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Breakthroughs in Indole and Indolizine Chemistry – New Synthetic Pathways, New Applications

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Additional information is available at the end of the chapter

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Abstract

Indole and indolizines (heterocyclic aromatic compounds structurally and chemically isomeric with indoles) are an important class of N-fused heterocyclic compounds due to their interesting biological and optical properties. Different strategies for generating diverse collections of small molecules with indole and indolizine moieties have been developed. They can be synthesized by means of classical and nonclassical pathways. The present study discusses the versatile nature of indole/indolizine derivatives, new green methods for their synthesis, their possible mechanism of action and also provides information about current/future prospects of the topics and different indole/indolizine derivatives in pharmaceutical/clinical trials. With the remarkable number of approved indole-containing drugs as well as the importance of the indolizine moiety, it can be easily concluded that indole and indolizine derivatives offer perspectives on how pyrrole scaffolds might be exploited in the future as bioactive molecules against a broad range of diseases.

Keywords: Indole, indolizine, bioactive heterocycles, green chemistry, functionalization, mechanism

1. Introduction

A great deal of research in heterocyclic chemistry concerns the development of strategies for efficient synthesis and the discovery of new methods of ring formation, since more than half of the biologically active compounds produced by nature contain a heterocyclic moiety as a fundamental unit in their structure. Also, heteroaromatic compounds are always of great importance for chemists and the identification and confirmation of highly potent and selective bioactive molecules is a decisive step both in academic and pharmaceutical research.

Heterocyclic compounds with a pyrrole cycle are significant both in materials and in medicinal chemistry [1]. Indoles and indolizines (heterocyclic aromatic compounds structurally and chemically isomeric with indoles) are important classes of N-fused heterocyclic compounds due to their interesting biological and optical properties. Although their chemistry is a well-established subject for researchers, they continue to attract much attention due to their diverse biological properties. Also, the correlation between indoles and indolizines has prompted speculation that indolizine analogs of biologically important indoles could conceivably have potent physiological activities [2].

Indoles and their derivatives are well-known as an important class of heterocyclic compounds, their core being a near-ubiquitous component of biologically active natural products, widespread in different species of plants, animals, and marine organisms. The indole is also well-known as one of the most important scaffolds for drug discovery, capable of serving as ligand for a diverse array of receptors and it has been a major focus of research [3]. Indole derivatives have the unique property of mimicking the structure of peptides and to bind reversibly to enzymes and exhibit significant physiological and pharmacological, industrial, and synthetic applications such as beneficial estrogen metabolism promoter in humans, anticarcinogenic properties, inhibitors of human prostate cancer cells, and free radical scavenging activities [1, 4]. The indole scaffold is widely used in antiviral drugs and reverse-transcriptase inhibitors, drugs used to treat HIV infection or AIDS, and in some cases hepatitis B. Meanwhile, a number of bis (indolyl) alkanes have received considerable attention because of their occurrence in bioactive metabolites of terrestrial and marine origin [5].

Indolizine is the core structure of many of the naturally occurring alkaloids such as swainsonine (a potent inhibitor of Golgi alpha-mannosidase II, an immunomodulator and a potential chemotherapy drug), monomorphine (might be used to lure ants to their doom), gephyrotoxin (muscarinic antagonist), and lamellarins (HIV-1 integrase inhibition and antibiotic activity) [6].

The indolizine synthetic derivatives also deserve special attention because of their pharmacological properties such as antibacterial, anti-inflammatory, antiviral and antileishmanial, analgesic and antitumor, antioxidant activities, aromatase inhibition, calcium entry blocking, histamine H3 receptor antagonist, and physicochemical properties such as strong fluorescence [6, 7].

Different strategies for generating diverse collections of small molecules with indole and indolizine moieties have been developed. They can be synthesized by means of classical and nonclassical pathways.

The development of simple, convenient, and an eco-friendly approach for the synthesis of these biologically important compounds is still in demand. For example, the very useful and green concept of a “click” reaction is a facile, selective, high-yield reaction under mild water-tolerant conditions with little or no by-products [8]. Cascade annulation reactions lead also to the formation of polycyclic fused six- and seven-membered heterocycles with indole and indolizine core [9].

Microwave irradiation, sonication, and solvent-free are green chemistry techniques that have been used for a variety of applications including organic synthesis. Microwaves and ultra-

sounds have been used as synthetic techniques for obtaining indole and indolizine derivatives in high-yield, higher reaction rate. The simplicity of the reactions using these techniques, the elimination of toxic solvents, and the synthesis carried out in a very short time period are particularly useful for the creation of diverse chemical compounds of “drug-like” molecules for biological screening [10].

Multicomponent reactions (MCRs) or tandem reactions have developed as a powerful tool for delivering the molecular diversity needed for the synthesis of interesting heterocyclic scaffolds, to efficiently construct a variety of intermediates possessing an indolyl or indolizyl subunit and are particularly attractive especially if they start from simple molecules [11].

The present study discusses the versatile nature of indole/ indolizine derivatives, new green methods for their synthesis, their possible mechanism of action, and also provides information about current/future prospects of the topics and different indole/indolizine derivatives in pharmaceutical/clinical trials.

2. Indoles

Indole derivatives are, perhaps, the most studied nitrogen heterocyclic systems because of interesting biological properties that received particular interest due to the reserpine alkaloid, one of the first drugs used for the treatment of central nervous system (CNS) disorders. Different substituted indoles are particularly important in pharmaceutical chemistry being capable to bind many receptors with high affinity exhibiting various pharmacological activities. Therefore, it is important to explore new synthetic reactions and evaluate various properties of indole derivatives.

2.1. Indole synthesis

To obtain biologically relevant N-hydroxyindoles, a prudent step would be to synthesize O-protected hydroxyindoles, to avoid their dimerization into kabutanes. Such were the premises of one study, presenting the annulation of nitrosoarenes with various alkylating and acylating agents, able to afford the desired compounds with excellent regioselectivity [4].

The synthesis of 3,3-dimethyl-2-amide indoles could be achieved through the I₂/DMSO promoted oxidative amidation reaction between 1,2,3,3-tetramethyl-3H-indolium iodide and secondary amines with moderate yields (Figure 1) [12].

Using a method involving four steps, 2-indole-3-yl-thiochroman-4-ones could be obtained (Figure 2), according to Song et al. In the final step, the Michael addition reaction of thiochrome and indole, an ionic liquid is used, to increase the yield, with the added advantage that it could be reused three times without a decrease of efficiency [13].

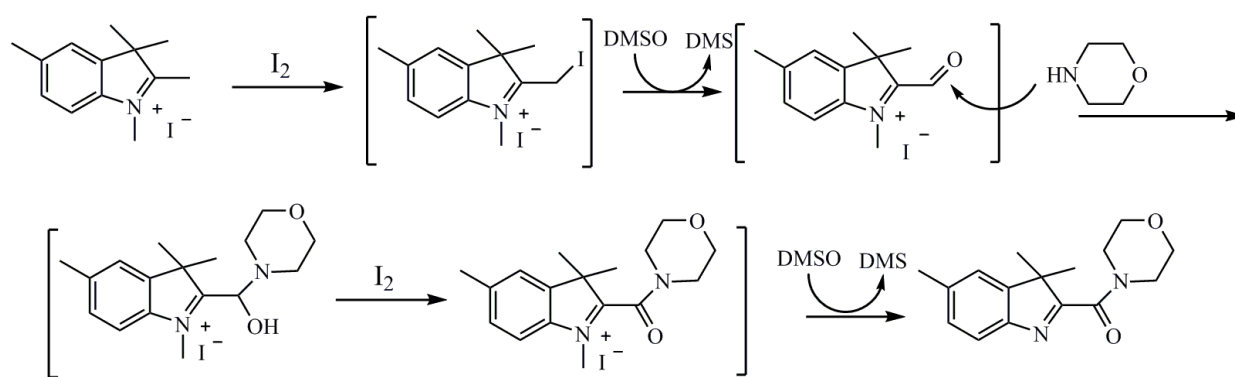


Figure 1. Synthesis of 3,3-dimethyl-2-amide indoles: mechanism [12]

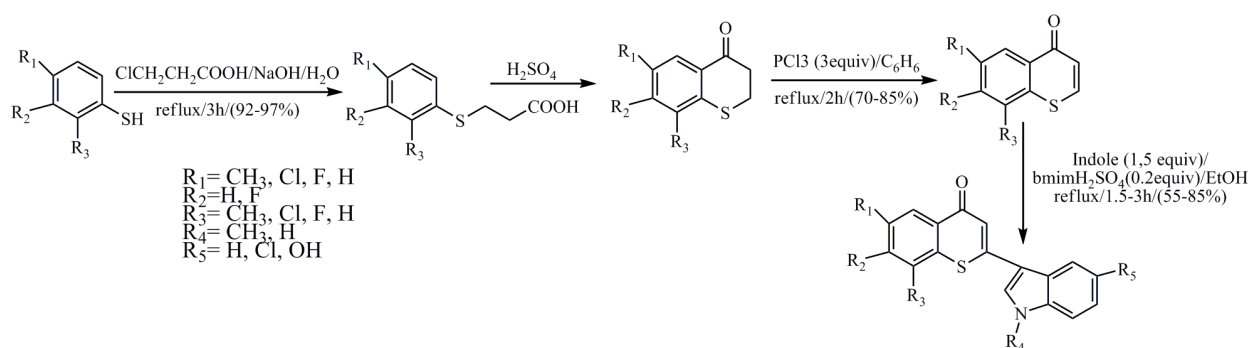


Figure 2. Synthesis of 2-indole-3-yl-thiocroman-4-ones derivatives [13]

2.2. Green methods for indole synthesis

Polyvinylsulfonic acid, a biodegradable and recyclable polymeric acid rarely used in organic transformations, could be used as a Bronsted acid catalyst in the synthesis of bis (indolyl) methane [14]. Another pathway to obtain this compound would be to employ a reusable resin, Indion Ina 225H, as catalyst of the substitution reaction between indoles and aldehydes (Figure 3), reportedly attaining excellent yields in short reaction times [15].

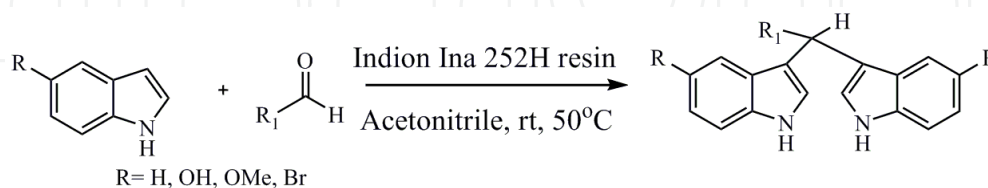


Figure 3. Synthesis of bis(indolyl) methane using a reusable resin, Indion Ina 225H [15]

Various carbonyl compounds, including ketones could also be building blocks for the much desired bis(indolyl)methanes, using catalytic amounts of iodine in the presence of sodium dodecylsulfate in aqueous solution above its critical micellar concentration and the protocol was also extended to afford 3-substituted indolyl ketones (Figures 4 and 5) [3].

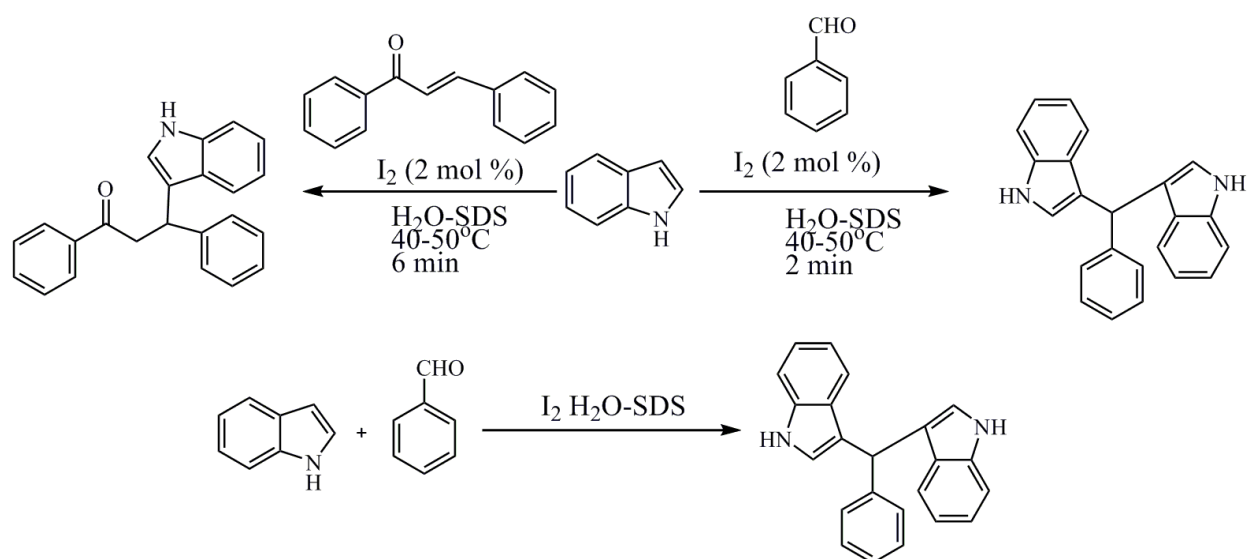


Figure 4. Synthesis of bis(indolyl)methanes, using catalytic amounts of iodine in the presence of sodium dodecylsulfate [3]

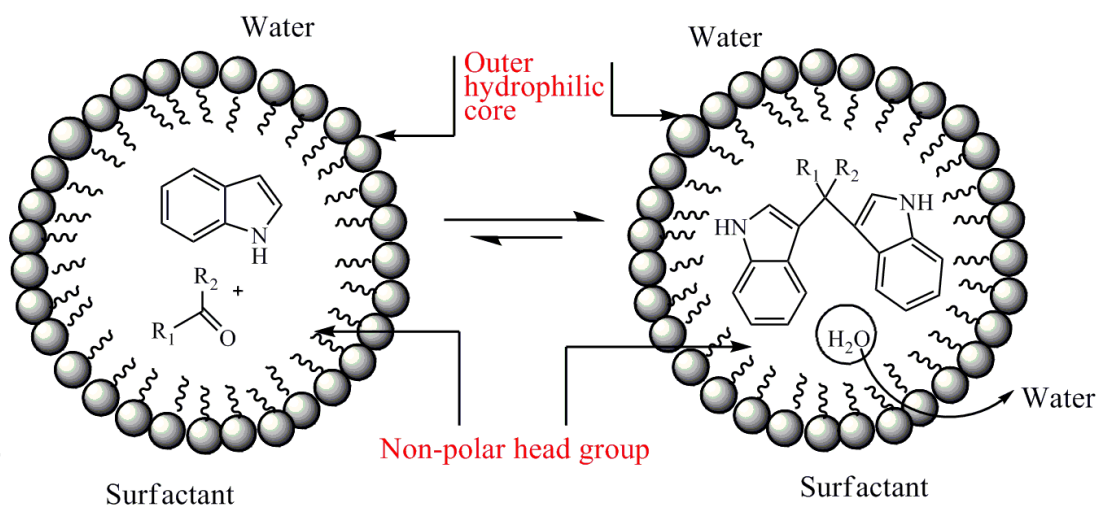


Figure 5. Iodine-catalyzed formation of bis(indolyl)methane from indole and aldehyde under aqueous micellar conditions [3]

3. Indolizine derivatives

The indolizine core has found numerous applications in the synthesis of biologically active compounds. Partially or completely reduced indolizine analogs are widely used in the synthesis of indolizidine alkaloids and related unnatural products. Among many other pharmacological uses, polycyclic analogs of indolizine, for example, have found a broad application as heterocyclic analogs of indene in the synthesis of ligands for transition metal

complexes. Although many methods have been developed for their synthesis, they are generally time-consuming or require the use of stoichiometric amounts of organometallic reagents, Lewis acids, expensive catalysts or potentially toxic solvents, which limits their economical applications. Accordingly, development of alternative catalytic methods for construction of these important heterocyclic cores is necessary [9].

3.1. Indolizines obtained via 1,3-Dipolar cycloaddition

The mechanism of obtaining condensed five-membered ring systems via 1,3-dipolar cycloadditions implies the reaction of a dipole, in this case an N-ylide generated in situ from a cycloimmonium halide and a base or another deprotonating agent followed by its addition to a dipolarophile, olefinic, or acetylenic [7].

N-ylides could be generated employing 1,2-epoxybutane as both solvent and deprotonation agent, or by using triethylamine in DCM, with ethyl propiolate or DMAD as dipolarophiles, or again coupling the ylide with acrylonitrile and using TPCD for the aromatization step, all methods with similar medium to good yields (Figure 6) [7]. Moderate yields, up to 22%, are reported when reacting DMAD with N-ylides generated from pyridinium salts and K_2CO_3 , using catalytic amounts of dicyclohexyl-18-crown-6 [16]. In another study, 20 substituted indolizines were obtained in just 30 min at room temperature, employing electron-deficient alkynes, in the presence of K_2CO_3 in DMF, with yields as high as 77% [17].

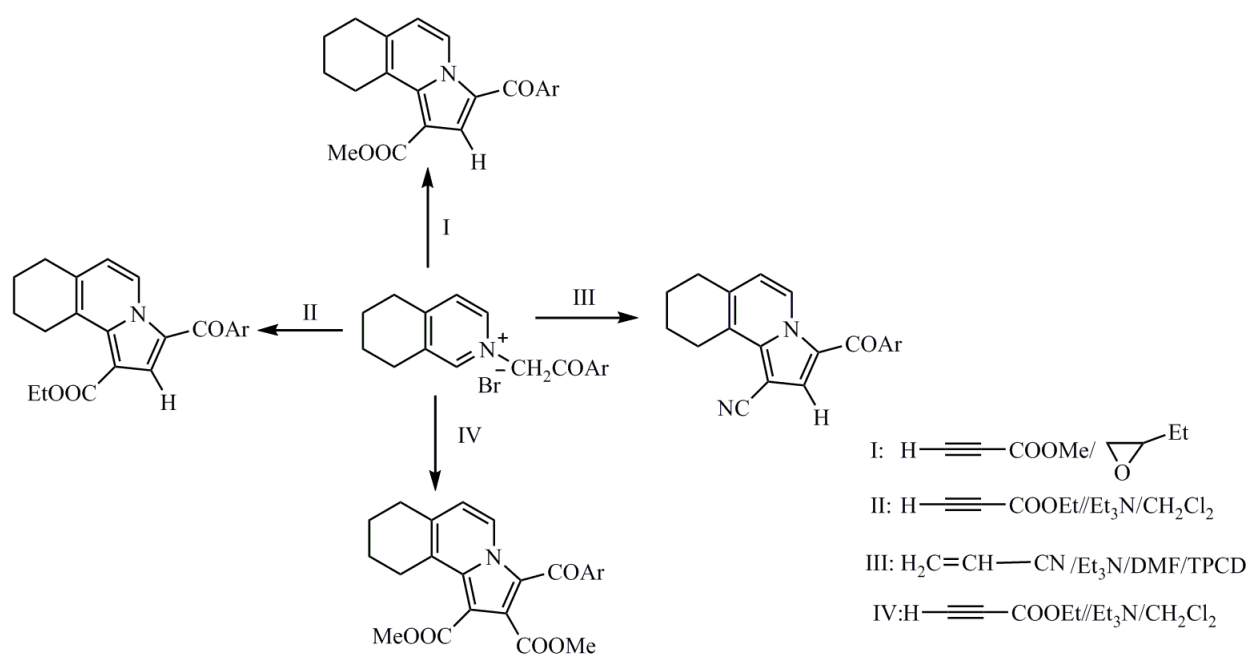


Figure 6. Synthesis of the new 7,8,9,10-tetrahydropyrrolo[2,1-a]isoquinolines [7]

The solvent could have a great impact on the reaction mechanism, as one study demonstrates, using substituted ethenes (E-1,2-di(alkylsulfonyl)-1,2-dichloroethene) as dipolarophiles (Figure 7). In aprotic solvents, the reaction takes place as a 1,3-dipolar cycloaddition, with

yields between 62 and 75% for the six indolizines obtained, but in protic solvents an addition–elimination reaction intervenes, leading to the competitive formation of furans, with indolizine yields as low as 9% [18].

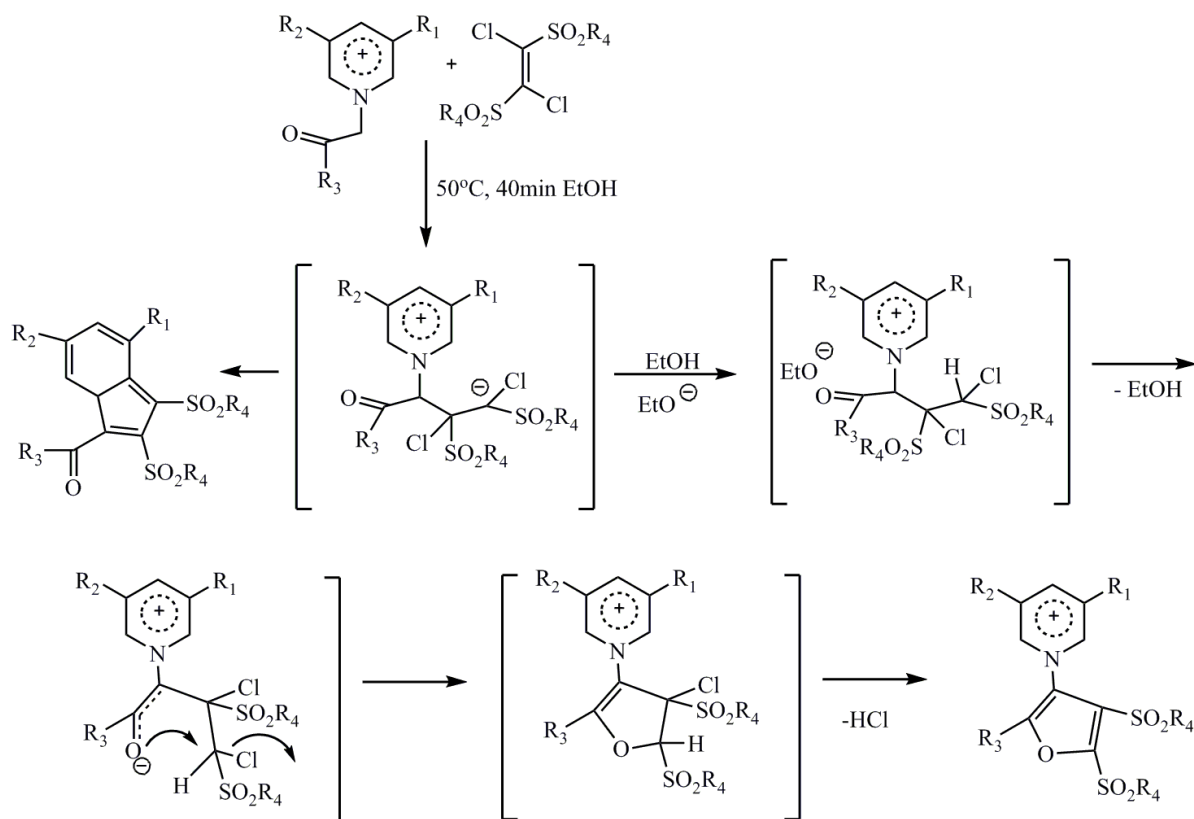


Figure 7. The reactions of pyridinium ylides with ethenes in EtOH [18]

3.2. Indolizines obtained via one-pot reactions

One-pot reactions imply obtaining the product in a single step, by adding all the necessary reagents in the same reaction medium, without having to isolate and purify any precursors of the desired product. This type of procedure offers advantages such as swiftness, the preparation of complex compounds from readily available material, simplification of workup and atom economy.

Mishra et al. present a method to obtain 1-aminoindolizines from aldehydes, secondary amines, and terminal alkynes, in a one-pot reaction (Figure 8). After testing several solvents and metal catalysts, the best results are obtained with CuCl in PEG, synthesizing 15 substituted indolizines with yields exceeding 70%, after 3–4 h reaction time [19].

Substituted 3-aminoindolizines could be obtained via one-pot multistep reactions, from 2-pyridine carboxyaldehyde and various nitriles, after 3 h reaction in toluene at 105°C, by adding 1.1 eq of Hantzsch ester as a hydride transfer agent and catalytic amounts of piperidinium acetate [20].

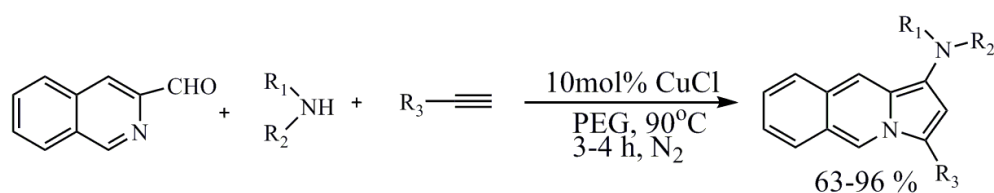


Figure 8. One-pot multicomponent synthesis of 1-aminoindolizines [19]

The synthesis of 2-acetyl-3-(phenylamino)indolizine-1-carboxamides could also be achieved in a single step (Figure 9), by combining pyridine-2-carbaldehyde, acetoacetanilide and isocyanides in toluene at reflux, with yields around 90% for the four compounds obtained [21].

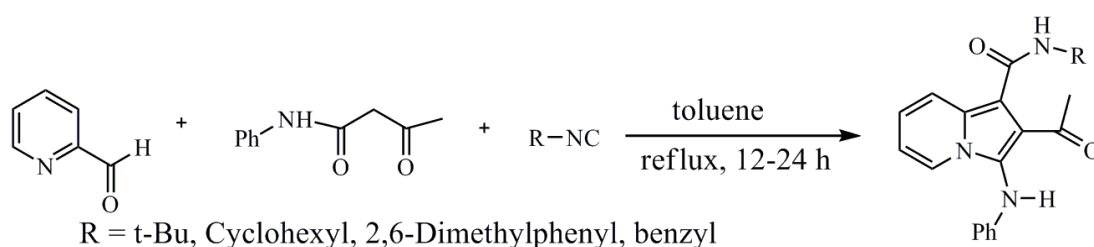


Figure 9. Synthesis of 2-acetyl-3-(phenylamino)indolizine-1-carboxamides via a three-component condensation [21]

A four-component tandem reaction is proposed by Zhenjun et al., by treating pyridine (or quinoline) with phenacyl bromides (or bromoacetophenones), ethyl glyoxalate, and Na_2CO_3 in refluxing acetonitrile. The resulting polysubstituted indolizines are obtained after 16 h of reaction time in moderate-to-good yields [22].

Seventeen polysubstituted indolizines could be obtained via a one-pot sequential addition-cyclodehydration-dehydrocyanation from 2-(1H-pyrrol-1-yl) nitriles with α,β -unsaturated carbonyl compounds (Figure 10) [23].

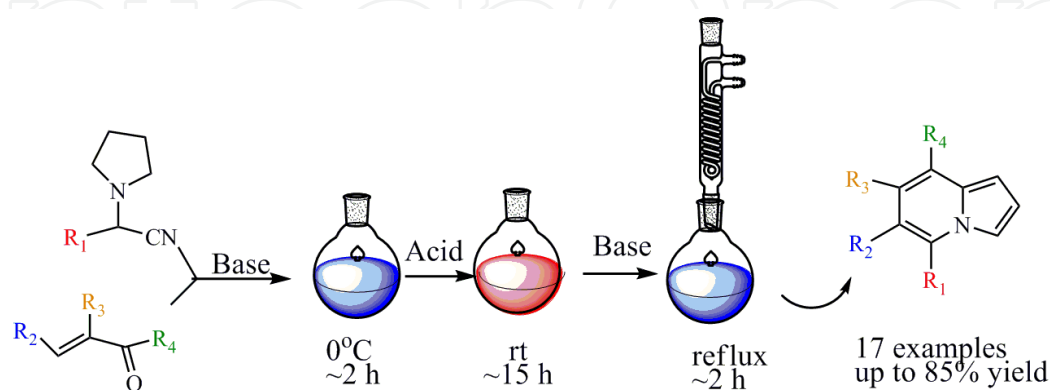


Figure 10. One-pot addition-cyclodehydration-dehydrocyanation of 2-(1H-pyrrol-1-yl) nitriles with α,β -unsaturated carbonyl compounds [23]

3.3. Novel approaches to indolizine synthesis

The indolizine core could be accessible starting from pyrrole, with strategies involving intramolecular aldol cyclization or domino Knoevenagel condensation, shown in Figure 11 [24].

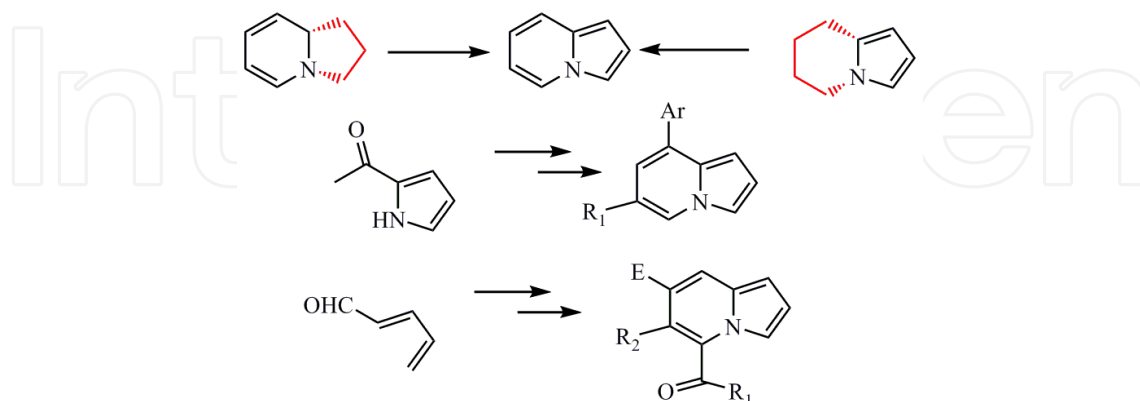


Figure 11. Possible synthetic approaches to indolizines [24]

Another [3+3] annulation approach employs allyl bromides derived from Morita-Baylis-Hilman adducts (Figure 12), with the conclusion that electron withdrawing groups, as substituents at the aromatic ring, contribute to successful ring closure and result in accordingly substituted indolizines [25].

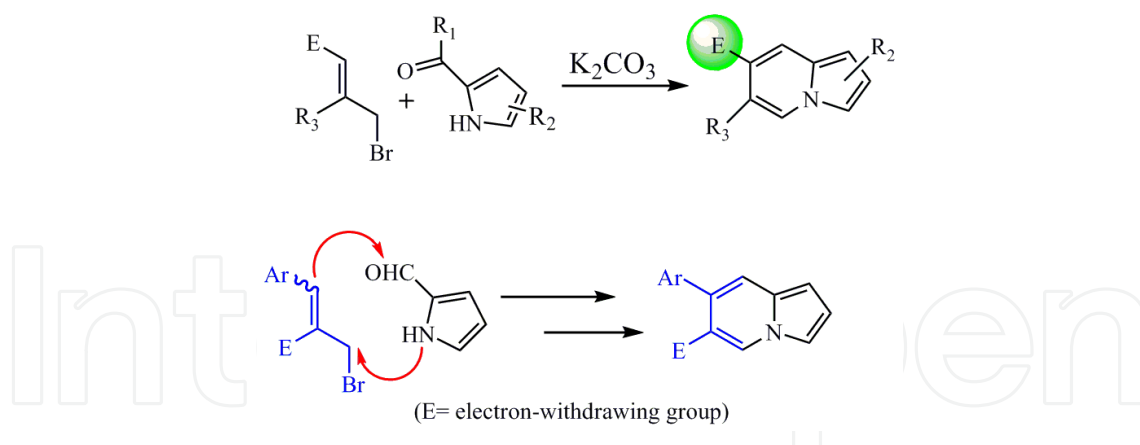


Figure 12. Design of new [3+3] annulation route to indolizines [25]

Novel 2-acyl-6-aryl substituted indolizines were obtained starting from 4-acyl-pyrrole-2-carbaldehyde and α , β -unsaturated esters, in the presence of K_2CO_3 in DMF, with yields between 42 and 68% after 8–12 h at 50°C [26].

Another possibility would be to perform a tandem oxidative C-H functionalization and 5-endo-dig cyclization, starting from 2-substituted pyridines and alkynes (Figure 13), which could be achieved with good yields using an Ag_2CO_3 reusable catalyst [27].

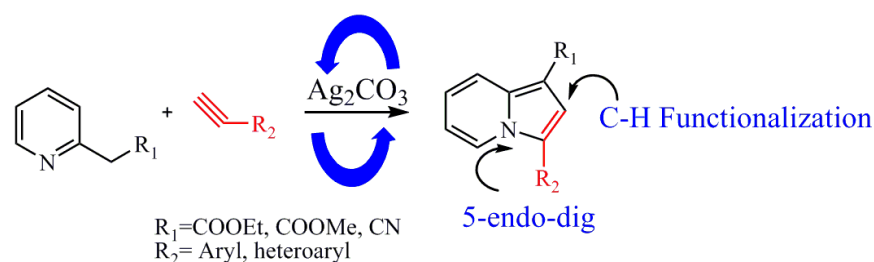


Figure 13. Silver-mediated oxidative C-H functionalization to synthesize indolizines [27]

Substituted pyridines and acetophenones lead to the formation of 1,2,3-triarylindolizines with moderate-to-excellent yields, promoted by I_2/DMSO at 100°C , the proposed mechanism for this reaction is presented in Figure 14 [28].

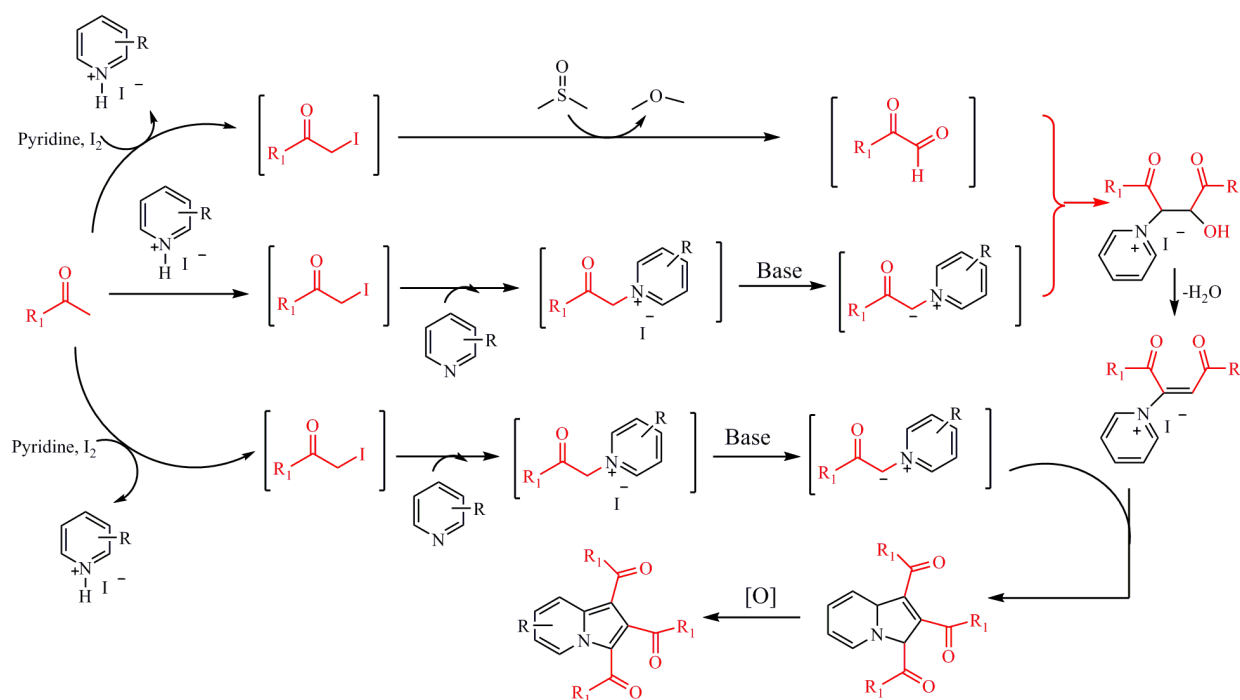


Figure 14. Formation of 1,2,3-triarylindolizines. Proposed reaction pathway [28]

3.4. Green methods for indolizine synthesis

During the synthesis of N-heterocycles there are many problems of health and safety in addition to the environmental problems caused by their use and disposition as waste. Green methods are a route towards increasing the efficiency of indoles and indolizines synthesis, and stride to use less toxic solvents, to reduce the stages of the synthetic routes and minimize waste as far as practically possible for sustainable development.

A potential method to make synthetic chemistry more environment-friendly would be to reuse catalysts, such as ion-exchanging resins. Amberlite-IRA 402 (OH) could be employed as the

ylide-forming base in the reaction between phenacyl pyridinium, quinolinium and isoquinolinium salts and alkynes (Figure 15) [29].

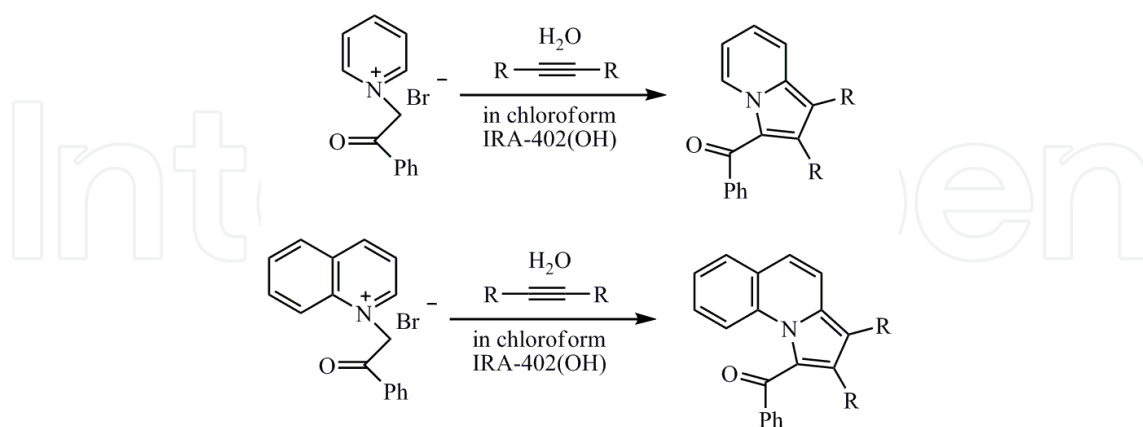


Figure 15. Synthesis of indolizines and pyrrolo [1,2-a] quinolines using alkynes [29]

Unconventional activation techniques, such as microwave irradiation, not only lead to shorter reaction times but generally increase the purity of the desired compound. One study presents the synthesis of 8 indolizine derivatives in an aqueous medium that were obtained in good yields after 1 min of irradiation at 300W [30].

Biocatalysis could be employed to aid the formation of indolizine derivatives in an aqueous medium, as seen in Figure 16. Ultrasound activation was compared to conventional heating, affording 7,7'-bis-indolizines with similar yields in much shorter reaction times [31].

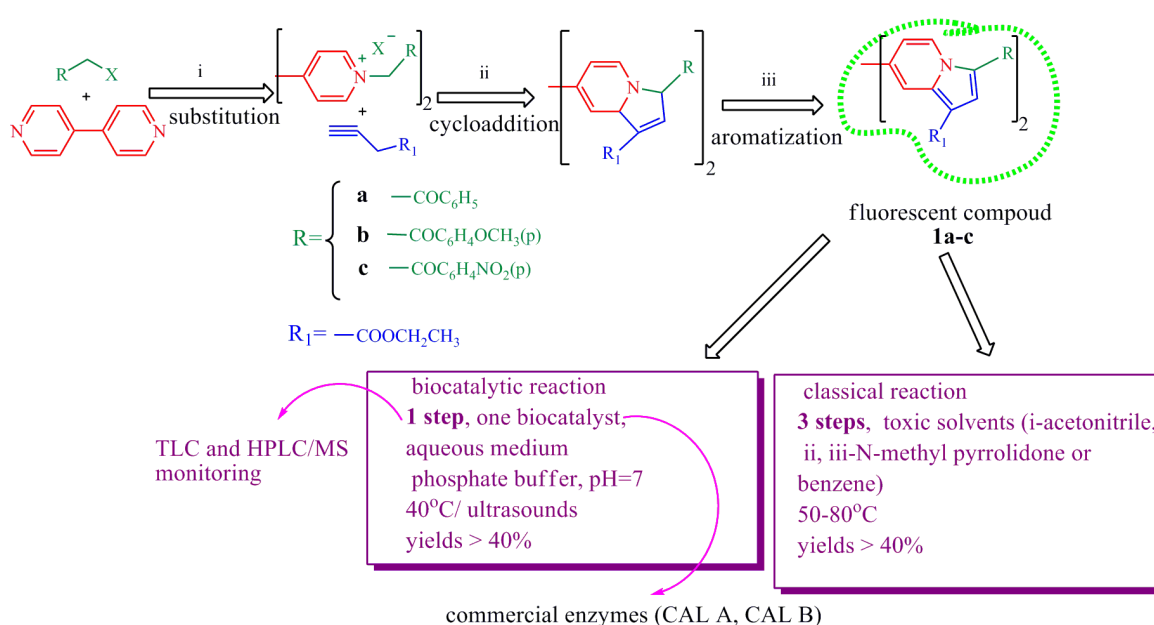


Figure 16. Synthesis of bisindolizines by biocatalytic reaction [31]

4. Indoles and indolizines functionalization

The Oxone-induced oxidation of indole-3-carbaldehydes and 5-halogenated analogs could lead to the formation of tryptanthrin derivatives (Figure 17), a highly functionalized biologically active natural product, at room temperature [32]. The phthalazine moiety could also be accessible with green methods, employing catalytic amounts of L-proline, with good yields and less than 2 h reaction time [33].

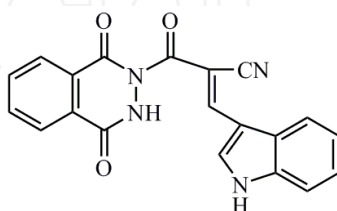


Figure 17. Tryptanthrin derivative [32]

The reaction between indole and formaldehyde could produce high yields of hemiaminals, with the added value of mild conditions, such as room temperature and an aqueous medium, in the presence of TBAF [34].

The most eco-friendly approach when it comes to solvent choices would be not to employ any solvents. Analogs of 3-alkylindole, for example, could be prepared in solvent-free conditions, using MgO nanoparticles as catalyst [35]. Bis(indol-3-yl)methanes could be synthesized in solvent-free grinding conditions, employing a reusable catalyst, phosphate-impregnated titania, obtaining yields as high as 93% [36].

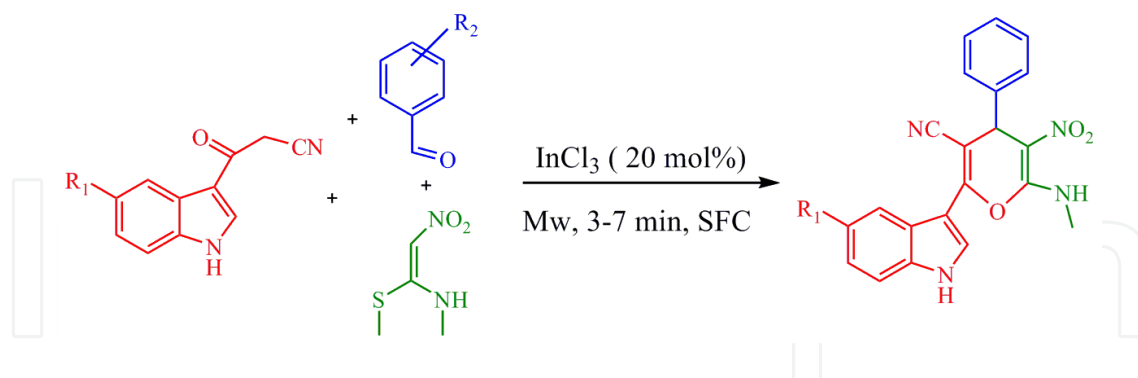


Figure 18. Synthesis of highly functionalized indolylpyrans [37]

Unconventional activation techniques could also be used for indole functionalization. Within 10 min, including reaction and purification time, 3-pyranyl indole derivatives could be obtained with good yields, through one-pot microwave-assisted reactions, with InCl_3 as catalyst (Figure 18) [37]. Indolyl chalcones could be prepared from indole-3-carboxaldehyde and heteroaryl active methyl compounds under conventional heating, but the yield was much improved and reaction time was drastically reduced (from more than 9 h to less than 15 min) when microwave irradiation was introduced [38]. Ultrasounds aid the selective formation of

11 3-selanylindole derivatives with good yields, proving superior to conventional heating and microwave irradiation for this synthesis [39].

Both indoles and indolizines could be functionalized via alkylation with enamides under mild conditions (Figures 19 and 20), using FeCl_3 , in short reaction times with good yields [2].

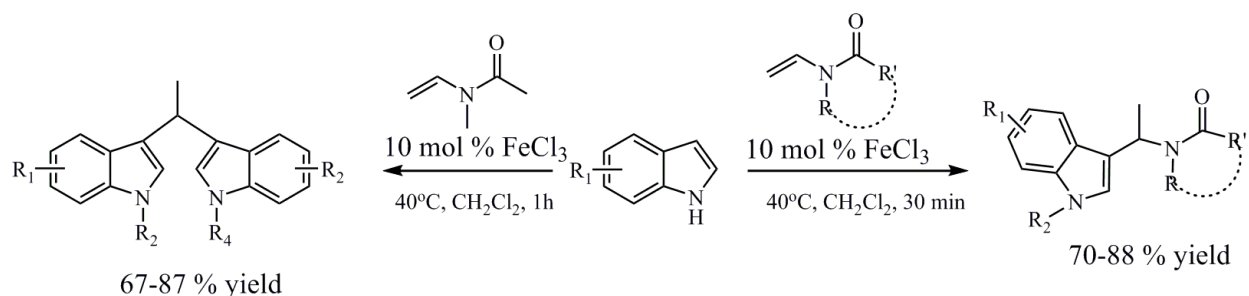


Figure 19. Iron-catalyzed alkylation of indoles with enamides [2]

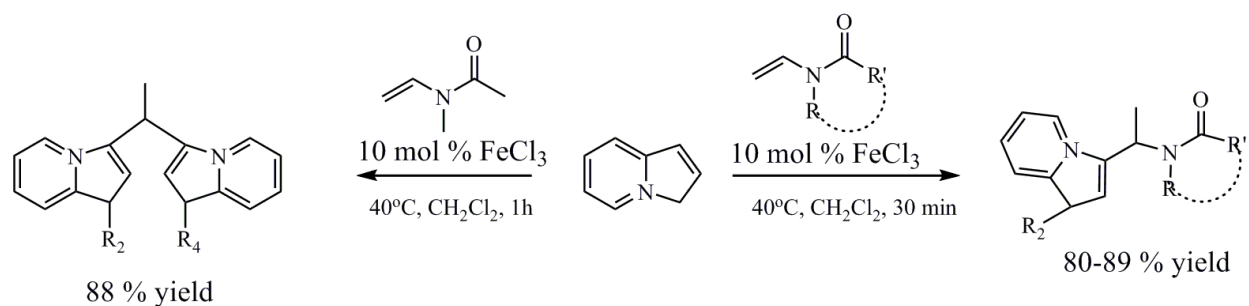


Figure 20. Iron-catalyzed alkylation of indolizines with enamides [2]

The Friedel-Crafts alkylation of indoles could also be performed in water, as presented in Figure 21, with yields as high as 97% in the presence of Keggin heteropoly acids, solid super-acid catalysts [40].

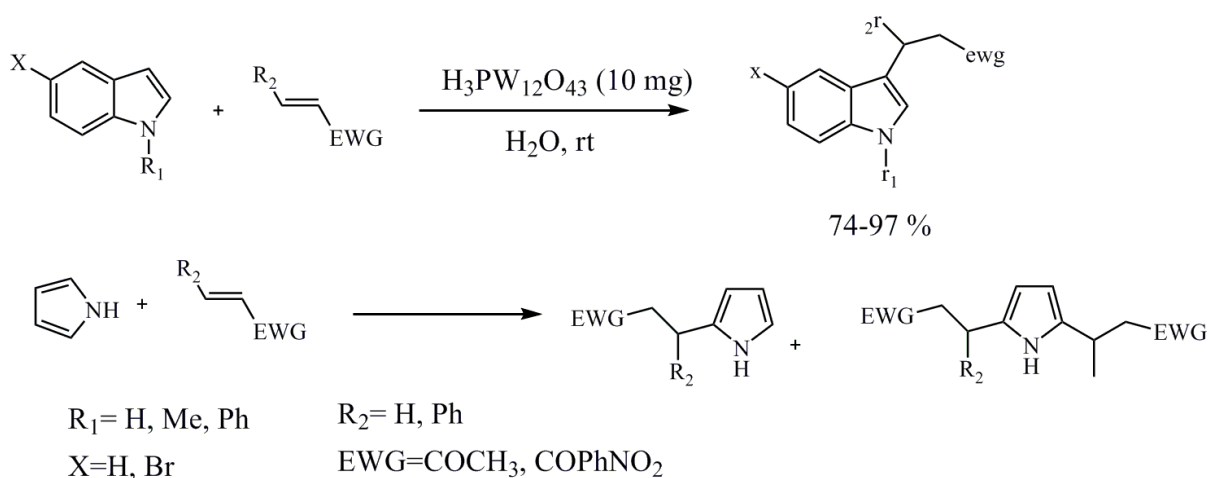


Figure 21. Friedel-Crafts alkylation of indole [40]

A novel approach presents the previously inaccessible regioselective formation of substituted pyrido[2,3-*b*]indolizine-10-carbonitriles, via a cascade transformation of α,β -unsaturated carbonyl compounds with a dimer of 1-(cyanomethyl) pyridinium chloride, in ethanol/water in the presence of sodium acetate [41].

5. Pharmaceutical applications

As we have seen so far, interesting pathways have been proposed for the synthesis of indoles and indolizines. Many of these molecules have subsequently been involved in tests to assess their biological activity. Natural compounds with these moieties have also attracted interest, not just as extracts, but as targets for total/semisynthesis or as frameworks for compound libraries. Next, we shall review some of the extremely diverse pharmaceutical applications of these derivatives, ranging from fluorescence probes, to antiviral, to anticancer molecules currently in clinical trials.

5.1. Natural and synthetic indoles

Lead by Cialis, there are seven indole-containing commercial drugs in the Top-200 Best Selling Drugs by US Retail Sales in 2012. Examples of indole derivatives marketed as antiviral drugs, for example, are Arbidol (a broad-spectrum antiviral with anti-influenza and immunomodulating effects) and Delavirine (a non-nucleoside reverse transcriptase inhibitor) [42].

Bisindoles, such as hamacanthin A, isolated from marine sponges (*Hamacantha* sp., *Spongosorites* sp.), or the more famous indole-3-carbinol (I3C), a compound found in cruciferous vegetables (cabbage, kale, cauliflower, broccoli, Brussels sprouts) and its bisindole metabolite, 3,3'-diindolylmethane (DIM), have displayed biological activities such as antimicrobial, antiparasitic, anti-inflammatory, and anticancer and are high up on the interest list of many researchers [43].

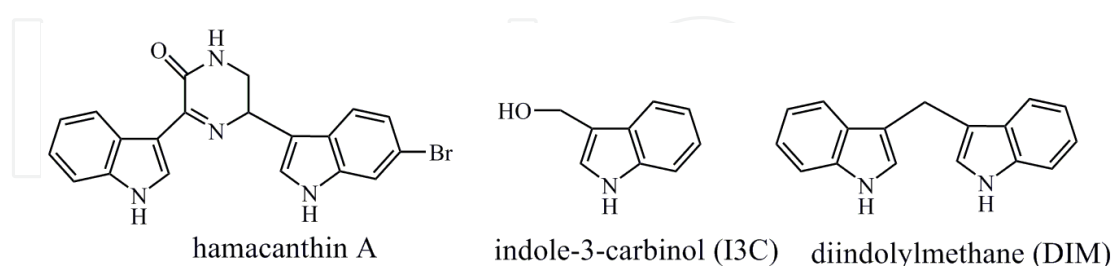


Figure 22. Natural indoles [50]

Some of the many studies published in this field have resulted in the elucidation of some of the mechanisms of their bioactivity. The influence of I3C, for example, on lung cancer cells, has been attributed to apoptosis via Fas activation and caspase-8 pathways and also cell-cycle arrest at the G₀/G₁ phase, and it was also shown that cancer preventive effects of I3C were mediated via modulation of the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway

[44]. I3C was also shown to induce the expression of phase I and II enzymes by the binding of the aryl hydrocarbon receptor (AhR) (Figure 23) [45].

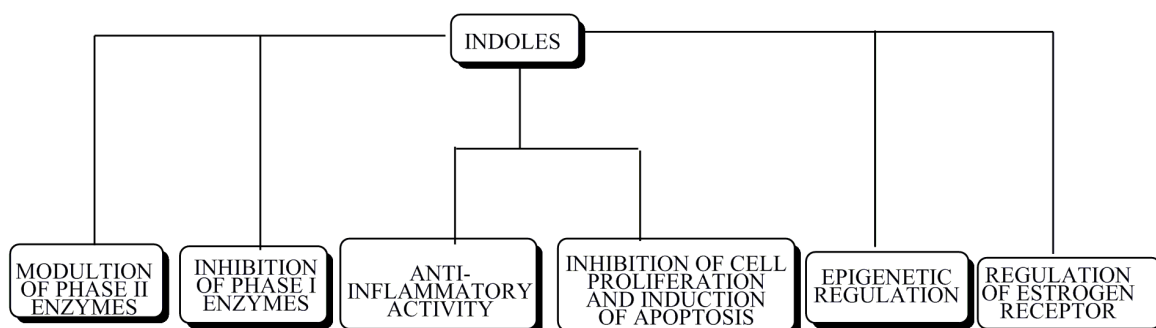


Figure 23. Biological activity pathways of indoles [45]

DIM has been found to increase bone mass by suppressing osteoclastic bone resorption, in physiological and pathological conditions [46]. DIM could also help prevent heart failure, as one study indicates the compound improves myocardial energy metabolism imbalance via AMPK α signaling [47].

Strychnine and brucine are well known for their toxic effect that manifests in the form of hypertension and violent convulsions. Brucine is also a proposed anticancer drug candidate, as it inhibits VEGF-induced cell proliferation, reducing p-VEGFR2 kinase activity and inhibiting neovascularization in vivo [48].

Other indole alkaloids, isolated from marine sources, such as coscinamides, dragmacidin D, topsentins, or even fungal sources, such as asterriquinone, have exhibited antiviral (anti-HIV), antimicrobial, antitumor activity, along with the inhibition of serine–threonine protein phosphatases or ascites hepatoma AH13, for example [49]. Such compounds, isolated from the *Strychnos* species, have also been found to inhibit quinine- and choloquinine-resistant *P. falciparum* [50]. One of the more studied indole alkaloids would be physostigmine, the template that led to the development of rivastigmine, globally licensed in 2006 to fight the symptoms of dementia associated with Parkinson's disease, also prescribed for the symptomatic treatment of Alzheimer's disease [51].

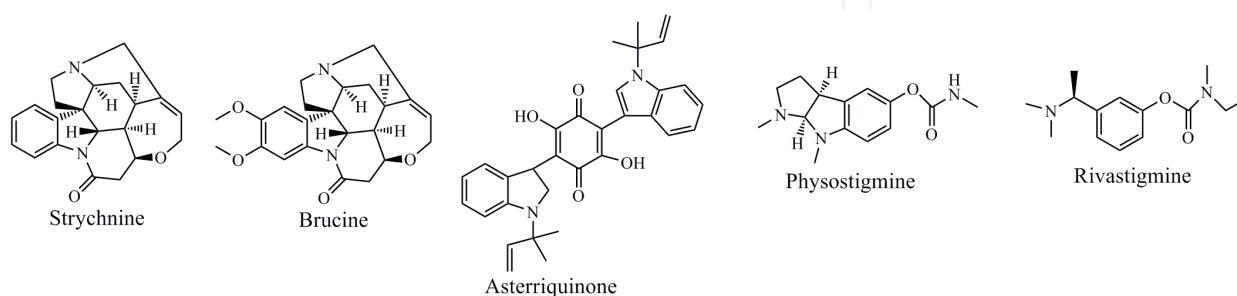


Figure 24. Indole alkaloids – strychnine, brucine, asterriquinone, physostigmine, and rivastigmine[50]

With methods of extraction developing since the 1960s, with many efforts concentrating on the efficiency and environmental impact of the process, terpenoid indole alkaloids and their pharmacological properties continue to attract attention as some of them are already marketed as anticancer, antihypertensive, or hypoglycemic agents, for example [52]. Some monoterpene indole alkaloids are in high demand, such as vinblastine (*Catharanthus roseus*) and camptothecin (*Camptotheca acuminata*, *Nothapodytes foetida*), currently used as chemotherapeutic drugs, and eyes have turned toward metabolic engineering. However, their biosynthetic pathways are still not fully elucidated and geneticists, chemists, and biotech specialists are scrambling to fill in the gaps, with resources such as cell- and organ-specific transcriptome databases on hand [53, 54].

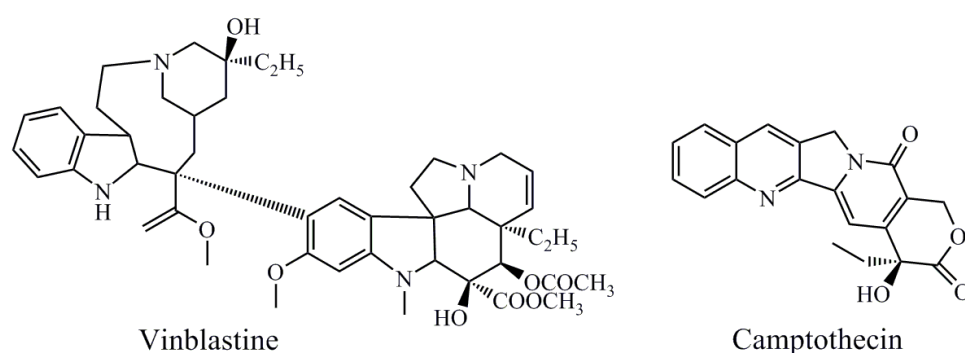


Figure 25. Indole alkaloids – vinblastine and camptothecin [50]

A novel class of indole-2-carboxylate derivatives was designed starting from the structure of pyrroloquinoline quinone, with two compounds (Figure 26) emerging as more potent anti-proliferants than the reference drugs, compounds that induced PARP cleavage and increased ROS generation dose-dependence [55].

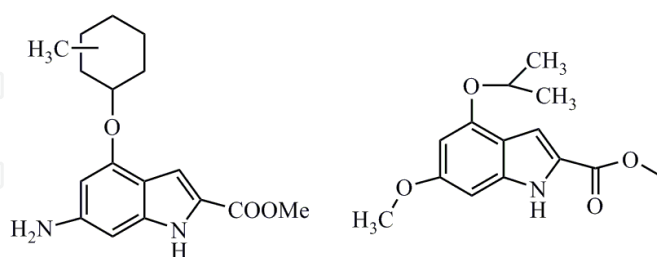


Figure 26. Indole-2-carboxylate derivatives [55]

Protein tyrosine phosphatases (PTP) are a novel, mostly untapped family of therapeutic targets, with implications in oncology (SHP2), autoimmunity (Lyp) or diabetes (PTP1B). X-ray crystal structural analysis has been performed on PTP-inhibitor complexes, revealing bicyclic benzofuran and indole-based salicylic acids as useful first steps toward the development of more potent inhibitors (Figure 27) [56].

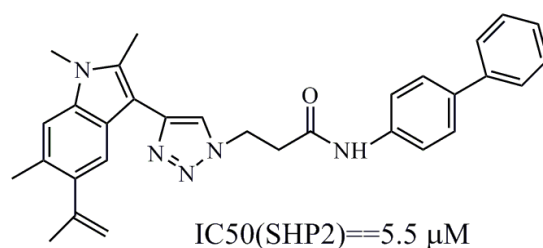


Figure 27. PTP-inhibitor [56]

Novel galantamine derivatives with indole moiety have exhibited an activity against acetylcholinesterase up to 95 times higher than the parent compound, with one promising lead binding in a region close to the peripheral anionic site of the enzyme, where the Ω-loop of amyloid beta peptide adheres [57].

Coronary heart disease, prevalent in industrialized regions, comes hand-in-hand with high levels of LDL-C ("bad cholesterol") and low levels of HDL-C ("good cholesterol"), treated mostly with statins, inhibitors of HMG-CoA reductase with dose-limiting hepato- and myotoxicity. However, the screening of a small indole chalcone fibrates library (Figure 28) has revealed three compounds with a more potent hypolipidemic effect than the standard drug, fenofibrate, coupled with high inhibition percentages of superoxide anions, hydroxyl radicals, and microsomal lipid-peroxidation [58].

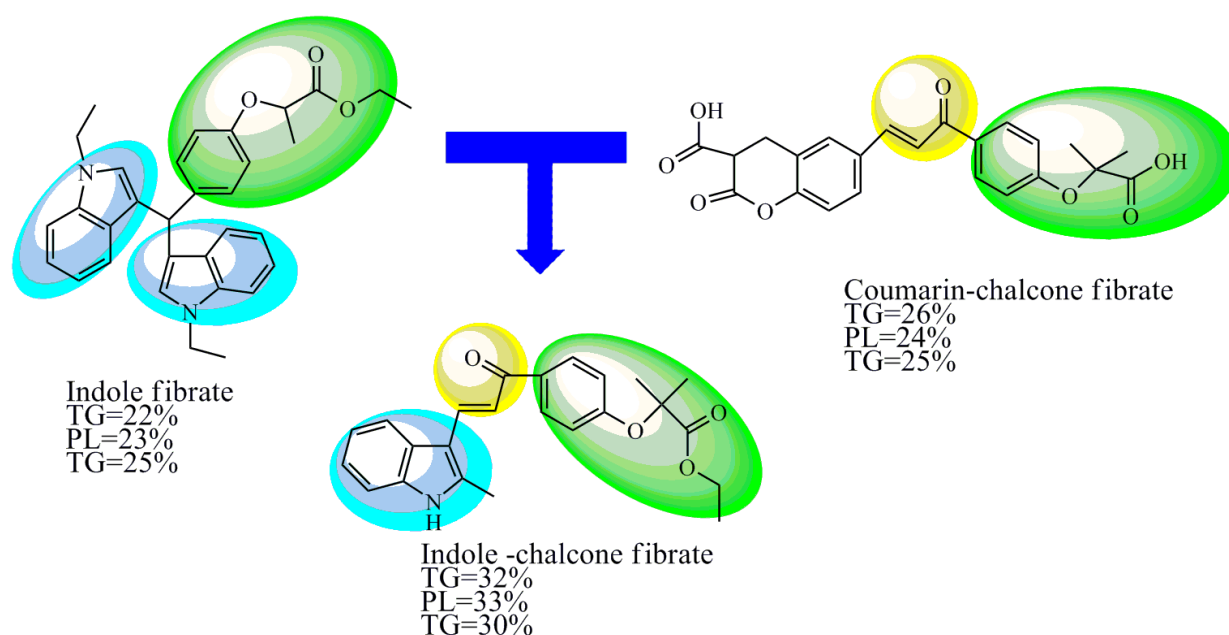


Figure 28. Indole chalcone fibrates [58]

Beneficial effects on lipid and also glucose metabolism were also reported concerning 1-(4-chlorobenzoyl)-5-hydroxy-2-methyl-3-indoleacetic acid (GY3), which increased glucose consumption and decreased lipid accumulation through AMPK activation in hepG2 cells, with

obvious implications in metabolic syndrome, type 2 diabetes, and nonalcoholic fatty liver disease [59].

Some indole derivatives also show promising antimicrobial activity. Five out of 24 bisindolylmethane Schiff base derivatives synthesized were found to specifically inhibit *Salmonella typhi*, *S. paratyphi A* and *S. paratyphi B*, even if the inhibition was moderate at best, when nitro or halogen substituents were introduced [43].

5.2. Natural and synthetic indolizines

Natural products derived from the indolizine core, such as castanospermine, swainsonine, or tylophorine, polyhydroxylated indolizidine alkaloids, have attracted much attention, struggles toward total synthesis, or analog design issues. Their biological properties range from the antiviral to the anticancer realm, with promising effects on autoimmune diseases [60].

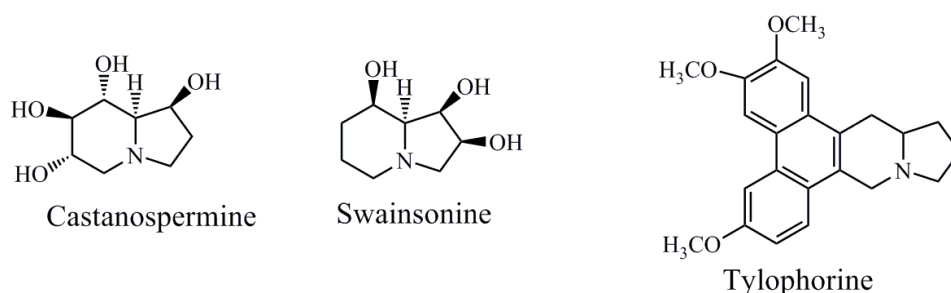


Figure 29. Indolizidine alkaloids [50]

For example, castanospermine glycoside analogs inhibit breast cancer cells MCF-7 and MDA-MB-231, inducing cell cycle arrest and apoptosis without impact on normal cell proliferation [61]. Some 5 α -substituted swainsonine analogs successfully inhibit Golgi α -mannosidase II, a key enzyme in the N-glycosylation pathway and a potential target for cancer chemotherapy, without much loss of activity by comparison with the parent compound [62]. Tylophorine was shown to inhibit VEGFR2 tyrosine kinase activity and its downstream signaling pathways, neovascularization, tumor angiogenesis and tumor growth, molecular docking simulations indicating that it could form hydrogen bonds and have aromatic interactions within the ATP-binding region of the VEGFR2 kinase unit [63].

In the indolizine nucleus, the six-membered ring suffers from low electron density, with a subsequent charge buildup in the five-membered ring, resulting in a large dipole moment and fluorescence properties. The influence of the substituents goes a long way into predicting a blue or red-shifted fluorescence; for example, the C-2 position could carry a lot of weight [26].

The 10 π conjugated planar electronic structure, exhibiting strong fluorescence properties, can be useful for DNA interaction studies. Such is the case of some indolizinyropyridinium derivatives, found to interact similarly to ethidium bromide, binding in the minor groove, but having its fluorescence partially quenched [64].

Switchable biosensors could be designed starting from Seoul-Fluor (Figure 30), an indolizine scaffold with three positions for different radicals: R1 and R2 substituents affect electronic perturbation; R3 could be a functional handle for bioconjugation, thus creating a versatile platform with tuneable emission wavelength and controllable quantum yield [65].

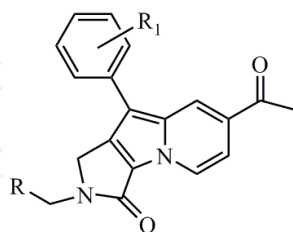


Figure 30. Indolizine biosensor: Seoul-Fluor [65]

Many indolizine derivatives have been proven to be worthy therapeutic agents, with a number of them undergoing clinical trials, notably five anticancer molecules that inhibit topoisomerase [66]. As is the case of photophysical properties, the substituents of the indolizine core can be tailored to suit the bioactivity requirements.

Following a SAR study, 49 indolizine derivatives were obtained and tested as potential HIV-1 infectivity factor inhibitors, one of which was found to exhibit an IC_{50} value of 11 μ M [67].

A feature that makes indolizine derivatives attractive is the design possibilities. The facile replacement of substituents could lead to more in-depth perception toward their effect upon desired bioactivity, solubility, or other properties sought [66].

Two new classes of indolizines fused with phenantroline skeletons were designed and synthesized, obtaining compounds with a coplanar structure, potentially able to interact with DNA through an intercalation mechanism, compounds that also possess good solubility in microbiological medium. Furthermore, one of the compounds exhibit, under aerobic conditions, activity against *M. tuberculosis* H37Rv, with an IC_{50} = 67 μ M. Two other compounds had a selective and significant antiproliferative activity (around 50%) against two breast cancer cell lines (MCF7 and T-47D) (Figure 31) [68].

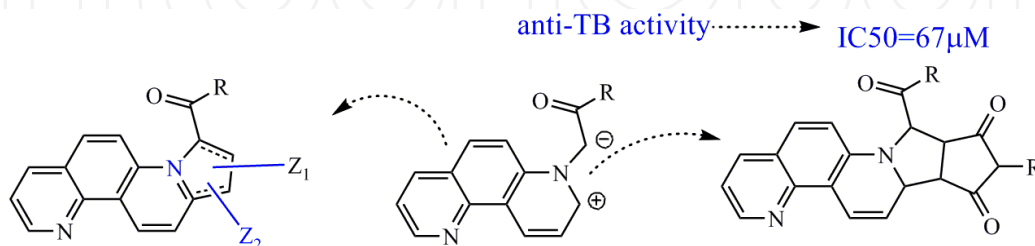


Figure 31. Indolizines fused with phenantroline skeletons active against *M. tuberculosis* and breast cancer [68]

During rational design efforts, concentrated on the identification of potential farnesyltransferase inhibitors (implications with respect to oncogenic Ras proteins), the replacement of the

triazole unit with the indolizine nucleus resulted in IC_{50} s in the low micromolar range. The substituents' influence on bioactivity and pharmacokinetic parameters was also investigated [69].

Rational design could be pushed even further, employing 3D-QSAR studies to yield pharmacophore models, as is the case for 15-lipoxygenase inhibitory activity. For this purpose, 47 indolizines with anti-15-LOX activity were used to obtain a statistically significant model [70].

The similarity of the two heterocycles has motivated researchers since 1967, when Harrell and Doerge postulated that indolizine analogs of bioactive indoles could possess similar or improved potency [66]. Such an endeavor was attempted with the synthesis of 1-(2-aminoethyl)-3-benzyl-7-methoxy-2-methylindolizine, an analog of indole derivative benanserine, the replacement of indole with indolizine proving to have no effect on anti-acetylcholinesterase activity but diminished the antihistamine and anti-5-hydroxytryptamine activity [66].

Ramatroban, 3-((3R)-3-[(4-fluorophenyl)sulfonyl]amino)-1,2,3,4-tetrahydro-9H-carbazol-9-yl)propanoic acid, is a well-known prostaglandin D₂ inhibitor and thromboxane receptor antagonist. Researchers from Merck and Amira have presented numerous ramatroban analogs with the indole moiety replaced with indolizine and aza-indole, both proving potential during SAR studies. Among them, a 4-aza-indole derivative (Figure 32) inhibited hCRTH2 with an IC of 6 nM and was active in a murine OVA-induced lung inflammation model [71-74].

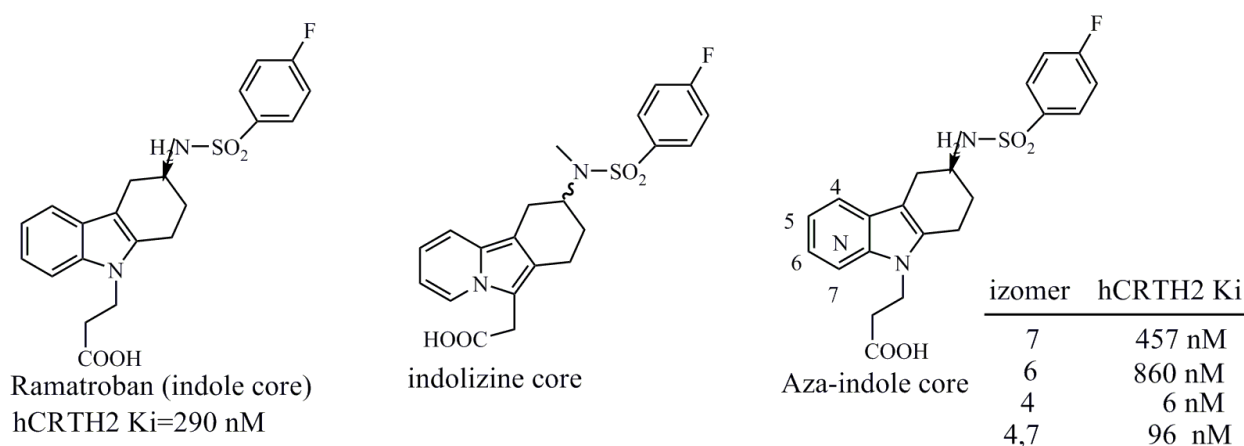


Figure 32. Tricyclic CRTH2 antagonist [74]

LE 300 is a selective antagonist for dopamine D₁/D₅ and serotonin 5-HT (2A) receptors, bearing an azecine ring fused to an indole ring on one side and a benzene moiety on the other side. New analogs of this compound were prepared, namely pyrrolo[2,3-g]indolizine, pyrrolo[3,2-a]quinolizine rings and their corresponding dimethylpyrrolo[2,3-d]azonine, and dimethylpyrrolo[2,3-d]azecine [75]. The study concludes that the indolizine and quinolizine derivatives show no activity concerning the receptors analyzed, while their azonine and azecine counterparts exhibited only weak antagonistic effects for serotonin and histamine receptors, remaining nonresponsive toward the four dopamine receptors tested.

Secretory phospholipases A2 (sPLA2s) is successfully inhibited by substituted indole and indolizine derivatives, as previously reported by Lilly and Shinogi researchers, with compounds like indoxam and Me-indoxam exhibiting favorable pharmacokinetic profiles [76-79]. Oslund et al. have prepared a set of benzo-fused analogs, among which they identified a compound that was the first reported potent inhibitor of groups IID and IIF sPLA2s and the most generally potent sPLA2 inhibitor reported to date (Figure 33) [80].

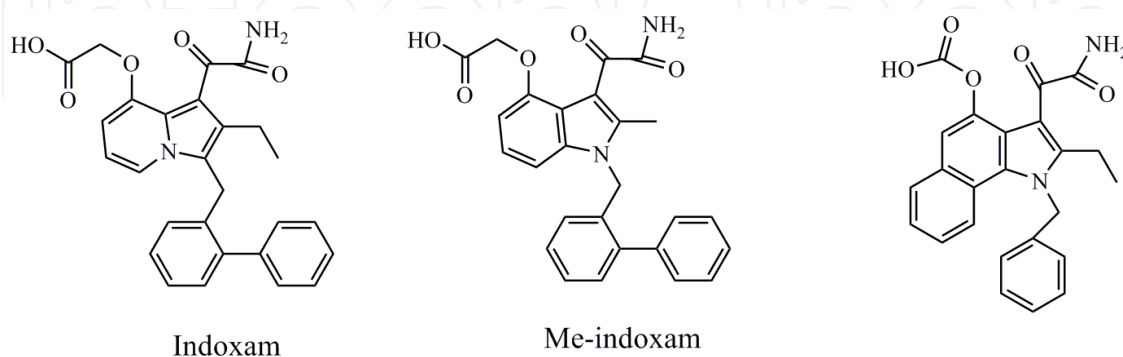


Figure 33. Substituted indole, indolizine, and benzo-fused indole inhibitors against human and mouse sPLA2 [80]

James et al. have prepared a series of indole and indolizine-glyoxylamides (Figure 34) and subsequently tested the compounds' cytotoxicity against cancer cell lines, identifying high antiproliferative activities, even in the case of multidrug-resistant phenotypes. After searching among numerous cores, with the goal to replace indole, the researchers synthesized a novel class of cancer agents with an indolizine core, with a lead compound that proved effective against multidrug-resistant cell lines such as MES-SA/DX5 and HL60/TX1000, resistant to treatment with Taxol [81].

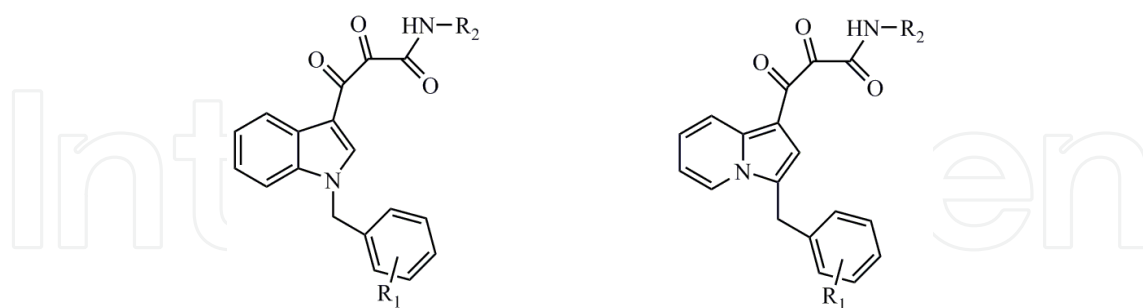


Figure 34. Indole- and Indolizine-glyoxylamide derivatives [81]

6. Conclusions

Considering the growing interest for biologically active compounds, we believe that in the future the search for novel indole and indolizine derivatives will result in the emergence of

new synthesis pathways and new and unexplored biologically active derivatives with pyrrole moieties.

Taking into account the importance of anticancer drugs, like vinblastine, irinotecan, topotecan, or camptothecin, the development of biologically active derivatives of new natural lead compounds containing indole and indolizine nucleus might be helpful in the design and development of novel and more potent anticancer drugs, antiviral agents, intercalating agents.

With the remarkable number of approved indole-containing drugs as well as the importance of the indolizine moiety, it can be easily concluded that indole and indolizine derivatives offer perspectives on how pyrrole scaffolds might be exploited in the future as bioactive molecules against a broad range of diseases.

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References

- [1] Yurovskaya MA, Alekseyev RS. New perspectives on classical heterocyclic reactions involving pyrrole derivatives (Review). *Chem. Het. Comp.* 2014;49(10):1400-1425.
- [2] Niu T, Huang L, Wu T and Zhang Y. FeCl₃-promoted alkylation of indoles by enamides. *Org. Biomol. Chem.* 2011;9:273.
- [3] Ganguly NC, Mondal P and Barik SK. Iodine in aqueous micellar environment: a mild effective ecofriendly catalytic system for expedient synthesis of bis(indolyl)methanes and 3-substituted indolyl ketones. *Green Chem. Lett. Rev.* 2012;5(1):73-81.
- [4] Ieronimo G, Mondelli A, Tibiletti F, Maspero A, Palmisano G, Galli S et al. A simple, efficient, regioselective and one-pot preparation of N-hydroxy- and N-O-protected

- hydroxyindoles via cycloaddition of nitrosoarenes with alkynes. Synthetic scope, applications and novel by-products. *Tetrahedron*. 2013;69:10906-10920.
- [5] Tabera DF, Tirunaharib PK. Indole synthesis: a review and proposed classification. *Tetrahedron*. 2011;67(38):7195-7210.
- [6] Matczak R, Koszarna B, Gryko DT. 1-(imidazo-1-yl)-indolizines, two-step synthesis and optical properties. *Tetrahedron*. 2014;70:7006-7009.
- [7] Caira MR, Popa MM, Draghici C, Barbu L, Dumitrescu D, Dumitrascu F. 7,8,9,10-tetrahydropyrrolo[2,1-a]isoquinolines in the search for new indolizine derivatives. *Tet. Lett.* 2014;55:5635-5638.
- [8] Sharma V, Kumar V. One-pot synthesis of animoindolizines and chalcones using CuI/CSP nanocomposites with anomalous selectivity under green conditions. *Med. Chem. Res.* 2014;23:3593-3606.
- [9] Chernyak N, Tilly D, Li Z and Gevorgyan V. Cascade carbopalladation-annulation approach toward polycyclic derivatives of indole and indolizine. *ARKIVOC*. 2011;76-91.
- [10] Singh MS, Chowdhury S. Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. *RSC Adv.* 2012;2:454-4592.
- [11] Outlaw VK, d'Andrea FB and Townsend CA. One-pot synthesis of highly-substituted N-fused heteroaromatic bicycles from azole aldehydes. *Org. Lett.* 2015;17(8):1822-1825.
- [12] Liu H, Chen H, Li Y, Lv Y, Cai J, Ji M. A novel and one-pot method for synthesis of unprecedented 3,3-dimethyl-2-amide indoles under metal-free conditions. *Tet. Lett.* 2015;56:2332-2335.
- [13] Song Y-L, Wu F, Zhang C-C, Liang G-C, Zhou G, Yu J-J. Ionic liquid catalyzed synthesis of 2-(indole-3-yl)-thiochroman-4-ones and their novel antifungal activities. *Bio-org. Med. Chem. Lett.* 2015;25:259-261.
- [14] Ekbote SS, Deshmukh KM, Qureshi ZS and Bhanage BM. Polyvinylsulfonic acid as a novel Bronsted acid catalyst for the synthesis of bis(indolyl)methanes. *Green Chem. Lett. Rev.* 2011;4(2):177-183.
- [15] Surasania R, Kalitaa D and Chadrasekhar KB. Indion Ina 225H resin as a novel, selective, recyclable, eco-benign heterogenous catalyst for the sythesis of bis(indol-yl)methanes. *Green Chem. Lett. Rev.* 2013;6(2):113-122.
- [16] Singh R, Panda G. An overview of synthetic approaches for heterocyclic steroids. *Tetrahedron*. 2013;69:2853-2884.
- [17] Sandeep C, Padmashali B, Kulkarni RS. Efficient synthesis of indolizines and new imidazo[1,2-a]pyridines via the expected cyclization of aromatic cycloimmonium

- ylides with electron deficient alkynes and ethyl cyanoformate. *Tet. Lett.* 2013;54:6411-6414.
- [18] Dontsova NE, Nesterov VN, Shestopalov AM. Effect of solvent nature on the regioselectivity of the reactions of pyridinium ylides with E-1,2-di(alkylsulfonyl)-1,2-dichloroethene. From the reaction of 1,3-dipolar cycloaddition to the reaction of nucleophilic addition-elimination (AdN-E1,5). *Tetrahedron*. 2013;69:5016-5021.
- [19] Mishra S, Naskar B, Ghosh R. CuCl catalyzed green and efficient one-pot synthesis of aminoindolizine frameworks via three-component reactions of aldehydes, secondary amines, and terminal alkynes in PEG. *Tet. Lett.* 2012;53:5483-5487.
- [20] Li L, Chua WKS. One-pot multistep synthesis of 3-aminoindolizine derivatives. *Tet. Lett.* 2011;52:1392-1394.
- [21] Ziyaadini M, Hazeri N, Maghsoodlou MT, Habibi-Khorassani SM, Willis AC. A novel one-pot domino reaction for the synthesis of 2-acetyl-3(phenylamino)indolizine-1-carboxamide derivatives. *Tet. Lett.* 2011;52:5774-5776.
- [22] Mao Z, Li X, Lin X, Lu P, Wang Y. One-pot multicomponent synthesis of polysubstituted indolizines. *Tetrahedron*. 2012;68:85-91.
- [23] Kucukdisli M and Opatz T. One-pot synthesis of polysubstituted indolizines by an addition/cycloaromatization sequence. *J. Org. Chem.* 2013;78:6670-6676.
- [24] Lee JH, Kim I. Cycloaromatization approach to polysubstituted indolizines from 2-acetylpyrroles: decoration of the pyridine unit. *J. Org. Chem.* 2013;78:1283.
- [25] Park S, Kim I. Electron-withdrawing group effect in aryl group of allyl bromides for the successful synthesis of indolizines via a novel [3+3] annulation approach. *Tetrahedron*. 2015;71:1982-1991.
- [26] Ge YQ, Gong XY, Song GJ, Cao XQ, Wang JW. The synthesis, characterization and optical properties of novel 2-acyl 6-arylindolizines. *Spectrochimica Acta A: Mol. Biomol. Spectrosc.* 2015;135:7-13.
- [27] Pandya AN, Fletcher JT, Villa EM, Agrawal DK. Silver-mediated synthesis of indolizines via oxidative C-H functionalization and 5-endo-dig cyclization. *Tet. Lett.* 2014;55:6922-6924.
- [28] Yang Y, Gao M, Zhang D-X, Wu L-M, Shu W-M, Wu A-X. Convergent domino synthesis of 1,2,3-triaroylindolizines from methyl ketones and pyridines via self-division of labor strategy. *Tetrahedron*. 2012;68:7338-7344.
- [29] Hazra A, Mondal NB, Maity A, Naskar S, Saha P, Paira R et al. Amberlite IRA-402 (OH) ion exchange resin mediated synthesis of indolizines, pyrrolo [1,2-a] quinolines and isoquinolines: antibacterial and antifungal evaluation of the products. *Eur. J. Med. Chem.* 2011;46:2132-2140.

- [30] Gopal MS and Anitha I. Aqueous phase microwave synthesis of some bisindolizines. *Int. J. Chem. Std.* 2014;2(4):35-38.
- [31] Dinica RM, Furdui B, Ghinea IO, Bahrim G, Bonte S and Demeunynck M. Novel one-pot green synthesis of indolizines biocatalysed by *Candida antarctica* lipases. *Mar. Drugs*. 2013;11:431-439.
- [32] Nelson AC, Kalinowski ES, Jacobson TL, Grundt P. Formation of tryptanthrin compounds upon Oxone-induced dimerization of indole-3-carbaldehydes. *Tet. Lett.* 2013;54:6804-6806.
- [33] Kumar PP, Reddy YD, Reddy CVR, Devi BR and Dubey PK. Green synthesis of novel (E)-2-(1,4-dioxo-1,2,3,4-tetrahydrophthalazine-2-carbonyl)-3-(1H-indol-3-yl)acrylonitriles. *Green Chem. Lett. Rev.* 2014;7(4):322-329.
- [34] Meshram HM, Thakur PB and Bejjam MB. An efficient synthesis of hemiaminal of indoles by using tetrabutylammonium fluoride (TBAF) in water as a reusable reaction media. *Green Chem. Lett. Rev.* 2013;6(1):95-100.
- [35] Hoseini-Sarvari M and Parhizgar G. Regioselective Friedel-Crafts alkylation of indoles with epoxides using nano MgO. *Green Chem. Lett. Rev.* 2012;5(3):439-449.
- [36] Talukdar D and Thakur AJ. A green synthesis of symmetrical bis(indol-3-yl)methanes using phosphate-impregnated titania catalyst under solvent free grinding conditions. *Green Chem. Lett. Rev.* 2013;6(1):55-61.
- [37] Kamalraja J, Perumal PT. Microwave assisted InCl₃ mediated regioselective synthesis of highly functionalized indolylpyran under solvent-free condition and its chemical transformation to indolyltriazolylpyran hybrids. *Tet. Lett.* 2014;55:3561-3564.
- [38] Siddiqui ZN, Farooq F and Musthafa TNM. A highly efficient, simple, and ecofriendly microwave induced synthesis of indolyl chalcones and pyrazolines. *Green Chem. Lett. Rev.* 2011;4(1):63-68.
- [39] Vieira BM, Thurow S, Brito JS, Perin G, Alves D, Jacob RG et al. Sonochemistry: an efficient alternative to the synthesis of 3-selanylindoles using CuI as catalyst. *Ultrasonics Sonochem.* 2015;27:192-199.
- [40] Heravia MM, Farda MV and Faghihi Z. Heteropoly acids-catalyzed organic reactions in water: doubly green reactions. *Green Chem. Lett. Rev.* 2013;6(4):282-300.
- [41] Proenc F, Costa M. A one-pot synthesis of substituted pyrido[2,3-b]indolizines. *Tetrahedron*. 2011;67:1071-1075.
- [42] Zhanga M-Z, Chena Q, Yang G-F. A review on recent developments of indole-containing antiviral agents. *Eur. J. Med. Chem.* 2015;89:421-441.
- [43] Imran S, Taha M, Ismail NH, Khan KM, Naz F, Hussain M and Tauseef S. Synthesis of novel bisindolylmethane Schiff bases and their antibacterial activity. *Molecules*. 2014;19:11722-11740.

- [44] Khan N, Mukhtar H. Dietary agents for prevention and treatment of lung cancer. *Cancer Lett.* 2015;359:155-164.
- [45] Riso P, del Bo C. Preventive effects of broccoli bioactives: role on oxidative stress and cancer risk. In: Preedy VR, editor. *Cancer: Oxidative Stress and Dietary Antioxidants*. Elsevier Inc; 2014. p. 115-125.
- [46] Yu TY, Pang WJ, Yang G-S. 3,3'-Diindolylmethane increases bone mass by suppressing osteoclastic bone resorption in mice. *J. Pharmacol. Sci.* 2015;127:75-82.
- [47] Deng W, Zong J, Wei L, Guo H, Cheng Z, Zhang R, et al. 3,3'-Diindolylmethane improves myocardial energy metabolism imbalance induced by pressure overload via AMPK α in mice. *Int. J. Cardiol.* 2014;177:235-237.
- [48] Saraswati S, Agrawal SS. Brucine, an indole alkaloid from *Strychnos nux-vomica* attenuates VEGF-induced angiogenesis via inhibiting VEGFR2 signaling pathway in vitro and in vivo. *Cancer Lett.* 2013;332(1):83-93.
- [49] Carbone A, Parrino B, Barraja P, Spanò V, Cirrincione G, Diana P, et al. Synthesis and antiproliferative activity of 2,5-bis(3'-Indolyl)pyrroles, analogues of the marine alkaloid Nortopsentin. *Mar. Drugs* 2013;11:643-654.
- [50] Aniszewski T. Biology of alkaloids. In: *Alkaloids – Chemistry, Biology, Ecology and Applications*. 2nd ed. Elsevier B.V.; 2015. p. 196-257.
- [51] Bhadra S, Dalai MK, Chanda J, Mukherjee PK. Evaluation of bioactive compounds as acetylcholinesterase inhibitors from medicinal plants. In: *Evidence-Based Validation of Herbal Medicine*. Elsevier Inc.; 2015. p. 274-300.
- [52] Goldhaber-Pasillas GD, Choi YH Verpoorte R. New methods of analysis and investigation of terpenoid indole alkaloids. In: *Advances in Botanical Research – New Light on Alkaloid Biosynthesis and Future Prospect*. 2013. p. 233-272.
- [53] Sirikantaramas S, Yamazaki M, Saito K. Camptothecin: Biosynthesis, biotechnological production and resistance mechanism(s). In: *Advances in Botanical Research – New Light on Alkaloid Biosynthesis and Future Prospect*. 2013. p. 139-161.
- [54] Salim V, De Luca V. Towards complete elucidation of monoterpene indole alkaloid biosynthesis pathway: *Catharanthus roseus* as a pioneer system. In: *Advances in Botanical Research – New Light on Alkaloid Biosynthesis and Future Prospect*. 2013. p. 1-37.
- [55] Ji X-Y, Xue S-T, Zhan Y-C, Shen J-J, Wu L-T, Jin J, et al. Design, synthesis and antiproliferative activity of a novel class of indole-2-carboxylate derivatives. *Eur. J. Med. Chem.* 2014;83:409-418.
- [56] He Y, Zeng L-F, Yu Z-H, He R, Liu S, Zhang Z-Y. Bicyclic benzofuran and indole-based salicylic acids as protein tyrosine phosphatase inhibitors. *Bioorg. Med. Chem.* 2012;20:1940-1946.

- [57] Atanasova M, Stavrakov G, Philipova I, Zheleva D, Yordanov N, Doytchinova I. Galantamine derivatives with indole moiety: Docking, design, synthesis and acetylcholinesterase inhibitory activity. *Bioorg. Med. Chem.* 2015;23:5382-5389.
- [58] Sashidhara KV, Dodda RP, Sonkar R, Palnati GR, Bhatia G. Design and synthesis of novel indole-chalcone fibrates as lipid lowering agents. *Eur. J. Med. Chem.* 2014;81:499-509.
- [59] Si M, Yan Y, Tang L, Wu H, Yang B, He Q, Wu H. A novel indole derivative compound GY3 improves glucose and lipid metabolism via activation of AMP-activated protein kinase pathway. *Eur J Pharmacol.* 2013;698:480-488.
- [60] Koskinen AMP and Kallatsa OA. Polyhydroxylated indolizidine alkaloids – an efficient synthesis of 1-deoxy-8,8a-di-epi-castanospermine. *Tetrahedron* 2003;59:6947-6954.
- [61] Allan G, Ouadid-Ahidouch H, Sanchez-Fernandez EM, Risquez-Cuadro R, Fernandez JMG, Ortiz-Mellet C, Ahidouch A. New castanospermine glycoside analogues inhibit breast cancer cell proliferation and induce apoptosis without affecting normal cells. *PLoS ONE.* 2013;8(10):76411.
- [62] Kuntz DA, Nakayama S, Shea K, Hori H, Uto Y, Nagasawa H, Rose DR. Structural investigation of the binding of 5-substituted swainsonine analogues to Golgi alpha-mannosidase II. *Chembiochem.* 2010;11(5):673-680.
- [63] Saraswati S, Kanaujia PK, Kumar S, Kumar R and Alhaider AA. Tylophorine, a phenanthraindolizidine alkaloid isolated from *Tylophora indica* exerts antiangiogenic and antitumor activity by targeting vascular endothelial growth factor receptor 2-mediated angiogenesis. *Mol Cancer.* 2013;12:82.
- [64] Gradinaru R-V, Luca A-M, Cretescu I, Danac R. Fluorescent conjugates: pH stability, dye-DNA interaction and biological activity. *REV. CHIM. (Bucharest).* 2010;61:9.
- [65] Kim E, Lee Y, Lee S and Park SB. Discovery, understanding, and bioapplication of organic fluorophore: A case study with an indolizine-based novel fluorophore, Seoul-Fluor. *Acc. Chem. Res.* 2015;48:538-547.
- [66] Sharma V, Kumar V. Indolizine: a biologically active moiety. *Med Chem Res.* 2014;23:3593-3606.
- [67] Huang W, Zuo T, Luo X, Jin H, Liu Z, Yang Z, et al. Indolizine derivatives as HIV-1 VIF–elonginC interaction inhibitors. *Chem. Biol. Drug. Des.* 2013;81:730-741.
- [68] Danac R, Al Matarneh CM, Shova S, Daniloaia T, Balan M, Mangalagiu II. New indolizines with phenanthroline skeleton: Synthesis, structure, antimycobacterial and anticancer evaluation. *Bioorg. Med. Chem.* 2015;23:2318-2327.

- [69] Dumea C, Belei D, Ghinet A, Dubois J, Farce A, Bicu E. Novel indolizine derivatives with unprecedented inhibitory activity on human farnesyltransferase. *Bioorg. Med. Chem. Lett.* 2014;24:5777-5781.
- [70] Sharma V, Kumar V. Pharmacophore mapping studies on indolizine derivatives as 15-LOX inhibitors. *Bulletin of Faculty of Pharmacy, Cairo University.* 2015;53:63-68.
- [71] Stearns BA, Baccei C, Bain G, Broadhead A, Clark RC, Coate H, et al. Novel tricyclic antagonists of the prostaglandin D2 receptor DP2 with efficacy in a murine model of allergic rhinitis. *Bioorg. Med. Chem. Lett.* 2009;19:4647.
- [72] Gervais FG, Sawyer N, Stocco R, Hamel M, Krawczyk C, Sillaots S, et al. Pharmacological characterization of MK-7246, a potent and selective CRTH2 (chemoattractant receptor-homologous molecule expressed on T-Helper Type 2 Cells) Antagonist. *Mol. Pharmacol.* 2011;79:69-76.
- [73] Gallant M, Beaulieu C, Berthelette C, Colucci J, Crackower MA, Dalton C, et al. Discovery of MK-7246, a selective CRTH2 antagonist for the treatment of respiratory diseases. *Bioorg. Med. Chem. Lett.* 2011;21:288.
- [74] Tumey N. CRTH2 antagonists. In: Levin JI, Laufer S, editors. *Anti-Inflammatory Drug Discovery*. RSC Publishing; 2012. p. 109-112.
- [75] Rostom SA. Novel fused pyrrole heterocyclic ring systems as structure analogs of LE 300: Synthesis and pharmacological evaluation as serotonin 5-HT(2A), dopamine and histamine H(1) receptor ligands. *Achiv Der Pharmazie.* 2010;343:73-80.
- [76] Dillard RD, Bach NJ, Draheim SE, Berry DR, Carlson DG, Chirgadze NY, et al. Indole inhibitors of human nonpancreatic secretory phospholipase A2. 1. Indole-3-acetamides. *J. Med. Chem.* 1996;39:5119-5136.
- [77] Dillard RD, Bach NJ, Draheim SE, Berry DR, Carlson DG, Chirgadze NY, et al. Indole inhibitors of human nonpancreatic secretory phospholipase A2. 2. Indole-3-acetamides with additional functionality. *J. Med. Chem.* 1996;39:5137-5158.
- [78] Draheim SE, Bach NJ, Dillard RD, Berry DR, Carlson DG, Chirgadze NY, et al. Indole inhibitors of human nonpancreatic secretory phospholipase A2. 3. Indole-3-glyoxamides. *J. Med. Chem.* 1996;39:5159-5175.
- [79] Hagishita S, Yamada M, Shirahase K, Okada T, Murakami Y, Ito Y, et al. Potent inhibitors of secretory phospholipase A2: Synthesis and inhibitory activities of indolizine and indene derivatives. *J. Med. Chem.* 1996;39:3636-3658.
- [80] Oslund RC, Cermak N and Gelb MH. Highly specific and broadly potent inhibitors of mammalian secreted phospholipases A2. *J. Med. Chem.* 2008;51(15):4708-4714.
- [81] James DA, Koya K, Li H, Liang G, Xia Z, Ying W, et al. Indole- and indolizine-glyoxylamides displaying cytotoxicity against multidrug resistant cancer cell lines. *Bioorg. Med. Chem. Lett.* 2008;18(6):1784-1787.