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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF THE 5-[2(3)-DIALKYLAMINO ALKOXY] ISATIN 3- THIOSEMICARBAZONES AND 5-[2(3)-DIALKYLAMINO ALKOXY] ISATIN-3-HYDRAZONE

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ABSTRACT:

In the present work, some new 5-[2(3)-dialkylaminoalkoxy] Indole 3-thiosemicarbazone 2-ones and 5-[2(3)-dialkylaminoalkoxy] Indole 3-hydrazone 2-one were prepared from 5-hydroxy isatin. 5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer method and it react with thiosemicarbazides/Hydrazine hydrate gives 5-hydroxy isatin 3- thiosemicarbazone/5-hydroxy isatin 3- hydrazone. 5-hydroxy isatin-3-hydrazone/ 5-hydroxy isatin 3- thiosemicarbazones were condensed with dialkylaminoalkylhalide by using William son synthesis to prepare the 5-[2(3)-dialkylaminoalkoxy] isatin 3- thiosemicarbazones and 5-[2(3)-dialkylaminoalkoxy] isatin-3-hydrazone 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, the 5-[2(3)-dialkylaminoalkoxy] isatin 3- thiosemicarbazones, 5-[2(3)-dialkylaminoalkoxy] isatin-3-hydrazones, Antimicrobial activity.

1. 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)-dialkylaminoalkoxy] isatin 3-thiosemicarbazones and 5-[2(3)-dialkylaminoalkoxy] isatin-3-hydrazones. 5-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 thiosemicarbazide hydrochloride/hydrazine hydrate for half an hour to get 5-Hydroxy isatin thioSemicarbazone/hydrazone. 5-hydroxy isatin-3-hydrazone/ 5-hydroxy isatin 3- thiosemicarbazones were condensed with dialkylaminoalkylhalide by using William son synthesis to prepare the 5-[2(3)-dialkylaminoalkoxy] isatin 3- thiosemicarbazones and 5-[2(3)-dialkylaminoalkoxy] isatin-3-hydrazone 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.

2. 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.

2.1Chemicals

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.

2.2Chemistry

Solvents were dried or distilled before use. Melting points were obtained on a Thoshniwallmelting 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. 1H NMR spectra were recorded on Bruckerspectrospin 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.

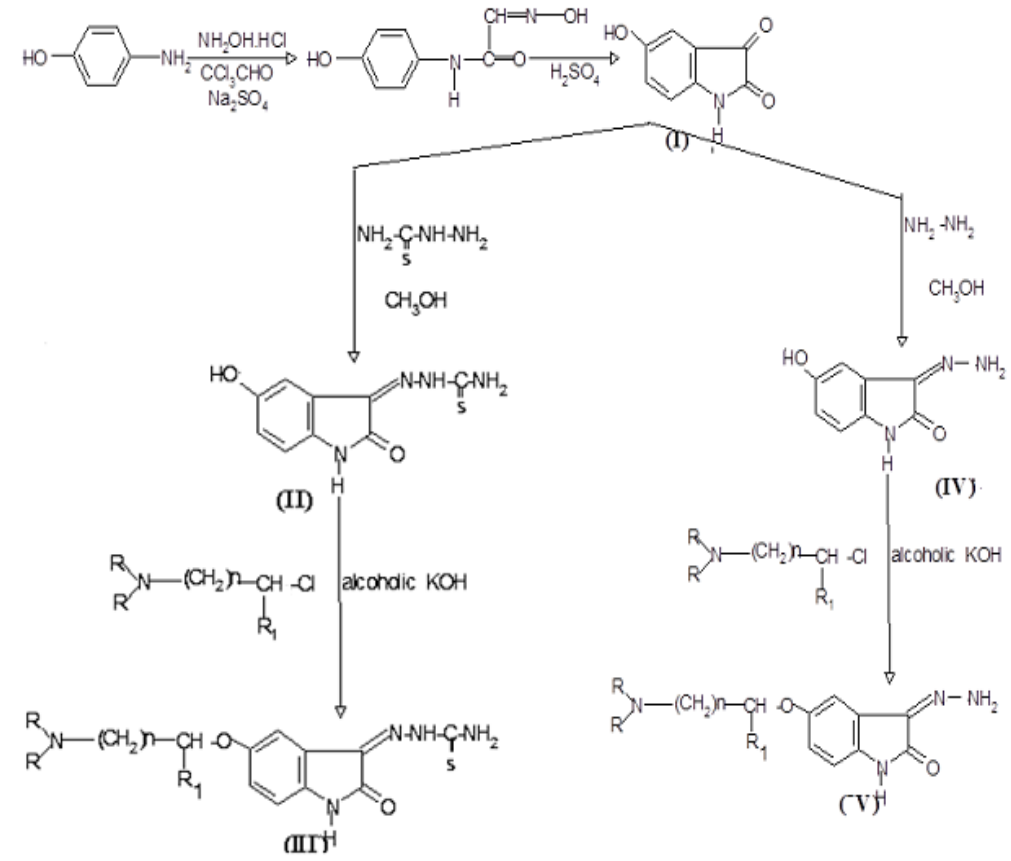
2.2.1Preparation of 5-Hydroxyindole 3-thiosemicarbazone 2-one (II) and 5-Hydroxyindole 2-hydrazone (IV)

5-Hydroxyisatin was heated under reflux in methanol containing two or three drops of acetic acid with thiosemicarbazide hydrochloride/Hydrazine hydrate for half an hour. The product thus separated was filtered and purified by recrystallization from suitable solvent. (Yield89%, m.p.270oc (II), Yield 90%, m.p.284 (IV)).

2.2.2 Preparation of 5-[2(3)-dialkyl amino alkoxy] Indole 3-thiosemicarbazone-2-one (III) and 5-[2(3)-dialkyl amino alkoxy] Indole 3-hydrazone-2-one (V)

A mixture of 5-Hydroxyindole3-thiosemicarba-zone2-one(II) /5-hydroxy indole 3-hydrazone 2-one(IV) (0.01 Moles) and dialkylaminoalkylhalide (0.01 Moles) placed in 10% alcoholic potassium hydroxide and this mixture was stirred at room temperature 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 recrystallization from hydro alcoholic mixtures to get a crystalline solid. Similarly other 5-Hydroxy Isatin derivatives as shown in **Scheme -1** were prepared and their melting points were determined in Open capillary tubes using Toshniwall melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC. The physical data of the title compounds were presented in **Table-1**. The compounds were characterized by spectral data.



5-Hydroxy- isatin- 3- thiosemicarbazone derivatives (III)

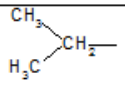
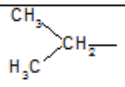
IIIa R=CH_3; R_1=H ;n=1
IIIb R=C_2H_5; R_1=H ;n=1
IIIc R=CH_3; R_1=H ;n=2
IIId R=CH_3; R_1= CH_3 ;n=1
IIIe R=CH_3-CH-CH_3; R_1=H ;n=1

5-Hydroxy-isatin- 3-hydrazone derivatives (V)

Va R=CH_3; R_1=H ;n=1
Vb R=C_2H_5; R_1=H ;n=1
Vc R=CH_3; R_1=H ;n=2
Vd R=CH_3; R_1= CH_3 ;n=1
VeR=CH_3-CH-CH_3;R_1=H ;n=1

Fig 1:Scheme

TABLE I: Physicaldata Of 5-[2(3)-Dialkyl Amino Alkoxy] Indole 3-Thiosemicarbazone-2-Ones(Iiia-Iiie) And 5-[2(3)-Dialkyl Amino Alkoxy] Indole 3-Hydrazone-2-Ones(Va-Ve)

S.No	Compound	R	R_1	N	X	M.F	% YEILD	M.P	M.Wt
1	IIIa	CH_3	H	1	$NNHCSNH_2$	$C_{13}H_{17}N_5O_2S$	91%	>320	307
2	IIIb	C_2H_5	H	1	$NNHCSNH_2$	$C_{15}H_{21}N_5O_2S$	86%	>320	335
3	IIIc	CH_3	H	2	$NNHCSNH_2$	$C_{14}H_{19}N_5O_2S$	93%	>320	353
4	IIId	CH_3	CH_3	1	$NNHCSNH_2$	$C_{14}H_{19}N_5O_2S$	85%	>320	353
5	IIIe		H	1	$NNHCSNH_2$	$C_{16}H_{24}N_5O_2S$	81.8%	>320	365
6	Va	CH_3	H	1	NNH_2	$C_{12}H_{16}N_4O_2$	92%	>320	248
7	Vb	C_2H_5	H	1	NNH_2	$C_{14}H_{20}N_4O_2$	83%	>320	276
8	Vc	CH_3	H	2	NNH_2	$C_{13}H_{18}N_4O_2$	92%	>320	294
9	Vd	CH_3	CH_3	1	NNH_2	$C_{13}H_{18}N_4O_2$	86%	>320	294
10	Ve		H	1	NNH_2	$C_{13}H_{26}N_4O_2$	82%	>320	306

3. SPECTRAL DATA

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

IR spectrum (KBr) of compound **(I)** exhibited absorption bands (cm-1) 3421.47 (OH), 1630.08 (C = O), 1548(Ar,C=C), 1282(C-O-C), 883.85-579.8 (Ar). **^{1}H NMR** (300 MHz, DMSO-d_6):13.3 (s,1H, OH), 10.36(s,1H,-CONH), 6.65-7.29 (m, 3 H, Ar-H). **Mass** spectrum of compound III showed molecular ion(M+) base peak at m/z (164.1).

Compound (**IIIa)** showed characteristic **IR** peaks at 3368.41(NH2), 3282.52(CONH), 1708(C=O), 1576(Ar C=C), 1263(C-O), 1085(C=S), 1576(C=N), 883.85 (Ar C-C).**^{1}H NMR** (300 MHz,DMSO-d_6): 11.36(s, 1H,CONH),7.29(s,2H,NH2), 7.03(s,1H,Ar-H), 7.20(d,1H,Ar-H), 7.94(d,1H,Ar-H), 3.2(t,2H, O-CH2), 2.9(t,2H, N-CH2),1.36(s, 6H,N-(CH3)2). **Mass** spectrum of compound **IIIa** showed molecular ion (M+) base peak at m/z 307. The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thiosemicarbazone from the molecule ion.

Compound (**IIIb)** showed characteristic **IR** peaks at 3368.41(NH2), 3282.52(CONH), 1165.96 (C=S), 1570.21 (Ar ,C=C), 1243(C-O-C), 845.51(Ar).**^{1}H NMR** (300 MHz, 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) 7.47-7.56(d,2H, NH_2),1.24 (m,6H,N-C-CH_3,1.12(t,N-CH_2).

Mass spectrum of compound **IIIb** showed molecular ion (M+) base peak at m/z 335. The mass spectrum shows its base peak at m/z 214 (100%) may be due to the fragmentation of the thiosemicarbazone from the molecule ion.

Compound (**IIIc)** showed characteristic **IR** peaks at 3368.41(NH2), 3282.52(CONH),1165.96(C=S), 1579.72 (Ar,C=C), 1266(C-O-C), 805.91(Ar).**^{1}H NMR** (300 MHz, DMSO-d_6):10.46(s,1H,-CONH),7.21-7.49(m,3 H,Ar-H), 7.51-7.56(d,2H, NH_2),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)$_2$). **Mass** spectrum of compound **IIIc**showed molecular ion (M+) peak at m/z 353 (100%). The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thiosemicarbazone from the molecule ion.

Compound (**IIId)** showed characteristic **IR** peaks at 3368.41(NH2), 3282.52(CONH),1165.96(C= S), 1546.86 (Ar,C=C),1245(C-O-C),812.71(Ar).**^{1}H NMR** (300MHz,DMSO-d_6):10.51(s,1H,-CONH),7.12-7.42(m,3H,Ar-H),7.51-7.56(d,2H,NH_2),2.76 (m,H,O-CH), 2.45(d,3H,R_1=CH_3), 2.31(d,1H,N-CH),1.44 (s,6H,N-(CH_3)$_2$). **Mass** spectrum of compound **IIId** showed molecular ion (M+) base peak at m/z 353(100%).The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thiosemicarbazone from molecule ion.

Compound (**IIIe)** showed characteristic **IR** peaks at 3368.41(NH2), 3282.52(CONH), 1165.96(C=S), 1576.34 (Ar,C=C),1228(C-O-C),814.53(Ar).**^{1}H NMR** (300 MHz, DMSO-d_6):10.26(s, 1H,-CONH), 7.34-7.51(m,3 H,Ar-H), 7.51-7.56(d,2H,NH_2),2.96 (t,2H,O-CH_2) ,2.82 (t,2H,N-CH_2), 1.35 (t, 2H,N-CH) ,1.21 (d,12H,C -(CH_3)$_2$). **Mass** spectrum of compound **IIIe** showed molecular ion (M+) peak at m/z 365 (100%). The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thosemicarbazone from the molecule ion.

Compound (**Va)** showed characteristic **IR** peaks at 3450.13(NH2), 146.46(CONH), 1708(C=O), 1268 (C-O-C), 1085(C=S), 1528(C=N).**^{1}H NMR** (300 MHz, DMSO-d_6): 11.36(s,1H,CONH),7.29(s,2H,NH2), 7.03(s,1H,Ar-H), 7.20(d,1H,Ar-H), 7.94(d,1H,Ar-H) 3.2(t,2H, O-CH2), 2.9(t,2H, N-CH2),1.36(s, 6H,N-(CH3)2). **Mass** spectrum of compound **Va** showed molecular ion (M+) base peak at m/z 248 (100%).It also

shows peak at m/z (71) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**Vb)** showed characteristic **IR** peaks at 3450.13(NH2), 146.46(CONH), 1685.96(C=O), 1600.96(C=N) 1570.21(Ar,C=C),1243 (C-O-C),845.51(Ar). **^{1}H NMR**(300MHz, 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)7.47-7.56(d,2H, NH_2), 1.24(s,10H,N-$(C_2H_5)_2$).

Mass spectrum of compound **Vb** showed molecular ion (M+) peak at m/z 276(100%).It also shows peak at m/z(99) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**Vc)** showed characteristic **IR** peaks at 3450.13(NH2), 146.46(CONH), 1698.96 (C=O), 1600.96 (C=N), 1579.72 (Ar, C=C), 1266(C-O-C),805.91(Ar).**^{1}H NMR**(300 MHz,DMSO-d_6):10.46(s,1H,-CONH), 7.21-7.49(m,3H,Ar-H), 7.51-7.56(d,2H, NH_2), 2.76(m,H,O-CH), 2.45(d,3H, R_1=CH_3),2.31 (d,1H,N-CH),1.44(s,6H,N-$(CH_3)_2$). **Mass** spectrum of compound **Vc** showed molecular ion (M+) base peak at m/z 294 (100%). It also shows peak at m/z (113) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**Vd)** showed characteristic **IR** peaks at 3450.13(NH2), 146.46(CONH),1698.96 (C=O),1600.96 (C=N)1546.86(Ar,C=C),1245(C-O-C), 812.71(Ar).**^{1}H NMR** (300 MHz, DMSO-d_6):10.51(s,1H,-CONH),7.12-7.42(m,3H,Ar-H),7.51-7.56 (d,2H, NH_2), 2.76 (m, 2H,O-CH_2), 2.45(t,3H,R_1=CH_3), 2.31 (m,1H,N-CH), 1.44 (s,6H,N-$(CH_3)_2$).**Mass** spectrum of compound **Vd** showed molecular ion (M+) base peak at m/z 294 (100%). It also shows peak at m/z (113) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**ve)** showed characteristic **ir** peaks at 3450.13(nh2), 146.46(conh), 1696.96 (c=o), 1600.96 (c=n), 1576.34(ar,c=c),1228 (c-o-c),814.53(ar). **^{1}h nmr**(300mhz, dmso-d_6):10.26(s,1h,-conh),7.34-7.51(m,3h,ar-h),7.51-7.56(d,2h, nh_2), 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-$(ch_3)_2$). **Mass** spectrum of compound **ve** showed molecular ion (m+) base peak at m/z 306(100%).it also shows peak at m/z (129) may be due to the fragmentation of the alkyl chain from the molecule ion.

4. 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)-dialkylaminoalkoxy] isatins and 5-[2(3)-dialkylaminoalkoxy] isatin -3-semicarbazones

S.No	Compound	*B. subtilis*	*E.coli*	*K.pneumoniae*	*S.aureus*
		Zone of Inhibition (in mm)			
1	IIIa	6.4	6.7	4.4	5.2
2	IIIb	8.0	8.9	5.8	5.3
3	IIIc	9.1	8.7	6.7	6.4
4	IIId	9.6	9.6	8.3	8.2
5	IIIe	8.3	10.0	9.6	10.1
6	Va	6.4	6.2	4.9	5.3
7	Vb	8.1	8.6	5.5	5.8
8	Vc	4.1	10.2	7.1	8.1
9	Vd	8.6	10.3	7.9	9.9
10	Ve	8.9	10.5	9.0	10.4
11	Ampicillin (10µg/cup)	13.5	14.75	13.9	14.8

Concentration of the test compound: 300µg/cup

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5. RESULTS AND DISCUSSION

Table-II shows the antibacterial activity data of 5-[2(3)-dialkylaminoalkoxy] Indole 3-thiosemicarbazone 2-ones and 5-[2(3)-dialkylaminoalkoxy] Indole 3-hydrazone 2-ones, which had significant antibacterial activity. Amongst them, compounds IIId, IIIc, Ve and Vd has been found to be relatively more effective against B. subtillis with a zone of inhibition of 9.6 mm, 9.1 mm , 8.9 mm, 8,6 mm respectively. Compounds Ve, Vd, Vc, IIIe and IIId relatively more effective against E.coli with the zone of inhibition of 10.5mm, 10.3mm, 10.2mm, 10mm and 9.6mm respectively. Compounds IIIe, Ve are more effective against K. pneumonia with a zone of inhibition of 97mm, 9.0mm respectively. Compounds

Ve, IIIe, Vd and IIId are more effective against S.aureus with a zone of inhibition of 10.4mm, 10.1mm, 9.9mm, and 8.2mm respectively.

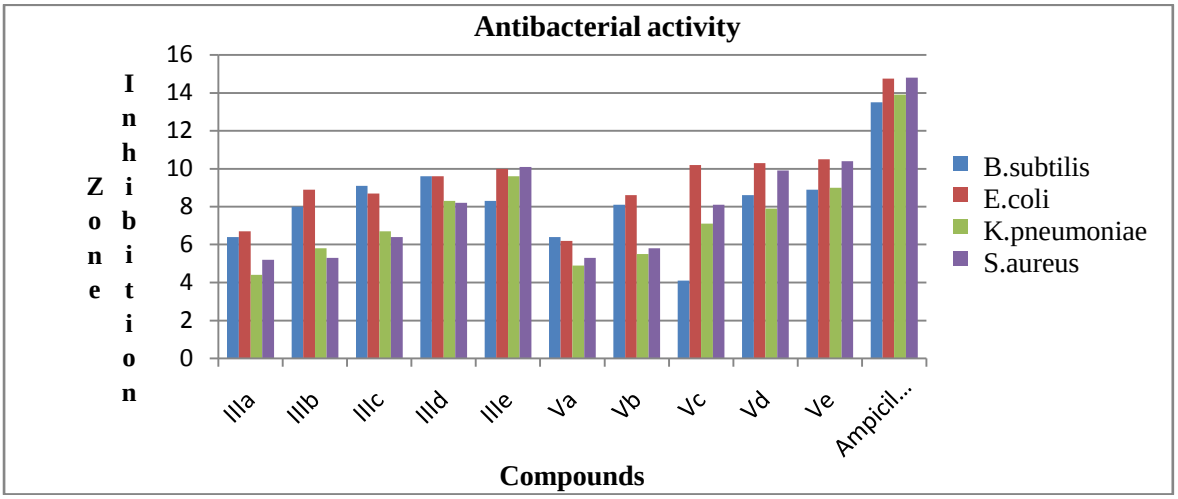

Figure 2: From the observed data that the compounds Vd, Ve and IIId, IIIe have shown more antibacterial activity. The compound IIIa, IIIb, IIIc, Va, Vb and Vc shows moderate anti-bacterial activity.

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