زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Synthesis Characterization and Biological Activities of Some New Isatine Derivatives

Research Project

Submitted to the department of (chemistry) in partial fulfillment of the requirements for the degree of B.A or BSc. in (chemistry)

by: Ameena Amer

Supervised By:

Assist. Lect. Hawzhin Yassin Hussen

April-2023

Supervisor recommendation

I am the student's supervisor, [**ameena amer adil**].

I support that the student has completed all the requirements for submitting the research drawn entitled [**Synthesis Characterization and Biological Activities of Some New Isatine Derivatives**] according to the numbered administrative order 3/1/5/1972 on 9th oct. 2022 in accordance with the instructions of Salahaddin university quality assurance and it is ready for discussion.

Supervisor full name with (**Assist. Laect.Hawzhin Yassin Hussen**)

Signature with date :2023-04-05

project lecturer

Dr. Dler D. Kurda

Dedication

I sincerely dedicate this study to my beloved parents, whose kindness I will always be unable to repay. Likewise, to all the professors who have grown weary of me ever since I was a student. And devoted to all of my friends, family, and loved ones.

Acknowledgment

First of all, thank God for helping us to conduct this research that nothing can be done without God's help, Then I would like to thank Assist. Laect. Hawzhin Yassin Hussen and Dr. Dler D.Kurda for their support and help in carrying out this project, and finally, thank you to all those who helped me, even if it was a little thing. Finally, thank you.

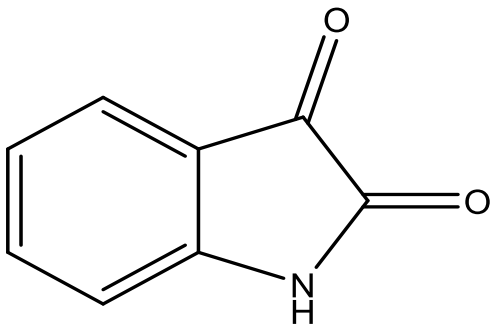
Abstract:

This research is consisting of clarify most the heterocyclic molecule isatin (1H-indole-2,3-dione) and its derivatives form a significant family of chemicals that can be employed as building blocks for the manufacture of pharmaceuticals. Since its discovery, a lot of research work has been done regarding the synthesis, chemical properties, and biological of isatin. The isatin moiety also demonstrates essential chemical processes such as oxidation, ring expansion, Friedel–Crafts reaction and aldol condensation. We have also outlined a number of recently documented biological properties, including anti-cancer, anti-bacterial, anti-diabetic, and others, that are demonstrated by isatin derivatives. Particular emphasis has been made to their anti-cancer activity.

Keyword: Isatine , Methods for Synthesis , Synthesis of Derivatives , Biological activities.

1.1. Introduction

Organic compounds of the heterocyclic class display a variety of biological and pharmacological properties. Isatin, sometimes referred to as indole quinone or indenedione and also known as 1H-indole-2,3-dione (1), is one such physiologically active heterocyclic molecule. It has two carbonyl groups in locations 2 and 3, as well as a nitrogen atom in position 1. Two cyclic rings—one with six members and the other with five—make up its structure. There are two flat rings. The aromatic ring has six members, while the anti-aromatic ring has five members.(Al-Khuzaie et al., 2022)



indoline-2,3-dione

(1)

The most widely used techniques for creating different isatin derivatives are those developed by Sandmeyer, Stolle, Gassman, and Martinet. In addition, several distinct and The preparation of isatin derivatives using recent published and discussed ecologically friendly synthetic techniques. (Ferraz de Paiva et al., 2021)

The chemical reactions that isatins go through also include Friedel-Crafts, ring expansion, oxidation reaction, and aldol condensation. Several medically necessary derivatives, such as tryptanthrin, indirubin, and 2-oxindoles, can be made using these chemical processes. A survey of the literature revealed that isatin and its components have anti-cancer, antibacterial, antifungal, anticonvulsant, antitubercular, and anti-HIV properties, as well as antioxidant, anti-inflammatory, and analgesic properties.(Al-Khuzaie et al., 2022)

This study concentrated on the isatin molecule since it is crucial for the synthesis of physiologically active chemicals that are employed in numerous pharmacological and medical applications. on compiling the most recent research on the creation, applications in chemistry and biology of isatin and its derivatives. (Ferraz de Paiva et al., 2021)

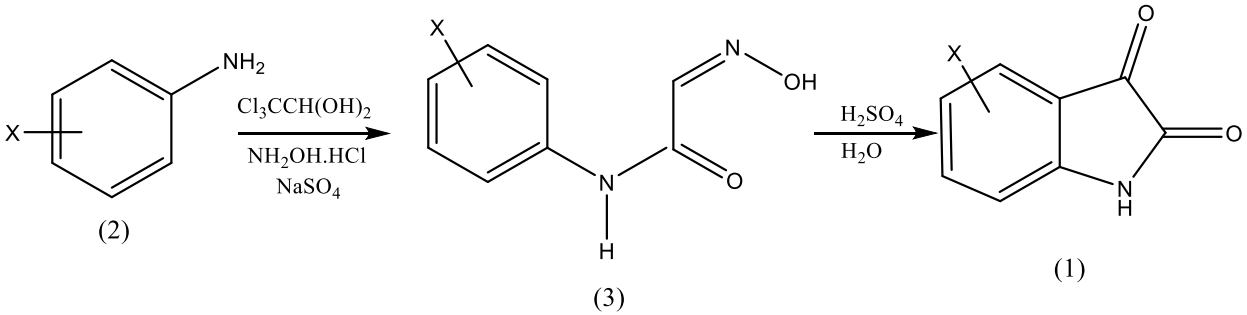
1.2. History

Isatin was first found by Erdmann and Laurent as an indigo oxidation byproduct generated from nitric and chromic acids (Erdmann, 1840; [4] Laurent, 1840). From water, alcohol, or acetic acid, it crystallizes as orange-red monoclinic prisms. Animals and plants both naturally contain isatin and its derivatives. It is a component of the parotid gland's secretions in Bufo frogs and is discovered in humans as a metabolic byproduct of the hormone adrenaline.[6] Melochia tomentosa, a Caribbean plant that causes tumors, produced 5-(3'-methylbut-2'-yl) isatin, while Chaetomium globosum produced methoxy phenylpentyl isatins (melosatin alkaloids). (Nath et al., 2020)

2.1. Different Methods for Synthesis of Isatin derivatives:

2.1.1. Sandmeyer method synthesis

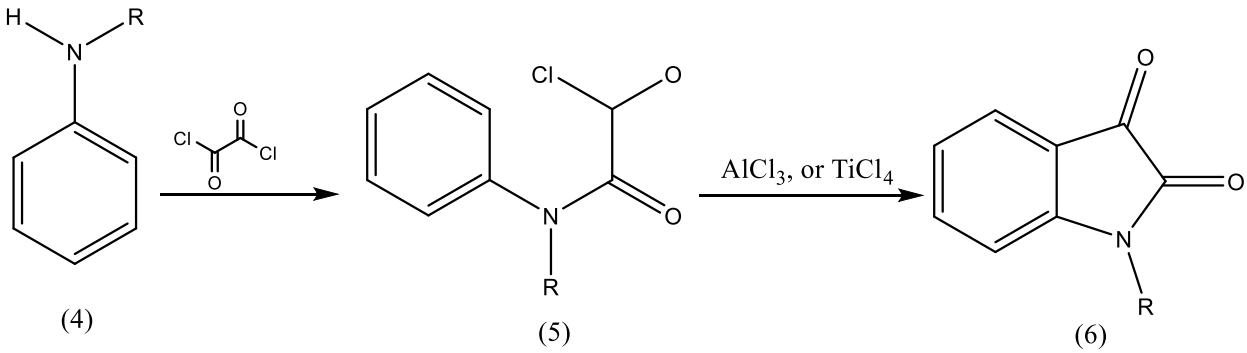
Isatin (1) were synthesized by Sandmeyer method the reaction of aniline (2) with chloral hydrate ($Cl_3CCH(OH)_2$) and hydroxylamine hydrochloride ($NH_2OH.HCl$) to form isonitrosoacetanilide(3) in an aqueous solution of sodium sulfate. Cyclization of isonitrosoacetanilide to isatin(1) is achieved after treatment with concentrated sulfuric acid. (Sandmeyer, 1919)



Scheme 1: Sandmeyer method for the synthesis of isatin

2.1.2. Stolle method synthesis

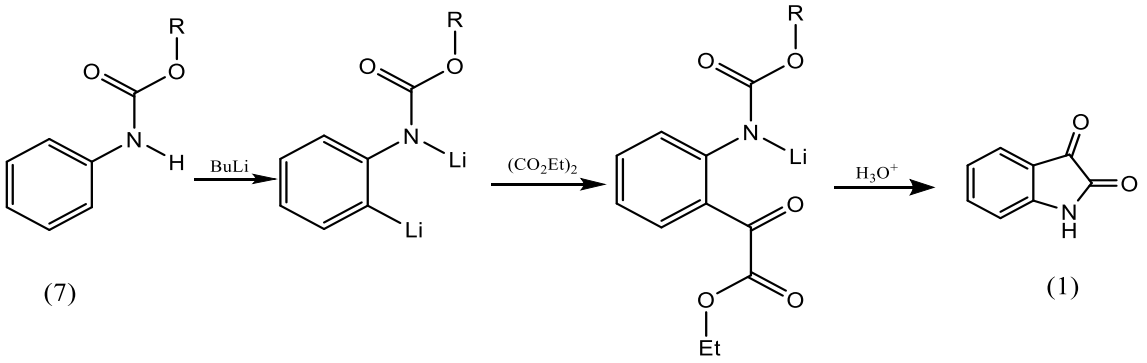
The compound of N-substituted aniline(4) was reacted with oxalyl chloride to form chlorooxalylanilide(5), which can then be cyclized by stoll method and Lewis acids such as (AlCl3, or TiCl4) to form N-aryl isatin(6) derivatives.(Stollé et al., 1922)



Scheme 2 Stolle method for the synthesis of isatin.

2.1.3. Meanwell and hewawasam method synthesis

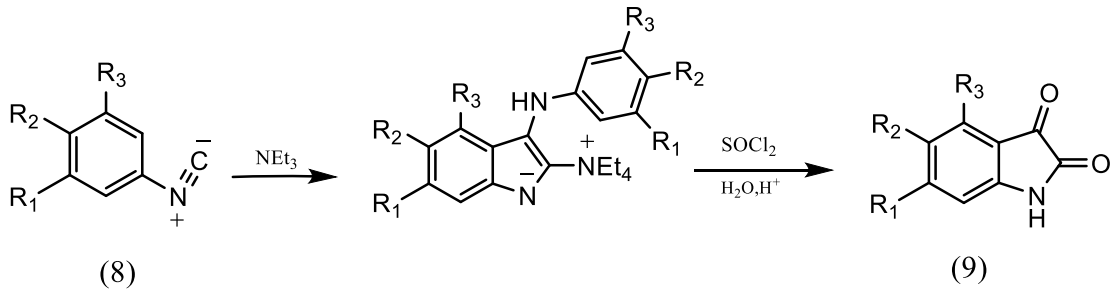
The compound (7) was reacted with ethyle oxalate by meanwell and hewawasam method for synthesis of isatin . After deprotection and cyclisation processes of the intermediate α-ketoesters by using HCl. The benefit of this method is regioselectivity of the 4- substituted isatins synthesis from meta-substituted anilines where the substituent is a metalation directing group such as an amino protected group . (Gassman et al., 1977)



Scheme 3: represents Meanwell and Hewawasam method for synthesis of isatin

2.1.4. Mironov method synthesis

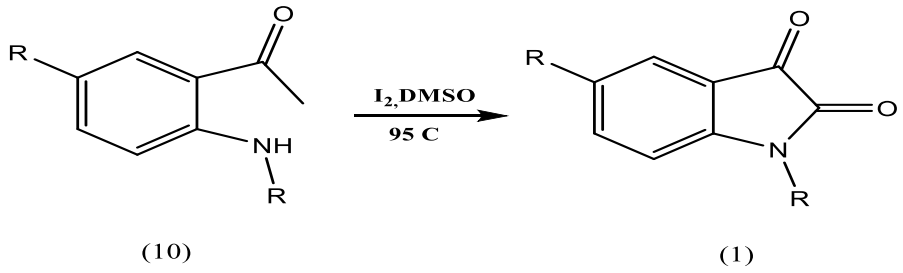
The Mironov method was synthesized of isatin derivatives. This method was based on the reaction of aromatic isocyanides with tertiary amines to produce 2-triethylammonio-3-arylaminoindolates which were then heated without isolation in excess thionyl chloride and hydrolyzed to yield the target isatins(9) .(Mironov and Mokrushin, 1998)



Scheme 4: Mironov synthesis strategy of isatins containing electron withdrawing groups

2.1.5. Oxidation reaction method synthesis

A new metal-free synthesis using I_2, DMSO as a catalyst was developed for the synthesized of N-substituted isatins. Through C-H bond activation and subsequent inter-cyclization, N-alkylated and N-arylated isatins can be made from 2-amino acetophenones(10) .(Reddy et al., 2014)

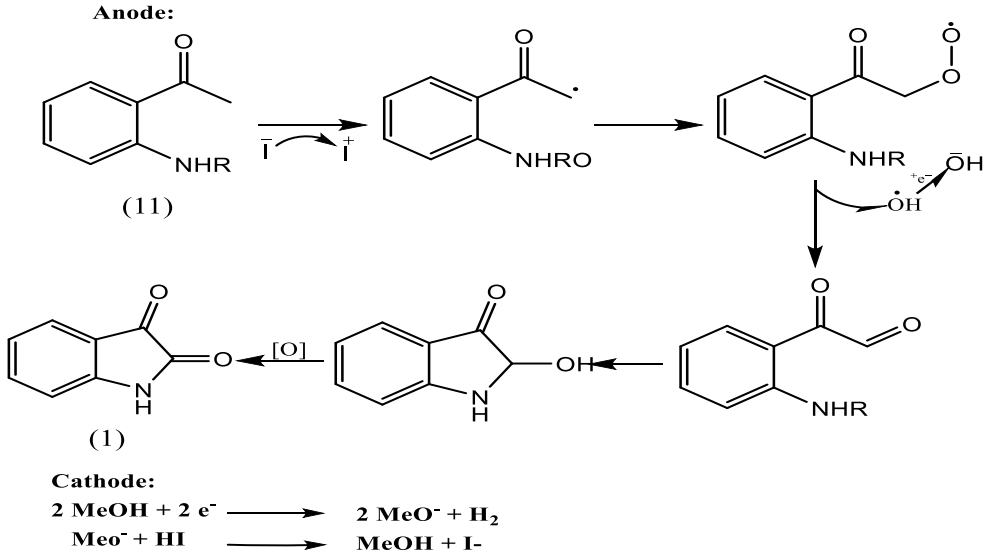


(10) (1)

Scheme 6: Synthesis of isatin by chemical oxidation reactions

2.1.6. Electrochemical oxidation method synthesis

The isatin synthesized via electrocatalytic oxidation of 2′- aminoacetophenones. 2′-aminoacetophenones undergo a C-H oxidation followed by an intramolecular C-N bond formation via a simple electrochemical oxidation in the presence of n-Bu4NI as the electrolyte and methanol as the solvent. This method produced various isatins of different substituted groups with good yields. (Qian et al., 2017)

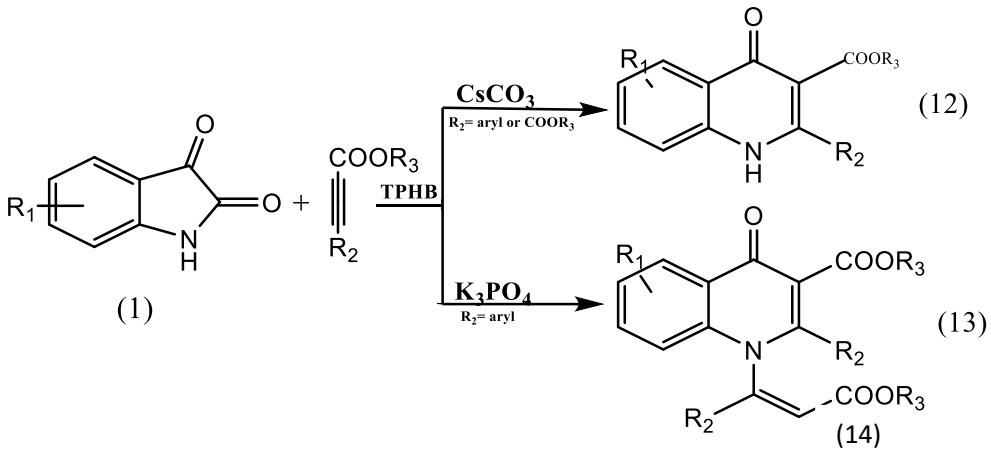


Scheme 5: Synthesis of isatin by electrochemical oxidation reactions

2.2. Synthesis of isatin derivatives

2.2.1 Synthesis of isatin derivative by oxidation reaction

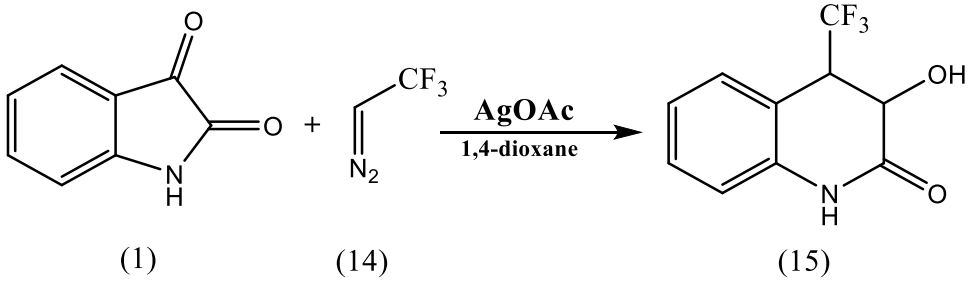
The compound (12) and (13) were synthesized an oxidative cyclization process using isatins and alkynes to prepare structurally diverse 4- quinolones. Intriguingly, Switchable access to substituted 1- vinyl-3-carboxylate-4-quinolones and 3-carboxylate-4- quinolones could be obtained by switching the reaction's base. (Jiang et al., 2018)



Scheme 7: Organocesium-catalyzed oxidation of isatin to isatoic anhydride

2.2.2. Ag-catalysed formation method synthesis

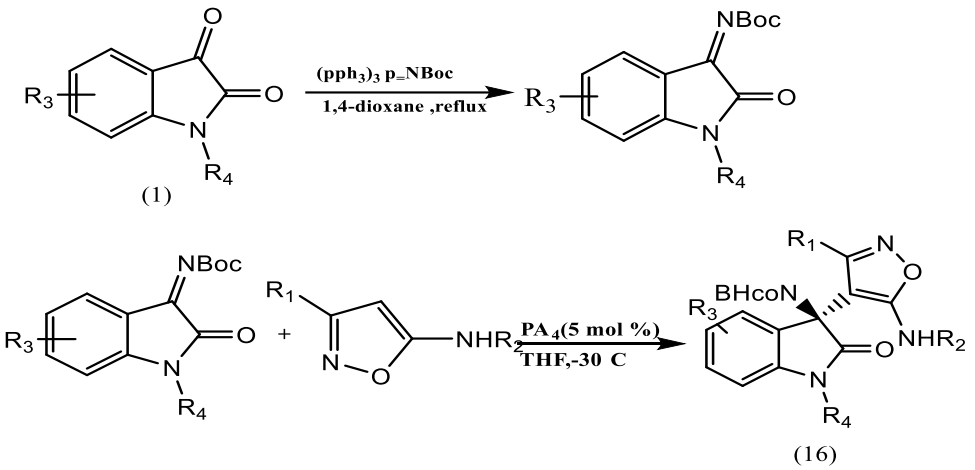
The compound (15) was synthesis by the reaction of triflurodiazoethane(14) and isatin (1). It is a simple and reliable Ag-catalyzed technique that effectively converts isatin ketoimines to 3-amino-4-trifluoromethylquinolinones(15) in high yield. (Jamali et al., 2020)



Scheme 8: Ag-catalysed formation of isoxazoloquinolines

2.2.3. Frieddle-craft alkylation method synthesis

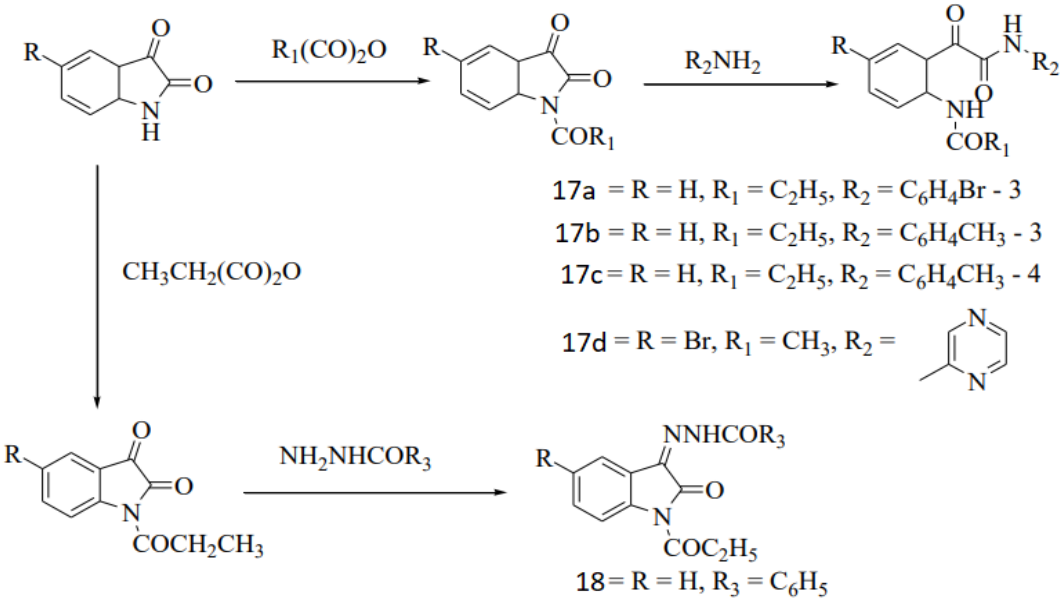
The 3-isoxazole 3-amino-oxindoles (16) with high yields and good to moderate enantioselectivity. Friedel-Crafts alkylation of isatins with pyrroles. (Liu et al., 2021)



Scheme 9: Friedel-Crafts alkylation of isatins with pyrroles to give oxindoles

2.2.4. Mass Spectrometry fragmentation pattern method synthesis

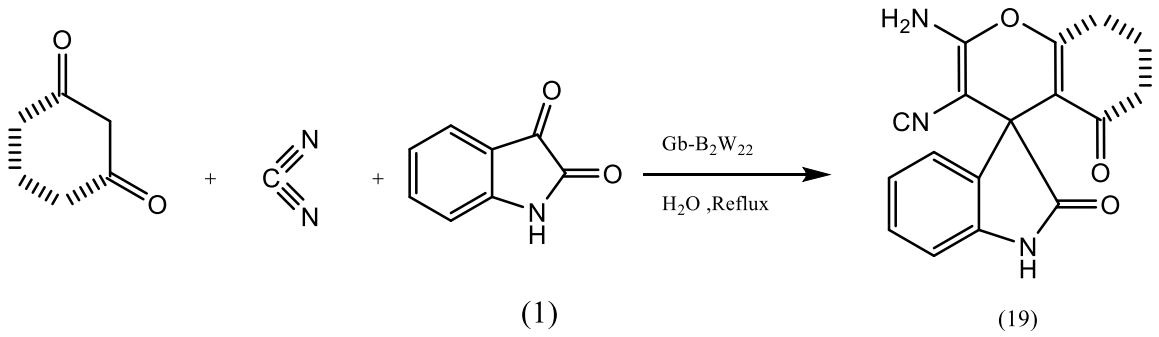
The derivatives of isatin 17a-17d and 18 were synthesized by condensation method.(Saleem et al., 2022)



Scheme (10). Mass Spectrometry fragmentation pattern of synthesized derivatives

2.2.5. Spiro-2-amino-4H-pryans method synthesis

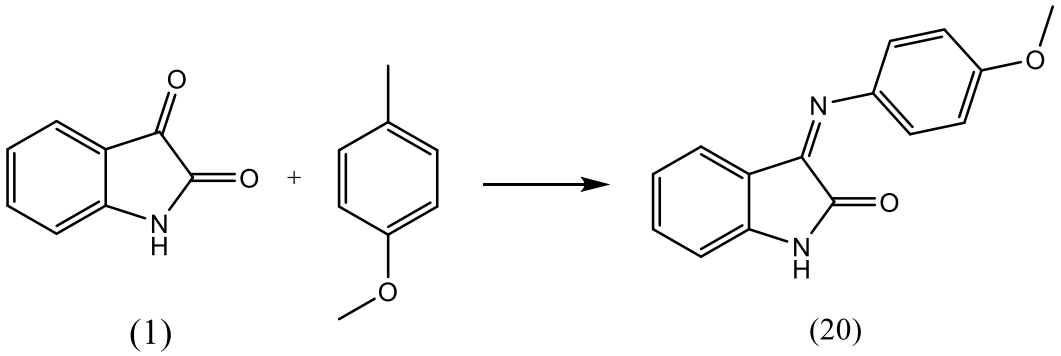
A combination of 1,3-diketone, carbonyl compound (either isatin or acenaphtoquinone), α-cyano compound (either malononitrile or ethyl cyanoactetate), and Gd-B2W22 was stirred in water at ambient temperature until the complete formation of the product was traced by TLC. (Daraie et al., 2022)



Scheme 11: Synthesis of spiro-2-amino-4H-pryans.

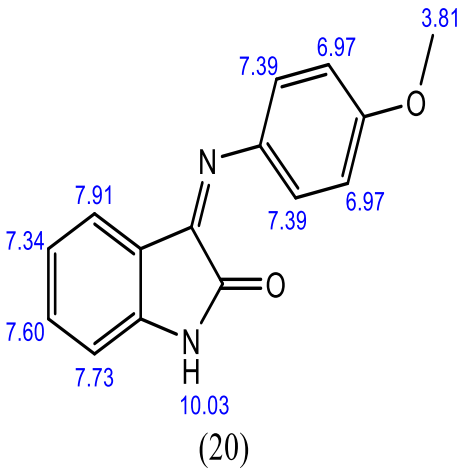
2.2.6. Substituted method synthesis

The isatin(1) was reacted with (1-methoxy-4-methylebenzene) that well synthesized (Z)-3-((4-methoxyphenyl)imino)indolin-2-one (20).(Daraie et al., 2022)

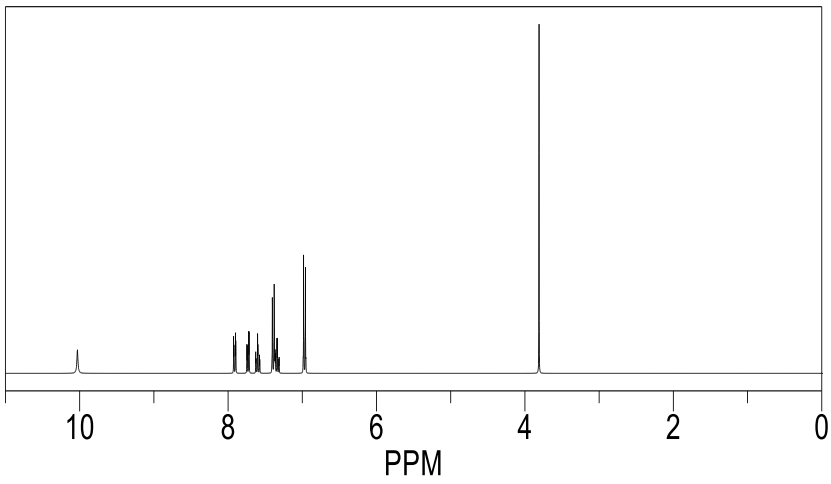


Scheme 12: synthesis Substituted reaction

ChemNMR ^{1}H Estimation



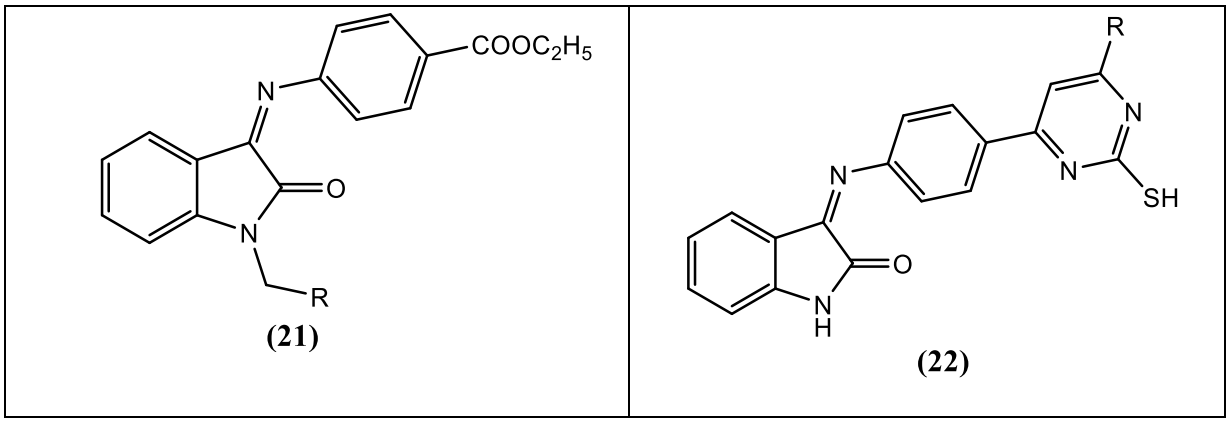
(20)



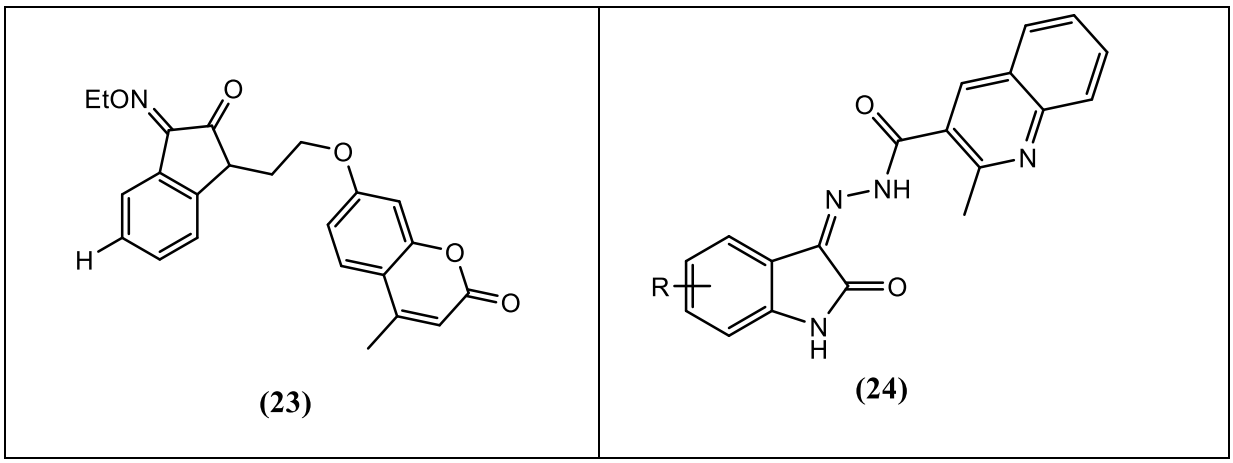
Estimation quality is indicated by color: good, medium, rough

3.1.. Biological application of isatin

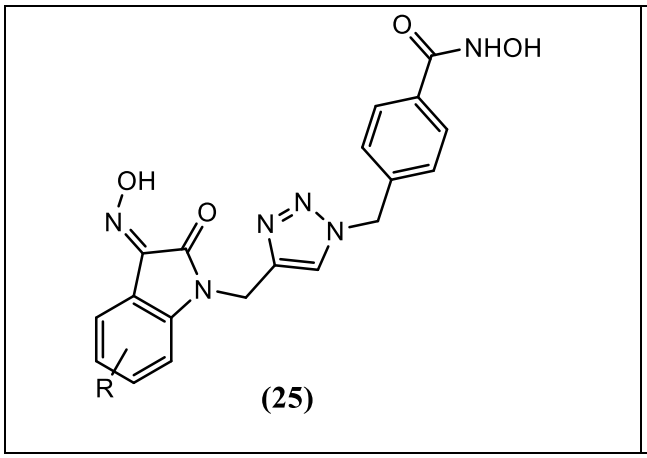
1. Anti-bacterial activity.(Meenakshi et al., 2014)



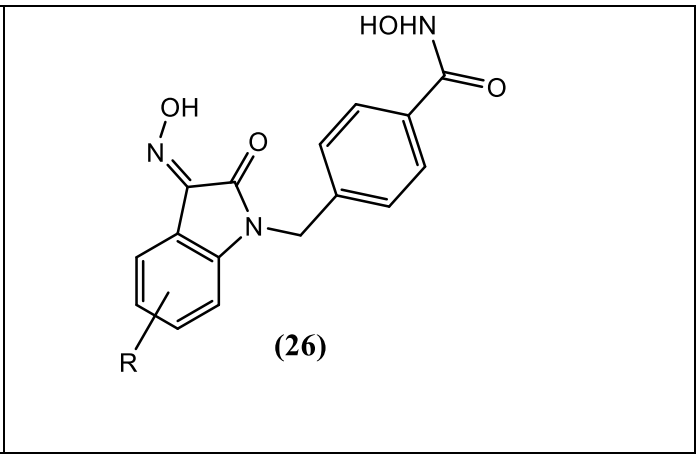
2. Anti-tuberculosis activity.(Maddela and Makula, 2016)



3. Isatins as histone deacetylases (HDACs) inhibitors. (Eldehna et al., 2017)

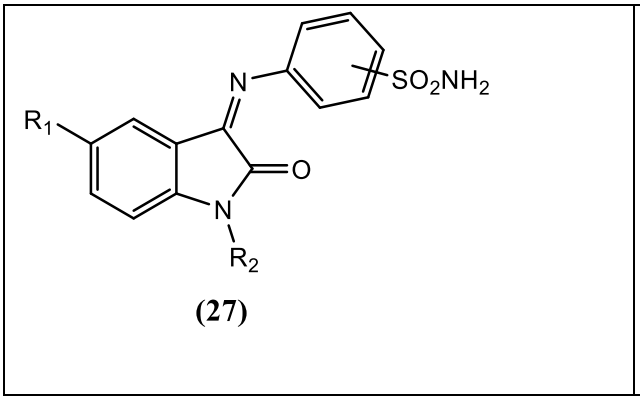


(25)

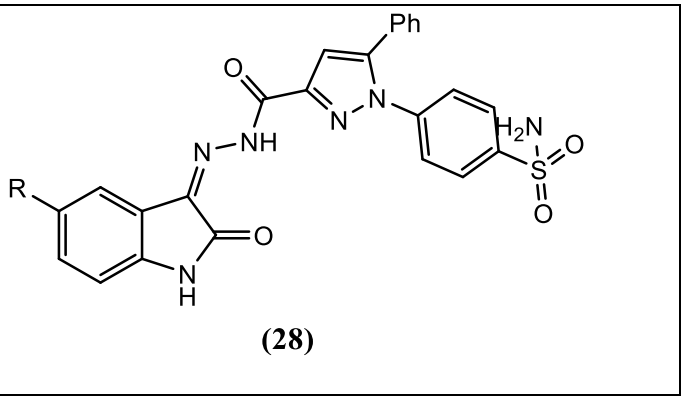


(26)

4. Isatins as carbonic anhydrase inhibitors.(Singh et al., 2017)

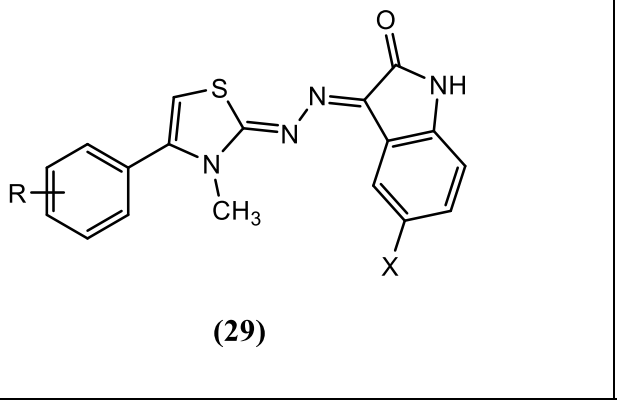


(27)

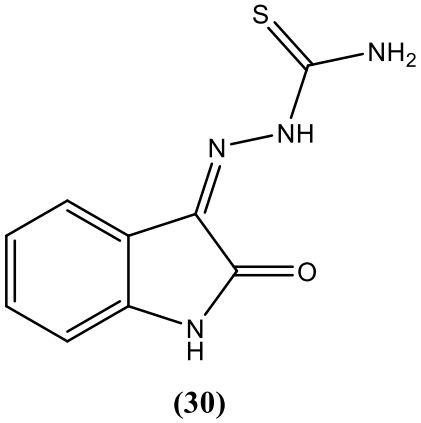


(28)

5. Anti-viral activity. (Meleddu et al., 2017)

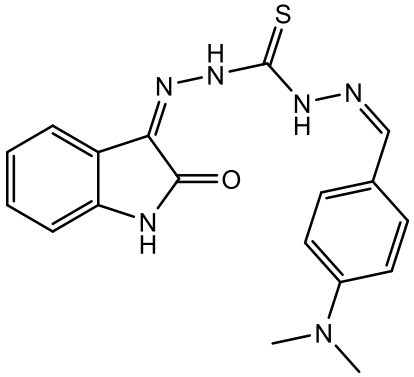


(29)

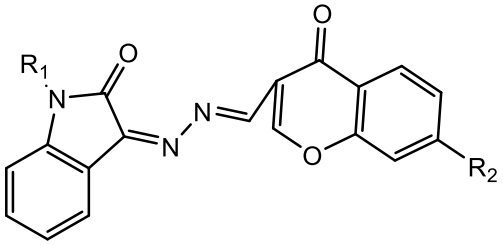


(30)

6. Anti-diabetic activity. (Kakkar, 2019)

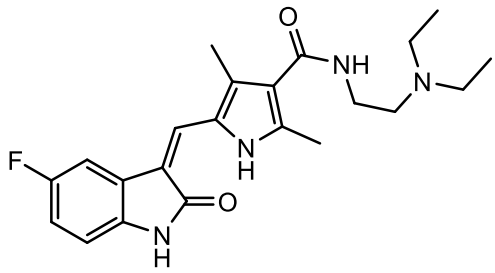


(31)

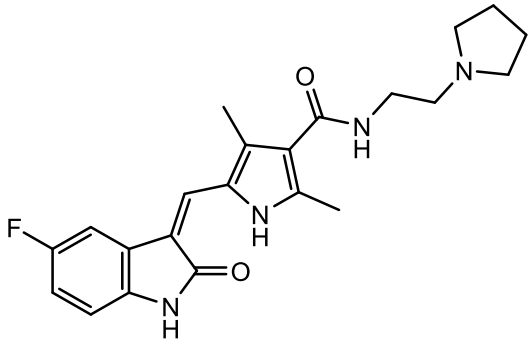


(32)

7. Anti-cancer activity. (Yousef et al., 2020)



(33)



(34)

4.Conclusion

Isatin is a significant molecule with distinctive biological characteristics that make it appropriate for numerous medical and pharmaceutical uses, such as an antibacterial, anticancer, and antidiabetic drug. In order to find innovative, environmentally acceptable ways to synthesize isatin and get beyond its challenges, research in this area has significantly increased. In addition, isatin reactions have received a great deal of attention since they open up a wide range of novel derivatives with potent biological properties that can be exploited in a wide range of biological and medicinal applications. For all of these reasons, isatin is a significant nucleus and opens up new study avenues.

5.References

AL-KHUZAIE, M. G., FAHAD, M. M. & AL-SAFI, A. J. 2022. Synthesis, Reaction and Biological Importance of Isatin Derivatives. *Biomedicine and Chemical Sciences,* 1**,** 193-206.

DARAIE, M., MIRZAEI, M., BAZARGAN, M., AMIRI, V. S., SANATI, B. A. & HERAVI, M. M. 2022. Lanthanoid-containing polyoxometalate nanocatalysts in the synthesis of bioactive isatin-based compounds. *Scientific Reports,* 12**,** 1-18.

ELDEHNA, W. M., ABO-ASHOUR, M. F., NOCENTINI, A., GRATTERI, P., EISSA, I. H., FARES, M., ISMAEL, O. E., GHABBOUR, H. A., ELAASSER, M. M. & ABDEL-AZIZ, H. A. 2017. Novel 4/3-((4-oxo-5-(2-oxoindolin-3-ylidene) thiazolidin-2-ylidene) amino) benzenesulfonamides: Synthesis, carbonic anhydrase inhibitory activity, anticancer activity and molecular modelling studies. *European journal of medicinal chemistry,* 139**,** 250-262.

FERRAZ DE PAIVA, R. E., VIEIRA, E. G., RODRIGUES DA SILVA, D., WEGERMANN, C. A. & COSTA FERREIRA, A. M. 2021. Anticancer compounds based on isatin-derivatives: strategies to ameliorate selectivity and efficiency. *Frontiers in molecular biosciences,* 7**,** 627272.

GASSMAN, P. G., CUE JR, B. W. & LUH, T.-Y. 1977. A general method for the synthesis of isatins. *The Journal of Organic Chemistry,* 42**,** 1344-1348.

JAMALI, M. F., GUPTA, E., KUMAR, A., KANT, R. & MOHANAN, K. 2020. Ag-Catalyzed Trifluoromethylative Ring Expansion of Isatins and Isatin Ketimines with Trifluorodiazoethane. *Chemistry–An Asian Journal,* 15**,** 757-761.

JIANG, S.-F., XU, C., ZHOU, Z.-W., ZHANG, Q., WEN, X.-H., JIA, F.-C. & WU, A.-X. 2018. Switchable Access to 3-Carboxylate-4-quinolones and 1-Vinyl-3-carboxylate-4-quinolones via Oxidative Cyclization of Isatins and Alkynes. *Organic letters,* 20**,** 4231-4234.

KAKKAR, R. 2019. Isatin and its derivatives: a survey of recent syntheses, reactions, and applications. *MedChemComm,* 10**,** 351-368.

LIU, H., YAN, Y., LI, M. & ZHANG, X. 2021. An enantioselective aza-Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived N-Boc ketimines. *Organic & Biomolecular Chemistry,* 19**,** 3820-3824.

MADDELA, S. & MAKULA, A. 2016. Design, synthesis and docking study of some novel isatin-quinoline hybrids as potential antitubercular agents. *Anti-Infective Agents,* 14**,** 53-62.

MEENAKSHI, K., GOPAL, N. & SARANGAPANI, M. 2014. Synthesis, characterization and antimicrobial activity of some novel Schiff and Mannich bases of isatin. *Int j pharm pharm sci,* 6**,** 318-322.

MELEDDU, R., DISTINTO, S., CORONA, A., TRAMONTANO, E., BIANCO, G., MELIS, C., COTTIGLIA, F. & MACCIONI, E. 2017. Isatin thiazoline hybrids as dual inhibitors of HIV-1 reverse transcriptase. *Journal of enzyme inhibition and medicinal chemistry,* 32**,** 130-136.

MIRONOV, M. A. & MOKRUSHIN, V. S. 1998. Reaction of aromatic isocyanides with triethylamine: a new method for the synthesis of indole betaines. *Mendeleev communications,* 8**,** 242-243.

NATH, R., PATHANIA, S., GROVER, G. & AKHTAR, M. J. 2020. Isatin containing heterocycles for different biological activities: Analysis of structure activity relationship. *Journal of Molecular Structure,* 1222**,** 128900.

QIAN, P., SU, J.-H., WANG, Y., BI, M., ZHA, Z. & WANG, Z. 2017. Electrocatalytic C–H/N–H coupling of 2′-aminoacetophenones for the synthesis of isatins. *The Journal of Organic Chemistry,* 82**,** 6434-6440.

REDDY, M. R., RAO, N. N., RAMAKRISHNA, K. & MESHRAM, H. 2014. I2–DMSO promoted intramolecular oxidative cyclization of 2-(aryl or alkyl amino)-acetophenones for the synthesis of isatins. *Tetrahedron Letters,* 55**,** 4758-4762.

SALEEM, M., AHMAD, M., MEHMOOD, R. F., SHAHEEN, A., QAISER, S., NIAZ, S. I., ALI, M., IRSHAD, M., MEHMOOD, S. & A ABUBSHAIT, S. 2022. Synthesis of Isatin Derivatives Exhibiting Antibacterial, Antifungal and Cytotoxic Activities. *Current Organic Synthesis,* 19**,** 748-756.

SANDMEYER, T. 1919. Über isonitrosoacetanilide und deren Kondensation zu Isatinen. *Helvetica Chimica Acta,* 2**,** 234-242.

SINGH, A., RAGHUWANSHI, K., PATEL, V. K., JAIN, D. K., VEERASAMY, R., DIXIT, A. & RAJAK, H. 2017. Assessment of 5-substituted isatin as surface recognition group: design, synthesis, and antiproliferative evaluation of hydroxamates as novel histone deacetylase inhibitors. *Pharmaceutical Chemistry Journal,* 51**,** 366-374.

STOLLÉ, R., BERGDOLL, R., LUTHER, M., AUERHAHN, A. & WACKER, W. 1922. Über N-substituierte Oxindole und Isatine. *Journal für Praktische Chemie,* 105**,** 137-148.

YOUSEF, M. A., ALI, A. M., EL-SAYED, W. M., QAYED, W. S., FARAG, H. H. & ABOUL-FADL, T. 2020. Design and synthesis of novel isatin-based derivatives targeting cell cycle checkpoint pathways as potential anticancer agents. *Bioorganic chemistry,* 105**,** 104366.