



## SYNTHESIS AND SEDATIVE-HYPNOTIC ACTIVITY OF NOVEL SERIES OF ISATIN HYDRAZONE AND ISATIN THIOSEMICARBAZONE DERIVATIVES

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### ABSTRACT

In the present work, some new 5-[2(3)-dialkylamino alkoxy] Indole 3-thiosemicarbazone 2-ones and 5-[2(3)-dialkylamino alkoxy] Indole 3-hydrazone 2-ones were prepared from 5-hydroxy isatin. The structures of the products were characterized by IR, NMR, MASS Spectral studies. Thus synthesized and characterized targeted compounds were further screened for their Sedative-Hypnotic activity by using Potentiation of Pentobarbitone induced Narcosis method. Among all the newly synthesized derivatives, Compound IIIa, IIIb and Compound Va,Vb potentiated the sedative-hypnotic activity very significantly , thus these compounds showed promising activity and compounds IIIb and Vb showed moderate sedative-hypnotic activity.

**Keywords :** Synthesis, 5-[2(3)-dialkyl amino alkoxy] Indole 3-hydrazone 2-one, 5-[2(3)-dialkylamino alkoxy] Indole 3-thiosemicarbazone 2-ones, Sedative-Hypnotic Activity.

### 1. INTRODUCTION

Isatins are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry. A variety of biological activities are associated with isatin including CNS activities as potentiation of Pentobarbitone induced narcosis[1], anticonvulsant activity and enzymatic inhibition activities[2]. Isatins are capable of crossing the blood-brain barrier [3]. Isatin, a heterocyclic compound was identified in animals as a major component of the endogenous monoamine oxidase inhibitor [4, 5]. Isatin (1H-indole-2, 3-Dione) is a synthetically versatile substrate, where it can be used for the

synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis. Isatin has also been found in mammalian tissues, and its function as a modulator of biochemical processes has been the subject of several discussions. A survey of literature reveals the advances in the use of isatin for organic synthesis during the last twenty -five years, as well as enormous importance of its biological and pharmacological properties.

## 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.

### 2.1. Chemicals

Dialkylaminoalkylhalides,Hydrazinehydrate,Thiosemicarbazide-hydrochloride 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.

### 2.2. 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 Thadman-mass-quantam API 400H mass spectrophotometer.<sup>1</sup>H NMR spectra were recorded on Bruker spectrospin 400 MHz spectrophotometer in DMSO-d<sub>6</sub>. 5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer[6] method It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitroso-acetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield.

### 2.3. Preparation of 5-Hydroxyindole 3-thiosemicarbazone 2-one(II) and 5-Hydroxyindole 2-hydrazone(IV)

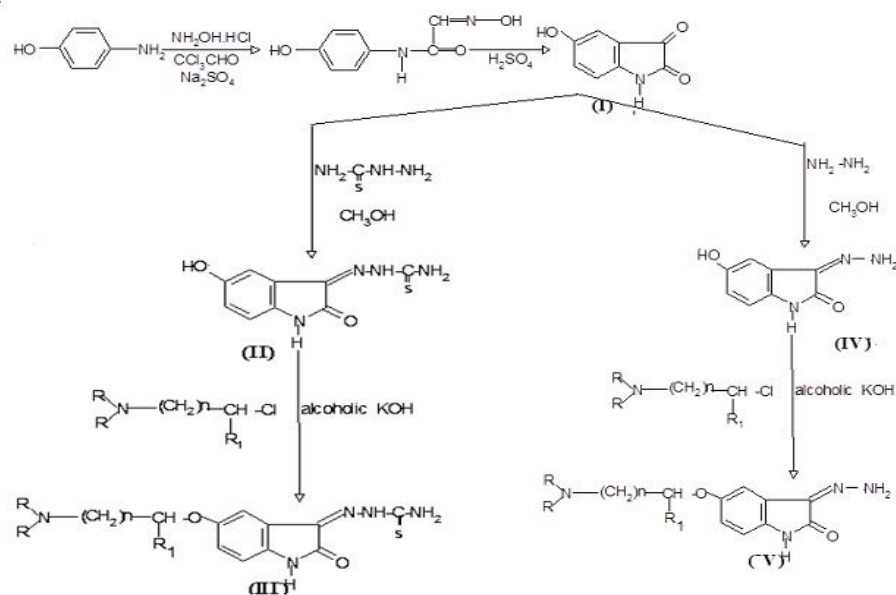
5-Hydroxyisatin was heated under reflux in methanol containing two or three drops of acetic acid with thiosemicarbazide hydrochloride/Hydrazine hydrate for half an hour. The product

thus separated was filtered and purified by recrystallization from suitable solvent. (Yield 89%, m.p. 270°C (II), Yield 90%, m.p. 284 (IV)).

#### 2.4 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-Hydroxyindole-3-thiosemicarbazone-2-one (II) / 5-hydroxy indole 3-hydrazone-2-one (IV) (0.01 moles) and dialkylamino alkylhalide (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 recrystallisation 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.



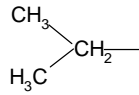
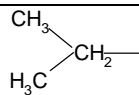
##### 5-Hydroxy- isatin- 3- thiosemicarbazone derivatives (III)

- IIIa R=CH<sub>3</sub>; R<sub>1</sub>=H ;n=1
- IIIb R=C<sub>2</sub>H<sub>5</sub>; R<sub>1</sub>=H ;n=1
- IIIc R=CH<sub>3</sub>; R<sub>1</sub>=H ;n=2
- IIId R=CH<sub>3</sub>; R<sub>1</sub>= CH<sub>3</sub> ;n=1
- IIIe R=CH<sub>3</sub>-CH-CH<sub>3</sub>; R<sub>1</sub>=H ;n=1

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

- Va R=CH<sub>3</sub>; R<sub>1</sub>=H ;n=1
- Vb R=C<sub>2</sub>H<sub>5</sub>; R<sub>1</sub>=H ;n=1
- Vc R=CH<sub>3</sub>; R<sub>1</sub>=H ;n=2
- Vd R=CH<sub>3</sub>; R<sub>1</sub>= CH<sub>3</sub> ;n=1
- Ve R=CH<sub>3</sub>-CH-CH<sub>3</sub>; R<sub>1</sub>=H ;n=1

**Table-1 Physical data 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 <sub>1</sub>	N	X	M.F	% YEILD	M.P	M.Wt
1	IIIa	CH <sub>3</sub>	H	1	NNHCSNH <sub>2</sub>	C <sub>13</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> S	91%	280	307
2	IIIb	C <sub>2</sub> H <sub>5</sub>	H	1	NNHCSNH <sub>2</sub>	C <sub>15</sub> H <sub>21</sub> N <sub>5</sub> O <sub>2</sub> S	86%	272	335
3	IIIc	CH <sub>3</sub>	H	2	NNHCSNH <sub>2</sub>	C <sub>14</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> S	93%	283	353
4	IIId	CH <sub>3</sub>	CH <sub>3</sub>	1	NNHCSNH <sub>2</sub>	C <sub>14</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> S	85%	264	353
5	IIIe		H	1	NNHCSNH <sub>2</sub>	C <sub>16</sub> H <sub>24</sub> N <sub>5</sub> O <sub>2</sub> S	81.8%	258	365
6	Va	CH <sub>3</sub>	H	1	NNH <sub>2</sub>	C <sub>12</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	92%	293	248
7	Vb	C <sub>2</sub> H <sub>5</sub>	H	1	NNH <sub>2</sub>	C <sub>14</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub>	83%	269	276
8	Vc	CH <sub>3</sub>	H	2	NNH <sub>2</sub>	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	92%	261	294
9	Vd	CH <sub>3</sub>	CH <sub>3</sub>	1	NNH <sub>2</sub>	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	86%	252	294
10	Ve		H	1	NNH <sub>2</sub>	C <sub>13</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub>	82%	248	306

## 2.5. 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<sup>-1</sup>) 3421.47 (OH), 1630.08 (C = O), 1548(Ar,C=C), 1282(C-O-C), 883.85-579.8 (Ar). **<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): 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<sup>+</sup>) base peak at m/z (164.1).

Compound (IIIa) showed characteristic **IR** peaks at 3368.41(NH<sub>2</sub>), 3282.52(CONH), 1708(C=O), 1576(Ar C=C), 1263(C-O), 1085(C=S), 1576(C=N), 883.85 (Ar C-C). **<sup>1</sup>H NMR** (300 MHz,DMSO-d<sub>6</sub>): 11.36(s, 1H,CONH),7.29(s,2H,NH<sub>2</sub>), 7.03(s,1H,Ar-H), 7.20(d,1H,Ar-H), 7.94(d,1H,Ar-H), 3.2(t,2H, O-CH<sub>2</sub>), 2.9(t,2H, N-CH<sub>2</sub>),1.36(s, 6H,N-(CH<sub>3</sub>)<sub>2</sub>). **Mass** spectrum of compound IIIa showed molecular ion (M<sup>+</sup>) base peak at m/z 307.

Compound (IIIb) showed characteristic **IR** peaks at 3368.41(NH<sub>2</sub>), 3282.52(CONH), 1165.96 (C=S), 1570.21(Ar,C=C), 1243(C-O-C), 845.51(Ar). **<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): 10.25(s, 1H,-CONH ), 7.03-7.45(m,3 H,Ar-H),2.99 (t,2H,O-CH<sub>2</sub>) ,2.72 (t,2H,N-CH<sub>2</sub>) 7.47-7.56(d,2H, NH<sub>2</sub>),1.24 (m,6H,N-C-CH<sub>3</sub>),1.12(t,N-CH<sub>2</sub>).

**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(NH<sub>2</sub>), 3282.52(CONH), 1165.96(C=S), 1579.72 (Ar,C=C), 1266(C-O-C), 805.91(Ar). **<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>):10.46(s,1H,-CONH),7.21-7.49(m,3 H,Ar-H), 7.51-7.56(d,2H, NH<sub>2</sub>),2.84 (t,2H,O-CH<sub>2</sub>) , 2.51 (m,2H, CH<sub>2</sub>),2.48 (t,2H,N-CH<sub>2</sub>), 1.25 (s,6H,N-(CH<sub>3</sub>)<sub>2</sub>). **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 (**IIIId**) showed characteristic **IR** peaks at 3368.41(NH<sub>2</sub>), 3282.52(CONH), 1165.96(C= S), 1546.86 (Ar,C=C),1245(C-O-C),812.71(Ar). **<sup>1</sup>H NMR** (300MHz,DMSO-d<sub>6</sub>):10.51(s,1H,-CONH),7.12-7.42(m,3H,Ar-H),7.51-7.56(d,2H,NH<sub>2</sub>),2.76 (m,H,O-CH) , 2.45(d,3H,R<sub>1</sub>=CH<sub>3</sub>), 2.31(d,1H,N-CH),1.44 (s,6H,N-(CH<sub>3</sub>)<sub>2</sub>). **Mass** spectrum of compound **IIIId** 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(NH<sub>2</sub>), 3282.52(CONH), 1165.96(C=S), 1576.34 (Ar,C=C),1228(C-O-C),814.53(Ar). **<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>):10.26(s, 1H,-CONH), 7.34-7.51(m,3 H,Ar-H), 7.51-7.56(d,2H,NH<sub>2</sub>),2.96 (t,2H,O-CH<sub>2</sub>), 2.82 (t,2H,N-CH<sub>2</sub>), 1.35 (t, 2H,N-CH) ,1.21 (d,12H,C -(CH<sub>3</sub>)<sub>2</sub>). **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(NH<sub>2</sub>), 146.46(CONH), 1708(C=O), 1268 (C-O-C), 1085(C=S), 1528(C=N). **<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): 11.36(s,1H,CONH),7.29(s,2H,NH<sub>2</sub>), 7.03(s,1H,Ar-H), 7.20(d,1H,Ar-H), 7.94(d,1H,Ar-H) 3.2(t,2H, O-CH<sub>2</sub>), 2.9(t,2H, N-CH<sub>2</sub>),1.36(s, 6H,N-(CH<sub>3</sub>)<sub>2</sub>). **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(NH<sub>2</sub>), 146.46(CONH), 1685.96(C=O), 1600.96(C=N), 1570.21(Ar,C=C), 1243(C-O-C), 845.51(Ar). **<sup>1</sup>H NMR**(300MHz, DMSO-d<sub>6</sub>): 10.25(s, 1H, -CONH), 7.03-7.45(m, 3H, Ar-H), 2.99(t, 2H, O-CH<sub>2</sub>), 2.72(t, 2H, N-CH<sub>2</sub>), 7.47-7.56(d, 2H, NH<sub>2</sub>), 1.24(s, 10H, N-(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>).

**Mass** spectrum of compound **Vb** showed molecular ion (M<sup>+</sup>) 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(NH<sub>2</sub>), 146.46(CONH), 1698.96 (C=O), 1600.96(C=N), 1579.72(Ar,C=C), 1266(C-O-C), 805.91(Ar). **<sup>1</sup>H NMR**(300 MHz, DMSO-d<sub>6</sub>): 10.46(s, 1H, -CONH), 7.21-7.49(m, 3 H, Ar-H), 7.51-7.56(d, 2H, NH<sub>2</sub>), 2.76(m, H, O-CH), 2.45(d, 3H, R<sub>1</sub>=CH<sub>3</sub>), 2.31 (d, 1H, N-CH), 1.44(s, 6H, N-(CH<sub>3</sub>)<sub>2</sub>). **Mass** spectrum of compound **Vc** showed molecular ion (M<sup>+</sup>) 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(NH<sub>2</sub>), 146.46(CONH), 1698.96 (C=O), 1600.96 (C=N), 1546.86(Ar,C=C), 1245(C-O-C), 812.71(Ar). **<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): 10.51(s, 1H, -CONH), 7.12-7.42(m, 3H, Ar-H), 7.51-7.56 (d, 2H, NH<sub>2</sub>), 2.76 (m, 2H, O-CH<sub>2</sub>), 2.45(t, 3H, R<sub>1</sub>=CH<sub>3</sub>), 2.31 (m, 1H, N-CH), 1.44 (s, 6H, N-(CH<sub>3</sub>)<sub>2</sub>). **Mass** spectrum of compound **Vd** showed molecular ion (M<sup>+</sup>) 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(NH<sub>2</sub>), 146.46(CONH), 1696.96 (C=O), 1600.96 (C=N), 1576.34(Ar,C=C), 1228 (C-O-C), 814.53(Ar). **<sup>1</sup>H NMR**(300MHz, DMSO-d<sub>6</sub>): 10.26(s, 1H, -CONH), 7.34-7.51(m, 3H, Ar-H), 7.51-7.56(d, 2H, NH<sub>2</sub>), 2.96(t, 2H, O-CH<sub>2</sub>), 2.82(t, 2H, N-CH<sub>2</sub>), 1.35 (m, 2H, N-CH), 1.21(d, 12H, C-(CH<sub>3</sub>)<sub>2</sub>). **Mass** spectrum of compound **Ve** showed molecular ion (M<sup>+</sup>) 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.

### 3. PHARMACOLOGY

#### 3.1 Effect of Pentobarbitone – Induced Narcosis [7-11]

Healthy adult albino swiss mice weighing between 20 and 28 g. were fasted for 24hrs. Before the experiment and were divided into groups of six animals each. The test compounds or standard diazepam (50mg/kg) were administered intraperitoneally. The control group of animals was given the vehicle. After 30 min, pentobarbitone sodium was administered,

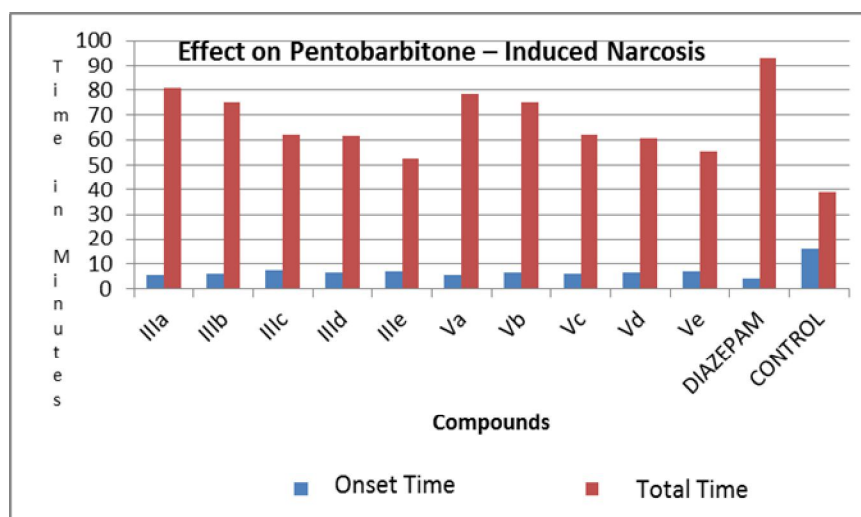


intraperitoneally to all groups of animals at a dose of 45 mg/kg. The time of onset of sleep after administration of test compounds and pentobarbitone sodium, the time of loss of righting reflex were recorded in all the groups of test animals and the effect on pentobarbitone sodium induced narcosis by the compounds was observed as shown in Table-3.

**Table2 Sedative-Hypnotic activity 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	Time of Onset of sleep (min)	Total sleeping time (min)
1	IIIa	5.36 ± 1.30	80.80 ± 2.87
2	IIIb	6.24 ± 0.82	75.31 ± 3.51
3	IIIc	7.25 ± 1.25	62.20 ± 4.25
4	III d	6.40 ± 2.10	61.45 ± 2.25
5	IIIe	7.15 ± 1.55	52.40 ± 4.10
6	Va	5.80 ± 3.20	78.40 ± 3.94
7	Vb	6.36 ± 1.25	75.38 ± 2.52
8	Vc	6.25 ± 0.84	62.20 ± 2.25
9	Vd	6.50 ± 2.20	60.80 ± 4.25
10	Ve	7.16 ± 3.20	55.60 ± 3.91
11	DIAZEPAM	4.34 ± 0.16	93.06 ± 1.20
12	CONTROL	15.69 ± 1.63	38.87 ± 3.48

n=6 animals per each group, dose 100mg/kg body weight



**Figure1. Sedative-Hypnotic activity 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)**

#### 4. RESULTS AND DISCUSSIONS

Physical data TLC, IR,  $^1\text{H}$  NMR and mass spectra confirmed the structures and purity of the synthesized compounds. All the title compounds decomposed before melting. All the synthesized compounds were evaluated for their in vivo Sedative-Hypnotic activity. It was observed that compounds **IIIa**, **Va**, **IIIb**, **Vb**, significantly reduced the onset of sleep induced by pentobarbitone, there by showed a promising sedative-Hypnotic activity, whereas the compounds **Vd**, **Ve**, **IIIc**, **Vc**, **IIId**, **IIIc,IIIe** showed moderately potentiated the pentobarbitone induced sedative –Hypnotic activity.

#### CONCLUSION

A new series of five 5-[2(3)-dialkyl amino alkoxy] Indole 2,3 dione derivatives were synthesized by reacting 5-hydroxyindole 2,3 dione schiff bases with 2-N,N di alkylamino alkyl halides. Evaluation of these compounds as sedative hypnotic activity revealed that the compounds **Va**(R=CH<sub>3</sub>), **Vb**(R=C<sub>2</sub>H<sub>5</sub>), **IIIa**(R=CH<sub>3</sub>) and **IIIb**(R=C<sub>2</sub>H<sub>5</sub>) with a dimethyl and diethyl amino ethyl chain derivatives was found to be relatively superior in sedative-hypnotic activity and other compounds(**IIIc**, **IVc**, **IIId**, **Vd**, **IIIe**, **Ve**) are next in the order of activity. This study reports the successful synthesis of the title compounds in good yields and moderate to potent sedative hypnotic activity of these derivatives containing isatin moiety which is comparable with standard drug Diazepam. It has been observed that the increased sedative hypnotic activity is attributed to the presence of pharmacologically active groups like thiosemicarbazide and dimethyl amino ethyl side chain.

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