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SYNTHESIS AND SEDATIVE-HYPNOTIC ACTIVITYOF NEW ISATIN DERIVATIVES

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ABSTRACT

In the present work, some new 3-(2-benzoylhydrazono)-[substituted amino]-2-oxoindoline-5-carboxamides and 3-(2-(3-aminobenzoyl)hydrazono)-[substituted amino]2-oxoindoline-5- carboximide derivatives were prepared from ethyl 2,3- dioxoindoline- 5-carboxylate.The newly synthesised derivatives were characterized by using the data of IR, 'H NMR and Mass Spectral analysis. Thus synthesised and characterized targetted compounds were further screened for their Sedative-Hypnotic activity by using Potentiation of Pentobarbitone induced Narcosis method.Among all the newly synthesized derivatives, Compound VIf and Compound VIIf potentiated the sedative-hypnotic activity very significantly , thus these compounds showed promising sedative-hypnotic activity and compounds VIb,VIIb and VIIe showed moderate sedative-hypnotic activity.

KEY WORDS

Synthesis, 3-(2-benzoylhydrazono)-[substituted amino]-2-oxoindoline-5-carboxamides, 3-(2-(3-aminobenzoyl) hydrazono)-[substituted amino]2-oxoindoline-5- carboximides, Sedative-Hypnotic activity.

1. INTRODUCTION

Isatins are an important group of heterocyclic compounds [1] 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, anti-convulsant 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].

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[5], 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 [6]. 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. EXPERIMENTAL

Melting points of all synthesized compounds were determined by open capillary tubes and are uncorrected. The IR spectra (KBr pellets) were recorded on Spectrum BX series model spectrometer for Compounds **VI** and **VII.** ^{1}H NMR spectra were recorded for compound **VIc** and **VIIc** on AV 300 MHz NMR Spectrometer, using TMS as internal standard. The mass spectra were recorded on -LCQ ion Mass spectrometer. The purity of the compounds were checked by Thin Layer Chromatography (TLC) on Merck Silica gel 60 F254 pre coated sheet using Chloroform and Ethyl acetate in 1:1 v/v.

2.1 Synthesis of ethyl 4 - (2-(hydroxyimino) acetamido) benzoate (ii)–To 90g (0.54mol) of chloral hydrate and 1200 ml of water crystallized sodium sulphate (1300 g) followed by a solution of appropriate aniline (ethyl 4-amino benzoate) (0.5mol) in 300 ml of water were added, to which 51.2g(43ml, 0.52 mol) of concentrated hydrochloric acid has been added to dissolve the aniline. Finally, a solution of hydroxylamine HCl, 110g (1.58mol) in 500 ml of water was added. The contents of the flask were heated on water bath so that vigorous boiling began in about 40 to 45 minutes. After 1 to 2 minutes of vigorous boiling the reaction was completed. During the heating period, some crystals of ethyl 4- (2-(hydroxyimino) acetamido) benzoate separated out. On cooling the solution in running water, the formed product was crystallized and was filtered under suction and air dried.

2.2 Synthesis of ethyl 2, 3- dioxoindoline - 5 - carboxylate (iii)

Sulphuric acid (600 g, 326 ml, sp.gr. 1.84) was warmed at 50^0C and to this 0.46mol of dry finely powdered ethyl 4 - (2-(hydroxyimino) acetamido) benzoate was added at such a rate so as to maintain the temperature between 60°C to 70°C but not higher and subjected to stirring. External cooling was applied at this stage so that the reaction could be carried out more rapidly. After the addition completed, the solution was heated to 80°C and maintained at that temperature for 10 minutes to complete the reaction. Then the reaction mixture was cooled to room temperature and poured up on 10 to12 times the volume of crushed ice while stirring. After standing for about half-an-hour, the product separated washed several times with small portions of cold water, several times to remove sulphuric acid.

2.3 Synthesis of ethyl (Z)- 3-(2-benzoylhydrazono)-2-oxoindoline-5-carboxylate (iv) and ethyl (Z)-3-(2-(3-aminobenzoyl) hydrazono)-2-oxoindoline-5-carboxylate (v)

(5, 0.01mol) benzoic acid hydrazide and ethyl 2,3-dioxoindoline-5-carboxylate (6, 0.01mol) were taken in methanol(20ml), 2 drops of glacial acetic acid was added and heated under reflux on a water bath for 8 to 12 h. The product ethyl (Z) - 3-(2 benzoylhydrazono)- 2-oxoindoline-5-carboxylate thus obtained was recrystallized from methanol.

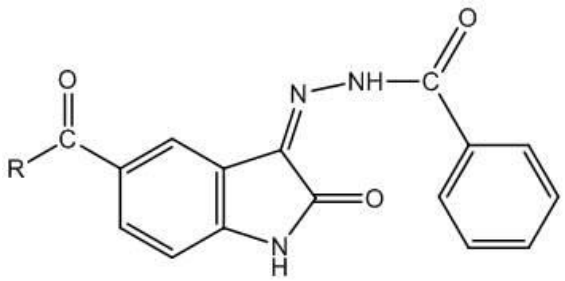
(5, 0.01mol) 4-amino benzohydrazide and ethyl 2,3-dioxoindoline-5-carboxylate (6, 0.01mol) were taken in methanol(20ml), 2 drops of glacial acetic acid was added and heated under reflux on a water bath for 8 to 12 h. The product ethyl (Z)- 3-(2-(3-aminobenzoyl) hydrazono)-2- oxoindoline-5- carboxylate thus obtained was recrystallized from methanol.

2.4 Synthesis of 3 - (2- benzoylhydrazono) - [substituted amino] 2 - oxoindoline- 5-carboximides (vi) and 3- (2- (3-aminobenzoyl) hydrazono)- [substituted amino] 2-oxoindoline-5- carboximides (vii)

A mixture of ethyl(Z)-3-(2-benzoylhydrazono)-2-oxoindoline-5-carboxylate(0.01M) and ethyl(Z)-3-(2-(3-aminobenzoyl)hydrazono)-2-oxoindoline-5-carboxylate(0.001) and substituted amines(0.01M) were taken in 50ml of methanol, heated under reflux on a water bath for 24-48hrs. The alcohol was reduced to half of its volume and cooled. The product separated was filtered and washed with small portions of cold alcohol first and then with cold water repeatedly and dried. The product was purified by recrystallization from methanol.

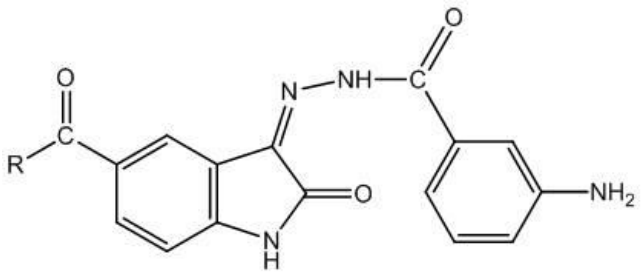
Adopting this procedure totally we have synthesized twelve new isatin derivatives. The yields, melting points and physical data of newly synthesized compounds were summarized in **Table-1 and Table-2.**

Table 1- Physical data of Synthesis of 3-(2-benzoylhydrazono)-[substituted amino] 2-oxoindoline-5-carboximides (VI):



S.No.	R	Molecular formula	Molecular weight	Compound	Melting point (°C)	Percentage yield
1.		$C_{22}H_{27}N_5O_4$	426.10	Via	200-203	77
2.		$C_{24}H_{31}N_5O_4$	454.21	VIb	190-192	75
3.		$C_{25}H_{33}N_5O_4$	468.24	Vic	210-212	74
4.		$C_{23}H_{29}N_5O_4$	440.18	VId	203-206	75
5.		$C_{22}H_{26}N_4O_4$	411.09	VIe	212-215	81
6.		$C_{22}H_{26}N_4O_4$	411.09	VIf	208-210	80

Table 2- Physical data of Synthesis of 3-(2-(3-aminobenzoyl) hydrazono)-[substituted amino]2-oxoindoline-5-carboximides(VII):



S.No.	R	Molecular formula	Molecular weight	Compound	Melting point (°C)	Percentage yield
1.		$C_{22}H_{29}N_6O_4$	442.10	VIIa	220-222	77
2.		$C_{24}H_{33}N_6O_4$	470.21	VIIb	193-195	72
3.		$C_{25}H_{35}N_6O_4$	484.24	VIIc	210-212	74
4.		$C_{23}H_{31}N_6O_4$	456.18	VIId	190-192	76
5.		$C_{22}H_{28}N_5O_4$	427.09	VIIe	202-204	80
6.		$C_{22}H_{28}N_5O_4$	427.09	VIIf	210-212	82

2.5 Effect of Pentobarbitone – Induced Narcosis [7-10]

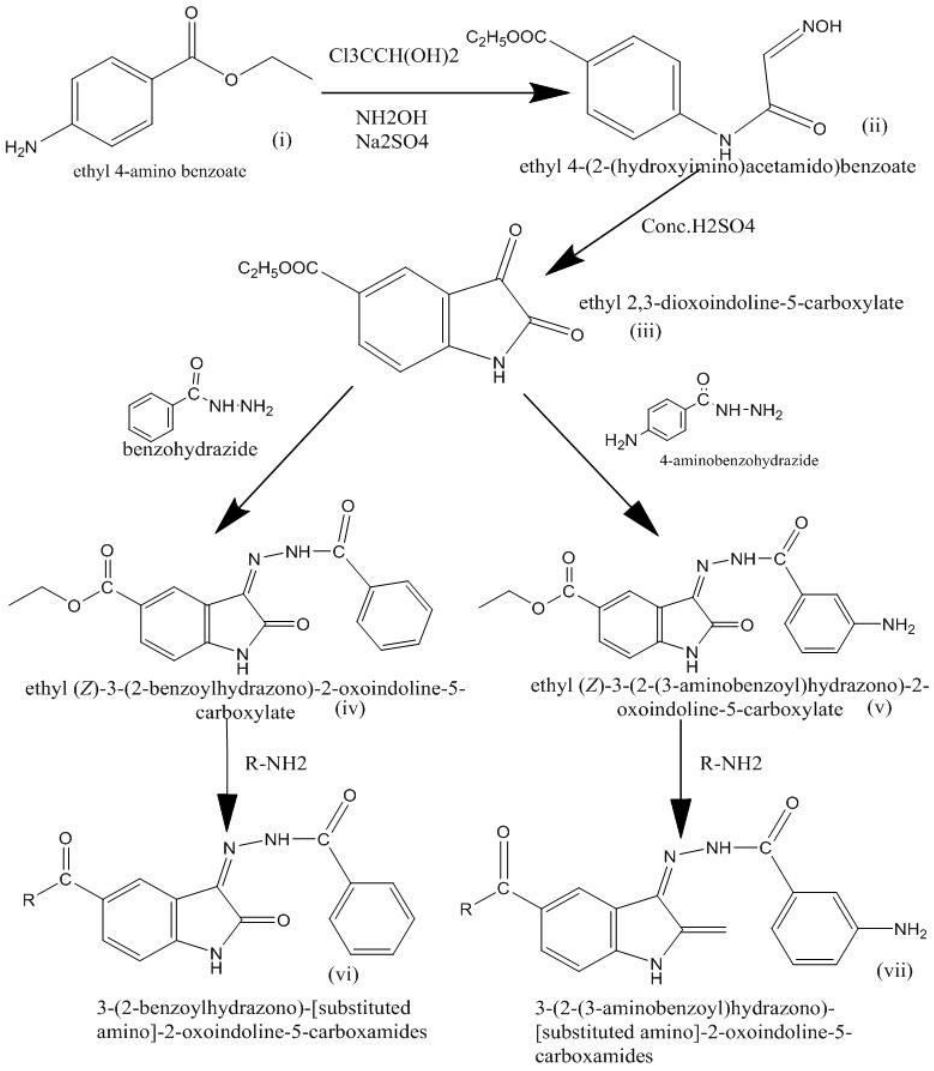
Healthy adult albino swiss mice weighing between 20 and 28 g. were fasted for 24hrs. Before the experiment and were divided into groups of six animals each. The test compounds or standard diazepam (50mg/kg) were administered intraperitoneally. The control group of animals was given the vehicle. After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

Table 3: Sedative-Hypnotic activity of 3-(2-benzoylhydrazono)-[substituted amino]2-oxoindoline-5-carboximides(vi) and 3-(2-(3-aminobenzoyl)hydrazono)-[substituted amino]2-oxoindoline-5-carboximides(vii)

Compound	Time of Onset of sleep (min)	Total sleeping time (min)
VIa	7.36 ± 1.30	60.80 ± 2.87
VIb	6.25 ± 0.84	75.31 ± 3.51
VIc	7.25 ± 1.25	62.20 ± 4.25
VId	6.50 ± 2.20	68.45 ± 2.25
VIe	7.15 ± 1.55	72.40 ± 4.10
VIf	6.80 ± 3.20	78.40 ± 3.94
VIIa	6.50 ± 2.20	62.20 ± 2.87
VIIb	7.36 ± 1.25	75.31 ± 3.51
VIIc	6.25 ± 0.84	62.20 ± 2.25
VIId	6.50 ± 2.20	60.80 ± 4.25
VIIe	7.15 ± 3.20	75.60 ± 3.91
VIIf	7.25 ± 1.25	76.10 ± 2.59
DIAZEPAM	4.34 ± 0.16	93.06 ± 1.20
CONTROL	15.69 ± 1.63	38.87 ± 3.48

SCHEME



2.6. Ethyl 2, 3-dioxoindoline-5-carboxylate :(III)

[11]The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3650(NH), 3323 (C-H), 1620 (C=O).

PMR spectrum (DMSO-d_6) of the compound has been found to exhibit proton signals (δ ppm) at: 1.30 (t, 3H,CH_3), 4.30(q,2H,CH_2), 7.8-8.2(d,2H,Ar-H), 8.4(S,1H,Ar-H), 7.95(d,2H,Ar-H), 7.54-7.62(t,3H,Ar-H), 10.87(s,1H,NH), 10.03(s,1H,NH).

Mass spectrum of compound (III) recorded its molecular ion peak at m/z 219.05.

2.7. 3-(2-benzoylhydrazono)-N-(3-(diethylamino) propyl)-2-oxoindoline-5- carboxamide : (VIc):

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3650(NH), 3323 (C-H), 1620 (C=O).

PMR spectrum (DMSO-d_6) of the compound has been found to exhibit proton signals (δ ppm) at:1.15(t,6H,CH_3),3.01(q,4H,CH_2),2.36(t,2H,CH_2),1.77(m,2H,CH_2),3.42(q,2H,CH_2),8.44(t,1H,NH),8.41(s,1H,Ar-H)7.9-8.2(d,2H,Ar-H),7.95(d,2H,Ar-H),7.54-7.62(t,3H,Ar-H),10.87(s,1H,NH),10.03(s,1H,NH).

Mass spectrum of compound (VIc) recorded its molecular ion peak at m/z 421.21.

3. RESULTS AND DISCUSSION

The preliminary studies on Sedative-Hypnotic activity of the new 3-(2-benzoylhydrazono)-[substituted amino] 2-oxoindoline-5-carboximides (vi) and 3-(2-(3-aminobenzoyl) hydrazono) - [substituted amino]2-oxoindoline – 5 - carboximides (vii) have generated some interesting data.

3.1. Sedative-Hypnotic activity

All the synthesized new isatin derivatives were evaluated for their Sedative-Hypnotic activity by using the standard Diazepam.

The investigation of Sedative-Hypnotic activity revealed that the tested compounds VIf and VIIf (R-N,N-dimethylethanamine) potentiated the sedative-hypnotic activity, there by showed a promising sedative-hypnotic activity, where as the compound VIb, VIIb(N,N-diethylethane-1,2-diamine) and VIIe (butan-1-amine)potentiated the sedative-hypnotic activity moderately towards Pentobarbitone induced Narcosis method.

Figure1: Graph showing Sedative-Hypnotic activity of 3-(2-benzoylhydrazono)-[substituted amino]2-oxoindoline-5-carboximides(vi) and 3-(2-(3-aminobenzoyl)hydrazono)-[substituted amino]2-oxoindoline-5-carboximides(vii).

4. CONCLUSION

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. It has been observed that the increased sedative-hypnotic activity is attributed to the presence of pharmacologically active group like N, N-dimethylethanamine side chain.

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