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REVIEW

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Synthesis of biologically active sulfonamide-based indole analogs: a review

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Abstract

The class of heterocyclic compounds exhibits a variety of pharmacological actions, long employed as an active ingredient in drug design and production. Indole and its derivatives are crucial in medicinal chemistry. Due to its physiological action, it has been gaining a lot of interest by exhibiting antibacterial, anticonvulsant, antifungal, antimalarial, antidiabetic, antidepressant, anticancer, and antimicrobial properties. The indole moiety constitutes a benzene ring fused with a pyrrole ring to form a bicyclic structure with a nitrogen atom as the major component and is produced by a variety of techniques. The sulfonamide analogs of indole usually referred to as sulfa medicines have recently been produced and exhibit strong antimicrobial actions. The goal of this work is to present the most recent methods for synthesizing indole-sulfonamide derivatives, together with data on their reported activities and synthetic scheme from 2010 to 2023. We anticipate that this review will help medicinal chemists rationally develop pharmacologically active derivatives of indole with sulfonamide scaffolds.

Keywords Indole, Sulfonamide-indole analogs, Synthesis, Biological activity, Review, Sulfonamide

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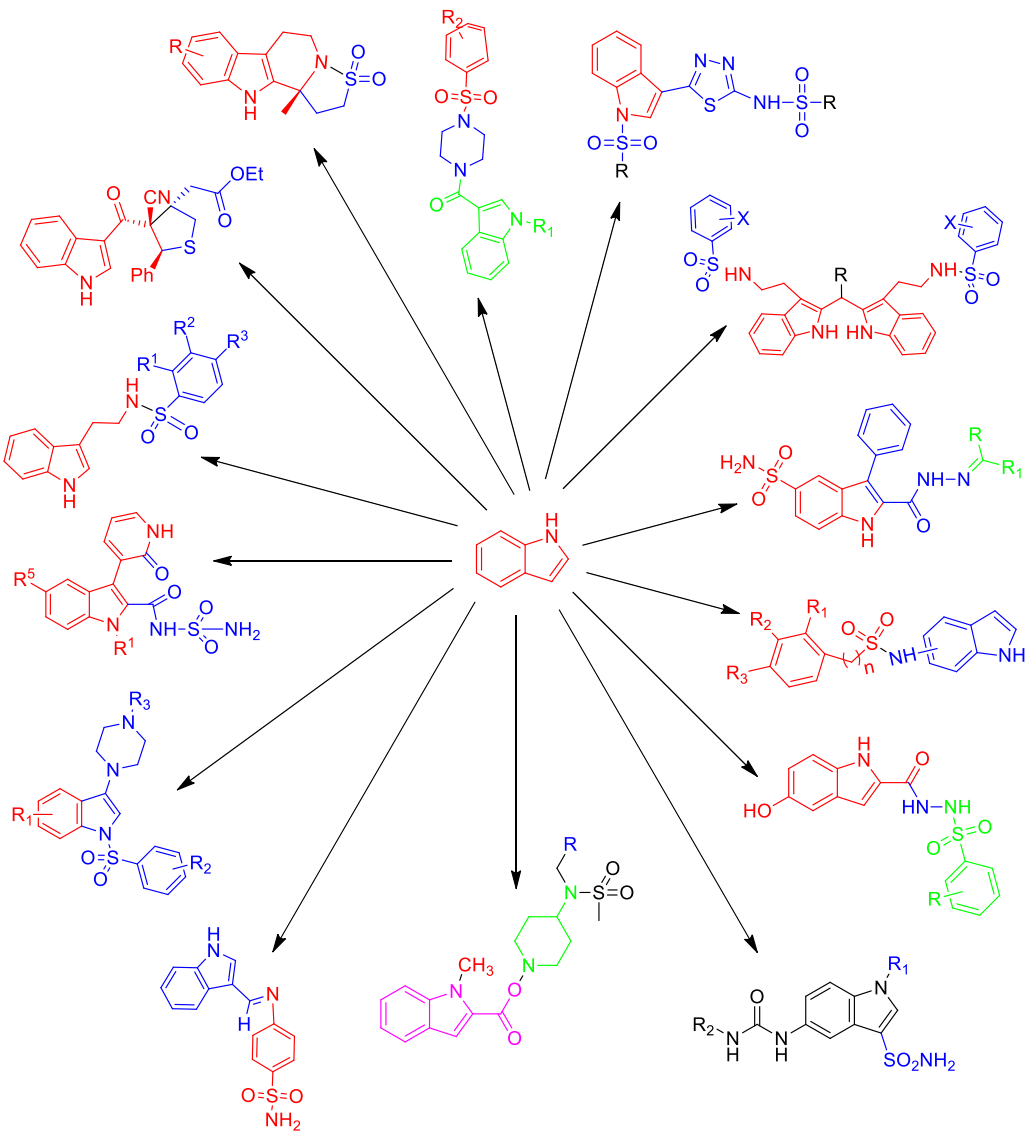
Graphical Abstract



Background

A large variety of heterocyclic molecules, including "Indole", is clinically active, making heterocyclic chemistry crucial in medication design [1]. In 1866, while researching the indigo dye, Baeyar and knop created indole for the first time [2]. Baeyar used reduced oxindole [3] to make indole. Indole, with the chemical formula "C_8H_7N", is often referred to as 1H-benzo[b] pyrrole [4]. The temperature at which indole melts is noted to be around 52 °C, while its boiling happens around 253 °C giving a solid crystalline structure of this compound, a bicyclic structure [5].

Some naturally occurring alkaloids have an indole ring. There have been claims that indole derivatives have biological effects and possess anti-inflammatory [6, 7], antitubercular [8–10], antidiabetic properties [11, 12], antioxidant [13, 14], anticancer [15–18], anticholinesterases [19, 20], and antiviral [21–23] properties. Indole-sulfonamide is thought to be a suitable pharmacophore equivalent for substituting active sites in drug design since it undergoes substitution, primarily at the C-3 position, and has hydrophilic properties similar to the sulfonyl group[24]. Indole is a relatively weak basic chemical. This results from the delocalization of the nitrogen lone

pair into the free-to-move-electronic system within the indole ring. As a result, the lone pair of electrons on nitrogen is not available for protonation and it becomes protonated at the C-3 position instead since this configuration is thermodynamically more stable due to the retention of aromaticity. As a result, it participates in a variety of chemical processes, including cycloaddition [25], carbon lithiation [26], oxidation [27], electrophilic substitution [28], and organometallic indole anion complexes. These processes are especially prevalent at the C-3 position. Indole is a solid at room temperature, and it naturally arises in human feces and gives out a fecal odor. However, it emits a floral smell at lesser concentrations and is a component of many perfumes, colognes, and coal tars [3]. In addition, indole has a role in several metabolic processes that take place within the body [29]. It controls spore formation, plasmid stability, drug resistance, biofilm development, and virulence, among other aspects of bacterial physiology [30].

Sulfonamides play a crucial role in pharmaceuticals and are physiologically active [31, 32]. Sulpha or sulfa medications are produced by the sulfonamide moiety's fundamental structure with corresponding reactants [33]. The greater potency demonstrated for developing novel characteristics of sulfonamides can also produce active derivatives. The chemistry of indole-carboxylic acid moiety [34] with that of sulfonamides can produce a pharmacologically active scaffold via different methods as reported in the literature.

Main text

Synthesis and biological evaluation of indolenyl sulfonamides

In 2010, by condensation, reacting indole-3-carboxaldehyde with various sulfonamides including sulfamethazine, sulfaguanidine, sulfadiazine, sulfisoxazole, sulfathiazole, sulfamethoxazole, and sulphanilamide seven novel indolenyl sulfonamides have been created [34]. The possible ligands for complexation with some specific divalent transition metal ions have been utilized as these manufactured compounds (copper, zinc, and cobalt). The findings of this inquiry were consistent with the indolenyl sulfonamides' proposed structures. It has been proposed that certain functional groups, including azomethine or hetero-aromatics [35], present in these compounds showed biological activity, which may be the cause of the molecules' increased hydrophobicity and liposolubility. Hence, all produced sulfonamides have potent antibacterial [36] and antifungal activities. This in turn increased the activity of the compounds and biological absorbance. This study played a pivotal role in synthesizing sulfonamide derivatives of indole with biological activities in a new way. The synthetic scheme, which was adopted for this study, is described below (Scheme 1).

Synthesis of N_1-arylsulfonyl-3-piperazinyl indole derivatives

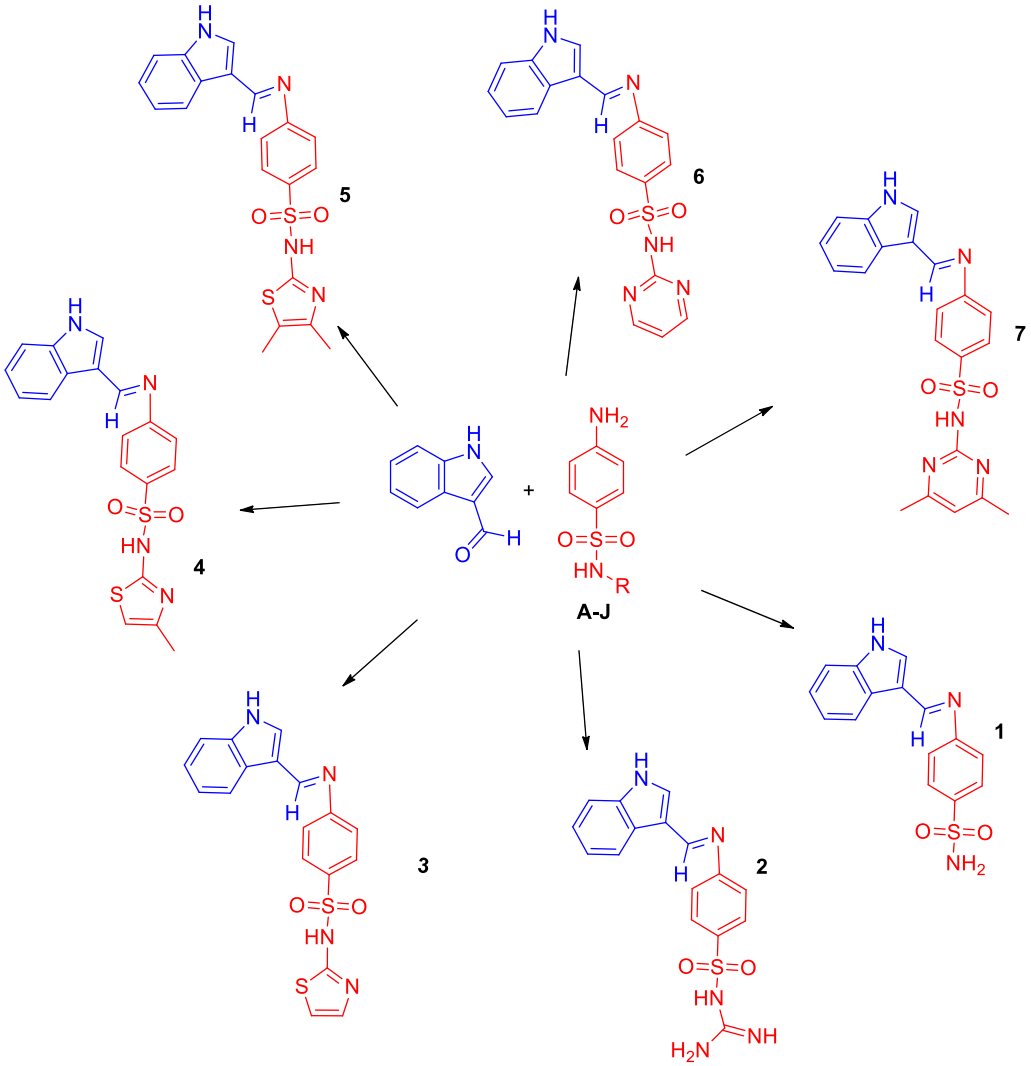
To create equivalent substituted N_1-acetyl-3-piperazinyl indole derivatives, sodium triacetoxyborohydride, *N*-alkyl piperazines, and titanium isopropoxide were reacted with the derivatives of substituted *N*-alkyl acetyl indoxyl. Further, the deacetylated product was produced by deacetylating these indole derivatives with simple under reflux such as NaOH and KOH. The *N*1 sulfonylation of indole was accomplished using several distinct techniques. Dimethylformamide (DMF) and sodium hydride were determined to be the most effective combination. As an alternative, it was discovered that potassium hydroxide and tetrahydrofuran (THF) were equally useful for producing target chemicals in high quantities. The synthetic mechanism followed a multistep route as all the reactants were treated in alternative ways and a good yield was determined at the end of the reaction. The conditions were closely monitored by various techniques and finally, a successful characterization yielded the product. The final product was further checked for any biological activity and it showed a positive result [37] (Scheme 2).

Synthesis of C2 acyl sulfonamide analogs of indole

In a study done by Anilkumar et al. [38], the majority of the analogs were successfully synthesized at the C2 location. Under simple conditions, hydrolysis of the C2 ester produced approximately quantifiable yields of the advanced intermediate. C2 acyl sulfonamide intermediates were produced after carbonyl di imidazole activation and then reacting alkylated sulfonamides. The last synthetic modification to generate analogs by demethylation in dioxane reflux was performed. A C2 acyl sulfamide analog was produced after treatment with sulfonylurea and a consecutive demethylation process. The formed sulfonamide-indole scaffold is highly potent in terms of biological significance. The schematic synthesis of the above-mentioned product is illustrated (Scheme 3).

Significance of Friedel–Craft reaction for the synthesis of indole sulfonamides

As possible anticancer medicines, Ratchanok and team created indole core structures using the Friedel–Craft reaction catalyzed by tungstosilicic acid hydrate in this study. Due to the catalyst's favorable environmental characteristics and simplicity, it has drawn a lot of attention. Here, the structure–activity relationship (SAR) of the synthesized indole analogs and their antiproliferative effect on cancer cell lines are reported [39]. The



Scheme 1 Synthesis of sulfonamide derivatives of indole

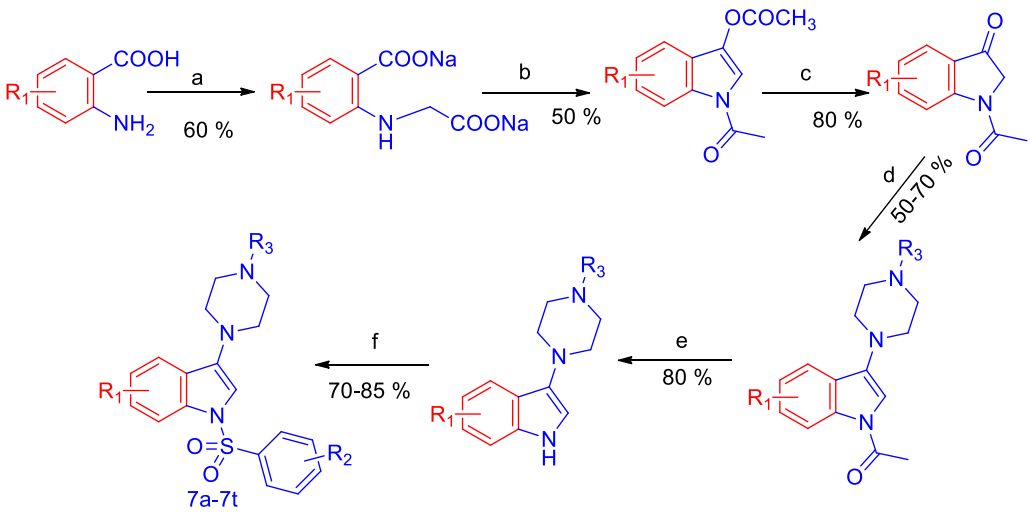
significance of this method was that the used Friedel–Craft reaction is utilized precisely to obtain a good yield. The mechanism of its synthesis was specific to producing a cytotoxic product with much wider applications as an agent. Its mechanism is environment-friendly and specific in action. Various methods including spectroscopic techniques [40] confirmed the formed product (Scheme 4).

Chiral squaramide-catalyzed cascade sulfa Michael addition reactions

Through an organocatalyzed addition process (Cascade sulfa Michael/Michael addition), Li et al. [41] discovered an enantioselective compound named (E)-3-aryl-2-(indol-3-ylcarbonyl) acrylonitriles. The catalysts used called chiral squaramide [42] helped to speed up this process and produced 3-substituted chiral indole scaffolds having 3 stereo centers of tetrahydrothiophene [43] in good to exceptional yields. With the best catalyst in place, further research was done to determine the best reaction conditions by examining the number of reactants, solvent interactions, and given temperature. The reaction was observed under optimal circumstances, and a noticeable impact was observed by the electronic interactions that the substituent had on the indole ring that resulted in an enantioselective product. The asymmetric reaction provided a highly specific environment for the reaction to grow in optimal conditions given the fact that the chiral indole derivatives were the ideal products (Scheme 5).

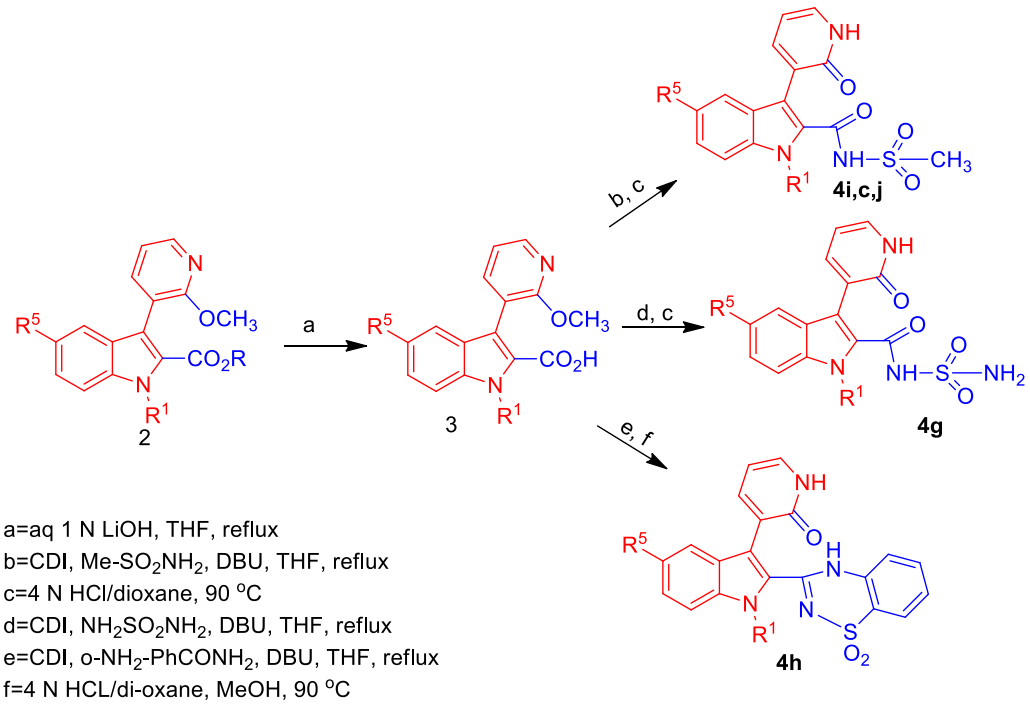
Two-step enantioselective synthesis of sulfonamide-indole derivatives via cascade cyclization reaction

Dixon and coworkers reported the synthetic route for the generation of highly enantioselective sulfonamide-indole



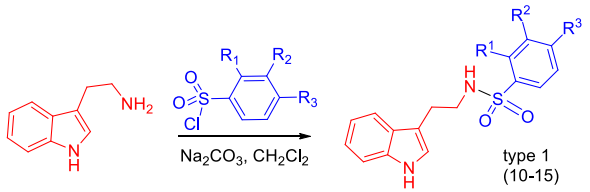
a=$ClCH_2COOH.H_2O$, NaOH, Heat
b=Acetic anhydride, Sodium acetate, H_2O, DMF, heat
c=Na_2SO_3, abs ethanol, heat
d=titanium isopropoxide, N-alkyl piperazine, $NaBH(OAc)_3$, ethanol, rt
e=KOH, ethanol, reflux
f=NaH, BNF, $ArSO_2Cl$, rt

Scheme 2 Compounds (7a-7t) synthesis



a=aq 1 N LiOH, THF, reflux
b=CDI, Me-SO_2NH_2, DBU, THF, reflux
c=4 N HCl/dioxane, 90 °C
d=CDI, $NH_2SO_2NH_2$, DBU, THF, reflux
e=CDI, o-NH_2-$PhCONH_2$, DBU, THF, reflux
f=4 N HCL/di-oxane, MeOH, 90 °C

Scheme 3 C-2 analogs general synthesis



Scheme 4 Synthesis of indole benzenesulfonamide derivatives (**10–15**)

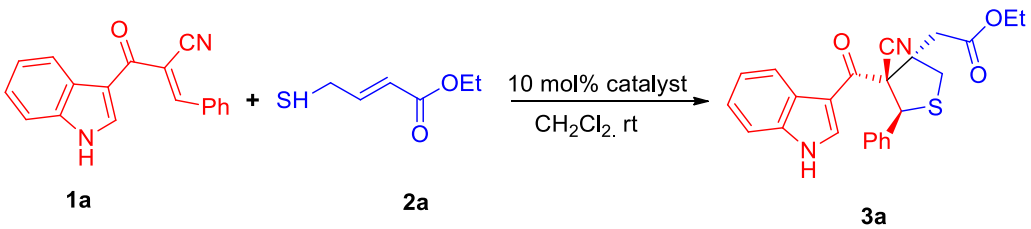
derivatives by a cyclization cascade reaction involving two steps in the synthesis, i.e. hydroamination and catalyzed cyclization [44]. Observed yield for this product by using toluene as a solvent ranged between 85 and 96%, and the whole reaction mixture was refluxed for about 20 h at the temperature of 20 °C. This reaction gave pure enantioselective [45] products which were obtained in pure form. The importance of this reaction was the selectivity of the product, and the formation of a cyclized product with a higher yield was reported (Scheme 6).

Sulfonamide-indole derivatives as antiproliferative agents: structure–activity relationship

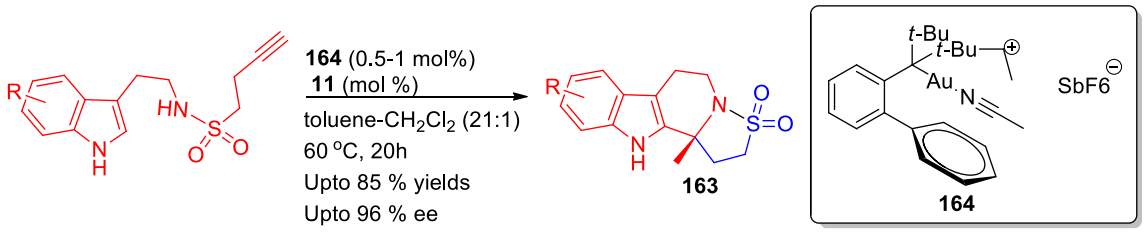
Ruo-Jun Man outlined a synthetic route for many new derivatives of indole with sulfonamide moiety, assessed their anticancer [46] and anti-tubulin capabilities, investigated their effects on cell division, cell death, and microtubule dynamics, and examined the structure–activity link [47]. He looked at the links between structure and activity by adding different substituents to the benzene and indole rings. Electron-donating groups inside the benzene ring of the compounds showed stronger antiproliferative [48] along with tubulin depolymerization effects [49]. Molecular docking and the 3D-QSAR model, which might be used to create novel compounds with stronger tubulin inhibitory action, also offered further knowledge. An evaluation of the antiproliferative activities of the synthesized derivatives along with a comparison was made between different moieties. Different functional groups had specific actions (either as an activator or as a poison) and were recorded. The significance of this study was the activities shown by the compounds on a large scale such as antiproliferative activity (Scheme 7).

Analysis of antibacterial activities of indole-sulfonamide analogs

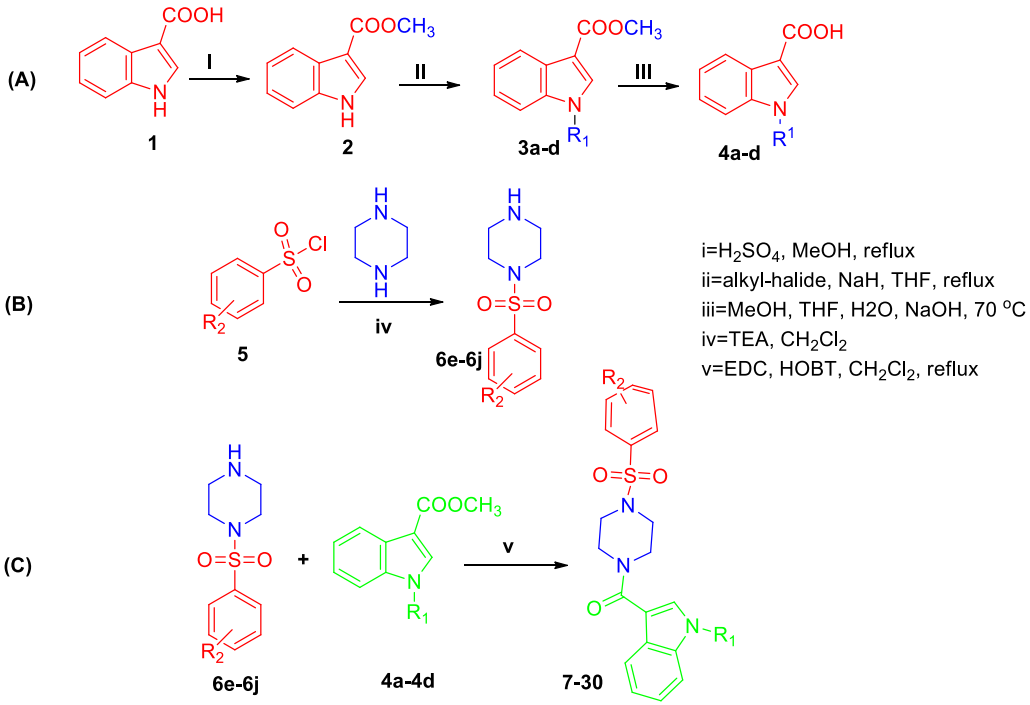
Recent work in 2017 described the production of sulfonamide analogs with the pyrimidine nucleus and tested them for cytotoxicity and antiamoebic activity [50]. Given the significance of these functional moieties, the author built a structure that included all the crucial components previously reported, with the idea that these structures would cooperate to increase therapeutic benefits. This work reported the synthesis of a novel compound named *N*-[5-(substituted-phenylsulfonyl)-1*H*-indol-3-yl] following the computational screening of 1, 3, and 4-thiadiazol-2-yl-substituted benzenesulfonamide that was also tested. Gram (+ve & −ve) pathogens like *S. epidermidis*, *E. coli*, and *P. mirabilis* were the ones against which the synthesized analogs were assessed for their antibacterial activity. The results showed that every component showed a wide range of activity based on Lipinski's rule of five. The artificial counterparts outperformed "Ciprofloxacin"



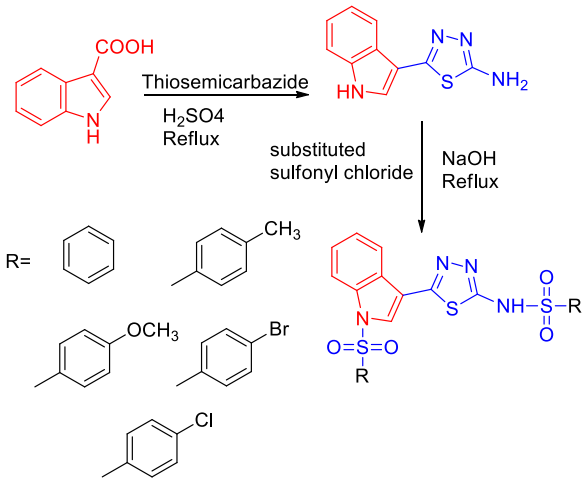
Scheme 5 Screening of different chiral organocatalysts



Scheme 6 Indole-derived sulfonamide enantioselective synthesis



Scheme 7 Synthetic route for an indole-sulfonamide moiety



Scheme 8 Systematic route adapted for the synthesis of compounds

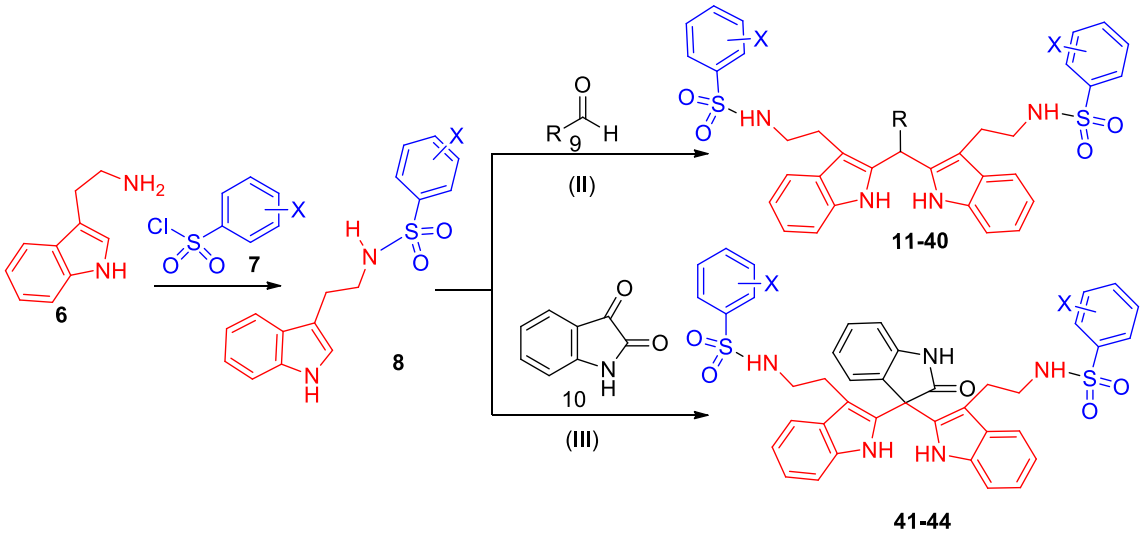
in terms of their activity. The significance of this study is the involvement of the indole nuclei in generating desired sulfonamide scaffolds as products (Scheme 8).

Synthesis of bis- and tris-indole sulfonamides via alkylation

Chemists have previously reported new sulfonamide-indole derivatives containing bis-indoles and tris-indoles [39, 51]. The main reaction involved the alkylation followed by condensation of N-benzylsulfonyl halides with tryptamines that led to the production of several novel indole-sulfonamide derivatives in moderate to good yields (40–68%) [52]. The target protein, aromatase, and the generated indole derivatives were examined for their binding modes using molecular docking. Molecular docking was the main characterization technique to verify the formed compound. This study helped generate the indole-sulfonamide scaffolds via a simple alkylation method of the alkyl halides. The addition of benzaldehyde in this reaction gave different moieties as described in the scheme below. Bis-indoles and tris-indoles were obtained in very good yield, and this reaction paved the way for the scientist to explore more of such compounds (Scheme 9).

Analyzing IR stretching vibrations in indole-sulfonamide derivatives

3-Phenyl-5-sulfonamide-1*H*-indole-2-carbohydrazide synthesis was reported by a team of scientists led by Kübra Demir-Yazıcı who synthesized this compound from sulfanilamide by diazotization reaction [53]. The reaction involved the generation of diazonium salt followed by condensation, cyclization, and ultimately treating it with hydrazines [54]. Further processing of the material with the proper carbonyl component (ketone or aldehyde) produced hydrazone derivatives. Melting temperatures and spectrum analysis were used to describe newly synthesized hydrazones. Compounds IR spectra



Scheme 9 Bis- and tris-indole derivatives with sulfonamide (**11–44**)

displayed NH stretching bands for hydrazine and sulfonamide groups at the indole ring at 3423 and 3138 cm^{-1}. Strong C=O stretching bands in the range of 1643–685 cm^{-1}, whereas the main compound as expected had a band at 1627 cm^{-1}, confirming the novel compounds' carbonyl functionalities. The sulfonamide group's symmetric and asymmetric SO_2 stretching vibrations displayed IR band values in the 1344–1311 cm^{-1} and 1176–1147 cm^{-1} range, respectively [55]. The reactivity was checked, but due to the time-lapse, it was left over. However, it was seen that a few of the sulfonamide-indole scaffolds showed carbonic anhydrase activities that were later examined (Scheme 10).

Synthesis of sulfonamide-indole compounds with aromatase-inhibitory activity

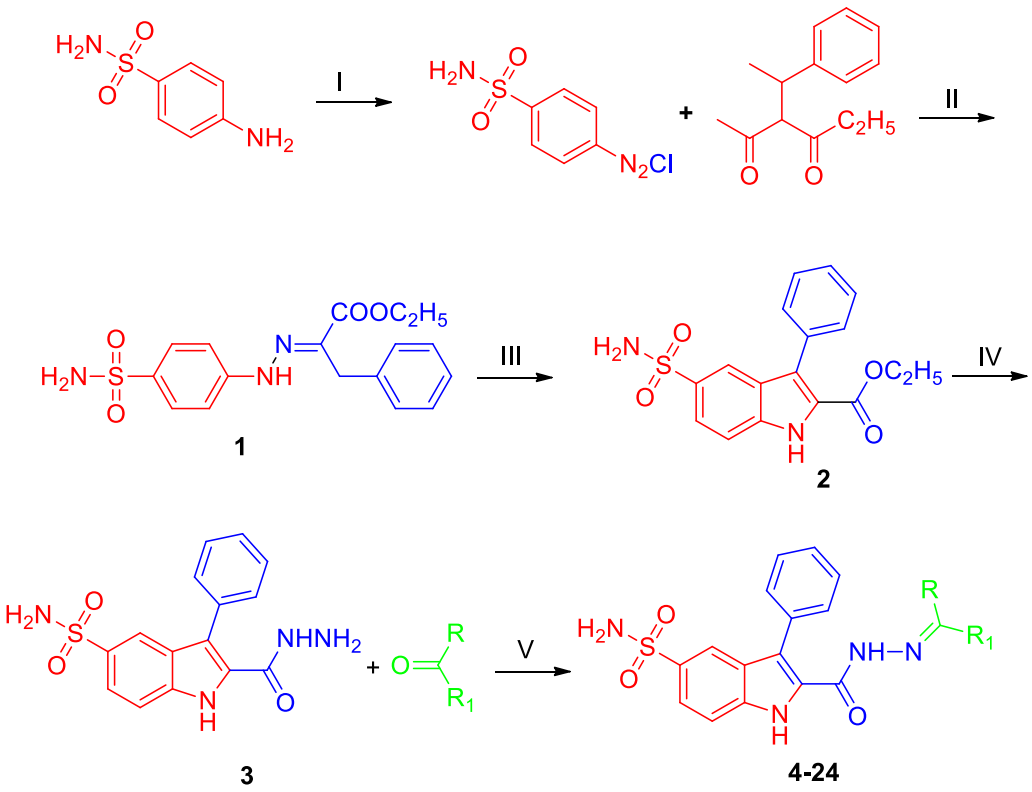
By reacting the suitable commercial indolamine and the commercial arylsulfonamide with $N(CH_3)_3$ in dry CH_2CL_2, holding the mixture for 2 h at the ice point, followed by 18 to 22 h standing at room temperature, the desired compounds were created[56]. Liquid chromatography provided the refined chemicals during the purification process. Aromatase inhibitors are used in the pharmaceutical management of postmenopausal women with early and metastatic breast cancer. Although aromatase inhibitors [57] are now used in medicine, generating new compounds with greater clinical efficacy and fewer negative effects is difficult. The docking study revealed that the active substances had interactions with the aromatase's residues. The synthesized indole-sulfonamide derivatives [58] showed aromatase inhibition activity, and it was observed by studying the heme group interactions of the aromatase enzyme with indole nuclei. This research is very significant because for the very first time, the AI is used parallel to the chemistry, and the products were screened for future significance (Scheme 11).

Indole-sulfonamide derivatives as potential acetylcholinesterase inhibitors

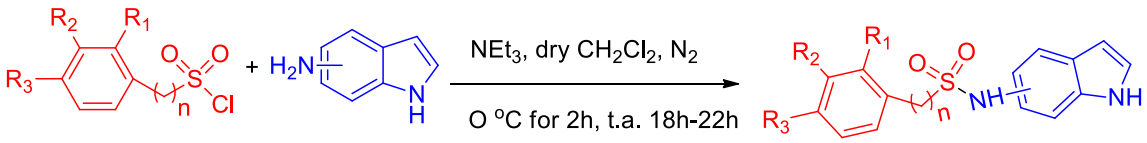
A new class of indole-sulfonamide derivatives exhibiting strong acetylcholinesterase (AChEs) inhibition was prepared using hydrazine and pyridine [59]. The molecular docking research showed that newly synthesized drugs interacted with enzymes very well at the active site. The IC_{50} values were by the data collected and reflected strong AChEs inhibition [60]. The significance of this study was mainly associated with the different aromatic residues attached to the parent indole-sulfonamide moiety, each of which had a specific AChEs action. The amount and placement, which different functional groups occupied inside the benzene ring, differed between the chosen compounds. These results marked the beginning of the creation of an effective analog that can treat Alzheimer's [61]. Further optimizing the most active molecules can create lead compounds. The simplicity of this study is reflected in the scheme illustrated below (Scheme 12).

Synthesis of sulfonamide-indole derivatives with carbonic anhydrase inhibition activity

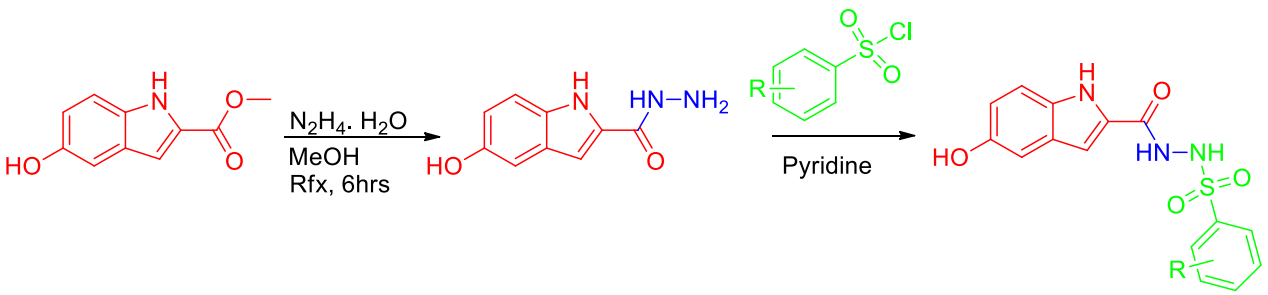
Priti Singh and her team designed a new strategy to produce a new moiety of sulfonamide-indole derivatives with carbonic anhydrase inhibition activity [62]. This strategy provided a new route for the synthesis of desired products. Indole-3-sulfonamide derivatives were synthesized using this strategy. The main synthetic approach



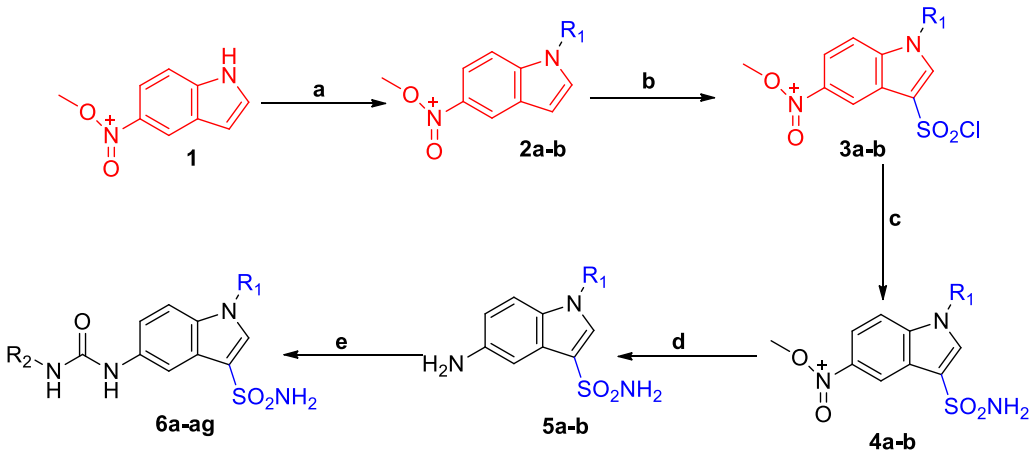
Scheme 10 Synthesis via diazotization of indole-sulfonamide scaffolds



Scheme 11 Sulfonamide-indole derivatives synthesis containing aromatase inhibition activity



Scheme 12 Sulfonamide analogs synthesis containing indole



Scheme 13 Carbonic anhydrase moieties of indole-sulfonamide

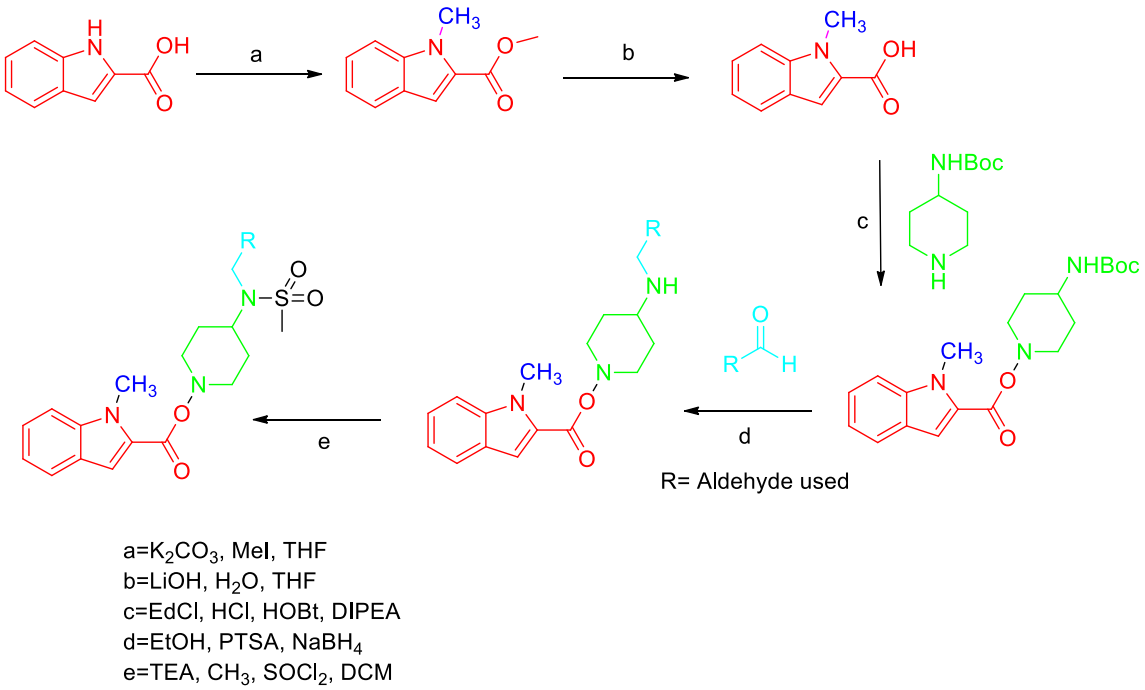
involved the *N*-alkylation of derivatives of 5-nitroindoles by using sodium hydride in a solvent of dimethylformamide (DMF) in the presence of anhydrous conditions [63]. Chlorosulfonic acid is used for the chlorosulfonation of the indole derivatives obtained in the previous step. *N*-alkylated indole-3-sulfonamide derivatives were synthesized in aqueous ammonia through an amination reaction with the amines [64]. In the presence of acetic acid and iron, the derivatives were reduced to obtain an intermediate that was then reacted with the isocyanates to get the desired product in good yield [65, 66]. Then the successful characterization was done, and it was revealed that the reaction obtained products in good amounts and the final product showed good biological activity, the carbonic anhydrase inhibition activity. The solvents and reagents used in this experiment were purified. The results were very much promising (Scheme 13).

Synthesis and antimicrobial evaluation of sulfonamide-based indole derivatives

In the study carried out by Khushbu Agarwal et al., a starting material with the name of 1*H*-indole-2 carboxylic acid was used to synthesize several novel indole derivatives based on sulfonamides [67]. By using specific characterization techniques like ^{1}H NMR [68], the structures of produced sulfonamide-based indole derivatives were verified. The most common indole derivative with acid was employed to carry out the reaction. The strategy involved the di-methylation of the *N*-alkylated indole-2-carboxylic acid [69], and then it was treated with methyl iodide (MeI) and K_2CO_3 leading to the formation of indole ester [70] which in the presence of tetrahydrofuran undergoes deprotection. The formed indole-acid derivative was then reacted with a commercially available reagent with the name of 4-ter-Butyloxycarbonyl (4-boc) piperidine amine followed by deblocking reaction to yield the final product [71]. The synthetic scheme shown below demonstrates the strategy that accompanied this reaction and how the desired products were obtained. The strategy is quite simple and easy to apply. The sulfonamide-indole derivatives were prepared by treating reactants in the presence of trimethylamine with alkyl sulfonamide halide in a very friendly environment. The produced indole-sulfonamide scaffolds showed to be effective antimicrobials. All of the produced derivatives exhibited positive activity against Gram Positive *Staphylococcus aureus* while showing inactivity against *Bacillus megaterium*, according to biological evaluation. Most of the products showed strong biological activity against Gram-negative bacteria excluding a few, while all of them showed an extremely strong effect against *Klebsiella pneumonia*. This study contributed to the field's ongoing indole derivative research (Scheme 14).

Conclusion

The current review emphasizes the synthesis and biological evaluation of indole-sulfonamide analogs from 2010 to 2023. The various synthetic routes including the Friedel–Craft reaction, cascade sulfa Michael addition reaction, enantioselective cascade cyclization reaction,



Scheme 14 Sulfonamide-indole-based derivatives synthesis

and alkylation reactions are schematically visualized for the better understanding of drug chemists. The infrared stretching vibrations are also reported. Furthermore, pharmacological activities such as antiproliferative, antibacterial, and antimicrobial are demonstrated with corresponding structure–activity relationships. Additionally, some of their inhibitory effects like aromatase, acetylcholinesterase, and carbonic anhydrase are also described. Using the literature findings mentioned above as a summary, we can state that indole exhibits a wide range of biological activities. Future research in the production of indole scaffolds is growing, and this literature will give a direction for drug design chemists to synthesize a new variety of active drugs.

Abbreviations

DMF	Dimethylformamide
THF	Tetrahydrofuran
SAR	Structure–activity relationship
3D-QSAR	Three-dimensional quantitative structure–activity relationship
AIs	Aromatase inhibitors
AChEs	Acetylcholinesterase
^{1}H NMR	Proton nuclear magnetic resonance

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Author contributions
IM contributed to the design of the study and drafted the paper; AA contributed to drafting the paper and critical revision of the article; and all authors have read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The authors declare no conflict of interest.

Competing interests
The authors declare that they have no competing interests.

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