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

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ABSTRACT

Sulphadiazinyl Schiff bases of isatin and derivatives and their Mannich bases were synthesized. Their chemical structure have been confirmed by IR, 1HNMR and 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.

Keywords: Antimicrobial activity , Sulphadiazine Schiff Bases.

Introduction- Isatin is an endogeneous compounds identified in humans that possesses a wide range og biological activities. It has long range of activities in CNS-MAO inhibition, anticonvulsant and axxiogenie. It effects as a Mao inhibitior is the protent in vitro action.

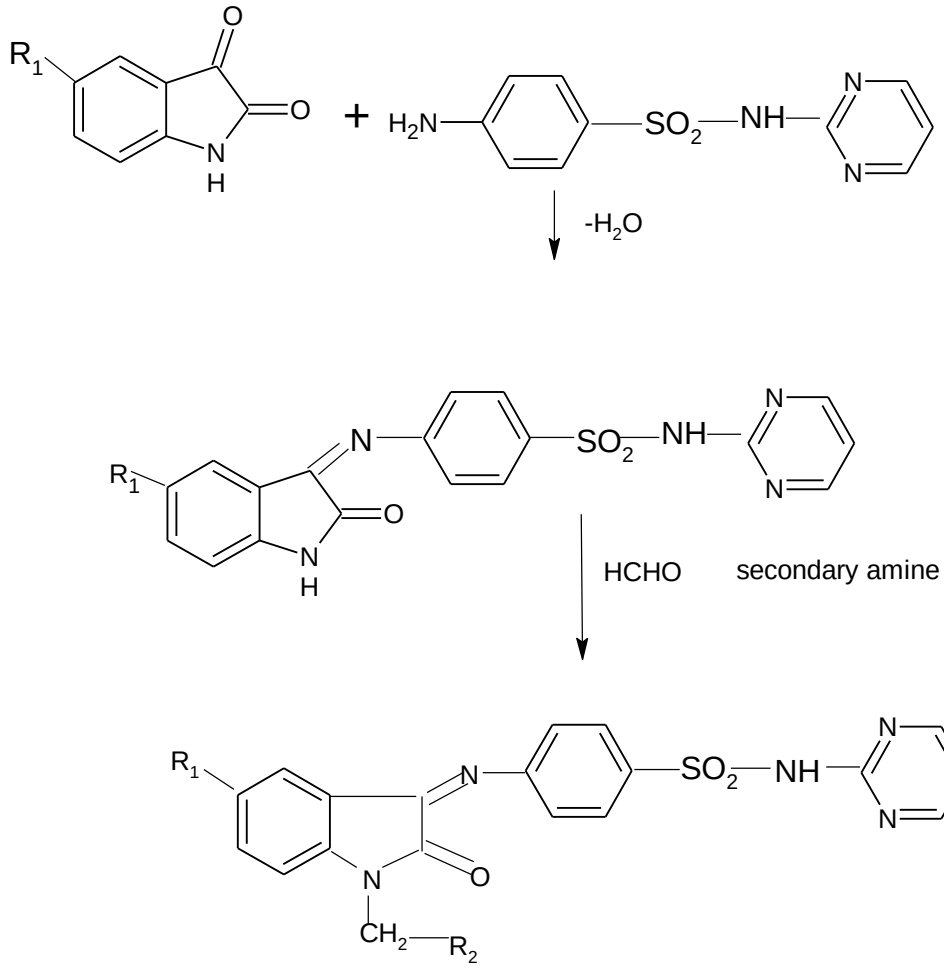
A series of p-substituted isatin semicarbazones have shown anticonvulsant activity in MES , scPTZ and scSTY tests. Various isatin N- mannich bases of isatin-3-thiosemicarbazenes have shown antiviral and tuberculostatic activity. Methisazone is an effective compound against variola and vaccinia viruses. 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 unsubstitued isatin. Pandeya and coworkers synthesized Schiff bases of isatin withy trimethoprim and their N-Mannich bases. All the synthesized compounds showed good activity against V.Cholerae, S.Boydii, E. faecilis and E. trades with MIC in range of 10-30 µg/ml.

Investigation of antimicrobial activity (against 28 pathogenic baecteria) 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. Among the synthesized compound 1-(piperdinomethyl)-5-bromo-3(3-(4-pyridyl)-5-mercapto-4(H)-1, 2, 4-triazolyl)iminoisatin showed the most favorable antimicrobial activity. None of the compounds showed the most appreciable anti HIV activity. The synthesized compounds were screened for anticonvulsant activity by MES, scMET-and strychnine induced seizure pattern tests. The synthesized compounds were tested for the sedative and hyphotie activity i. e potentiation or antagonisation by pentobarbitone induced harcosis in rats.

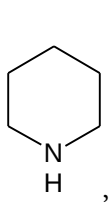
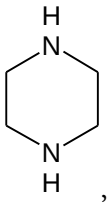
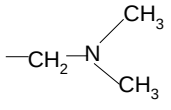
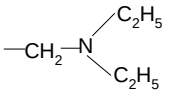
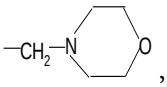
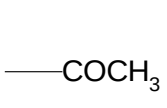
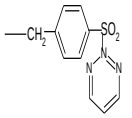
EXPERIMENTAL WORK - The synthetic work is mainly concerned for the preparation of condensation compounds i e N-metylacetylisatin-3-semicarbazones and 5-substituted N-methyl/acetyl isatin-semicarbazones.

1.Synthesis of 3-(4-Sulphadiazinyl) isatin. Equimolar quantities (.02 mol) of isatin (2.80gm) and sulphadiazine(6 gm) was dissolved in warm alcohol and refluxed on a steam bath for 2 hours. After standing for 24 hours at room temperature the product was collected by suction filtration. Yield 72% M.P 240 ^{0} C **compound I-** Elemental analysis for $C_{18}H_{31}N_5O_3S$; Found C: 56.60, H: 3.02, N: 12.16; Calcd. C: 56.68, H:3.44, N:18.45. IR(KBr, cm^{-1}): 3500-3300-NHsymmetric stretching, 1650 cm^{-1} -c=o stretching (amide) 1670-1400 cm^{-1} – ring skeletal vibration, 1150-C-N stretching (amide), 900-690-aromatic C-H stretching, out of plane. HNMR (DMSO-d_6 ppm ∂8.5-doublet(2 protons), 7.6-doublet (2 protons) 7.0-triplet(1 proton) , 6-7-doublet(2 protons). Similarly, 3-(4-sulphadiazinyl)-5-chloroisatin was prepared using appropriate moles of 5-chloroisatin and sulphadiazine. Charactersation data are given in Table-1

2. Synthesis of N- Mannich Bases. N- Mannich bases were prepared by condensing equimolar properties of the appropriate sulphadiazinyl isatin derivatives with secondary amine and formaldehyde. Scheme-1



R_1= H, Cl

R_2 = H, Cl,  ,  ,  ,  ,  ,  , 

Scheme-1

3.Synthesis of N-(diethyl aminomethyl)-3-(4-sulphadiazinyl) isatin.(Compound VI). Diethylamine (.004 mol) was added dropwise with cooling shaking to the slurry consisting-3-(4-sulphdiazinyl isatin) (.004 mol, 1.516 g) ethanol (5 ml) and 35% formalin (.34 ml). The reaction mixture was allowed to stand at room temperature for 20 minutes. At the end of this time, the contents were cooled and products thus separated was filtered and recrystallized from ethanol. Yield : 1.5 g (88.7%)

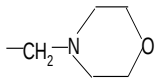
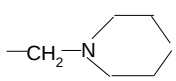
Elemental analysis for $C_{23}H_{25}N_6O_3S$; Found C: 55.36, H:4.9 , N: 19.01 Calcd. C: 55.35, H:4.78, N:19.12. Ultraviolet spectrum:λmax(nm): 266,248,242. IR spectrum showed absorption bands (cm^{-1})n at 3410-3350(NH symmetric stretching), 1620 (>V=O), 1580-1400(ring skeletal vibration), 1330 (SO_2symmetric stretching)n 1260-1080(amine C-N stretching) 1160(SO_2 symmetric stretching) and 940-860 (aromatic C-H and of the plane). ^{1}HNMR (DMSO-d_6 ppm) : 7.6-doublet (2 proton) 8.5-doublet (2 protons), 7.0- triplet (2 protons)2.9-singlet(2 protons) due to presence of different moieties in $C_{23}H_{25}N_6O_3S$. Similarly, other Mannich base 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 ar 500 µg concentrationin 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, Aspergillns (A. flavus) and Dermatophyton (Microsporum gypseium) by cup-plate diffusiontechniques. Most of the compounds were found to be inactive, but they showed activity on Candida albicans. The results are given in Table-3

Table-1

Characterization Data

S.No.	Compounds/mf	R1	R2	Mp/yield	Rf/Rm
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 $C_{24}H_{24}N_6O_3$	H		181-184 (83.6)	0.774 (-0.5348)
III	N-(1-piperzinomethyl)-3-(4-sulphadiazinyl)isatin $C_{24}H_{24}N_6O_3$	H		130-134 (78.5)	0.772 (-0.4525)
IV	N-(1-piperzinomethyl)-3-(4-	H		128	0.738

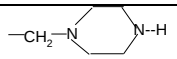
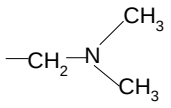
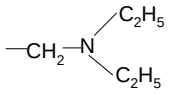
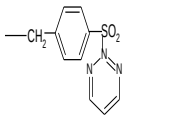
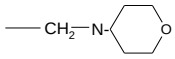
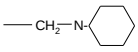
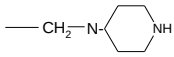
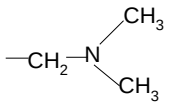
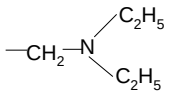
	sulphadiaznyl)isatin $C_{23}H_{23}N_7O_3S$			(88.4)	(-0.8530)
V	N-(Dimethylaminomethyl)-3-(4-sulphadiazinyl)isatin $C_{23}H_{21}N_6O_3S$	H		232 (91.8)	0.821 (-0.5867)
VI	N-(Diethylaminomethyl)-3-(4-sulphadiazinyl)isatin $C_{23}H_{25}N_6O_3S$	H		248 (80.6)	0.798 (-0.8179)
VII	N-Acetyl-3-(4-sulphadiazinyl)isatin $C_{20}H_{15}N_5O_4S$	H		150-154 (90.8)	0.66 (-0.3430)
VIII	N-(4-sulphadiazinylmethyl)-3-(4-sulphadiazinyl)isatin $C_{29}H_{23}N_9O_5S_2$	H		220 (85.4)	0.800 (-0.6021)
IX	3-(4- sulphadiazinyl)-5-chloro isatin $C_{18}H_{12}N_5O_3SCl$	Cl	H	213 (85.0)	0.801 (-0.6260)
X	N-(1-Morpholinomethyl)-3-(4-sulphadiazinyl)-5-chloroisatin $C_{23}H_{22}N_6O_3SCl$	Cl		226 (91.7)	0.782 (-0.5540)
XI	N-(1-piperidinomethyl)-3-(4-sulphadiazinyl)-5-chloro isatin $C_{24}H_{24}N_6O_3SCl$	Cl		190 (88.0)	0.830 (-0.6848)
XII	N-(1-piperinomethyl)-3-(4-sulphadiazinyl)-5chloro isatin $C_{23}H_{23}N_7O_3SCl$	Cl		225 (95.8)	0.820 (-0.8290)
XIII	N-(Dimethylaminomethyl)-3-4-(4-sulphadiazinyl)-5-chloroisatin $C_{21}H_{20}N_6O_3SCl$	Cl		220 (90.1)	0.821 (-0.7467)
XIV	N-(Diethylaminomethyl)-3-(4-sulphadiazinyl)-5-chloroisatin $C_{23}H_{24}N_6O_3SCl$	Cl		208 (90.0)	0.921 (-1.2127)
XV	N-Acetyl-3-(4-sulphadiazinyl)-5-chloroisatin $C_{20}H_{15}N_5O_4SCl$	Cl		214 (78.2)	0.620 (-0.2024)

Table-2

Antibacterial Activity of Sulphadiazinyl Bases of Isatin

S.No.	VC	EC	Ps	ST	KI	SP	SF
Isatin	100	100	0	0	120	110	0
5-Chloroisatin	130	140	110	110	170	120	130
Sulphadiazinyl	**0**	200	120	120	200	200	200
I	289	120	0	0	300	-	260
II	290	100	130	130	340	-	300
III	348	220	130	130	320	-	270
IV	310	210	0	0	-	-	250
V	290	160	180	180	300	-	260
VI	350	180	220	220	270	-	240
VII	300	130	170	170	300	-	210
VIII	290	130	120	120	320	-	270
IX	130	120	120	120	160	100	340
X	150	150	130	130	220	120	290
XI	150	220	130	130	210	120	300
XII	130	210	130	130	180	120	310
XIII	200	150	110	110	200	130	350
XIV	210	200	140	140	180	110	360
XV	180	180	150	150	200	0	240

VC= Vibrocholerae, EC= E. coli , Ps=Psendomonas

KI=Klebsiella SP= S.Paratyphoid SF=S. faecelis

Table-3. Antifungal Activity of Sulphadiazine Bases of Isatin

Compounds	Zone of Inhibition at 500µg×10 mm
Isatin	120
Chloroisatin	160
Sulphadiazine	-
I	-
II	-
III	150
IV	-
V	100
VI	-
VII	-
VIII	-
IX	180
X	160
XI	200

XII	210
XIII	200
XIV	150
XV	180

Results And Conclusion: **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-chloroisatin exhibited very good activity against *Pseudomonas*,the activity of cholroisatin and sulphadiazine being zero. Compound III and VI exhibited maximum activity against *V.cholerae* , compound IX against *S. facelis* and pseudomonas and compounds II against *Klebsiella.*

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