International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.9, No.07 pp 516-522, 2016

Synthesis and Spectroscopic Studies on the new Schiff Base Derived from the 1:1 condensation ofIsatinwith Amines and itsEvaluating biological activity

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Abstract : A series of Schiff base derivatives have been synthesized by condensed of isatin and amines(amino pyridine,5-methyl amino pyridine,4-methyl amino quinolin ,aminobenzotiazol,4-aminoantipyrine, fluoren-9(9aH)-ylidene)hydrazine) in ethanol in the presence of acetic acid as catalyst to yield the Schiff base derivatives (I-V) , The structure of synthesized compounds has been established on the basis of their spectral (FT-IR ,Mass ,^{1}H,^{13}C-NMR,elemental analysis)data.The purity of the compounds was confirmed by TLC. All these compounds were evaluated for their In vitro activity against several microbes (*Staphylococcus aureus, Escherichia coli, Bacillus subtilis*and*Klebsiella pneumonia*).
Keywords: Schiff bases, isatin, amines, Spectral study, antibacterial activities.

Introduction

Isatin (indole-2, 3-dione) is an endogenous compound, widely distributed in mammalian tissues and body fluids[1]. In the brain the highest levels have been found in the hippocampus[2], and an immune cytochemical staining revealed its specific localization within particular cells. *In vivo* isatin administration causes a range of dose-dependent behavioral effects[3], including angiogenesis and increased water retention. In vitro, isatin is a potent inhibitor of both atrial natriureticpeptide (ANP)-stimulated, membrane-bound guanylatecyclase and nitric oxide-stimulated soluble guanylate cyclase[4]. It is an inhibitor of monoamine oxidase B (IC_{50}3-8 LM) and of atrial natriuretic peptide receptor binding (0.4 LM) at levels that may be in the physiological range[5].Isatin is well known as a pharmacological agent having a range of action in the brain and it is protective against certain types of infections. Isatin derivatives are reported to show other biological activities, such as, anti-bacterial[6, 7], anti-fungal[8, 9], anti-HIV[10,11,12], muscle relaxant[13], anti-allergic[14], and anti-inflammatory[15] activities. Schiff bases are used as substrates in the preparation of a number of biologically active compounds. Moreover, Schiff bases derived from variousHeterocycles have been reported to possess anti-fungal[16], anti-cancer[17], cytotoxic[18], and anti-convulsant activities[19]. The chemistry of isatin and its derivatives is particularly interesting because of their potential application in medicinal chemistry. Schiff bases of isatin derivatives have been reported to demonstrate a variety of biological activities, such as, anti-inflammatory[20], anti-convulsant[21], anti-HIV[22], anti-bacterial[23], anti-fungal[24], and anti-depressantactivities[25]. These observations have led to the conception that a series of some different novel Schiff bases of isatin were synthesized using different amines and their chemical structures were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy, and Elemental analysis. These compounds were screened for their analgesic properties. The results of such studies are discussed in this article.

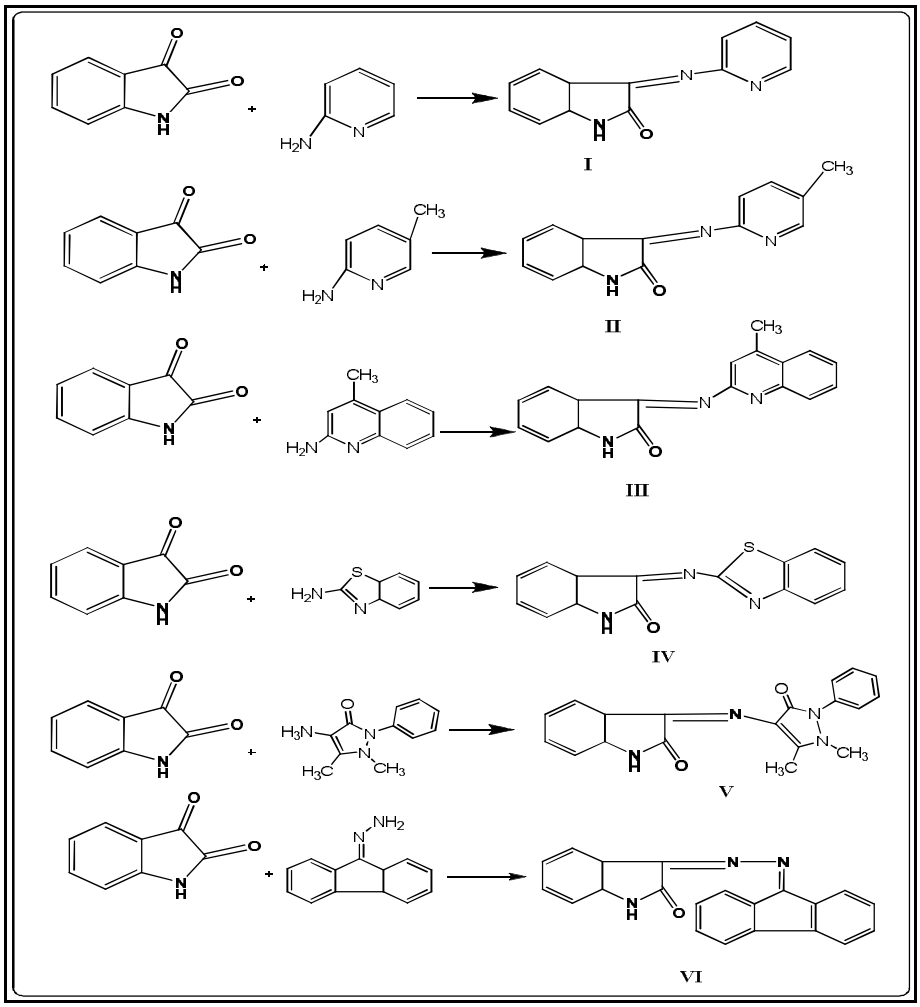
Experimental

Reagents and Apparatus

All the chemicals used were of AnalaR grade and procured from Sigma-Aldrich and Fluka.Metal salts were purchased from E. Merck and were used as received. Distilled water was used in extraction experimental. The solvents were saturated with each other before use in order to prevent volume changes of the phases during extraction. All compounds were routinely checked by TLC on silica gel G plates using Mixture of petroleum ether/ethyl acetate (7:3; 6:4; 5:5 by V/V) used as mobile phase and the developed plates were visualized by UV light, iodine vapour and KMnO4 solution. The C, H, and N were analyzed on a Carlo-Erba 1106 elemental analyzer. The IR spectra were recorded on Jusco 300 instrument in KBr pellets. ^{1}H,$^{13}C$and the 2DNMR Spectra were recorded on a Bruker (Avance) 300MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent Standard Bruker software was used throughout.Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz. . LC-Mass spectrawere recorded on a BrukerDaltonics LC-MS Spectrometer,

Methods of preparation:

Synthesis of Schiff bases of Isatin**:**Equimolar quantity of isatin (0.005mol) and substituted aromatic amine (0.005mol) were added into 30ml of absolute ethanol containing 2-3 drops of glacial acetic acid in 100ml round bottomed flask. The reaction mixture was refluxed for 3-4 hour at the refluxing temperature. The solvent was then distilled off and the product obtained was recrystallized from chloroform to give theSchiff base derivatives Scheme (1)[26,27].



Scheme1

The physical properties,elemental analysis data and spectral data shown in Tables (**I,II,III,IV**).

Table (I) Physical properties of compounds (I-VI) .

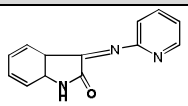
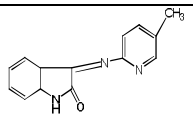
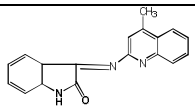
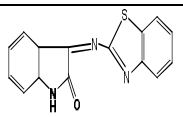
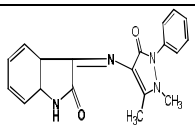
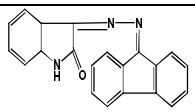
Comp. No.	structure	M.P (^{0}C)	Yield (%)	Molecular Weight	*Molecular formula*	colour	U.V($CHCl_3$) λ max (nm)
I		**228**	80	255	$C_{13}H_{11}N_3O$	White	298
II		**172**	60	239	$C_{14}H_{13}N_3O$	White	298
III		**199**	75	289	$C_{18}H_{15}N_3O$	White	304
IV		**248**	63	281	$C_{15}H_{11}N_3OS$	White	314
V		**212**	70	334	$C_{19}H_{18}N_4O_2$	White	288
VI		**266**	80	325	$C_{21}H_{15}N_3O$	Red	316

Table (II) FT-IR Spectral data for compounds (I-V)

Comp. No.	υ (C–H) cm^{-1}	υ(C=C) cm^{-1}	C=O υ cm^{-1}	*C=N* cm^{-1}	*Others*
I	3189.4	1579.56	1735.25	1635	
II	3178.23	1610	1720.65	1625	
III	3174.91	1620	1715.63	1638	
IV	3168.25	1595.23	1724	1640	
V	3145	1592	1723.04	1625.13	1720.60cm^{-1}(C=O),
VI	3060.5	1546.9 –1496.78	1722	1642	1635.23 (C=N)

Table (III)Elemental Analysis (C.H.N) of synthesis Compounds

compounds	Calc.			Found		
	H%	N%	C%	H%	N%	C%
I	4.92	18.66	69.30	4.90	18.62	69.66
II	5.48	17.56	70.28	5.40	17.50	70.44
III	5.23	14.52	74.72	5.20	14.62	74.80
IV	3.94	14.94	64.04	3.80	14.90	64.44
V	5.43	16.76	68.25	5.42	16.78	68.33
VI	4.65	12.91	77.52	4.60	12.95	77.60

Table (IV) ^{1}H-NMR and ^{13}C-NMR spectral data for some of the prepared compounds.

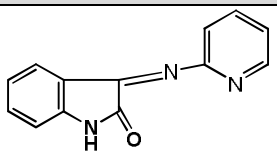
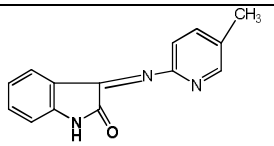
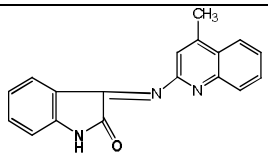
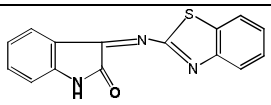
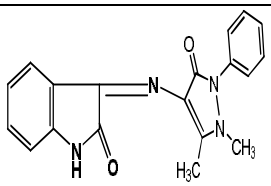
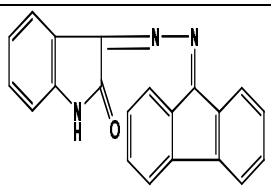
Compd. No.	Compd. Structure	^{1}H-NMR spectra data	^{13}C-NMR spectra data
I		^{1}H-NMR: 7,7.66,7.40,8.52(4H,Ar-pyridine),7.26,7.50,7.81,7.86 (4H,Ar-benzen),8.01(NH)	^{13}C-NMR 116.1,137.3,119.5,145.0,160.6(5C, Ar-pyridin) ,150.1(C=O),117.7,141.2,119.4,131.2,124.4,129.4(6C,Ar-benzene),163.5(C=N)
II		^{1}H-NMR:2.31(s,3H,$\underline{CH_3}$-Ar),6.91,7.57,8.33 (,3H,Ar-pyridin) ,7.26,7.50,7.81,7.86 (4H,Ar-Benzene) ,8.01(NH)	^{13}C-NMR:18(CH_3-Ar) ,151.1,158.3,115.3,136.4,132.1 (5C,Ar-pyridin) 117.7 ,141.2 ,119.4,131.2, 124.4, 129.4 (6C,Ar-Benzene),150.3 (C,2C=O),163.5(C=N),18(C,CH_3),
III		^{1}H-NMR: 2.61(s,3H,CH_3),7.24,8.16,7.59,7.75,7.95(m,4H,Apyridinr),7.81,7.26 , 7.50,7.86 (m,4H ,Ar-Benzene) ,8(H,NH)	^{13}C-NMR:19.6($\underline{CH_3}$-Ar) 114.8,145.5,175.3,126.8,147.8,124.2,126.5,129.29,129.2(9C,Ar) 117.7,141.2,129.4,124.4,131.2,119.4,141.2(6C,Ar-Benzene) 150.1 (C,2C=O), 163.5(C=N)
IV		^{1}H-NMR: 8.01,7.53,7.53,8.18(4H,Ar),7.26,7.50,7.86,7.81(4H,Ar),8(1H,NH)	^{13}C-NMR: 121.8,124.5,125.3,121.6,148.7,125.8(6C,Ar),174.6(C-N),163.5(C=N),150.1(C=O),117.7,141.2,119.4,131.2,124.4,129.4(6C,Ar)
V		^{1}H-NMR:6.90,7.35,7.37(5H,Ar),3.11 (3H,CH3),2.44(3H,CH3),8(H,NH),7.81,7.26,7.56,7.86(4H,Ar)	^{13}C-NMR:34.9(1C,$\underline{CH_3}$-N) ,13(1C,CH_3),150.1($\underline{C}$-C=O) ,150.2(CH_3-$\underline{C}$-N) ,139.8(C=O), ,129.2,122.8.8,129.2,123.9,160.7 (6C,Ar), 117.7,141.2,119.4,131.2,124.4,129.4(6C,Ar-isatine)
VI		^{1}H-NMR: 8.03,7.58,7.68,7.95,7.54,7.64,7.90,8.47(8H,Ar-fluorene),7.26,7.50,7.86,7.81(4H, Ar-isatine),8(H,NH)	^{13}C-NMR :129.7,127.7,131.5,121.2,143,130.1,143,121.2,131.5,127.7,129.7(12 C,Ar) ,164.6 (C,$\underline{C}$=N),169(C,C=O)138(C=N),117.7,141.2,119.4,131.2,124.4,129.4(6C,Ar-isatine)

Table (V) Antimicrobial activity of N substituted isatine

Compound	Zone of inhibition (mm)			
	Gram positive bacteria		Gram negative bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumonia*
I	**9.5±0.13**	**7±0.11**	**6.5±0.37**	**6.5±0.26**
II	**10±0.25**	**9±0.22**	**7±0.33**	**6±0.14**
III	**12±0.36**	**13±0.11**	**6±0.11**	**6±0.36**
IV	**13±0.33**	**14±0.23**	**5.9±0.23**	**8±0.12**
V	**11±0.23**	**15±0.11**	**7±0.45**	**6±0.26**
VI	**10±12**	**10±0.13**	**8±0.12**	**7±0.13**
Ciprofloxacin*	**14±11**	**9±0.12**	**9±0.23**	**7.5±0.36**

Data aremean ± SDofthreeindependentexperiments. * Positive control

Result and Discussion

The product (I-IV) was formed from the reaction of one molecule of isatine and mole of amine. The infrared of products exhibited characteristic peak at 1723.25 cm^{-1} due to ν (C=O) group and no absorption band due to NH_2 group. Compound (V) show absorption at (1720.60) cm^{-1}due to (C=O). Compound (VI) show absorption at (1635.23)cm^{-1}due to (C=N) The UV spectra showed λmax at 298-316.

^{1}H-NMR for compounds (I-VI)shows multiplesignals at (7.26-7.86 ppm) due to aromatic proton of isatine. ^{1}H-NMR for compounds (II,III)show single signal at (2.31,2.61ppm) due to(CH_3)group,also ^{1}H-NMR for compounds (V) show single signal at (2.44,3.11ppm) due to(CH_3)group and ^{1}H-NMR for compound (VI) show signals at (7.03-7.47 ppm) due to aromatic proton of a fluorenering

^{13}C-NMR of compounds (I-VI) showed signals at (117.7-131.3ppm) due to aromatic carbons ofisatine and signal at (150.3ppm) due to Imidic C=O**.** ^{13}C-NMR spectrum of compound (I) showed signal at (116.1,137.3,119.5,145.0,160.6ppm) due to aromatic carbons of pyridine, ^{13}C-NMR spectrum of compound (II) showed single signal at (18 ppm) due to CH_3 group ,and signal at (151.1,158.3,115.3,136.4,132.1ppm) due to aromatic Carbone of pyridine ^{13}C-NMR spectrum of compound (III) showed single signal at (19.6ppm) due to ($\underline{CH_3}$-Ar), and signal at (114.8,145.5,175.3,126.8,147.8,124.2,126.5,129.29,129.2) ppm due to aromatic carbons of aromatic ring of (quinoline). ^{13}C-NMR spectrum of compound (IV) showed signals at(121.8,124.5,125.3,121.6,148.7,125.8 ppm) due to aromatic carbons of benzothiazole.^{13}C-NMR spectrum of compound (V) showed single signals at(34.9,13ppm) due to CH_3 group and signal at (139.8ppm) due to (C=O) and signals at (129.2,122.8.8,129.2,123.9,160.7 ppm) due to aromatic carbons ofdimethyl-2-phenyl-pyrazol-3-one, ^{13}C-NMR spectrum of compound (VI) showed signal at(129.7,127.7,131.5,121.2, 143,130.1,143, 121.2,131.5,127.7,129.7ppm) due to aromatic carbons of fluorene[28,29,30].

Antimicrobial Activity

The antimicrobial activity of both categories of compounds was determined by the disc diffusion method[31]. The in vitro antimicrobial activity was carried out in two gram positive bacteria, and two gram negative bacteria. The gram positive bacteria used were *Staphylococcus aureus* and *Bacillus subtilis*, gram negative bacteria used were *Escherichia coli* and *Klebsiella pneumonia*.

The compounds were tested at a concentration of 100µg/mL in Dimethylsulfoxide. The zoneof inhibition was compared after 24 hrs of incubation at 37°C against Ciprofloxacin (100µg/mL) as standards for comparison of antibacterial activity **(**Table V) In general, all synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism *S. aureus, B. subtilis, E. coli*and *K. pneumonia*, peculiar against (*S. aureus*and*B. subtilis*)Figure 1.

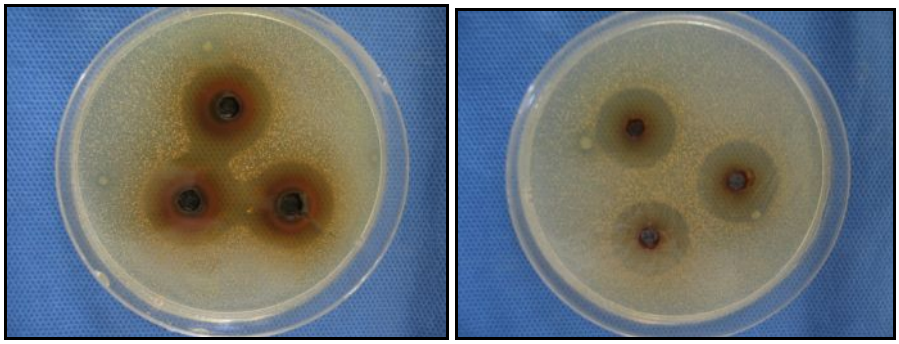


Figure 1: Photograph showing antibacterial studies of the schiff bases against *S. aureus*

Conclusions

The main aim of the present study is to synthesize and investigate the antimicrobial and anti corrosion activity of new heterocyclic derivatives containing phthalimide ring with the hope of discovering new structures serving as potential broad spectrum antimicrobial agents and anti-corrosion agents. Compounds (**I-VI**) which contain functional moiety is most potent against bacterial it's showed good antimicrobial activity.

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