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A REVIEW ON RECENT ADVANCES IN CHEMISTRY, SYNTHESIS AND BIOLOGICAL APPLICATIONS OF ISATIN DERIVATIVES

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ABSTRACT

Indole and its derivatives have engaged a unique place in the chemistry of nitrogen heterocyclic compounds. The recognition of the plant growth hormone, heteroauxin, the significant amino acids, tryptamine & tryptophan and anti-inflammatory drug, indomethacine are the imperative derivatives of indole which have added stimulus to this review work. Isatin (1H-indole-2,3-dione), an indole derivative of plant origin. Although it is a naturally occurring compound, but was synthesized by Erdmann and Laurent in 1840 before it was found in nature. Isatin is a versatile precursor for many biologically active molecules and its diversified nature makes it a versatile substrate for further modifications. It is concerned in many pharmacological activities like anti-malarial, antiviral, anti-allergic, antimicrobial etc; isatin and its derivatives have been also found to demonstrate promising outcomes against various cancer cell lines. This review provides a brief overview on the recent advances and future perspectives on chemistry and biological aspects of isatin and its derivatives reported in the recent past.

Keywords: Isatin, indole derivative, anti-malarial, anti-allergic, anti-viral.

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INTRODUCTION

A large number of naturally occurring compounds, like alkaloids, were found to possess indole nucleus. In medicinal chemistry, isatin is considered as a privileged scaffold with broad spectrum of medicinal properties and vast possibility to undergo chemical transformation.[1] Isatin (1H-indole-2,3-dione) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids.[2]

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives.[3] 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 Couroupitaguianensis, 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 of adrenaline. 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-2'-yl)isatin was isolated from *Streptomyces albus* and 5-(3'-methylbuten-2'-yl)isatin from *Chaetomium globosum*.[4] Isatin has also been found to be a constituent of coal tar. Isatins (1H-indole-2,3-dione) are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as raw material for drug synthesis.[5] Isatins have also been found in mammalian tissue and their function as a modulator of biochemical processes has been the subject of several discussions.[6]

Chemistry of Isatin (1H-indole-2,3-dione)

Many synthetic methodologies have been described for the conversion of isatins to other heterocyclic systems.[7] This chemistry can be generalized as one of the following strategies

a) Partial or total reduction of the heterocyclic ring, leading to indoles and derivatives.

b) Oxidation of the heterocyclic ring. For example, conversion of isatin to isatoic anhydride, with

subsequent conversion to other heterocyclic systems as shown in Figure 1.

c) Nucleophilic addition at position C-3, which may be further followed by a cyclization process, with or without N1-C2 bond cleavage (Figure 2); or by a *spiro*-annelation at position C-3 as seen in Figure 2.

d) Nucleophilic substitution at position C-2, leading to the opening of the heterocyclic ring. This process may be followed by an intramolecular or by an intermolecular *exo-trig* cyclization as seen in Figure 3 and Figure 4.

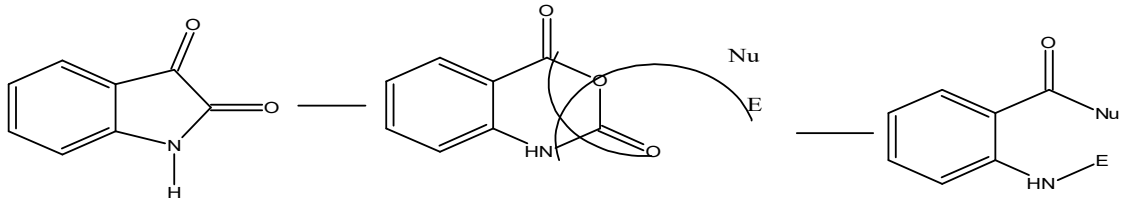

Figure 1

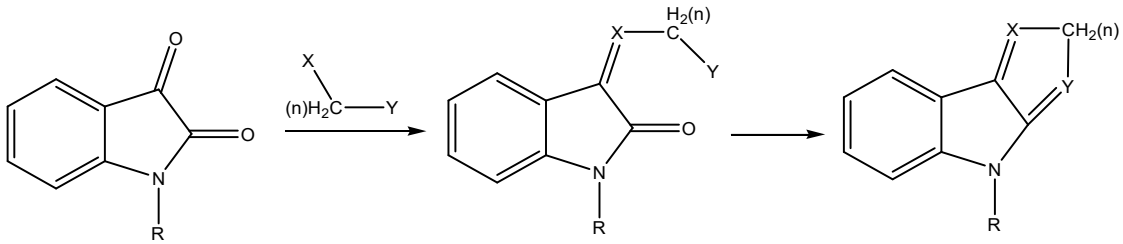

Figure 2

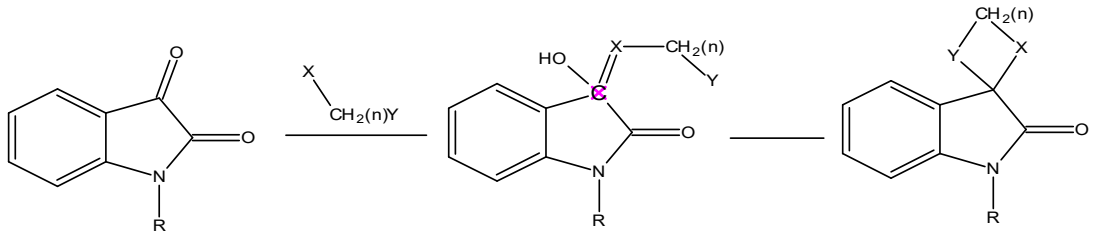

Figure 3

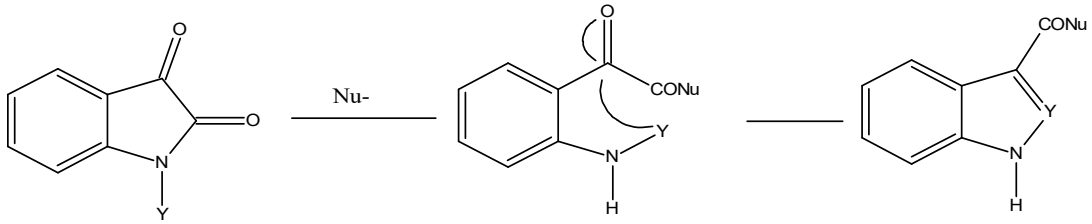

Figure 4

Synthesis of Isatin (1H-indole-2,3-dione)

Sand meyerisatin synthesis: It 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 as given in Figure 5.[8]

Stolleisatin synthesis: 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 TiCl4 has also been used in this method as seen in Figure 6.[9]

Martinet isatin synthesis: 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 as clearly seen in Figure 7.[10]

Gassman isatin synthesis: This methodleads to formation of substituted isatin(40 81% yield)by the formation and subsequent

oxidation of an intermediate 3- methylthio-2-oxindole as seen in Figure 8.[11]

Metalation of anilide isatin synthesis: The recent method for synthesis of isatin is based on ortho-metalation (DoM) of N-pivaloyl- and N-(t-butoxycarbonyl)-anilines. The 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 as observed in Figure 9.[12]

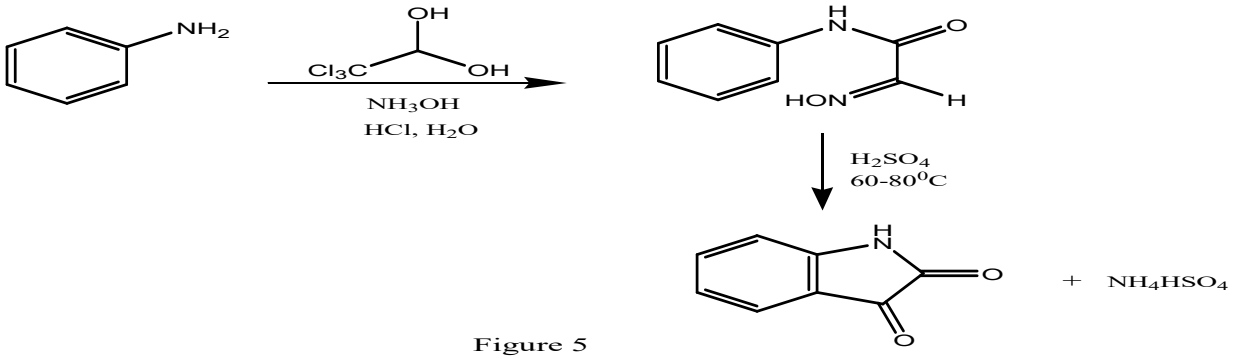

Figure 5

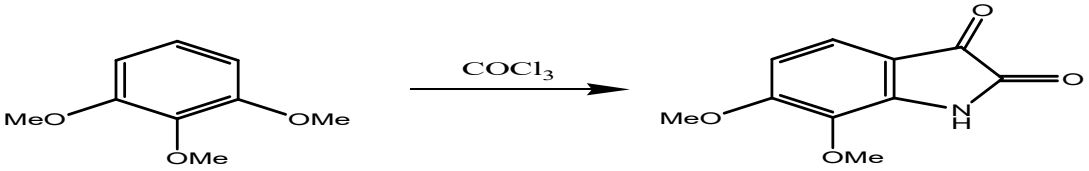

Figure 6

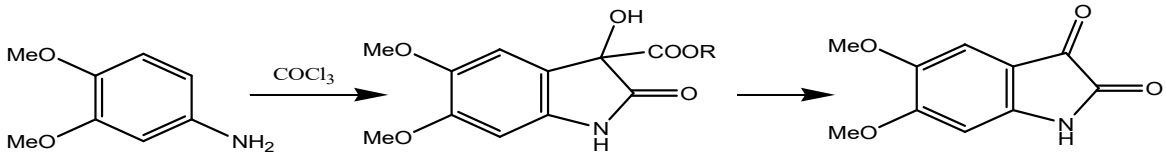

Figure 7

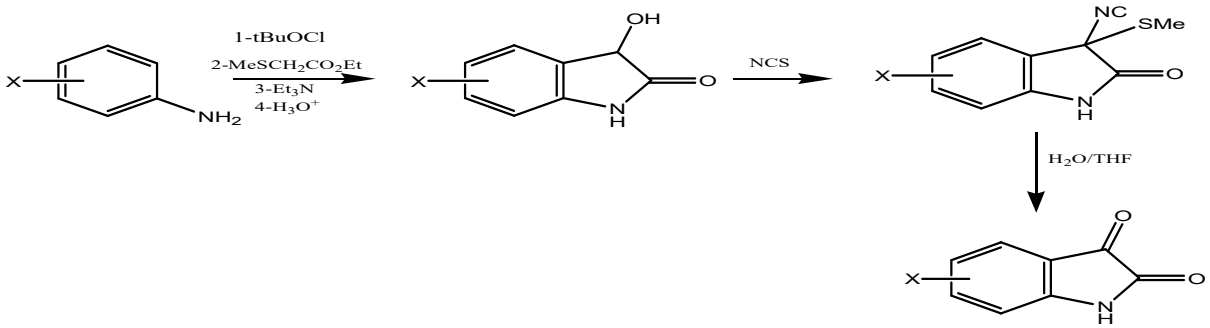

Figure 8

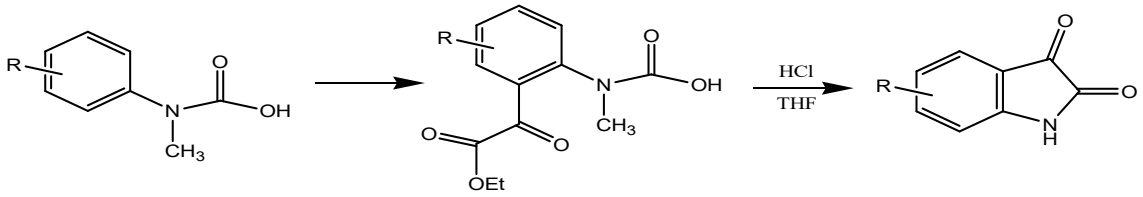

Figure 9

Biological application of Isatin (1H-indole-2,3-dione)

Isatin (1H-indole-2,3-dione) derivatives have been associated with diverse biological activities, some of them are given in Figure 10. Respiratory synctial viral infections can be among the reasons of asthma in infants while during in vitro and in vivo studies (E)-1-((1-(4-fluorobutyl)-1H-benzo[d]imidazol-2-yl)methyl) -3-(hydroxyimino)indolin-2-one [2] derivatives have been described effective against respiratory synctial viral infection.[13] Therefore, a more comprehensive and targeted research is required to find out potential drug molecules against asthma from the isatin derivatives.[14] Isatin and its derivatives have been found effective against a variety of cancer cell lines and possess cytotoxic activity such as 3,3-bis(4-hydroxyphenyl)indolin-2-one [3].[15]

Synthesis, characterization and anticonvulsant activity of novel schiff base of isatin derivatives done by condensation of imesatin with different aromatic aldehydes. All the synthesized compounds screened for anticonvulsant 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 [4] showed excellent anticonvulsant activity with lower dose in MES as well as in ScMet methods.[16]

In vitro studies conducted on Plasmodium falciparum W2 strain, triazole and substituted indole derivatives of isatin like 1-(4-(4-((4-(2-(7-chloroquinolin-4-yl)hydrazinyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)butyl)-3-hydroxyindolin-2-one [5] have been stated as effective antimalarial agents.[17] (Z)-1-((1-isopentyl-1H-benzo[d]imidazol-2-yl)methyl)-3-(methoxyimino)indolin-2-one [6] shows a good potential against a variety of viruses. During *in vitro* studies, isatinoxime ethers have been reported for their cytotoxicity and inhibitory activity against Respiratory Syncytial Virus (RSV), which produces infection in children under 2 years of age and may causes death.[18] One-pot synthesis of spiroxindoles derived from isatin such as (R)-2'-amino-6'-(1H-indol-3-yl)-2-oxospiro[indoline-3,4'-pyran]- 3',5'-dicarbonitrile [7] has been reported to exhibit good and moderate antimicrobial activity against various bacterial and fungal strains.[19]

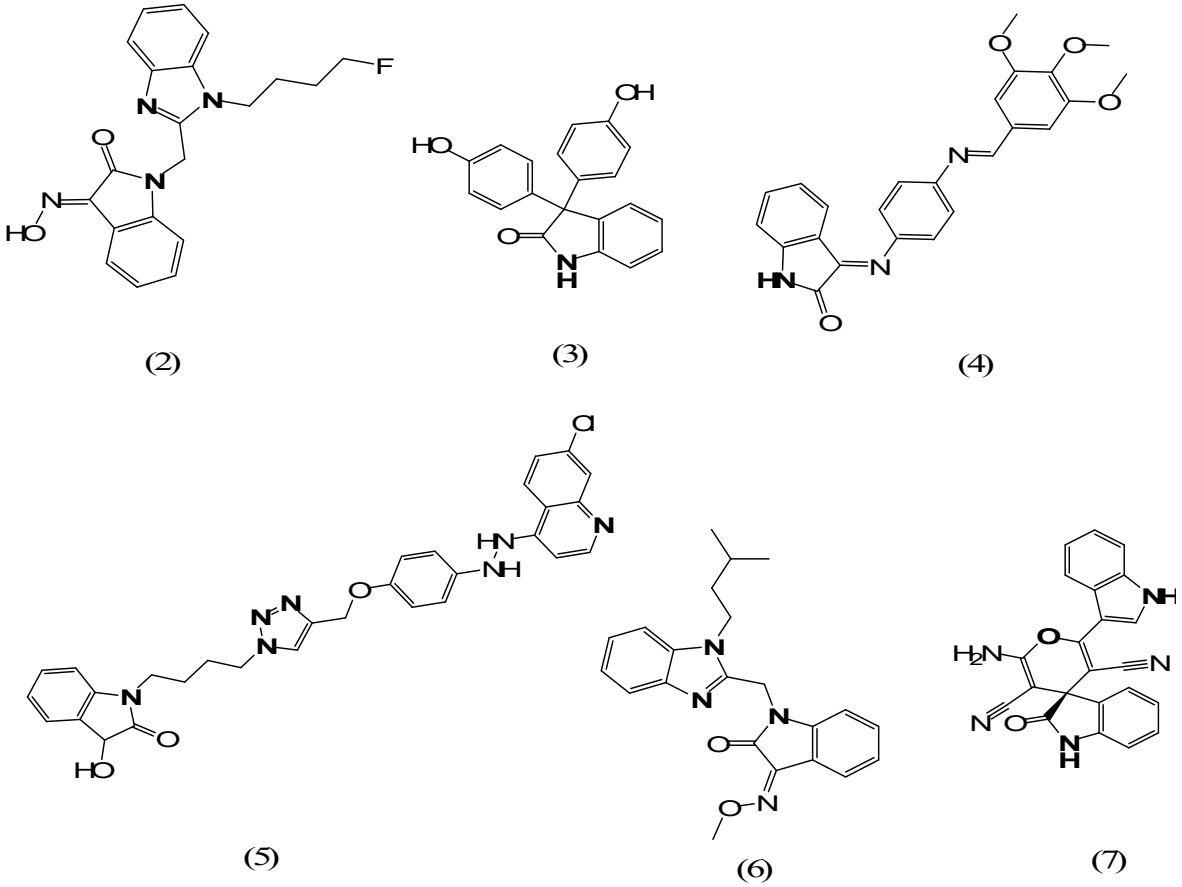

Figure 10: Some of biologically active derivatives of Isatin (1H-indole-2,3-dione)

Different biological activities of 1H-indole-2,3-dione are shown in Figure 10. 5-substituted-3-(4-arylimino)-1-[5-mercapto(1,3,4-oxadiazolyl)] -methyl-indol-2-one have been synthesized by heterocyclization of 5-substituted-3-(4-arylimino)-2-oxo-1- indole acetylhyrazide on treatment with CS2 in ethanolic KOH.

All the compounds were evaluated for their in-vitro antibacterial activity against *S. aureus*, *B subtilis*, *E. coli*, *P. vulgaris* and antifungal against *C. albicans*, *A. niger* standard strains using disc diffusion method. The synthesized compounds showed good antibacterial and antifungal activity.[20] (3Z)-5-bromo-1-methyl-3-[(4-nitrophenyl)imino]-1,3-dihydro-2H-indol-2- one was synthesized by reacting 5-substituted N-methyl/N-acetyl isatin and aromatic amine with glacial acetic acid and was shown to possess good anticonvulsant activity.[21] Bis-diisatin [3,3′] furan synthesized on treatment with furan in presence of diethylamine under intensive stirring. The compounds were evaluated for cytotoxicity study on the brine shrimp as a test organism.[22]

Novel series of Schiff bases of 5-subsituted Isatin and N-acetyl isatin synthesized by using different substituted aromatic aldehydes. These synthesized compounds were investigated for analgesic activity by tail immersion method and anti-inflammatory activity by carrageenan-induced paw oedema method.[23] 1-[N,N-dimethylaminomethyl]isatin-3-[1'(6"-chloro benzothiazol-2"-yl)] synthesized by reacting 3-[-1-(-6-chloro benzothiazol-2 yl)thiosemicarbazone] and formalin with dimethylamine. The synthesized compounds were screened for anti-HIV activity at HIV-1(III B) in MT-4 cells.[24]

Schiff bases of N-methyl and N-acetyl isatin derivatives were synthesized and studied the behavioral effects of isatin, a putative biological factor in rhesus monkeys. Isatin, one of the constituents of tribulin, a postulated endocoid marker of stress and anxiety, has been shown to induce anxiety in rodents.[25]

3-p-(p-(alkoxycarbonyl)phenyl) carbamoyl)phenyl)imino-1-aminomethyl-2-indolinones with antitubercular activity had been synthesized and investigated against *M. tuberculosis* H37Rv. 2-{(benzalamino-4-hydroxybenzyl) (1,3,4)-oxadia zino[6,5-b]} Indole derivative synthesized by condensing 2-Amino-4-[(1,3,4)oxadiazino[6,5- b]indole-3-yl]-phenol with various aromatic aldehydes which shows diuretic activity.

Synthesis and evaluation of antioxidant activities of some novel isatin derivatives and analogs were reported. A series of novel Schiff bases of isatin were synthesized by condensation of imesatin with different aromatic aldehydes. The isatins were synthesized by reaction of isatin with p-phenylenediamine. The chemical structures of the synthesized compounds were confirmed by means of IR, 1H-NMR, mass spectroscopy, and elemental analysis.

These compounds were screened for antioxidant activity by DPPH radical scavenging activity. In this method, the compound 3-(4-(4-dimethylaminobenzylideneamino) phenylimino) indoline-2-one showed highest antioxidant activity because of the presence of electron donating group.

CONCLUSION

Isatin is a molecule with great synthetic versatility and enormous pharmacological potential that has been intensively investigated by different research groups all over the world. Several structural modifications of the basic core of this molecule have been made, such as ring and alkyl group addition. These modifications often take advantage of the distinct reactivities of the two carbonyls and the N-H group.

In addition to the synthesis of novel compounds, new methods of obtaining isatins have been explored by researchers. The focus of this review was to summarize the recent literature published about isatin and its derivatives. These heterocyclic molecules are among the fastest developing areas of interest for synthetic chemists and pharmacists. Some of the properties including, antiviral antiasthamatic, anticancer, MOA-inhibitor and antimicrobial, however, as mentioned earlier, isatin derivatives have good potential and a broad spectrum of application against various cancer cell lines, therefore, synthesis and investigation of new isatin derivatives is an active area of research and has the potential for the development of pharmacologically active molecules.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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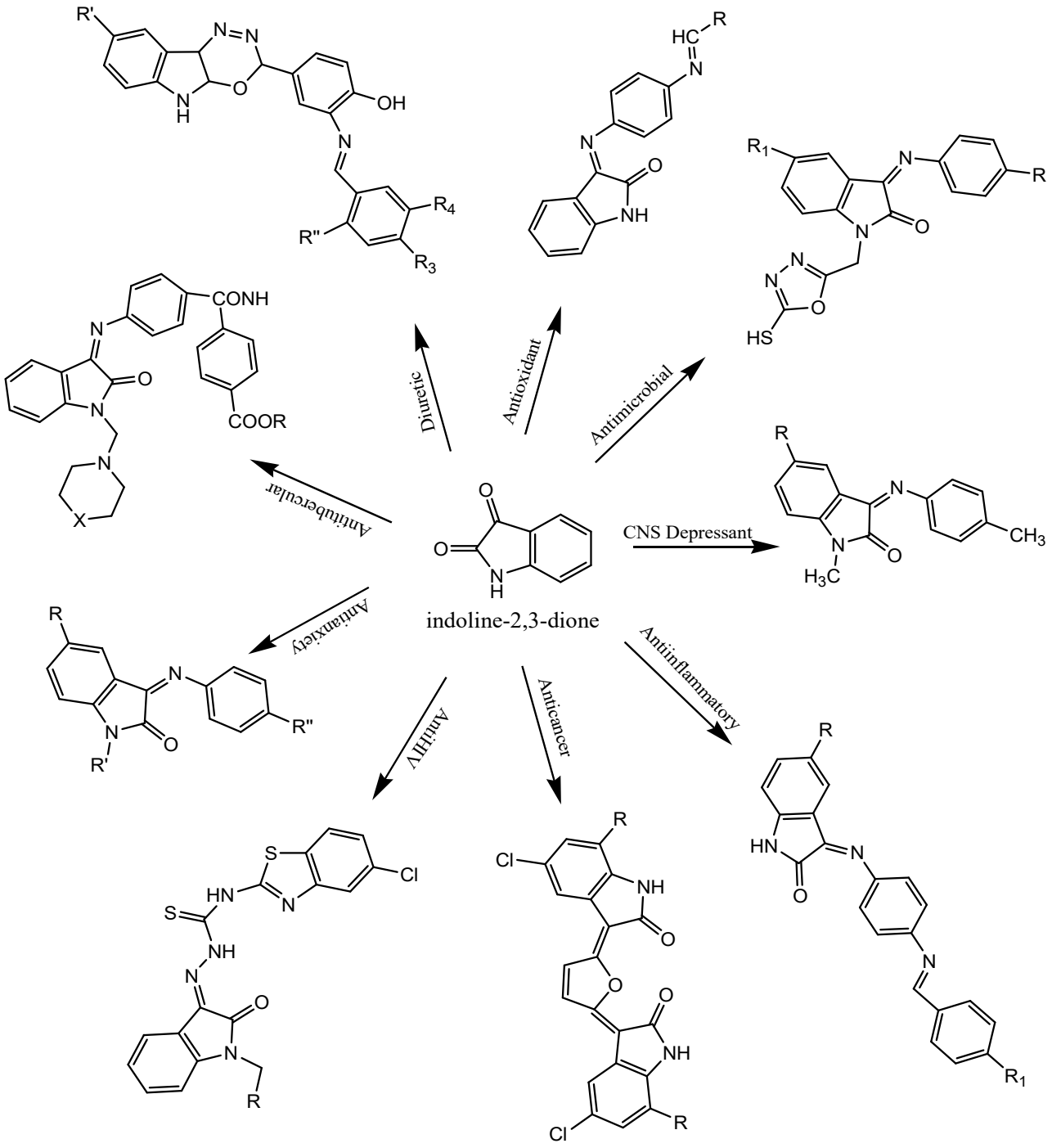

Figure 11: Different biological activities shown by 1H-indole-2,3-dione

REFERENCES

1. Langdon SR, Brown N, Blagg J. Scaffold diversity of exemplified medicinal chemistry space. Journal of Chemical Information and Modeling. 2011; 51(9):2174-2185.

2. González A, Quirante J, Nieto J. Isatin derivatives, a novel class of transthyretin fibrillogenesis inhibitors. Bioorganic & Medicinal Chemistry Letters. 2009; 19(17):5270-5273.
3. DeSimone R, Currie K, Mitchell S, Darrow J, Pippin D. Privileged Structures: Applications in Drug Discovery. Combinatorial Chemistry & High Throughput Screening. 2004; 7(5):473-493.
4. Pakravan P, Kashanian S, Khodaei MM, Harding FJ. Biochemical and pharmacological characterization of isatin and its derivatives: From structure to activity. Pharmacological Reports. 2013; 65(2):313-335.
5. Johansson H, Jørgensen TB, Gloriam DE, Bräuner-Osborne H, Pedersen DS. 3-Substituted 2-phenyl-indoles: privileged structures for medicinal chemistry. RSC Advances. 2013; 3(3):945-960.
6. Ghosh AK, Brindisi M. Organic Carbamates in Drug Design and Medicinal Chemistry. Journal of Medicinal Chemistry. 2015; 58(7):2895-2940.
7. Bissantz C, Kuhn B, Stahl M. A medicinal chemist's guide to molecular interactions. Journal of Medicinal Chemistry. 2010; 53(14):5061-5084.
8. Loloiu G, Loloiu T, Maior O. Chemistry of isatin. Synthesis of 2,3-diketo-1H-pyrol[2,3-b]-dibenzo-p-dioxin. Revista de Chimie. 1998; 49(12):861-864.
9. Da Silva JFM, Garden SJ, Pinto AC. The Chemistry of Isatins: A Review from 1975 to 1999. Journal of the Brazilian Chemical Society. 2001; 12(3):273-324.
10. Hewawasam P, Meanwell NA. A general method for the synthesis of isatins: Preparation of regiospecifically functionalized isatins from anilines. Tetrahedron Letters. 1994; 35(40):7303-7306.
11. Pandeya SN, Sriram D, Nath G, De Clercq E. Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. Farmaco. 1999; 54(9):624-628.
12. Kumar K, Carrère-Kremer S, Kremer L, Guérardel Y, Biot C, Kumar V. 1 H -1,2,3-Triazole-tethered isatin-ferrocene and isatin-ferrocenylchalcone conjugates: Synthesis and in vitro antitubercular evaluation. Organometallics. 2013; 32(20):5713-5719.
13. Busse WW, Lemanske RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet. 2010; 376(9743):826-834.
14. Pandeya SN, Smitha S, Jyoti M, Sridhar SK. Biological activities of isatin and its derivatives. Acta Pharmaceutica. 2005; 55(1):27-46.
15. Raj R, Biot C, Carrère-Kremer S, et al. 7-chloroquinoline-isatin conjugates: Antimalarial, antitubercular, and cytotoxic evaluation. Chemical Biology & Drug Design. 2014; 83(5):622-629.
16. Prakash CR, Raja S, Panneer Selvam T, Saravanan G, Karthick V, Dinesh Kumar P. Synthesis and anti-microbial activities of some novel schiff bases of 5-substituted isatin derivatives. Rasayan Journal of Chemistry. 2009; 2(4):960-968.
17. Raj R, Gut J, Rosenthal PJ, Kumar V. 1H-1,2,3-Triazole-tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates: Synthesis and antimalarial evaluation. Bioorganic & Medicinal Chemistry Letters. 2014; 24(3):756-759.
18. Dawson-Caswell M, Muncie HL. Respiratory syncytial virus infection in children. American Family Physician. 2011; 83(2):141-145.
19. Nandakumar A, Thirumurugan P, Perumal PT, Vembu P, Ponnuswamy MN, Ramesh P. One-pot multicomponent synthesis and anti-microbial evaluation of 2′-(indol-3-yl)-2-oxospiro(indoline-3,4′-pyran) derivatives. Bioorganic & Medicinal Chemistry Letters. 2010; 20(14):4252-4258.
20. Bari SB, Mahajan BM. Synthesis and pharmacological evaluation of some isatin based novel spiroheterocycles for anticonvulsant activity. Research Journal of Chemistry and Environment. 2008; 12(3):85-89.
21. Singh R, Sharma S, Banarasi B. Synthesis, Characterization And Evaluation Of 2-Imino Benzothiazole Derivatives As Anticonvulsant Agents. International Journal of Pharmaceutical Sciences and Research. 2014; 5(5):213-217.
22. Arifuzzaman M, Kandahary RK, Islam MR. Cytotoxicity study of reaction products between isatin and furan. Bangladesh Journal of Pharmacology. 2009; 4(2):96-100.
23. Chinnasamy R, Sundararajan R, Govindaraj S. Synthesis, characterization, and analgesic activity of novel schiff base of isatin derivatives. Journal of Advanced Pharmaceutical Technology & Research. 2010; 1(3):342.
24. Pandeya SN, Sriram D, Nath G, de Clercq E. Synthesis, antibacterial, antifungal and antiviral activityevaluation of some new bis-Schiff bases of isatin and their derivative. Pharmaceutica Acta Helvetiae. 74 11. 1999; 74-78.
25. Palit G, Kumar R, Patnaik GK, Bhattacharya SK. Behavioural effects of isatin, a putative biological factor, in rhesus monkeys. Biogenic Amines. 1997;13(2):131-142.

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