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Review Article

Carbazole derivatives: an attractive scaffold in anticancer lead discovery.

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ABSTRACT

Cancer is one of the leading chronic diseases with a high mortality rate worldwide. Current statistical studies on cancer estimates from the World Health Organization (WHO) in 2020, cancer is the first or second leading cause of death. Although cancer remains a devastating diagnosis, several decades of preclinical progress in cancer biology and biotechnology have recently led to the successful development of several biological agents that substantially improve survival and quality of life for some patients. For over half a century, the carbazole skeleton has been the key structural motif of many biologically active compounds including natural and synthetic products. Carbazoles have taken an important part in all the existing anti-cancer drugs because of their discovery in a large variety of organisms, including bacteria, fungi, plants, and animals. Several natural or synthetic polycyclic molecules with carbazolic nuclei, which show attractive anticancer properties were approved, and their biological activities and their specificity, obtaining cytotoxic agents effective in a panel of various cancer cell lines. The most described carbazole anti-tumor agents were classified according to their structure, starting from the tricyclic–carbazole motif to fused tetra-, penta-, hexa- and heptacyclic carbazoles. This review also highlights the key advancements of Carbazole and its derivatives for cancer therapy and exploration of emerging directions in clinical development that have the potential to impact clinical care in the future in search of cancer therapy.

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INTRODUCTION

The heterocycles are inextricably tied to the periods of life [1]. The role of heterocycles in the production of molecules or drugs is a critical area of medicinal chemistry/Pharmaceutical chemistry [2]. There are several heterocyclic compounds with biological activity, including vincristine, morphine, chloroquine, meperidine, and sulfadiazine. Overages of the history of organic synthesis, heterocyclic sulfur, and nitrogen compounds have piqued chemists' curiosity [3-4]. Carbazole is a heterocyclic aromatic chemical molecule. It is tricyclic in structure, with two 6-membered benzene rings connected on each side by a five-membered nitrogen-containing ring. Carbazole and its derivatives are a sizable family of heterocyclic nitrogen compounds that are often found in nature (Figure 1) [5].

Figure 1 illustrates the numerous carbazole groups and these are found in a range of naturally occurring medicinal active compounds [6], e.g., carbazomycins and murrayafoline A. Series of carbazole derivativesand N-substituted carbazoles have been synthesized (oxazinocarbazoles, isoxazolocarbazolequinone, pyrido-carbazolequinone, tetrahydro carbazoles, benzocarbazoles furo - carbazoles

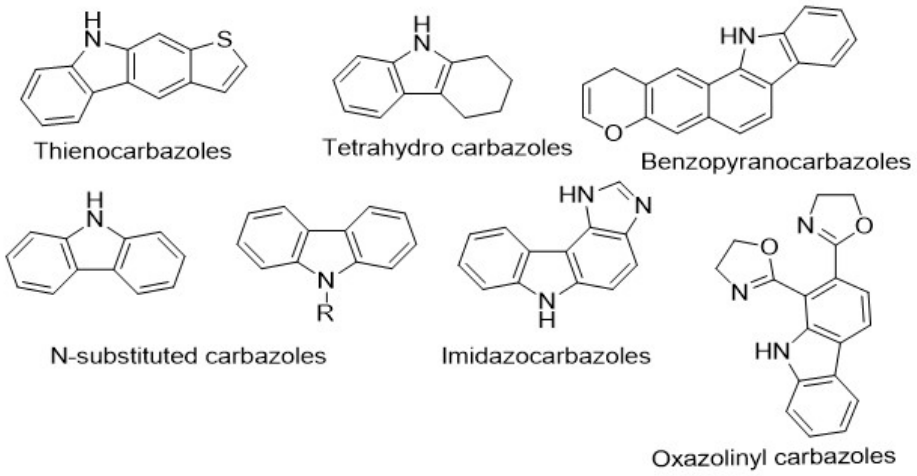

Figure 1. Structures of Various Classes of Carbazoles.

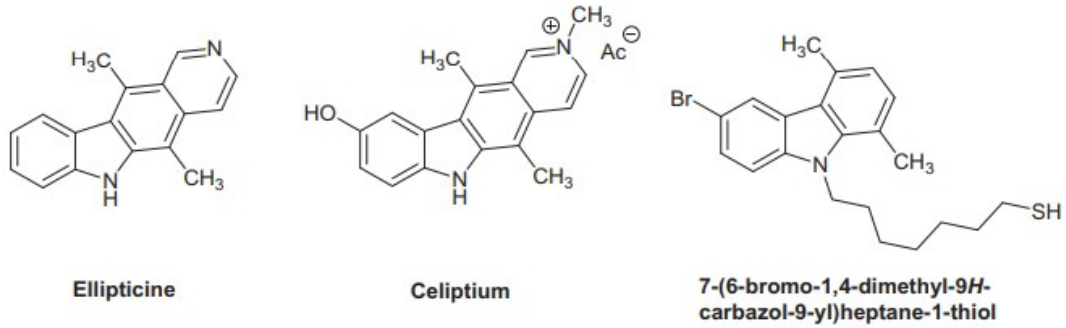

Figure 2. Chemical structures of ellipticine, elliptinium acetate (*Celiptium* VR) and a 6-bromo derivative of carbazole.

pyridocarbazoles, pyrrolo-carbazoles. indolocarbazoles oxazolinyl carbazoles thienocarbazoles, imidazocarbazoles, thiazolocarbazoles, benzopyrano-carbazoles, benzofurano-carbazoles and are well known for their various therapeutical actions such as antioxidant, anti-inflammatory, antibacterial, antitumor, anticonvulsant, antipsychotic, antidiabetic, larvicidal properties, etc. The current study focuses on the pharmacological activities of carbazole and conceptualizes the potency of N-substituted carbazole [7, 8, 9, 10].

Cancer is the leading cause of morbidity and mortality globally. About 10 million deaths were reported in 2020. The new cases of cancer were Lung carcinomas (2.21 million), Breast cancer (2.26 million), Colorectal cancer (1.93 million), prostate cancer (1.41 million), non-melanoma skin cancer (1.20 million), and gastric cancer (1.09 million) are reported worldwide in the year 2020 [11, 12]. Cancer is a chronic problem that is rapidly expanding in the 21st era and is estimated to influence more than 22 million individuals by 2030 [13, 14]. In apoptosis, triggers of caspases (cysteine-aspartic proteases, cysteine aspartases, or cysteine-dependent aspartate-directed proteases) lead to intercellular activation of target substrates [15]. The ability to promise drug targets in chemotherapy rapidly proliferates cells during cell division, thus these novel agents might also target normal cells that grow quickly like those in the hair follicles, gastrointestinal tract, and bone marrow along with cancer cells. Attributable to this, some characteristic outcomes occur, along with loss of hairs, canal distress, and less white blood corpuscle count [16, 17, 18].

Carbazole derivatives

Many carbazole derivatives and related compounds have been studied. More interestingly, three derivatives have obtained marketing authorization with anti-cancer drug status in different countries. Ellipticine, which was discovered in 1959 (Figure 2) [19].

The third derivative recently approved in 2017 by the FDA [20] and the EMA [21] is midostaurin (Novartis), described mainly as the first fms-like tyrosine kinase 3 (FLT3) inhibitor for newly diagnosed acute myeloid leukemia (AML) and for advanced systemic mastocytosis [22, 23].

Compared to the previously recent published reviews, we focused this article on the carbazole derivatives exerting anti-tumour activity reported from 2012 to

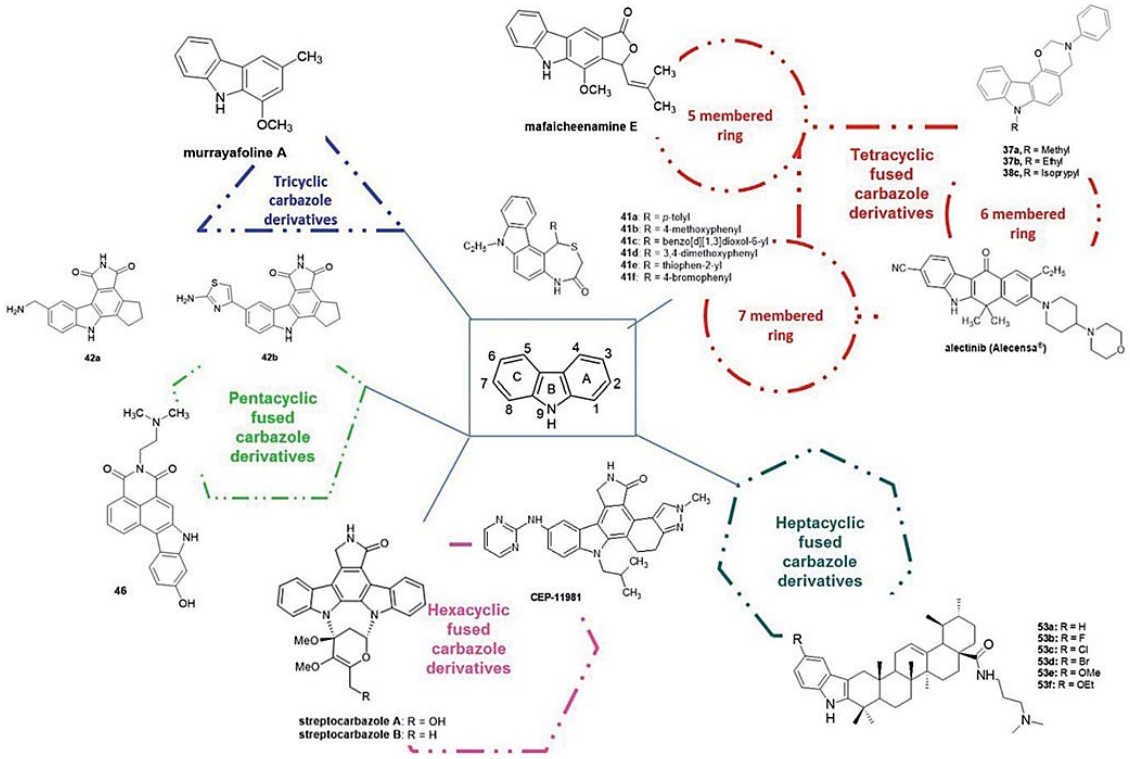

Figure 3. Main frameworks of biologically active carbazole alkaloids.

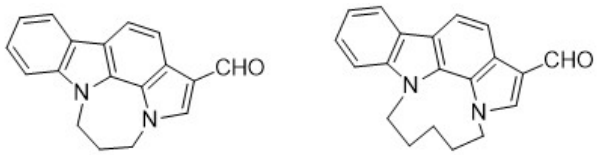

Figure 4. Structures of N1-N10 bridged pyrrolo-carbazoles.

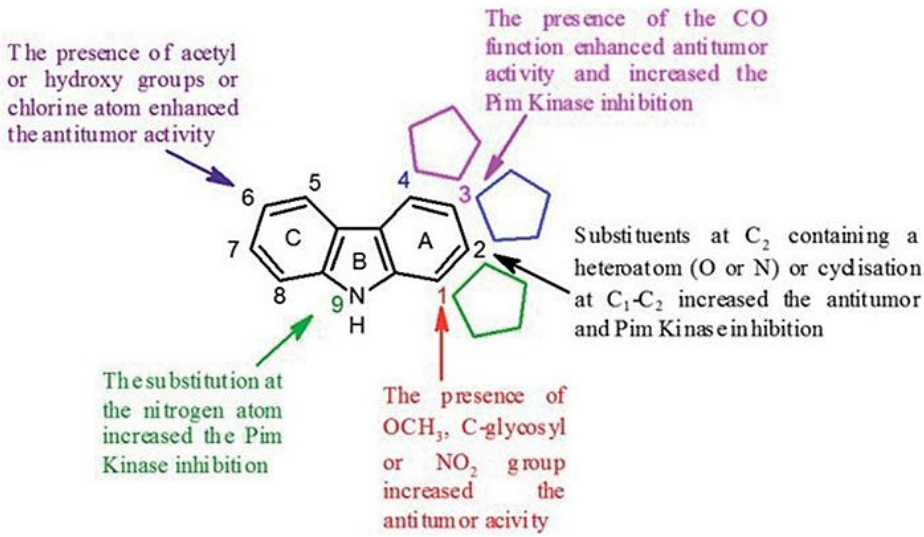

Figure 5. SAR study of tetracyclic carbazoles containing a 5-membered ring.

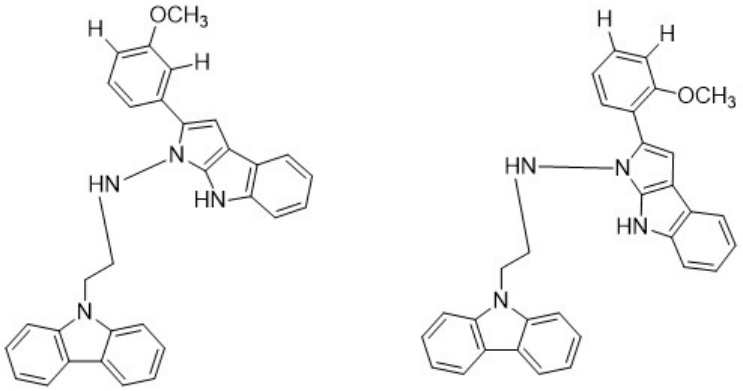

Figure 6. Structures of hydrazinoacetyl carbazoles.

to 2018, and we critically collected the most significant data. The term "carbazole" includes both the tricyclic molecular skeleton and diverse fused carbazoles including tetracyclic (with 5-, 6- and 7-membered rings), pentacy clic, hexacyclic and finally heptacyclic fused carbazoles (Figure 3). Several databases, bibliographic information (articles) from namely ScienceDirect, Scifinder, Pubmed and Web of Science as well as technological (patents) information from INPI Patents Database, European Patent Office (EPO), as well as the World Intellectual Property Organization (WIPO), were used as literature sources. The increased interest in the use of carbazole derivatives for the cancer therapy can also be expressed in the research of patents.

Pim-kinases assay a variety of proteins involved in critical biological processes such as cell cycle progression and apoptosis. It has been shown that overexpression of PIM-kinase results in carcinogenesis in human leukemia and lymphoma. Additionally, pim-kinases are recognized to be crucial targets for the development of novel anticancer drugs. Akue-Ge produced a series of carbazoles replaced with N. Giraud et al. produced pyrrolo-carbazoles derivatives.

The capacity of these drugs to suppress pim-kinases has been determined. The chemicals and showed significant activity against the IPC-81 cell line of acute myeloid leukemia, which is an excellent predictor of leukemia, with nanomolar inhibitory capabilities (Figure 4).

A study found that P7C3 also protects mature neurons in brain regions outside of the hippocampus. P7C3 blocks 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mediated cell death of dopaminergic neurons in the substantia nigra of adult mice, a model of Parkinson's disease (PD). Dose-response studies demonstrates that the P7C3 analog P7C3A20 blocks cell death with even greater potency and efficacy, which parallels the relative potency and efficacy of these agents in blocking apoptosis of newborn neural precursor cells of the dentate gyrus. P7C3 and P7C3A20 display similar relative effects in blocking 1-methyl-4-phenylpyridinium (MPP(+))-mediated death of dopaminergic neurons in Caenorhabditis elegans, as well as in preserving C. elegans mobility following MPP(+) exposure. In-vivo screening assay also protects dopaminergic neurons of the substantia nigra following exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a mouse model of Parkinson's disease. Here, we provide evidence that an active analog of P7C3, known as P7C3A20, protects ventral horn spinal cord motor neurons from cell death in the G93A-SOD1 mutant mouse model of amyotrophic lateral sclerosis (ALS). The detailed SAR study of tetracyclic carbazoles is expressed in figure 5.

The anticancer activity of Compound (34, 35) produced by Kumar et al. was evaluated in cell laryngeal lines (HEP2) and Ehrlich's Ascites Carcinoma (EAC) cells. The chemicals were discovered to be effective against tumor cell lines (Figure 6). The reason behind this can be linked with EDG which enhances the fundamental properties of the molecule.

CONCLUSION

Carbazole derivatives exhibited potential antiproliferative activity against different cancer cell lines by diverse mechanisms, inclusive of arresting cell cycle and inducing apoptosis, and several anticancer agents are carbazole-based compounds. Thus, carbazole derivatives represent a fertile source for the discovery of novel anticancer therapeutic agents. Over the past numerous years, various carbazole hybrids have been developed as potential anticancer agents. The present review focuses on the recent progress, from 2016 until now, in the knowledge of anticancer properties, structure-activity relationships, and mechanisms of action of carbazole hybrids to provide a basis for the development of relevant therapeutic agents.

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