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Development of Novel Indole Molecules for the Screening of Anti-inflammatory Activity

K.Swathi* and M. Sarangapani
Medicinal Chemistry Laboratory, University College of Pharmaceutical Sciences, Kakatiya University, Wararagal-506009, A.P., India

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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 anti-inflammatory activity. Some of these compounds showed good anti-inflammatory activity compared with standard compounds.

Key Words: Synthesis, 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-diones, Antiinflamatory activity.

INTRODUCTION

Isatin is an endogenous compound isolated in 1998 and reported[1] to possess a wide range of central nervous system activities. Surendranath pandya[2] 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[3], antibacterial[4-6] and MAO inhibitory[7], antihistaminic[8]activity. It is evident from the literature survey that Isatin derivatives dialkylamino alkyl derivatives showing more promising anti-inflammatory activities. Keeping in view of these two molecular moieties viz., 5-hydroxy isatin and dialkylamino alkyl (Resembles diphenhydramine), 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 anti-inflammatory activity.

We are reporting in the present communication the synthesis and characterization of some new compounds: 5-[2 (3)-dialkylamino 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 anti-inflammatory activity and the structures of these compounds were identified by IR, NMR and Mass Spectrums.

***Corresponding author.**
K.Swathi
Medicinal Chemistry Laboratory,
University College of Pharmaceutical Sciences,
Kakatiya University,
Wararagal-506009, A.P., India

EXPERIMENTAL

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

Caragenan, Indomethacin, 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.

Preparation of 5-[2(3)-dialkylamino alkoxy] Indole 2,3 dione derivatives:

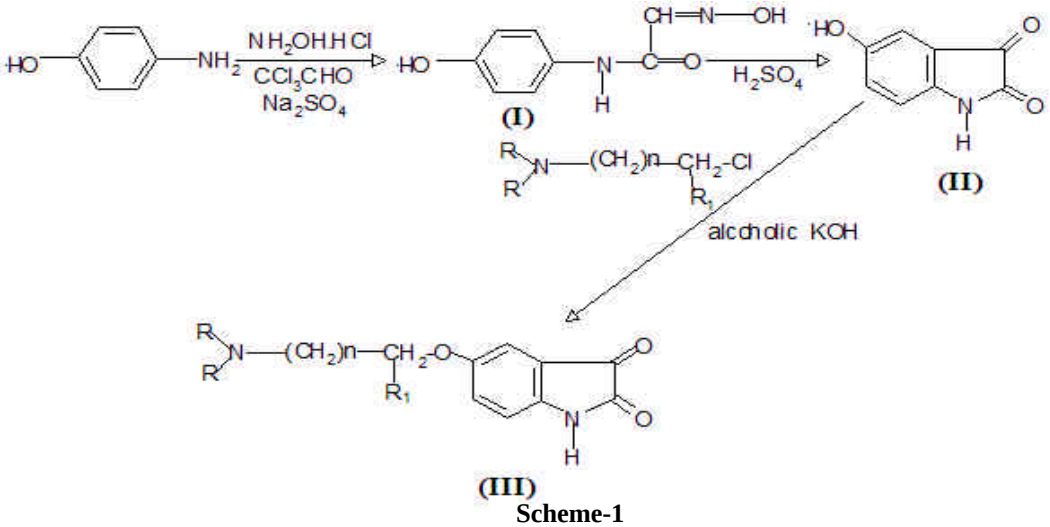
A mixture of 5-hydroxyisatin (0.01 moles) and dialkylamino alkylhalide

(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 recrystalisation 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:

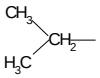
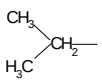
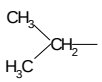
The compounds have been characterized by the spectral data IR, PMR and Mass.

IR spectrum (KBr) of compound **(III)** 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). Its PMR spectrum (DMSO, **III**) showed characteristic peaks at (δ ppm) 300 MHz 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).



Scheme-1

Table- 1: Characterization Data of 5 - [2(3) -Dialkylamino Alkoxy] Indole 2, 3-Diones

S.No	Compound	R	R_1	n	X	M.F	% 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	252
3	IIIc	CH_3	CH_3	1	O	$C_{13}H_{16}N_2O_3$	93%	<320	248
4	IIId	C_2H_5	CH_3	1	O	$C_{15}H_{20}N_2O_3$	85%	<320	276
5	IIIe		H	1	O	$C_{16}H_{22}N_2O_3$	81.8%	<320	290
6	IIIf	CH_3	H	2	O	$C_{13}H_{16}N_2O_3$	93%	<320	248
7	IIIg	C_2H_5	H	2	O	$C_{15}H_{20}N_2O_3$	75%	<320	276
8	IIIh		H	2	O	$C_{17}H_{24}N_2O_3$	74%	<320	304
9	IIIi	CH_3	H	0	O	$C_{11}H_{12}N_2O_3$	85%	<320	220
10	IIIj	C_2H_5	H	0	O	$C_{13}H_{16}N_2O_3$	90%	<320	238
11	IIIk		H	0	O	$C_{15}H_{22}N_2O_3$	75%	<320	276

Compound (**IIIa)** showed characteristic IR peaks at 3276(NH), 1651.96 (C=O), 1569.82 (Ar ,C=C), 1276(C-O-C), 1080(C-N), 2860(C-C), 807.93(Ar). Its PMR spectrum (DMSO, **IIIa**) showed characteristic peaks at (δ ppm) 300 MHz 10.36(s, 1H,-CONH), 7.21(d, H,Ar-H), 7.26(d, H,Ar-H), 7.01(s, H,Ar-H),3.2 (t,2H,O-CH_2) ,2.9 (t,2H,N-CH_2), 1.36 (s,6H,N-$(CH_3)_2$). Mass spectrum of compound **IIIa** showed molecular ion (M+) base peak at m/z 234 (100%).It also shows peak at m/z (72) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIb)** showed characteristic IR peaks at 3274(NH), 1681.53 (C=O), 1570.21 (Ar ,C=C), 1243(C-O-C), 1084(C-N), 2890(C-C), 845.51(Ar). Its PMR spectrum (DMSO, **IIIb**) showed characteristic peaks at (δ ppm) 300 MHz 10.25(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.99 (t,2H,O-CH_2) ,2.72 (t,2H,N-CH_2) , 1.24 (s,4H,N-$(CH_2$ -C)$_2$), 1.22 (s,6H,(N-C-$CH_3)_2$). Mass spectrum of compound **IIIb** showed molecular ion (M+) base peak at m/z 252 (100%).It also shows peak at m/z (90) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIc)** showed characteristic IR peaks at 3274(NH), 1651.96 (C=O), 1579.72(Ar ,C=C), 1266(C-O-C), 1095(C-N), 2898(C-C), 805.91(Ar). Its PMR spectrum (DMSO, **IIIc**) showed characteristic peaks at (δ ppm) 300 MHz 10.46(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),2.84 (m,H,O-CH) , 2.51 (d,3H, R_1=CH_3),2.48 (d,2H,N-CH_2), 1.25 (s,6H,N-$(CH_3)_2$).

Mass spectrum of compound **IIIc** showed molecular ion (M+) base peak at m/z 248 (100%).It also shows peak at m/z (86) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIId)** showed characteristic IR peaks at 3257(NH), 1679.64 (C=O), 1546.86 (Ar ,C=C), 1245(C-O-C), 1180(C-N), 2960(C-C), 812.71(Ar). Its PMR spectrum (DMSO, **IIId**) showed characteristic peaks at (δ ppm) 300 MHz 10.51(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),2.76 (m,2H,O-CH) , 2.45 (t,3H, R_1=CH_3), 2.48 (d,2H,N-CH_2), 1.24 (s,4H,N-(CH_2-C)$_2$), 1.22 (s,6H,(N-C-CH_3)$_2$). Mass spectrum of compound **IIId** showed molecular ion (M+) base peak at m/z 276 (100%). It also shows peak at m/z (114) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIe)** showed characteristic IR peaks at 3257(NH), 1689.46 (C=O), 1576.34 (Ar ,C=C), 1228(C-O-C), 1170(C-N), 2870(C-C), 814.53(Ar). Its PMR spectrum (DMSO, **IIIe**) showed characteristic peaks at (δ ppm) 300 MHz 10.26(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),2.96 (t,2H,O-CH_2) ,2.82 (t,2H,N-CH_2), 1.35 (s, 2H,N-$(CH)_2$) ,1.21 (d,12H,N-C -$(CH_3)_2$). Mass spectrum of compound **IIIe** showed molecular ion (M+) base peak at m/z 290 (100%).It also shows peak at m/z (128) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIf)** showed characteristic IR peaks at 3286(NH), 1651.96 (C=O), 1566.82 (Ar ,C=C), 1266(C-O-C), 1150(C-N), 2910(C-C), 808.93(Ar). Its PMR spectrum (DMSO, **IIIf**) showed characteristic peaks at (δ ppm) 300 MHz 10.46(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),3.2 (t,2H,O-CH_2) ,2.9 (t,2H,N-CH_2), 3.01(m,2H,C-CH_2-C), 1.36 (s,6H,N-$(CH_3)_2$). Mass spectrum of compound **IIIf** showed molecular ion (M+) base peak at m/z 248 (100%).It also shows peak at m/z (86) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIg)** showed characteristic IR peaks at 3274(NH), 1681.53 (C=O), 1570.21 (Ar ,C=C), 1243(C-O-C), 1210(C-N), 2885(C-C) 845.51(Ar). Its PMR spectrum (DMSO, **IIIg**) showed characteristic peaks at (δ ppm) 300 MHz 10.25(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.99 (t,2H,O-CH_2) , 3.04(m,2H,C-CH_2-C), 2.72 (t,2H,N-CH_2) ,1.23 (s,4H,N-(CH_2-C)$_2$), 1.21 (s,6H,(N-C-CH_3)$_2$). Mass spectrum of compound **IIIg** showed molecular ion (M+) base peak at m/z 276 (100%).It also shows peak at m/z (114) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIh)** showed characteristic IR peaks at 3257(NH), 1689.46 (C=O), 1576.34 (Ar,C=C), 1228(C-O-C), 1280(C-N), 2970(C-C) 814.53(Ar). Its PMR spectrum (DMSO, **IIIh**) showed characteristic peaks at (δ ppm) 300 MHz 10.26(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.96 (t,2H,O-CH_2) , 3.06(m,2H,C-CH_2-C),2.82 (t,2H,N-CH_2), 1.35 (s, 2H,N-$(CH)_2$) ,1.21 (d,12H,N-C -$(CH_3)_2$). Mass spectrum of compound **IIIh** showed molecular ion (M+) base peak at m/z 304 (100%).It also shows peak at m/z (142) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIi)** showed characteristic IR peaks at 3276(NH), 1651.96 (C=O), 1569.82 (Ar, C=C), 1276(C-O-C), 1089(C-N), 2865(C-C) 807.93(Ar). Its PMR spectrum (DMSO, **IIIi**) showed characteristic peaks at (δ ppm) 300 MHz 10.36(s, 1H,-CONH), 7.21(d, H,Ar-H), 7.26(d, H,Ar-H), 7.01(s, H,Ar-H) , 2.8 (s,2H,N-CH_2-O), 1.36 (s,6H,N-$(CH_3)_2$). Mass spectrum of compound **IIIi** showed molecular ion (M+) base peak at m/z 220 (100%).It also shows peak at m/z (58) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIj)** showed characteristic IR peaks at 3274(NH), 1681.53 (C=O), 1570.21. (Ar ,C=C), 1243(C-O-C), 1180(C-N), 2940(C-C), 845.51(Ar). Its PMR spectrum (DMSO, **IIIj**) showed characteristic peaks at (δ ppm) 300 MHz 10.25(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.78 (s,2H,N-CH_2-O)1.24 (s,4H,N-(CH_2-C)$_2$), 1.22 (s,6H,(N-C-CH_3)$_2$)

Mass spectrum of compound **IIIj** showed molecular ion (M+) base peak at m/z 238 (100%).It also shows peak at m/z (76) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIk)** showed characteristic IR peaks at 3257(NH), 1689.46 (C=O), 1576.34 (Ar ,C=C), 1228(C-O-C), 1165(C-N), 2970(C-C), 814.53(Ar). Its PMR spectrum (DMSO, **IIIk**) showed characteristic peaks at (δ ppm) 300 MHz 10.26(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.76 (s,2H,N-CH_2-O), 1.35 (s, 2H,N-$(CH)_2$) ,1.21 (d,12H,N-C -$(CH_3)_2$). Mass spectrum of compound **IIIk** showed molecular ion (M+) base peak at m/z 276 (100%).It also shows peak at m/z (114) may be due to the fragmentation of the alkyl chain from the molecule ion.

IN VIVO EXPERIMENTS

Anti-inflammatory activity

Carrageenan - induced rat paw edema method[9] was employed for evaluating the anti inflammatory activity of the synthesized compounds . Wister Albino rats of either sex weighing approx 200- 300 gm, were housed in clean polypropylene cages and kept under room temperature (25±2°C), and relative humidity 40-50% in a 12 h light-dark cycle. Food was withdrawn 12 h before and during experimental hours. In this study, the animals were divided into groups as shown in the Table-2. Acute inflammation was produced by sub plantar injection of 0.1ml of 1% suspension of Carrageenan in normal saline, in the right hind paw of the rats. After Intra peritoneal administration of the test compounds, the paw volume was measured Plethysmometrically at 1, 2, 3, and 4 h intervals. Indomethacin 5mg/kg in normal saline was used as standard drug.

Table 2: Antiinflammatory activity of 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-dione derivatives

Compound	1hr	% inhibition	2hr	% inhibition	3hr	% inhibition	4hr	% inhibition
IIIa	0.54	36.29	0.43	48.91	0.51	64.7	0.43	75.4
IIIb	0.54	35.6	0.51	47.9	0.48	62.9	0.48	74.3
IIIc	0.72	16.6	0.56	32.6	0.55	57.6	0.53	70.5
IIId	0.74	13.1	0.68	30.6	0.63	51.5	0.55	69.4
IIIe	0.76	11.7	0.70	28.5	0.63	51.5	0.55	68.4
IIIf	0.72	15.4	0.68	32.6	0.65	50.45	0.56	68.8
IIIg	0.63	22.5	0.58	37.9	0.56	54.9	0.45	72.1
IIIh	0.62	27.2	0.48	40.8	0.50	61.5	0.43	71.1
IIIi	0.67	20.1	0.53	34.7	0.53	58.2	0.46	71.4
IIIj	0.67	22	0.65	33.6	0.56	56.9	0.48	70.3
IIIk	0.67	24	0.63	35.7	0.58	55.3	0.51	70.6
Indomethacin	0.63	25.8	0.53	45.9	0.48	63.07	0.43	76.1
Control	0.85	-	0.98	-	1.3	-	1.8	-

RESULTS:

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 antiinflamatory activity. Among the compounds were subjected to antiinflamatory activity and it was observed that compounds **IIIa** and **IIIb** showed more promising activity **IIIg,IIIh,IIIi,IIIk,IIIj and IIIc** were found to be next in the order of reducing the duration of inflamation. **IIIc** and **IIId** compounds also exhibited moderatere protective activity against carrageenan induced inflamation.

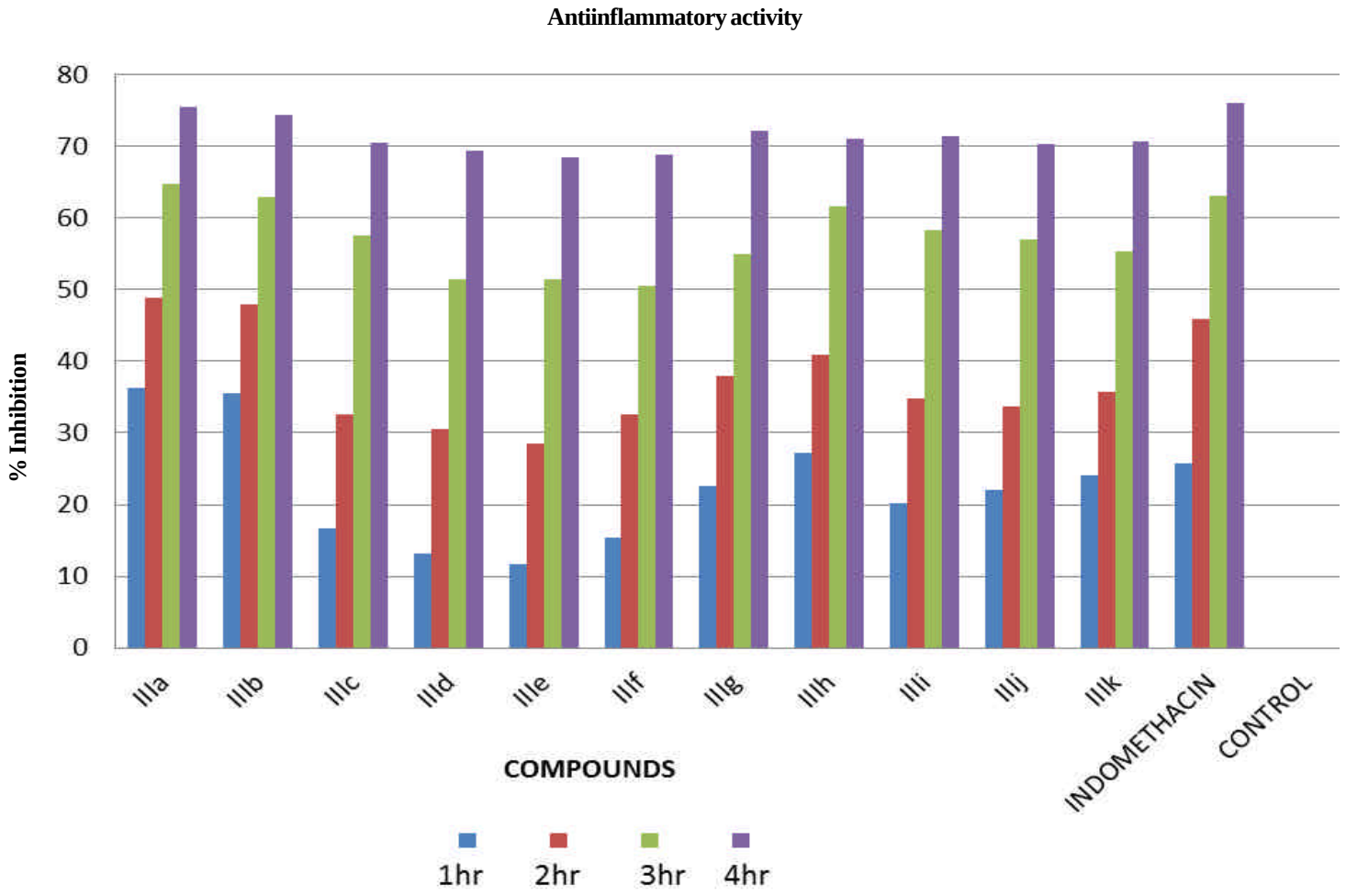


Figure1: Graph showing Antiinflammatory activity of 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-dione derivatives

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 antiinflamatory with a dimethyl (**IIIa)**,di ethyl(**IIIb**) amino ethyl chain derivatives was found to be relatively superior in antiinflamatory activity and other compounds(**IIIg,IIIh,IIIi,IIIk,IIIj and IIIc**) are next in the order of activity.

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