BioGecko

Vol 12 Issue 03 2023

ISSN NO: 2230-5807

RECENT ADVANCES IN THE SYNTHESIS AND APPLICATIONS OF INDOLE FUSED DERIVATIVES: A BRIEF REVIEW

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Abstract
In this review researcher focuses recent advances of indole in multicomponent processes for the synthesis of fused heterocyclic compounds, **covering last four years since 2018 to 2022**.
Indole is one of the most versatile and ubiquitous nitrogen-based heterocyclic scaffolds, it is often used as a building block in the synthesis of many chemical compounds.Because of their usefulness in medicine and biological processes, heterocyclic molecules like indole are very relevant.Particularly, the past decade have seen an increase in the synthesis of indole derivatives as researchers have attempted to achieve promising new heterocycles with chemical and biomedical relevance through the design of polycyclic structures by the incorporation of multiple fused heterocyclic scaffolds. Some of the environmentally friendly methods that are overtaking conventional methods for the synthesis of indole and their fused derivatives include the use of ionic liquids, water (solvent), use of solid acid catalyst, microwave irradiation technique, and some other. Furthermore, substituted indoles fused compounds have enormous potential in many other fields.

Key words: Heterocyclic compound, Indole, synthesis, biological potential

Introduction

Today, the majority of molecules are heterocyclic, therefore studying them is becoming more popular. Among the heterocycles, indole-based compounds have a wide range of uses in the fields of medicine, agrochemistry, dyes, etc. Indole derivatives have numerous applications as sanitizers, corrosion inhibitors, copolymers, anti-cancer, anti-HIV, anti-cancer, anti-inflammatory, anti-tubercular, anti-microbial, anti-viral, anti-cancer, and anti-tumor medications (1-4).With a variety of pharmacological actions owing to various modes of action, indole is an exceptional heterocyclic molecule, a privileged scaffold, and a flexible pharmacophore.Many compounds with crucial biological roles have bicyclic heterocyclic structures; indole is particularly flexible due to its structure. Indole nucleus also act as inhibitor like Hepsin inhibitor,Histone deacetylase inhibitor, Phosphodiesterase 4 (PDE4) inhibitor, Urease inhibitor and VEGFR-2 tyrosine kinase inhibitor, Aromatase inhibitor, etc (5).An indole, also known as benzopyrrole, is an organic molecule with the formula C8H7N that has been noted as a key building block in the area of medicinal chemistry because of the fusion of its six-membered benzene ring with the five-membered nitrogen-containing pyrrole ring (4,6).

In terms of chemistry, Indole is just slightly basic. As a result of nitrogen lone-pair delocalization into the -electronic system, which may move freely around the indole ring, this occurs.Therefore, owing to the preservation of aromaticity, the protonation of C-3 is more thermodynamically preferable than that of N-1, and the lone pair of electrons on nitrogen is not readily available for protonation. That's why the C-3 position is a centre for a wide range of chemical processes, including electrophilic substitution, organometallic indole anion complexes, carbon lithiation, oxidation, cyclo-addition, and more besides.At room temperature, indole is a solid. It is the odorous compound found naturally in human stool. At lesser concentrations, however, it gives a floral aroma and is used in perfumes, colognes, and even coal tar In addition to this, indole participates in a wide variety of essential metabolic processes. Spore formation, plasmid stability, drug resistance, biofilm development, and virulence are only few of the bacterial physiological processes that are controlled by this protein (6).

Chemical synthesis of Indole

The Indole nucleus may be synthesised using many conventional techniques, some of which have been reported in the below. It requires a variety of beginning materials and strategies (1,6-8), such as:-

- Julia indole synthesis
- Fischer indole synthesis
- Reissert indole synthesis
- Baeyer-Emmerling indole synthesis
- Larock indole synthesis
- Bartoli indole synthesis
- Madelung indole synthesis
- Fukuyama synthesis
- Leimgruber-Batcho

Over the last five years, researchers have studied and proposed novel approaches for the synthesis of indole fused derivatives/compounds and also involving the wide range of efficient catalysts. Some mentioned in below-

Ozdarska k. et al. (2022) demonstrated that depending on the substitution at position 3 of the indole, NH tricyclic pyridazinoindolone scaffold in yields ranging from satisfactory to excellent. Although an EWG moiety is present at the C-3 position, the indole cycle's nucleophilic capacity at the C2 position is still there, providing access to the required tricyclic skeleton in aadequate yield and allowing access to the active molecule. To make this family of tricyclic cyclic backbones, however, this cyclization of N-aminoindole species seems to be an unrefined, elegant, and straightforward synthesis method. The synthesis of HDAC inhibitors and the application of indole chemistry to alkaloid derivatives (tricyclic ABE backbone) may both be of interest. In summary, Using an intra-molecular electrophilic aromatic substitution and a simple/effecient acid catalyst, a tricyclic derivative obtained and Selective inhibition of class IIa vs class I HDAC enzymes may be achieved by the use of a terminal capping group, such as the pyridazinoindolone scaffold, which is bulky enough to selectively bind in the cavity of histone deacetylase 7 (HDAC7) without impacting HDAC1 (9).

Shourkaei F.A. et al. (2022) researcher offers to make a indole-fused diketopiperazine derivatives, researchers provide a two-step process based on cyclizing Ugi adducts in the presence of trimethylamine. This process does not need a metal catalyst. Simple Ugi condensation was used to start the reaction, which was then followed by a modest intramolecular nucleophilic hitting in a single pot. Under basic circumstances and with excellent yield, the synthesis procedure included a Ugi four-component reaction involving tryptophanate, 1H-indole-2-carboxylic acid, benzaldehyde derivatives, and isocyanide derivatives. An effective method for creating novel biological molecules is described in this literature (10).

Kaur Manpreet et al (2021) discovered/described that novel synthetic approach including the production of intramolecular C(sp^2) N bonds under a modified Cadogan reaction for the creation of previously unreported 1,4-dihydropyrazolo[4,3-b]indoles (6) and their derivatives (7, 8). The synthesis of products through the nitrene process was justified using DFT simulations.
Micromolar quantities of the active compounds were fatal to three different types of cancer cell lines: lung (A549), colon (HCT-116), and breast (MDA-MB-231, and MCF-7). Aggressive MDA-MB-231 cancer cells were killed by the compound when it was synthesised. 7a, 7b, and 6h was shown to cause ROS production as well as change their mitochondrial membrane potential in biological research. It was later discovered that these chemicals were either specific for Topo I (6h) or Topo II (7a, 7b) Inhibitor (11).

Ma Jiaoli et al (2021) α-Aminophosphonate moieties was synthesized in a set of new indole derivatives as antitumor medications.Most of the compounds and derivatives were shown to have moderate to high anticancer activity in an MTT test against human hepatocellular carcinoma/liver cancer (Hep G2) and human gastric cancer cells (MGC-803). When compared to the different compounds, C5 was shown to be more effective in inhibiting HepG2 than 5-fluorouracil. Compound B7 inhibited MGC-803 more potently than 5-fluorouracil, which is noteworthy.Results showed that these compounds might be auspicious and leading bioactive molecules act as potential anticancer medicines (12).

Chatterjee et al (2020) revealed that N-arylation of 5-aminopyrazoles catalysed intramolecularly by copper for the first time. A method for the synthesis of pyrazolo[3,4-b]indoles with extensive substituent groups.The indole backbone may be modified with halogens, alkyl, or methoxy groups. With this method, one's make a wide variety of substituted pyrazolo[3,4- b]indoles with a small to large indole core.In addition, pyrazolo[1,5-a]benzimidazoles are synthesised by selective N-arylation of unsymmetrical (electron-rich) diaryl bromides to form pyrazole. From pyrazole precursors, pyrazolo[3,4-b]indoles may be synthesised in a safe and practical manner. (13).

H. Zhang-Xu et al (2020) novel thiosemicarbazone indole derivatives was developed and synthesised. On five cancer cells, most of the chemicals showed modest to high anti-cancer activity (PC3, EC109, DU-145, MGC803, MCF-7). When compound 16f was tested against normal WPMY-1 cells, it was shown to be highly selective for PC3 cells and to have antiproliferative effects. In preliminary mechanistic experiments, compound 16f was shown to have the potential to inhibit prostate cancer cell proliferation and colony growth (PC3, DU-145) in a dose-dependent manner. In addition, the stimulation of the MAPK signalling pathway by derivative 16f resulted in G1/S cycle seize and death, which mightlinked to ROS buildup. Molecule 16f also inhibited tumour development in a xenograft model including PC3 cells and showed no harm in animals when tested in vivo. Overall, analogue 16f may be considered a possible lead molecule for the invention of a novel anti-prostate cancer medication based on its biological activity assessment (14).
Tokala R. et al (2020) synthesized thiadiazolo-carboxamide bridging -carboline-indole hybrids, noteworthy cytotoxic drugs were developed by combining conspicuous features. The synthesized compound were tested on several cancer cell lines (A549), MDA-MB-231 (BT-474), HCT-116 (HTP-1), and MDA-MB-231 in combination with 12c showed that 12c had the most powerful cytotoxicity in vitro of any of the produced novel compounds (12a–k) (A549). Additionally, a chemical known as 12a was shown to be very cytotoxic to the lung cancer (A549) cell line. These two compounds, 12c and 12a, were further tested for their ability to block DNA intercalative topoisomerase-IIa. Compound 12c's antiproliferative action was further assessed in A549 cells using conventional apoptosis tests, which revealed concentration-dependent nuclear, morphological, and membrane potential depolarization, as well as the externalisation of phosphatidylserine, in the mitochondria. Compound 12c inhibited lung cancerous cell migration in vitro, as shown by cell cycle analyses and wound healing evaluation. Compound 12c inhibited cell cycle growth in A549 cells in the G0/G1 phase in a dose-dependence manner. Compound 12c's safety profile was revealed by screening oppose a normal human lung epithelium cell line. very remarkable. Intercalative binding in the active pocket of topo-II is further confirmed by molecular modelling studies. Additional favourable drug-like features of the synthesised compounds were discovered by in silico forecast of physiochemical parameters.
This work was focus on putting together several pharmacological features of developed compounds that may be appropriately derivatized to signal their advancement as prospective anticancer medicines (15).
Al-Wabli et al (2020) Using different spectroscopic techniques, the new synthesised isatin-indole molecular compounds 5a–s was identified and their potential as antiproliferative agents in vitro was determined. In vitro anti-proliferative property of compound 5m was shown against three human cancerous cell lines. This chemical was seven times more effective than sunitinib. Compound 5m was subjected to extensive pharmacological testing in order to learn more about the anti-proliferative mechanism of this family of drugs. Compound 5m induced the number of cells in the G1 phase while reduce the number of

cell in the G2/M and S phases. Furthermore, compound 5m decreased the quantityof phosphorylated retinoblastoma protein found in a dose-dependent manner. B cell translocation gene 1, cell cycle-associated proteins includes cyclin B1, cyclin D1, and phosphorylated cyclin-dependent kinase 1, and a pro-apoptotic protein such as Bcl-2-associated X protein gene, as well as initiated caspase-3, were all increased by compound 5m. The oral toxicity of compounds 5a-s was shown using ADME predictions. As a result, compounds 5a–s might be used as a novel anti-proliferative principle/lead chemicals in chemotherapy (16).

Varvuolyte et al (2020) discovered a hybrid pyrazole-indole fluorescent compounds 5, 7, and 10 were prepared from commercially available chemicals. Wittig-Ramirez olefination, Vilsmeier-Haack formylation, and ligand-free Heck-Sonogashira palladium-catalyzed cross-coupling processes were utilised to synthesise the compounds. 3-(hexyloxy)-1-phenyl-1H-pyrazole-4-carbaldehyde 1 and 5-(iodo-3,3-dimethyl-2-(3-iodopropyl)-2H-indole 4 Using PdCl2(PPh3)2, CuI as a co-catalyst, and triethylamine as a base, we get compound 5 with a 60% yield and anti-cancer properties.Two-step synthesis of the fluorescent 3H-indole derivative 7 was carried out, commencing with the identical aldehyde 1. Alkene 6 was obtained in 84% yield in the first phase of the Wittig process. When the methyltriphenylphosphonium iodide solution in toluene was titrated with a hydrochloric acid base, the resulting methyltriphenylphosphorane was employed as the yield source. A modified technique from the literature was used to carry out the ligand-free palladium-catalysed Heck reaction of 6 with the aforementioned derivative 4, resulting in a yield of 62 percent for the target product 7. In order to prolong the πconjugation of the 3H-indole derivatives and thereby create a bathochromic shift in the fluorescence emission, alkene 6 was formylated under Vilsmeier-Haack conditions, yielding,-unsaturated aldehyde 8. Then, compound 8 passed through a Wittig reaction to create 4-[(1E)-buta-1,3-dien-1-yl]-3-(hexyloxy)-1-phenyl-1H-pyrazole 9 in 52% yield. Finally, under the aforesaid ligand-free Heck reaction conditions, compound 9 was coupled with 4 to generate the highly luminous 3H-indole derivative 10 in 25% yield.The required chemical 7 was extracted in a modest yield of 62 percent using a technique described in the literature.

Newly synthesised Two human cancer cell lines, K562 (chronic myeloid leukaemia) and MCF-7 (breast cancer), were tested for sensitivity to pyrazole-indole conjugates 5, 7, and 10. While the chemicals themselves had low cytotoxicity, examination of the treated cells under a fluorescence microscope revealed some interesting effects, discovered that the light-exposed treated cells began to die, indicating that they had photodynamic anticancer capabilities and the most powerful chemical, 7, elicited a robust photodynamic response. In this literature researcher revealed that fluorescent pyrazole-indole hybrids may offer as an attractive source of photosensitizing chemicals with anticancer action(17).

Shaik et al (2020)finding novel medications, indole motifs are among the most important scaffolds andreported the synthesis and in vitro examination of novel N-substituted indole derivatives (1-3) with anti-microbial/bacterial activity. The aforementioned compounds have been synthesised successfully from readily accessible building blocks. Using the disc diffusion technique, tested for antibacterial and antifungal properties using novel strains of S. aureus, E. coli, and C. albicans. Most notably, 4-(1-(2-(1H-indol-1-yl) ethoxy) pentyl)-N,N-dimethyl aniline (1) was shown to be the most powerful of the analogues tested, demonstrating a level of inhibition greater than that of the widely used standard medication chloramphenicol.Compound 1, which contains butyl substituents, was shown to be more selective than its similarly related structural relatives two and three (2).

Ali Imran et al (2018)synthesized a simple and easy micellar "nano" indole heterocyclic compound with anti-cancer activity. Ultra voilet spectroscopy, ^{1}H NMR, FT-IR, and Mass spectroscopy was used to analyse the produced compounds 11–23. During adduct formation, the produced chemicals bind to DNA's minor grooves. Compounds 11–23 high intercalation Kb values revealed that they bind to DNA by electrostatic attraction, according to hypochromism. 11-23 showed remarkable anticancer activity against the cancer cell

line HepG2/C3A. The DLC and DLE percentages was good. Lipinski's rule of five was followed by compounds 11–23. Cancers can be treated with compounds 11–23 (18).

Rezvanian et al (2018) discovered a One-Pot Synthesis of spiro[indoline-3,4'- pyrano-pyrazole] Iodine-Catalyzed Derivatives/compounds. It was produced using a simple, efficient, and effective synthetic technique.Moreover, this amazing technique generates new spiropyranopyrazole compounds in excellent to high yield. This method is easier to use and better for the environment because it doesn't involve using poisonous or dangerous solvents. This innovative technique allows for the creation of five new bonds in a single sequence (19).

Conclusion

The work concluded that the several methods wasexistfor preparing the indole fusedcompounds and its derivatives. These Synthesis/methods using green chemistry norms typically employs gentle reaction conditions, less hazardous ingredients, active catalysts, procedures that do not need the use of solvents or are mediated by water, and produces high yields of the product of interest in a shorter amount of time than conventional methods.The indole ring system is a very prevalent and important category of heterocycle found in nature.The indole ring system is particularly interesting to chemists since it is included in a number of useful synthesised medicinal compound. It should be noted that many of the cited works in this review are published within the past decade is evidence of the continuous significance of indoles and the accessibility of "something novel" for their synthesis.

Source of Funding- Self Funded

Conflict of Interest- Nil

Acknowledgement- The author would like to thank all his mentors. The notes compiled here are collected over a period of time and may have been reproduced verbatim. Apologize to all researchers if in-advertently failed to acknowledge them in the references.

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