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Design, synthesis and biological evaluation of 5-[2(3)-dialkylamino alkoxy] indole 2,3-diones as new antihistamine agents

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Abstract

In the present work, some new 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-diones were prepared from 5-hydroxy isatin. A mixture of 5-hydroxy isatin, dialkylamino alkylhalide in alcoholic potassium hydroxide was stirred at room temperature for 6 hours to get the 5-[2(3)-dialkylamino alkoxy] Indole 2,3-diones. The structures of the products were characterized by IR, NMR, MASS Spectral studies. All the compounds were evaluated for Antihistaminic activity by Histamine chamber method.

Key words: Synthesis, 5-[2(3)-dialky amino alkoxy] indole 2, 3-diones, antihistaminic activity.

Introduction

Isatin is an endogeneous compound isolated in 1998 and reported[1] to possess a wide range of central nervous system activities. In the last few years, Isatin derivatives have been discovered which show potential hypnotic[3], antibacterial[4-6] and, antihistaminic[7]activity.

It is evident from the literature survey that Isatin derivatives dialkylamino alkyl derivatives showing more promising antihistaminic activity. Keeping in view of these two molecular moieties viz., 5-hydroxy isatin and dialkylamino alkyl (Resembles chloramphenicol), it is our endeavor to bring such important moieties into a single molecular frame as a model for molecular conjunction by appropriate synthetic routes and to screen them for antihistaminic activity.

We are reporting in the present communication the synthesis and characterization of some new compounds: 5-[2(3)-dialky amino alkoxy] Indole 2, 3-diones

5-Hydroxyisatin condensed with dialkylamino alkyl halide by using Williamson synthesis to prepare the *5*-[2(3)-dialkylamino alkoxy] Indole 2, 3-dione derivatives. All the compounds of the series have been screened for antihistaminic activity and 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

Leptazole, Diazepam, 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 Thadmam-mass-quantam API 400H mass spectrophotometer.^{1}H NMR spectra were recorded on Brucker spectrospin 400 MHz spectrophotometer in DMSO-$d_{6.}$

5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer[8] 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.

Synthesis of 5-[2(3)-dialkyl amino alkoxy] Indole 2,3 dione derivatives:

A mixture of 5-hydroxyisatin (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 recrystallization from hydro alcoholic mixtures to get a crystalline solid. Similarly other 5-Hydroxy Isatin derivatives 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 –I. The compounds were characterized by spectral data.

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

Compound IIIa
IR (KBr, cm-1): 3276(NH), 1651.96(C=O), 1569.82(Ar, C=C), 1276(C-O-C), 807.93(Ar); ^{1}H NMR (300 MHz, DMSO-d_6):10.36(s, 1H, -CONH), 7.01-7.29(m, 3H, Ar-H), 3.2(t, 2H, O-CH_2 s), 2.9(t, 2H, N-CH_2), 1.36(s, 6H, N-$(CH_3)_2$).

Mass spectrum showed molecular ion (M+) base peak at m/z 231 (100%). It also shows peak at m/z (71) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound IIIb
IR (KBr, cm^{-1}): 3274(NH), 1681.53(C=O), 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, 3H, Ar-H), 2.99(t, 2H, O-CH_2 s), 2.72 (t, 2H, N-CH_2), 1.24 (s, 10H, N-$(C_2H_5)_2$).

Mass spectrum showed molecular ion (M+) base peak at m/z 263 (100%). It also shows peak at m/z (71) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound IIIc
IR (KBr, cm-1): 3274(NH), 1651.96(C=O), 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), 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-$(CH_3)_2$).

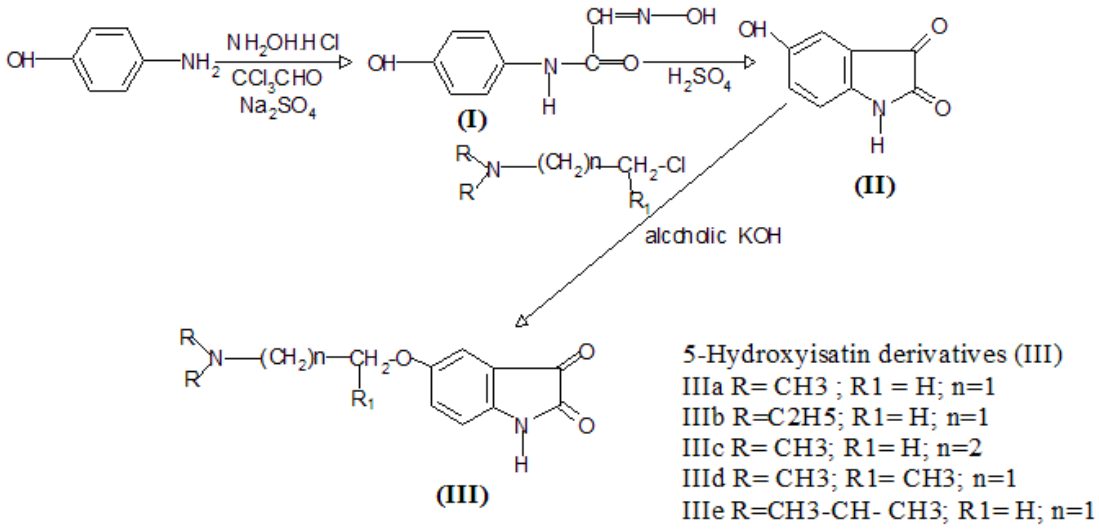
Mass spectrum showed molecular ion (M+) base peak at m/z 247 (100%).

Compound IIId
IR (KBr, cm-1): 3257(NH), 1679.64(C=O), 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), 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 showed molecular ion (M+) base peak at m/z 247 (100%).

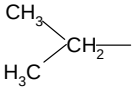
Compound IIIe
IR (KBr, cm-1): 3257(NH), 1689.46(C=O), 1576.34(Ar, C=C), 1228(C-O-C), 814.53(Ar); ^{1}H NMR (300 MHz, DMSO-d_6):10.26(s, 1H, -CONH), 7.34-7.51(m, 3H, Ar-H), 2.96(t, 2H, O-CH_2 s), 2.82 (t, 2H, N-CH_2), 1.35(s, 2H, N-CH), 1.21 (d,12H, C-$(CH_3)_2$).

Mass spectrum showed molecular ion (M+) base peak at m/z 291 (100%).It also shows peak at m/z (71) may be due to the fragmentation of the alkyl chain from the molecule ion.



Scheme-1

Table- 1: Characterization data of 5 - [2(3) -dialkylamino alkoxy] indole 2, 3-diones

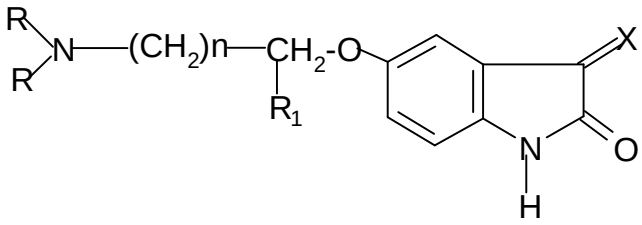
S.No	Compound	R	R_1	N	X	Chem.formula	Yield (%)	M.P	M.Wt
1	**IIIa**	CH_3	H	1	O	$C_{12}H_{14}N_2O_3$	91%	<320	234
2	**IIIb**	C_2H_5	H	1	O	$C_{14}H_{18}N_2O_3$	86%	<320	262
3	**IIIc**	CH_3	H	2	O	$C_{13}H_{16}N_2O_3$	93%	<320	248
4	**IIId**	CH_3	CH_3	1	O	$C_{13}H_{16}N_2O_3$	85%	<320	248
5	**IIIe**		H	1	O	$C_{16}H_{24}N_2O_3$	81.8%	<320	292

Anti histaminic effect of drug on guinea pigs:[9]
Materials: Histamine aerosol apparatus with compressor, sphygmomanometer and nebulizer**,** Histamine1%, Chlorpheniramine maleate(40mg\ml), saline.

Method: The instrument consist of a transparent box of a perspex devided by a perforated wall in to two.There is a small hole to spray aerosol .The spray is done using a nebulizer which is connected to a spygmomanometer and the compressor. One side of the box has a movable partition to remove the aerosol. Guenea pigs of identical weight are selected for the experiment. The test compounds suspended in normal saline were administered at a dose of 100 mg/kg body weight i.p .The aerosol containing histamine (1%) is spreader by nebulizer into the chambers and the time was recorded till the animal show dyspnoea and convulsions. The lid was quickly opened to remove aerosol and the animal is allowed to recover. The control group animals received only vehicle (Normal saline). One group of animals was administered chlorpheniramine as a standard, (i.p 4 mg/kg). After 30 minutes, repeated the experiment as done earlier noted the

fall of time of animals before and after test compounds and chlorpheniramine treatment respectively. The results are presented in Table-II and Graph-I.

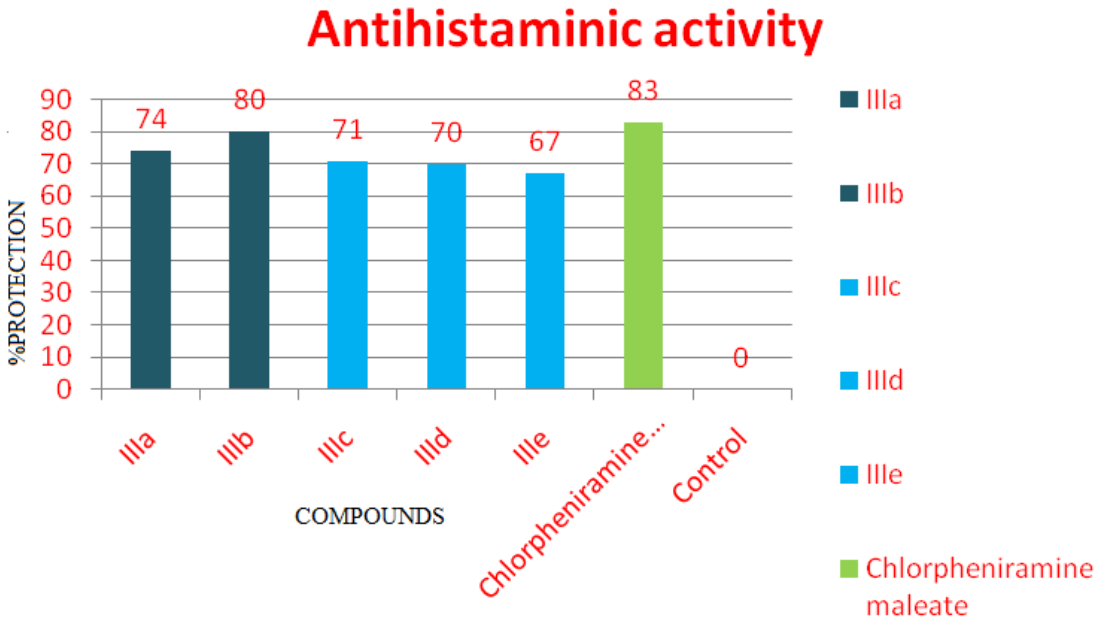
Table-2: Antihistaminic activity of 5-[2(3)-dialkylamino alkoxy] isatins and 5-[2(3)-dialkyl amino alkoxy] isatin -3-semicarbazones



Compound	Protected time	%Protection
IIIa	562	74
IIIb	720	80
IIIc	502	71
IIId	476	70
IIIe	446	67
Chlorpheniramine maleate	835	83
Control	145	0

Number of animals n=6

The compounds were tested at a dose of 100mg/kg (b.w)



Results and discussion

Physical data TLC, IR, ^{1}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 anticonvulsant and skeletal muscle relaxant activity. Out of all the tested compounds (IIIa, IIIb, IIIc, IVa, IVb and IVc), compounds IIIa ($R=CH_3$) and IIIb ($R=C_2H_5$) showed more protection against Histamine aerosol induced convulsions**.** IIIc, IIId exhibited moderate protective activity and IIIe showed mild protective 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 with 2-N,N di alkylamino alkyl halides.Evaluation of these compounds as antihistaminic activity revealed that the compounds (IIIa,IIIb) with a dimethyl and diethyl amino ethyl chain derivatives was found to be relatively superior in antihistaminic activity and other compounds(IIIc, IIId, IIIe) are next in the order of activity.

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