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SYNTHESIS AND ANTHELMINTIC ACTIVITY OF ISATIN DERIVATIVES AGAINST *PHERITIMA POSTHUMA*

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ABSTRACT

Some new Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino) benzene sulphonamide) has been synthesized from isatin & different p-substitute aniline. In the next step, I (a-h) on treatment with isatin, sulfanilamide and reflux with glacial acetic acid Synthesis of carbamimidoyl - 3 – (2-oxo-indalin-3 – yl- indene amino) benzene sulphonamide (a-h) In the last step, which on mannich reaction with piperidine and formaldehyde gave(N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino) benzene sulphonamide) (a-h) under microwave irradiation at a power of 140 watts. MW irradiation led to higher yields in much less time than that by conventional method. The newly synthesized compounds were characterized on the basis of elimental analysis, IR, H NMR, and mass spectra. All the synthesized isatin derivatives have been investigated for their anthelmintic activity.

Key Words: Microwave, conventional, Synthesis, Isatin, Anthelmintic activity.

INTRODUCTION

Generation of different heterocyclic derivative has created a boom in the field of medicinal chemistry. Different heterocyclic compounds have shown various biological activities such as antibacterial, antifungal, antiviral, analgesic, anti-inflammatory, Anthelmintic activity and thus can be used as a lead in the discovery of new drug molecule. An important aspect of medicinal chemistry is to establish a relationship between chemical structure and biological activities. Hundreds of thousands of new drugs are prepared annually throughout the word. Many of them are entered in pharmacological screening to determine whether they have useful biological activity or not. This process of random screening resulting in the identification of new lead compounds. The most serious problem in designing of more efficacious drugs is how to minimize its toxicity and maximize its pharmacological action (Whehui Wu *et al*., 2003) & Zongru Guo, 2006).

Isatin (1H-indole-2, 3-Dione) is a synthetically versatile substrate, where it can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis. Isatin has also been found in mammalian tissues, and its function as a modulator of biochemical

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processes has been the subject of several discussions. The advances in the use of isatin for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported in this review and in the accompanying supplementary information (Siritron Simoom *et al*., 2006).

It is evident from literature that isatin derivatives are known to be associated with broad spectrum of biological activity like anti-inflammatory, antibacterial, antifungal analgesic, Anthelmintic activity. In view of these facts and as a continuation of our work in the laboratory, prompted us to synthesize some new 5-mercapto-2-(3-(4-fluorophenyl imino)-1-methyl indole-2-one)-1, 3, 4-oxadiazole. All the synthesized compounds were screened for their in vitro Anthelmintic activity was tested.

a. Synthesis of Isatins

Isatin (1H-indole-2, 3-dione, Figure 1) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids.

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. Three reviews have been published regarding the chemistry of this compound: the first by Sumpter, in 1954, a second by Popp in 1975 and the third on the utility of isatin as a precursor for the synthesis of other heterocyclic compounds3. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives.

These properties are more fully detailed in the supplementary material. In nature, isatin is found in plants of the genus Isatis, in Calanthe discolor LINDL. and in Couroupita guianensis Aubl, and has also been found as a component of the secretion from the parotid gland of Bufo frogs, and in humans as it is a metabolic derivative ofadrenaline8. Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant Melochia Tomentosa as well as from fungi: 6-(3'-methylbuten-2yl) isatin was isolated from Streptomyces albus and 5-(3'-methylbuten-2'-yl) isatin from Chaetomium globosum. Isatin has also been found to be a component of coal tar (Xuesen Fan and Yongmin Zang, 2003).

b. Helminths

The World Health Organization estimates that a staggering two billion people harbour parasitic worm infections. Parasitic worms also infect livestock and crops, affecting food production with a resultant economic impact. Despite this prevalence of parasitic infections, the research on the anthelmintic drug is sparse. Helminths have complex life-cycles, special knowledge of which is required for the treatment of the infections caused by them (Bennett PN and Brown MJ, 2000). The present paper reports the Synthesis and Anthelmintic activity of Isatin Derivatives.

RESULT AND DISCUSSION

Chemistry

(N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino) benzene sulphonamide) has been synthesized from isatin & different p-substitute aniline. In the next step, I (a-h) on treatment with isatin, sulfanilamide and reflux with glacial acetic acid Synthesis of carbamimidoyl - 3 – (2-oxo-indalin-3 – yl- indene amino) benzene sulphonamide (a-h) In the last step, which on mannich reaction with piperidine and formaldehyde gave(N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino) benzene sulphonamide) (a-h) under microwave irradiation at a power of 140 watts. The product recrystalised with ethanol.

Materials and methods

All starting materials were from different manufactured company like (sd.fine chemicals, SDFCL, Lobachem etc.) And all the materials used without further purification all reactions were monitored by thin- layer-chromatography using TLC sheet coated with silica gel GF254 spots were visualized with UV light.

Scheme of Synthesis

Experimental protocols

a. Chemistry

Reagents and chemicals were from sd.fine chemicals, SDFCL, Lobachem of highest purity available, and were used without further purification. All the synthesized 3 phenyl iodole derivatives produced and purified in laboratory as described earlier. Melting points are recorded in open capillary one ended tubes and are uncorrected. The IR spectra (KBr) were recorded on a Shimadzu FTIR-8300, spectrophotometer. The 1H-NMR spectra were recorded on a Bruker Advance-400 MHz spectrometer.

***b. Synthesis of carbamimidoyl** - 3 – (2-oxo-indalin-3 – yl-indene amino) benzene sulphonamide*

Equimolar quantity of 0.01 moles of Substituted isatin and sulfanilamide are dissolved in 40 ml of ethanol. Than 2ml glacial acetic acid is added and refluxed for 8-12 hrs.The

content is poured on crushed ice.The crystalline product was collected by filtration, dried and recrystallised (result of slurry Schiff base).

***c. Synthesis of (N-carbamimidoyl** 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino) benzene sulphonamide)*

Slurry consist of 1.505 gm of Schiff base containing the acidic amino group of Isatin, 5 ml THF and 2 ml 37% HCHO, mix.To this, add piperidine 0.425 gm dropwise with cooling and shaking. And Stand at room temperature for one hour with occasional shaking. Than Warm on steam bath for 15 minute and Cool the content then mannich ppt. Obtain. The Precipitate Recrystalise with petroleum ether.

Py .a. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-fluro) benzene sulphonamide) Yield 63%, mp 192-194 ^{0}C, IR (KBr) v max in cm^{-1} 1670(C=O), 1236(C-F), 1592(C=N), (C-H), 1592 1600(C=C).^{1}H-NMR (CH; 7.76, 7.81, 7.26, 7.22), Solubility-DMSO, H_2O.Rf-0.713.

Py.b. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-chloro) benzene sulphonamide). Yield 56.5%, mp 202-205 ^{0}C, IR (KBr) v max in cm^{-1} 1732(C=O), 1588 (C=N), 2945 (C-H), 1597(C=C) 722 (C-Cl); H-NMR (CH; 7.81, 7.76, 7.50, 7.22), solubility- DMSO, $CHCl_3$. Rf-0.652.

Py. c. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-bromo) benzene sulphonamide). Yield 54.9%, mp 204-206 ^{0}C, IR (KBr) v max in cm^{-1} -2565(S-H), 715 (C-S), 3450 (N-N), 1655 (C=O) 585 (C-Br); H-NMR (CH; 7.86, 7.81, 7.21, 7.23), solubility-DMSO, water. Rf -0.712.

Py. d. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-hydroxy) benzene sulphonamide). Yield 60.5%, mp 207-209 ^{0}C, IR (KBr) v max in cm^{-1} 3415 (N=N), 3300 (N-H), 1678(C=O), 2876(C-H) 1529 (C-OH); ^{1}H-NMR (CH; 7.86, 7.50, 6.99, 7.81), solubility- DMSO,H_2O,$CHCl_3$. Rf 0.743.

Py. e. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-methyl) benzene sulphonamide). Yield 57%, mp 207-209 ^{0}C, IR (KBr) v max in cm^{-1} 2890(C-H), 1622(C=N), 1336 (C-N) 2590(S-H), 3081 (C-CH_3); ^{1}H-NMR (7.81, 7.23, 7.22), Solubility-DMSO,H_2O, Rf-o.743.

Py. f. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-methoxy) benzene sulphonamide) Yield 60%, mp 199-202 ^{0}C, IR (KBr) v max in cm^{-1} 2820(C-H), 1728(>C=O), 1336 (C-N) 2586(S-H) 2873(C-OCH_3); ^{1}H-NMR (7.21, 7.50, 7.22), Solubility-DMSO,H_2O, Rf-0.712.

Py. g. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-nitro) benzene sulphonamide) Yield 57.1%, mp 203-205 ^{0}C, IR (KBr) v max in cm^{-1} 1732(C=O), 1634 (C=N), 2945 (C-H), 1597(C=C) 1345 (C-NO_2); ^{1}H-NMR (CH; 7.81, 7.76, 7.86, 7.23), solubility- DMSO, $CHCl_3$. Rf-0.612.

Py.h. Synthesis of (N-carbamimidoyl 1-4-(2-oxo-1-(piperidine-1-ylmethyl) indolin-3-ylidineamino-5-amino benzene sulphonamide) Yield 61.5%, mp 209-211 ^{0}C, IR (KBr) v max in cm^{-1} -2565(S-H), 715 (C-S), 3450 (N-N), 1655 (C=O) 1581 (C-NH_2); ^{1}H-NMR (CH; 7.86, 7.81, 7.21, 7.23), solubility-DMSO, water. Rf -0.702.

Anthelmintic activity

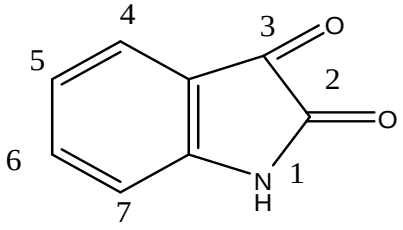
The anthelmintic activity was performed according to the method of Ghosh et al. (Ghosh *et al*., 2005) on adult Indian earthworm *Pheritima posthuma* as it has anatomical and physiological resemblance with the intestinal roundworm parasites of human beings. The eighteen Indian earthworms (approximately equal size) were divided into a group of three consisting of six earthworms in each group. The earthworms were released into 50 ml of desired formulation (Girme *et al*., 2006; Dash *et al*., 2002).

Standard: Piperazine citrate (10 mg/ ml)

Test: Isatin derivatives SKa,b,c,d,e,f,g,h (10 mg/ ml).

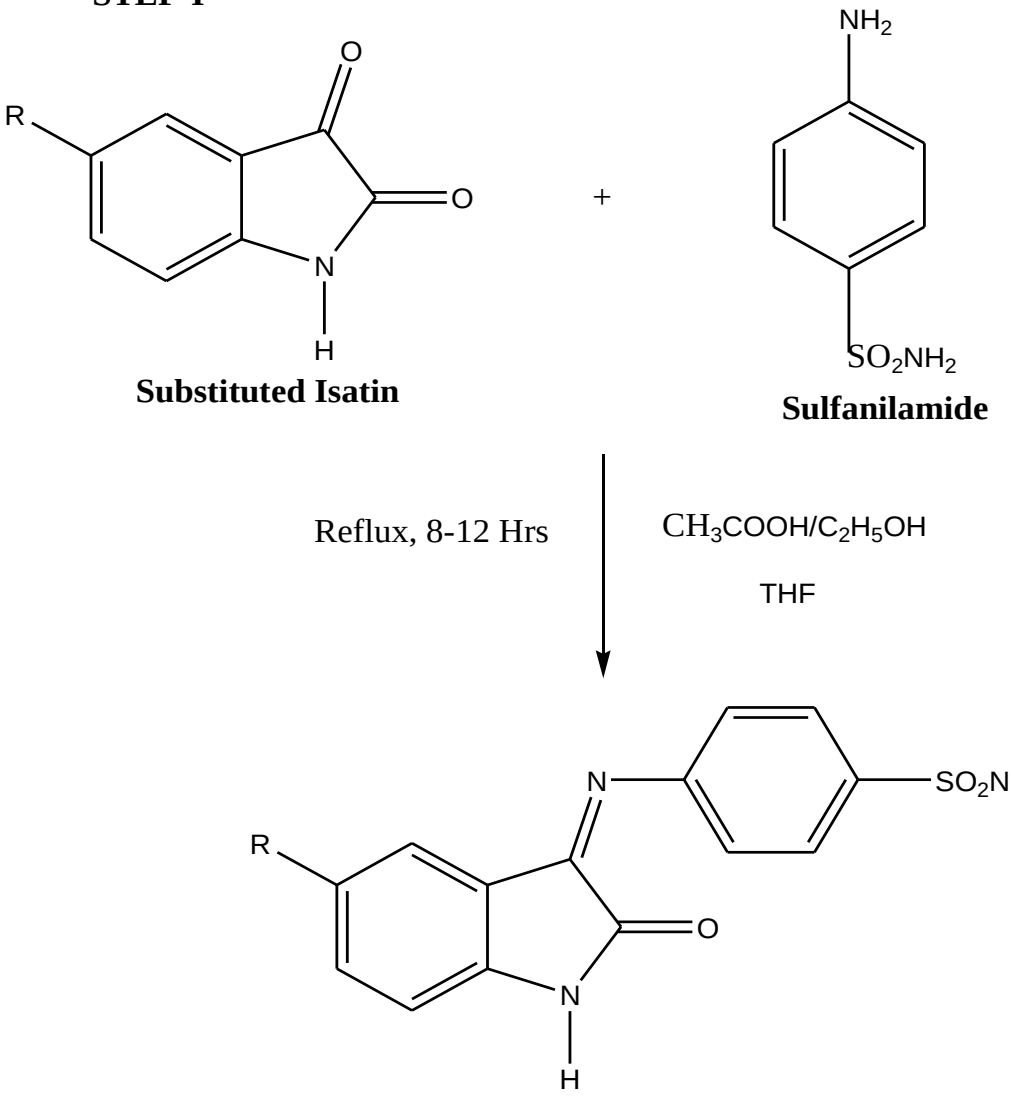
Observations were made and the time taken to paralyse or cause the death of individual worms was recorded. Paralysis was said to occur when the worms did not receive even normal saline. Death was concluded when the worms were seen to lose their motility followed with fading away of their body colour. Results are shown in Table-1.

Figure 1. Structure of Isatin



Scheme of Synthesis

STEP-I



Substituted Isatin **Sulfanilamide**

Carbamimidoyl-3-(2-oxoindolin-3-ylidine amino) benzene Sulfanamide

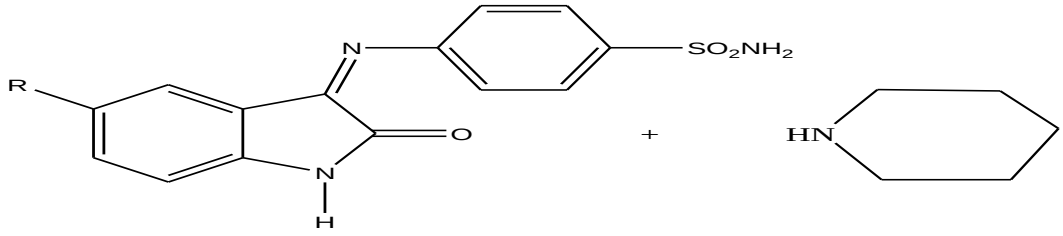
Here,

CH_3COOH - Acetic Acid

C_2H_5OH - Ethanol

THF -Tetra Hydro Furan

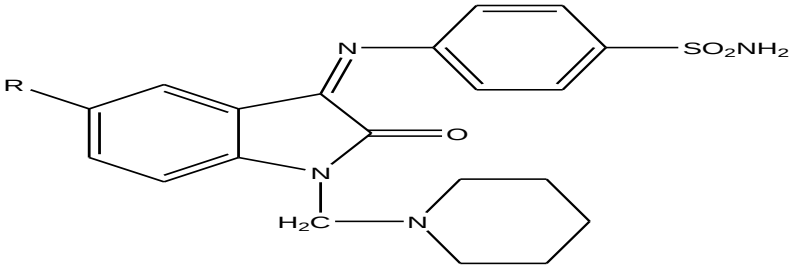
STEP II



Carbamimidoyl-3-(2-oxoindolin-3-yl -idine amino) benzene Sulfanamide

Piperidine

THF HCHO



MANNICHBASE

(N-Carbamimidoyl-4-(2-oxo-1-(piperidine -1-ylmethyl) indolin-3-ylidine amino) benzene Sulfanamide)

Here.

THF - Tetra Hydro Furan

HCHO - Formaldehyde

.

Table 1. Anthelmintic activity of isatin derivatives

Compound	Time taken for paralysis(min)	Time taken for death of worms (min)
SKa 10 mg/ ml	10.28±1.5	56.10±2.6
SKb 10 mg/ ml	16.14±2.62	30.39±3.24
SKc 10 mg/ ml	72.59±1.67	125.15±2.29
SKd 10 mg/ ml	59.26±3.5	225.45±2.47
SKe 10 mg/ ml	38.22±2.8	85.49±1.58
SKf 10 mg/ ml	30.14±3.17	62.28±3.28
SKg 10 mg /ml	20.32±2.2	62.15±3.7
SKh 10 mg/ ml	12.45±1.45	54.24±2.42
Piperazine citrate 10 mg/ ml	9.45±1.25	21.56±1.23

*Values are expressed as mean ± SEM (n=5), *p<0.001 denotes significance with respect to the control group using one way ANOVA followed by Dunnet's test.*

CONCLUSION

In conclusion, we have synthesized some Isatin derivatives (Py a-h) and evaluated these compounds for their Anthelmintic activities. The simple Isatin derivatives Py c, Py e, Py f, Py h were concluded as most potent derivatives in all the cases.

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