broth; bacteria were inoculated into test tubes containing 10 mL of nutrient broth. One loopful of bacteria and fungi were transferred aseptically to each of the test tubes. The test tubes were incubated at 37°C for bacteria and 25°C for fungi for 24 hr. This is referred to as seeded broth. [11]

(b) Standardization of seeded broth (viable count)

1 mL of the 24 hr seeded broth of each strain was diluted with 99 mL of sterile normal saline containing 0.05% TWEEN 80 (8 drops of TWEEN 80 in 1000 mL of normal saline). From that 1 mL was further diluted to 10 mL with sterile normal saline. This was continued till 102, 104, 105 up to 1010

dilution of the seeded broth was obtained.

The dilutions were studied by inoculating 0.2 mL of each dilution on to the nutrient agar at 30 - 40°C. After inoculation it was transferred into Petri dish before it gets solidified. All the Petri dishes were incubated for 24 h at 37°C for bacteria and 25°C for fungi.[12] The number of well-formed colonies on the plates was counted. The seeded broth was then suitably diluted to contain between 107–108 microorganisms/mL. This was designated as working stock, which was used for antimicrobial studies.

Zone of Inhibition of the synthesized compounds

Inoculate the previously prepared working stock appropriate to the assay with requisite quantity of suspension of the micro-organism, to the medium at a temperature between 40oC and 50°C and immediately pour the inoculated medium into petridishes to give a depth of 3 to 4 mm.The dishes were specially selected with bottoms and were placed on a level surface so as to ensure that there was a uniform thickness. The Petri dishes were allowed to be sterilized at 160 – 170°C for 1 hr, before use as shown in Table 2.

Table No. 2.Zone of inhibition of the synthesized compounds

Compounds	Zone of inhibition (in mm)											
	S.aureus		S.epidermis		B .cerus		K .pneumonia		P .aeroginosa		E .coli	
	100	200	100	200	100	200	100	200	100	200	100	200
3a	25	29	25	28	24	31	20	25	22	29	22	25
3b	20	20	28	25	20	28	18	21	20	23	18	20
3c	21	19	25	22	19	25	17	20	21	24	19	21
3d	20	20	26	24	20	26	18	23	20	26	20	24
3e	28	23	31	31	23	31	19	24	28	33	23	29
3f	24	23	29	32	23	29	19	23	24	32	24	26
3g	24	24	18	24	24	18	18	23	24	26	26	27
3h	25	22	19	20	22	19	18	23	25	24	31	25
3i	21	24	18	19	24	18	19	24	21	24	29	24
3j	22	25	19	20	25	19	17	22	22	20	18	22
Ciprofloxacin 100µg/ml	36		39		39		36		35		37	

The paper disc (Whatman No.2) was cutdown into small disc (6mm diameter) and sterilized at 180°C for 30 mts in hot air oven impregnated with the test and standard drug separately. The dried discs were placed on the surface of the medium. [13] After all the drugs are added Petri dishes were left standing for 1 to 4 hr at room temperature, as a period of pre-incubation diffusion to minimize the effects of variation in time between the application of different solutions. All the Petri dishes were incubated for 24 hr at the required temperatures, i.e., 37°C for bacteria and 25°C for fungi. After incubation the diameters of the circular inhibition zones were measured and from these values minimum inhibitory Concentration and biological activities were calculated.

Determination of MIC

Agar Streak Dilution Method

MIC of the synthesized compound was determined by agar streak dilution method. A stock solution of the synthesized compound (100 µg mL-1) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for anti-bacterial activity and sabouraud dextrose agar medium for anti-fungal activity). A specified quantity of the medium (40-50°C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. [14] Suspension of the microorganism were prepared to contain approximately 105 cfu mL-1 and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37°C for 24 h and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate as shown in Table 3

Antiinflammatory Activity

The activity was performed by following the procedure of Winter et al on groups of six animals each.Edema was induced in the rats by injecting carrageenan (0.05 ml,1% w/v in 0.9%saline) into the subplantar tissue of the right hind paw.One group was kept as control and treated with propylene glycol. The animals of standard drug treated groups were pretreated with standard drug and test copounds given orally 1 h before the carrageenan injection,respectively.The paw volume (ml) was measured before carrageenan injection and 0,1,2 and 3 h thereafter,usingplethysmometer.The percentage antiinflammatory activity was calculated according to formula given below.

% Antiinflammatory activity = (1-Vt/Vc) x 100(where Vt and Vc are the volumes of edema in drug treated and the control groups,respectively).The results are tabulated in Table – 3

Table No.3 Minimum Inhibitory Concentration of Synthesized Compound

Compound	mg kg $^{-1}$p.o.	% inhibition of edema	Compound	mg kg $^{-1}$p.o.	% inhibition of edema
3a	25	15.5	3f	25	14.9
	50	31.1		50	30.2
3b	25	12.1	3g	25	15.6
	50	24.8		50	32.1
3c	25	13.2	3h	25	13.2
	50	26.8		50	26.8
3d	25	12.5	3i	25	14.2
	50	24.8		50	28.8
3e	25	12.8	3j	25	14.8
	50	25.6		50	30.8

Conclusion

In the present study attempt was made to synthesize the derivatives of 6*H*–Indolo[2,3-b]quinoxalinesfrom Schiff base as intermediate. The compounds are 3a–3j . All the compounds were characterized and confirmed by IR, ^{1}H NMR, and Mass spectra. Antibacterial activity of synthesized compounds was tested against both gram positive and gram negative bacteria and the standard drug used

for the study was ciprofloxacin. The compounds with nitro substitution showed better activity. piperdine, piperzino, morpholino substitutions at NR position produced good antibacterial activity The antiinflammatory activity of the synthesized compounds with piperzine, diethylamino, dimethylamino, morpholino substitutions at NR position produced good inflammatory activity where as other copounds were moderately active at the dose level of 50 mg/kg.

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