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Research Article

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 5-[2(3)-DIALKYLAMINO ALKOXY] INDOLE 2, 3-DIONES AND 5-[2(3)-DIALKYLAMINO ALKOXY] INDOLE 2-ONE, 3-SEMICARBAZONES

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ABSTRACT

In the present work, some new, *5*-[2(3)-dialkylamino alkoxy] Indole 2,3-diones and 5-[2(3)-dialkylamino alkoxy] Indole 2-one,3-semicarbazones were prepared.5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer method and it react with semicarbazides gives 5-hydroxy isatin 3- semicarbazone. 5-hydroxy isatin/ 5-hydroxy isatin 3- semicarbazones were condensed with dialkylamino alkylhalide by using William son synthesis to prepare the *5*-[2(3)-dialkylamino alkoxy] Indole 2, 3-dione and 5-[2(3)-dialkylamino alkoxy] Indole 2-one, 3-semicarbazone derivatives. The structures of the products were characterized by IR, NMR, and MASS Spectral study. All the compounds were evaluated for Antimicrobial activities. Some of these compounds showed good antibacterial activities compared with standard compounds.

Keywords: Synthesis, 5-[2(3)-dialky amino alkoxy] Indole 2, 3-diones, 5-[2(3)-dialky amino alkoxy] Indole 2-one, 3-semicarbazones, Antimicrobial activity

INTRODUCTION

Surendranath pandya[1] et al. reported the synthesis and anticonvulsant activity of some novel n-methyl/acetyl,5-(un)-substituted isatin-3-semicarbazones. In the last few years, Isatin derivatives have been discovered which show potential hypnotic[2], antibacterial[3-6], MAO inhibitory[7], antioxidant[8] activity.

We are reporting in the present communication the synthesis and characterization of some new compounds: 5-[2(3)-dialky amino alkoxy] Indole2, 3-diones, 5-[2(3)-dialky amino alkoxy] Indole2-one, 3-semicarbazones5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer method[9]. 5-Hydroxyisatin was heated under reflux in methanol containing two or three drops of acetic acid with semicarbazide hydrochloride for half an hour to get 5-Hydroxy isatin Semicarbazone. 5-Hydroxyisatin and 5-Hydroxy isatin semicarbazone condensed with dialkylamino alkyl halide by using Williamson synthesis to prepare the 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-dione and 5-[2(3)-dialkylamino alkoxy] Indole 2-one, 3-semicarbazone derivatives. All the compounds of the series have been screened antibacterial activity, the structures of these compounds were identified by IR, NMR and Mass Spectrums.

MATERIALS AND METHODS

The compounds were mostly synthesized by conventional methods and described in experimental selection and also by the methods established in our laboratory.

Chemicals

Dialkyl amino alkylhalides purchased from Sigma- Aldrich Chemicals Private Limited, Hyderabad, India. p-amino phenol, hydroxylamine hydrochloride, sodium sulfate were purchased from Merck Chemicals Private Limited, Hyderabad, India.

Chemistry

Solvents were dried or distilled before use. Melting points were obtained on a Thoshniwall melting point apparatus in open capillary tubes and are uncorrected. The purity of the compounds were ascertained by TLC on silica gel –G plates(Merck).Infrared spectra(IR) were recorded with KBR pellet on a Perkin-Elmer BX series, Infrared spectrophotometer. Mass spectra were recorded by the direct inlet method on Thadmammass- quantam API 400H mass spectrophotometer.[1]H NMR spectra were recorded on Brucker spectrospin 400 MHz spectrophotometer in DMSO-d6.

5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer method It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when

treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield.

1 Preparation of 5-Hydroxy Indole 3- semicarbazone 2-one

5-Hydroxyisatin was heated under reflux in methanol containing two or three drops of acetic acid with semicarbazide hydrochloride for half an hour. The product thus separated was filtered and purified by recrystalization from suitable solvent

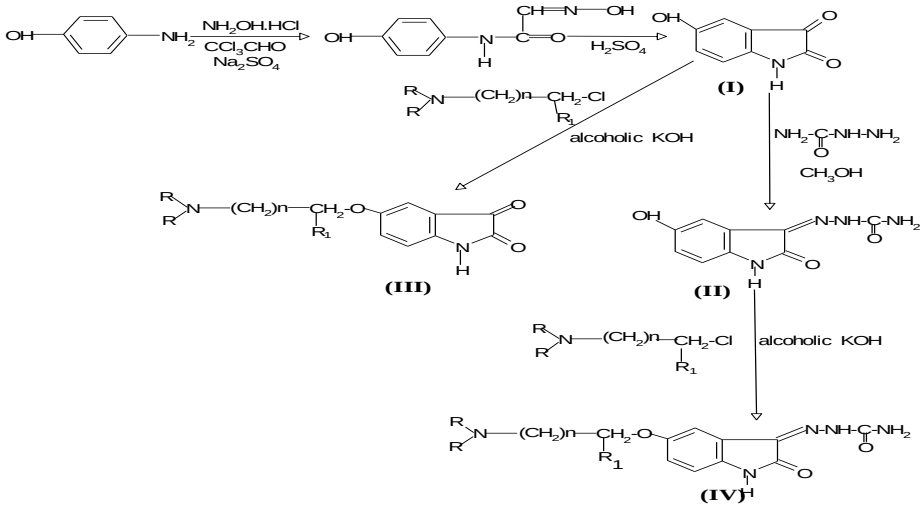
2 Preparation of 5-[2(3)-dialkyl amino alkoxy] Indole 2,3-dione, 5-[2(3)-dialkyl amino alkoxy] Indole 2-one,3-semicarbazone derivatives

A mixture of 5-Hydroxyisatin/5-Hydroxyisatin-3-semicarbazone (0.01 moles) and dialkylamino alkylhalide (0.01 moles) placed in 10% alcoholic potassium hydroxide and this mixture was heated under reflux on water bath for 6 hours .The alcohol was reduced to half of its volume and cooled. The product separated was filtered, washed with small portions of cold alcohol repeatedly and dried .It was purified by recrystalisation from hydro alcoholic mixtures to get a crystalline solid.

Adopting these procedure 10 compounds of 5-OH-Isatin derivative was prepared. The physical data of the title compounds were presented in Table –I. The compounds were characterized by spectral data.

Similarly other 5-Hydroxy Isatin derivatives were prepared and their melting points were determined in Open capillary tubes using Toshniwal melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC.

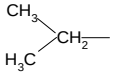
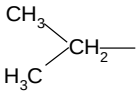
SCHEME



5-Hydroxyisatin derivatives (III)
IIIa R= CH3 ; R1 = H; n=1
IIIb R=C2H5; R1= H; n=1
IIIc R= CH3; R1= H; n=2
IIId R= CH3; R1= CH3; n=1
IIIe R=CH3-CH- CH3; R1= H; n=1

5-Hydroxyisatin-3- semicarbazone derivatives (IV)
IVa R= CH3 ; R1= H; n=1
IVb R=C2H5; R1= H; n=1
IVc R= CH3 ; R1= H; n=2
IVd R= CH3 ; R1=CH3; n=1
IVe R=CH3-CH- CH3 ; R1= H; n=1

Table- I.:Characterization Data Of 5 -[2(3) -Dialkylamino Alkoxy] Indole 2,3-Diones And 5-[2(3) -Dialkylamino Alkoxy] Indole-3-Semicarbazone- 2-Ones

S.No	Comp ound	R	R_1	N	X	M.F	% YEILD	M.P	M.Wt
1	IIIa	CH_3	H	1	O	$C_{12}H_{14}N_2O_3$	91%	<320	234
2	IIIb	C_2H_5	H	1	O	$C_{14}H_{18}N_2O_3$	86%	<320	262
3	IIIc	CH_3	H	2	O	$C_{13}H_{16}N_2O_3$	93%	<320	248
4	IIId	CH_3	CH_3	1	O	$C_{13}H_{16}N_2O_3$	85%	<320	248
5	IIIe		H	1	O	$C_{16}H_{24}N_2O_3$	81.8%	<320	292
6	IVa	CH_3	H	1	$NNHCONH_2$	$C_{13}H_{17}N_5O_3$	92%	<320	291
7	IVb	C_2H_5	H	1	$NNHCONH_2$	$C_{15}H_{21}N_5O_3$	83%	<320	319
8	IVc	CH_3	H	2	$NNHCONH_2$	$C_{14}H_{19}N_5O_3$	92%	<320	365
9	IVd	CH_3	CH_3	1	$NNHCONH_2$	$C_{14}H_{19}N_5O_3$	86%	<320	365
10	IVe		H	1	$NNHCONH_2$	$C_{17}H_{27}N_5O_3$	82%	<320	349

SPECTRAL DATA

The compounds have been characterized by the spectral data IR, PMR and Mass.

1. *5-Hydroxy indole 2, 3 di one (III).* Yield - 90.2%; ^{1}H NMR (DMSO- d_6): 13.3 (s, 1H, OH), 10.36(s, 1H,-CONH), 6.65-7.29(m, 3 H, Ar-H) ; MS (ESI), m/z =164 [M+ 1]; IR (KBr): 3421.47 (OH), 1630.08 (C = O), 1548 (Ar, C=C), 1282(C-O-C), 883.85-579.8 (Ar) cm-1.

2. *5-[2(3)-dimethyl amino ethoxy] Indole 2, 3 di one (IIIa).* Yield - 91%; ^{1}H NMR (DMSO- d_6): 10.36(s, 1H,-CONH), 7.01-7.29(m,3 H,Ar-H),3.2 (T,2H,O-CH_2) ,2.9 (t,2H,N-CH_2), 1.36 (s,6H,N-$(CH_3)_2$); MS (ESI), m/z =231 [M+ 1]; IR (KBr): 3276(NH), 1651.96 (C=O), 1569.82 (Ar ,C=C), 1276(C-O-C), 807.93(Ar).

3. *5-[2(3)-diethyl amino ethoxy] Indole 2, 3 di one (IIIb).* Yield - 86%; ^{1}H NMR (DMSO- d_6). 10.25(s, 1H,-CONH), 7.03-7.45(m,3 H,Ar-H),2.99 (t,2H,O-CH_2),2.72 (t,2H,N-CH_2) , 1.24 (s,10H,N-$(C_2H_5)_2$).; MS (ESI), m/z =263[M+ 1]; IR (KBr): 3274(NH), 1681.53 (C=O), 1570.21 (Ar, C=C), 1243(C-O-C), 845.51(Ar).

4. *5-[2(3)-dimethyl amino propoxy] Indole 2, 3 di one (IIIc).* Yield - 93%; ^{1}H NMR (DMSO- d_6). 10.46(s, 1H,-CONH), 7.21-7.49(m,3 H,Ar-H),2.84 (t,2H,O-CH_2) , 2.51 (m,2H, CH_2), 2.48 (t,2H,N-CH_2), 1.25 (s,6H,N-$(CH_3)_2$) ; MS (ESI), m/z =247[M+ 1]; IR (KBr): 3274(NH), 1651.96 (C=O), 1579.72 (Ar ,C=C), 1266(C-O-C), 805.91(Ar).

5. *5-[2(3)-dimethyl amino isopropoxy] Indole 2, 3 di one (IIId).* Yield - 85%; ^{1}H NMR (DMSO- d_6). 10.51(S, 1H,-CONH), 7.12-7.42(m, 3H, Ar-H),2.76 (m,1H,O-CH) , 2.45 (d, 3H, R_1=CH_3), 2.31 (d,2H,N-CH_2), 1.44 (s,6H,N-$(CH_3)_2$; MS (ESI), m/z =247[M+ 1]; IR (KBr): 3257(NH), 1679.64 (C=O), 1546.86 (Ar , C=C), 1245(C-O-C), 812.71(Ar).

6. *5-[2(3)-diisopropyl amino ethoxy] Indole 2, 3 di one (IIIe).* Yield - 81%; ^{1}H NMR (DMSO- d_6). 10.26(s, 1H,-CONH), 7.34-7.51(m, 3H,Ar-H),2.96 (t,2H,O-CH_2), 2.82 (t,2H,N-CH_2), 1.35 (m, 2H,N-CH) ,1.21 (d,12H,C -$(CH_3)_2$) ; MS (ESI), m/z =291[M+ 1]; IR

(KBr): 3257(NH), 1689.46 (C=O), 1576.34 (Ar , C=C), 1228(C-O-C), 814.53(Ar).

7. *5-[2(3)-dimethyl amino ethoxy] Indole 2-one, 3-semicarbazone (IVa).* Yield - 92%; ^{1}H NMR (DMSO- d_6). 10.36(s, 1H,-CONH), 7.01-7.29(m,3 H,Ar-H),3.2 (t,2H,O-CH_2) ,2.9 (t, 2H,N-CH_2), 1.36 (s, 6H, N-$(CH_3)_2$); 7.41-7.46(s, 2H, NH_2) ,11.36(s, 1H, NH); MS (ESI), m/z =291[M+ 1]; IR (KBr): 1651.96 (C=O), 1569.82 (Ar, C=C), 1276(C-O-C), 807.93(Ar).

8. *5-[2(3)-diethyl amino ethoxy] Indole 2-one, 3-semicarbazone (IVb).* Yield - 83%; ^{1}H NMR (DMSO- d_6). 10.25(s, 1H,-CONH), 7.03-7.45(m, 3H,Ar-H),2.99 (t, 2H,O-CH_2) ,2.72 (t, 2H,N-CH_2) ,1.24 (s, 10H,N-$(C_2H_5)_2$), 7.41-7.46(s,2H, NH_2) ,11.36(s,1H, NH); MS (ESI), m/z =317[M+ 1]; IR (KBr): 3274(NH), 1681.53 (C=O), 1570.21 (Ar, C=C), 1243(C-O-C), 845.51(Ar).

9. *5-[2(3)-dimethyl amino propoxy] Indole 2-one, 3-semicarbazone (IVc).* Yield - 92%; ^{1}H NMR (DMSO- d_6). 10.46(s, 1H, -CONH), 7.21-7.49(m, 3H,Ar-H), 2.84 (t, 2H, O-CH_2), 2.51 (M,2H, CH_2), 7.41-7.46(s, 2H, NH_2), 11.36(s, 1H, NH), 2.48(t, 2H, N-CH_2), 1.25 (s, 6H, N-$(CH_3)_2$). MS (ESI), m/z =363[M+ 1]; IR (KBr): 3274(NH), 1651.96 (C=O), 1579.72(Ar, C=C), 1266(C-O-C), 805.91(Ar).

10. *5-[2(3)-dimethyl amino isopropoxy] Indole 2-one, 3-semicarbazone (IVd).* Yield - 86%; ^{1}H NMR (DMSO- d_6). 10.51(s, 1H,-CONH), 7.12-7.42(m, 3H, Ar-H), 2.76 (m, 2H, O-CH_2), 7.41-7.46(s, 2H, NH_2), 11.36(s, 1H, NH), 2.45 (t, 3H, R_1=CH_3), 2.31 (m, 1H, N-CH), 1.44 (s, 6H, N-$(CH_3)_2$). MS (ESI), m/z =363[M+ 1]; IR (KBr): 3257(NH), 1679.64 (C=O), 1546.86(Ar, C=C), 7.41-7.46(d, 2H, NH_2), 11.36(s, 1H, NH) 1245(C-O-C), 812.71(Ar).

11. *5-[2(3) - diisopropyl amino ethoxy] Indole 2-one, 3-semicarbazone (IVe).* Yield - 82; ^{1}H NMR (DMSO- d_6). 10.26(s, 1H, -CONH), 7.34-7.51(m, 3H, Ar-H), 2.96 (t, 2H, O-CH_2), 7.41-7.46(s, 2H, NH_2), 11.36(s, 1H, NH), 2.82(t, 2H, N-CH_2), 1.35(m, 2H, N-CH), 1.21 (d, 12H, C-$(CH_3)_2$). MS (ESI), m/z =347[M+ 1]; IR (KBr): 3257(NH), 1689.46 (C=O), 1576.34 (Ar, C=C), 1228(C-O-C), 814.53(Ar).

ANTIBACTERIAL ACTIVITY [10,11].

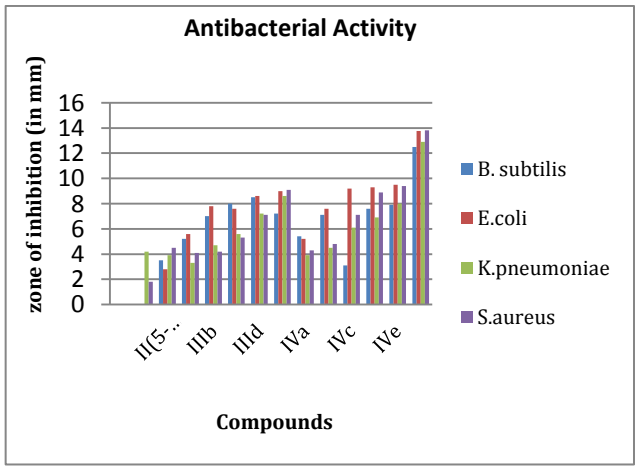
All the compounds have been evaluated for their antibacterial activity against both gram-positive and gram-negative bacteria and the results are presented in Table- II. The results of the evaluation have been compared with a broad-spectrum antibiotic Ampicillin as the standard drug.

Table- II:Antibacterial Activity Of 5-[2(3)-Dialkylamino Alkoxy] Isatins And 5-[2(3)-Dialkylamino Alkoxy] Isatin -3-Semicarbazones

S.No	Compound	*B. subtilis*	*E.coli*	*K.pneumoniae*	*S.aureus*
		Zone of Inhibition (in mm)			
1	I (5-Hydroxyisatin)	-	-	4.2	1.8
2	II(5-Hydroxyisatin-3-semicarbazone)	3.5	2.8	3.9	4.5
3	IIIa	5.2	5.6	3.3	4.1
4	IIIb	7.0	7.8	4.7	4.2
5	IIIc	8.0	7.6	5.6	5.3
6	IIId	8.5	8.6	7.2	7.1
7	IIIe	7.2	9.0	8.6	9.1
8	IVa	5.4	5.2	3.9	4.3
9	IVb	7.1	7.6	4.5	4.8
10	IVc	3.1	9.2	6.1	7.1
11	IVd	7.6	9.3	6.9	8.9
12	IVe	7.9	9.5	8.0	9.4
13	Ampicillin(10µg/cup)	12.5	13.75	12.9	13.8

RESULTS AND DISCUSSION

Table-II shows the antibacterial activity data of 5-Hydroxyisatin (III) and 5-Hydroxyisatin 3-semicarbazone (IV) derivatives, which had significant antibacterial activity. Amongst them, compounds IIId, IIIc, IVe and IVd has been found to be relatively more effective against *B. subtillis* with a zone of inhibition of 85 mm, 79 mm , 76 mm, 72 mm respectively. Compounds IVe, IVd, IVc, IIIe and IIId relatively more effective against *E.coli* with the zone of inhibition of 95mm, 93mm, 92mm, 90mm and 86mm respectively. Compounds IIIe, IVe are more effective against *K. pneumonia* with a zone of inhibition of 86mm, 80mm respectively. Compounds IVe, IIIe, IVd and IIId are more effective against *S.aureus* with a zone of inhibition of 94mm, 89mm, 91mm, and 71mm respectively.



From the observed data that the compounds IVd, IVe and IIId, IIIe have shown more antibacterial activity. The compound IIIa, IIIb, IIIc,IVa, IVb and IVc shows moderate anti bacterial activity where as compound I & II has very less anti bacterial activity against *K.pneumonia* and *S.aureus* and whereas no antibacterial activity was observed against *E.coli* and *B.subtillis*.

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