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An Endogenous Heterocyclic Compound Isatin.

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ABSTRACT

Isatin, also called as 1H-Indole-2, 3-Dione is a compound which is endogenous in nature having eight carbon atoms. It is versatile in nature and distributed in tissues and body fluids. Isatin is a naturally occurring heterocyclic class of compound with an indole ring and two oxo groups in its ring system. Isatin is a naturally occurring compound, but was synthesized by Erdmann and Laurent in 1840 before it was found in nature. It is a useful scaffold which undergoes a variety of chemical transformations, but however its structure is relatively simple. In this article is a review of some methods of synthesis and physical and chemical properties isatin. There is also a description about its various activities like antiviral, anti-inflammatory, anticonvulsant, CNS-MAO inhibition, anxiogenic and antitumor activities, antimicrobial, antitubercular, inhibition of glucose and amino acid uptake. Diverse activities of Isatin include fibrinolytic, muscle relaxant, immunosuppressant, anti-thrombotic activity and antiallergic.It also acts as an inhibitor of various protein kinase families, mainly that of tyrosine kinase receptors and serine/threonine specific protein kinase such as the cycline dependent kinases which is an effect of its indole ring.

Keywords: Isatin, structural activity relationship, Anti-inflammatory, Antitubercular, CNS-MAO inhibition.

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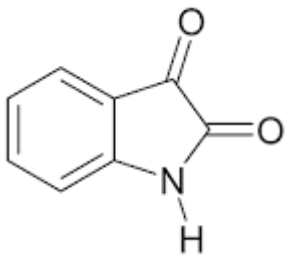
INTRODUCTION

Isatin is a chemical compound with a heterocyclic indole ring with a molecular formula $C_8H_5O_2N$.It is an eight membered ring consisting of 1 nitrogen atom,8 carbon atoms,2 oxygen atoms and 5 double bonds. Isatin is a naturally occurring compound, but was synthesized by Erdmann and Laurent in 1841[1] before it was found in nature. Naturally it is found in plants of *isatis* genus and the species *Melochia tomentosa* Aubl, *Couroupita guianensis* and *Boronella koniamboensis,* egg masses of Australian mollusc *Dicathais orbita* and in the parotid gland secretions of *Bufo* frog [2-5].



PHYSICAL PROPERTIES

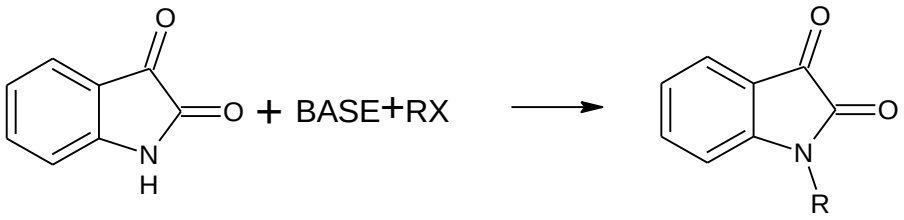
Isatin occurs in nature as an orange solid and has a molecular weight of 147.13g/mol [6]. It has a melting point of 193-195^{0}C and 202-203^{0}C.It is readily soluble in polar organic solvents such as methanol, acetone, acetonitrile, DMSO, DMF and ethyl acetate [7], partially soluble in CH_2Cl_2, $CHCl_3$, slightly soluble in water and not soluble in non-polar organic solvents such as hexane, toluene, benzene.

CHEMICAL PROPERTIES

Isatin undergoes N-Alkylation, N-Arylation, N-Acylation, N-Sulphonation, Monohalogenation, Chlorination, Oxidation, Reduction, Pfitzinger reaction, Nitration and Benzylation.

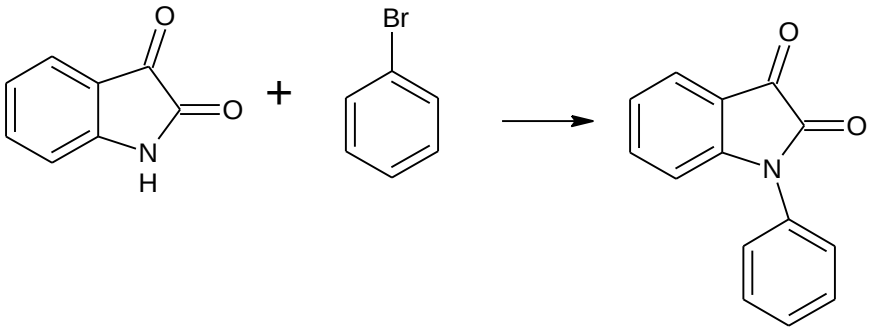
N-Alkylation

N- Alkyl isatin is prepared by reacting sodium salt with sulphates or alkyl halides [8].



N-Arylation

N-Arylisatin is prepared from reaction with triphenyl bismuth actetate $(Ph_3Bi(OAc)_2$ and copper oxide (CuO) under inert atmosphere or from arylbromide and copper oxide [9].



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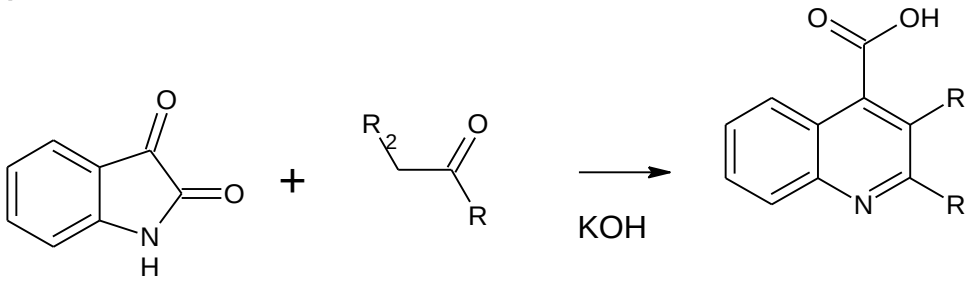
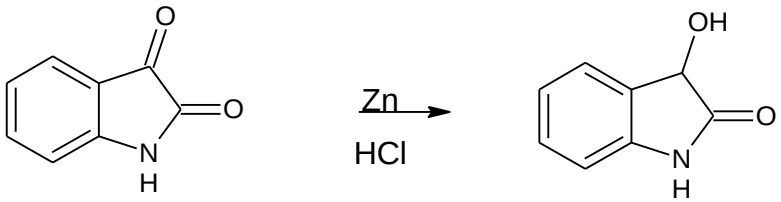
Pfitzinger reaction

Isatin reacted with a carbonyl compound in presence of a base will give substituted quinoline-4-carboxylic acid [10].



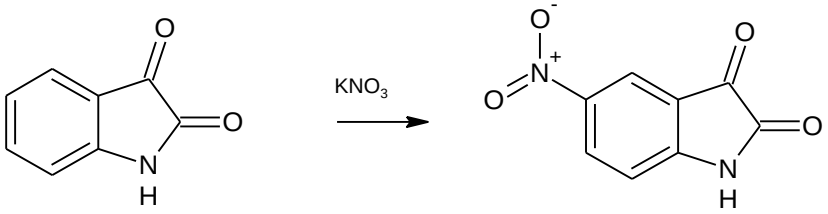
Reduction

Isatin undergo reduction in presence of reducing agent such as Zn and HCl to yield 3-hydroxy-1, 3-dihydro-2H-indol-2-one-methane [11].



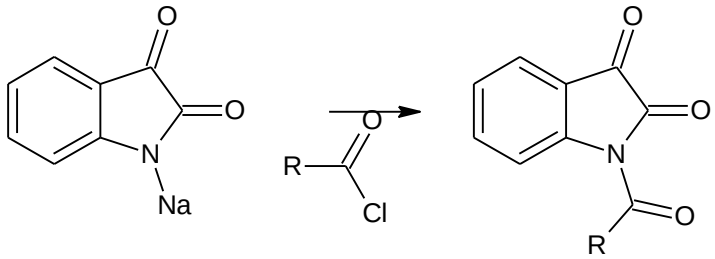
Nitration

5-Nitroisatin is produced by adding con.$H2SO_4$ drop wise to a solution of Isatin at 0-5^{0}c over a time period of 1 hour [12].



N-Acylation

N-Acylation is synthesized by using sodium salt of isatin and acyl chloride or anhydide under reflux [13].



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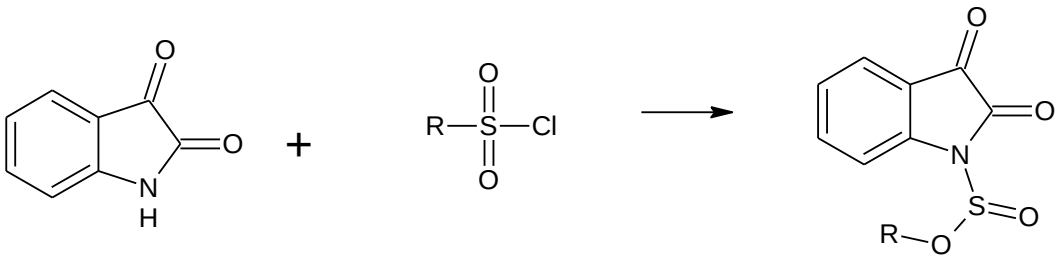
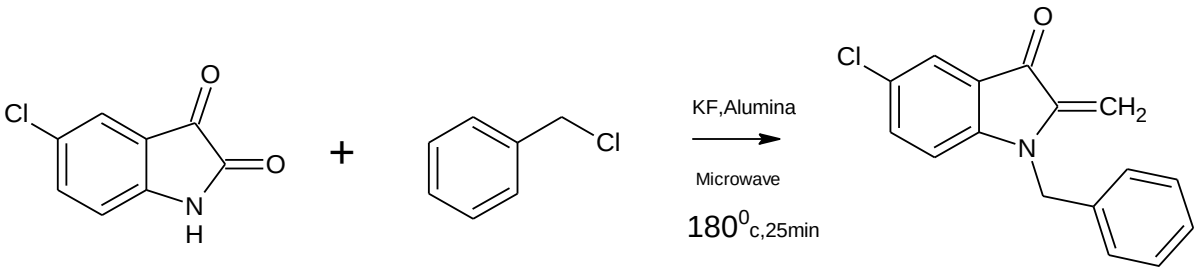
N-Sulfonylation

The reaction between sulfonyl chloride and isatin yields N-sulphonylisatin [14].



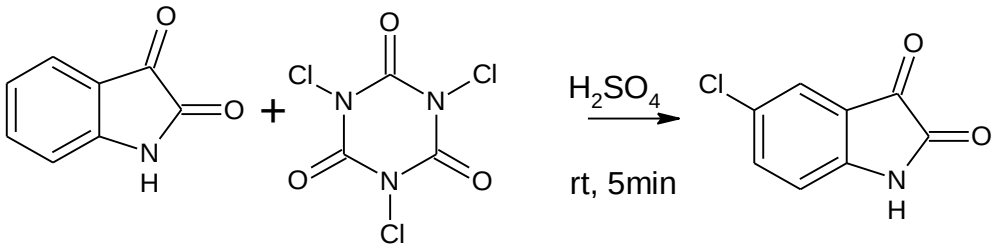
N-Benzylation

N-Benzylation of isatin is done by the reaction of isatin 1-a, b with chlorobenzyl 20 or bromobenzyl 21 under microwave irradiation or solid support of KF/alumina [15].



Chlorination

Chlorination of isatin was done by the reaction of N-Chloramide or N-Chlorimide and N-Chlorosaccharide in a heterogenous medium. It occurs at C-5 position [16].



Monohalogenation

Monohalogenation of isatin is attained by the reaction between isatin and N-Halosaccarines in the presence of silicon dioxide at room temperature [17].

Oxidation

Isatin in presence of chromium trioxide converted into isatoic anhydride, the anhydride form of isatin. The oxygen atom introduced between two adjacent carbonyl group is obtained from the oxidizing agent. This should not cause significant decomposition to the system [17].

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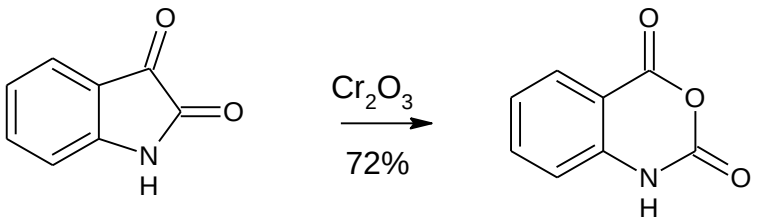
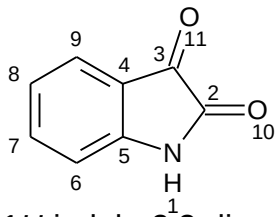


STRUCTURAL ACTIVITY RELATIONSHIP

When a halogen group (e- donating) is introduced to the R1 position of isatin, a more active compound can be obtained.5, 6 and 7 subtitutions improve CNS activity. Anticancer activity of isatin can be enhanced by nitrating the C5 position. Cytotoxicity mildly increases by the addition of methoxy group.

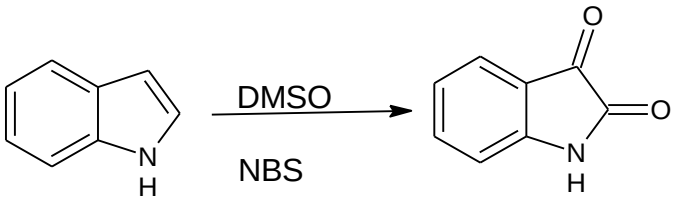
Halogenation of isatin at 5th position gives 5-Bromo, 5-Iodo, 5-Fluro isatin. Unsubstituted isatins are 5-10 times less active than halogenated Isatins. Substitution of Phenyl ring at 3rd position increases the anti-microbial activity [18].



1*H*-indole-2,3-dione

SYNTHESIS OF ISATIN AND ITS DERIVATIVES

Take a clean-3-necked round bottom flask and add a mixture containing Indole, NBS, and DMSO.This mixture is stirred for 60^0c for 6hours.Then under reduced pressure, it is stirred at a temperature above 80^0c for 16 hours. The reaction mixture was poured into water. Dichloromethane is used for the extraction and the product is dried over $MgSO_4$ and purified by chromatography [19].



Sandmayer isatin synthesis

The reaction between aniline and chloral hydrate along with hydroxylamine hydrochloride in the presence of sodium sulphate to form isonitrosoacetanilide.After isolation it is treated with concentrated sulphuric acid [20].

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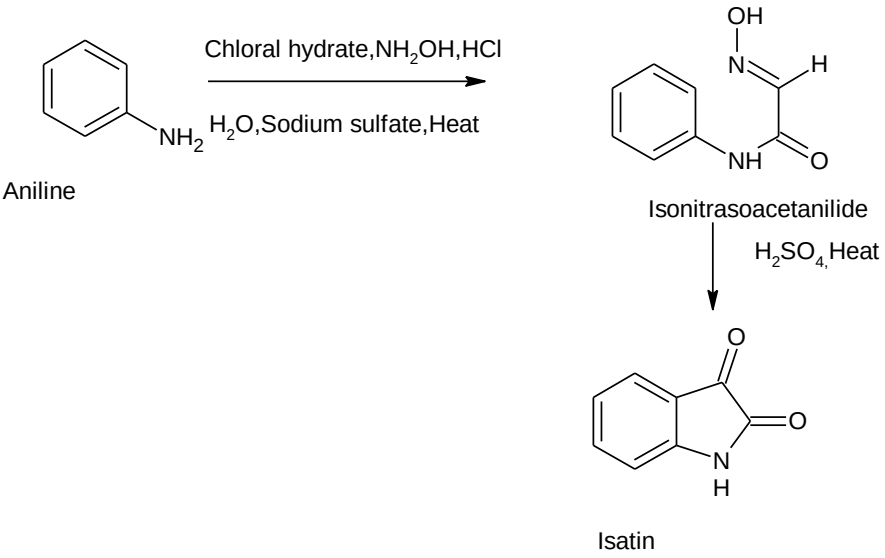
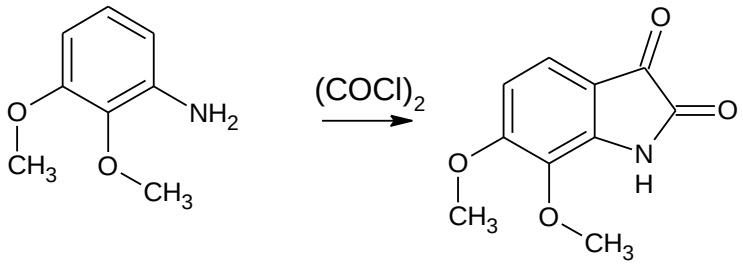


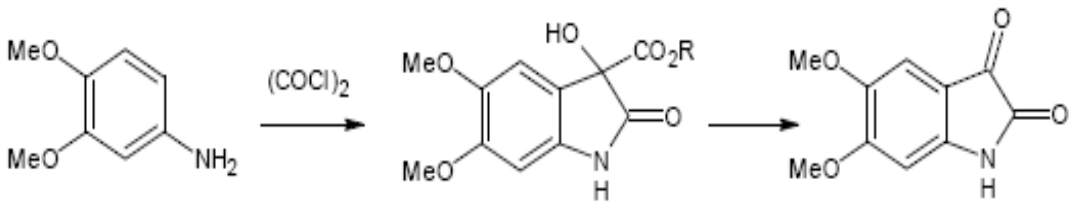
Stollen isatin synthesis

Here the aniline is treated with oxalyl chloride to from chloroxalylanilide which is an intermediate that in the presence of Lewis acid undergoes cyclisation [21].



Martinet isatin synthesis

It involves the reaction of an aminoaromatic compound in the presence of an acid with either an oxomalonate or its hydrate yield a derivative of 3-(3-hyroxy-2-oxindole) carboxylic acid which on oxidative decarboxylation gives isatin [22].



SYNTHESIS OF ISATIN DERIVATIVES

Synthesis of 1-Benzoyl indole-2, 3-dione

A solution of sodium carbonate (0.025mol) in 5mL of water was added into a mixture of Isatin (0.01mol) and benzoyl chloride (0.01mol) in 20 mL of ethanol. Then it was refluxed for 2-3 hrs. The reaction mixture precipitate was filtered after cooling. It is then dried and recrystallized with ethanol.

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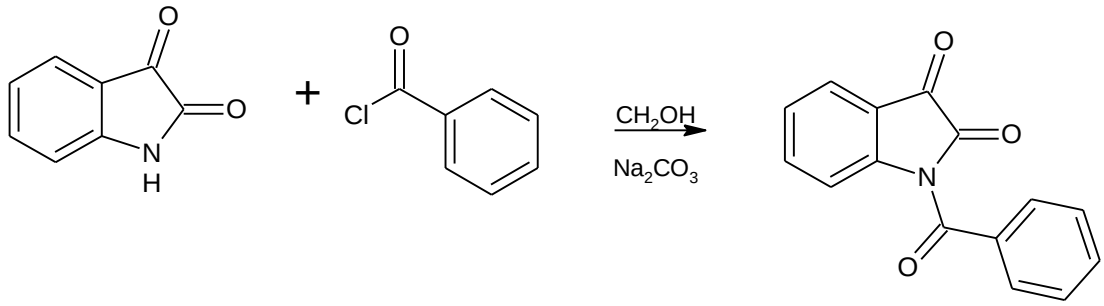
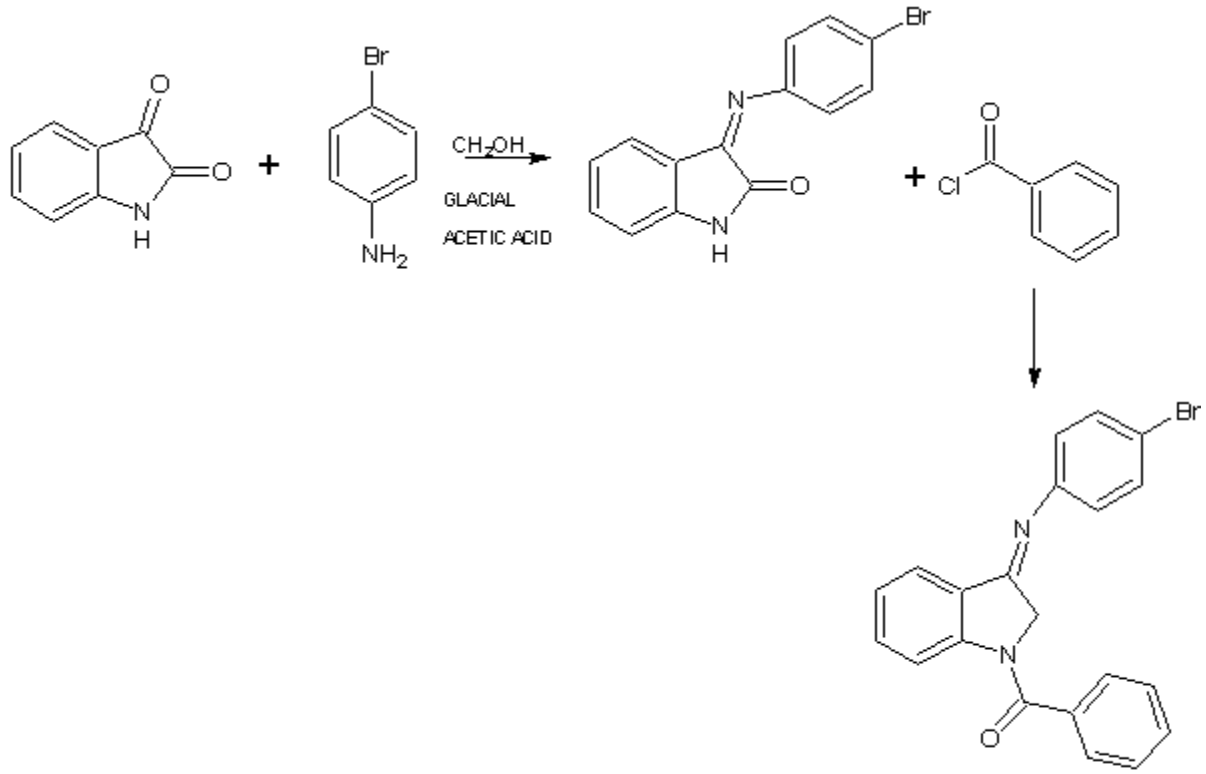


Synthesis of 1-benzoyl-3-(4-bromophenylimino) indolin-2-one

The mixture of Isatin (0.005mol) and p-bromoaniline (0.005mol) were added into 20 mL of ethanol (absolute) containing a few drops glacial acetic acid. Then it is treated with benzoyl chloride and sodium carbonate in presence of ethanol.



ACTIVITIES OF ISATIN

CNS ACTIVITY

CNS depressant activity

[23] Isatin is a CNS-MAO inhibitor, anticonvulsant and anxiogenic. It has most potent action as mono amine oxidase inhibitor till date [24].With an inhibitory concentration of 3µg/mL, it acts as a selective MAO B inhibitor. At concentrations higher than 3µg/mL it inhibits other enzymes like alkaline phosphatases. Isatin possess antiseizure activity and potentiates antiseizure activity of propranolol in rodents. At a low dose of 15mg/kg Isatin prolongs pentylenetetrzole (PTZ) induced seizures and also acts as an anxiogenic. While at higher doses of 80 mg/kg it turns into a anticonvulsant and sedative. The brain serotonin levels are significantly raised [25].

Anticonvulsant activity

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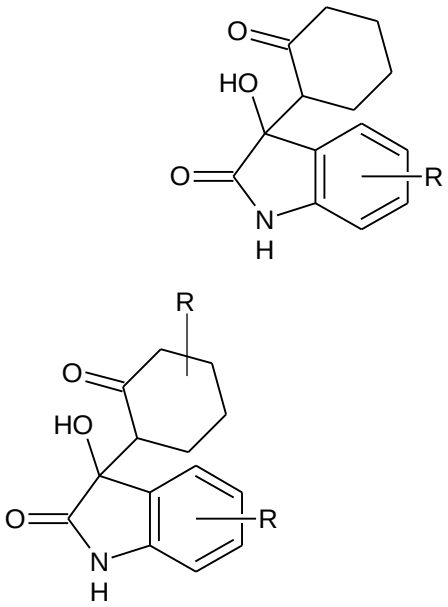
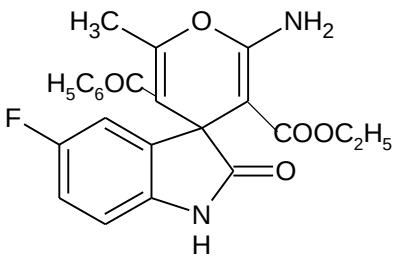
A) Isatin has anxiogenic properties occuring within a narrow intraperitoneal dose range of 15-20 mg/kg as reported by Bhattacharya and Chakraborthi. At higher dose it exhibited significant anticonvulsant activity against both 3MPA (Mercapto Propionic Acid) and Pentylenetetrazol (PTZ) induced clonic convulsions. They have also found that Isatin inhibits memory facilitating, anxiolytic and diuretic actions of ANP administered intacerebroventricularly. It also functions as a potent antagonist to anti-natriuretic peptide (ANP) [26].
B) The effect of isatin as an inhibitor on amygdaloid kindling in rats, seizure and anticonvulsant effect in convulsion model was studied by Li et al.Isatin given at a dose of 50-200mg/kg intraperitoneal significantly raised focal after-discharge threshold, seizure severity was reduced in kindled rats [27].
C) A series of cyclohexane and other cyclic ketone derivatives of isatin were prepared and screened for anticonvulsant activity by Pajouhesh et al pentylenetetrazole seizure threshold test activity was shown by a considerable number of analogues [28].



Cyclic ketone derivative of isatin

D) A series of condensed compounds were synthesized by reacting a heterocyclic system like isatin or 5-fluro isatin with ethyl cyano acetate and substituted ketones by Jain and Banzal. This compound showed anticonvulsant activity in rats [29].



Heterocyclic derivatives of isatin

E) In the treatment and prevention of epilepsy and migraine indoles, like 1-[5-(2-thienyl methoxy-1H-indole-3-yl)] propan-2-amine reported were used[30].
F) Substituted indole- 2-carboxylate as invivo potent antagonist acting on strignine insensitive glycine binding site were synthesized by Difabio et al. and further in mice, their potency to inhibit convulsions induced by N-methyl-D-aspartate (NMDA) invitro were evaluated [31].

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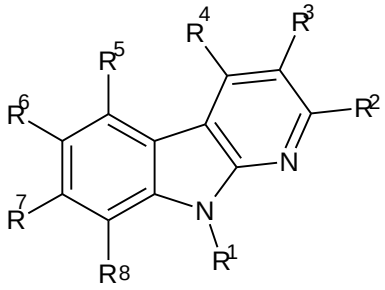
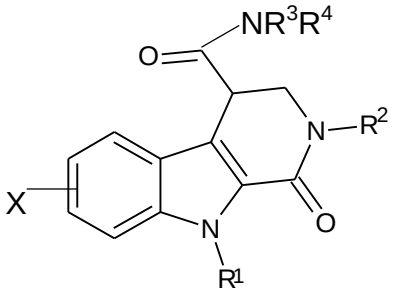
G) pyrido[2,3-b] indoles which treat a disease through the metabotropic glutamate receptor system in CNS were prepared by Olesen and Kansrup.The compounds were also useful treating diseases of CNS such as epilepsy, parkinsonism and senile dementia [32]



Pyrido [2, 3-b] indoles

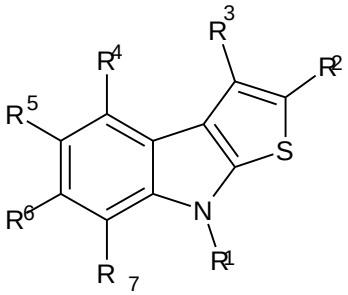
H) Pyrroloindoles and indolethiazipines were evaluated for anti-convulsant, analgesic, anti-inflammatory and ulcerogenic activity. Potent anti-convulsant and analgesic activity were shown by all compounds [33].



1H-pyrido [3, 4-b] indole-4-carboxamide derivatives.

1H-pyrido [3, 4-b] indole-4-carboxamide derivatives were prepared by Evanno et al and assist for anxiolytic, hypnotic and anticonvulsant activity [34]

1. Thieno [2, 3-b] indoles and pyrido [2, 3-b] indoles were prepared by Jakobsen et al as antagonist acting on metabotropic glutamate receptor. It is therefore useful in epilepsy senile dementia and parkinsonism [35].



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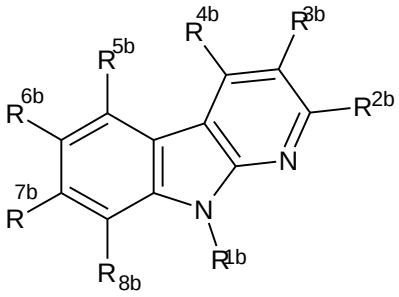


Thieno [2, 3-b] indoles and Pyrido [2, 3-b] indoles.

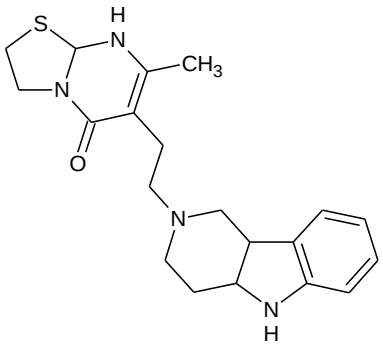
3. Anxiogenic and other CNS activity

The behavioral effect of isatin was studied by Palit et al, a considered biological factor in rhesus monkeys. Isatin is a constituent of tribulin which is has shown to induce anxiety in rodents and is a postulated endocoid marker of stress and anxiety [36].The effect of isatin in vitro on inhibition of human MAO A and B was studied by Medvedev et al. Most analogues were found to be less potent than Isatin [37].

The requirement for co-planar structures of Isatin substituents at C2 and C3 positions for selective inhibition of MAO A was revealed through QSAR (Quantitative Structure Activity Relationship) analysis. Through substantial experimental and clinical investigations it was shown by Hamaue et al that Isatin is an endogenous inhibitor of MAO A [38]. It also possess physiological properties for stress and anxiety. Isatin has also acetyl choline esterase (AchE) inhibitory effect. The effect of Isatin administered exogenously and its effect on levels of Acetyl choline and dopamine in rat brain was studied. It was indicated that endogenous Isatin may play a role in the maitenance of brain levels of Acetyl choline by increasing dopamine levels. In conditions of stress like in exposure to extreme cold and acute food deprivation , it was reported by Tozawa and Veki the markedly increased urinary excretion of Isatin in urine [39].

The synthesis of Isatin N-2(-alkly-benzoxazole-5-carbonyl) hydrazones and their screening for analgesic, antidepressant and H1-antihistaminic activity was carried out by Sarangapani and Reddy [40].

Hexahydropyrido (4, 3-b) indoles were synthesized by Kennis et al [41].



The above compound was found to have antagonistic activity against central dopamine and serotonin in combined apomorphine, tryptamine and nor-epinephrine test in rats.

CHEMOTHERAPEUTIC ACTIVITY

Antimicrobial activity

Isatin-N-mannich bases of isatin-3-thiosemicarbazone derivatives, investigated by Varma and Nobles against viral, fungal and bacterial organisms [42].Anti-viral and tuberculostatic activity is shown by thiosemicarbzones of different carbon compounds. Three thiosemicarbazones derivatives were toxic to cancer cells and two compound were active against poliovirus type II, gram positive bacteria, fungi and yeast.

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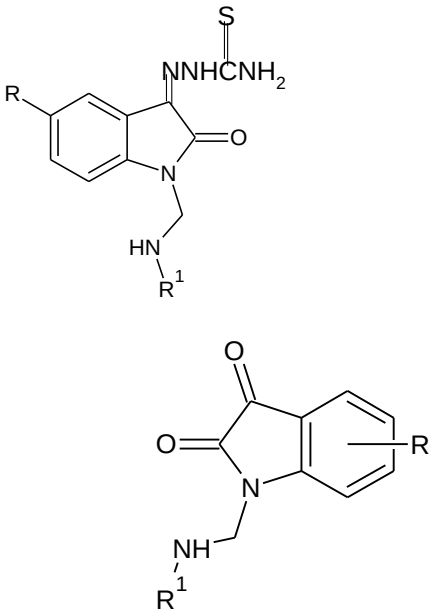
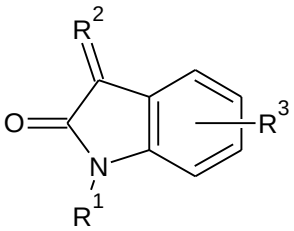
Isatin N-Mannich bases were also prepared by them.



Nine compounds were found to exhibit activity against Polio II virus, one of them displayed activity against four different viruses, and two had activity against all four classes of organisms.
A series of congenic Isatin N-mannich bases and their evaluation were carried out by Kupinic et al [43].



Most of the above synthesized Isatin mannich bases had inhibitory effect on Gram-negative bacteria and fungi but moderate effect on growth of gram positive bacteria. Three compounds had potent activity against Gram positive bacterium Micrococcus flavus.

Amino methylation was carried out on position 1 of a series of 5-haloisatins and introduction of hydrazine groups at 3rd position was carried out by Maysinger et al [44].The prepared compounds were tested for their activity against fungi and bacteria. Presence of halogen at position 5 and amino moiety at position 1 had more activity than unsubstituted Isatin.

Anticancer activity

Isatin has ability to kill cancer cells or cause cytotoxicity on a particular compound. They are also found to intercalate between DNA base pairs and inhibit ribonucleoprotien telomerates.3-o-nitrophenyl hydrazones of isatin were prepared by Popp and Pajouhesh and found to be inactive against L-1210 lymphoid leukemia and active against Walker carcinoma-256 intramuscularly [45].

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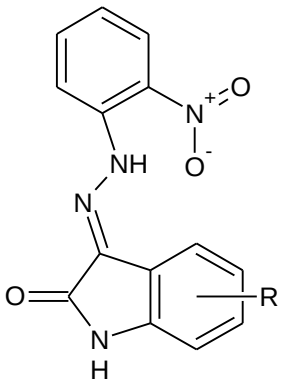
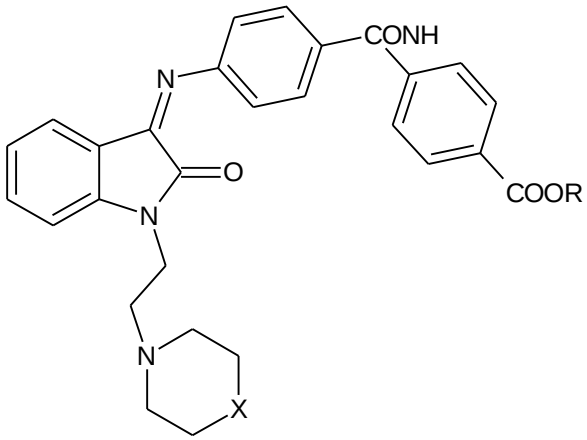


Five compounds tested for antiluekaemic activity against p388 lymphocytic leukemia in mice and di-Mannich base with dimethyl amino group showed highest activity in the tested compounds. A bromine group in position 5 of the aromatic ring of isatin increased the activity in the parent molecule to a smaller extent.

MISCELLANEOUS ACTIVITY

1. Anti-tubercular activity

1-nonyl-7-phenyl-1H-indol-2.3-dione synthesized by Ramachandran was active against Mycobacterium tuberculosis [46].3 [-p-(p-(alkoxycarbonyl)-phenyl) carbamoyl)]-phenyl) imino-1-aminomethyl-2-indolinones synthesized by Varma and Pandya was investigated for its antitubercular activity against M.tuberculosis H_{37} Rv [47].



N-Mannich bases of Isatin prepared from dipiperidine by Collino and Volpe exhibited fibrinolytic, muscle-relaxant, antiallergic, antihistaminic, immunosuppressant and antithrombis activities [48].

2. Inhibitor of glucose, amino acid uptake

Isatins competitively inhibited (27-40%) Na+-dependent L-Lysine in rat intestine. Isatin was unaffected by SH group reacting agents. Isatin also inhibited Na+-K+-ATPase in the intestine invitro but has no effect on enzyme action in vivo [49].

Isatin has antagonistic effect on histamine induced bronchoconstriction activity. It also has cardio inhibitory effect, hypertensive, respiratory depressant and diuretic effects. It doesn't have any effect on inflammation and gastric activities

CONCLUSIONS

This article deals with introduction of Isatin along with its chemistry and its physical and chemical properties. We further discuss about the synthesis of Isatin and its derivatives. We have also explored the common pharmacological properties. From the study we were able to know that Isatin compounds are potent chemical moieties with wide range of activities and presently many derivatives of Isatin are under research study.

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