CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1034541

Available online at: http://www.iajps.com Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME NOVEL 3-HYDRAZONE-1H-BENZOINDOL-2(3H)-ONES

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Abstract

A novel analogue of 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives were synthesized by condensation of 1H-benzoindole-2, 3-dione with various hydrazine derivatives in the presence of methanol. The synthesized compounds were characterized by IR, 1HNMR spectroscopy and newly synthesized compounds evaluated for their antimicrobial studies.

Keywords: *Hydrazine, Methanol, Spectroscopy, Antimicrobial activity.*

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*Please cite this article in press as R. Vasanthi et al , **Synthesis, Characterization and Antimicrobial Evaluation of Some Novel 3-Hydrazone-1H-Benzoindol-2(3H)-Ones**, Indo Am. J. P. Sci, 2017; 4(10).*

INTRODUCTION:

Heterocyclic compounds play an important role in medicinal chemistry and drug synthesis. A large number of heterocyclic compound are essential to life various compounds such as alkaloids, antibiotics, essential amino acids, the vitamins, hemoglobin, the hormones and a large number of synthetic drugs and dyes contain heterocyclic ring systems by heterocycles. Isatin (1H-indole-2, 3-dione) belonging to a class of heterocyclic compound and it was first discovered by Erdmann[1] and Laurent [2] in 1841, independently as a product from oxidation of indigo by nitric and chromic acids. Isatin and several of their derivatives have been generally associated with various biological and pharmacological properties such as antibacterial [3-5], antifungal [6,7], antiviral [8,9], anti-HIV [10,11],CNS [12-14] and cytotoxic activities [15]. Keeping this in view as the main objective, the present project has been to synthesize 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives by condensation of 1H-benzoindole-2, 3-dione with various hydrazine derivatives. The newly synthesized compounds were characterized by spectroscopic methods and screened for their biological activity.

MATERIALS AND METHOD:

All the chemicals used in synthesis of new isatins were obtained from standard commercial sources. Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems were indicated at appropriate places. All the melting points were determined in open capillaries using Boitus melting point apparatus, expressed in ^{o}C and were uncorrected. The 1HNMR spectra of the compounds were recorded on Bruker spect, 400 MHZ NMR spectrophotometer using TMS as an internal standard and the values were expressed in δ ppm.

EXPERIMENTAL PROCEDURE

1. Synthesis of 1H-benzoindole-2, 3-dione (III):

a. Synthesis of 2-(hydroxyimino)-N-(naphthalene-4-yl)acetamide(II) – General Procedure:

In a 5 lit. R.B. flask were placed chloralhydrate (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 alpha-Naphthyl amine (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 contents of flask were heated about 45 minutes. After 1-2 minutes of vigorous boiling the reaction was complete. It was filtered under suction, air dried and purified by recrystallization from methanol.

b. Synthesis of 1H-benzoindole-2, 3-dione (III) – General Proceudre:

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 naphthylisonitrosoacetanilide (0,46 mol)(II) was added at such a rate so as to maintain the temperature between 60 and 70^{0} C. Then, the reaction mixture was cooled to room temperature and poured on crushed ice. 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.

2. Synthesis of 3-Hydrazone-1H-benzoindol-2(3H)-one (IV) [16]:

Equimolar quantity (0.004 mol) of Naphthylisatin (III) and different hydrazine derivatives were dissolved in 10 ml of warm methanol and refluxed for 30-90 min. After standing for approximately 24hr at room temperature, the products were separated by filteration, vaccum dried and recrystallized from warm methanol. The synthesis of title compounds could be achieved by the Scheme – I.

ANTIMICROBIAL ACTIVITY [17]

The new series of 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives (IVa-e) for antibacterial and antifungal activity.

Antibacterial activity:

The antibacterial activity of title compounds was assayed against four different strains of bacteria by agar diffusion method. Solution of test compounds were prepared by dissolving 10 mg each in dimethylsulfoxide (DMSO,10ml).A reference standard for Gram-positive and Gram-negative bacteria was made by dissolving accurately weighed quantities of Ampicillin in DMSO (10 µg/ml).

The nutrient agar medium was sterilized by autoclaving at 121 ^{o}C (15 lb/sq.inch) for 15 min. Petri-plates, tubes and flasks plugged in cotton were sterilized in hot-air oven at 160 ^{o}C for an hour. Into each sterilized Petri-plate (10 cm diameter), about 27 ml of molten nutrient agar medium inoculated with the respective strain of bacteria (50 µl of inoculum into each plate) was transferred aseptically. In each plate, three discs of 6 mm diameter were made with a sterile borer. These solutions at concentrations (200 µg/ml, 150 µg/ml, 100 µg/ml) was added to respective disc aseptically and labeled accordingly. The plates were kept undisturbed for 1 hour at room

temperature to allow the diffusion of the solution properly in the nutrient agar medium. After incubation of the plates at 37 ± 1 ºC for 24 hours, the diameter of zone inhibition surrounding each of discs was measured with the help of an antibiotic zone reader. All the experiments were carried out in triplicate. Simultaneously, controls were maintained employing 0.1 ml of DMSO to observe the solvent effects and the results were represented in Table. No.1

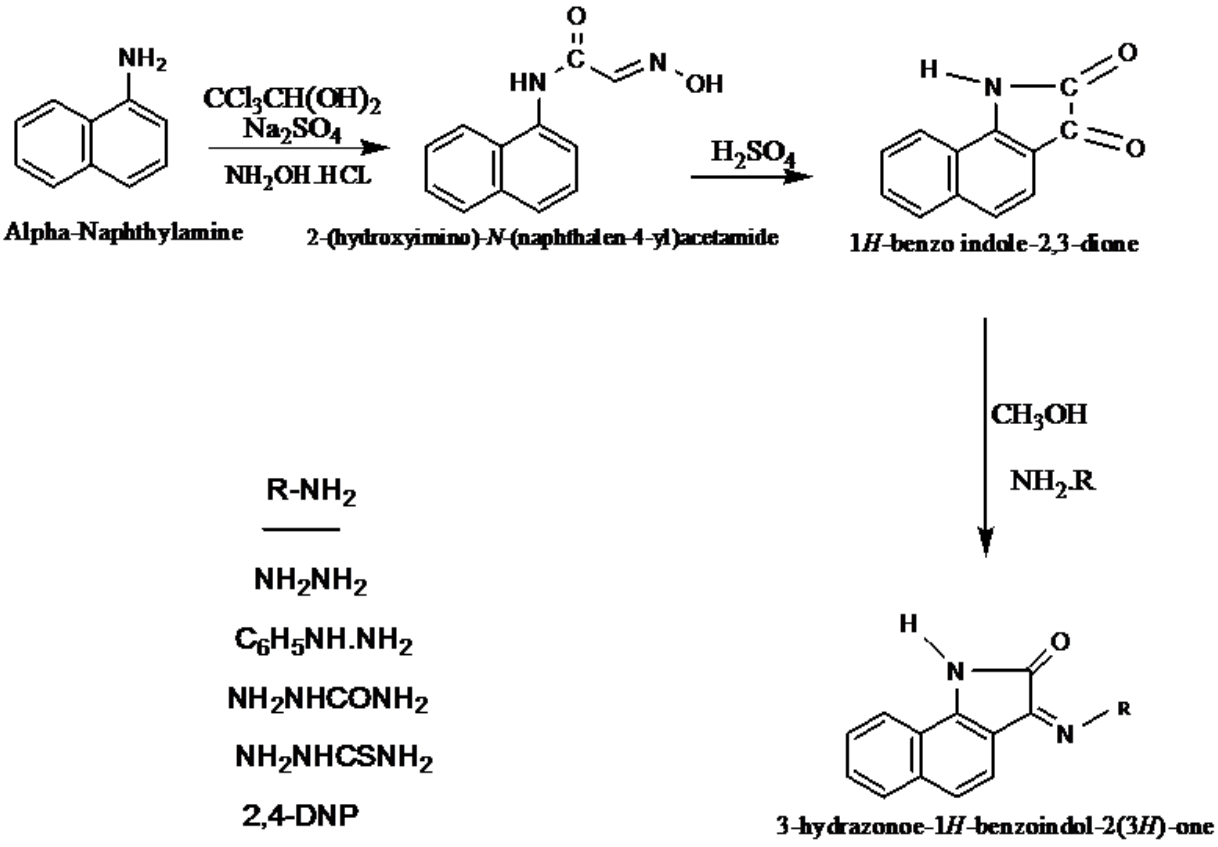
Antifungal activity:

The antifungal screening of synthesized compounds against two strains of organism ***Candida albicans and Yeast*** were used.

The solution of test compound was prepared by a similar procedure described under the antibacterial activity. A reference standard solution of Clotrimazole (10 µg/ml) was prepared by dissolving 10 mg of Clotrimazole in 10 ml of dimethylsulfoxide (DMSO).

The SDA medium was sterilized by autoclaving at 12 (15 lb/sq.inch) for 15 min. the Petri-plates were sterilized in hot-air oven at 160º C for an hour. Into each sterilized Petri-plate about 27 ml of molten SDA medium was added. Incubated at 30 ºC for 2 days. After 2 days of incubation, the medium free of contaminations was spreaded with 50 µl of 48 hours culturing. After solidification of the cups of 6 mm diameter were made in each plate with sterile borer. Accurately 50 µl of 200 µg, 150 µg, 100 µg concentrations of test solution was transferred to the respective Petri-plates aseptically and labeled accordingly. The reference standard 50µl was also added to the discs in each plate. Then the plates were incubated at 25 ºC for 48 hours at inverted position. The diameter of zone of inhibition was read with help of an antibiotic zone reader. The experiment was performed in triplicate and the results were represented in Table. No.2

SCHEME-I



RESULTS AND DISCUSSION

Physical data of 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives (IV)

S.No.	Compd	Substituents R-NH_2	Mol. Formula	Mol. Weight	M.P.(^{0}C)	Yield (%)
1.	Iva	-$NH.NH_2$	32	1.33g	140-144	67
2.	IVb	$C_6H_5NH.NH_2$	108	1.36g	146-148	54
3.	IVc	$NH_2NHCONH_2$	75	1.16g	128-132	61
4.	IVd	$NH_2NHCSNH_2$	91	1.63g	120-124	48
5.	IVe	2,4-DNP	198	2.56g	152-154	56

Spectral data of 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives (IV)

S.No.	Compound	IR-(cm^{-1})	NMR- δ (ppm)
1.	Iva	N-H= 3370, C=O-1643, C=C-1596, C=N-1490, N-N-967.	7.37-7.68 (m, 6H, Ar-H), 6.08 (s, 1H, NH pyrrolidine), 6.35-6.47 (m, 3H, NH).
2.	IVb	N-H= 3370, C=O-1643, C=C-1596, C=N-1490, Ar C-N-1330, N-N-967	7.35-8.24 (m, 11H, Ar-H) 6.52 (s, 1H, NH pyrrolidine) 6.22-6.31 (m, 2H, NH)
3.	IVc	- N-H= 3370, C=O-1643, C=C-1596, C=N-1490, N-N-967	7.46-7.88 (m, 6H, Ar-H) 6.47 (s, 1H, NH pyrrolidine) 6.26-6.44 (m, 4H, NH)
4.	IVd	- N-H= 3370, C=O-1643, C=C-1596, C=N-1490, C=S-1335, N-N-967	7.29-7.38 (m, 6H, Ar-H) 6.40 (s, 1H, NH pyrrolidine) 6.31-6.45 (m, 4H, NH)
5.	IVe	-N-H= 3370, C=O-1643, C=C-1596, NO_2=1556, N-N-967	7.27-8.35 (m, 9H, Ar-H), 6.45 (s, 1H, NH pyrrolidine), 6.64 - 6.72 (m, 2H, NH).

Antibacterial activity:

The antibacterial activity of new 3-Hydrazone-1H-benzoindol-2(3H)-one derivative was screened against 4 different strains of bacteria by agar diffusion method.

Table 1: Antibacterial activity of 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives at different sub concentrations.

			Zone of inhibition (in mm)			
S. No	Compound No	Conc in µg/ml	B. subtilis	S. aureus	E.coli	P.vulgaris
1	IVa	100	8	10	8	9
		150	10	12	10	10
		200	13	13	11	12
2	IVb	100	9	8	7	8
		150	11	10	9	9
		200	12	11	10	11
3	IVc	100	11	10	9	8
		150	13	12	12	11
		200	16	14	14	13
4	IVd	100	7	8	8	9
		150	12	10	10	11
		200	14	12	11	14
5	IVe	100	10	12	11	13
		150	14	13	12	13
		200	16	15	15	14
6	AMPICILLIN	10	18	16	17	19

Antifungal activity:

The antifungal activity of 3-Hydrazone-1H-benzoindol-2(3H)-one derivative has been screened against 2 strains of fungi by agar diffusion method.

Table 2: Antifungal activity of 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives (IV) at different concentrations.

			Zone of inhibition (in mm)	
S. No	**Compound No**	**Conc in µg/ml**	**Candida albicans**	**Yeast**
1	IVa	100	9	9
		150	12	10
		200	13	12
2	IVb	100	8	8
		150	9	10
		200	11	12
3	IVc	100	9	8
		150	10	11
		200	12	13
4	IVd	100	9	8
		150	10	10
		200	12	11
5	IVe	100	10	8
		150	11	10
		200	12	11
6	FLUCANAZOLE	10	15	16

CONCLUSION:

The new substituted 3-Hydrazone-1H-benzoindol-2(3H)-one derivatives were synthesized by condensation of 1H-benzoindole-2, 3-dione with various hydrazine derivatives and synthesized compounds were characterized by physical and spectral analysis. All the compounds were screened for antibacterial & antifungal activity at the concentration of 100 µg/ml, 150 µg/ml & 200 µg/ml. The compounds of this series have been relatively active against bacterial and fungal strains. The compounds IVc and IVe showed significant action among the series of compound against bacteria and fungi. This promising result gave us scope for further work in this area.

ACKNOWLEDGEMENT

The authors are thankful to Nalanda College of Pharmacy, Nalgonda for providing necessary facilities to carry out the present research work.

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