Recent Advancement in Synthesis of Isatin as Anticonvulsant Agents: A Review

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Abstract

Isatin (1*H*-indole-2,3-dione) and its analog, are versatile substrates which acts as a precursor for large number of pharmacologically active compounds, thus having a significant importance in the synthesis of different heterocyclic compound.Isatin shows varity of biological activities such as antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic.This review focused on isatin synthetic methods and its biological activity as anticonvulsant. An Isatin derivative shows potent anticonvulsant activity at low concentration among all the derivatives, Schiff bases are found to be most potent anticonvulsant agent.

Introduction

Isatin (1*H*-indole-2, 3-Dione) consist of indole nucleus and two types of carbonyl groups i.e. keto and lactam group. It has been discovered 150 years ago and now known as oxindole and Endogenous polyfunctional heterocyclic compounds. It was first investigated by Erdman [1] and Laurent [2] in 1841 as a product from the oxidation of indigo by nitric and chromic acids [3] (Scheme 1).

Isatin [4] and Popp [5] is used for synthesis of heterocyclic compounds [6]. In nature, isatin is found in plants of the genus *Isatis* [7], in *Calanthe discolor LINDL* [8] and in *Couroupita guianensis Aubl* [9]. It has also been found as a component of the secretion from the parotid gland ofBufo frogs [10], and in humans it is a metabolic derivative of adrenaline [11-13]. Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxyphenylpentylisatins) obtained from the Caribbean tumorigenic plant *Melochia tomentosa* [14-16] as well as from fungi: 6-(3'-methylbuten- 2'-yl)isatin was isolated from *Streptomyces albus* [17] and 5- (3'-methylbuten-2'-yl) isatin from *Chaetomium globosum* [18]. Isatin has also been found to be a component of coal tar [19]. Isatin has a wide varity of pharmacological activities such as antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic [6.9,11,13]. Different research group attempted study on isatin synthetic aspect [6,11] . Other research group attempted study of istain biological activity [11-13]. In this review we focused on different sites of reactivity of this moiety; its structural confirmation data, different sites of action (mechanism of action) its pharmacological activity as anticonvulsants.

Structural Aspects

Crystallographic data

The crystallographic data represents that it is planar; with a large bond length of 1.55 Å between the two carbonyls. The lone pair electron repulsion between the oxygen atoms [20,21] was responsible for such a large bond length which was subsequently checked by comparison of bond length between cis and trans 1, 2-diketones and no difference was observed [22]. A similar bond length was observed for 1-acetylisatin [23], 1-α-chloroacetylisatin [24] , diethyl (2,3-dihydro-2-oxo-3- indolylidene) propanedioate [25] , 1,1'-oxalylbisisatin [26] and 1-methylisatin [27], as well as in derivatives where C-3 is tetrahedral, such as 3,3-dichloro-1H-indol-2(3H)-one [28] and 5'-bromospiro-[1,3-dioxolano-2,3-indolin]-2'-one [29], as well as in 3-m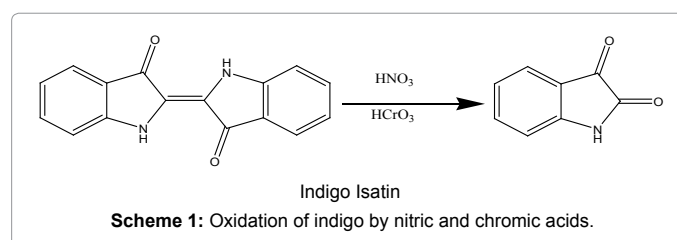ethyleneoxindoles [30] (Table 1) and in products obtained by nucleophilic ring opening of 1-acetylisatin, where the 1,2-dicarbonyl system assumes a s-trans conformation [31].

Infrared spectroscopy

The I.R. of isatin shows two strong bands at 1740 and 1620 cm-1 corresponding to the carbonyl stretching vibrations. A broad band was found at 3190 cm-1 due to N-H stretching, accompanied by some sub-bands, representing N-H in-plane bending [32-34]. The ν C=O values modified by N-alkylation, but N-acetylation leads to a hypsochromic shift of the lactam absorption by 50-70 cm-1, and the ketone band shifts to 1750 cm-1, as a result of conjugation between nitrogen lone pair and acetyl group [35].

1H NMR spectroscopy

The 1H NMR spectrum of isatin show the signals of the aromatic

Indigo   Isatin
Scheme 1: Oxidation of indigo by nitric and chromic acids.

X	R1	R2	C_2-C_3
O	H	H	1.55
O	Ac	H	1.538
O	Me	H	1.545
Cl , Cl	H	H	1.556
OCH$_2$CH$_2$O	H	Br	1.539
CHCH=C(CH$_3$)$_2$	H	H	1.508

Table 1: Bond length between C2 and C3 if X is changed [32].

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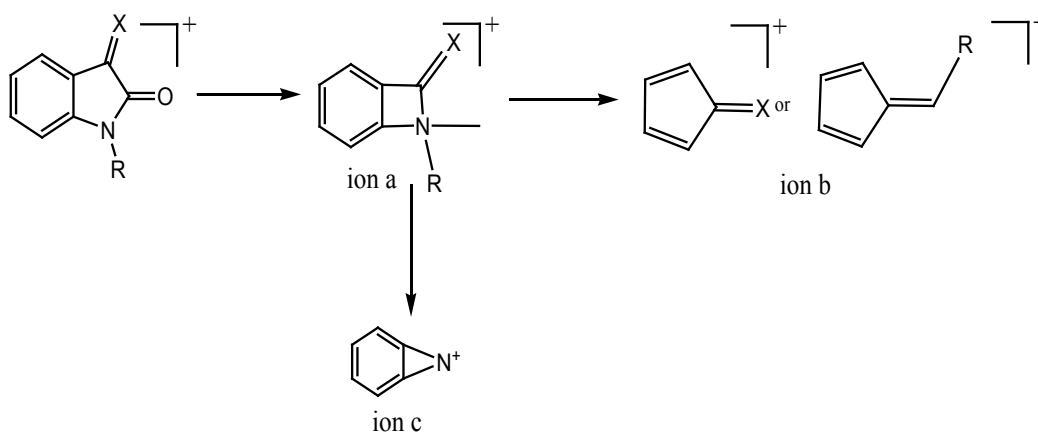
nucleus signals at 6.86 (doublet), 7.00 (triplet), 7.47 (doublet) and 7.53 (triplet) ppm (DMSO-d6), corresponding to H-7, H-5, H-4 and H-6 respectively. N-alkylation does not affect this pattern, whereas N- acetylation leads to a downfield shift of all the signals, but most significantly of H-7 due to the carbonyl group having anisotropic effect. In the same way, 3-methyleneoxindoles bearing cyano groups represents downfield shift of H-4 by about 0.6-1.0 ppm [36,37] (Table 2).
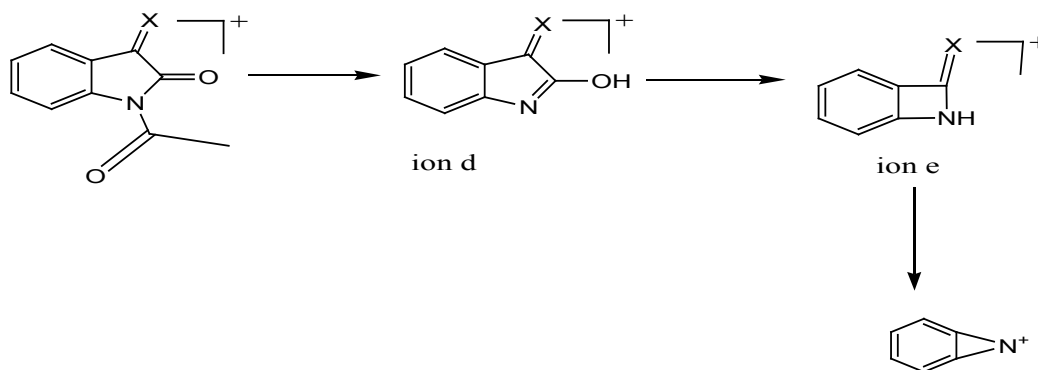
Mass spectrometry

The electron-impact mass spectra of isatin [38], 1-alkylisatins [39] and its derivatives, such as hydrazones [40], show an intense molecular ion peak. In case of 3, 3-disubstituted oxindoles [41], the base peak represents the loss of the substituent at C-3. A peak corresponding to the loss of CO (ion a) can be observed, but its intensity can be decreased with the increase in size of the alkyl chain of 1-alkylisatins [42]. Ion usually loses HCN, leading to a fulvene ion (ion b). An arene aziridine is also observed (ion c), which arises from a second loss of CO [43-45]. The ions b and c are also observed in the gas-phase pyrolysis of isatin [46]. In a general manner, the mass spectra of 3-substituted isatins show a sequential loss of neutral molecule [47] (Scheme 2).

A peak corresponding to the loss of CO is not found in the mass spectra of isatin-3-oximes, this is attributed to a Beckmann rearrangement of the molecular ion leading to a heterocyclic ring opened ion [48]. In the case of the acetylated derivatives, the molecular ion is usually of low intensity. The fragmentation pattern includes loss of ketene (ion d) and of CO (ion e) (Scheme 3).
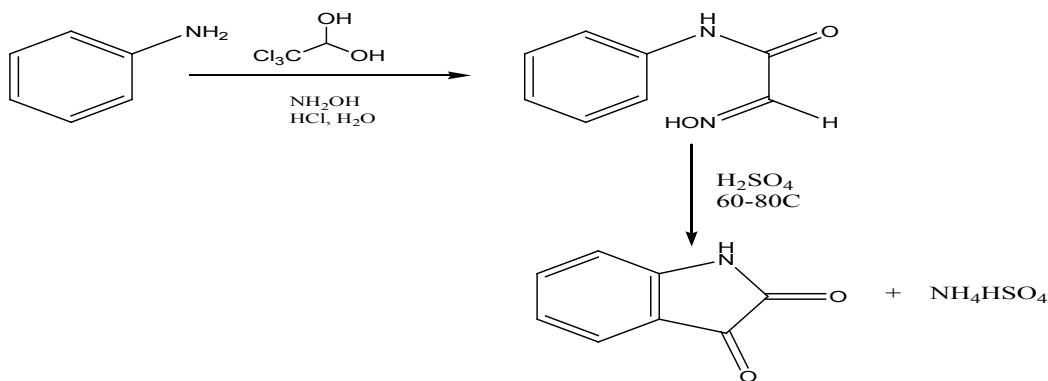
Synthetic Methods

Methods

1. Then Sand meyerisatin synthesis [49]: Synthesis of isatin. was carried out by reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate leads to formation of an isonitrosoacetanilide, which is isolated on treatment with concentrated sulfuric acid to obtain isatin of >75% overall yield [49] (Scheme 4).

2. The Stolleisatin synthesis [50]: Anilines are reacted with oxalyl chloride to form an intermediate named chlorooxalylanilide which is then cyclized in the presence of a Lewis acid, usually $BF_3.Et_2O$ or aluminum chloride, although $TiCl_4$ has also been used in this method [50] (Scheme 5).

X	R	H-4	H-5	H-6	H-7	CH_3CO	Solvent
O	H	7.50d	7.07t	7.60t	6.92d	-	DMSO-d6
O	Me	7.59d	7.12t	7.61t	6.91t	-	DMSO-d6
O	Ac	7.27d	7.33t	7.70t	8.38d	2.73s	DMSO-d6
$C(CN)_2$	H	7.87d	7.12t	7.59t	6.94d	-	DMSO-d6

Table 2: NMR data of isatin is presented [32].

Scheme 2: Mass spectra of 3-substituted isatins show a sequential loss of neutral molecule.

Scheme 3: Fragmentation pattern includes loss of ketene (ion d) and of CO (ion e).
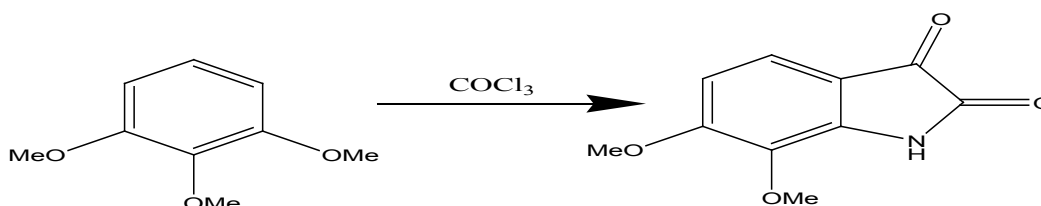
3. The Martinet isatin synthesis [51]: Isatin was synthesized by the reaction of an amino aromatic compound with an oxomalonate ester or its hydrate in the presence of an acid to form a 3-(3-hydroxy-2-oxindole) carboxylic acid derivative which on further oxidative decarboxylation yields isatin [51] (Scheme 6).

4. The Gassman isatin synthesis [52]: This methodleads to formation of substituted isatin(40-81% yield)by the formation and subsequent oxidation of an intermediate 3- methylthio-2-oxindole [52] (Scheme 7).
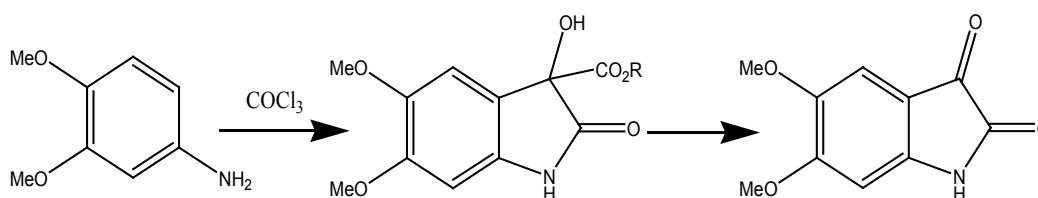
5. Metalation of anilide isatin synthesis [53]: The recent method for synthesis of isatin is based on ortho-metalation (DoM) of N-pivaloyl- and N-(t-butoxycarbonyl)-anilines. The
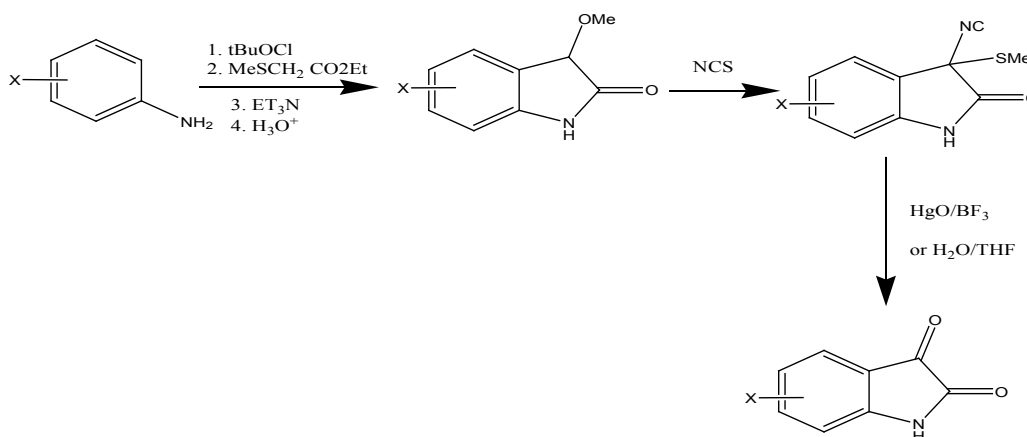

Scheme 4: Sand meyerisatin syntheses [49].

Scheme 5: Stolleisatin syntheses [50].

Scheme 6: Martinet isatinsyntheses [51].

Scheme 7: Gassman isatin syntheses [52].

dianions are treated with diethyl oxalate and then isatins are obtained after deprotection and cyclisation of the intermediate a-ketoesters. The advantage of this method is being regioselective for the synthesis of 4-substituted isatins from meta-substituted anilines [53] (Scheme 8).

Structure activity relationship

Natasarito vaska et al. proposed that if R1 is substituted by halo groups (electron donating) than more active compound is obtained [54]. Thomson et al. proposed that Substitution at 5, 6, and 7 improves the CNS activity [55]. Nitration at C5 enhanced the anticancer activity by a factor of 4, while the addition of a methoxy group mildly increases the cytotoxicity. Furthermore, halogenation yielded the most active compounds, with 5-bromo-, 5-iodo-, and 5-fluoroisatin being 5-10 times more active than the unsubstituted parent compound [56] (Figure 1). N- Alkylation and acylation can be done on position 1st. If substituted phenyl ring is substituted at 3rd position than it enhances antimicrobial activity [55]. Thomson et al. proposed that a little variation at 3rd position may produce different degree of biological activity [55]. Prakash et al. suggested thatformation of Schiff base on reaction with aromatic amine leads to formation of compound with anticonvulsant activity [57].
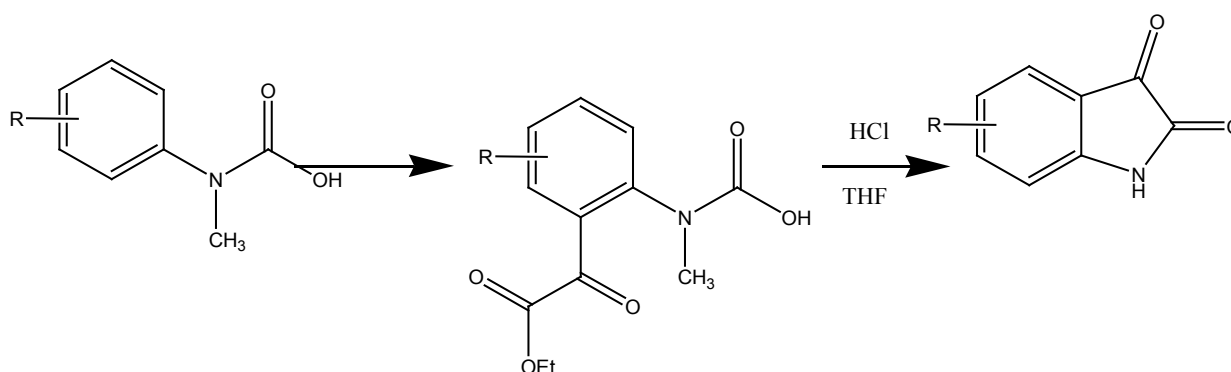
Chemical reactivity of isatin

N-Alkylation: N-alkylation of isatins was discovered by different methods, among which they are commonly alkylated by allowing isatin sodium salt to react with alkyl halides or sulphates [58,59]. Isatin sodium salt was prepared by reaction of isatin with sodium hydride, using DMF [60] or toluene under reflux [61]. Some other methods use potassium carbonate in DMF [62,63] or in acetone [64] for salt formation of isatin. The use of CaH_2 in DMF was also reported [65] and this method was proposed to be used for the synthesis of both mono and bis-N-alkylisatins. The *N*-substituted isatin derivatives were also synthesized by reactions between isatin and halohydrocarbon,

these reactions carried out in the presence of NaOEt using EtOH as solvent or in the presence of NaH using DMF as solvent [66]. N-Alkyl substituted isatin derivatives are known to have anticancer activity [67-69]. In 2003, N-alkyl isatin was found to induce apoptosis in human cancer cell lines, but not in normal cells [67]. Vine et al. [70] synthesised a series of di-brominated N-substituted isatins which shows the increased potency of the halogenated isatins and also revealed that N-methylation enhance the cytotoxicity of the parent compound [56]. In 2008 [71] different reaction conditions for N- alkylation of isatin were proposed using ethyl chloroacetate as alkylating agent. Na_2CO_3, K_2CO_3, Cs_2CO_3, CaH_2, TEA, LiOH, NMM, NaOEt were used as bases and DMF, DMA, HMPT, MeCN, DMSO and NMP were used as polar aprotic solvents. The best results were obtained by the use of K_2CO_3 or Cs_2CO_3 and a few drops of DMF or NMP.Other than this microwave method for synthesis of N-alkylated [71]. Isatin was also discovered in this method an equimolar quantity of isatin and halohydrocarbon was taken to which K2CO3 as catalyst was added and DMF is used as solvent, and then exposed to microwave radiations [71]. In 2011 N-substituted isatin was synthesized and characterized to have antioxidant activity [57].

N-Arylation: N-Arylisatin could synthesized from isatin in quantitative yields by reaction with $Ph_3Bi(OAc)_2$ andCuO under an inert atmosphere [72] or from aryl bromides and cupric oxide [73].

N-Acylation: N-Acylisatins were synthesized by different methods i.e. by using Acyl chlorides or anhydrides under reflux, either alone [74] or using perchloric acid in benzene, triethylamine in benzene [35], pyridine in benzene [75], or triethylamine in chloroform [76,77] as catalysts; or it can also be obtained by conversion of isatin to sodium isatide using NaH in toluene under reflux and reaction with acyl chlorides [63]. The use of diacyl chlorides, such as oxalyl chloride [78], octanedioyl or nonanedioyl chlorides [79], leads to formation of a bis-acylisatins. 2, 2-dimethylmalonyl chloride used to obtain 2, 2-dimethylmalonyl-bis-isatin was failed, and led to form an unusual

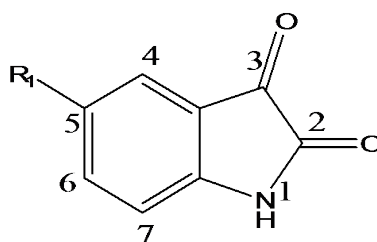**Scheme 8:** Metalation of anilideisatin synthesis [53].

Figure 1: Isatin.

tricyclic compound which was characterized by spectroscopic methods and by X-ray diffraction [26] (Scheme 9).
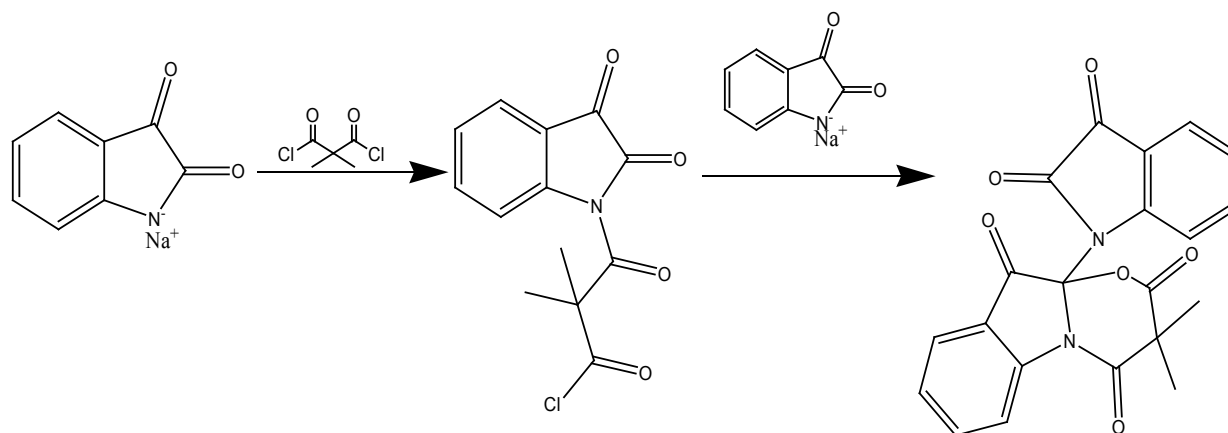
N-Sulfonylation: The reaction of isatin and sulfonyl chlorides helps to synthesize N-Sulfonylisatin by applying the same methodologies as used forsynthesis of 1-acylisatins. For example, 1- tosylisatin was formed in 71-74% yield by mixing tosyl chloride with isatin in presence of Et_3N or with the sodium salt of isatin [80].

N-Haloderivatives: The treatment of isatin with sodium hypochlorite in acetic acid leads to 1-chloroisatin, an effective mild oxidizing agent for the conversion of alcohols to aldehydes and ketones [81] and of indoles to 3-chloroindoles without formation of by-products [82]. N-[phenyliodine(III)] bisisatin can be obtained from the sodium salt of isatin and phenyliodine (III) bistrifluoroacetate in 85% yield. This compound is a member of a group of iodine (III) imides, which possess mild oxidizing properties [83].
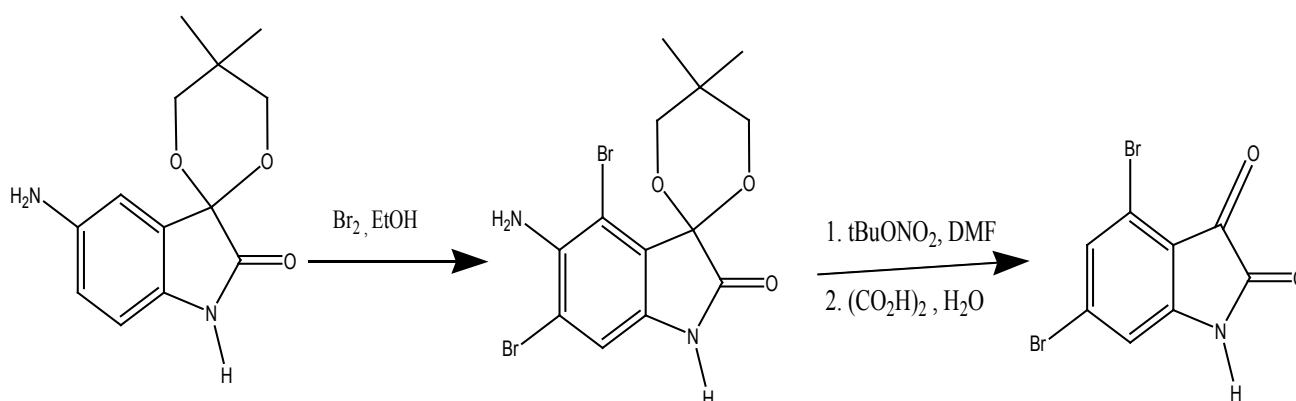
Reactivity: The isatin with substituent attached to the aromatic ring are usually obtained from functionalized anilines, it can be synthesized by electrophilic aromatic substitution. Nitration of isatin using the sulfonitric mixture yields 5-nitroisatin [84]. The bromination of isatin in an acid catalyzed reaction gives 5, 7-dibromo-3, 3-dialkoxyoxindoles using alcohol as solvent [85]. Micro scale mono-brominationis achieved at position 5 by using N-bromoacetamide in acetic acid medium [86]. Palladium-catalyzed Suzuki cross-coupling reaction [87] facilitate arylation by the use of aryl or heteroary lboronic acids led to formation of 5-Bromoisatins 4, 6-dibromoisatin, a key intermediate in the

synthesis was prepared by bromination in ethanol of a 5-aminoisatin derivative [88] (Scheme 10).

Substitution of fluorine group at 5th position was found to increase the biological activity. For example, Vine et al. reported an *in vitro* cytotoxicity for a range of mono-substituted isatins on a human monocyte-like, histiocytic lymphoma cell line [70]. Structure activity relationship (SAR) studies revealed that substitution at position 5 was favored over positions 4, 6 or 7, leading to greater cancer cell killing ability. By increasing the number of electron-withdrawing groups on the ring such as dibromo-, tribromo-, iodo- and nitro substitution on isatin led to enhance the overall biological activity against the human cancer cell lines up to 100-fold from that of the parent molecule [88]. Banerji et al. proposed microwave method for substitution at C-3 position by diamines was discovered which leads to formation of imesatins [89]. Sourabh Bhardwaj et al. suggested antimicrobial activity of Schiff bases of isatin and isatin derivatives. This procedure was modified for the synthesis of title compounds offers reduction in the reaction time, operation simplicity and easy work-up [90]. I.-J. Kang et al. proposed that isatin on 3rd position when substituted with thiosemicarbazonesis found to be as potent herpes simplex virus inhibitors. Thiourea moiety of thiosemicarbazone was found to be potent antiviral agent [91]. Gangarapu et al. discovered a microwave assisted substitution at 3rd position of isatin by Thiocarbohydrazide. These New Isatin Derivatives arealso known as Monothiocarbohydrazones which are Cytotoxic and Chemopreventive Agents [92].

Scheme 9: Formation of a bis-acylisatins.

Scheme 10: 5, 7-dibromo-3, 3-dialkoxyoxindoles.

Biological Aspects

Mechanism of action: isatin

Isatin was identified as major constituent of tribulin, it is a low-molecular-weight inhibitor of Monoamine Oxidase Type-B (MAO-B) [93]. If urinary concentration of isatin is increased in patients it is considered as the diagnostic marker of Parkinson's disease and severity of the disease. Isatin plays an important role in the regulation of acetylcholine (Ach) in brain by increasing the level of Dopamine (DA) under stress [94,95]. Tribulin contains metabolites of isatin [96], but physiological and pathological roles of isatin and tribulin are yet not clear. Due to exercise [97] and old age [98] tribulin levels are found to be increased in humans. Tribulin excretion in human is found to be higher in females than males [99]. Tribulin appears to be enhanced in different conditions such as stress, agitation, or anxiety. Thus these observations represents that during the stress, activated catecholamine-synthesizing cells and corticotropin- releasing factor cells involved in isatin production [100] plays central roles in stress responses. Tribulin acts on central benzodiazepine receptors, and hence suggested to be an anxiety-promoting agent [101]. The potency of tribulin as mono amino oxidase (MAO inhibitory) and benzodiazepine-receptor-binding inhibitors isfound to be roughly equal [102]. It is found to be a selective MAO-B inhibitor. At much higher concentrations, it may also inhibit other enzymes, such as alkaline phosphatase [103]. Tribulin is obtained by extraction from the tissue and body fluids with ethyl acetate. It has been suggested that dietary tryptophan can be converted into an indole by the gut flora and then transported to the liver where it is oxidized. Kumar *et al.* (1988) [104] suggested that isatin inhibits acetylcholine esterase (AChE) activity in rat brain. The physiological role of isatin is to regulate acetylcholine (ACh) levels in the rat brain, the levels of ACh, choline (Ch), and DA in rat tissues after 2 h of administration (50 or 200 mg/kg, i.p.) was further elucidated , according to it ACh and Ch levels in the striatum receiving isatin increased significantly [104]. In other words, at a single dose isatin simultaneously increased the ACh and DA levels in the WKY striatum. *In vitro* study suggests that, isatin induced an approximate 93% inhibition of MAO and a 5% inhibition of AChE in the rat brain which can be concluded as isatin has a higher affinity for MAO than AChE. Isatin administration also increased Ch, an AChE metabolite of ACh, in many brain regions. These results suggested that isatin increased ACh levels not by inhibiting AChE activity but rather by affecting another pathway [105]. It affects the central nervous system. Isatin has been shown to inhibit a number of enzymes in various tissues, such as acid phosphatase [106], alkaline phosphatase, and xanthine oxidase, hyaluronidase [107] as well as MAO. In a variety of tests isatin are found to have antiseizure activity [108], it also enhances the antiseizure action of propranolol [109]; and its physiological effects protect against stress and certain infections. Yuwiler [110] also found that isatin can acts as benzodiazepine blocker. The most potent action of isatin is the inhibition of the atrial natriuretic peptide (ANP) binding to its receptor. Isatin attenuates ANP-stimulated guanylatecyclase activity in the rat brain, heart, and kidney [110]. Recently it was also suggested that the anxiogenic effect of isatin can be explained by its antagonism of ANP. Isatin and derivatives display diverse pharmacological activities. The biological and pharmacological properties of isatin and its derivatives have led to extensive use of these compounds as key intermediates in organic synthesis. Literature surveys reveal that various derivatives of isatin possess diverse activities such as antioxidant and anti-inflammatory [111], antimicrobial [112], antituberculosis [113], anticancer [114], anti-HIV [115], antiviral [116], anticonvulsant [117,118] activities. Isatin is a core constituent of many alkaloids and drugs as well as dyes, pesticides and analytical reagents. Among all these activities anticonvulsant activity of isatin is discussed below briefly:

Anticonvulsant activity

Kumar et al. [119] found that a little variation at para position of the phenyl ring having chloro and nitro substituted compounds (Figure 2) i.e. 2a and 2brespectively have excellentanticonvulsant activity compared to that of the substitution at any otherposition. Among the synthesized compounds such as (1b) 3, 4-dihydro-2-(4-nitro phenyl) imidazo(4,5,6), indol and (1c) 2-(4-chloro phenyl) -3, 4-dihydro-imidazo (4,5,6) indole showed excellent anticonvulsant activity.

Prakash et al. [120] reported (Figure 3) Synthesis, characterization and anticonvulsant activity of novel schiff base of isatin derivatives. They are synthesized by condensation of imesatin with different aromatic aldehydes. All the synthesized compounds screened foranticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet).Among all the synthesized compounds, 3-(4-(3,4,5-trimethoxy benzylideneamino) phenylimino) indoline-2-one showed excellentanticonvulsant activity with lower dose in MES as well as in ScMet methods.

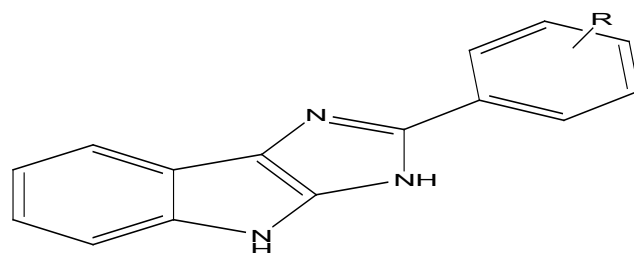Veerasamy et al. [121] reported the Synthesis of 3-cycloalkanone-3,

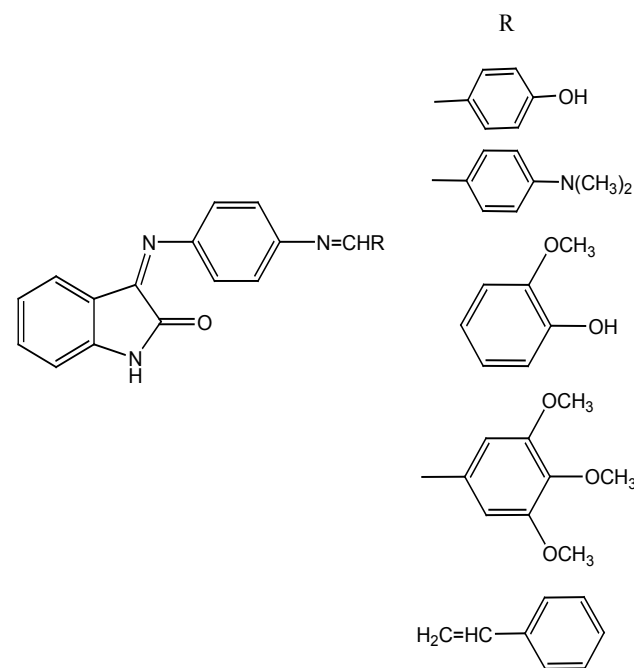**Figure 2:** Phenyl indoloimidazolederivatives [119]. (2a = 4-nitrophenyl; 2b = 4-chlorophenyl).

Figure 3: A series of novel Schiff base of isatin derivatives [120].

4-hydroxy-2-oxindolesderivatives where X can be bromo or chloro. These derivatives showed the MES testand PTZ test. Compound 24a was active in PTZ seizurethreshold test (PTZ), thus act as a potential anticonvulsant (Figure 4).

Subudhi et al. [122] reported anticonvulsant and antimicrobial activity of Cu (II), Zn (II) and Co (II) complex of isatin 3-Glycine.Isatin and glycine have inhibitory effects on central nervous system and to capitalize these features metal complexes of isatin-3-glycine were prepared and evaluated for anticonvulsant activity. Among them Cu (II) complex were found to be most active (Figure 5).

Ragavendran et al. [123] reported the synthesis of *N*-aryl/alkylidene-4-(1, 3-dioxo-1, 3-dihydro-2*H* isoindol-2-yl) butanoylhydrazides/butanamides which was further analyzed for anticonvulsant activity. Compounds were ineffective in MES test up to 300 mg/kg. These compounds were found to be more potent when compared to standard drug phenytoin and ethosuximide, and were effective at dose 30 mg/kg (Figure 6).

Sridhar et al. [124] reported the Synthesis of 3-(4-chlorophenylimino)-5-methyl-1, 3-dihydro-indole-2-one. The synthesized compounds were active inMES test and found to be more potentwhen compared to standard drug phenytoin and ethosuximide. Among all 23b was found to be most activecompound and showed 87% protection at 100 mg/kg doselevel (Figure 7).

Palluotto et al. [125] Synthesize a series of 2-aryl-2, 5 dihydropyridazino[4, 3- b]indol-3(3H)ones (Figure 8) among them some showed potent anticonvulsant activity (Figure 8).

Campagna et al. [126] Synthesize a series of a 2-aryl -2, 5-dihydropyridazino [4, 3-b] indol-3(3H) ones (Figure 9) among all
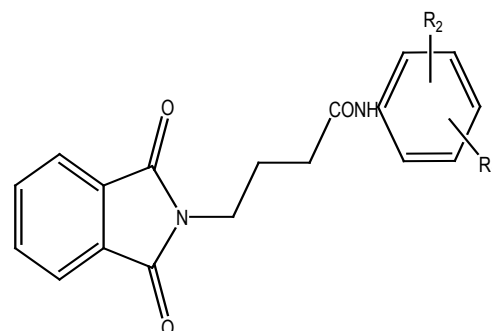
Figure 6: *N*-aryl/alkylidene-4-(1, 3-dioxo-1,3-dihydro-2*H* isoindol-2-yl) butanoylhydrazides/ butanamides(R$_1$= 2-CH$_3$, 3-Cl, R$_2$= 4-CH$_3$, 2-CH$_3$) [123].
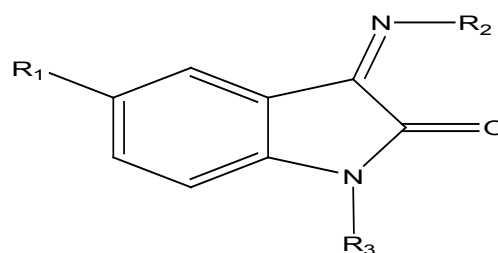
Figure 7: 3-(4-chloro-phenylimino)-5-methyl-1, 3-dihydro-indole-2-one derivative [124]. (R$_1$ =H, CH$_3$, CH$_3$, 4-methylphenyl, 4-chlorophenyl, 1-naphthyl, R$_3$ =H).

Figure 8: 2-aryl-2, 5 dihydropyridazino[4, 3- b]indol-3(3H)ones derivative [125]. (R=H, R$_1$=p-Cl, p-Br, p-OCH3, p-Cl, R$_2$=H, CH3).

X= Br, Cl

Figure 4: 3-cycloalkanone-3, 4-hydroxy-2-oxindolesderivatives [121].

Figure 5: Metal complexes of isatin-3-glycine (M=Cu,Zn,Co) [122].

compounds having X= H, Cl, Br group were found to be potent against pentylenetetrazole (PTZ) and induced seizures in mice .

Popp et al. [127] studied Comparative anticonvulsant activity of different compounds (Figure 10). They found that 3-hydroxy-3-acetonyloxindole (10 A) have greater anticonvulsant activity than 3-hydroxyl-3-pehenacycloindole (10 B). The compounds 3-acetonyldeneoxindole (11A) and 3-acetophenylideneoxindole (11B) haveless anticonvulsant activity. Another compound 3-cyclohexenonyloxindole (11C) have enhanced activity in MES screen from 300 to100 mg/kg. Thus compound 3-hydroxy-3-cyclohexanonyloxindole (10C) was found to have potent anticonvulsant drug showing activity at 300 mg/kg by body weight in the MES test.

Muller et al. [128] were found that oxindole, isatin and

Figure 9: 2-aryl -2, 5-dihydropyridazino [4, 3-b] indol-3(3H) ones [126]. (X=H, Cl, Br).

Figure 10: Comparative anticonvulsant activity of different compounds.

NmethylIsatin-3-thiosemicarbazene injected (1/p) in the rat,inhibited monoamine oxides in liver homogenate, Isatin-3-hydrazone was much less effective as an inhibitor,introduction of Br group at the position 5 in certain analogne safforded 5-bromoisatine, 5-bromo-N-methylisatin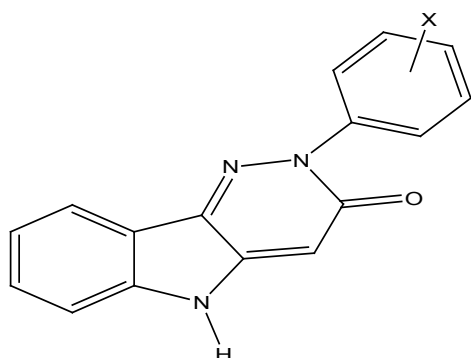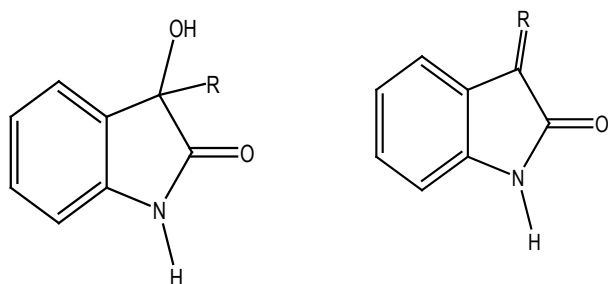 and 5-bromoisatin-3-hydrazone. The bromo group markedly increased the inhibitory effectiveness of the unsubstituted compounds.

Applications

Isatin is known as a colouring agent for amino acid proline, it leads to formation of a blue derivative [129]. It was used in pollens for the determination of the level of aminoacid [130-133] and other vegetal materials [134] by using paper chromatography. It has been used in a colourimetric screening test of human serum for hyperprolinemia [135], in a colourimetric assay of HIV-1 proteinase [136] and also for the estimation of the age of bones in crime investigations [137]. Isatin-3-hydrazone is studied for colourimetric determination of steroids [138,139]. Another application of isatin is steroid analysis and it can be used as coloured marker in the Sephadex LH-20 chromatographic separation of steroidal blood components [140,141]. For the detection of amino acid by thin layer chromatography a fluorogenic derivative of isatin is reacted with tryptophan [142,143]. It is useful for the detection of 3, 4-dehydroproline, which is oxidized by isatin and further reacted with p- dimethylaminobenzaldehydeto to give a coloured derivative [144]. 1-Chloromethylisatin has been used as a derivatizing agent for alcohols [145], small chain [146] and fatty carboxylic acids [147], and amines, including indole [148]. Isatin is also used in determination of the enzymatic activity of ketopantoyl-lactone reductase [149-151] and other fungal carbonyl reductases [152].

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