Review Article

INDOLIZINE DERIVATIVES: RECENT ADVANCES AND POTENTIAL PHARMACOLOGICAL ACTIVITIES

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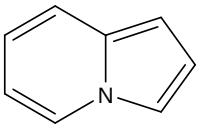
ABSTRACT

Indolizine derivatives possess valuable biological activities and have been studied for their psychotropic anti-inflammatory, analgesic, antimicrobial, antiexudative, anti inflammatory, anti-tumour (alkylating) agents and hypoglycemia activities. Many substituted indolizines are subject of extensive researches due to biological, medicinal, photographic and other useful applications. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity. Thus, the chemistry, synthesis and properties of this fused system and its analogues have been frequently reviewed. In this review, the recently synthesized indolizine derivatives possessing important pharmacological activities have been highlighted.

Keywords: Indolizine derivatives, Potential pharmacological activities.

INTRODUCTION

Organic compounds containing two condensed rings (5- and 6-membered) and a bridging nitrogen atom are known as indolizines. Indolizines are such parent system, which contain ring junction nitrogen and very rare in nature. Indolizines are structurally and chemically isomeric with indoles. It is this analogy between indole and indolizine nucleus that has prompted speculation that indolizine analogs of biologically important indoles could conceivably have potent physiological activity.[1-2]



indolizine

Figure 1

This system is isoelectronic with indole and represents a group of heterocyclic compounds structurally related to purines. Therefore, indolizines can be considered as a 10-π electron system. A lot of modifications, observations and investigation have been reported in this area. Several biologically active indolizines were reported to possess biological activities like anti-inflammatory[3], hypoglycemic activities.[4-5] Other activities reported are $5HT_3$ receptor antagonist[6], anti acetylcholine[7], CNS depressant activity[8], estrogen receptor binding[9], anti-oxidant property[10-11], antimicrobial and analgesic activity.[12-13] Many amino acid derivatives with an active indolizine nucleus have been utilized in cancer therapy.[14-15] Lise-Lotte Gunderson, Ayele H. Negussie and Frode Rise synthesized various derivatives of α-hydroxybenzyl substituted indolizines which shows anti mycobacterial activity.[16]

The indolizine ring system is an important structural motif frequently found in natural products and has been used as an important skeleton in pharmaceutics because of their interesting and promising biological properties. Synthetic indolizines have found wide-spread application in drug design efforts, biological, and pharmaceutical research.[17]

In recent years the synthesis of indolizines has been the object of much research, owing to the great interest primarily derived from the presence of these heterocyclic structures in several alkaloids isolated from the skin extracts of Neotropical frogs. Although several methods of synthesis of racemic indolizine derivatives have been published, a limited number of enantio selective syntheses have been reported.[18]

PHARMACOLOGICAL ACTIVITIES

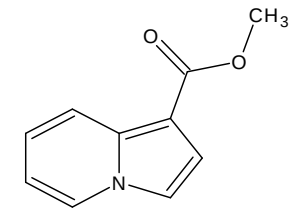
Indolizine display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules. Considerable interest has been focused on the indolizine structure. The discovery of this class of drugs provides an outstanding case history of modern drug development and also points out the unpredictability of pharmacological activity from structural modification of a prototype drug molecule. It is having a variety of medicinal applications. Indolizine derivatives carrying different substituents in the nucleus ring are associated with a wide range of biological activities including anticancer, antibacterial, antifungal, anti-cholinergic and anti-histaminic, anti tubercular activity. Their derivatives were also found to exhibit cytotoxic and CNS depressant activity.[19]

Anti-microbial and Anti-tubercular activity

Gundersen *et al.,* synthesized a series of 1-Substituted indolizine derivatives and screened for their inhibitory activity against M.tuberculosis H37Rv. They reported compounds were first screened at concentration of 6.25g/mL. MIC values as well as toxicity against VERO cells were determined whenever the inhibition of M.tuberculosis growth in the initial screening was 90% or higher.[20-21]

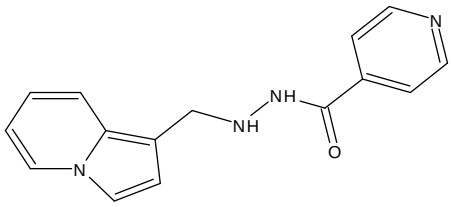
Srikanth *et al.,* synthesized a series of indolizine-1-Carboxylate derivatives and also screened for antibacterial activity against E.coli, P.aeruginosa, and S.aureus. They reported all the synthesized compounds have shown antimicrobial activity and reported N'-(pyridine-4-carbonyl) indolizine-1-carbohydrazide derivatives shows anti-tubercular activity against the Mycobacterium tuberculosis H37Rv strain using Lowenstein-Jensen Medium and Isoniazid, Pyrazinamide and Ethionamide as standard drugs.[22]

A.Hazra *et al.,* synthesized a new series of indolizine derivatives and studied their antimicrobial activity. The micro organisms used in this study consisted of 13 strains of bacteria namely Bacillus subtilis UC564, Staphylococcus aureus 25923, Streptococcus faecalis 29212, Micrococcus luteus AGD1, Escherichia coli ATCC25938, Klebsiella pneumonia J/I/4, Pseudomonas aeruginosa ATCC27853, Vibrio cholera 7201, Vibrio parahaemolyticus 72016, Shigelladysenteriae 3, Shigella flexneri DN13, Salmonella typhi DIRW, and Salmonella typhimurium 11.[23]



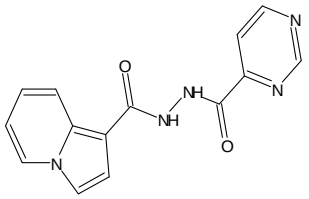
methyl indolizine-1-carboxylate

Figure 2



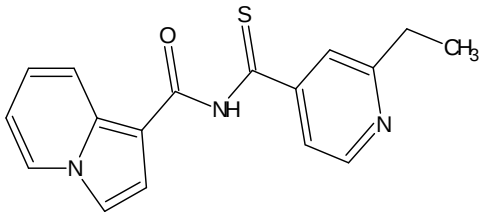
N'-(indolizin-1-ylmethyl)isonicotinohydrazide

Figure 3



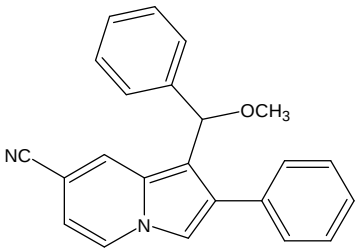
N-(pyrimidin-4-ylcarbonyl)indolizine-1-carbohydrazide

Figure 4



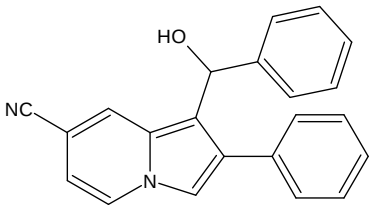
N-[(2-ethylpyridin-4-yl)carbonothioyl]indolizine-1-carboxamide

Figure 5



1-[methoxy(phenyl)methyl]-2-phenylindolizine-7-carbonitrile

Figure 6



1-[hydroxy(phenyl)methyl]-2-phenylindolizine-7-carbonitrile

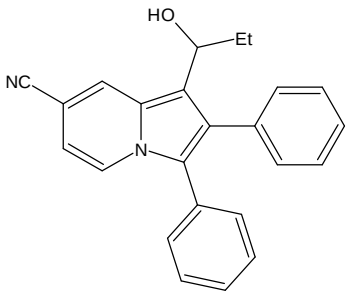
Figure 7

Anti fungal activity

Gundersen *et al.,* synthesized a series of Indolizin-1-yl (phenyl) methanone derivatives and screened for their anti fungal activity. Antifungal studies were carried out on four strains of fungi, viz. Aspergillusniger, and Candidaalbicans, Candidatropicalis, and Cryptococcus neoformans.[24]

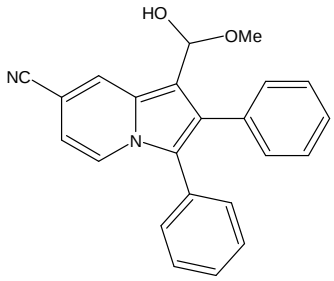
P. Sharma *et al.,* reported in vitro antimicrobial and anti fungal activity of a series of 1-substituted indolizin derivatives and they were investigated against several representative pathogenic bacteria and fungi.[25]

T. Weide *et al.,* synthesized a series of 3-substituted indolizine-1-carbonitrile derivatives and screened for their anti fungal activity and as phosphatase inhibitors.[26]



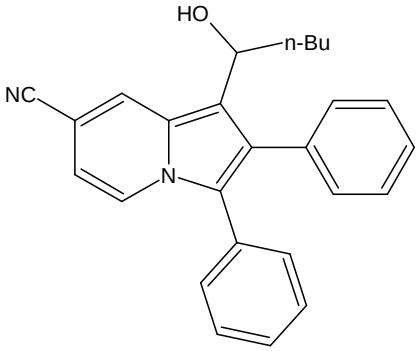
1-(1-hydroxypropyl)-2,3-diphenylindolizine-7-carbonitrile

Figure 8



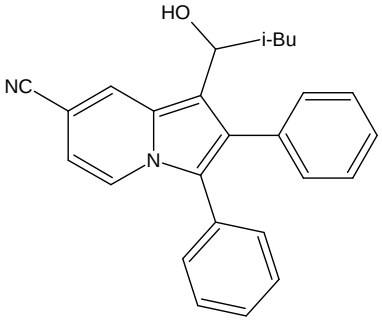
1-[hydroxy(methoxy)methyl]-2,3-diphenylindolizine-7-carbonitrile

Figure 9



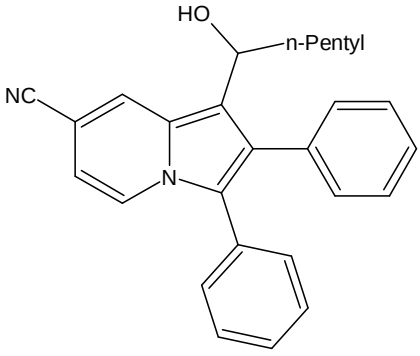
1-(1-Hydroxypentyl)-2, 3-diphenylindolizine-7-carbonitrile

Figure 10



1-(1-Hydroxy-3-methylbutyl)-2, 3-diphenylindolizine-7-carbonitrile

Figure 11



1-(1-hydroxyethyl)-2,3-diphenylindolizine-7-carbonitrile

Figure 12

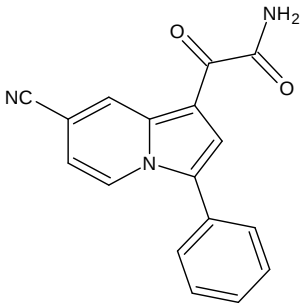
A.Hazra *et al.,* synthesized a new series of 3-Benzoyl-indolizine-2-carboxylic acid methyl ester derivatives and studied for their anti fungal activity. Antifungal studies were carried out against thirteen bacterial and four fungal strains. All the synthesized compounds showed dual antibacterial and antifungal efficacy.[27]

Anti cancer activity

D. A. James *et al.,* synthesized a class of indole - and indolizine-glyoxylamides derivatives and demonstrate their substantial in vitro anti-proliferative activities against cancer cell lines, including multidrug resistance (MDR) phenotypes. The in vitro cytotoxic effects have been demonstrated across a wide array of tumor types of various origins (e.g., breast, colon, uterine).

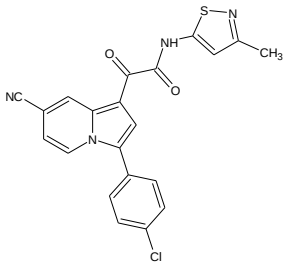
Li *et al.,*. have synthesized and studied a series of N-heterocyclic indolyl glyoxylamides and found compounds possessing activity against cancer cell lines including MDR cell lines. These compounds also showed significant in vivo activity in cancer models. These findings support the continued investigation of this class of compounds as anticancer agents.[28]

Bacher *et al.,* first reported the activity of D-24851 (now known as Indibulin) and its mechanism of action has been extensively studied. The mechanism of action was shown to be through the destabilization of microtubules in cancer cells but the tubulin binding site is not the same as the well-known vincristine and colchicines binding sites. It has also been reported that indibulin has activity against MDR cell lines, oral bioavailability, and no neurotoxicity.[29]



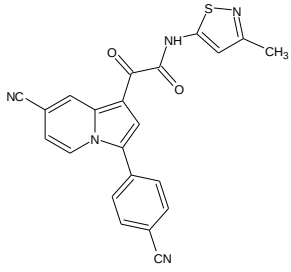
2-(7-cyano-3-phenylindolizin-1-yl)-2-oxoacetamide

Figure 13



2-[3-(4-chlorophenyl)-7-cyanoindolizin-1-yl]-*N*-(3-methylisothiazol-5-yl)-2-oxoacetamide

Figure 14

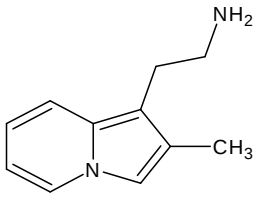


2-[7-cyano-3-(4-cyanophenyl)indolizin-1-yl]-*N*-(3-methylisothiazol-5-yl)-2-oxoacetamide

Figure 15

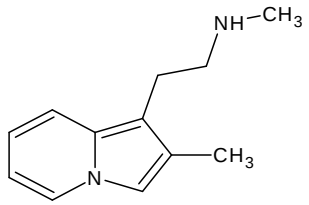
Anti-histamine and Central nervous system (CNS) depressant activities

Gian Mario *et al.,* have been synthesized 1-(2-aminoethyl)-2-methylindolizine and some N-alkyl derivatives. Preliminary pharmacological evaluation showed that these compounds exhibited anti-acetylcholine, anti-histamine and central nervous system (CNS) depressant activities.[30]



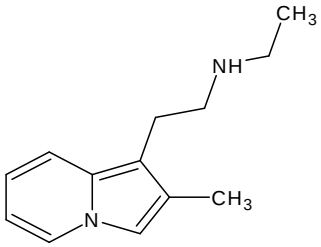
2-(2-methylindolizin-1-yl)ethanamine

Figure 16



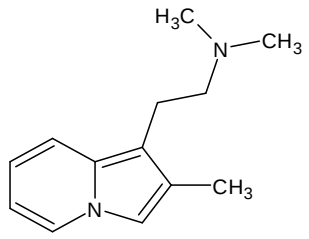
N-methyl-*N*-[2-(2-methylindolizin-1-yl)ethyl]amine

Figure 17



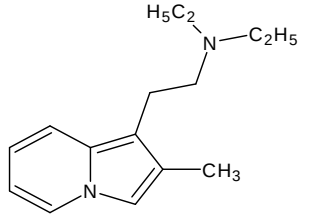
N-ethyl-*N*-[2-(2-methylindolizin-1-yl)ethyl]amine

Figure 18



N,*N*-dimethyl-*N*-[2-(2-methylindolizin-1-yl)ethyl]amine

Figure 19



N,*N*-diethyl-*N*-[2-(2-methylindolizin-1-yl)ethyl]amine

Figure 20

CURRENT ASPECT OF INDOLIZINE DERIVATIVES

Most of the synthesized compounds exhibited good activity against the studied set of microorganisms. Since a fewer species have been used in this study, it is warranted to screen these compounds with varied species and resistant strains. All the compounds showed very good antituberculars activity even at less concentration. Hence, it is evident that the substituted indolizine derivatives are potent candidates for extensive Antitubercular studies. The synthesized derivatives inhibited the growth of mycobacterium tuberculosis strain (H37RV) and shown good anti microbial activity against E.coli, P.aeruginosa, S.aureus and E.fecalis. Recently T.Weide *et al.,* synthesized a series of 3-substituted indolizine-1-carbonitrile derivatives and act as tyrosine phosphatase inhibitors (PTPs). The development of small-molecule inhibitors of PTPs is emerging only very recently as a rapidly growing area of investigation in clinical biology and medicinal chemistry. Therefore, PTP1b is currently a major target of medicinal chemistry research in the pharmaceutical industry.

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REFERENCES

1. William HB, Doerge RF, Mannich bases from 2-Phenylindolizines-I, J Pharm Sci., 56, 1967, 225-8.
2. Swinborne FJ, Hunt JH, Klinkert G., Adv Heterocyclic Chemistry, 23, 1978, 103-7.
3. Kalman RK, Doerge RF, p-substituted 1, 2-Diphenylindolizines as anti-inflammatory agents, J pharm Sci., 61, 1972, 949-51.
4. De AU, Saha BP, Indolizines II, search for potential oral hypoglycemic agents, J Pharm Sci., 64,1975, 249-52.
5. De AU, Saha BP., Search for potential oral hypoglycemic agents, J Pharm Sci., 62, 1973, 1897-8.
6. Jose B, Fake CS, Joiner GF, Kini FD, Miner WD, 5HT3 receptor antagonists, indazole and indolizine-3 carboxylic acid derivatives, J Med Chem., 30, 1987, 2317-9.
7. Ippolito A, Claudi F, Gulini U, Micossi L, Indolizine derivatives with biological activity for 3-(2-aminoethyl)-2-methylindolizine and their N-alkyl derivatives, J Pharm Sci., 68, 1979, 321-4.
8. William HB, Doerge RF., Mannich bases from 2-Phenylindolizines-II, J Pharm Sci, 56(9), 1967, 1200-2.
9. Jorgenson AS, Jacobsen P, Christiansen LB, Bury PS, Synthesis and estrogen binding activities of novel pyrrolo(2,1,5-cd)indolizine derivatives, Bioorg and Med Chem Lett., 10, 2000, 2383-6.
10. Dalhus B, Gundersen LL, Rise F, Bast A et al., Synthesis of 1-substituted-7-cyano-2,3-diphenylindolizines and evaluation of Antioxidant Properties, Eur J Org Chem., 37, 2003, 63-70.

11. Baidya M, Das AK., Synthesis and pharmacological screening of some indolizinamido glutamine derivatives, Ind J Het Chem., 9, 14, 2004, 81-2.
12. Mukerjee I, Das AK, Synthesis and antimicrobial activity of mannich bases of indolizine analogues, Orient J Chem., 2(22), 2006, 339-42.
13. Das AK, Som S., Synthesis and evaluation of some 3-benzoylindolizine-1- carboxamides as possible anti-inflammatory and analgesic agents, Orient J Chem. 2(22), 2006, 415-20.
14. P. Olejníkova, L. Birošová , L. Švorc, Antimicrobial and Antimutagenic Properties of Newly Synthesized Derivatives of Indolizine, Sci Pharm., 77, 2009, 216.
15. Wani MC, Nicholas AW, Wall ME. Plant antitumor agents, J Med Chem., 30, 1987, 2317-9.
16. Gunderson LL, Neguisse AH, Rise F., Mycobacterial activity of 1-Substituted indolizine, Archiv der pharmazie., 336, 2002, 191-5.
17. Flitsch, W. In Comprehensive Heterocyclic Chemistry, Katritzky, A. R., Rees, C.W., Eds., Pergamon Press, Oxford, 4, 1984, 443.
18. Daly, J W, Spande, T F. In Alkaloids Chemical and Biological Perspectives, S W, Ed., Wiley. New York, 1986, l-274.
19. Johnson, T. O.; Ermolieff, J, Jirousek, M. R. Protein tyrosine phosphatase 1B inhibitors for diabetes, Nat. Rev., Drug Discovery, , 1, 2002696.
20. Gundersen, Negussie, A.H., Rise, F., Synthesis of indolizine derivatives with selective antibacterial activity against Mycobacterium tuberculosis., European journal of pharmaceutical sciences, 30, 2007, 26–35.
21. Gundersen, L.-L., Malterud, K.E., Negussie, Indolizines as novel potent inhibitors of 15-lipoxygenase, Bioorg. Med. Chem., 11, 2003, 5409–5419.
22. Srikanth Lingala, Raghunandan Nerella, Ratnakar Cherukupally, Synthesis and comparative Anti-tubercular activity of Indolizine derivatives, International Journal of Pharmaceutical Sciences Review and Research., 6(2), 2011, 128-131.
23. A. Hazra, Mondal, Arindam Maity, Subhendu, 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, European Journal of Medicinal Chemistry, 2011, 1-9.
24. Hurst, J., Melton, T., Wibberley, D.G., A simple synthesis of *3*-deoxy-D-erythro-pentose, J. Chem.Soc., 1965, 3, 2948–2955.
25. P. Sharma, Kumar, Shikha, Studies on synthesis and evaluation of quantitative structure–activity relationship of 5-[(3-chloro-4,4-disubstituted-2-oxoazetidinyl)(N nitro) amino]-6-hydroxy-3-alkyl/aryl[1,3]-azaphospholo[1,5-a]pyridin-1-yl-phosphorusdichlorides., Bioorg. Med. Chem. Lett., 15, 2005, 937–943
26. Weide, Lars Arve, Heino, 3-Substituted indolizine-1-carbonitrile derivatives as phosphatase inhibitors, Bioorg. Med. Chem. Lett., 16, 2006, 59–63.
27. Lemke, T.L., Antiparasitic agents. In: Williams, D.A., Lemke, T.L. (Eds.), Foye's Principles of Medicinal Chemistry, 5th ed. Lipincott Williams and Wilkins, Philadelphia, 2002, 867.
28. D. A. James, Keizo, Hao Li, Guiqing, Zhiqiang, Indole- and indolizine-glyoxylamides displaying cytotoxicity against multidrug resistant cancer cell lines, Bioorg. Med. Chem. Lett., 18, 2008, 1784–1787.
29. Morita K, Yamamoto, Iwata H, Synthesis of indolizine derivatives, Biochem. Pharmacology, 22,1973, 111-5.
30. Gian Mario, Francesco and Fabrizio, Indolizine derivatives with biological activity, 1-(2-Aminoethyl)-2-methylindolizine and its N-alkyl derivatives, Eur. J. Med. Chem., 23, 1988, 291-294.

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