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Bioactive Indole Heterocycles and their Synthetic Routes: A Comprehensive Review

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Abstract

Indole analogues are very significant and useful heterocycles, with numerous applications in synthetic organic chemistry, material chemistry, medicinal chemistry, and natural product chemistry. Based on existing data, researchers have been focusing on developing indole-based molecules with new biological and pharmacological effects, since many well-known drugs like tadalafil, sumatriptan, rizatriptan, Fluvastatin etc have indole core. In this review article, we have described the general features and reactivity pattern at different positions of indole ring. In addition to this, different synthetic approaches for the preparation of a series of biologically as well as synthetically challenging complex heterocyclic molecules having indole is also discussed.

Keywords: Indole, Heterocycles, Synthesis, Bioactivity, Organic Molecules.

Introduction

Many organic and medicinal chemists are actively involved in the synthesis of indole analogues nowadays. (1) For the first time, Adolf von Baeyer used zinc dust to separate indole from oxindole in 1866. (2) Because many pharmaceutical applications are well documented, chemists can use accelerated methods to synthesize interesting indole compounds. (3) Indole based heterocyclic substances that are useful in our daily lives are sanitizers(4), pharmaceuticals (5,6), bioactive substances (7,8), corrosion inhibitors (9,10), pigments (11), copolymers (12,13), and construction blocks in the production of organic compounds. (14-16) To produce heterocycles, multicomponent reactions have been frequently used, and MCRs are an excellent tool for constructing a varying set of base materials with potentially interesting biological functions in organic compounds. (17-20) The MCR technique is appealing because of its ease of use, high selectivity, and high yield while requiring minimal requirements for synthesis. Indole frameworks have long been established for their utility in the synthesis of novel medicinal molecules. (21-23)

Adolf von Baeyer, a German scientist, developed a number of techniques for indole synthesis using oxindoles and zinc dust. (24) The molecular structure of indole (25) was then proposed by him, and it is known as the Fischer Indole Reaction, which was published for the first time in 1869. It was first recognised as the best and most efficient method for synthesising indoles in 1883. (26) Indole is a benzopyrrole with the benzene and pyrrole rings fused at the

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2- and 3-positions of the pyrrole nucleus. Many organic compounds, such as fungal metabolites, indole alkaloids, as well as marine organic products, include the indole ring (Fig 1). (27) In the world of pharmacy, the indole core has been discovered to be a very active core since various natural compounds with indole as their fundamental ring have been discovered to be therapeutic drugs. Indole derivatives have been discovered to have antibacterial, (28) antibiotic, (29) anti-inflammatory, (30) analgesic, (31) antiviral, (32) antimalarial, (33) chemotherapeutic, (34) antifungal, (35) anti-tubercular, (36) and antioxidant properties. (37) The compounds also show agonistic effects on various receptors, including the Liver x receptor (LXR) and the 5-HT1D (5-hydroxytryptamine) receptors.

Due to the general unique capacity of the resultant molecules to replicate the molecules of peptides as well as bind reversibly to subunits, heterocyclic chemistry is one of the most important sources for novel molecules with wide biological processes. (38-41) The true value of heterocyclic compounds, according to researchers and scientists, is their capacity to create a library based on a single core scaffold and screen it against various receptor proteins, yielding several active molecules. It is possible to build nearly infinite variations of fused heterocyclic compounds, resulting in innovative polycyclic frameworks with various physical, chemical, and biological properties. Because of the ability to combine them, the geometric fusion of several rings into one well-defined stiff polycyclic structure promises a high level of system expertise. In advancement of our research into the synthesis of heterocycles and multi-component reactions, and because so many reactions are used in the preparation of indole-based heterocycles, this review covers the most recent applications of indole in the synthesis of heterocycles from 1975 to till date. (42-47) The reactivity of indoles' C-3 carbon atom in electron-donating reactions is discussed first, followed by the MCRs at the N-position of indoles reacting as a nucleophilic attack to yield substituted indole derivatives. Indole cycloaddition processes, including cycloaddition events involving the C2-C3 p-bond as well as the C-N sigma bond. Finally, the various indole and derivative-based reactions are examined. (48-51)

Reactivity Patterns of Indole

The indole molecule is a heterocycle that is easy to react with several activated olefins. As far as chemical reactivity is concerned, the indole is active at four different places, as indicated in Fig 2, involving nitrogen atom 1, carbon atom 3, the C2-C3 p-link, and the C2-N sigma link. Strong acids, such as hydrochloric acid, can help to protonate the indole more easily in comparison to the N-atom because they protonate the C3 position. Another reaction involving indole derivatives is the cyclo-addition reaction. Indole's C2-C3 p-bond is prone to cycloaddition processes, while the C2-N sigma bonding has also been seen to catalyse cycloaddition processes.

Various natural chemicals, such as tryptophan 3, have indole as a parent nucleus. Indole-3-acetic acid 7 is a plant-based hormone that is created when tryptophan is degraded in higher plants. Because of their vast range of biological and therapeutic applications, indole derivatives are of great interest. In this paper, we attempt to summarise the essential therapeutic activities of indole compounds. (52) The role of indole alkaloids like tryptophan in animal and human nutrition is well established. In animals, Serotonin 5 is a key neuron transmitter, and Reserpine 6 is a blood pressure medicine and tranquilizer. Mitomycin 4 and its analogues have long been used in the treatment of cancer, and the usage of indole-3-acetic acid 7 as a heteroauxin known as a plant growth hormone has helped to strengthen indole chemistry (53,54), with the synthesis and separation of indoles from nature rising dramatically (Fig 3). The following are some of the important drugs with an indole moiety that are utilised as pharmacological agents: Sumatriptan 8, Tadalafil 9, Rizatriptan 11, and Fluvastatin 10. (54) (Fig 4).

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As a result of crucial findings, this review provides a thorough examination of contemporary indole nucleus applications in a variety of biological domains. Fungi infect many people every year, but their impact on the global burden of illness is largely overlooked, and many of them produce small illnesses that kill just as many people as tuberculosis or dengue. (55) This is attributed to an increase in the number of people who have a compromised immune system or who are immunocompromised due to immunodeficiency, chemotherapy, or transplantation. Additionally, due to overuse or improper administration of drugs, bacterial diseases have become more resistant to them, potentially resulting in a global health disaster. (56) In addition to this, Methicillin and Vancomycin are most commercially accessible drugs, which are no longer usable against the current care facility illnesses. As a result, these drugs were only used to treat the most serious cases. As a result, these drugs are generally used for treating the most challenging illnesses as a way to stop the spread of resistance. (57-59) Mitomycin is a type of biologically active indole alkaloid, and its compounds are getting popular due to their widespread use as chemotherapeutic drugs and their good antimicrobial activities. (60,61)

Compounds with a modified specificity profile can produce distinct and very few undesirable side effects when used in accordance with a strategic plan. (62) According to the literature study, triazole-indole hybrid molecules have already been produced and are regarded as having outstanding properties. (63) Furthermore, it was shown that a free N-H in the aromatic ring was needed for antimicrobial activities against E. coli, K. pneumoniae, and P. aeruginosa. (64) Because of its nontoxicity, broad protection, and good pharmacological qualities, the nucleus of triazole analogues has received a lot of attention (65), and it was discovered that adding the sulfur atom, which is an electron rich particle in the triazole ring, greatly improves the biological activity of the target molecules. (66) This is because the sulfur particles influence lipophilicity and electronic structure in the triazole ring, resulting in increased transmembrane diffusion and interaction with macromolecular substrates. (67)

Main text: synthetic approach of bioactive indoles

The Fischer indole synthesis was a very crucial and effective approach for the development of a range of indole intermediates and physiologically active chemicals for over a century. For synthetic organic chemists, the synthesis and bioactivity of indoles were of prominent emphasis, and numerous methods for their manufacture have been discovered. Many reactions are metal-based synthesis that takes place at room temperature in the presence of various catalysts, whereas others are acid and base catalyst-based reactions. Some of the most important are phase transfer reactions.

Metal-mediated synthesis

Organic molecule formation depends heavily on metals and their oxides, which catalyse many reactions in different ways. Sarkar et al. synthesized 2-phenyl-2,3-dihydroisoindolinones using regioselective cyclization, CuI (Copper Iodide) as catalysts, and PTS (Platinum Monosulfide) analogues of methan-1-yl-1-ylidene-diphenol as ligands. Under aerobic circumstances, the reaction involved a one-pot multicomponent process using indoles, which are 4-Iodo-N-phenylbenzamide and terminal alkynes, followed by a nucleophilic addition (Scheme 1). (68) J. J. Jennings revealed the formation of indolylmalonamides through a 3-component reaction involving indole, chromene-3-carboxylates, and amines in the presence of a Lewis acid catalyst, $La(OTf)_3$ (Scheme 2). When exposed to long-wavelength UV rays, indolylmalonamide molecules demonstrated remarkable fluorescence properties (366 nm). (69)

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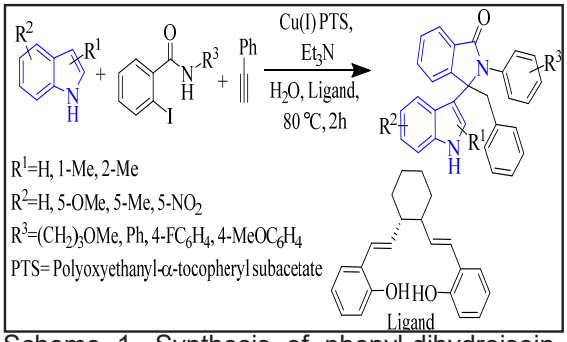
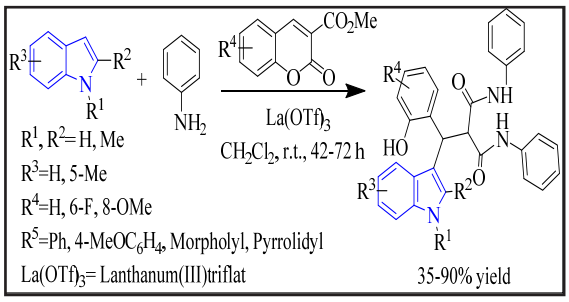
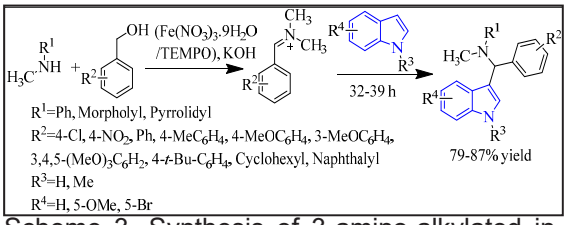


Scheme 1. Synthesis of phenyl-dihydroisoindolinones derivative.

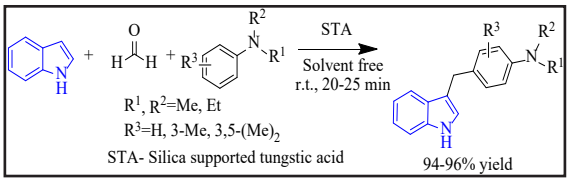


Scheme 2. Synthesis of indolylmalonamides derivative.

The one-pot, three-component Mannich type reaction involving the combination of amines, alcohols, and indoles as proposed by Singh et al. is an extremely effective way to synthesize 3-amino-alkylated indole derivatives. In the presence of $Fe(NO_3)_3.9H_2O$/TEMPO(2,2,6,6-tetramethylpiperidin-1-yl)oxyl as a catalyst, amines and alcohols were treated with potassium hydroxide in toluene to produce iminium ions. After that, the iminium ion interacted with indoles to form a new 3-substituted indole compound (Scheme 3). (70-72) Shinde and Jeong discovered the reaction of indole and formaldehyde with tertiary aromatic molecules in the presence of silica-supported tungstic acid (STA) as a catalyst support under solvent-free conditions to synthesize amino arylated indole. For the synthesis of such amino arylated indole analogues, this technique was carried out using a 3-component Mannich method and Friedel-Crafts additions (Scheme 4). (73)

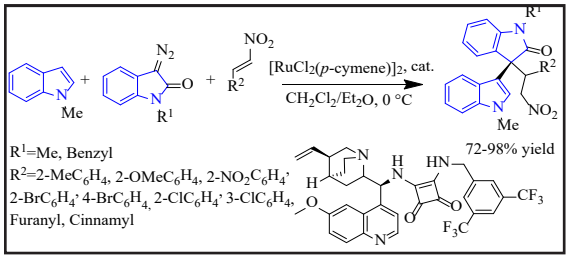


Scheme 3. Synthesis of 3-amino-alkylated indoles derivative.



Scheme 4. Synthesis of amino arylated indole derivative.

Chen et al. also revealed the preparation of bis-indole variants using N-Methyl indole, diazooxindole, and nitrostyrene via an asymmetrical addition reaction in the presence of [Ru] as well as squaramide ($O_2C_4(NH_2)_2$) as catalysts (Scheme 5). (74)



Scheme 5. Synthesis of variants of bis-indole derivative.

Acid-catalysed synthesis

A catalytic process is explained as the method of changing the rate of a chemical reaction by using a catalyst that is not modified throughout the chemical process. Catalysis pathways can be categorised as either selective or generalized, depending on the different molecules that behave like acids or bases.

Jiang and Yan have demonstrated a three-component procedure for the formation of analogues such as tetrahydro-1H-in-

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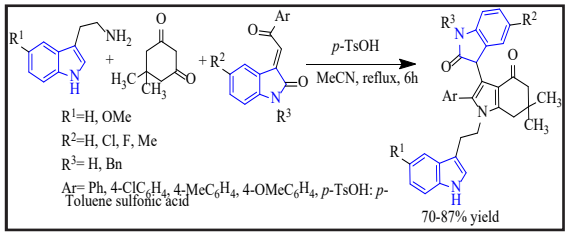
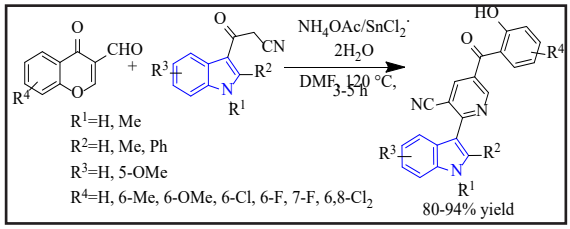
dolin-2-ones. In this synthesis (Scheme 6), a one-pot condensation reaction of indole using dimedone as well as 3-phenacylideneoxindoles in vaporising acetonitrile (MeCN) utilising p-toluene sulfonic acid (p-TsOH) acts as a motivator well as 3-phenacylideneoxindoles in vaporising acetonitrile (MeCN) utilising p-toluene sulfonic acid (p-TsOH) acts as a motivator. (75) The bifunctional indole-3-yl pyridines were manufactured by Poomathi and coworkers via an effective one-pot synthesis of formyl-chromones with ammonium acetate in dimethylformamide (DMF) with stannous chloride mediation (Scheme 7). (76)

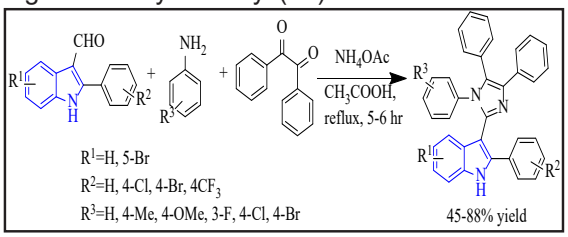


Scheme 6. Synthesis of tetrahydro-1H-indolin-2-ones derivative.

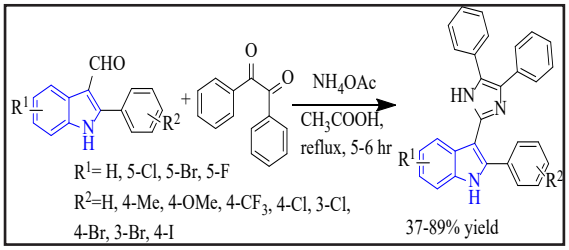


Scheme 7. Synthesis of indole-3-yl pyridines derivative.

Naureen et al. used a one-pot multi-component condensation technique to develop indole-based tetra-aryl-imidazoles. This method (Scheme 8) employs the reaction of indole-3-carbaldehydes, anilines, and benzyls in acetic acid in the presence of ammonium acetate. The anti-urease action of the produced molecules was tested, and the results were positive. (77) Naureen et al. further developed analogues of 2-phenyl-1H-indoles by condensing formyl indole, benzil, and ammonium acetate under refluxing acetic acid conditions (Scheme 9). The compounds were tested for a-glucosidase inhibitory activity and considered to have high inhibitory efficacy. (78)

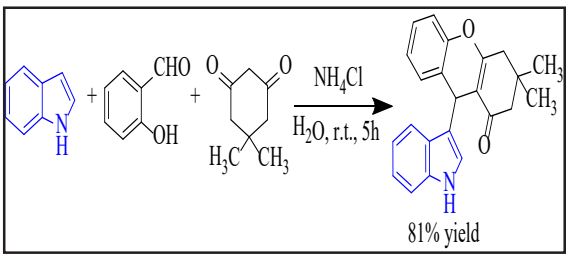


Scheme 8. Synthesis of tetra-aryl-imidazoles derivative.



Scheme 9. Synthesis of phenyl-1H-indoles derivative.

Bhattacharjee et al. used ammonium chloride as a promoter in the one-pot synthesis of indole using salicylaldehyde and dimedone to produce analogues of tetrahydro-1H-xanthen-1-one (Scheme 10). (79) So and Mattson demonstrated the preparation of glycine products using chiral based phosphoric acid as a catalyst. The multi-component linking processes of indole compounds, nitro-diazoester, or anilines in methyl tert-butyl ether (MTBE), which acts as a solvent, have been used in this method (Scheme 11). (80)



Scheme 10. Synthesis of analogues of tetrahydro-xanthenone.

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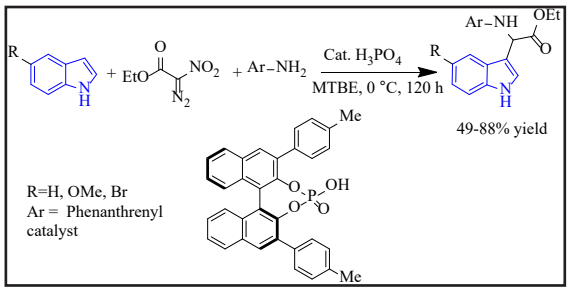
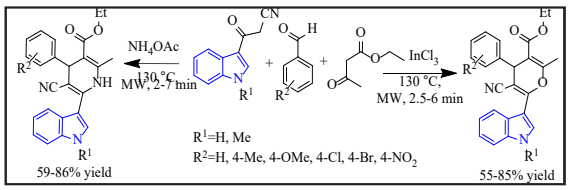
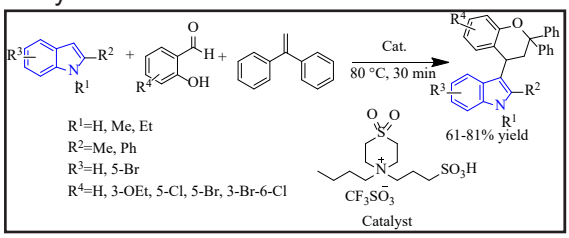


Scheme 11. Synthesis of glycine derivative.

Borah et al. synthesized the functionalized indole derivatives obtained via one-pot multicomponent synthesis of analogues of aldehydes, cyanoacetyl-indoles, as well as ethyl acetoacetate, with the addition of indium chloride ($InCl_3$) under microwave irradiation. The one-pot reaction was performed after NH_4OAc was employed as the source of ammonia in this process, producing the analogues of indole (Scheme 12). (81) Taheri et al. employed a sulfone-containing Bronsted acid (ions-based liquid), in a one-pot reaction combining indole, salicylaldehydes, and 1,1-diphenylethylene to make substituted chromane compounds (Scheme 13). (82)



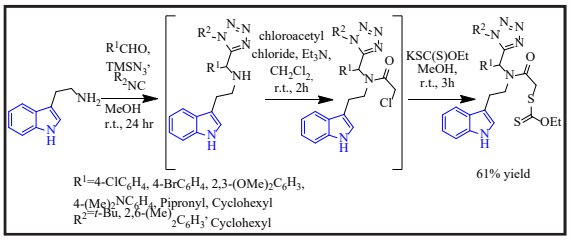
Scheme 12. Synthesis of analogues of cyanoacetyl-indoles.



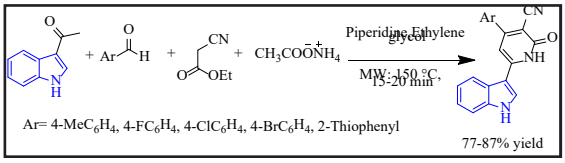
Scheme 13. Synthesis of substituted chromane derivative.

Base-catalysed synthesis

Gordillo-Cruz et al. showed several steps to synthesize 3-substituted indoles (Scheme 14) using 3-aminomethylindole chlorobenzene and $TMSN_3$ (trimethylsilyl azide). The first step was cyclization/substitution, which was subsequently N-acylated using chloro-acetyl chloride to produce stage B, which was further treated with potassium ethyl xanthogenate salts to produce the final compound xanthates. (83) Sayed et al. reported the synthesis of different 6-indolylpyridine-3-carbonitriles via a one-pot multi-component strategy in the presence of a catalyst. The reaction involves 3-acetylindole, aldehydes, ethyl cyanoacetate, and ammonium acetate (Scheme 15). They show good anti-proliferative properties of the synthesized compound. (84)



Scheme 14. Synthesis of xanthates derivative.

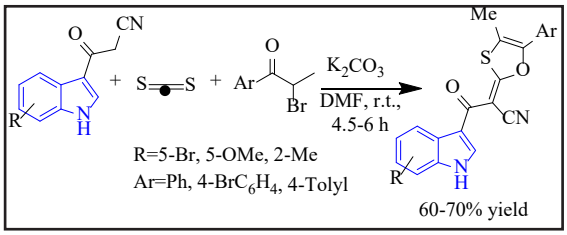


Scheme 15. Synthesis of 3-acetylindole derivative.

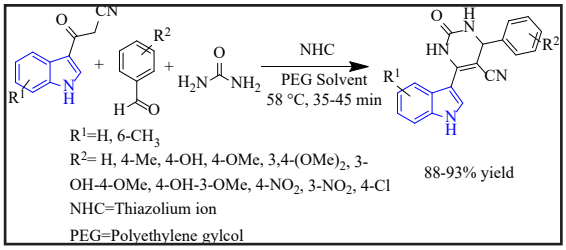
Liu et al. revealed the synthesis of two carbon-tethered compounds that are analogues to the pair of 1,3-oxathiole-indoles. The method involves a three-component domino [3+2] heterocyclization procedure with indole, carbon disulfide, and substituted a-bromo propiophenones (Scheme 16). (85) According to Fatma et al., combining cyanoacetyl-indoles with an arylaldehyde and urea in the presence of PEG-400 (polyethylene glycol) and the catalytic amount of thiazolium anion based on the N-heterocyclic carbene (NHC) resulted in a diverse set of tetrahydropyrimidine analogues.(86)

Viola et al. developed the new coumarin substituted indole derivatives by microwave irra-

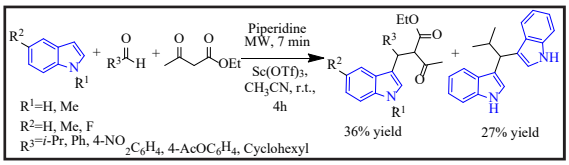
diating indole, salicylaldehyde, and malonates at room temperature in the presence of piperidine and Scandium triflate (Scheme 18). The main drawback of this reaction is that the compounds show very low yields. (87)



Scheme 16. Synthesis of 1,3-oxathiole-indole derivative.

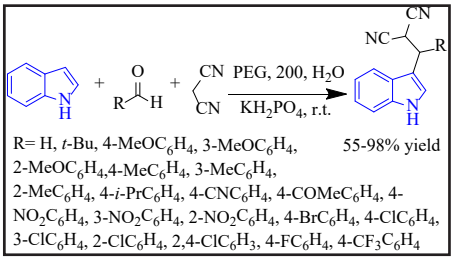


Scheme 17. Synthesis of tetrahydro pyrimidine based carbonitriles derivative.



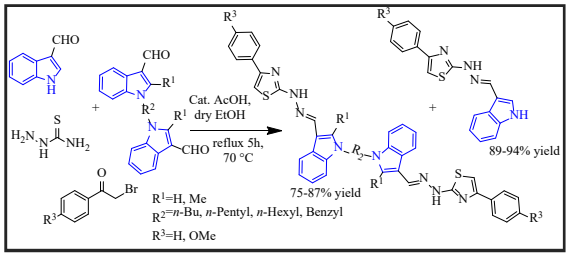
Scheme 18. Synthesis of coumarin derivative.

Wan et al. produced 3-substituted indole compounds in good to exceptional yields using polyethylene glycol (PEG) as a supporting base, in a 3-component reaction involving aldehydes, indoles, as well as malononitrile (Scheme 19). (88)



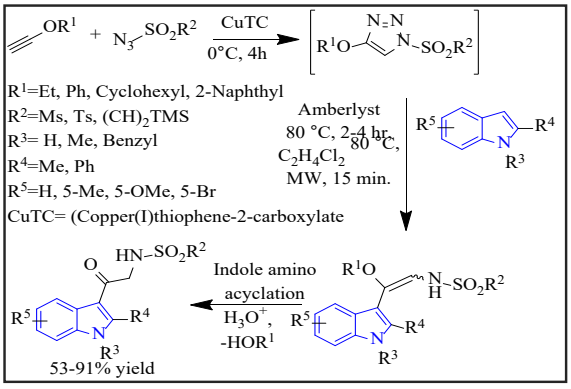
Scheme 19. Synthesis of analogue of 3-indole.

For the synthesis of new mono- as well as the bis-hydrazineyl thiazole analogues, Mahmoodi et al. conducted a one-pot cyclo-condensation using thiosemicarbazide and 3-formyl indole with the addition of a promotor such as acetic acid (Scheme 20). In vitro anti-bacterial activity against Gram-positive & the Gram-negative pathogens was examined for the synthesized derivatives. The thiozole analogue containing methoxy as a donor agent demonstrated potent antimicrobial activity against gram-positive pathogens. (89-91)



Scheme 20. Synthesis of hydrazineyl thiazole derivative.

Slight aminoacylation of indoles was established by Alford et al. for the preparation of oxo-tryptamines using a multicomponent procedure with ynol ethers and sulfonyl azides. (Scheme 21). First, ynol ethers and sulfonyl



Scheme 21. Synthesis of oxo-tryptamines.

azides were used to make derivatives of N-sulfonyltriazoles, which were then treated with indoles. For the a-aminoacylation of enols, the amino ketone was converted to enol ethers. (92)

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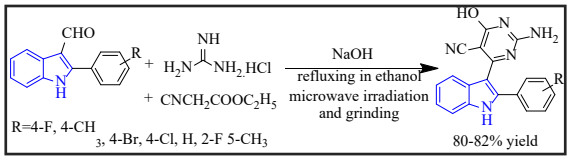
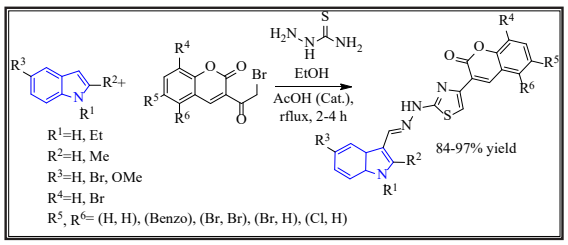
Gupta et al. synthesized the hydroxy pyrimidine compounds via one-pot synthesis of indole-3-aldehyde derivatives, ethyl cyanoacetate, and guanidine HCl. The reaction was tested under three different conditions: microwave irradiation, grindstone technology, and boiling (Scheme 22). The antimicrobial activity of the items was tested against harmful microbes and found to be relatively mild. (93)

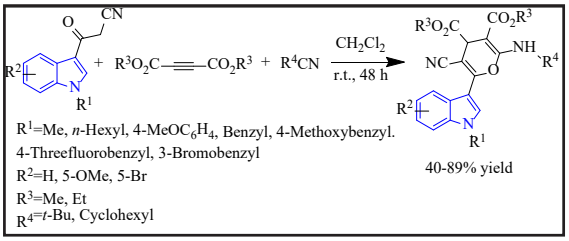


Scheme 22. Synthesis of hydroxy pyrimidines compounds.

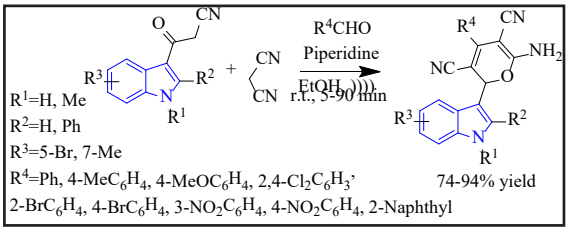
According to Gali et al., a range of indole integrated thiazolyl coumarins have been produced utilising a catalyst proportion of acetic acid in a reaction that involves indole variants, thiosemi-carbazides, and derivatives of chromen-2-ones (Scheme 23). [94] For the synthesis of analogues of 4H-pyran that have an indole scaffold, Song et al. demonstrated the [3+3] cyclization of analogues of cyanoacetyl-based indoles with DMAD & isocyanides (Scheme 24). (95) Chen and co-workers studied the effective preparation of substituted indole-pyran compounds using a one-pot mechanism of aldehydes, 3-cyanoacetyl indoles, and malononitrile with the addition of piperidine, which acts as a promotor. The reaction is carried out under ultrasonic irradiation at room temperature (Scheme 25). Thiamine hydrochloride, which is vitamin B_1 & CTAB were also used as promoters in this process, giving 92–94% products. (96)



Scheme 23. Synthesis of thiazolyl coumarins.



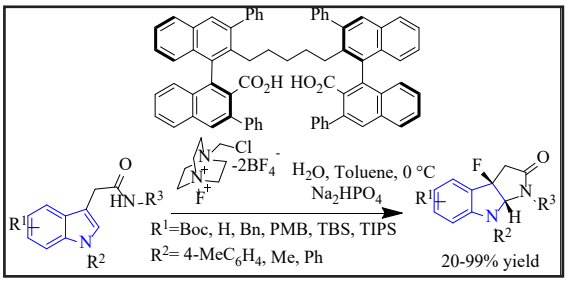
Scheme 24. Synthesis of 4-H-pyran derivative.



Scheme 25. Synthesis of substituted indole-pyran compounds.

Phase transfer catalyst mediated synthesis

A different type of catalyst is a catalytic reaction with phase-transfer catalytic conditions. Ionic reactants are regularly soluble in an aqueous solution but insoluble in an organic liquid in the absence of a phase-transfer catalyst (PTC). The accelerator acts as a solvent, dissolving the ions in the organic solvent. Hiromichi et al. discovered fluorocyclization based indole analogues with the help of a dianionic phase-transfer catalyst. In this process, the author produces pyrroloindoline compounds, which are highly enantioselective under a modest synthesis method. (Scheme 26). (97)



Scheme 26. Synthesis of pyrroloindoline derivative.

The diastereoselective preparation of

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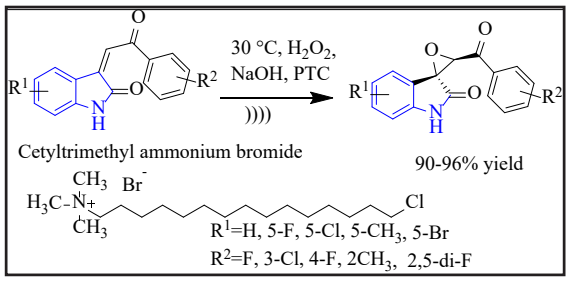
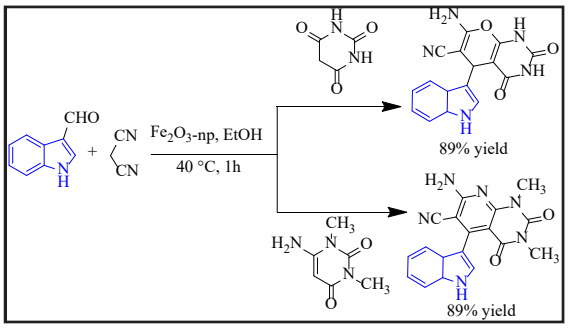
fluorine-containing [indole-3,2-oxirane] derivatives by using phase transfer catalyst (PTC) acetyl-trimethyl ammonium bromide was revealed by Dandia et al. The developed method was novel and eco-friendly for the manufacture of different indole-based heterocycles. The protocol involves aqueous ultrasonic irradiation for the epoxidation of indole-2-one analogues, which produce analogues of 3-benzoyl-2(1H)-ones (Scheme 27). (98)



Scheme 27. Synthesis of benzoyl-2(1H)-ones derivative.

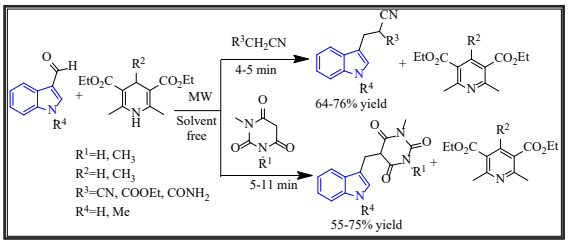
Miscellaneous

M. Kidwai et al. unfolds the formation of pyrano[2,3-d] pyrimidines as well as the pyrido[2,3-d] pyrimidines by using magnetic particles (Fe_3O_4-NPs). The processes were carried out in ethanol using a 3-component one-pot process involving malononitrile, indole & barbituric acids as well as the 6-amino uracil analogues. (Scheme 28). (99)

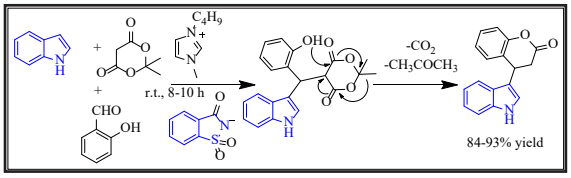


Scheme 28. Synthesis of pyrano[2,3-d] pyrimidines & analogues of pyrido[2,3-d] pyrimidines.

Baruah et al. described the formation of 3-alkylated indole analogues (Scheme 29). In a convection-driven 3-component reaction of alkyl nitriles, indole-3-aldehydes, as well as barbituric acids using DPH (1,4-dihydropyridines) analogues. (100) Atul et al. developed imidazolium saccharinate via multicomponent reaction between indole, salicylaldehyde and cyclic active methylene derivatives using ionic liquids. The study revealed that decarboxylation enhanced the properties of indoles and dihydrocoumarin, which give coumarin-based analogues of indole (Scheme 30). (101)



Scheme 29. Synthesis of alkylated indole derivative.



Scheme 30. Synthesis of imidazolium saccharinate.

Khalafi-Nezhad et al. demonstrated the utilisation of trimethylsilyl-chloride as a multipurpose catalyst for a one-pot, three-component reaction to produce analogues of xanthen-(9H)-ones from the reaction of indole and analogues of di-carbonyls. (Scheme 31). (102) The author developed a novel diastereoselective domino cyclization method using post-Ugi gold as the promotor for diastereoselective domino cyclization to synthesize variously substituted spiroindolines in Scheme 32. The Ugi reaction of propargylamine, acids, indole-3-aldehydes, or isocyanides yields a very high number of molecules that react with $Au(PPh_3)SbF_6$ in chloroform ($CDCl_3$) to form spiro-indolines in moderate yields. (103,104)

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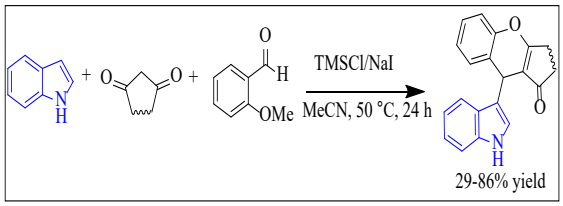
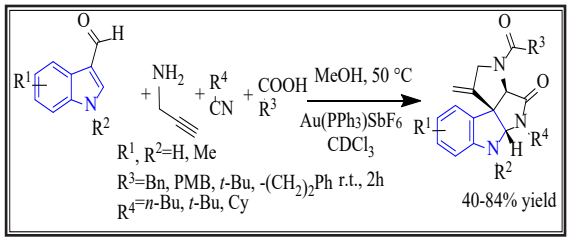
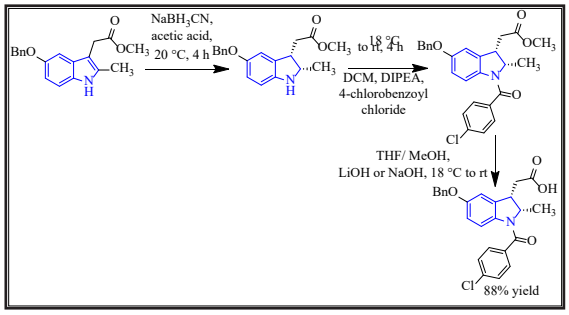


Scheme 31. Synthesis of xanthen-4-(9H)-ones derivative.

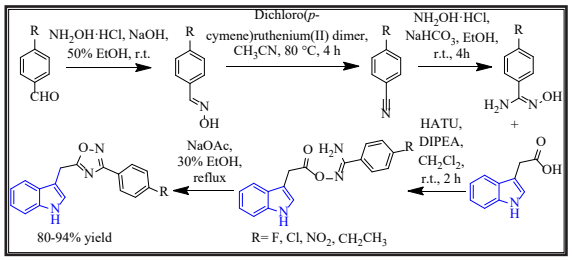


Scheme 32. Synthesis of derivative of spiroindolines.

The newly synthesized indole derivative, 1-(4-chlorobenzene)-5-hydroxy-2-methyl-3-indoleacetic acid, was shown to have insulin-sensitizing and glucose-lowering properties. Scheme 33 represents the seven-step synthesis of a product from para-nitrophenol. The final compound revealed the strongest hypoglycemic activity of any indole-3-butyric acid derivative. However, because of the presence of a 2,3-double bond, the amide bond of the final compound is easily hydrolyzed. (105) The 1,2,4-oxadiazole ring linked to the indole scaffold distinguishes phidianidines. They were first isolated from the aeolid opisthobranch mollusk Phidiana militaris in 2011, according to Gavagnin et al. (106). These indole compounds had strong cytotoxicity as well as neuroprotective properties as typical secondary metabolites. Furthermore, the findings indicated that they were both T-cell protein tyrosine phosphatase (TCPTP) and protein tyrosine phosphatase 1 B (PTP1B) inhibitors. Furthermore, structure-activity relationships (SAR) and molecular docking analyses of 40 different phidiandine analogues revealed that a 1,2,4-oxadiazole ring was required for PTP1B inhibitory activity. Scheme 34 (107) depicts the function-oriented synthesis of PTP1B inhibitory analogues.

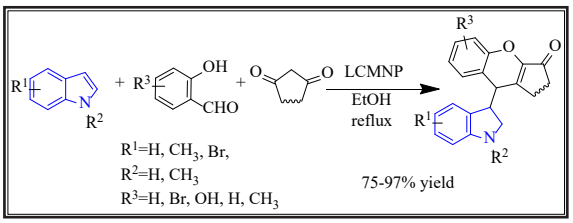


Scheme 33. Synthesis of derivative of indole-3-butyric acid.



Scheme 34. Synthesis of derivative of phidianidines.

Since many years, researchers have been studying the synthesis of 9-(1H-indol-3-yl) xanthen-4-(9H)-ones derivatives (Scheme 35), it is a class of multifunctional heterocyclic chemicals with an indole ring, and their inhibitory activity on a-glucosidase [108].



Scheme 35. Synthesis of 9-(1H-indol-3-yl) xanthen-4-(9H)-ones derivatives

Conclusion

In medicinal chemistry and drug development, indole and its derivatives have proven to be excellent target molecules. They can be found in a broad range of organic sources,

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and novel indole derivatives are produced on a regular basis. Because these scaffolds bind to a broad range of proteins, their production represents a possible route to new lead molecules. The pharmacological actions of indole scaffolds have been highlighted in this review. The remarkable biological and physiological activity of such indoles makes them potential candidates for microbe-borne diseases and other health problems like Alzheimer's disease. The indole is a very versatile nucleus in the pharmacological sector, as evidenced by the therapeutic potential of indole analogues. As a result, the information is expected to aid in the development of novel compounds with improved bioactive components, as well as novel synthetic methodologies.\

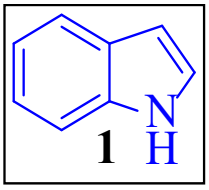

Fig 1 Structure of indole.

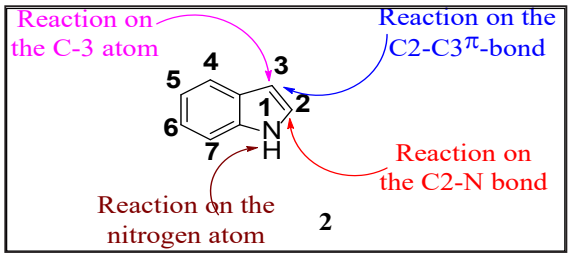

Fig 2. Active of carbon nitrogen in indole compound.

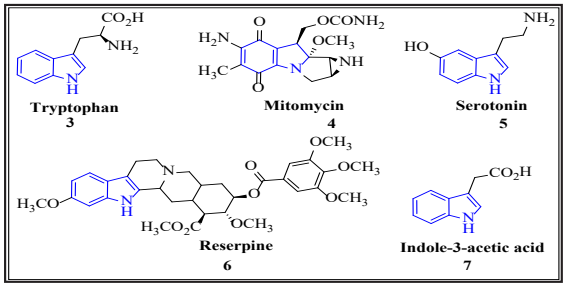

Fig 3. The structure of indole alkaloids.

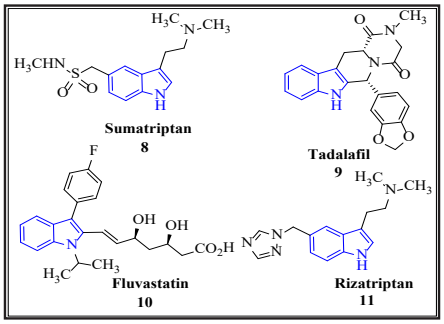

Fig 4. The structure of some pharmacological agents.

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Abbreviation

- 5-HT1D- 5-Hydroxytryptamine receptors
- DMF-Dimethylformamide
- DPH-1,4-dihydropyridines
- LXR- Liver x receptor
- NHC- *N*-heterocyclic carbene
- PEG- Polyethylene glycol
- PTC-Phase transfer catalyst
- PTP1B- Protein tyrosine phosphatase 1 B inhibitors
- PTS- Platinum monosulfide
- *p*-TsOH- *p*-toluene sulfonic Acid
- SAR- Structure activity relationship
- STA- Supported tungstic Acid
- TCPTP- T-cell protein tyrosine phosphatase
- $TMSN_3$-Trimethylsilyl azide