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Review Article

Recent Advances in the Synthesis of Indolizines and their Derivatives

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Abstract *- The synthesis of indolizine via conventional methods, reaction necessitates several hours and some under reflux conditions, and the usage of expensive catalysts like palladium, copper, rhodium, titanium and silver. These reactions are typically time-consuming, mandating prolonged reflux conditions and the usage of hazardous solvents to nature. Although, with these significant resources, the yield obtained is satisfactory. Furthermore, it also makes the synthesis cost-effective, but it also punishes the environment due to the hazardous waste generated. In this study, we report that synthesising indolizine by adapting a green technique over the conventional method would diminish environmental impact while boosting efficiency and perpetuity in indolizine synthesis.*

Keywords *- Bioactive, 1,3-Dipolar cycloaddition eco-friendly microwave, Indolizine, Diseases, Illness.*

1. Introduction

The synthesis of N-fused cyclic heteroatom has enthralled research for over a century [1], as these classes of motifs have been significant frame-structure cores in numerous natural drugs and synthetic pharma cores, manifesting a wide range of significant biological potential [2]. Among these heterocyclic compounds, indolizine being a compound bearing one pyrrole ring and one pyridine ring coupled together with nitrogen being a fused atom (figure 1), which is quite sparse in nature. Additionally, these compounds are structural and chemical isomers of indole [3]. The homogeneity between indolizine and indole nuclei has led to the motifs of indolizine derivatives having an efficient biological potential, and the presence of indole boosts physiological activities [4]. It is isoelectronic with heterocyclic compounds and indole akin to purines and has a 10-π electron system.

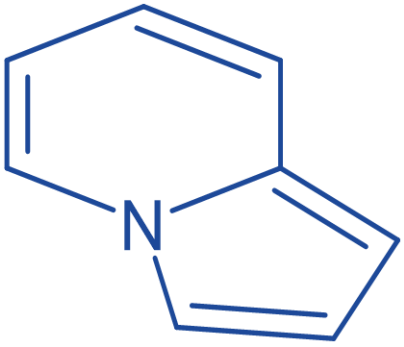

Fig. 1 Structure of indolizine

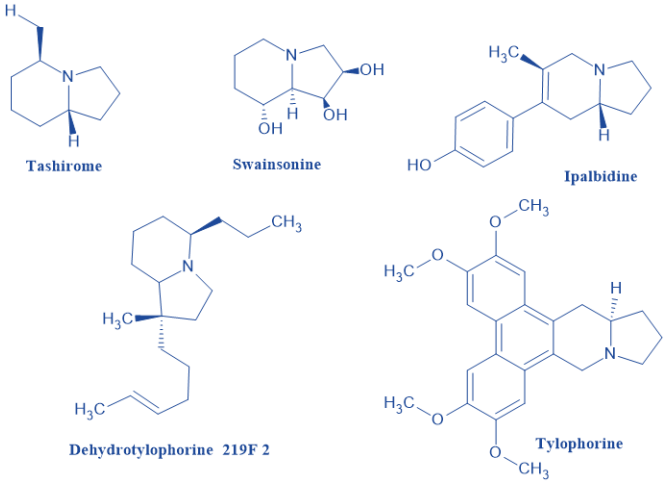

Fig. 2 Naturally occurring alkaloids of indolizine derivatives

There are a variety of forms of indolizine motifs isolated from insects, animals, marine life and microbes. Example (±) Swainsome [5], camtothecin [6], tashirome [7], (D) ipalbidine [8] and dehydrotylophorine [9, 10] (Figure 2). The noteworthiness of indolizine in drug design has made them essential for synthetic and medicinal organic therapeutic applications and is emerging with different precise substitution patterns. Various indolizine derivatives have been proclaimed to display a wide spectrum of applications in various fields such as biology, food industries, pharmaceuticals, chemistry and medicine [11]. This series of bridge-headed N-linked heterocyclic compounds exhibit potential biological activities

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such as antioxidant, antimicrobial [12], anticancer, calcium-entry blocking, photoluminescence, anti-inflammatory and enzyme inhibition [13]. These derivatives are also studied in material science due to their electric properties and fluorescence. The interesting bioactive properties and scarcity of compounds from natural sources have made most researchers focus on developing variant methods to synthesise these compounds [14].

There is a diverse array of the synthetic routes for indolizine that can divided into the Tschichibabin reaction, 1,3 dipolar cycloaddition reaction, intermolecular cyclisation using acetic anhydride, and the formation of C_1-C_9, C_8-C_9 and C_3-C_4 bonds. Cyclisation involves metals such as palladium, gold, silver and copper as catalysts. Furthermore, numerous procedures start with nitrogen substrates in six-membered rings, such as quinoline, pyridine, and isoquinoline. The initial method for the synthesis of indolizine molecule includes dipolar cycloaddition reaction of pyridinium and related heteroatomic ylides with electron-deficient alkynes or alkenes, in addition to cyclisation of pyridine cycloisomerisation transformations and Scholtz reactions [15].

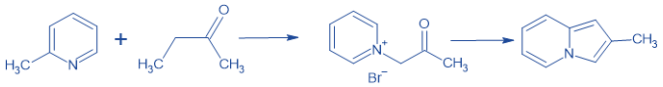
Beneath several decades, organic synthesis by green chemistry has been seized/clinched with scientific discipline. The congruity in green chemistry has been mastered in the benignant chemical process amid several new technologies contemplated per year. In the present scenario, the inquisitors in both savants and industry are continually encouraged to move on with environmentally benignant methods for procreating desired opportune molecules. Amid the generous principle of green chemistry, utilizing “safer solvents” and “energy efficiency” can be chosen as the prominent principle for synthetic inquisitors [16-19].

On the other hand, for many chemical processes, a predominant effect on nature is achieved through heating or cooling methods to master this adversity. Herein, we have approached with an efficient method, i.e., by microwave irradiation, which is proven to be 100 times faster than with conventional method (oil bath, etc.) and ease the chemical reaction. Gedye and co-workers first synthesized it in 1986 [20]. Microwaves generally depend on the endowment of the reaction mixture to intuitively consume microwave energy, taking advantage of “microwave dielectric heating” phenomena such as dipolar polarization or ionic conduction mechanisms [21,22].

The dominance of this method over the conventional method is due to the lower solvent consumption, reaction time, purity, high yield, efficiency, reduced by-product formation, and minimal impact on the environment and human health. This work reviews the synthesis of indolizine; adapting the green technique over the conventional method would diminish environmental impact while boosting efficiency and perpetuity in indolizine synthesis.

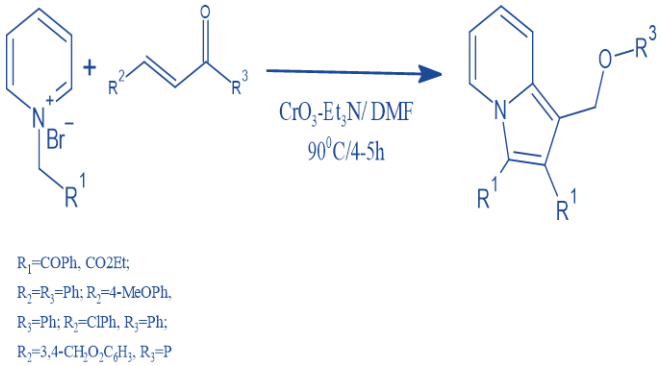
2. Background Study of Indolizine

The synthesis of homologous benzoindolizine fell back in 1912 by Scholtz [23]. Reacting 2-methyl pyridine with acetic anhydride at 200-220^{0}C resulted in a product called “picolide”, which yielded a colourless crystalline solid after hydrolysis; subsequently, it was identified as a compound that exhibited weakly basic properties but was not found to be derivative of pyridine. Furthermore, the molecule exhibited the characteristics of pyrroles and indoles and had an empirical formula (C8H7N), which is indole and isoindole. Revieing the observation, Scholtz posited the pyrrolopyridne structure for the compound and coined it as “pyrrocoline”; thereafter, Angeli named pyroindoles [24,25]. The veracity of Scholtz’s was confirmed by Diels and Alder [13], who confirmed the presence of four doubled bonds with catalytically reducing pyrrolocoline as a derivative. The derivative reacted with cyanogen bromide yielded a product similar in all respects to a (+) colicine (-) colicine previously synthesized by Loffler et al. At present, the compound earlier known as pyrrocoline or pyrindole is known as indolizine (Scheme 1).



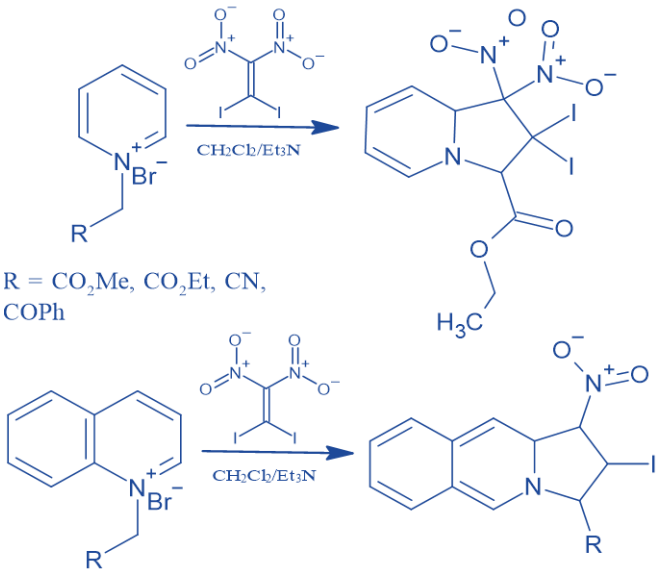
Scheme 1: Reagent (i) $(CH_3CO)_2$

Pyridinium N-ylides and isoquinolinium N-ylides treated with chalcone undergo 1,3-dipolarcycloaddition reaction in the presence of chromium trioxide or triethylamine to afford yields of 1-benzoyl-2-arylindolizine [42-76%] and 1-benzoyl 2-arylpyrrolo[1,2-*a*]quinoline [47-59%] (scheme-2) respectively [26].



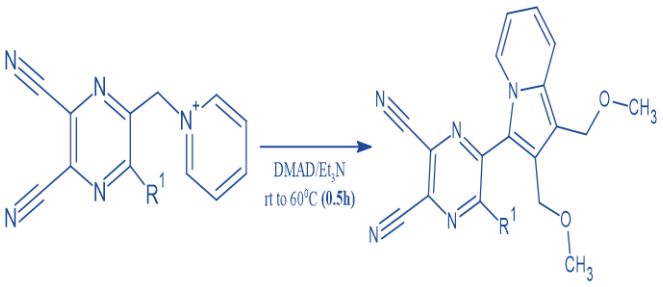
Scheme 2: Reaction conditions (i) CrO_3-Et_3N/ DMF, (ii) 90^{0}C/4-5h

The synthesis of nitro halogen substituted indolizine derivatives and pyrrolo[1,2-*a*]isoquinoline has been synthesised with moderate yields, 1,1-diodo-2,2-dintroethylene with pyridinium and isoquinolinium ylides contains, methylene group undergo 1,3-dipolarcycloaddition reaction. Pyridinium ylide with a carboethoxy group yielded 42%, while one with a benzoyl group yielded 16% (Scheme 3) [27].



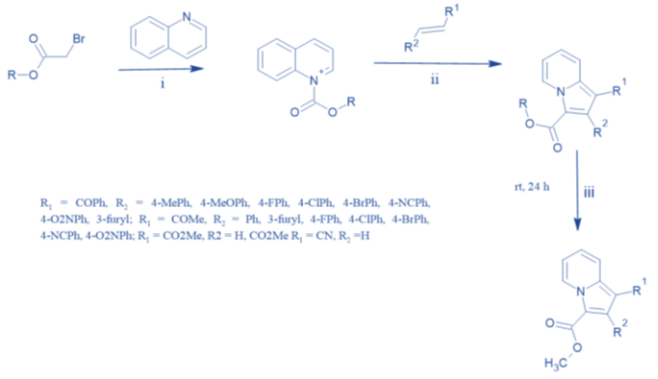
Scheme 3: Preparation of indolizine derivatives and pyrrolo[1,2-*a*]isoquinoline undergoing 1,3-dipolarcycloaddition reaction, respectively.

The synthesis of indolizine containing 5,6-dicyanopiperazines was yielded with moderate yield by the reaction of dimethyl acetylenedicarboxylate (DMAD) with dicyanopyrazine containing pyridinium ylides. In this study, methyl acrylate was used as a dipolarophile. The synthesis of indolizine with cationic pyridinium substituted derivative had been carried under the basic conditions from pyridinium ylides from asymmetric diqutarenary salts of 4, 40-bipyridine underwent cycloadditon reaction with ethyl propiolate with moderate yields (Scheme 4).



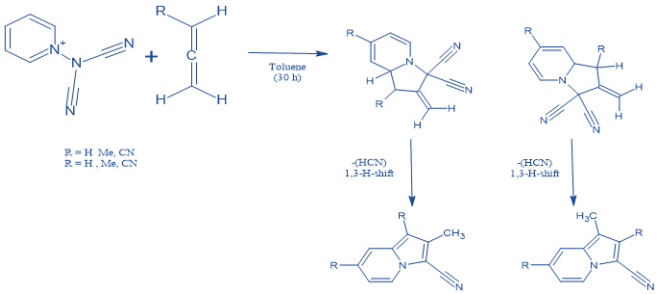
Scheme 4: Reaction Condition (i). DMAD/Et_3N (ii)60^{0}C (0.5h)

Quinolinium salt with polyethylene glycol in the presence of tetrakispyridinecobalt (II) dichromate, which acts as an oxidant reacted with active alkenes, undergoes 1,3-dipolar cycloaddition reaction to yield indolizine with low to moderate yields (scheme 5) [28].



Scheme 5: Reaction Conditions; i). CH_2Cl_2, rt, overnight, ii) K_2CO_3, TPCD, DMF, 90°C, overnight iii) 1% KCN/CH_3OH

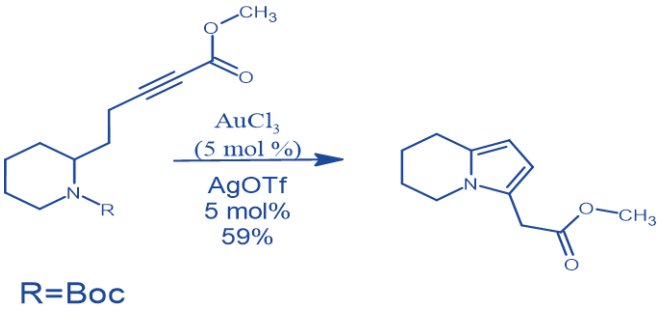
1-acylpyrrolo[2,1-*a*]isoquinoline and 1-acylpyrrolo[1,2-*a*]quinoline derivatives of the total of twenty-five compounds were synthesised with yields ranging between 29-78%, it has been synthesised by synthesised by one-pot reaction, in the presence of oxidant tetrakispyridinecobalt (II) dichromate treated with quinolinium and isoquinolinium ylide with maleic anhydride in a regioselective manner [29]. The synthesis of 3-cyano-1-methyl-2-phenylindolizines and 3-cyano-2-methyl-1-phenyl indolizines were synthesised by 1,3-sigmatropic and 1.3-dipolar cycloaddition reaction, followed by dehydrocyanation which yielded the very low product (Scheme 6) [30].



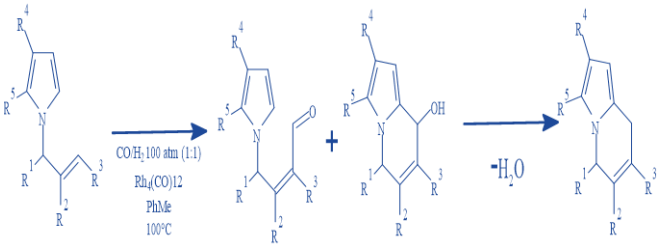
Scheme 6: Reagent used; Toluene, (30 h)

3. Synthesis of Indolizine by Metal-Catalysed

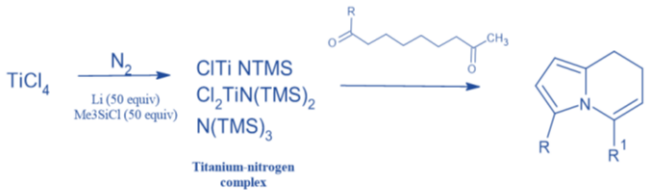
The 3-substituted 5, 6, 7, 8-tetrahydroindolizine was synthesized by cyclisation of N-Boc azacyclohexene having a propargylic ester using a composition of gold (III) chloride and silvertrifluromethanesulfonate as a catalyst (Scheme 7) [31]. Synthesis of 6-methyl-5,6-dihydroindolizine with 3 or 2-ethyl derivatives. A one-pot process was carried out using rhodium-catalyzed tandem hydroformylation (scheme 8), dehydration and cyclisation derived from starting material 1-(-2-methyl-2-propenyl)pyrrole. Molecular nitrogen fixation in which a minimal amount of titanium-complex was used to synthesise indolizine derivatives to form moderate to good yield (Scheme 9) [32]. A significant method was employed by palladium-copped, which cycloisomerises azaheterocycles, constituting a propargylic substituent that yields indolizine. It demonstrates monmorine the application of this method (Scheme 10) [33].



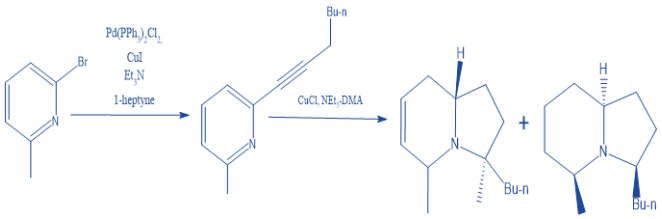
Scheme 7: 3-substituted 5, 6, 7, 8-tetrahydroindolizine was synthesized by the conversion of azacyclohexene having a propargylic ester using a composition of gold (III) chloride and silvertrifluromethanesulfonate as a catalyst.



Scheme 8: Reaction condition; (i). CO/H_2 100 atm (1:1), $Rh_4(CO)_{12}$, PhMe, 100°C



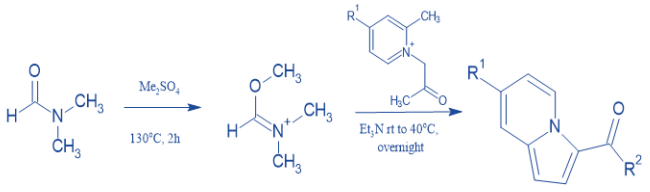
Scheme 9: Molecular nitrogen fixation in which a minimal amount of titanium-complex was used to prepare indolizine



Scheme 10: Palladium-copped, which cyclodimerizes azaheterocycles constituting propargylic substituent yielding indolizine.

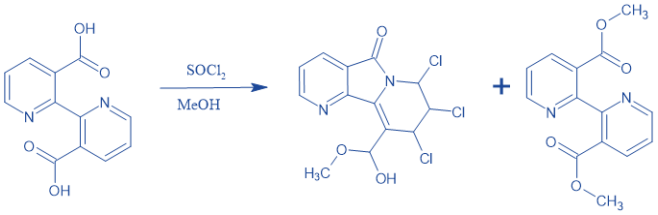
4. Synthesis of Indolizine by Other Reaction Methods

The 3- acylated indolizine was synthesized by reacting and adducting from dimethyl sulphate and dimethyl formamide with picolonium salts yielding 40-60% (Scheme 11) [34]. Chiral enantiomeric formed by the reaction of thionyl chloride with 2,2'-bipyridine3,3-dicarboxylic acid then was reacted with methyl 7,89-trichloro 6, 7, 8, 9-tetrahydro-5-oxopyrido-[2,3-a]indolizine-10-carboxylate with a yield of 37% (Scheme 12) [35]. In recent studies, indolizine was prepared readily from 2-(pyridine-2yl)acetyl motifs using (trimethylsilyl)diazomethane; the reaction was carried at r.t, yielding 2-derivatives of indolizine substituents (39-75%) and 1,2-cyclohexane-fused indolizine (Scheme 13) [36]. Lee and Co-workers synthesized a series of fifteen indolizine derivatives by treating 5-endo-dig 5 -and -endo-trig idocyclisation reactions in the presence of allylic and propargylic esters, respectively (Scheme 14) [37, 38]. Steve and the team synthesised 3-aminoindolizidine, undergoing ring contraction. The ring contraction of 3-azido-4-oxo-4H-quinolinizine-1-carboxylate and 3-azido-1-cyano-4H-quinolinizine-4-one in presence of acetic acid, stirred for 14hrs led to yield 3-(acetylamino)indolizine-1-carboxylate and 3-(acetylamino)indolizine-1-carbonitrlie respectively (Scheme 15) [39].



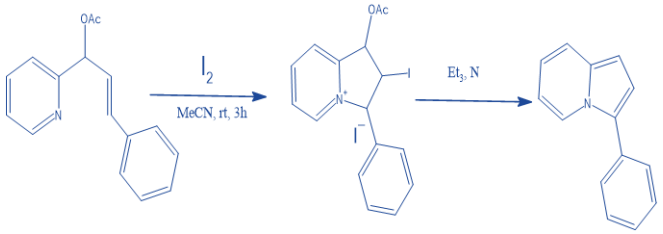
R_1 =H; R_2 = Ph, 3-CNPh, 4-CNPh, 4-MeOPh, 3-MeOPh, 4-ClPh, 4-O_2NPh, 4-FPh, 4-MePh, 3,4-Cl_2Ph, 4-(2-Pr)Ph, 4-MeO_2CPh, 4-CF3Ph, 5-chlorothien-2-yl.
R_1 =NO_2, R_2 = 4-CNPh; R1 =Et, R_2 = 4-CNPh, R_1 =MeO; R_2 = 4-ClPh;
R_1 =CO2Me, R_2 = 4-CNPh; R_1 =$MeOCH_2O$, R_2 = 4-CNPh

Scheme 11: Reaction Condition (i). Me_2SO_4, 130 °C, 2h (ii). Et_3N rt to 40°C, overnight

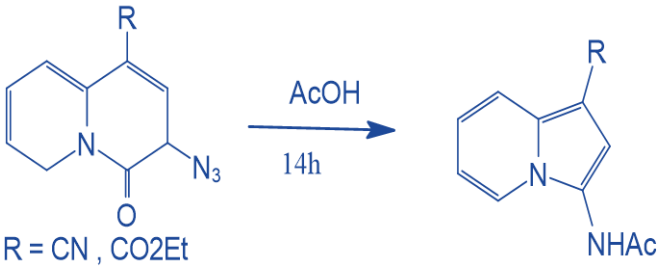


Scheme 12: Reaction Condition (i). $SOCl_2$, MeOH

Scheme 13: Reaction Condition (i). $TMSCHN_2$, MeOH, MeOH, rt, 24h



Scheme 14: Reaction Condition (i) I_2, MeCN, rt, 3h,



Scheme 15: Reaction Condition (i). AcOH, 14 hrs

5. Synthesis of Indolizine by Eco-friendly Methods

In our research, we report deploying a green technique to synthesise indolizine. One of our research projects adapted green techniques for the synthesis of indolizine derivatives by eco-friendly method, in which indolizine derivatives were synthesized by undergoing cyclisation of dipolarophiles with cycloimmonium ylides using water as a solvent and base at 80 ^{0}C. The synthesized compounds **1a**, **1b** and **1c** were evaluated for their potential against *anopheles arabienes* larvae, with temphos as the standard at 4 µg/mL. Motif 1a showed 93%, 1b exhibited 81%, and 1c showed 95% activity, examining the potential for controlling mosquito larvae [40].

Furthermore, we have synthesized indolizine derivatives by greener technique via the one-pot method in which phenacyl bromide, 3-bromoquinoline and triethyl amine were used as a base in the minimal amount of acetone to yield 4-bromo-(substituted-methoxy) pyrrolo[1,2-*a*]quinoline derivatives in high yield with trim in time as compared with conventional time. These derivatives were assessed for antibacterial potential against six different bacterial strains. Out of which **2a**, **2b** and **2c** have shown antibacterial potential (figure 3). Certainly, compound **2d** has shown the utmost inhibition zone compared to left-out compounds against both gram-positive and gram-negative bacteria.

The structure might bind with the extracellular and soluble proteins present on the bacterial cell wall and form the complex. Furthermore, the compound has shown noteworthy free radical scavenging activity with the highest inhibition at 100 µg/mL [41]. Lise-Lotte Gundersen et al. synthesized derivatives of indolizine and examined their potential antioxidant activity against lipoxygenase isolated from soyabeans.

Among all the derivatives, compound 3a has shown an effective potential antioxidant with an IC 50 value of 15±2 µM. SAR evaluation predicted that the electron-donating group of aryl substitution coupled with the sulfonates contributed to the potency activity of compound 3a. [42]. KingT et al. has synthesised motifs of hydrazide-hydrazone linked with quinoline ring irradiated under microwave radiation have shown noteworthy antimicrobial, especially 2-Propyl-(N’ -(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene) quinoline-4-carbohydrazide compound has displayed most potential gram-negative and gram-positive organism as a significant potential antimicrobial agent, ranging MIC value ranging from 3. 13 to 0. 39 µg/mL against six different organisms [43]. Rajesh Raju et al. have prepared indolizine derivatives with green practice using ionic liquid undergoing cycloaddition reaction to yield indolizine derivatives. The compounds have displayed high potential against COVID-19 protease and considered their use in antiviral agents [44].

From these studies, we report that green technique methods are more dominant than conventional techniques, which involve generating more waste, using hazardous solvents, and adapting costlier metal catalysts, thus posing a risk to the environment. By modifying the eco-friendly principle, it’s not only possible to achieve excellent yields rather, but it also minimizes the environmental impact. To our understanding, we provide some of the reactions that have exhibited the effectiveness of green synthesis.

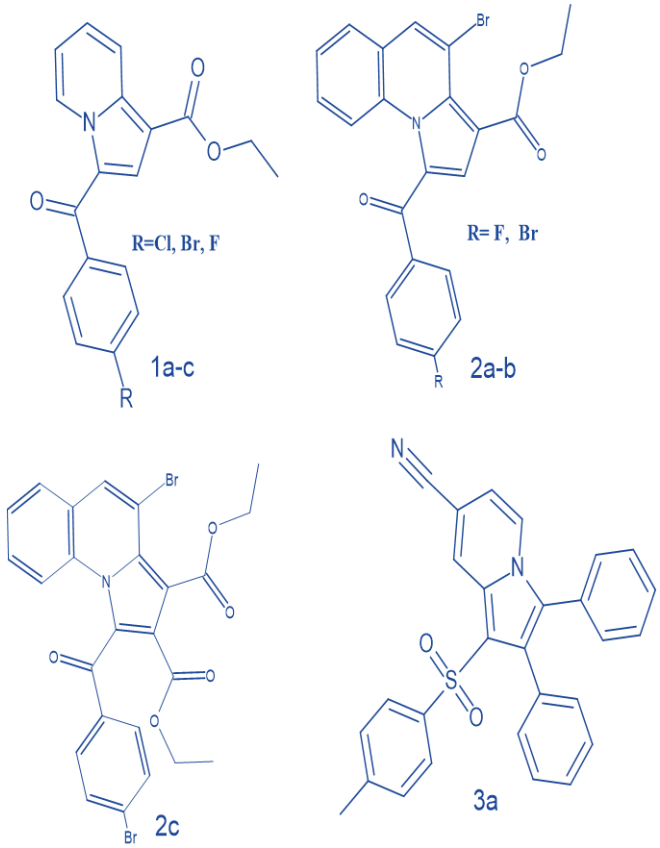
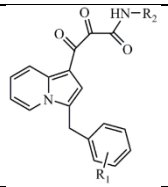
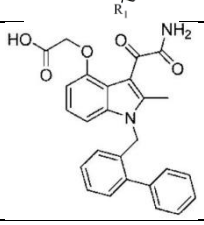
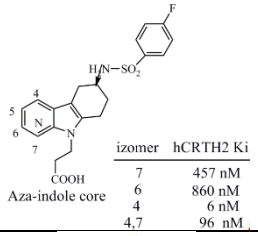
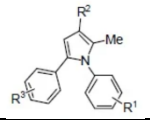
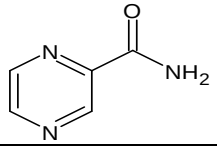
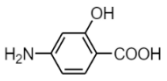
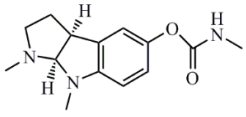
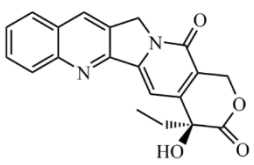
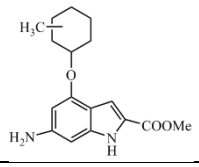


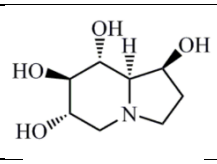
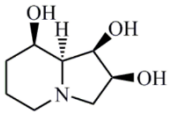
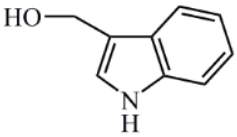
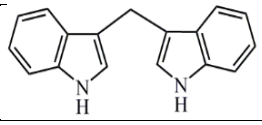
Fig. 3 Analogues of indolizine tested for various potentials

6. Pharmaceutical Applications

According to the previous results, researchers have highlighted that the prepared indoles and indolizines could be studied in terms of biological activities. Table 1 shows the different types of indole/indolizine derivatives that could be used in pharmaceutical trials due to their interesting biological behaviors.

Table 1. Structure and description of different indole/indolizine derivatives

Compound	Description	Structure
Indolizine-glyoxylamides	Exhibited excellent anti-proliferative activities against breast, uterine and colon cancer cell lines [41].	
Me-indoxam	It indicated inhibition against mice and humans (mGIIC, mGIIE, hGIIA, mGIIA, hGIIE, hGV, and mGV sPLA$_2$s) with low nanomolar potency [42].	
Aza-indole derivative	Inhibited hCRTH2 (IC=6nM) Active in murine OVA-induced lung inflammation [43].	
1,5-diarylpyrroles	Anti-tubercular and anti-inflammatory agents [44]	
Pyrazinamide (PZA)	PZA is an anti-mycobacterial drug Principle product (M. tuberculosis fatty acid synthase type I), such as palmitic acid [45], is inhibited with PZA (88%).	
p-aminosalicylic acid	Excellent agent against M. tuberculosis [46].	
physostigmine	It can be used to fight Alzheimer's disease and Parkinson's disease [47]	
Camptothecin	chemotherapic drugs can be used in metabolic engineering [48].	
Indole-2-carboxylate	As anti-proliferate agents, they could be used to induce PARP cleavage [49]	

Castanospermine	Showed anti-viral properties Fight for autoimmune diseases [50]	
Swainsonine	Displayed anticancer behaviours Fight for autoimmune diseases [50]	
Indole -3-carbinol	Could be observed in cabbage, Brussels sprouts, kale and broccoli [51]. Showed anti-inflammatory and anticancer properties.	
3,3-diindolylmethane	Exhibited anti-microbial and anti-parasitic properties [51]	

7. Conclusion

The encroachment to "environmentally friendly technique" has been conceived towards ongoing ecological methods in organic chemistry. Eco-friendly methods, which are fundamental to "green chemistry", approach the use of biological systems and enhance the technique to reduce the environmental impact.

These methods incorporate microwave radiation, which provides direct radiation on the molecule, which leads to direct heating, fastens reaction time, and lowers the formation of byproducts compared to the conventional technique. Using a thermos-shaker or sonicate enhances the reaction rate by reducing the need for hazardous chemicals or, certainly, reaction carried without a catalyst, eliminating the need for a toxic and expensive catalyst, streamlining the process and lowering the waste. The minimum use of hazardous solvents further decreases the environmental impact and elevates safety. Overall, eco-friendly methods significantly advance over traditional chemical synthetic techniques in efficacy, safety, and earth-friendliness.

Future Perspectives

The synthesis of indolizine derivatives using microwave irradiation has several advantages over the conventional heating method. These advantages include enhanced yield and purity, reduced reaction time and lead to more reproducible results. Also, this method of synthesis aligns with the green chemistry principles.

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