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Synthesis and Biological Activity of Sulphadiazine Schiff's Bases of Isatin and their N-Mannich Bases

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Sulphadiazinyl Schiff bases of isatin (and derivatives) and their Mannich bases were synthesized. Their chemical structures have been confirmed by IR, ^{1}H NMR and by elemental analysis. Antimicrobial evaluation were done against pathogenic bacteria and fungi. Nearly all the synthesized compounds exhibited antimicrobial activity against gram positive and gram negative bacteria at 500 µg concentration.

Key Words: Antibacterial activity, Sulphadiazine Schiff bases.

INTRODUCTION

Isatin is an endogenous compound with a long history and a broad range of pharmaceutical actions. It has long range of actions in CNS-MAO inhibition, anticonvulsant and anxiogenic. It effects as a MAO inhibitor is the potent *in vitro* action[1-4]. Isatin selectivity damages *Echinococcus multilacularis* and it may have role in chemotherapy of infections caused by parasites[5]. Some Mannich bases of isatin appear to act as antifungal, antibacterial and antiviral agents[6]. Some Mannich bases of isatin appear to act as antifungal, antibacterial and antiviral agents[6]. A series of 5-halo groups were introduced in position-3. Synthesized N-Mannich bases and hydrazones (Schiff bases) were tested against various bacteria and fungi. Halogen in position-6 and amino moiety in position-1 showed better activity than unsubstituted isatin[7]. Pandeya and coworkers[8] synthesized Schiff bases of isatin with trimethoprim and their N-Mannich bases. All the synthesized compounds showed good activity against *V. cholerae, S. Boydii, E. faecelis* and *E. tards* with MIC in the range of 10-25 µg/mL.

Investigation of antimicrobial activity (against 27 pathogenic bacteria) and anti HIV activity of 3-(4-pyridyl)-4-amino-5-mercapto-4(H)-1,2,4-triazole Schiff base of N-Mannich base of isatin were done. 5-Chloro and 5-bromo isatin derivatives were reported by Pandeya *et al.*[9]. Among the synthesized compounds 1-(piperdinomethyl)-5-bromo-3-(3′-(4″-pyridyl)-5-mercapto-4(H)-1′,2′,4′-triazolyl]imino isatin showed the most favourable antimicrobial activity. None of the compounds showed the most appre-

ciable anti HIV activity. Keeping this in mind some new Schiff bases of isatin and their Mannich bases were synthesized and were tested against many microbes *viz.*, *V. cholerae, E. coli, Pseudomonas, S. typhi, Klebsiella, S. paratyhphoid, C. albicans, S. Faecelis, etc*.

EXPERIMENTAL

Isatin has been procured by IDPL, India. 5-Chloroisatin was synthesized by cyclization of *p*-chloro isonitrosoacetanilide (m.p. 247-249ºC).

Synthesis of 3-(4-sulphadiazinyl)isatin: Equimolar quantities (0.02 mol) of isatin (2.94 g) and sulphadiazine (5 g) was dissolved in warm alcohol and refluxed on a steam bath for 1 h. After standing for *ca.* 24 h at room temperature, the product was collected by suction filteration. Yield 7 g (93.3 %) and m.p. 240ºC (**compound I**).

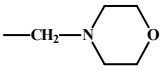
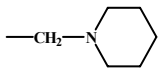
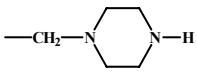
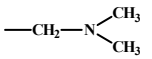
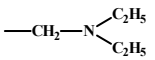
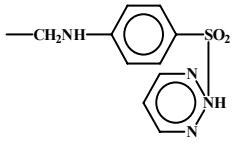
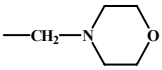
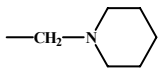
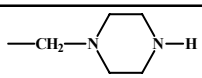
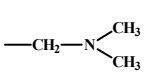
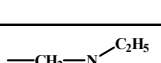
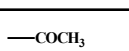
Elemental analysis for $C_{18}H_{13}N_5O_3S$; Found: C: 56.60, H: 3.03, N: 12.17; Calcd. C: 56.69, H: 3.43, N: 18.47. IR (KBr, cm^{-1}): 3500-3300-NH symmetric stretching, 1650 cm^{-1} -C=O stretching (amide), 1670-1400 cm^{-1} - ring skeletal vibration, 1320-1260 -SO_2 symmetric stretching, 1150 -C-N stretching (amides), 900-690 -Aromatic C-H stretch, out-of-plane. H NMR (DMSO-d_6 ppm (δ)]: 8.5 -doublet (2 protons), 7.6 -doublet (2 protons), 7.0 -triplet (1 proton), 6.7 -doublet (2 protons). Simiarly, 3-(4-sulphadiazinyl)-5-chloroisatin was prepared using appropriate moles of 5-chloroisatin and sulphadiazine. Characterization data are given in Table-1.

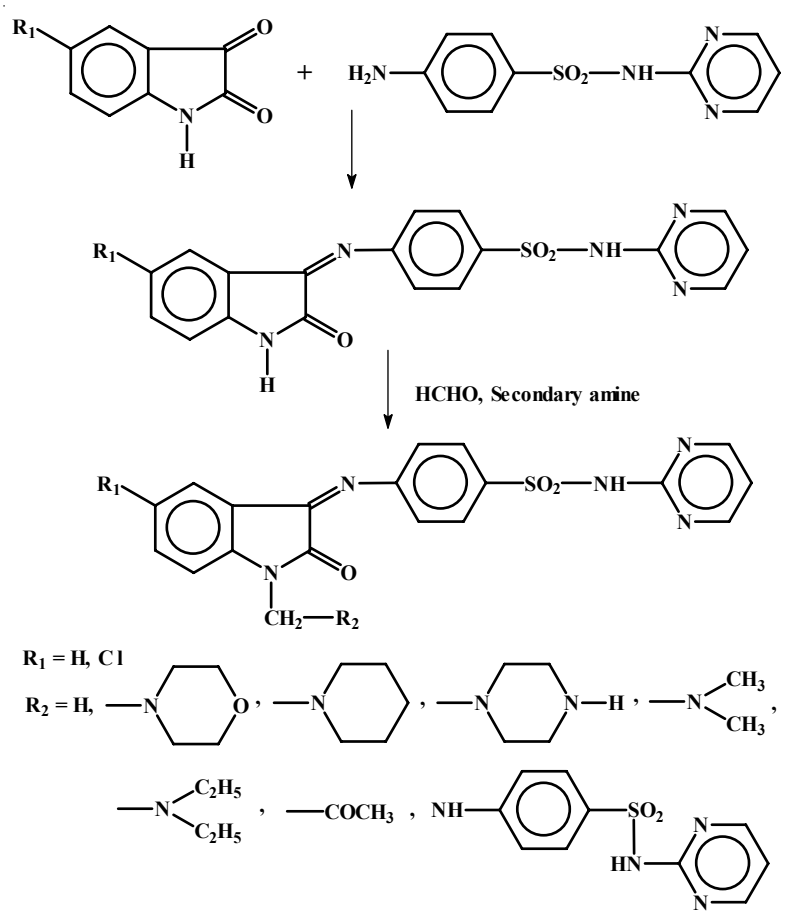
Synthesis of N-Mannich bases: N-Mannich bases were prepared by condensing equimolar proportions of the appropriate sulphadiazinyl isatin derivatives with secondary amine and formaldehyde (**Scheme-I**).

Synthesis of N-(dimethylaminomethyl)-3-(4-sulphadiazinyl)isatin (Compound V): Dimethylamine (0.004 mol, 0.2 mL) was added dropwise with cooling shaking to the slurry consisting 3-(4-sulphadiazinyl isatin) (0.004 mol, 1.516 g), ethanol (5 mL) and 37 % formalin (0.36 mL). The reaction mixture was allowed to stand at room temperature for 1 h with occasional shaking after which it was warmed on steam bath for 15 min. At the end of this period, the contents were cooled and products thus separated was filtered and recrystallized from ethanol. Yield: 1.6 g (91.7 %), m.p. 230ºC.

Elemental analysis for $C_{21}H_{21}N_6O_3S$; Found: C: 57.36, H: 4.8, N: 19.01; Calcd. C: 57.67, H: 4.81, N: 19.22. Ultraviolet spectrum: λ_{max} (nm): 268, 250, 244. IR spectrum showed absorption bands (cm^{-1}) at 3410-3390 (NH symmetric stretching), 1650 (>C=O), 1590-1410 (ring skeletal vibration), 1330 (SO_2 symmetric stretching), 1260-1090 (amine C-N stretching), 1160 (SO_2 symmetric stretching) and 940-860 (aromatic C-H and of the plane). ^{1}H NMR (DMSO-d_6 ppm (δ)]: 7.6 -doublet (2 protons), 8.5 -doublet (2 protons), 7.0 -triplet (2 protons), 7.6 -doublet (2 protons), 3.5 (broad peak,

TABLE-1
CHARACTERIZATION DATA

S. No.	Compounds / m.f.	R_1	R_2	m.p. (°C) / Yield (%)	R_f / R_m
I	3-(4-Sulphadiazinyl)isatin ($C_{18}H_{13}N_5O_3S$)	H	H	240 (93.3)	0.783 (-0.5573)
II	N-(1-Morpholinomethyl)-3-(4-sulphadiazinyl)isatin ($C_{23}H_{22}N_6O_4S$)	H		181-183 (83.6)	0.771 (-0.5346)
III	N-(1-Piperzinomethyl)-3-(4-sulphadiazinyl)isatin ($C_{24}H_{24}N_6O_3$)	H		130-132 (78.8)	0.771 (-0.4520)
IV	N-(1-Piperzinomethyl)-3-(4-sulphadiazinyl)isatin ($C_{23}H_{23}N_7O_3S$)	H		130 (89.1)	0.739 (-0.8531)
V	N-(Dimethylaminomethyl)-3-(4-sulphadiazinyl)isatin ($C_{23}H_{21}N_6O_3S$)	H		230 (91.7)	0.812 (-0.5967)
VI	N-(Diethylaminomethyl)-3-(4-sulphadiazinyl)isatin ($C_{23}H_{25}N_6O_3S$)	H		248 (80.8)	0.798 (-0.8179)
VII	N-Acetyl-3-(4-sulphadiazinyl)isatin ($C_{20}H_{15}N_5O_4S$)	H		150-152 (90.6)	0.693 (-0.3536)
VIII	N-(4-Sulphadiazinylmethyl)-3-(4-sulphadiazinyl)isatin ($C_{29}H_{23}N_9O_5S_2$)	H		220 (87.7)	0.800 (-0.6021)
IX	3-(4-Sulphadiazinyl)-5-chloro)isatin ($C_{18}H_{12}N_5O_3SCl$)	Cl	H	215 (87.0)	0.809 (-0.6269)
X	N-(1-Morpholinomethyl)-3-(4-sulphadiazinyl)-5-chloroisatin ($C_{23}H_{22}N_6O_3SCl$)	Cl		225 (92.7)	0.782 (-0.5547)
XI	N-(1-Piperidinomethyl)-3-(4-sulphadiazinyl)-5-chloroisatin ($C_{24}H_{24}N_6O_3SCl$)	Cl		190 (88.2)	0.832 (-0.6948)
XII	N-(1-Piperinomethyl)-3-(4-sulphadiazinyl)-5-chloroisatin ($C_{23}H_{23}N_7O_3SCl$)	Cl		230 (97.8)	0.821 (-0.8294)
XIII	N-(Dimethylaminomethyl)-3-4-(4-sulphadiazinyl)-5-chloroisatin ($C_{21}H_{20}N_6O_3SCl$)	Cl		222 (90.3)	0.851 (-0.7567)
XIV	N-(Diethylaminomethyl)-3-(4-sulphadiazinyl)-5-chloroisatin ($C_{23}H_{24}N_6O_3SCl$)	Cl		210 (90.3)	0.941 (-1.2027)
XV	N-Acetyl-3-(4-sulphadiazinyl)-5-chloroisatin ($C_{20}H_{15}N_5O_4SCl$)	Cl		219 (81.3)	0.636 (-0.2424)



Scheme-I

methyl protons), 2.9 -singlet (2 protons) due to presence of different moities in $C_{21}H_{21}N_6O_3S$. Simiarly, other Mannich bases were also prepared (Table-1).

Antibacterial study: The synthesized compounds were screened for their antibacterial activity against gram positive and gram negative bacteria by cup-plate diffusion techniques. The compounds were tested at 500 µg concentration in DMSO, using nutrient Agar as the medium. The results are presented in Table-2.

Antifungal study: The compounds were screened for their antifungal activity against *Candida albicans*, *Aspergillus* (*A. flavus*) and *Dermatophyton* (*Microsporum gypseium*) by cup-plate diffusion techniques. Most of the compounds were found to be inactive, but they showed activity on *Candida albicans*. The results are given in Table-3.

TABLE-2
ANTIBACTERIAL ACTIVITY OF SULPHADIAZINE BASES OF ISATIN

S. No.	VC	EC	Ps	ST	Kl	SP	SF
Isatin	100	100	120	0	120	110	0
5-Chloroisatin	130	140	0	110	170	120	140
Sulphadiazine	0	200	0	120	200	210	210
I	290	120	–	0	330	–	270
II	290	100	–	130	350	–	300
III	350	210	210	130	320	–	270
IV	310	210	210	0	–	–	250
V	290	150	270	170	300	–	260
VI	350	190	–	210	270	–	240
VII	300	140	–	160	300	–	200
VIII	290	140	240	120	320	–	280
IX	130	110	280	120	180	110	320
X	150	150	220	130	230	130	290
XI	150	220	280	140	200	120	300
XII	130	210	310	140	190	120	310
XIII	200	160	270	110	200	130	350
XIV	210	200	300	140	170	110	380
XV	180	190	330	150	200	0	220

VC = *Vibrio cholerae*, EC = *E. coli*, Ps = *Pseudomonas*, ST = *S. typhi*, Kl = *Klebsiella*, SP = *S. paratyphoid*, SF = *S. faecelis*.

TABLE-3
ANTIFUNGAL ACTIVITY OF SULPHADIAZINE BASES OF ISATIN

Compounds	Zone of inhibition at 500 µg × 10 mm (*C. albicans*)	Compounds	Zone of inhibition at 500 µg × 10 mm (*C. albicans*)
Isatin	140	**VII**	–
Chloroisatin	180	**VIII**	–
Sulphadiazine	–	**IX**	190
I	–	**X**	170
II	–	**XI**	200
III	160	**XII**	210
IV	–	**XIII**	200
V	100	**XIV**	150
VI	–	**XV**	180

RESULTS AND DISCUSSION

All the synthesized compounds were analyzed by spectral techniques, IR, UV and NMR spectra.

Almost all the synthesized compounds exhibited antibacterial activity against gram positive and gram negative bacteria at 500 µg concentration. Schiff base of isatin and 5-chloro isatin exhibited very good activity against *Pseudomonas*, the activity of chloroisatin and sulphadiazine being zero. Compounds **III** and **VI** exhibited miaximum activity against *V. cholerae*, compound **IX** against *S. faecelis* and *Pseudomonas* and compound **II** against *Klebsiella*.

Except compound **III** (piperidine Mannich base of isatin) none of the other compounds in isatin series exhibited activity against *Candida albicans*. Derivatives of chloroisatin exhibited good activity againt *Candida albicans*, sulphadizine being totally inactive.

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