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# INDOLIZINE: A COMPREHENSIVE REVIEW OF THEIR CHEMISTRY, SYNTHESIS AND APPLICATION

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## ABSTRACT

Indolizines are a unique class of bridgehead nitrogen-fused heteroaromatic compounds. They act as bioisosteres of indole, which is an important structure in medicinal chemistry. Their rigid aromatic framework, resonance stabilisation, and strong fluorescence support various chemical and biological uses. Improvements in synthetic methods, such as the Tschitschibabin reaction, 1,3-dipolar cycloadditions, and metal-catalysed cyclisations, have made it easier to create different indolizine derivatives with better yields and selectivity. Substituted indolizines show remarkable stability and resistance to nucleophilic attack, while still being highly reactive toward electrophiles. Biologically, indolizine derivatives have a wide range of activities, including antidiabetic, antimicrobial, anti-inflammatory, anticonvulsant, anticancer, antioxidant, and enzyme-inhibitory effects. They are notably effective as potent 15-lipoxygenase inhibitors. Their versatility goes beyondpharmacology into material science, where their fluorescence and stability increase their usefulness. Although some reactive sites remain underexplored, ongoing research is expanding the structural diversity and therapeutic potential of indolizines. Together, these

compounds continue to be valuable structures that drive progress in drug discovery and functional materials.

**KEYWORDS:** Indolizine, Tschitschibabin reaction, Anti-Microbial, Anti-Viral, Bioisostere of Indole.

## INTRODUCTION

Indolizine is a heteroaromatic ring system that belongs to the class of bridgehead nitrogen–fused heterocycles. It serves as a bioisostere of indole, a scaffold widely encountered in numerous natural products, pharmaceuticals, and approved commercial drugs. Compounds containing indolizine exhibit a broad spectrum of biological activities and have also found significant applications in material science. Further, the potent pharmacological activities of synthetic and natural indolizine derivatives also included Mycobacterium tuberculosis, anti-inflammatory, anticonvulsant, antiviral, antibacterial, analgesic, antileishmanial, antitumor, anti-mutagenic and antioxidant activities as well as glycosidase inhibitors.

Numerous studies and reviews have explored indolizine synthesis and applications since its first report in 1890. Indolizine hybrids show diverse biological activities and hold promise as prodrugs for many diseases. Continuing our focus on **bioactive heterocycles,**[58–61] we present an overview of indolizine pharmacology, emphasizing their inhibitory activities reported from the last decade up to March 2020.[1][2][3][4]

## CHEMISTRY OF INDOLIZINE

The synthesis of indolizine compounds by dipolar cycloaddition reactions takes place by deprotonation of the pyridinium salt. In this system, the intermediate 1,3-pyridinium dipole is generated and undergoes a spontaneous cycloaddition with electron-deficient alkynes, alkenes, and allenes. In the specialised literature, the synthesis of indolizine derivatives by cycloaddition reactions is presented, and in the last decade, notable improvements have been made in the catalytic conditions and reaction yields.

Douglas et al. proposed the synthesis of indolizine derivatives in up to 89 % yield in a single-step process. This cycloaddition synthesis reaction of indolizine by an *in situ* generated pyridinium ylide was developed using pyridine precursors, alkynes and diazoesters, while the catalyst was an iron complex.

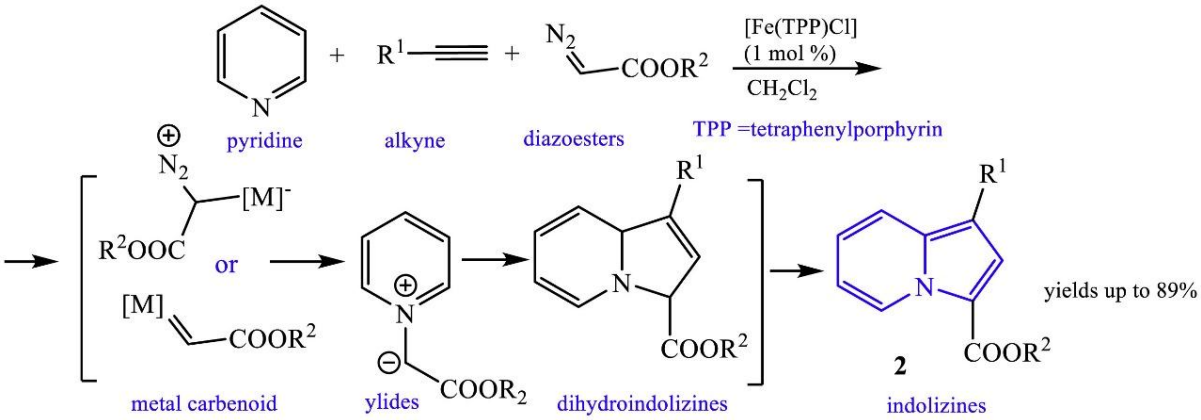
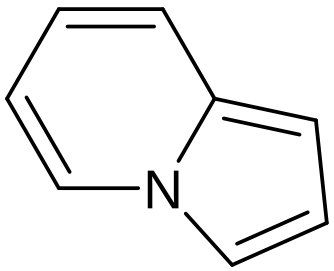



**Figure.1**

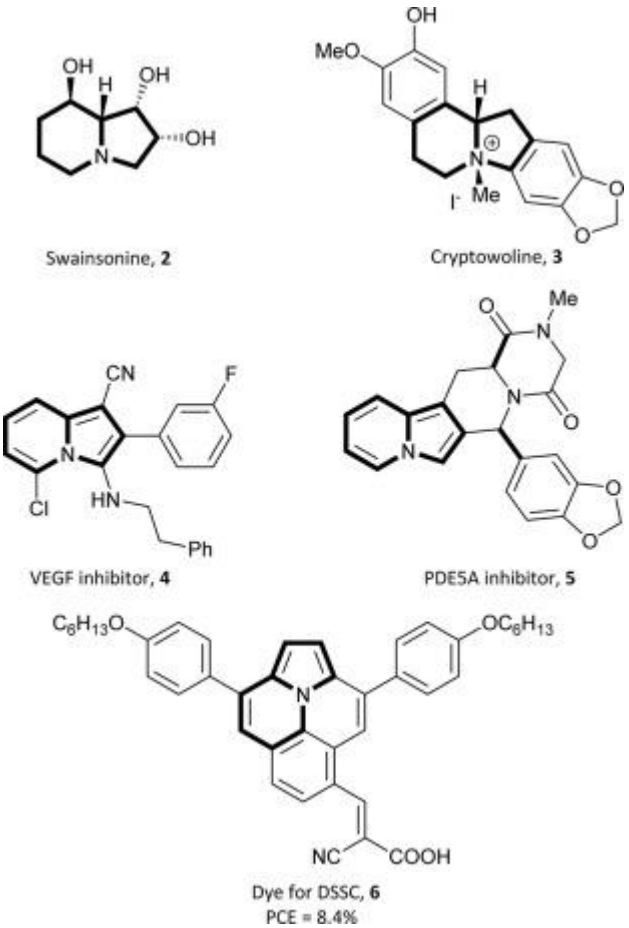
Despite the existence of an enantio- and diastereoselective route for the synthesis of cis-indolizine lactones 4, the evaluation of racemates and trans isomers potentially expands the possibilities of finding compounds on a first biological screening. The C1 reactivity of indolizines has scarcely been explored since it is less reactive than C3, and few methods are available for the synthesis of C1-free, C3-substituted indolizines.[5][6][7][8]

## STRUCTURE, PHYSICAL AND CHEMICAL PROPERTIES

An early argument that any resonance stabilization in indolizines is simply due to the presence of the pyrrole ring, the parent indolizine was first considered to be the best represented structure. However, the resonance energy (RE) calculated for indolizine was found to be 0.29 kcal/mol, which is larger than the total RE of pyrrole (0.23 kcal/mol). Furthermore, NMR studies have conclusively established delocalisation throughout both rings. Therefore, indolizine is now considered to be best represented by a resonance hybrid to which the canonical structures contribute. X-ray analysis has shown the crystal structure of the bis-indolizine to be nearly planar and the observed bond lengths to correlate well with the Huckel molecular orbital (HMO) bond orders. HMO calculations give the decreasing order of the electron density as: 3> 1 > >8a > 5 > 2 > 7> 6 on the ring carbons.



The partially or more often wholly hydrogenated derivatives of indolizine can be frequently found as backbones in many bioactive natural products such as swainsonine 2 [2a] or cryptowoline 3 (Fig. 2).[2b] Moreover, their synthetic derivatives have been found to exhibit a variety of biological activities, including as a potential inhibitor of vascular endothelial growth factor (VEGF) and for neuropilin-1 (NRP1) synergy (4),[3a] as agents with antibacterial, antiviral, anti-inflammatory properties,[3b–d] as well as phosphodiesterase V inhibitors (5),[3e] histamine H3 receptor antagonists,[3f] or as selective chemical probes for the bromodomains BAZ2A and BAZ2B.[3g] Indolizine derivatives have also been investigated for their suitability as dyes for dye sensitized solar cells (DSSC) (6)[4a] or organic light emitting devices (OLEDs),[4b,c] owing to their appreciable photophysical properties [18]




## PHYSICAL PROPERTIES

The parent indolizine and its alkyl derivatives are either low-melting solids or high-boiling liquids. It is sensitive to air, light and volatile in steam. However, when a phenyl group is attached at the 2nd or 5th position, the indolizines are found to be stable solids and

nonvolatile in steam. Most indolizines are highly fluorescent and show feeble basic properties.[19][20]

## CHEMICAL PROPERTIES

Reference has already been made to the structure of indolizines and, in particular, to its delocalized orbitals. Indolizines readily undergo electrophilic substitution and show resistance to nucleophilic attack. In their chemical reactivity, indolizines resemble pyrroles, indoles, and isoindoles. The following section deals with reactions of indolizines with electrophiles, oxidation, reduction, and other miscellaneous reactions.[20][21]

## BIOLOGICAL ACTIVITY

Antidiabetic activity

De Au and Shah BP (1975) specified the aminoalkylindolizine synthesis and evaluated the compounds for hypoglycaemic and antineoplastic activity in Ehrlich ascites carcinoma. The compounds (I-V) (Figure. 2) were found to possess good inhibitory activity.[7] [8]

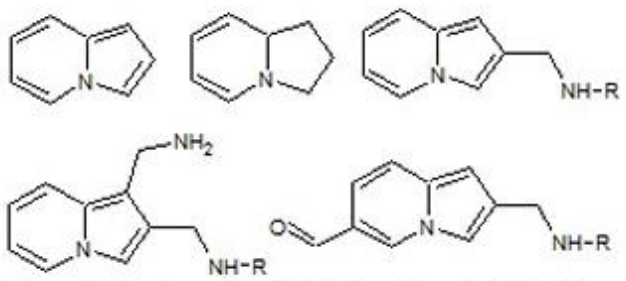



**Figure 2**: Structure of anti-diabetic amino alkyl indolizines.

### Antimicrobial Activity

The ion exchange resin mediated synthesis of indolizines, quinolines and isoquinolines. Synthesised heterocyclic derivatives were evaluated for antibacterial and antifungal studies against thirteen bacterial and four fungal strains. The results revealed that three derivatives (4a, 4b, 7a) are effective against all thirteen strains and notably, one indolizine derivative. (10) (Figure 3) showed dual antibacterial and antifungal efficacy. The compounds were screened against four different bacterial strains such as Staphylococcus aureus, Mycobacterium smegmatis, Salmonella typhimurium and Escherichia coli. Additionally, the compounds were also tested for sensitivity against a model yeast Candida parapsilosis and some model filamentous fungi Aspergillus fumigatus, Alternaria alternata, Botrytis cinerea

and Microsporum gypseum. Some of the derivatives showed selective toxicity to Gram-positive bacteria S. aureus.[8][9]

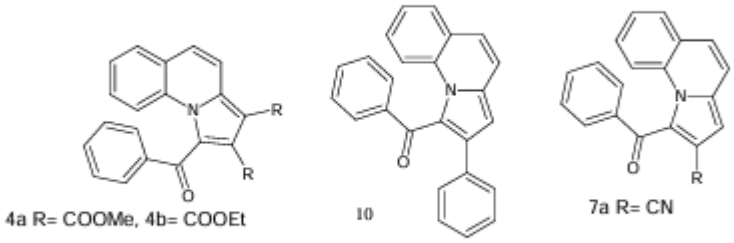



**Figure 3:** Structure of anti-bacterial & anti-fungal indolizine (10) derivativ

**Anti-Inflammatory Activity**

Pavan Srivastava (2015) et al., reported the bio-isosteric replacement of pyridine with bicyclic Indolizine. The derivatisation resulted in compounds with good anti-inflammatory activity. Five of the synthesised compounds (IND004, IND005, IND006, IND007 and IND008) showed significant inhibition of oedema in carrageenan and arachidonic acid-induced paw oedema model at a dose equimolar to diclophenac sodium. Kamal M. Dawood and coworkers (2006) synthesised benzofuran derivatives 3, 8a–b (Figure 4), 14b, and 17c. The derivatives were screened for anticonvulsant and anti-inflammatory activity. Some of them were found to possess anticonvulsant and anti-inflammatory activities.[10][11]

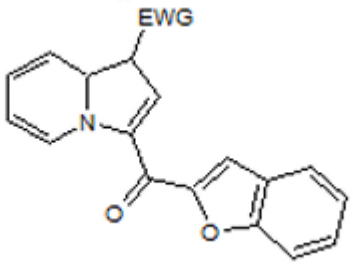



**Figure 4: Structure of active anti-inflammatory indolizine moiety.**

**Anti-Cancer Activity**

Danac, R and associates (2015) reported a feasible study of indolizines fused with phenanthrolone skeleton. The compounds were screened against an NCI 60 human tumor cell life panel. Two derivatives (4b & 6a) (Figure 15) showed selective and significant antitumor growth inhibitory activity against breast cancer (MCF7 and T-47D) and a slightly moderate

activity against some forms of Leukemia, Non-Small Cell Lung Cancer, Renal Cancer and Breast Cancer (MDA-MB-468). David A. James, (2008) demonstrated the SAR studies of a series of indole- and indolizine-glyoxyl amides and invitro anti-proliferative activities against cancer cell lines, including multidrug resistance (MDR) phenotypes. The invitro cytotoxic effects have been demonstrated across a wide array of tumor types of various origins (e.g., breast, colon, uterine) including cell lines that show resistance to Taxol.[11]

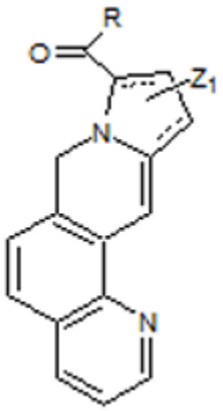



**Figure 5: Structure of indolizine-fused phenanthroline anti-cancer agents.**

**LOX Inhibitors**

Vikas Sharma and Vipin Kumar found that indolizine derivatives were identified as 15-lipoxygenase (15-LOX) inhibitors by pharmacophoric modeling approach tool. Solomon Teklu and associates A number of indolizine 1-sulfonates have been prepared by cyclization of cyclopropenones with pyridines followed by trapping of the intermediate 1-indolizinol with a sulfonyl halide, and examined as inhibitors of 15-lipoxygenase (15-LO). The compounds display IC50 values between 15 and 42 µM; all are more active than the well-known 15-LO inhibitor quercetin (IC50 51 lM). A wide variety of substituents are well tolerated. The enzyme inhibition was not affected by pre incubation or the presence of a detergent and no significant particle formation was observed.[12]

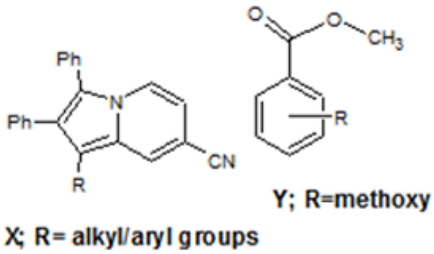


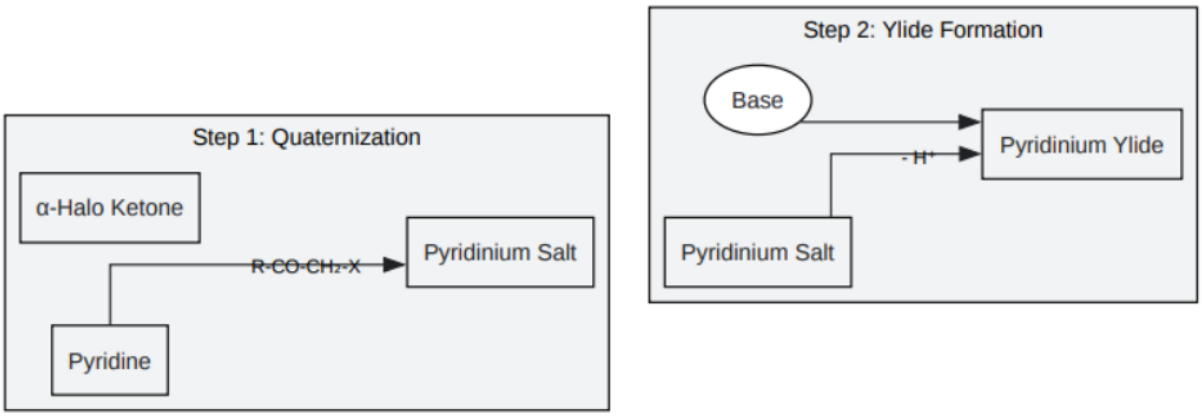

**Figure 6: Structure of indolizines15-LOX inhibitor.**

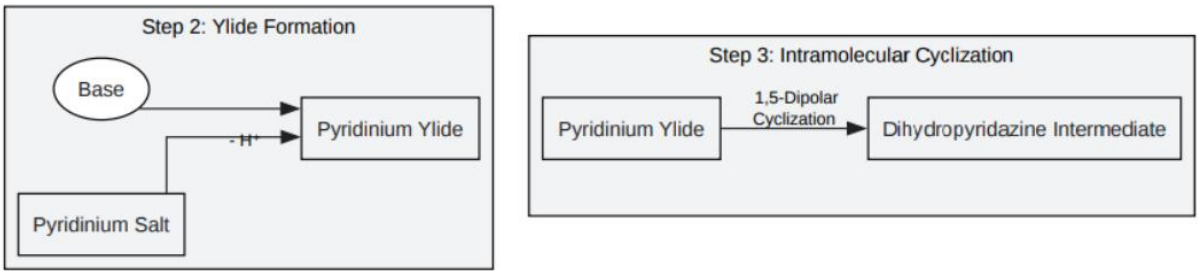
## SYNTHESIS OF INDOLIZINE

Indolizines have been synthesised over time by various classical methods, being a class of compounds among the important nitrogen-containing heterocycles, with a system of 10 π delocalized electrons that confers the aromatic character. The various synthesis pathways for indolizine compounds are mainly the Tschitschibabin reaction, cycloaddition reactions, intramolecular cyclisations, metal-catalysed C–H functionalization reactions, cycloisomerisation from 2-pyridine derivatives and trans-cyclisation of pyridotriazoles with alkynes. The synthesis of indolizines has been the subject of numerous studies, and common strategies for the preparation of aromatic indolizines involve substrates containing nitrogen in the six-membered ring, such as pyridine, quinoline and isoquinoline, but some methodologies also start from other derivatives such as pyrrole.[13]

### 1. Tschitschibabin reaction

The first laboratory synthesis of unsubstituted indolizine was described in 1910 by Scholtz by the reaction of α-picoline (2-methyl pyridine) with acetic anhydride, and then the addition of acid.[5,66] The mechanism of reactions initiated by Scholtz was proposed only in 1929 by Stepanow and Tschitschibabin. One of the classical approaches to the synthesis of indolizine compounds frequently used is the Tschitschibabin (also mentioned as Chichibabin) reaction, which consists of the quaternization of pyridine-2-substituted with α-halo gen-carbonyl compounds and an intramolecular cyclisation of pyridinium salts promoted in the presence of a base. The Tschitschibabin method is still used for the synthesis of substituted indolizines, with several notable improvements since its development.[13]






## 2. Synthesis of indolizines by 1,3-dipolar cycloadditions

The synthesis of indolizine compounds by dipolar cycloaddition re actions takes place by deprotonation of the pyridinium salt. In this system, the intermediate 1,3-pyridinium dipole is generated and undergoes a spontaneous cycloaddition with electron-deficient alkynes, alkenes, and allenes. In the specialized literature, the synthesis of indolizine derivatives by cycloaddition reactions is presented, and in the last decade, notable improvements have been made in the catalytic conditions and reaction yields. Douglas et al. proposed the synthesis of indolizine derivatives in up to 89 % yield in a single-step process.[16] [17][18]

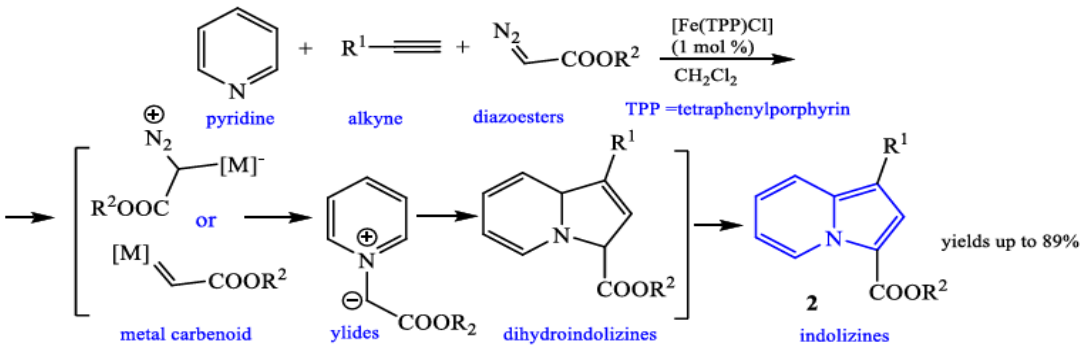



**Figure 6: Synthesis of indolizines through catalytically generated intermediate pyridinium ylides.**

## 3. Cyclisations forming C3–N4 bond

The synthesis of indolizines from propargylic pyridines, which has been optimized over time, represents an attractive approach through cycloisomerization, cyclization or arylation in the presence of catalysts such as Pt, Cu, Ag, Au, In, Pd, Ru, Ag and I 2 and heating in a polar protic solvent.[14][15]

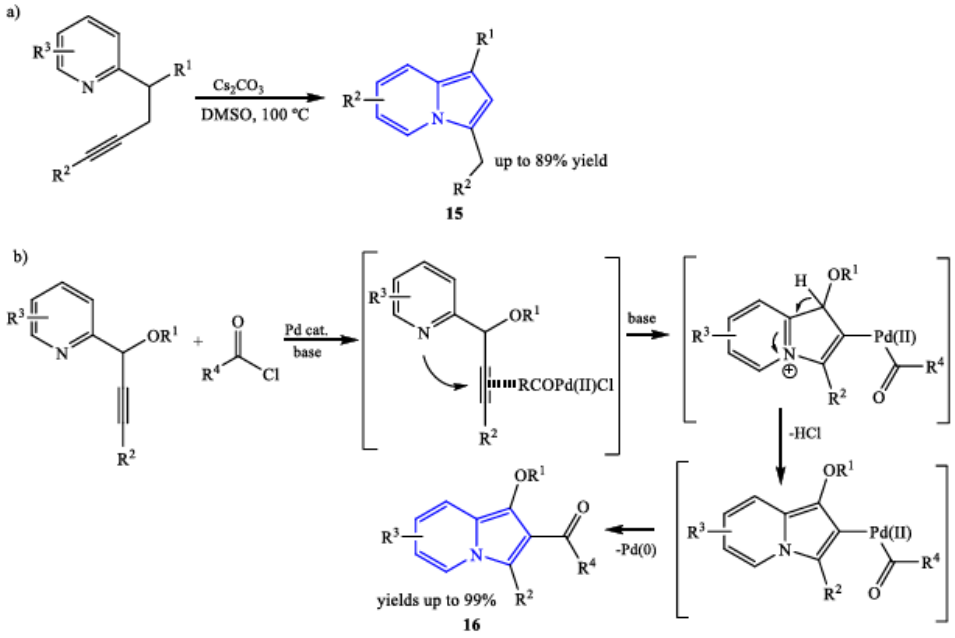



**Figure 7: Synthesis of indolizines from propargylic pyridines: a) Cesium carbonate mediated cycloisomerization of homopropargyl pyridines leading to indolizines 15.**

## CONCLUSION

Indolizines constitute an important class of nitrogen-containing heterocycles with a rigid aromatic framework that supports extensive chemical and biological versatility. Advances in classical and modern synthetic strategies—ranging from the Tschitschibabin reaction to 1,3-dipolar cycloadditions and metal-catalysed cyclizations—have greatly improved access to structurally diverse indolizine derivatives. Their physicochemical properties, including stability upon appropriate substitution and strong fluorescence, further enhance their utility.

Biologically, indolizine derivatives exhibit a wide spectrum of activities, including antidiabetic, antimicrobial, anti-inflammatory, anticonvulsant, anticancer, antioxidant, and enzyme-inhibitory effects. The development of indolizine hybrids and selective enzyme inhibitors, such as 15-LOX inhibitors, underscores their promise in drug discovery. Despite limited exploration of some reactive positions, notably C1, ongoing research continues to reveal new structural opportunities and therapeutic potential.

Overall, indolizines remain highly valuable scaffolds in medicinal chemistry and materials science, with continued advancements expected to drive further innovation and application.

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