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Research Paper

SYNTHESIS, CHARACTERIZATION AND EVALUATION OF ANTICANCER ACTIVITY OF PHENANTHRIDINE DERIVATIVES

Sunita Purohit*, Raghvendra Singh Bhadauria, Gunjan Jadon, Awadh Kishor, MD Zeeshan

*Department of Pharmaceutical Chemistry, Shrinathji Institute of Pharmacy, Nathdwara, Raj. India

Phenanthridines are important class of heterocyclic compounds owing their presence in wide variety of alkaloids, pharmaceuticals and bioactive compounds.Compounds incorporating such motif possess various biological activities including antiprotozoal, antiviral, nematocidal, antitumor, antibacterial, antifungal and cytotoxic activities.Cancer and infectious diseases are major public health problems worldwide due to the continuous emergence of drug resistance. It is imperative to search for new antimicrobial and anticancer agents from a natural source that could either overcome or avoid the multi-drug resistance.The benzo[c]phenanthridine alkaloids have attracted much attention due to their broad bioactivities such as anticancer, antimicrobial, and anti-inflammatory activities. In view of diverse traditional uses and its attractive bioactive chemical compounds.Sanguinarine and chelerythrine are the best-known benzo[c]phenanthridine alkaloids, most frequently studied for their antitumor effects.The molecular mechanism of action of these compounds has been often attributed to inhibition of topoisomerases, which are also targeted by the related compounds nitidine and fagaronine.DNA damage induces various responses, including stabilization and activation of tumor suppressor protein.

KEY WORDS –Phenanthridine, dihydropyrrolo [1,2-f] phenanthridines, Sanguinarine.

INTRODUCTION

Heterocyclic rings have played an important role in medicinal chemistry, serving as key templates central to the development of numerous important therapeutic agents. The urgent requirement for discovery of potent novel drugs to treat the scourge of cancer and to tackle the looming issue of resistance to antibiotics is a big challenge for medicinal chemists for this endeavour to succeed, the development of novel class of compounds, with unique mechanism of action, as therapeutics is urgently required. Phenanthridines are an important class of nitrogenous heterocyclic compounds with extensive 40 applications in the realm of medicinal and material chemistry.Phenanthridines are the heterocyclic aromatic compounds containing three six membered ring structures with nitrogen atom. In recent years, phenanthridine derivatives with non-flat, three dimensional (3-D) skeletons have attracted great interest as a result of their interesting biological and medicinal assets.It is now well established that the complexity of a molecule can be correlated to its medicinal relevance, since molecules with 3-D scaffolds are presumed to more adequately fit into the 3-D active sites of the receptors of the target biopolymers.Many recently isolated, naturally

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occurring, biologically important alkaloids have been found to possess non-flat phenanthridine-like skeletons further highlighting the importance of such molecules. Moreover, many synthetic non-flat phenanthridine molecules like 5,6-dihydrophenanthridenes and 1,2,3,12b-tetrahydroimidazol [1,2-] phenanthridines have also been found to exhibit significant bioactivity such as anti-tumour, antibacterial, anti-leukemic, fungicidal and anti-HIV activities.Compounds containing phenanthridine nucleus at various levels of reduction occur widely in nature.

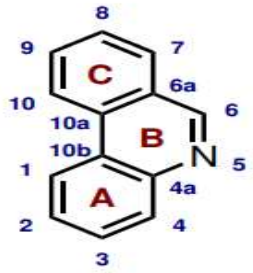

Figure 1: Structure of Phenanthridine

DOCKING

The completion of the human genome project has resulted in an increasing number of new therapeutic targets for drug discovery. At the same time, high-throughput protein purification, crystallography and nuclear magnetic resonance spectroscopy techniques have been developed and contributed to many structural details of proteins and protein–ligand complexes. These advances allow the computational strategies to permeate all aspects of drug discovery today, such as the virtual screening (VS) techniquesfor hit identification and methods for lead optimization. Compared with traditional experimental high-throughput screening (HTS), VS is a more direct and rational drug discovery approach and has the advantage of low cost and effective screening. VS can be classified into ligand-based and structure-based methods. When a set of active ligand molecules is known and little or no structural information is available for targets, the ligand-based methods, such as pharmacophore modeling and quantitative structure activity relationship (QSAR) methods can be employed. As to structure-based drug design, molecular docking is the most common method which has been widely used ever since the early 1980s. Programs based on different algorithms were developed to perform molecular docking studies, which have made docking an increasingly important tool in pharmaceutical research.The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behaviour of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as *pose*) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively.

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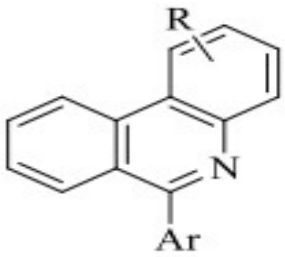
REVIEW OF LITERATURE

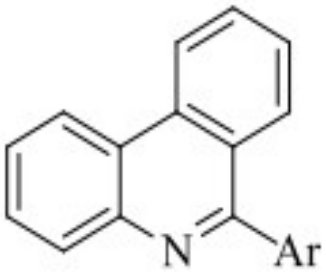
Wang et al. reported a cascade approach to 6-arylphenanthridine from aromatic aldehyde, aniline and benzenediazonium-2-carboxylate The in situ generated benzyne from benzenediazonium-2-carboxylate underwent a [4+2] cycloaddition reaction with the imine formed from aromatic amine and aldehyde to give dihydrophenanthridine. Finally, dehydrogenation in the reaction medium gave the 6-arylated phenanthridine in quantitative yields.



1.

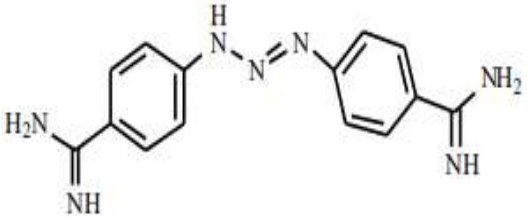
Pritchard and co-workers synthesis Palladium catalysed phenanthridine from imidoyl selenides This was the first report of palladium insertion into the C-Se bond. The palladium insertion into the imidoyl selenides followed by intramolecular cyclization and subsequent aromatization via the elimination of HSePh lead to the formation of substituted phenanthridines.

Mauro Cesar Isoldi, Maria Aparecida Visconti and Ana Maria de Lauro Castrucci studied Anti-Cancer Drugs: Molecular Mechanisms of Action,the advance in knowledge of intracellular



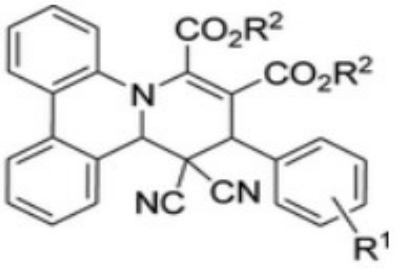
2.

biochemical alterations produced by malignant transformation has led man closer to the definitive control of cancer, by developing more efficient, less toxic and more specific drugs.



3.

Hossein mehrabi Synthesized Functionalized Pyrido[1,2-*f*] phenanthridines from Phenanthridine, Activated Acetylenes, and Arylidenemalononitriles, the zwitterions generated from phenanthiridine and dialkyl acetylenedicarboxylatesreact with a variety of arylidenemalononitriles, affording substituted pyrido[1,2-*f*] phenanthridines.



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AIM AND OBJECTIVE

In the pharmaceutical field, there has always been and will continue to be a need for new and novel chemical entities with diverse biological activities. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interesting compounds of widely different composition. We must always continue to search for drugs which exhibit clear advantages over the already existing respective drugs. Such advantages may be:

- A qualitative or quantitative improvement in activity,
- A partial or total absence of undesirable side effects,
- A lower toxicity,
- More nutritive value,
- Improved stability and
- A decrease in production cost.

PLANOFWORK

1. Synthetic Studies

Part A: Synthesis of 2-aminophenyl boronic acid

Part B: Synthesis of phenanthridine

Part C: Synthesis of Dihydropyrrolo [1-2f] Phenanthridine

2. Physicochemical Studies

Melting point determination

Thin layer chromatography (TLC)

Rotational and Vibrational absorption spectra (IR)

Nuclear Magnetic Resonance spectra (1H-NMR and 13C-NMR)

Elemental Analysis

3. Pharmacological Studies

Anticancer activity

SUMMARY AND CONCLUSION

In summary, an efficient, catalyst-free, multicomponent strategy for synthesis of 2-amino phenyl boronic acid, phenanthridine and dihydropyrrolo[1,2-f] phenanthridines was developed. These synthesized compounds were found to exhibit considerable in vitro anti-cancer and DNA cleavage activity. compound as a promising candidate with promising anticancer and DNA nuclease activity and the same would be further evaluated in the future against additional cancer cell lines animal models of cancer. Efficient, multi-component synthesis of dihydropyrrolo[1,2-f] phenanthridine derivatives in excellent yields, at room temperature using ethanol as a solvent. Aromatic or heterocyclic aldehydes, malononitrile, phenanthridine and tert butyl isocyanide were used as substrates for the reaction. The reaction was highly regio- and stereo-selective. Work-up procedure included only simple filtration and washing of the crude product residue leading to the isolation of highly purified products.

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