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Biological Potentials of Carbazole Derivatives: A Review

Babita Kumari[1], Sucheta[1*], Arpana Rana [2], Sheo Mohan Singh[3], Abhijit Debnath[4]

[1] School of Medical and Allied Sciences, K.R. Mangalam University, Sohna - Gurugram, Haryana 122103 ,
[2]Advanced Institute of Pharmacy, Palwal, Haryana, India
[3]International Center for Stem Cells, Cancer and Biotechnology (ICSCCB) New Delhi, India
[4]Noida Institute of Engineering and Technology (Pharmacy Institute), NIET Pharmacy Institute, Greater Noida,Uttar Pradesh, India

Corresponding author

Dr. Sucheta
Associate Professor
KR Mangalam University,
Sohna - Gurgaon Rd, Gurugram,
Sohna Rural, Haryana 122103
Contact: Sucheta568@gmail.com

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Abstract:

The carbazole framework serves as a pivotal structural element in numerous biologically active compounds, both synthetic and natural. Its wide array of biological activities and therapeutic applications has garnered considerable attention in research circles. Carbazole stands out as a promising base material for the synthesis of innovative drugs, given its strong pharmacophoric features and ring structure. Consequently, there's a burgeoning interest in crafting various carbazole derivatives as potential candidates for improved drug therapies across different diseases. This review offers a fresh approach for scientists to investigate this nucleus's possibility and create a new class of medications with improved therapeutic characteristics. Emphasizing the pharmacological activities of carbazole already documented by researchers, this review serves to consolidate existing knowledge and spur further advancements in diverse fields. Finally, this work provides a means by which scientists might design and create carbazole compounds with intriguing pharmacological properties.

Keywords: Carbazole, Carbazole derivatives, Antimicrobial, Antiepileptic, Anticancer

Introduction:

Carbazole is classified as a heterocyclic molecule that contains nitrogen. It has a tricyclic structure with two benzene rings connected by a five-membered ring on both sides that contains nitrogen. Many naturally produced biologically active substances, such as murrayafoline A and carbazomycins, contain the carbazole ring. Several carbazole derivatives have been synthesized, including furo-carbazoles, thiazolocarbazoles, thienocarbazoles, imidazocarbazoles, pyridocarbazoles, benzocarbazoles, oxazinocarbazoles, benzofurano-carbazoles, tetrahydrocarbazoles, pyrrolocarbazoles, oxazolinylcarbazoles, indolocarbazoles, benzopyrano-carbazoles, and N-substituted carbazoles. Carbazole derivatives have garnered significant attention in research due to their extensive versatility. They serve as promising candidates for drug development aimed at treating a variety of diseases. Derivatives of carbazoles show a variety of pharmacological properties, such as anti-inflammatory, antiprotozoal, antibacterial, anti-histaminic, antioxidant, anti-tubercular, anti-epileptic, hepatoprotective, antifungal, anti-HIV, anti-cancer and sedative properties. Additionally, they possess the ability to inhibit topoisomerase II, further augmenting their therapeutic potential [1-2]. Carbazole derivatives serve as crucial intermediates in the synthesis of numerous compounds and serve as foundational materials for development of new drug. The versatility of carbazole enables the formation of various derivatives possessing intriguing biological properties, attributed to the presence of pharmacophoric moieties. Several carbazole-based medications are commercially marketed, including ollivacine, ellipticine, alectinib, celiptium and datelliptium among others [1].

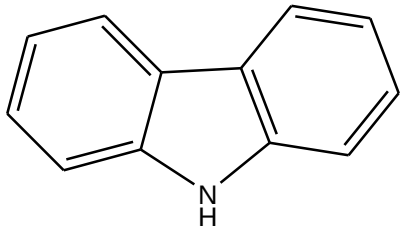


Figure 1: Carbazole

Biological Potentials of Carbazole Derivatives

Antimicrobial potential

The carbazole ring is a structural motif seen in a variety of naturally occurring pharmaceutical compounds. The carbazole skeleton has recently been used to create macrocyclic diamides containing thia- and oxy-linkage systems. These compounds represent novel structural elements with potential biological significance. A recent study assessed the antibacterial and antifungal activities of six novel compounds with similar structural characteristics. Salmonella typhi, Staphylococcus aureus, Proteus vulgaris, and Proteus mirabilis were the four human pathogenic bacteria used to evaluate the antibacterial activity of these substances [1]. A number of N-substituted carbazoles were examined to determine their antifungal and antibacterial properties. Adding a 1,2,4-triazole moiety to carbazoles was found to increase their antifungal activity against Candida albicans, with a MIC of 2 to 4 μg/mL. Moreover, it was noted that the presence

of an imidazole moiety enhanced the antibacterial efficacy against a variety of strains, including Bacillus subtilis, Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli, and methicillin-resistant Staphylococcus aureus, with MIC ranging from 1 to 8 µg/mL. Additionally, the carbazole triazolium molecule, which is the quaternization product of triazole, demonstrated exceptional antifungal and antibacterial activity against all tested microorganisms, with MIC values ranging from 1 to 64 µg/mL. sulphonamides [9-(substituted phenyl-sulphonyl)-4-(oxiran-2yl-methoxy)-9H-carbazole] and N-substituted carbamates were synthesized and evaluated for antibacterial and antifungal potential [3].

Numerous compounds showed significant antifungal and antibacterial properties against Bacillus subtilis, Escherichia coli, and Aspergillus niger as well as against Candida albicans and Fusarium oxysporium. At a dose i.e 100 µg/mL, the compounds exhibited zones of inhibition with a diameter ranging from 12.6 to 22.3 mm, indicating high antibacterial activity [4]. The synthesis and investigation of N9-(hydrazinoacetyl)-carbazoles revealed their possible antibacterial action.These include 1-carbazole-9-yl-2-(4-nitro-phenyl)-4,5-diphenyl-1H-1-yl-amino)-ethanone and 1-carbazole-9-yl-2-(substituted phenyl), which are probazole derivatives with imidazole and indole-imidazole moieties.[4,5-b] the 1,4-dihydroimidazole compound indol-1-ylEspecially efficient against Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae, and Escherichia coli were ethanones. These substances demonstrated zones of inhibition with diameters between 10.4 and 15.3 mm and minimum inhibitory concentrations (MIC) between 6.2 and 50 µg/mL, indicating their potential as strong antibacterial agents [5]. One compound called Incentrom A may be useful in locating chromosome-specific yeast growth inhibitors. This is an opportunity to create innovative antifungal medication formulations. Its mechanism of action depends on how it interacts with specific chromosomal structures called kinetochores (protein complexes) and centromeres (DNA segments), which are essential for chromosome segregation [1]. A million people succumb to malaria every year, making it one of the deadliest parasite infections. Plasmodium parasites are responsible for the spread of malaria. Variants of Plasmodium falciparum are among of the deadliest parasites. Certain raw root extracts from the Clausena harmandiana plant, however, exhibit antiplasmodial qualities against these strains. This activity is due to the carbazole component present in the extracts.

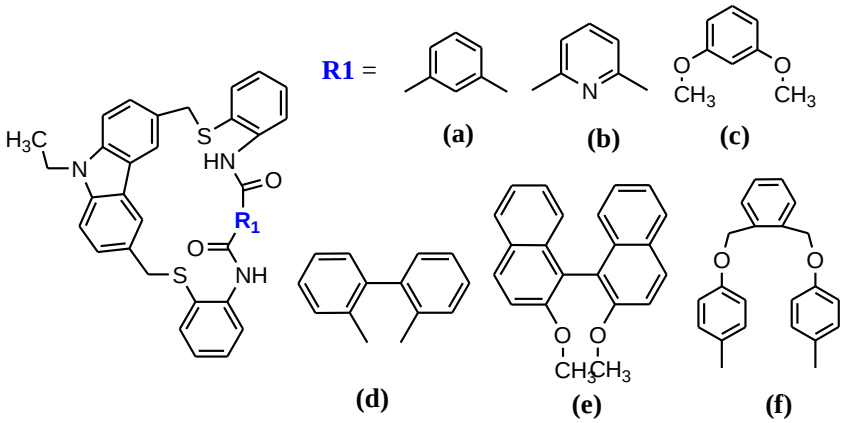


Figure 2: Structures of carbazolophanes (a-f)

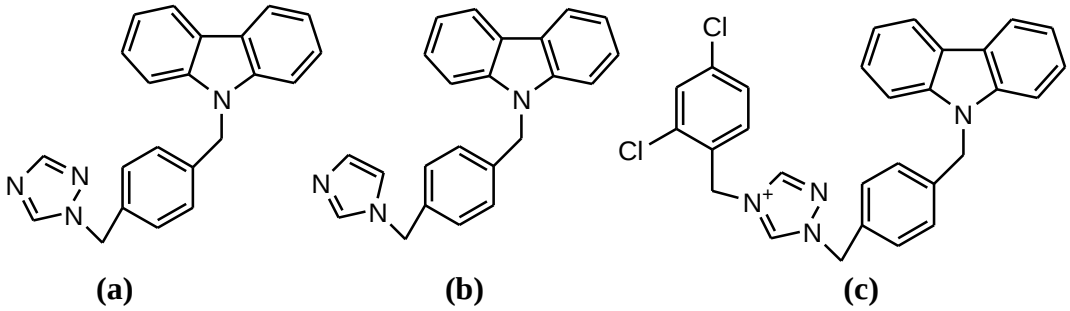


Figure 3: Structures of imidazole and triazole carbazoles (a-c)

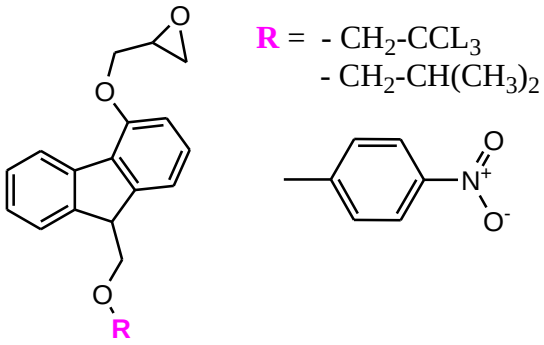


Figure 4: Structures of carbamate carbazoles

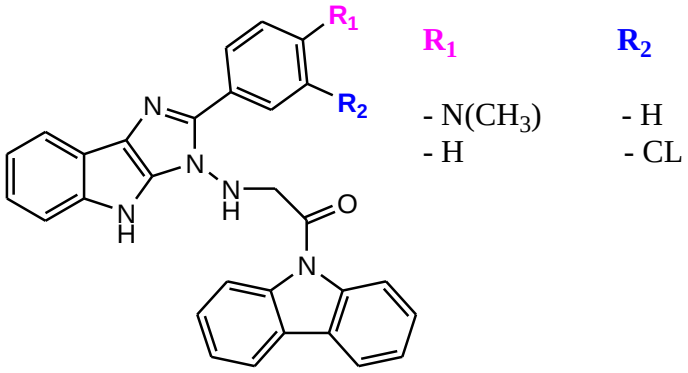


Figure 5: Structures of hydrazinoacetyl carbazoles

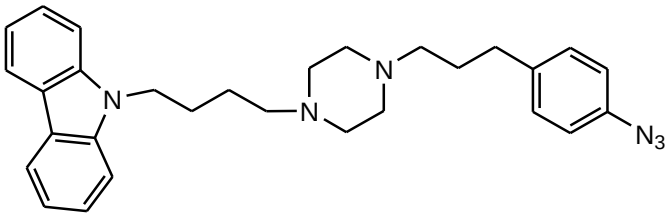


Figure 6: Structure of Incentrom A

Neurological disorders

Neural stem cells (NSCs) have the ability to differentiate into various nervous system cells, including neurons and glial cells, owing to their multipotency. NSCs provide wounded or dysfunctional cells with food and protection in addition to their capacity for differentiation. They have the ability to migrate, moving to far-off locations where they have been injured. Moreover, NSCs promote endothelial cells' and astrocytes' increased release of SDF-1 in injured tissues, which facilitates the healing process.

In terms of central nervous system (CNS) regeneration and repair, mammals have a limited potential. In adult mammals, neurogenesis primarily occurs in two areas: the subventricular zone (SVZ), which borders the lateral ventricles of the brain, and the subgranular zone (SGZ) of the dentate gyrus, which is located in the hippocampus. Because neural stem cells (NSCs) continue to undergo neurogenesis throughout adulthood, using them to treat neurological disorders including Parkinson's illness, multiple sclerosis, and Alzheimer's syndrome is a promising idea. Nevertheless, despite this promise, NSC clinical applications have not yet produced positive results. Using chemical or genetic therapies to promote endogenous neurogenesis and neuroprotection is another strategy. In addition to their therapeutic potential as innovative treatment options, small compounds that can either slow down neuronal death or promote neurogenesis and neuroprotection are of great interest because they are useful tools for understanding the mechanisms underlying neurogenesis. A neurological disorder called Alzheimer's disease (AD) progressively weakens the central nervous system. It manifests as dementia, noticeable behavioral anomalies that are often linked to cortical shrinkage, and a progressive loss of cognitive ability. As of right now, there are no drugs that can stop or reverse the disease's course. The main goal of pharmacological therapies is to reduce the symptoms of cognitive decline and memory impairment. Alzheimer's disease (AD) affects more than 35 million people worldwide and is currently on the rise in those 65 years of age and above. Many factors, such as abnormal tau protein phosphorylation, dysfunction of beta-amyloid protein metabolism, disruption of cholinergic function, and the involvement of oxidative stress and inflammatory processes, are strongly linked to the pathophysiology of AD. According to a well recognized notion, beta-amyloid (Ab) peptides more especially, those with 40 and 42 residues—that are produced when the amyloid precursor protein is cleaved are essential for the onset and course of Alzheimer's disease. Alzheimer's disease (AD) has been linked to the aggregation of monomeric beta-amyloid (Ab) peptides into insoluble plaques, also called senile plaques, which cause neuronal cell death. These plaques build up on blood vessel walls as well as in brain tissue at the microscopic level. The digestive enzymes beta-secretase and gamma-secretase successively break down the amyloid precursor protein (APP) to create Ab peptides. In particular, a crucial step in the release of these Ab isoforms is catalyzed by the gamma-secretase complex. There is possibility for preventing AD by focusing on this mechanism. In recent years, tremendous progress has been made in the development of effective beta-sheet breakers and formation of fibrils inhibitors that can stop beta-amyloid (Ab) monomers from aggregating into oligomeric and fibrillar structures. These compounds must exhibit permeability across the blood-brain barrier (BBB), minimal neurotoxicity, and good stability in vivo in order to be considered

clinically viable. Among the substances studied, a carbazole derivative proved a noteworthy inhibitor of the production of Alzheimer's beta-amyloid fibrils [1].

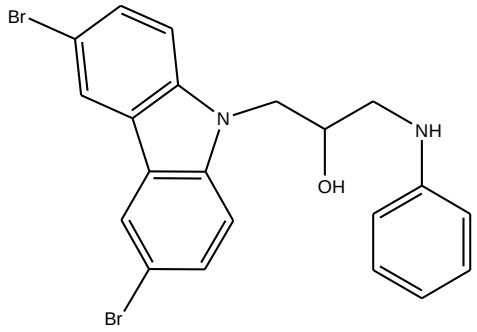


Figure 7: Structure of aminopropyl carbazole P7C3

Anti-Epileptic and Antinociceptive Activities

The most prevalent neurological condition, epilepsy is characterized by episodes of excessive, fleeting neuronal discharges. It is predicted to impact up to 50 million people globally, or 1.0% of the population. According to recent studies, a significant portion of patients on anti-epileptic medications show resistance to available treatment options. Because of this, scientists are working to find substances that are both more powerful and less hazardous in order to treat seizures and enhance patients' quality of life. Introduced and evaluated for their analgesic and anticonvulsive qualities, N-substituted carbazoles have demonstrated promise. The derivative 2-(2,3-dimethyl-phenyl)-amino-benzoic acid may have been the origin of one particular molecule's strong antiepileptic potential at a dose of 20 mg/kg. Moreover, analgesic effects of these substances have been identified [6].

Anticancer activity

Over the past few decades, cancer has become one of the most concerning diseases in the world. Pim kinases regulate many proteins connected to significant biological processes like the advancement of cell cycles and apoptosis, a process that is a type of programmed cell death that occurs in multicellular organisms. This includes abnormal cells proliferating and invading the body without control, which results in the development of tumors.. The Moloney murine leukemia virus's proviral integration site is located in Pim. Pim kinases have been observed to be overexpressed in human colon, pancreatic, lymphoma, prostate, and leukemia malignancies; these findings imply a role for Pim kinases in carcinogenesis. These results suggest that Pim kinases are valuable targets for the development of novel anticancer medications [7]. N-substituted pyrrolocarbazoles have remarkable efficacy as inhibitors of Pim kinase activity, as seen by their IC50 values, which span from 46 to 75 nM. Additionally, these compounds demonstrate potent antiproliferative activity, as demonstrated by their ability to effectively impede the growth of the following human cancer cell lines: PC3, DU145 (prostatic carcinoma), and PA1 (ovarian carcinoma). Their MIC values, which vary from 8 to 20 μM, emphasize their potential as potential medications against the proliferation of cancer cells [8]**.** Many compounds

such as 1-carbazole-9-yl-2-(substituted phenyl)-1,4-dihydroimidazo-4,5-indole-1-yl-amino-ethanones have been developed produced and tested for their antiomic effects against laryngeal cancer cell lines HEP2 and Ehrlich's Ascites Carcinoma cells. These substances have shown efficacy against tumor cell lines. The inclusion of an electron donor group, which probably increases the compound's basicity while lowering its acidity, may be the cause of the observed activity [5]. N-substituted carbazoles were found to be effective against tumor cells in an inquiry into their potential as anti-tumor agents, employing A549 cell lines as a model. Interestingly, the insertion of a fluoro group at the para-position dramatically improved the compound's anticancer activity, highlighting the significance of this modification [9]. N-substituted carbazoles have been synthesized and their antitumor potential evaluated. Particularly, N-[(methyl)(piperazin-1-yl)substituted phenyl] is a 5-[(9H-carbazol-9-yl)-methyl] derivative. It's been found that -1,3,4-oxadiazol-2-amines are effective against human breast cancer cell lines, particularly MCF-7 cell lines which contain progesterone, estrogen, and glucocorticoid receptors. Derivatives of pyridocarbazole have been demonstrated to have anti-HIV and anti-cancer properties. Ellipticine and its regioisomeric annulated indol and carbazole derivatives, and which feature a pyrido[4,3-b]carbazole framework, are a noteworthy class of drugs with potential anticancer activity [10]. Numerous experimental researches have shown that ellipticine and its derivatives' cytotoxic mechanism and antitumor efficaciousness are significantly influenced by their size, shape, and planarity. Particularly, positions 9 and N-2 are thought to be necessary for activity, whereas positions 1 and 11 are more adaptable and can take in some structural alterations. 9-methoxyellipticine, for instance, has demonstrated potential against several human tumor cell lines, with leukemia being its most effective target. Conversely, a quaternary pyridinium salt called ellipticinium acetate was developed specifically to treat metastatic breast cancer [11].

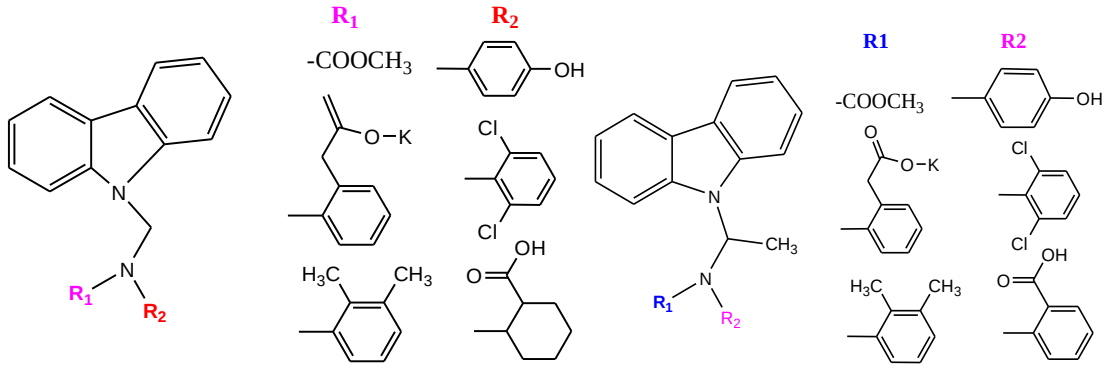


Figure 8: Structures of N-alkyl-carbazoles

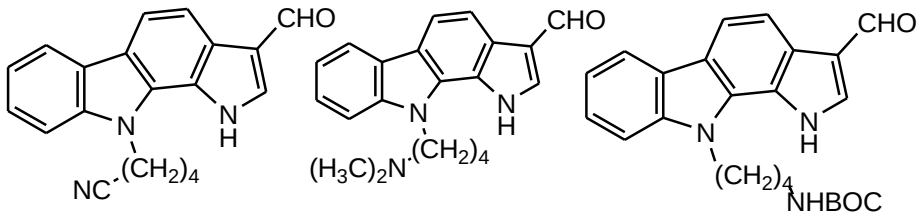
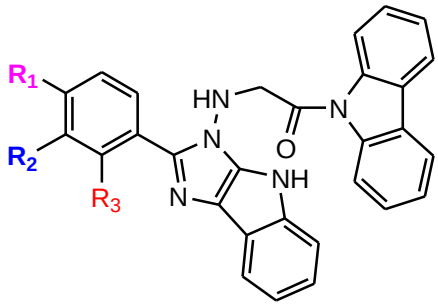


Figure 9: Structures of pyrrolo-carbazoles



R_1	R_2	R_3
-H	$-OCH_3$	-H
-H	-H	$-OCH_3$

Figure 10: Structures of hydrazinoacetyl carbazoles

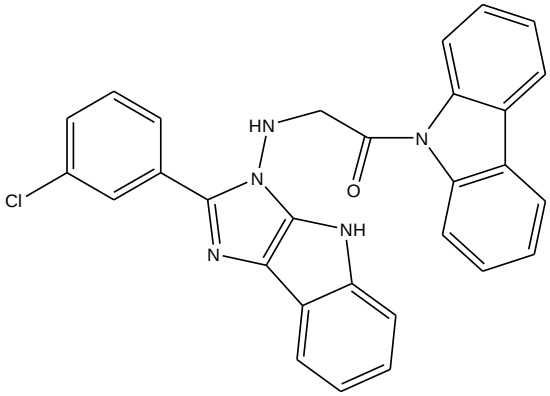
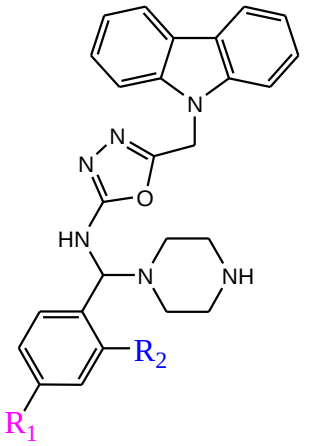


Figure 11: Structure of imidazo-indole carbazole



R_1	R2
-NO2	-H
-Cl	-H
-H	-Cl
-OCH3	-H
-F	-H

Figure 12: Structures of piperazinyl-oxadiazole carbazoles

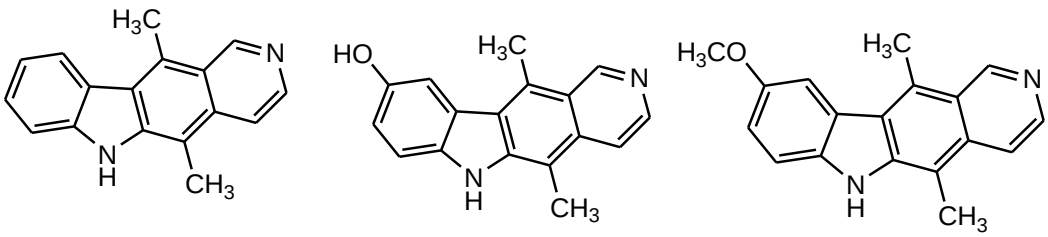


Figure 13: Structures of ellipticine and its derivatives

Conclusion:

Studies reveal that carbazoles has several advantageous attributes, including anticonvulsant, antibacterial, anticancer, analgesic, and anti-inflammatory effects, among other anticipated effects. This indicates that the presence of strong pharmacophoric groups and ring locations within the carbazole nucleus makes carbazoles highly promising for the development of novel medicines. Different functional groups can be substituted in the carbazole rings to create a variety of unique carbazole derivatives with a range of biological functions. As a result, carbazoles offer an advantageous platform for the development of novel pharmaceuticals.

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Conflict of interest: None

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