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Design and synthesis of novel Schiff bases of Isatins as antioxidants

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ABSTRACT

Isatin is a unique molecule possessing both amide and keto carbonyl groups. Apart from this, it has an active hydrogen atom attached to nitrogen (or oxygen) and an aromatic ring which should substitute at 5- and 7-positions. Derivatives of isatin are known to have cytotoxicity against human carcinoma cell lines. This compound therefore, has a potential to be used as a chemotherapeutic agent against cancer. This study was done to investigate the antioxidant activity of some novel isatin derivatives. All the new isatin derivatives employed in the investigation have been found to have antioxidant activity. All the compounds were tested at 20, 40,60,80,100 µg/ml concentrations and the results were compared with the standard drug (Ascorbic acid) at the same concentrations. Amongst them, none of the compounds were found to be less active than standard of ascorbic acid.

Keywords: Isatin, antioxidant activity, Ascorbic acid.

INTRODUCTION

Isatin and several of their derivatives have been generally associated with various biological and pharmacological properties. The synthesis of a large number of isatin derivatives have been described to obtain biologically potent compounds. In fact, an exhaustive literature survey reveals that isatins are potential synthons for building synthetically a variety of chemical systems known for their broader biological and / or pharmacological properties [1-5]. The presence of the indole nucleus found to have various pharmacological activities like antimicrobial, anti-oxidant, antiviral, anticonvulsant, anticancer activities etc. [6-24]

Therefore, keeping this in view as the main objective, the present project has been aimed to synthesize new isatins with other important aromatic systems and moieties by molecular conjunction, by adopting appropriate synthetic routes. Purification and characterization of all the new compounds including those of intermediates and finally evaluate the new compounds for their antioxidant activity by standard methods. [25-26]

EXPERIMENTATION

Scheme for the synthesis of new isatin derivatives

In view of the biological prominence of the mannich base of isatin and nitrogen mustards it is planned to synthesize new isatin nitrogen mustard derivatives containing the following molecular structure. (figure.1)

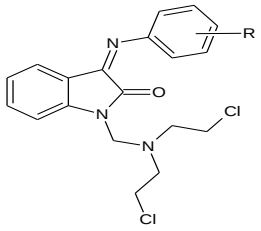


Fig.1.1{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)1,3-dihydro-2H-indole-2-one)

The compound has been synthesized as per the scheme given below.

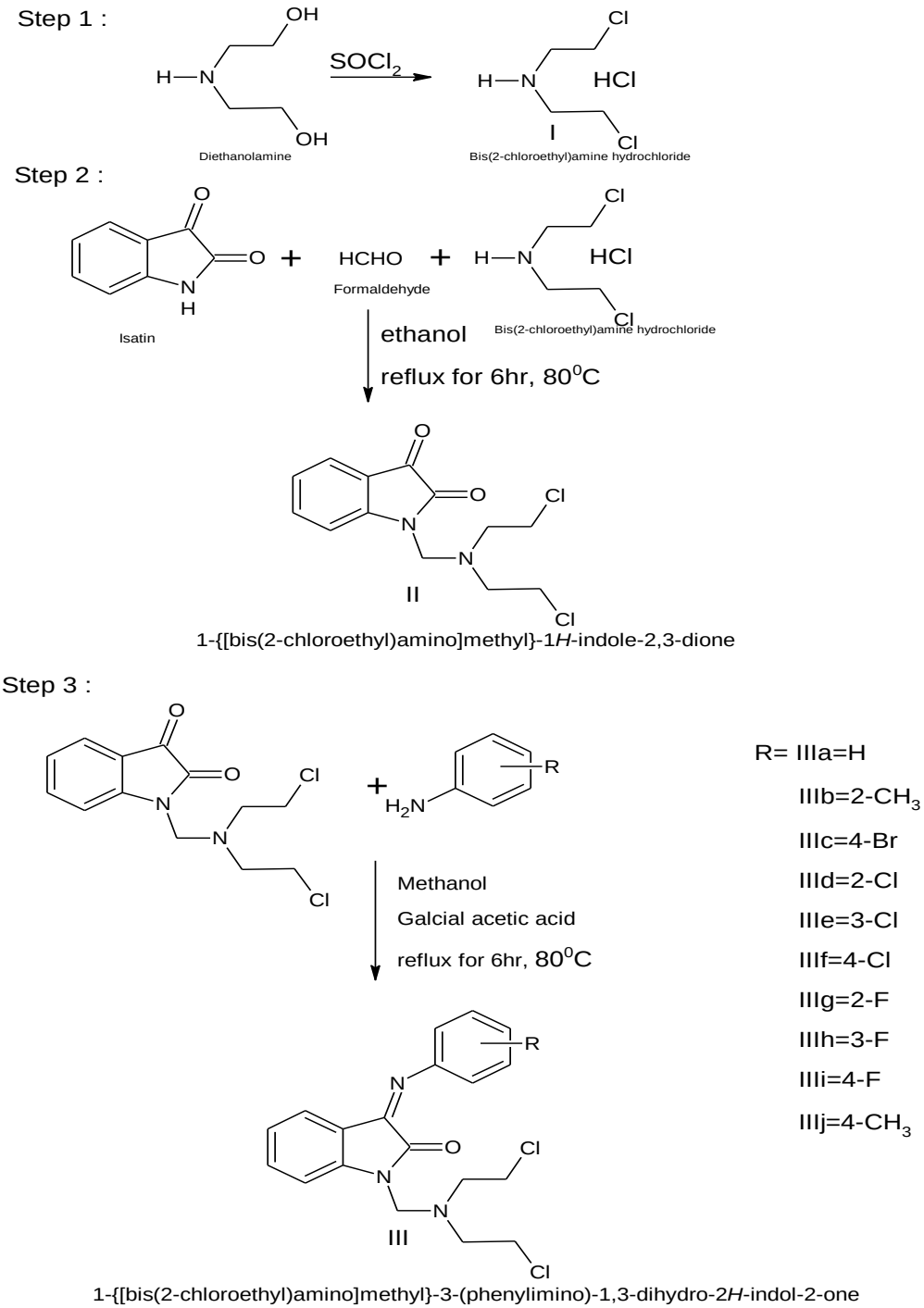


Figure.2. Scheme for synthesis of new Isatin derivatives

SYNTHESIS

Chemicals Required

Diethanolamine, Thionylchloride, Isatin, Formaldehyde, Ethanol, Aniline derivatives, Methanol, Sodium sulphate.

Synthesis of bis(2-chloroethyl)aminehydrochloride (I)

To the excess of Thionylchloride, Diethanolamine (3:1) was added and stirred for 30min at 0^0 C. The reaction mixture was heated slowly to evaporate excess Thionylchloride. White colour solid was obtained.

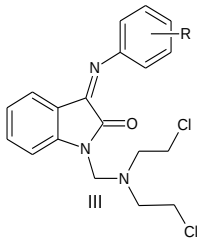
Synthesis of 1-{[bis(2-chloroethyl)amino]methyl}-1H-indole-2,3-dione(II)

The mannich condensation was done by the following procedure. A mixture of equimolar concentration of Isatin (0.010 moles; 1.47g), Formaldehyde (0.010 moles; 0.3g, 1 mL), Bis(2-chloroethyl)aminehydrochloride (0.010 moles; 1.42g) was refluxed in ethanol (50 mL) for 6hrs at 80^0 C. After filtering the filtrate was concentrated to one third its volume, dried over sodium sulfate. The residue was recrystallized from ethylacetate-petroleum ether gave pure material.

Synthesis of 1-{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)1,3-dihydro-2H-indole-2-one(III)

1-{[bis(2-chloroethyl)amino]methyl}-1H-indole-2,3-dione(II)(0.0005moles; 0.150g) was condenced with Aniline derivatives (0.0005 moles) in methanol (20mL) and trace amount of glacial aceticacid for about 8hrsat 80^0 Cto get respective1-{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)1,3-dihydro-2H-indole-2-one(III).(figure3) and the physical data for the synthesized compounds were reported in Table1.

PHYSICAL DATA FOR THE SYNTHESISED COMPOUNDS



1-{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)-1,3-dihydro-2*H*-indol-2-one

Figure 3. Structure of Synthesized Isatin derivatives

Table.1 Physical characterization of the synthesized compounds (IIIa-IIIj):

Compound	Substituents (R)	Mol.Formula	Colour	m.r (ºC)	Yield (%)	Mol.Wt
IIIa	H	$C_{19}H_{19}Cl_2N_3O$	Orange	280-285	70	376
IIIb	2-CH_3	$C_{20}H_{21}Cl_2N_3O$	Red	254-258	62	390
IIIc	4-Br	$C_{19}H_{18}BrCl_2N_3O$	Brown	272-276	65	455
IIId	2-Cl	$C_{19}H_{18}Cl_3N_3O$	Orange	238-240	55	410
IIIe	3-Cl	$C_{19}H_{18}Cl_3N_3O$	Orange	>300	67	410
IIIf	4-Cl	$C_{19}H_{18}Cl_3N_3O$	Yellow	268-273	70	410
IIIg	2-F	$C_{19}H_{18}Cl_2FN_3O$	Orange	201-203	77	394
IIIh	3-F	$C_{19}H_{18}Cl_2FN_3O$	Yellow	255-	73	394

				260		
IIIi	4-F	$C_{19}H_{18}Cl_2FN_3O$	Brown	>300	45	394
IIIj	4-CH_3	$C_{20}H_{21}Cl_2N_3O$	Orange	250-256	60	390

ANTIOXIDANT ACTIVITY

Antioxidant

An agent that prevents or inhibits oxidation. Antioxidants are substances that protect cells from the damaging effects of oxygen radicals, highly reactive chemicals that play a part in atherosclerosis, some forms of cancer and reperfusion injuries.

DPPH method

A simple method that has been developed to determine the antioxidant activity [25-26] of the drug utilizes the stable 2,2- diphenyl-1-picrylhydrazyl(DPPH) radical. The odd electron in the DPPH free radical gives a strong absorption maximum at 517nm and is purple in colour. The colour turns from purple to yellow as the molar absorptivity of the DPPH radical at 517nm reduces from 9660 to 1640 when the odd electron of DPPH radical becomes paired with hydrogen from a free radical scavenging antioxidant to form the reduced DPPH+H^+. The resulting decolourisation is stoichiometric with respect to the number of electrons captured. Antioxidant compounds may be water soluble, lipid soluble, insoluble or bound to cell walls. Hence extraction efficiency is an important factor in quantification of antioxidant activity of foods. Ascorbic acid (as the reference standard) and the sample are reacted with DPPH solution in methanol/water for 30mins at 35^0C in a test tube and the absorbance changes are measured at 517nm.

Preparation of standard solution

Ascorbic acid was used as standard for antioxidant activity. The weight equivalent to concentrations of 20, 40, 60, 80 and 100 µg/ml was weighed and dissolved in methanol.

Preparation of test solution

Stock solutions of samples were prepared by dissolving 10 mg of test sample in 9.5 ml of methanol and 0.5ml of DMSO to give concentration of 1000µg/ml. From the above stock solutions the concentrations of 20, 40, 60, 80 and 100 µg/ml were prepared by dissolving equivalent quantity in methanol.

Method

To 1 ml of 0.135 mM DPPH prepared in methanol was added 1.0 ml of test compounds ranging from 20-100 µg/ml. The reaction mixture was vortexed thoroughly and left in dark at room temperature for 30 min. The absorbance was measured colorimetry at 517 nm. The scavenging ability of the test compounds was calculated using the standard equation.

The IC_{50} values were given in table. The amount of DPPH radical was calculated following this equation:

% inhibition of DPPH = $[A_0 - A_s]/A_0 \times 100$

Where A_0 is the absorbance of control and A_s is the absorbance of sample. Standard drug is Ascorbic acid.

RESULTS AND DISCUSSION

In this study, we have synthesized a new series isatin derivatives. Yields of all synthesized compounds were good. The structure of isatin has been the subject of numerous investigations.

The presence of amine group at positon 1 in isatin and free amine group of bis(2-chloroethylamine and formaldehye reacts to give mannich base,1{[bis(2-chloroethyl)amino]methyl}-1H-indole-2,3-dione(II). The presence of carbonyl group at position 3 in 1-{[bis(2-chloroethyl)amino]methyl}-1H-indole-2,3-dione(II)and free amino group of the aniline derivatives furnishes reaction site at position 3 for condensation reaction. The title compounds were synthesized by condensation reactions of II and aniline derivatives to give **1-{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)1,3-dihydro-2H-indole-2-one(III)**. (figure3.)

All the above reactions are briefly summarized in scheme.All the derivatives were subjected to antioxidant activity (DPPH method). All the new isatin derivatives employed in the investigation have been found to have antioxidant activity. All the compounds were tested at 20, 40,60,80,100µg/ml concentrations and the results were compared with the standard drug (Ascorbic acid) at the same concentrations. Table 2 shows the antioxidant activity

data of**1-{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)1,3-dihydro-2H-indole-2-one.**

All the derivatives were having antioxidant activity.Figure.4 shows bar graph between microgram per ml concentration of compounds required for 50% inhibition of standard and the test compounds. Amongst them, none of the compounds were found to be active than standard (ascorbic acid). The compound IIIi was found to be more active than all the compounds tested.The compound IIIa was found to be least active than all the compounds tested.

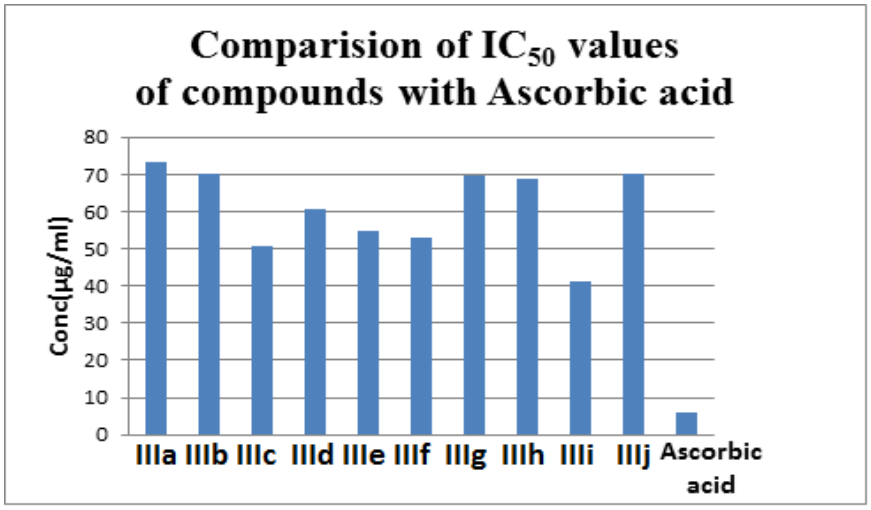


Figure.4. Comparisons of Anti oxidant activity of Synthesized compounds and Ascorbic acid standard drug

Table 2.Antioxidant activity of 1{[bis(2-chloroethyl)amino]methyl}-3-(phenylimino)1,3-dihydro-2H-indole-2-one(III a-j):

S.NO	Compound	R	IC_{50} (µg/ml)
1	IIIa	H	73.36
2	IIIb	2-CH_3	70.01
3	IIIc	4-Br	50.61
4	IIId	2-Cl	60.75
5	IIIe	3-Cl	54.80
6	IIIf	4-Cl	52.88
7	IIIg	2-F	69.91
8	IIIh	3-F	68.77
9	IIIi	4-F	41.22
10	IIIj	4-CH_3	70.16
11	standard	Ascorbic acid	5.84

CONCLUSION

Ten title compounds were synthesized (IIIa-j) and were analyzed by physical and spectral data (FT-IR, NMR, Mass).Yield of the compounds synthesized by above method was good. The synthesized derivatives gave satisfactory results for various evaluations like TLC, melting point, spectral data, and antioxidant activities. All the derivatives were screened for antioxidant activity and the results were compared with the standard drug Ascorbic acid. All the series of the compounds showed antioxidant activity. Compound **IIIi**(R=4-F) was found to be more effective antioxidant. Therefore, this study would be a fruitful matrix for the development of novel class of antioxidant and cytotoxic agents.

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