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Research Article

SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITIES OF OXADIAZOLE DERIVATIVE

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ABSTRACT

Isatin chemically known as 1H-indole-2,3-dione. It is a unique molecule possessing both amide and keto carbonyl groups. Isatin and its derivatives having several pharmacological actions. In the present study some Isatins derivatives have been synthesized. The chemical structures of the synthesized compounds were confirmed by using spectral and elemental analysis methods and developed some pharmacological evaluations.

KEY WORDS: *Isatins, Pharmacological actions, Oxadiazole derivative.*

INTRODUCTION

Isatin chemically known as 1H-indole-2,3-dione. It was discovered by Erdmann [1] and Laurent [2] in 1841, independently as a product from oxidation of indigo by nitric and chromic acids. In nature, isatin is found in plants of the genus *Isatin* [3], in *Calanthe discolor* [4] and in *Couroupita guianensis* [5]. Isatin (**I**) 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 was substituted at 5- and 7-positions. It exists in a tautomeric form (II) and these functional characteristics play an important role in governing the various reactions of the molecule.

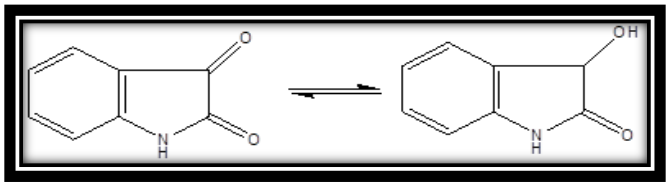

Fig. 1: Chemical Synthesis of Isatin

Isatins were synthesized by different methods: Some examples are

(I). The Sandmeyer Methodology: The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin It consists of reaction of aniline with chloral hydrate and hydroxylamine HCl in aqueous sodium sulfate to form an iso-nitrosoacetanilide, which after isolation, when treated with H_2SO_4, furnishes isatin.

(II). The Stolle Procedure: In this method, anilines react with oxalyl chloride to form an intermediate chloro-oxalylanilide which can be cyclized in the presence of a Lewis acid, usually aluminium chloride or $BF_3.Et_2O$, although $TiCl_4$ has also been used to give the corresponding isatin.

(III). The Martinet Isatin Synthesis: The Martinet procedure for the synthesis of indole-2,3-diones involves the reaction of an amino aromatic compound and either an oxomalonate ester or its hydrate in the presence of an acid to yield a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative which after oxidative decarboxylation yields the respective isatin.

Isatin and several of their derivatives have been generally associated with various biological and pharmacological properties such as antibacterial [6-8], antifungal [9-11], antiprotozoal [12, 13], antiviral [14-16], anthelmintic [17, 18] and CNS activities [19, 20].

MATERIALS AND METHODS

Experimental Procedure:

I. Synthesis of 1*H* benzo[e]indole 2, 3-dione:

A. Synthesis of isonitrosoacetanilide (II) Procedure:

In a 5 lit. R.B. flask were placed chloral hydrate (0.54 mol) and 1200 ml of water. To this solution, were then added crystallized sodium sulphate (1300 g) followed by a solution of an α-naphthylamine (0.5 mol) (I) in 300 ml of water and concentrated hydrochloric acid (0.52 mol). Finally, a solution of hydroxylamine HCl (1.58 mol) in 500 ml of water was added. The content of flask was heated over a wire-gauge by a mecker burner, so that vigorous boiling begins in about 45 minutes. After 1-2 minutes of vigorous boiling the reaction was complete. During the heating period itself the crystals of isonitroacetanilide started separating out. On cooling under the current of water the entire product was solidified. It was filtered under suction, air dried and purified by recrystallization from suitable solvent (s).

B. Synthesis of 1H benzo[e]indole 2, 3-dione Procedure:

Sulphuric acid (600 g, d. 1.84, 326 ml) was warmed to 50° C in a one-litre R.B. flask fitted with an efficient mechanical stirrer and to this, finely powdered and isonitrosoacetanilide (0.46 mol) (II) was added at such a rate so as to maintain the temperature between 60 and 70° C, but not higher. External cooling was applied at this stage so that the reaction could be carried but more rapidly. After the addition of isonitroso compound was completed, the temperature of the solution was raised to 80° C and maintained at that temperature for 10 min, to complete the reaction. Then, the reaction mixture was cooled to room

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temperature and poured on crushed ice (2.5 kg). After standing for about half-an-hour, the product separated was filtered, washed several times with small portions of cold water and dried. Purification of the compound was effected by recrystallization from methanol.

A. Synthesis of Semicarbazone – General Procedure:

5gm of semicarbazide HCl & 4.5gm of anhydrous sodium acetate was added to 25ml of water, heated gently until a clear solution was obtained. A solution of 5ml of appropriate aromatic aldehydes in 25ml of rectified spirit was added and warmed. This mixture was heated gently on a water bath for 15min. This semicarbazone was rapidly crystallized out in the solution still being heated. It was washed thoroughly with water and dried.

B. Synthesis of 1, 3, 4-Oxadiazole –General Procedure:

A solution of appropriate aromaticaldehyde semicarbazone (1 gm) and anhydrous sodium acetate was prepared. 10 ml of Br_2 was mixed with 40 ml of acetic acid. The above solution was added drop wise into the slurry with constant stirring until a yellow colour was produced. Then the stirring was continued for about 15 min. and cooled. Crushed ice was added to the above solution, filtered and dried.

Synthesis of 3 (1', 3', 4'-oxadiazol-2'-yl-imino)-1H-benzo[e]indol-2-one 1- derivatives:

Equimolar quantity (0.01 mol) of isatin, 1, 3, 4-oxadiazole (0.01 mol) and few drops of glacial acetic acid (0.01 mol) were dissolved in 10 ml of warm methanol and refluxed for 4 hrs. After standing for approximately 24 hr at room temperature, the products were separated by filtration, vacuum dried and recrystallized from warm methanol. The synthesized compounds have been characterized by the physical & spectral data.

The overall reaction involving the formation of isatin derivatives are shown in Table. 1.

Table No. 1: Synthesis of 3 (1', 3', 4'-oxadiazol-2'-yl-imino)-1H-benzo[e]indol-2-one 1- derivatives

S. No.	MOLECULAR FORMULA	MELTING POINT (0 C)	PERCENTAGE YIELD
1	R=H,R1=C6H3-(OCH)3	125-127	45
2	R=C6H5, R1=CH3	147-149	66
3	R=C6H5, R1=C2H5	160-162	58
4	R=C2H5, R1=C2H5	124-125	50
5	R=H, R1= C6H4-Br	126-128	56
6	R=H, R1=C6H4-OH	140-142	68
7	R=H,R1=C6H3N(CH3)2	158-160	82
8	R=H, R1=C6H3(OH)3	149-154	52

Spectral analysis:

3-(5'-phenyl-1', 3', 4'-oxadiazol-2'-ylimino)-1H-benzo[e]indol-2-one:

IR (KBr, cm^{-1}): 3166 (NH), 1576, 1597 (C=N), 1529 (C=C), 1368 (C-N), 1034 (C-O-C), 1625 (C=O), 1564 (Ar- C=C); ***^{1}H-NMR (δ ppm):*** 8.7 (1H, s, NH), 7.23-7.69 (5H, m, C- 4, 5, 7, 8,9), 7.17-7.21 (4H, m, C- 6, 3'', 4'' and 5''), 6.53-6.58 (2H, S, C-2''' and C-6''').

3-(5'-(4''-chlorophenyl)-1',3',4'-oxadiazol-2'-ylimino)-1H-benzo[e] indol-2-one:

IR (KBr, cm^{-1}): 3401 (NH), 1500, 1602 (C=N), 1579 (C=C), 1358 (C-N), 1056 (C-O-C), 1642 (C=O), 1564 (Ar- C=C), 855 (C-Cl); ***^{1}H-NMR (δ ppm):*** 8.4 (1H, s, NH), 6.84-7.53 (6H, m, C- 4, 5, 6, 7, 8,9), 7.60 (2H, s, C-2'' and C-6''), 7.75 (2H, s, C-3'', and C-5'').

3-(5'-styryl-1', 3',4'-oxadiazol-2'-ylimino)-1H-benzo[e]indol-2-one:

IR (KBr, cm^{-1}): 3250 (NH), 1590, 1598 (C=N), 1660 (C=C), 1358 (C-N), 1056 (C-O-C), 1680 (C=O), 1564 (Ar- C=C), 3020 (=C-H); ***^{1}H-NMR (δ ppm):*** 8.1 (1H, s, NH), 6.94-7.43 (6H, m, C- 4, 5, 6, 7, 8,9), 5.4 (1H, s, 1''), 6.4 (1H, s, 2''), 7.30 (2H, s, C-2''' and C-6'''), 7.31 (2H, s, C-3''', and C-5'''), 7.21(1H, C-4'')

Biological Activities:

Antibacterial Activity:

The 3-(substuited hydrazeno)-1H-benzo indol-2(3H)-one derivatives were studied for antibacterial activity [21, 22] on microorganisms by using cup plate method.

The test organisms were subculture using nutrient agar medium. The tubes containing sterilized medium were inoculated with respective bacterial strain. After incubation at 37 ^{0}C+ 1^{0}C for 18 hrs, they were stored in the refrigerator. Into each sterilized petriplate (20 cm diameter), 125 ml of molten nutrient agar medium was poured which was already inoculated with the respective strain bacteria (5ml of inoculum to 250 ml of nutrient agar medium) aseptically. The plates were left at room temperature aseptically to allow the solidification.

Each test compound (100 & 150 mg) was dissolved in dimethyl sulfoxide (5 ml, AnalR grade) at a concentration of 1000 µg/ml. Ciprofloxacin solution was also prepared at a concentration of 1000 µg/ml in dimethyl sulfoxide. The solutions of each test compound, control and reference standard (0.1ml and 0.15 ml) was added separately in the cups and the plates were kept undisturbed for at least 2 hours in the refrigerator to allow the diffusion of the solution properly into nutrient agar medium. Petri dishes were subsequently incubated at 37 + 1^{0}C for 24 hrs. After incubation, the diameter of zone of inhibition surrounding each of the cups was measured with the help of an antibiotic zone reader. All the experiments were carried out in triplicate. The results are presented in Table-II.

Table No. 2: Antibacterial activity of 3-(substuited hydrazono)-1H-benzo indol-2(3H)-one derivatives

S.NO	COMPOUND NO	CONCENTRATION (µg/ml)	ZONE OF INHIBITION (mm)			
			B. subtilis	*K. pneumonia*	*P. vulgaris*	*S. aureus*
1	A1	100	10	10	13	12
		150	10	10	14	11
2	A2	100	11	13	12	11
		150	12	12	12	12
3	A3	100	11	12	12	14
		150	13	11	13	13
4	A4	100	14	13	12	13
		150	14	13	12	12
5	A5	100	10	10	11	16
		150	11	10	11	18

NOTE: - Average zone diameter of triplicates in mm.

RESULTS AND DISCUSSION

All synthesized compounds were tested for their *Invitro* antibacterial activity by using the agar diffusion method. It has been observed that all the tested compounds showed mild to moderate activity against the bacteria. Whereas compound A1 -1, A2-2, A3-3 and A5 were found to be most promising antibacterial activity among the series of compounds and compound A5 shows highest activity at 150µg/ml.

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