Unleashing The Power of Isatin: A Comprehensive Review of its Dynamic Reactions and Innovative Applications in Modern Chemistry

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ABSTRACT

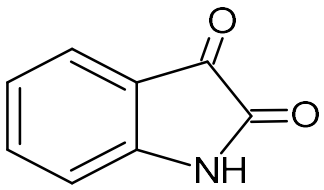
One of the potential heterocyclic chemical molecules is isatin (1H-indole-2,3-dione), which serves as the starting point for variety of derivatives with oxindole moiety also it shows various biological and pharmacological activities. The structural modification of the compounds improves its efficiency. We have covered the chemical characteristics, structural modifications, spectrum analyses, and a few commercial and biological applications of isatin variations in this review.

Keywords: Anticancer, Isatin, Luminescent sensor, spectra, Tribulin

INTRODUCTION

By utilizing nitric acid and chromic acid to oxidize indigo, Erdmann and Laurent first identified isatin as a by-product. It is an orange-red substance with a monoclinic prism crystal structure that crystallizes from water, alcohol, or acetic acid and melts at 200 °C[1]. Isatin is a metabolic product of the hormone adrenaline that is present in humans. Moreover, it is a part of the fluid made by the parotid gland in Bufo frogs[2]. Isatin scaffold is primarily utilised for anticancer treatments and is used in numerous organic synthesis processes. Chemotherapy is currently the most popular and effective cancer treatment[3]. Isatin has an extensive pharmacological profile, and researchers continue to use these heterocyclic moieties—either individually or in combination—to identify

new medications[4]. Isatin otherwise called as tribulin is a structural combination of a six-membered benzene ring and a nitrogen-containing five-membered ring, all of which are on the same plane but differ in that one is aromatic and the other is anti-aromatic. Isatin can exist in two structural isomers, the lactam structure as well as the lactim structure, as revealed by Baeyer in 1882[5]. The various tribulin derivatives have been shown to have a wide range of pharmacological features, including anticancer[6], anticonvulsant[7], antidepressant[8], antimicrobial[9], antiviral[10], and anxiolytic activities[11]. Molecular docking research of isatin variants as Epidermal growth factor receptor inhibitors[12] and anti-inflammatory substances[13], as well as the powerful anti-inflammatory effects of Indocin, Lodine, and tenidap, compelled all of us to isatin derivatives can be found in many different types of colours, agricultural chemicals, and medications, especially in physiologically active compounds. The research has garnered a lot of curiosity and pharmacology of isatin derivatives for their variety of actions due to its special size and privileged electronic characteristics.[14]



2,3-dioxoindoline

Fig.1. structure of isatin (tribulin)

1. CHEMICAL PROPERTIES

Different reactions happen when isatin is positioned differently[15]. The carbonyl group at the C2 position can also be investigated for the formation of spirocyclic substances, indigo, and indirubins, while the carbonyl group at C3 can be transformed into the effective imine or hydrazone variants as well as used for the synthesis of spirocyclic compounds and oxindoles[16]. The NH group can undergo N-alkylation[17], N-arylation[18], and N-acylation[19] in this way. When isatin reacts with carbamyl-urea, imine is produced with several free amino-containing substances relatively quickly by the addition of glacial acetic acid (fig.2).[20]

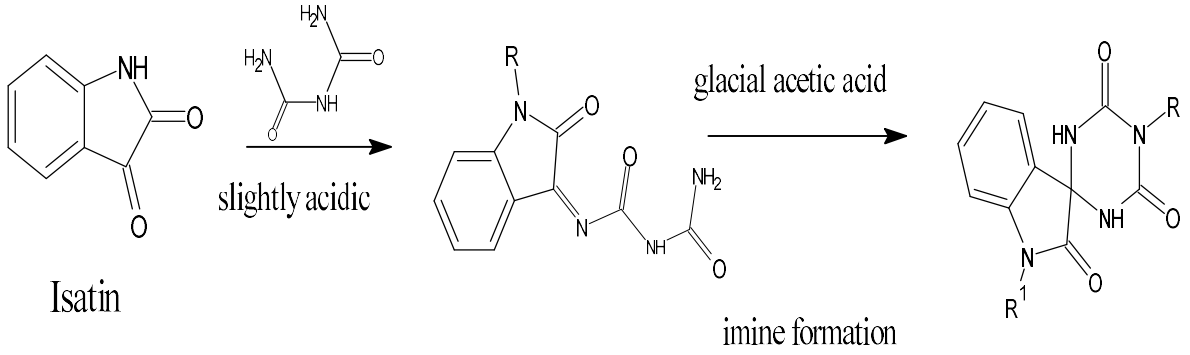


Fig.2

Another is the Wittig reaction, which produces alkenes by employing phosphonium ylide at the third position of isatin(fig.3).[21,22]

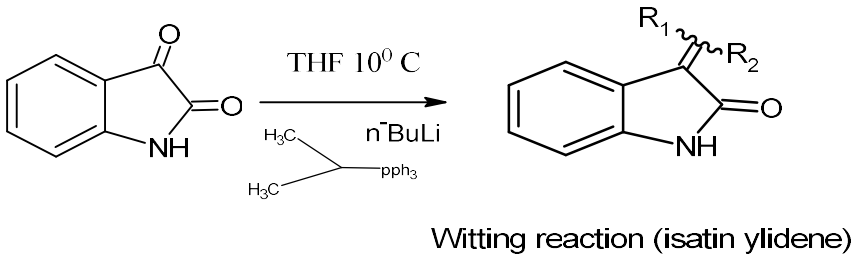


Fig.3

It is feasible to change isatin into oxindole at the third position carbonyl atom by first converting it to 3-hydroxy isatin and then going through reduction (fig.4).[23]

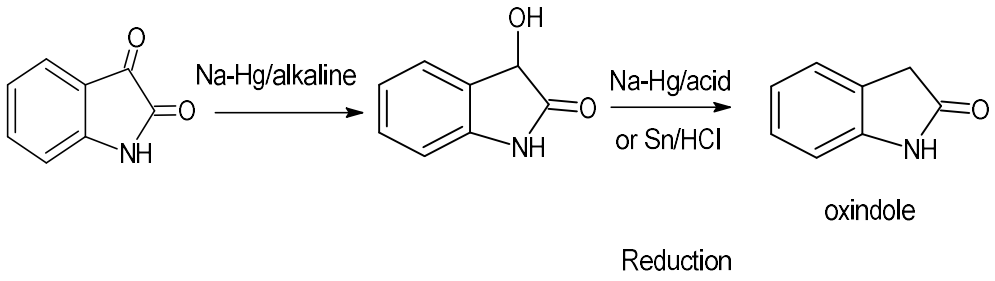


Fig.4

Isatin can have its first -NH position alkylated or acetylated with the use of a base in DMF solvent. The second position can be converted into O-alkylated Regio isomers with an alkyl halide in the presence of silver salts (fig.5).[24]

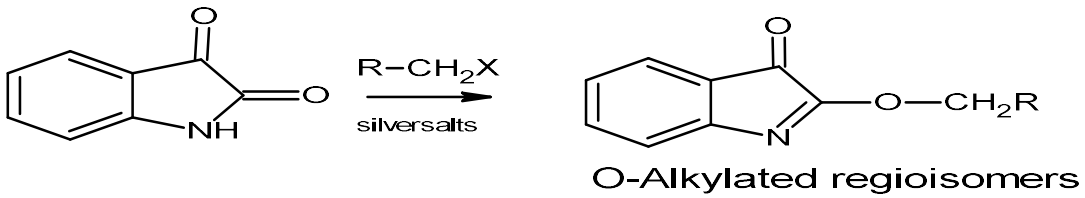


Fig.5

Isatin can be made from anthranilic acid, but if chromium trioxide/acetic acid or hydrogen peroxide are present, it may also be turned back into anthranilic acid through oxidation(fig.6).[25]

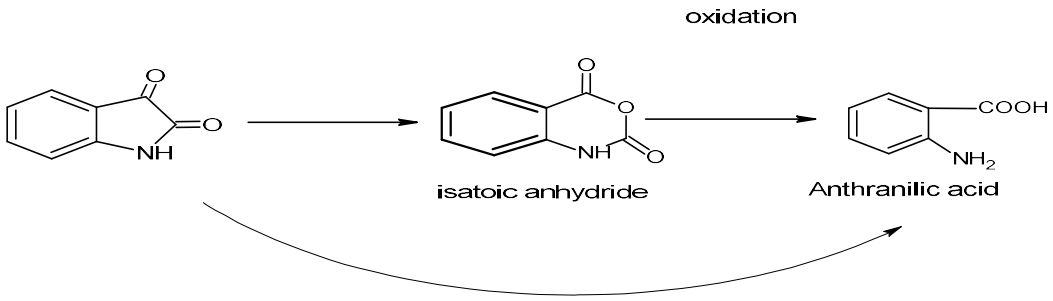


Fig.6

Borane in THF and an alkyl halide react to produce N-alkylated indole when sodium hydride is present. Additionally, it produces 3-alkyl indole when lithium aluminium hydride and alkyl lithium are present(fig.7).[26]

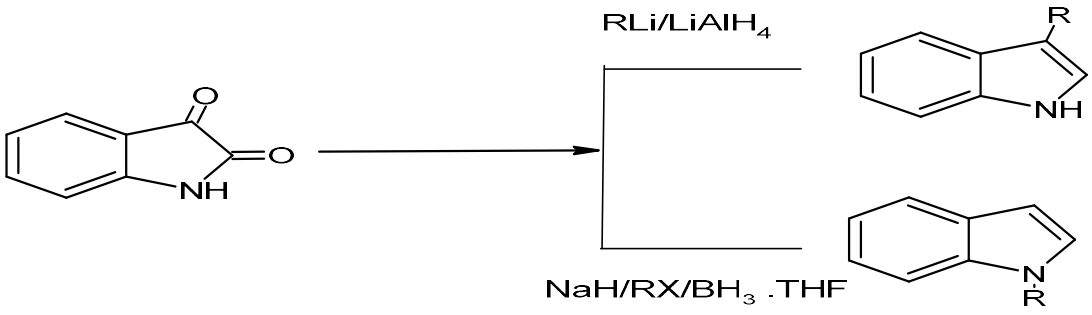


Fig.7

At the fifth position of isatin, electrophilic general substitution processes such halogenation, nitration, or sulphonation take place.

2. STRUCTURAL MODIFICATIONS

Variety of substituents at any point of its core structure, numerous tribulin variants have been created with the goal of creating effective and selective therapeutic medicines[27]. The most plausible positions appear to be at C3 and C5, C6, or C7 in the phenyl ring. A variety of substituents at N1, C3, and any C in the benzene ring modified their characteristics(fig.8)[28]. Position at C3-substituted tribulin, like thiosemicarbazones, oxindoles and their derivatives, imines and hydrazones, have been synthesized[29].

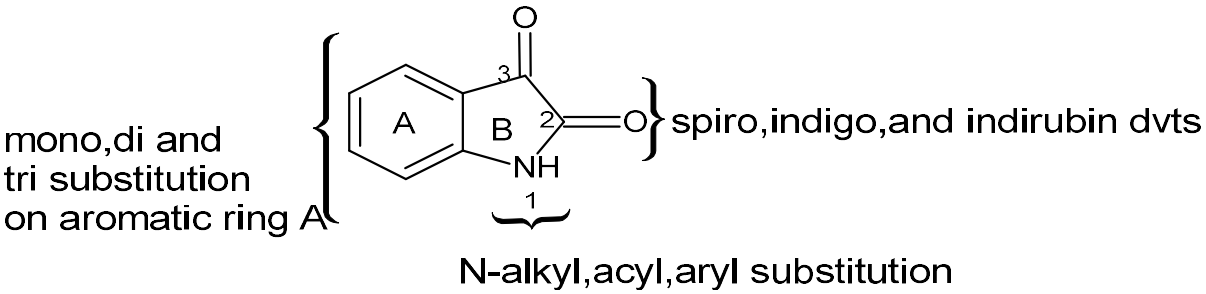


Fig.8

Many unique isatin derivatives were produced by three-direction modifications on the N-1, C-3, and C-5 positions of the isatin structure.[30]. The link between structure and activity was examined using antimicrobial susceptibility assays towards Gram-positive (S. aureus), Gram-negative (E. coli), and methicillin-resistant Staphylococcus aureus (MRSA) bacteria, as well as in vitro enzymatic inhibition studies using E. coli.[31]. It was discovered that the changes made to these 3 locations might significantly increase the antibacterial effectiveness and enzyme inhibitory actions.[32]

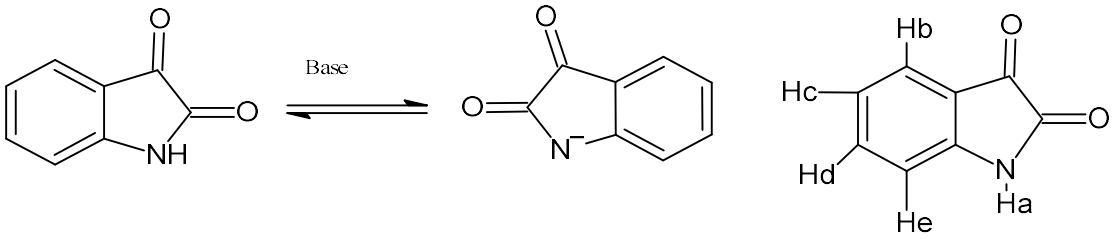
For improving an organic compounds characteristic for certain uses requires structural alterations in the form of adding electron-accepting or electron-donating substituents, more lipophilic or hydrophilic groups, or delocalizing the electron density[33]. At various places in the oxindole core, a variety of coordinating groups were added to control the reactivity of isatin-derivatives as antiproliferative agents[34]. In particular, N donor groups were added into the isatin ring core (imines, amines, hydrazines, hydrazones, oximes, and thiosemicarbazones)[35]. It has recently been reported that isatin can be hybridized with other anticancer pharmacophores, such as imines,

azoles, quinolines, quinazolines, sulphonamides, and coumarins, to create appealing frameworks for new anticancer medications that are more effective and less harmful.[36]

3. SPECTRAL STUDIES

Isatin has a maximum absorption in the UV-visible spectrum between 260 - 350 manometers, which corresponds to an aromatic ring-driven transition. The maximal absorption and band intensity in this region are determined by the aromatic ring's donor or acceptor capacity. The maximum band changes bathochromically as the ring's donor capacity rises[37]. The n $\rightarrow\pi^*$ and intramolecular charge transfer (ICT) transitions of the free electron pairs of nitrogen and oxygen correlate to a relatively weak absorption band in the range of 350 nm to 600 nm. In a basic solution, a new bathochromically shifted band in the range of 400 nm to 750 nm appears in place of the long-wavelength absorption bands in the region of 350 nm to 600 nm. This new band is the result of an azanion formation(a). A doublet at 7.47 ppm and 6.86 ppm, corresponding to Hb and He, respectively, may be seen in the isatin ^{1}H-NMR spectra(b). At about 11.03 ppm, the hydrogen atom (Ha) bound to nitrogen is visible as a singlet. At about 7.05 ppm and 7.57 ppm, respectively, the protons Hc and Hd display triplets. The protons of the azanion (Hb, Hc, Hd, and He) move downfield in the ^{1} H-NMR spectrum as a result of deprotonation of NH in the isatin moiety.[38]

Additionally, the isatin's infrared spectra(fig.9) exhibits two powerful bands at 1740 and 1620 cm^{-1}, which stand in for the carbonyl stretching vibrations. When N-H is stretched, a broad band with a few sub bands appears at 3188 cm^{-1}, which shifts to 2370 cm^{-1} when N-H is deuterated.[39]



(a) (b)

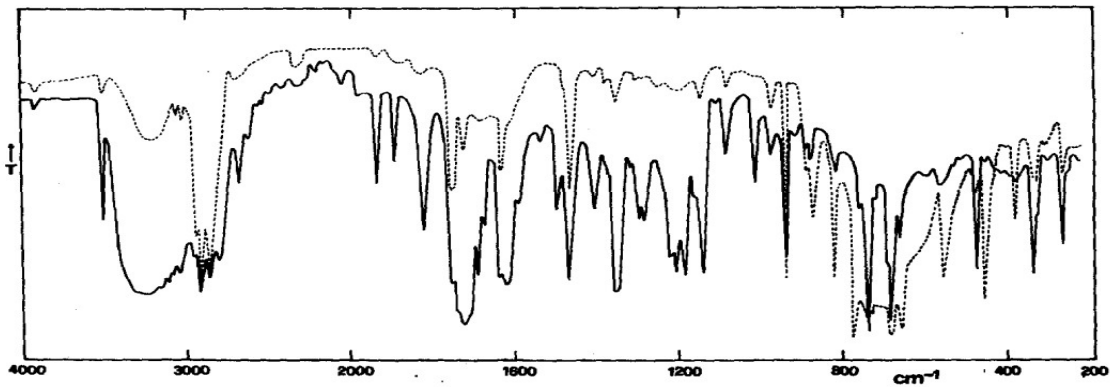


Fig. 9. Polarised IR spectra of isatin

In the mass spectra of N-alkyl isatin with a normal C1-C10 chain, it is shown that as the alkyl radical is lengthened, the intensity of the peaks characteristic for isatin and N-methylisatin decreases, whereas the intensity of the peak formed by the sequential loss of a CO group by the molecular ion and a portion of the radical as a result of cleavage of the bond at the carbon atom increases (fig.10). N-alkyl isatin with chains beginning with more than two C atoms exhibit fragments due to cleavages in their spectra, both without and with hydrogen atom migration.[40]

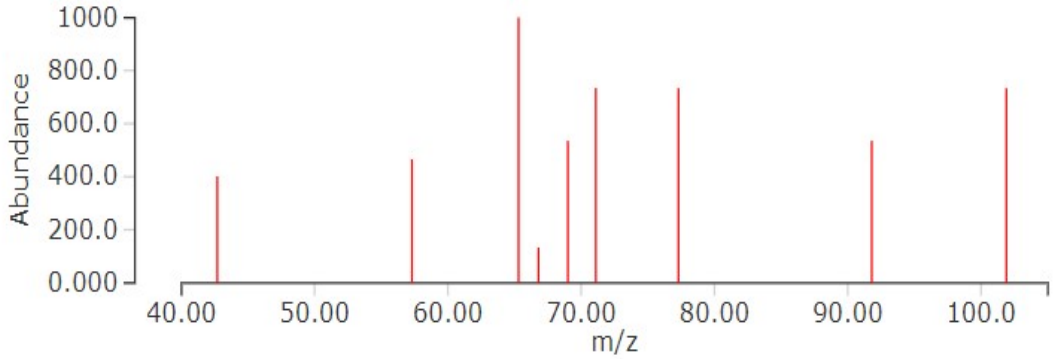


Fig. 10. Mass spectrum of isatin

4.INDUSTRIAL APPLICATIONS OF ISATIN

CORROSION INHIBITORS

Iron and steel corrosion is a significant industrial issue. It has been observed that organic molecules with heteroatoms like N, O, and S work well as inhibitors against the rusting of steel in acidic environments[41]. It has been reported that derivatives of isatin and their Mannich bases are effective corrosion inhibitors for steel and aluminium.[42] Three recently created isatin derivatives have been tested in hydrochloric acid to see how well they inhibit corrosion on carbon steel. With an increase in concentration, these compounds performed more effectively as inhibitors. The chemical was readily protonated in HCl solution to generate a cation-ionic form, which was then adsorbed at the metal surface via the already-adsorbed chloride ions[43]. It has been observed that a number of N-substituted isatin-based thiosemicarbazones effectively inhibit corrosion on the steel surface in 1 M HCl. Additionally, in this instance, the concentration of the inhibitor grew along with the corrosion efficiency.[44]

LUMINESCENT SENSOR/PROBE

One of the most active areas of research for chemists is the detection and measurement of metal ions in biological systems and the environment. Particularly highly harmful pollutants, such as heavy metal ions like Hg (II), Cd (II), and Pb (II), must be quickly detected in order to protect the environment, the general people, and the safety of food. The detection of Hg (II) in water has recently been reported using isatin functionalized nano porous SBA-15 as a selective fluorescent probe. SBA-15 displayed remarkable selectivity for Hg (II) over a number of other metal ions in aqueous conditions with a detection limit of 3.7 10-6 M. 45 Moreover, it has the ability to detect Hg (II) in a pH range from 4 to 10. In a different work, Hg (II) was specifically detected over a variety of transition metals and heavy metal ions in an ethanol-Tris buffer environment using a novel fluorescent probe based on an isatin-rhodamine hybrid..[46] In addition to Hg (II) detection, an isatin-based Schiff base sensor, with limits of detection in the range of 2-3 μM and 7-9 μM, respectively, has been developed for the detection of Cu^{2+} and S^{2-} in human blood serum.[47] A rhodamine-isatin-based sensor (RIH)was reported by Goswami et al. in order to detect $Al3^{+}$ in aqueous medium. For the purpose of detecting the pyrophosphate anion, the complex created (RIH-$Al3^{+}$) also functions as a fluorescence chemo sensor.[48]

DYES

Dye is a common colouring chemical used in the cotton and textile industries. It also has a significant impact on contemporary electronics. Isatin and its derivatives, such as indigo (a derivative with a C-2 substitution) and isoindigo (a derivative with a C-3 substitution), are adaptable natural dyes. The textile industry has utilized indigo as a vat dye, which is likely the oldest and most well-known dye[49]. Due to their electron-accepting qualities, indigo and its many derivatives, including Tyrian purple, indigo carmine, and indirubin, have applications in field effect transistors. They are also employed as food colorants in the food business[50]. An isomer of indigo called isoindigo has been utilized to make electro-active materials for organic electronics[51]. Materials for organic photovoltaics are produced by adding isoindigo to a scaffold made of π-conjugated polymers[52]. In this regard, it has been suggested that pyrazine-fused isoindigo dye is a promising component for creating donor-acceptor conjugated polymers for optoelectronic applications.[53]

5.BIOLOGICAL ACTION

5.1 ANTICANCER ACTIVITY

The 1,2,3-triazole is a common moiety with adaptability and biodiversity that can be used to make novel medications. It can improve the pharmacological, pharmacokinetic, and physicochemical properties of compounds[54]. Moreover, compounds containing 1,2,3-triazoles, like cefatrizine and carboxy amido-triazole, can be used to treat a variety of tumours, playing a vital role in the framework of cancer control. [55] The combination of isatin with 1,2,3-triazole thus opens the door to the development of novel anticancer medications. When compared to their unsubstituted analogues, hybrids with methoxy at the phenyl ring (R2) did not increase activity, but electron-donating bulky aryl groups at the C-5 position (R1) of the isatin moiety were favoured to electron-withdrawing groups. (fig.11).[56]

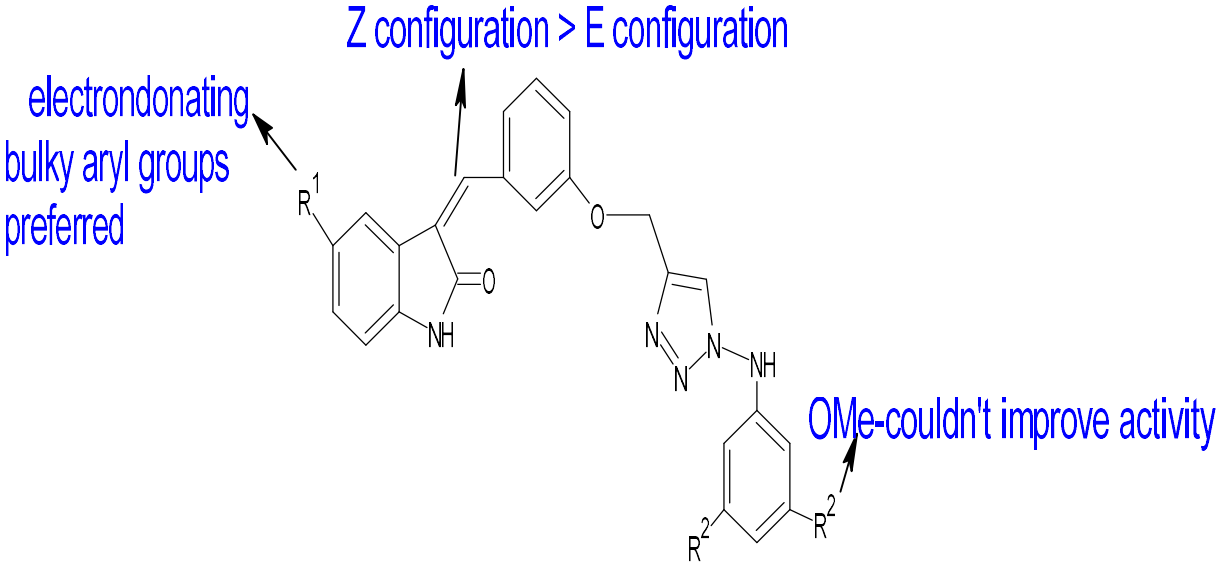


Fig.11

The pharmacological features of thiazole or thiazolidinone compounds include anticancer action, and several anticarcinogenic drugs, like tiazofurin and bleomycin, contain thiazole or thiazolidinone moiety. So, the isatin thiazole or thiazolidinone derivatives could serve potential novel anticancer agents[57]. The SAR showed that the thiazole component was essential for the high activity and that switching from thiazole to phenyl caused a substantial decrease of activity. It was advantageous to the activity to introduce halogen atoms into the isatin motif's C-5 location, with Cl > Br > H making the largest relative contributions. Comparing the activity of the substituted compounds to the unsubstituted analogues, those with electron-donating methyl at the thiazole skeleton shown increased activity. At the para position of the phenyl ring on the thiazole moiety, an electron-donating or electron-withdrawing group could be added to decrease the activity (fig 12).[58]

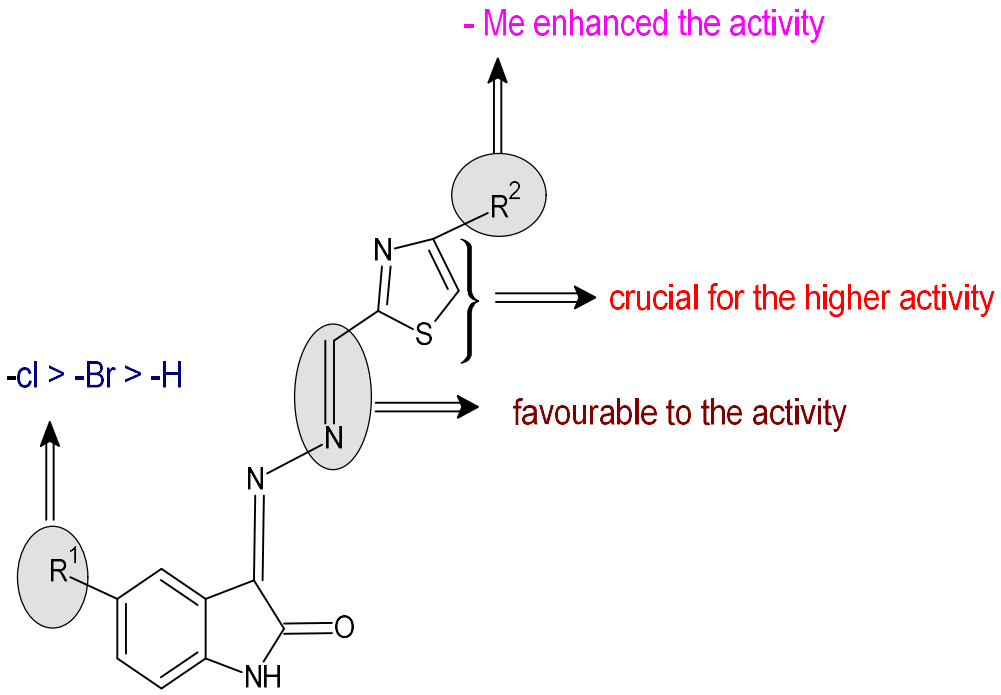


Fig.12

isatin and the pyrazole/pyrazolidine/pyrazolone motif may hybridize to create new anticancer substances with a variety of action mechanisms. A panel of 60 human cancer cell lines, including leukaemia, lung, colon, central nervous system (CNS), melanoma, kidney, ovarian, breast, and prostate cancer cells, were very sensitive to the isatin-thiazolidinone-pyrazoline hybrids[59]. The SAR showed that adding a substituent to the isatin moiety's N-1 position was detrimental to the activity, whereas adding an electron-donating methyl or an electron-withdrawing chloro or bromo at the C-5 position was advantageous. Naphthalen-2-yl may replace the substituted phenyl ring at the C-3 position of the pyrazoline fragment, and both electron-withdrawing and electron-donating groups were accepted at the R_4 position (fig.13).[60]

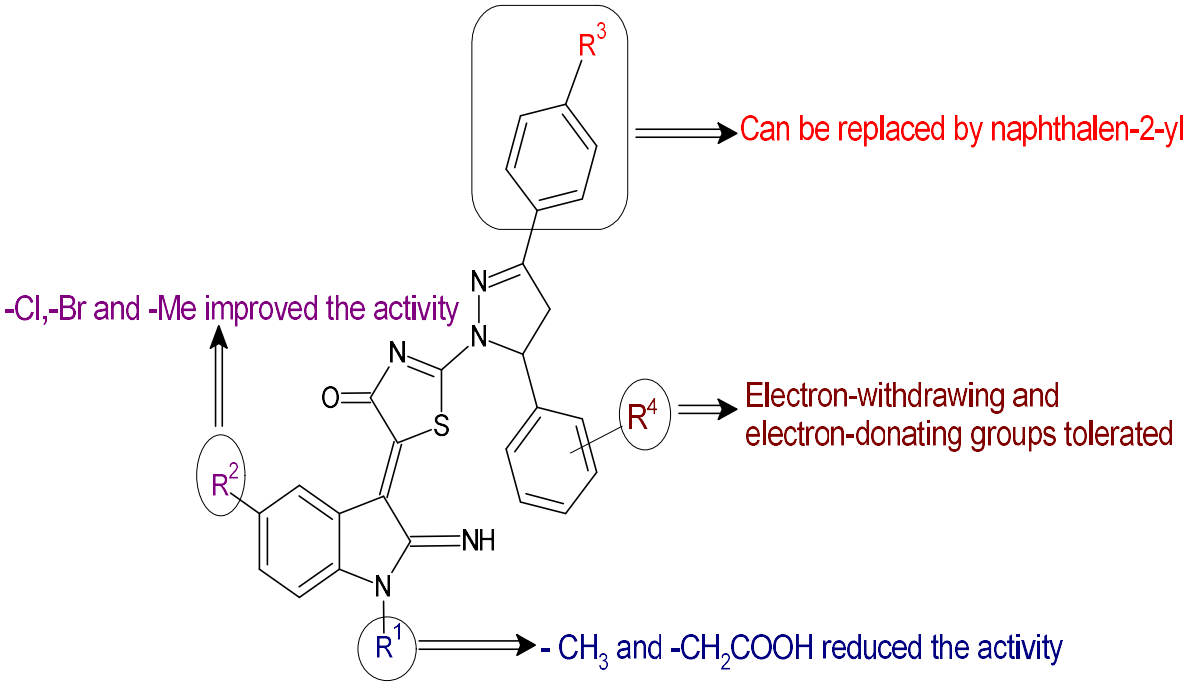


Fig.13

Isatin-imidazole or benzimidazole or imidazolone hybrids may be an appropriate choice for the discovery of new anticancer candidates, which may be active against both drug-sensitive and drug-resistant cancers[61]. Imidazole/benzimidazole/imidazolone derivatives such as pretomanid and delamanid exhibited great potency against both drug-sensitive and drug-resistant pathogens, even multidrug resistant organisms[62]. Despite showing promising activity against MCF-7 cancer cells, the isatin-benzimidazole hybrids were not as effective as doxorubicin[63]. As hybrid demonstrated the maximum activity, the SAR indicated that inserting a diphenyl amino group for the nitrogen-containing heterocycles at the N-1 position of the isatin motif was advantageous for activity. When compared to unsubstituted analogues, the anticancer SAR of hybrids showed that sulphur at the X position of the imidazolone fragment was superior to oxygen and bromo at the C-7 position (R) of the isatin moiety could increase activity. The activity of hybrids might be increased by adding halogen atoms to the isatin moiety's C-5 position (fig.14).[64]

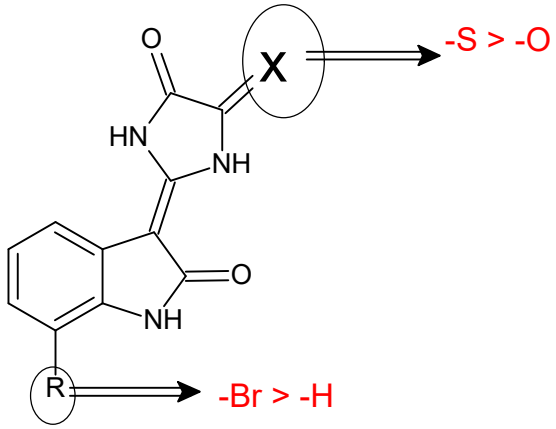
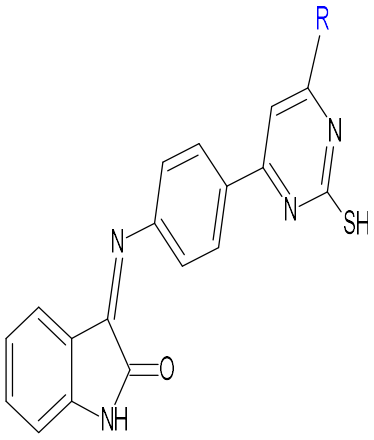


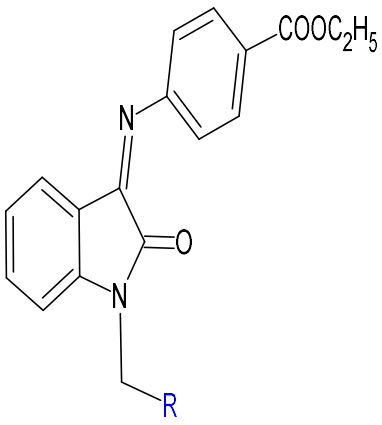
Fig.14

5.2 ANTIBACTERIAL ACTIVITY

Isatin derivatives are being extensively investigated by researchers for their antibacterial activity since they have therapeutic potential against a variety of harmful microorganisms. Numerous studies, it has been claimed that the isatin and its derivatives' Schiff and Mannich bases have strong antibacterial properties.[65] For a number of Schiff bases of isatin, the antibacterial and antifungal activity against Gram positive (Staphylococcus aureus and Bacillus subtilis), Gram negative (Escherichia coli and Proteus vulgaris), and fungi (Candida albicans and Aspergillus Niger) were studied in vitro (**A** & **B**). Findings showed that these substances considerably slowed the development of the microorganisms B. subtilis, S. aureus, and E. coli. Compound A-6 demonstrated considerable anti-fungal action in addition to the anti-bacterial activity, comparable to the conventional medication clotrimazole.

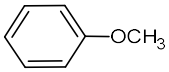
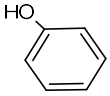
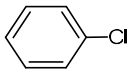
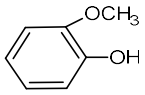
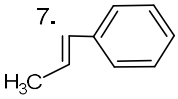


(A)

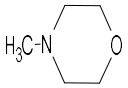
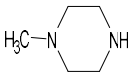
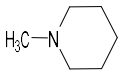
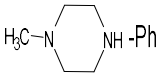


(B)

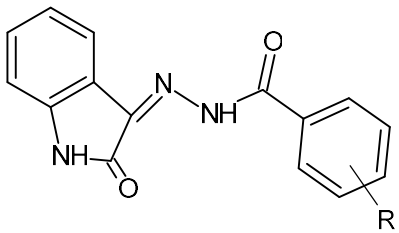
R for compound A

1. 
2. 
3. 
4. 
5. 
6. 
7. 

R for compound B

1. $-N(Me)_2$
2. $-N(Et)_2$
3. $-N(Ph)_2$
4. 
5. 
6. 
7. 

In a different study, kanamycin and chloromycetin were used as the usual medications while seven isatin derivatives (**C**) were evaluated against E. coli, P. aeruginosa, B. subtilis, and S. aureus. The findings showed that compound Ca (R = 3-F) displayed superior anti-bacterial activity against E. coli and P. aeruginosa, while compound Cb (R = 3-Cl) and Cc (R = 3-Br) demonstrated stronger anti-bacterial activities against S. aureus.[66]



(C)

In another study, it was discovered that the isatin compounds thiosemicarbazone and dispiropyrrolidine inhibit Mycobacterium tuberculosis expansion[67]. According to research

conducted in vitro, isatin-3- phenylhydrazone exhibits greater antibacterial efficacy than the reference drugs amoxicillin and norfloxacin against Proteus vulgaris, Proteus aeruginosa, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus[68]. Additionally, it has been shown that the one-pot synthesis of spiroxindoles produced from isatin exhibits good and moderate antibacterial efficacy against a variety of bacterial and fungal strains[69]. However, it has been noted that metal complexes of lanthanides can modify a number of variables, such as the molecule's lipophilicity, to boost the antifungal potential of isatin bishydrazones.[70]

5.3 ANTIVIRAL ACTIVITY

Isatin exhibits strong potential against numerous viruses. For their cytotoxicity and inhibitory effect against the Respiratory Syncytial Virus (RSV), which infects infants under 2 and may be fatal, isatinoxime ethers have been studied in vitro[71]. 5-fluoroisatin derivatives have been reported to exhibit strong inhibitory effect on Vero clone CCL-81 cells that have been pre-treated with vesicular stomatitis virus during in vitro tests[72]. One of the isatin derivatives, ID45, has been reported to have good potential for reducing viral growth and hindering the process of virus-induced apoptosis. Recently, substituted hydrazine derivatives of isatin have been stated to have good antiviral potential against Coxsackie virus B3, which is a primary cause of viral myocarditis and results in sudden death [73].

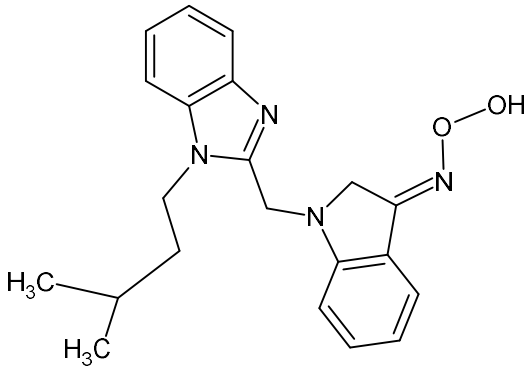


Fig.15

5.4 ANTIDIABETIC ACTION

Diabetes mellitus (DM), often known as diabetes or hyperglycaemia, is a syndrome that is defined by an abnormally slow metabolism and high blood sugar levels (hyperglycaemia) that are either caused by low amounts of the hormone insulin or by an abnormal resistance to the effects of insulin. The new chemical 1-(4-(di methylamino) benzylidene)-5-(2-oxoindolin-3-ylidene)-thio-carbohydrazone (fig.16) has been shown to have anti-diabetic properties. Blood glucose levels significantly decreased after the chemical was given to diabetic rats in single doses of 50 and 100 mg kg1 in a dose-dependent manner.[74]

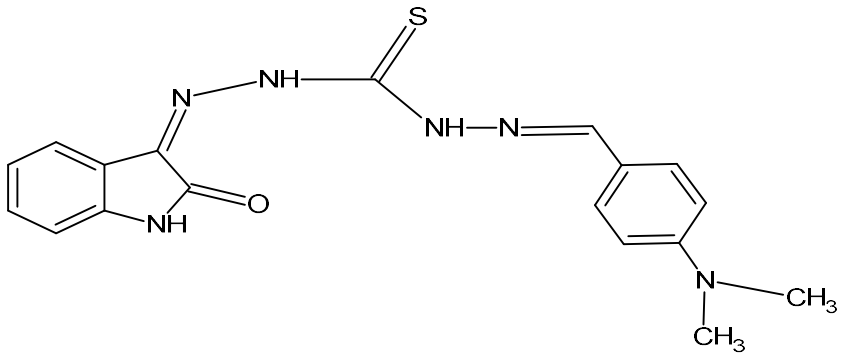


FIG.16

5.5 MONO AMINE OXIDISE INHIBITION

Monoamine oxidase (MAO) is a group of enzymes that uses dopamine as a substrate to catalyze the oxidation of serotonin and norepinephrine. MAO activity in the human brain rises with aging and is linked to neurodegenerative diseases like Parkinson's disease[75]. Research on the synthesis and evaluation of MAO inhibitors is ongoing, and isatin has been identified as a reversible inhibitor of the MAO isozyme(fig.17)[76]. Furthermore, isatin derivatives with substitutions at positions C5 and C6 are reversible inhibitors of MAO-(A and B); nevertheless, isatin derivatives with substitutions at positions C5 and C6 benzyloxy have been described as MAO-B inhibitors with IC50 values of 0.103 M and 0.138 M, respectively[77].

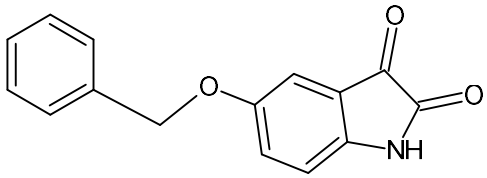


FIG.17

5.6 ANTHELMINTIC ACTIVITY

With a 5 g/ml concentration, a new series of tetradentate Schiff bases was created and tested for anthelmintic activity against the earthworm (Pheretima posthuma)[78]. From various substituted chalconised indole-2,3-diones made from various chalconised isatin, a number of new isatin derivatives were created. According to some substances, Pheretima posthuma is resistant to anthelmintic activity. Different 3-(2- hydrazino benzothiazoles)-substituted Indole-2-one derivatives were produced, and all of the resulting substances were tested for their anthelmintic potential using adult Indian earthworms (Pheretima postuma).[79]

5.7 ANTI-TUBERCULAR AGENTS

Isatin is a versatile lead molecule for developing a possible anti-tubercular agent because it has been observed that isatin derivatives have anti-tubercular activity. Natural products make up some of these derivatives. Tryptanthrin, an alkaloid from the Chinese herb Strobilanthes cusia, demonstrated substantial activity against MTB H37Rv (1mg/l), for instance[80]. A new non-nucleoside reverse transcriptase inhibitor with antimycobacterial qualities was created as an isatin-imino lead chemical for the efficient treatment of AIDS and AIDS-related TB. We created Schiff bases from derivatives of isatin and nalidixic acid carbohydrazide. Four Mycobacterium strains—Mycobacterium intercellulare, Mycobacterium xenopi, Mycobacterium chelonae, and Mycobacterium smegmatis—were tested for the synthesized derivatives' anti-TB efficacy. The studied compounds showed only weak anti-TB efficacy [81].

5.8 ANTI-ANXIETY ACTIVITY

Isatin derivatives that work as anti-anxiety medications include 5-hydroxy isatin, isatinic acid, Spiro benzodiazepines, Schiff bases of N-methyl and N-acetyl isatin, and others. The aromatic ring of isatin was hydroxylated to create a new class of 5-hydroxy isatin derivatives, which had a minor antianxiety effect[82].

6. CONCLUSION

One of the most actively studied topics in synthetic and medicinal chemistry continues to remain isatin. Organic chemists are developing a number of unique and environmentally friendly methods of synthesising isatin derivatives due to the medical applications linked with them. More research into these reactions could be done in order to create such new compounds. It is possible to investigate isatin further for industrial use, particularly as a fluorescence probe. As a selective fluorescent probe for the detection of Hg (II) in water, it has been described. The new isatin derivatives display promising anti-cancer, anti-viral, anti-anxiety, anti-bacterial, anti-diabetic, anti-TB, MAO-inhibition activity and other properties. Isatin is an essential nucleus owing to all of these characteristics, which also present new research opportunities.

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