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Research Article

SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITIES OF THIADIAZOLE DERIVATIVE

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ABSTRACT

Isatin (indole-2, 3-dione) is an endogenous compound, widely distributed in mammalian tissues and body fluids. 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.

KEYWORDS: *Isatin, Antifungal, Thiadiazole Derivative.*

INTRODUCTION

It is evident from literature that isatin derivatives are known to be associated with broad spectrum of biological activity like antibacterial [1], anti-inflammatory [2], analgesic [3], anti-viral [4], anti-fungal [5], anti-tubercular [6], anti-depressant [7]. Isatin hydrazones have been reported to possess anticonvulsant [7] activity also. In view of these facts and as a continuation of our work in the laboratory, prompted us to synthesize some new isatin derivates (Thiadiazole). All the synthesized compounds were screened for their *in vitro* anti-fungal activity [8].

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 50^0 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 70^0 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 80^0 C and maintained at that temperature for 10 min, to complete the reaction. Then, the reaction mixture was cooled to room 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.

C. 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.

D. 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.

Synthesis of 1, 3, 4-Thiadiazole (VII):

a. Synthesis of Thiosemicarbazone (VI) – General Procedure:

5 gm of thiosemicarbazide HCl & 4.5 gm of anhydrous sodium acetate was added to 25 ml of water, heated gently until a clear solution was obtained. A solution of 5 ml of appropriate aromatic aldehydes in 25 ml of rectified spirit was added and warmed. This mixture was heated gently on a water bath for 15 min. This thiosemicarbazone was

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rapidly crystallized out in the solution still being heated. It was washed thoroughly with water and dried.

b. Synthesis of 1, 3, 4-Thiadiazole (VII):–General Procedure:

A solution of appropriate aromatic aldehydes, thiosemicarbazone (1gm) and anhydrous sodium acetate was prepared. 10 ml of Br_2 was mixed with 40ml 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 15mins and cooled. Add crushed ice to the above solution, filter and dried.

III. Synthesis of 3-(1',3',4'-thiadiazol-2'yl-imino)-1H-benzo[e]indol-2-one (VIII):

Equimolar quantity (0.01 mol) of isatin (III), 1, 3, 4-Thiadiazole (VII) (0.01 mol) and few drops of glacial acetic acid (0.01 mol) were dissolved in 10 ml of warm methanol and refluxed for 4hrs. 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 1*H* benzo[e]indole 2, 3-dione

S.NO	NAME OF THE STRUCTURE	MELTING POINT (0 C)	PERCENTAGE YIELD
1	phenyl	297±2^{0}C	32.17
2	4''-chlorophenyl	305±2^{0}C	0.64
3	Styryl	234±2^{0}C	28.55
4	4''-nitrophenyl	230±2^{0}C	45
5	dimethylamino)phenyl	248±2^{0}C	37
6	4''-fluorophenyl	225±2^{0}C	31.42
7	3''-methoxyphenyl	215±2^{0}C	11.86
8	3'',4''-dimethoxyphenyl 3	276±2^{0}C	17.38

Spectral Analysis:

3-(5'-phenyl-1',3',4'-thiadiazol-2'yl-imino)-1H-benzo[e]indol-2-one:

IR (KBr, cm^{-1}): 3235 (NH), 1603 (C=N), 1475 (C=C), 1230 (C-N), 748 (C-S), 1709 (C= O); ***^{1}H-NMR (δ ppm):*** 8.01 (1H, s, NH), 7.12-7.75 (6H, m, C-4, 5, 6, 7, 8, 9), 7.55 (5H, s, C-2'' and 6''), 7.31 (3H, m, C-3'', 4''and 5''); ***^{13}C-NMR (δ ppm):*** 169.59 (C-2), 158.31 (C-3), 128.26 (C-3a), 118.63 (C-4a), 123.79 (C-4), 112.19 (C-5 and 6), 116.65 (C-7), 114.39 (C-7a), 129.43 (C-8), 132.11 (C-9), 131.50 (C-9a), 148.06 (C-2˙), 146.06 (C-5˙), 144.01 (C-1¨), 128.01 (C-2¨ and 6¨), 129.01 (C-3¨ and 5¨), 124.01 (C-4¨).

3-(5'-(4''-chlorophenyl)-1',3',4'-thiadiazol-2'yl-imino)-1H-benzo[e] indol-2-one:

IR (KBr, cm^{-1}): 3172 (NH), 1620 (C=N), 1537 (C=C), 1358 (C-N), 753 (C-S), 1675 (C=O), 918 (C-Cl); ***^{1}H-NMR (δ ppm):*** 7.92 (1H, s, NH), 7.12-7.67 (6H, m, C- 4, 5, 6, 7, 8, 9), 7.49 (2H, s, C-2'' and 6''), 7.28 (3H, m, C-3'' and 5'').

3-(5'-styryl-1',3',4'-thiadiazol-2'yl-imino)-1H-benzo[e]indol-2-one:

IR (KBr, cm^{-1}): 3400 (NH), 1641 (C=N), 15794(C=C), 1348 (C-N), 655 (C-S), 1628 (C= O); ***^{1}H-NMR (δ ppm):*** 7.85 (1H, s, NH), 7.05-7.72 (6H, m, C- 4, 5, 6, 7, 8,9), 7.29 (2H, s, C-2''' and 6'''), 7.20 (2H, m, C-3''',5'''), 7.16 (1H, m, C-4''), 5.62 (1H, s, C-1''), 6.61 (1H, s, C-2'').

Antibacterial activity:

From the above results it is evident that all the isatins synthesized, showed antibacterial activity(9-10) at both 100 µg and150 µg levels but the zones of inhibition not higher than the standard. Among the compounds tested, NT-14 was found to be more potent against *B.subtilis* and *E.coli* at both the dose levels tested. This compound was also active against *S.aureus* and *P.vulgaris*. Compounds NT-05, NT-11 and NT-12 also showed antimicrobial activity (11) at the dose levels tested.

The results also indicate, in general, a simple aryl group in the place of substituted aryl group contributes favorably to the inhibitory activity. Compounds with more number of electron releasing or electron with drawing substituents on the aromatic ring at different positions can be synthesized to draw meaningful conclusions with respect to the influence of electronic effects on the antimicrobial activity, as the present study could not establish clearly the influence of such groups.

However, a close look at the substituents on the aryl moiety of the isatins synthesized in the present study and their influence on antimicrobial activity, it is evident that a dimethylamino group present at the *para* position and a 3,4,5-trimethoxy substitution on the phenyl ring contributed to an increase in the antimicrobial activity.

Antibacterial activity:

Since thiadiazoles & isatins have been reported to possess antimicrobial activity, the new isatins prepared in the present work were tested for antimicrobial activity.

The same protocols and procedures that have been followed in Chapter-II are used to study antibacterial activity of newly synthesized isatin compounds **(1-15)**. The results are presented in **Table 2.**

Antifungal Activity:

The same protocols and procedures that have been followed in Chapter-II are used to study antifungal activity of thiadiazoles. The results are presented in **Table 3.**

Table No. 2: Antibacterial activity of Isatin derivatives (compounds NT-1 to NT-15)

Compound	Zone of inhibition (in mm)							
	B.subtilis		*S.aureus*		*E.coli*		*P.vulgaris*	
	100 µg	**150 µg**	**100 µg**	**150 µg**	**100µg**	**150 µg**	**100 µg**	**150 µg**
Standard	20	24	20	22	19	21	16	**18**
Control	-	-	-	-	-	-	-	**-**
NT-1	06	09	08	09	07	10	09	**11**
NT-2	13	16	12	15	11	14	12	**14**
NT-3	09	11	07	09	08	11	06	**09**
NT-4	12	15	11	14	10	13	12	**14**
NT-5	12	14	11	14	12	15	09	**10**
NT-6	14	16	11	12	13	16	12	**14**
NT-7	10	13	09	11	08	11	07	**09**
NT-8	12	14	09	11	10	12	11	**13**

NT-9	11	12	13	15	10	12	09	**12**
NT-10	11	13	10	12	08	10	09	**11**
NT-11	12	14	11	14	10	12	09	**10**
NT-12	10	12	09	12	10	12	09	**10**
NT-13	09	12	08	12	09	11	08	**11**
NT-14	16	18	14	16	12	14	13	**15**
NT-15	**13**	**16**	**12**	**15**	**11**	**14**	**12**	**14**

Note: "–" No zone of inhibition

Table No. 3: Antifungal activity of Isatin derivatives (compounds NO-1 to NO-15)

Compound	Zone of inhibition (in mm)			
	A.niger		*P.crysogenum*	
	100 µg	150 µg	100 µg	150 µg
Standard	20	23	20	22
Control	-	-	-	-
NT-1	06	09	08	10
NT-2	15	19	15	18
NT-3	08	11	10	14
NT-4	14	19	14	16
NT-5	12	16	13	17
NT-6	14	18	13	17
NT-7	11	14	12	15
NT-8	13	16	15	17
NT-9	10	15	13	15
NT-10	10	14	12	15
NT-11	13	18	14	17
NT-12	11	13	12	16
NT-13	06	08	10	13
NT-14	16	19	16	20
NT-15	16	20	14	18

Note: "– "No zone of inhibition

RESULT AND DISCUSSION

Thiadiazoles & isatins have been reported to possess antimicrobial activity and antifungal activity; the new isatins prepared in the present work were tested for antimicrobial activity. Compounds NT-05, NT-11 and NT-12 also showed better antimicrobial activity and NT-02, NT-05 and NT-14 showed better antifungal activity.

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