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REVIEW ON: B CARBOLINE AS AN POTENTIAL ANTINEOPLASTIC AGENT

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ABSTRACT

Cancer is the leading cause of death worldwide and places a significant strain on the healthcare system. Chemotherapy is one of the many treatment approaches that are crucial to addressing the difficulties of treating cancer, particularly when it is discovered at a late stage. Nonetheless, restrictions such severe side effects and drug resistance linked to current medications have spurred the creation of innovative chemotherapeutic medicines. Indole alkaloids with a tricyclic pyrido [3, 4-b] indole ring in their structure is known as b-carbolines. b-Carboline derivatives have established themselves as promising lead compounds for the synthesis of various anticancer active agents due to their widespread availability from natural sources, structural flexibility, quick reactivity, and interaction with varied anti-cancer targets such as DNA (intercalation, groove binding, etc.), enzymes (GPX4, topoisomerases, kinases, etc.), and proteins (tubulin, ABCG2/BRCP1, etc.). The synthesis and isolation, anticancer activity, mode of action, and surface area ratio (SAR) of different compounds containing b-carboline, as well as its derivatives and congeners, are covered in the current review.

KEYWORDS: b carboline, DNA topoisomerase, Peganum harmala, (Zygophillaceae, combilexin.

INTRODUCTION

Nowadays, cancer is one of the main causes of death and a major financial strain on the global healthcare system. It could be the result of environmental factors, genetic interferences, or a mix of the two. Out of over 100 distinct types of cancer, the most common types are colon, lung, breast, and prostate cancer. Another significant cause of death is cancer of the mouth and throat, which may be related to tobacco smoking. Natural goods, which are

incredibly diverse, are essential to human life and daily activities, including the treatment of health issues.[1]

Cancer treatment is one of the biggest medical challenges of our day. The World Health Organization (WHO) states that neoplastic disease is the primary cause of death worldwide in terms of mortality. breast, lung, colon, and rectal cancers were the most frequent cancer types.[2]

Many laboratories across the world are conducting extensive research initiatives to test plant extracts for anticancer potential. b Carbolines are a form of indole alkaloids that have an indole ring with a tricyclic pyrido structure. The primary method of classifying alkaloids, be they synthetic or natural, is based on the presence of a six-membered ring nitrogen. totally aromatic carbolines are the name for unsaturated carbolines, whereas dihydrocarbolines (DHCs) and tetrahydro carbolines (THCs) are the names for partially or totally saturated alkaloids.

Interestingly, compared to the comparable monomers, bivalent β-carboline alkaloids elicited significantly more bioactivity. Consequently, this indicates that bivalent chemicals ought to be the focus of future study due to their superior medicinal potential.[3]

The requirement for novel therapeutic agent

Combination therapy is the present state of cancer therapeutics since it prevents resistance from developing and outperforms single-drug therapy. Since cancer progenitor cells can induce remission and are frequently resistant to medications, eliminating them should be the next stage in the process of curing cancer.

It is essential to carry out more study to comprehend the fundamental causes of cancer drug resistance and to find treatments that can cure tumors without raising the risk of resistance.[4]

As a result of their inhibition of DNA topoisomerase, compounds have demonstrated encouraging anticancer effects. Twelve novel B carbolines hybrids were created, and eight of these compounds were chosen for further investigation based on their in vitro anticancer activity against sixty human sub-cancer cell lines from nine primary panels at NCI USA, as part of the drug discovery program. The compounds were tested at a single high dose.[5]

Because DNA is essential for cell division (replication) and maintenance (transcription), it is a primary target in cancer therapy. New chemical entities (NCEs) that target DNA can be exceptional examples of powerful chemotherapeutics. Beyond this, avoiding apoptosis is a distinctive feature of cancer that is becoming increasingly common, and as a result, substances that trigger apoptosis may one day become effective anticancer drugs. In light of these facts, research into the creation of new substances that target DNA and cause apoptosis is essential to the effective treatment of cancer.

The β-carboline alkaloids, which have a tricyclic pyrido indole ring structure, were naturally extracted from Peganum harmala (Zygophillaceae) seeds. In addition to their anticancer activity, these alkaloids were reported to have pharmacological and therapeutic qualities, such as anti-Alzheimer, anticonvulsant, antifungal, antibacterial, Anti plasmodial, antiviral, antiplatelet, and ant mutagenic activities.[6]

Carboline sourced from ocean

Some prospective anticancer lead compounds have been found in marine organisms, which are major natural sources. The ascidian Eudistoma olivaceous from the Caribbean was discovered to be a rich source of b-carbolines and eudistomins A-Q that are biologically active. Ritterella sigillinoides, an ascidian from New Zealand, was isolated and its eudistomins K biologically active and tested for anticancer activity against L1210, A549, HCT-8, and P388 cell lines.[4]

Cell Culture and Cell lines

The American Type Culture Collection ATCC (Manassas, Virginia, USA) provided the human non-small-cell lung cancer (NSCLC) cell line NCI-H460, the human breast cancer cell line T47D, and the human colorectal carcinoma cell line HCT-116. The cells were cultured at 37 °C in a humid environment with 5% CO2 and 95% air, supplemented with 10% (v/v) heat-inactivated fetal bovine serum, 2 mM glutamine, 10 mM HEPES buffer (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), 100 U/ml streptomycin, and 100 U/ml penicillin. 1106 cells were planted into fresh flasks after the cells were removed for subculturing using a 0.25% trypsin-EDTA (ethylenediamine tetra-acetic acid) solution.[7]

Agents that target dna

Intercalating agent

Numerous studies have demonstrated the biological and pharmacological effects of b-carbolines in both prokaryotic and eukaryotic cells. These effects are attributed to the drugs' capacity for DNA intercalation, which can modify the enzymatic activity involved in DNA repair processes or influence DNA replication.

Inhibitors of topoisomerase

The production of podophyllotoxin-linked b carboline congeners as possible DNA topoisomerase II inhibitors and anticancer medicines.

Bilexins The molecules in the combilexin class have dual mode DNA binding characteristics, meaning that they can bind to both DNA intercalation and minor grooves. These compounds may exhibit great selectivity and enhanced DNA binding affinity as a result of this bimodal mechanism.

Kinases as the intended target

Protein kinases use ATP to phosphorylate amino acids, which modifies a protein's structure and makes it active. This process controls the biological activity of proteins. Because kinases are essential for controlling a number of cellular processes, including apoptosis, cell motility, DNA damage and repair, and proliferation, they can occasionally operate as oncogenes. For this reason, protein kinase inhibitors are interesting candidates for cancer treatment.

Ferroptotic agent

The iron-dependent, programmed cell death known as ferroptosis is primarily identified by the build-up of lipid peroxides. Synthetic lethal screening was used to identify RSL3 as a potent inducer of ferroptosis, with an IC50 value of 0.02 mM for Calu-1 cells and 2 mM for BJeLR cells.[4]

Studies on dna-topo i inhibition

It has been determined that Topo I may be the target of various anticancer medications now in clinical use. Since topo I is involved in the processes of replication and proliferation, cancer cells have been shown to produce more topo I than normal cells. During a typical cell cycle, topo I generally cuts single-stranded DNA and rejoins the phosphate backbone to regulate changes in the structure of DNA. There are two known mechanisms by which topo I

inhibition occurs. The inhibitors can either attach to DNA directly and change its structure so that topo I is unable to identify it, or they can bind to DNA and change its structure.[8]

Compounds are used in cancer chemoprevention to either stop the growth of cancer cells or change the carcinogenic process.[9]

The β-carboline and three-cyclic tetrahydro-β-carboline (THBC) ring system is a fundamental structural component in medicinal chemistry, revealing a variety of pharmacologically significant alkaloids that are extracted from a variety of natural sources.[10]

The ways in which β-carboline works

β-carboline compounds use a variety of methods to demonstrate their anticancer properties. They primarily work by blocking DNA topoisomerases and cyclin-dependent kinases (CDKs) through DNA intercalation. Cytochrome P450, monoamine oxidase A, mitogen activated protein kinase-activated protein kinase 2 (MK-2), polo like kinase-1 (PLK1), IκK (IκB kinase complex), kinesin Eg5, dual enzyme tyrosine phosphorylated and regulated kinase, benzodiazepine, serotonin, dopamine, and imidazoline receptors are additional targets that have been reported to be involved.[11]

The alkaloid β-carboline and anthraquinone molecules have been identified for their intriguing biological properties, such as their ability to reduce inflammation.[12]

The cytotoxic activities of β-carboline nucleus were increased by substituting suitable substituents at position-9; the regulation of cytotoxic potencies was mostly dependent on the N2-benzyl substituent on the β-carboline core.[13]

Most bioactive metal complexes are generally thought to have DNA as their main target. The discovery of molecular directing metal complexes towards enzymes or protein-protein interactions has garnered a lot of attention.[14]

b-carbolines bind to CDK directly and stop the kinase activity. Numerous compounds of b-carboline cause multi-phase cell cycle arrest in a way that is concentration dependent.[15]

It is now necessary to create novel anticancer agents due to the ineffectiveness of current chemotherapy and its negative side effects.[16]

B-carbolines that fight cancer and target several biological targets b-carboline-combretastatin carboxamide conjugates and assessed their anticancer efficacy in order to investigate a novel class of cytotoxic medicines. Using many tumor cell lines, including HeLa, DU-145, and A-549, all of the synthesized compounds were examined for their cytotoxic potential using the SRB test. Etoposide and harmine were employed as positive controls.

All of the compounds had IC50 values between 1.01 and 50 Mm, indicating moderate to good activity.

Certain bcarboline derivatives, such as N-methylated b-carbolines, have the potential to be endogenous neurotoxins, while their N-nitroso derivatives have the ability to be endogenous mutagens and carcinogens. B-carboline alkaloids, both endogenous and exogenous, are constantly present in human bodies. Therefore, it is crucial to research how to address these elements in terms of their pharmacological and biological activities, and we should bear this in mind when developing new drugs in order to minimize their negative effects.[4]

Analysis of the cell cycle

The cell cycle, which is often split into four phases: DNA synthesis (S phase), mitosis (M phase), and G1 and G2 with differing length gaps, regulates the change from quiescence to cell proliferation.

Carcinogenesis is the term commonly used to explain disruptions in the cell cycle. One of the primary methods of treating cancer is the inhibition of the tumor cell cycle. Researchers were motivated to conduct additional research after β-carbolines exhibiting anticancer efficacy, including harmane, harmine, harmaline, and callophycin. Research findings indicated that β-carbolines had anticancer efficacy via multiple mechanisms, such as DNA insertion, inhibition of topoisomerases I and II, halting cell mitosis, and so forth.[17]

CONCLUSIONS

A synopsis of b-carboline's biological activity has been given in this review. The biological processes and structural-activity correlations of b carboline compounds have also been covered. A highly significant class of pharmacologically active moiety with a broad range of anticancer action via several mechanisms is b-carboline. When developing b-carbolines as chemotherapeutics, the main goals were to minimize undesirable side effects and resistance

development while also improving potency and stabilizing the pharmacokinetic profile and metabolism.

There have been reports of evidence indicating the widespread occurrence of b-carbolines and their derivatives in nature.

Additionally, b-carboline alkaloids, which are present in cooked meals, tobacco smoke, and plants that are used as drugs and hallucinogens, are constantly present in the environment.

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