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A Concise Review on Carbazole Derivatives and its Biological Activities

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Abstract:
Carbazole skeleton is the key structural motif of many biologically active compounds including synthetic and natural products. Carbazole has a good attention in the field of research study due to the wide spectrum of biological activity and therapeutic applications. Carbazole is a good lead compound for the synthesis of novel drugs.There is a growing interest in the synthesis of several carbazole derivatives as better drug candidates for the treatment of various diseases. Carbazole contains a strong pharmacophoric moiety and ring structure which attracts the researcher to this nucleus for the synthesis of novel drugs. Through this review, it introduces a new way for a researcher for introducing this nucleus and develop a novel class of drugs who have better therapeutic profile. In this review, it mainly discusses about the pharmacological activity of carbazole which has already been discussed by the researcher. These reports have resulted in a great number of contributions in diverse areas of interest. This study may produce a new way for the researchers to design and develop carbazole derivatives with good pharmacological activities.

Keywords: Anticancer , antiepileptic, antimicrobial , carbazole

INTRODUCTION:

Carbazole is a nitrogen containing heterocyclic compounds. It has a tricyclic structure, that consists of two 6 membered benzene ring fused on either side with a nitrogen-containing five membered ring. Carbazole and its derivatives are very important type of nitrogen containing heterocyclic compounds that are widespread in nature. The Carbazole ring is present in a variety of naturally occurring medicinally active substances e.g., carbazomycins and murrayafoline A. Various carbazole derivatives such as benzocarbazoles, oxazinocarbazoles, tetrahydrocarbazoles, furo-carbazoles, pyridocarbazoles, pyrrolocarbazoles, indolocarbazoles, oxazolinylcarbazoles, thienocarbazoles, imidazocarbazoles, thiazolocarbazoles , benzopyrano-carbazoles, benzofurano-carbazoles and N-substituted carbazoles have been synthesized and are well known for their pharmacological activities.Several research studies are focused on carbazole nucleus due to their wide applicability. Carbazole derivatives are promising drug candidate for the treatment of various diseases. The pharmacological activities exhibited by carbazolesare anti-cancer, antibacterial, antifungal, anti-inflammatory, anti-histaminic, antioxidant, hepatoprotective, anti-HIV, antiprotozoan, anti-tubercular, anti-epileptic and sedative properties, or topoisomerase II inhibition ability.[1,2]

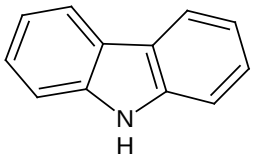


Figure 1: Carbazole

Carbazole derivatives act as intermediate for the synthesis of many compounds and also it is the starting material for the design of novel drugs. Carbazole forms different derivatives with interesting biological properties due to the presence of better pharmacophoric moiety. There are a number of carbazole based drugs commercially available in the market such as ellipticine,ollivacine, datelliptium, alectinib, celiptium etc.[1]

PHARMACOLOGICAL ACTIVITIES OF CARBAZOLE DERIVATIVES

1. Antimicrobial activities.

Carbazole ring is present in various natural medicinal active substances. More recently macrocyclicdiamides based on carbazole skeleton with thia- and oxy-linkage systems have been synthesized. Six new compounds with the structural elementsof biological importance showed significant antibacterialand antifungal activity . Antimicrobial activities of compounds were tested against four human pathogenic bacteria such as *Proteus mirabilis, Proteus vulgaris, Staphylococcus aureus* and *Salmonella typhi.*[1]

It was reported the antibacterial and antifungal activities of series of *N*-substituted carbazoles. It has been observed that introduction of 1,2,4-triazole moiety in carbazoles resulted in an increase of antifungal activity against *C. albicans*, with a minimum inhibitory concentration (MIC) of 2–4 μg/mL. The introduction of an imidazole moiety seems to be favourablefor antibacterial efficacy against *S. aureus*, *B. subtilis*, *E. coli*, methicillin resistant *S. aureus*(*MRSA*), *P. aeruginosa* and *B. proteus*(MIC 1–8 μg/mL). The quarternisation product of triazole ie.,carbazole triazolium compound, exhibited excellent antibacterial and antifungal activities against all strains with MIC values ranging from 1 to 64 μg/mL.[3]

N-substituted carbamates [(substituted phenyl/aliphatic-4-oxiran-2yl-methoxy)-9*H*-carbazole-9- carboxylate] and sulphonamides [9-(substituted phenyl-sulphonyl)-4-(oxiran-2yl-methoxy)-9*H*-carbazole] have been synthesized and evaluated for their antimicrobial activities.Certain compounds showed excellent antibacterial activities against *S. aureus*, *B. subtilis*, *E. coli* and antifungal activities against *A. niger*, *C. albicans* and *F. oxysporium*. The zones of inhibition were found to be in the range of 12.6–22.3 mm in diameter at a concentration of 100 μg/mL.[4]

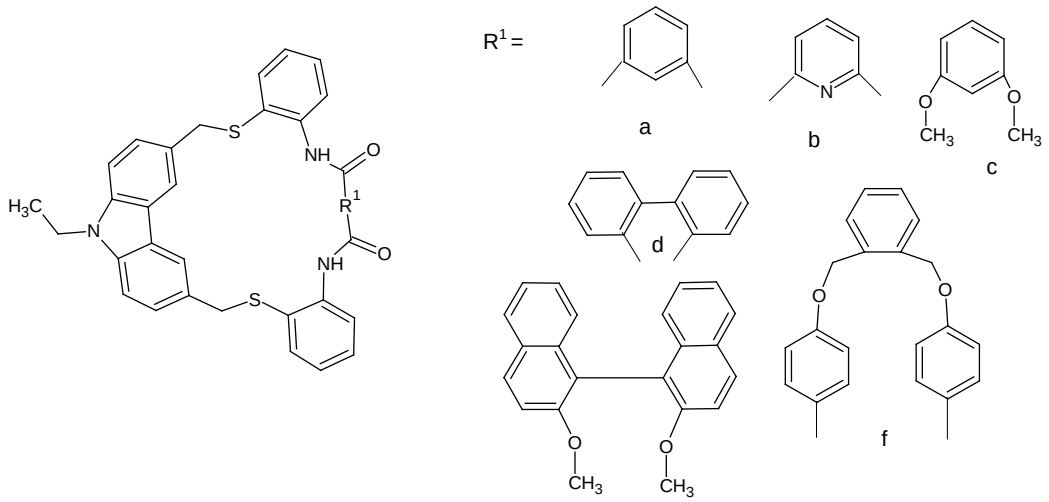
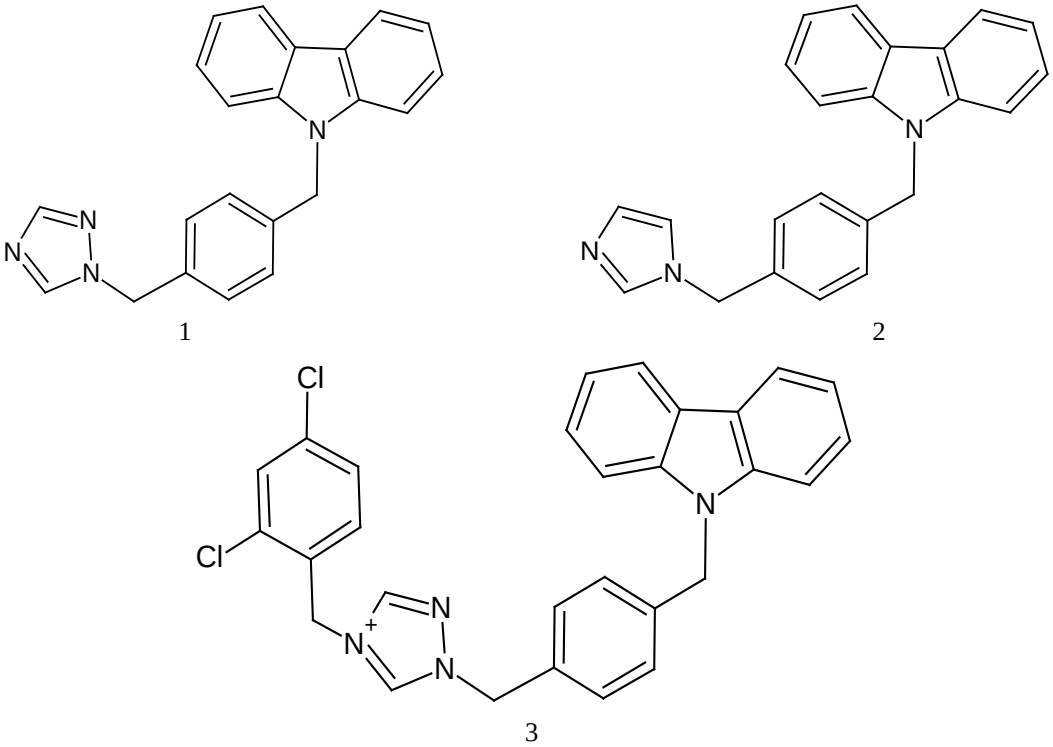


Figure 2: Structures of carbazolophanes (a-f)



1 2 3

Figure 3. Structures of imidazole and triazole carbazoles **1**–**3**

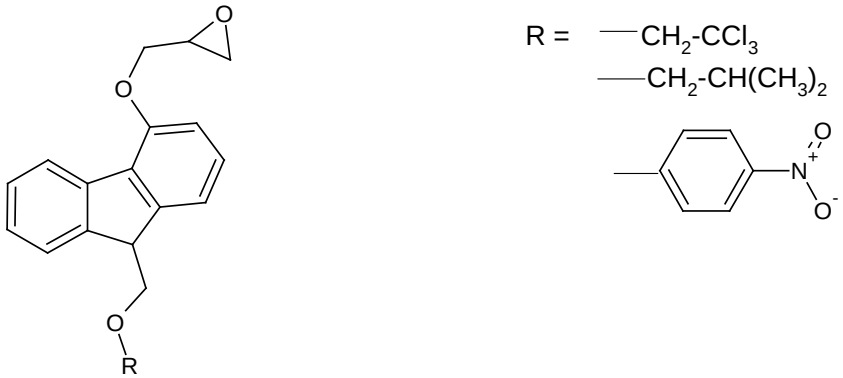


Figure 4. Structures of carbamate carbazoles

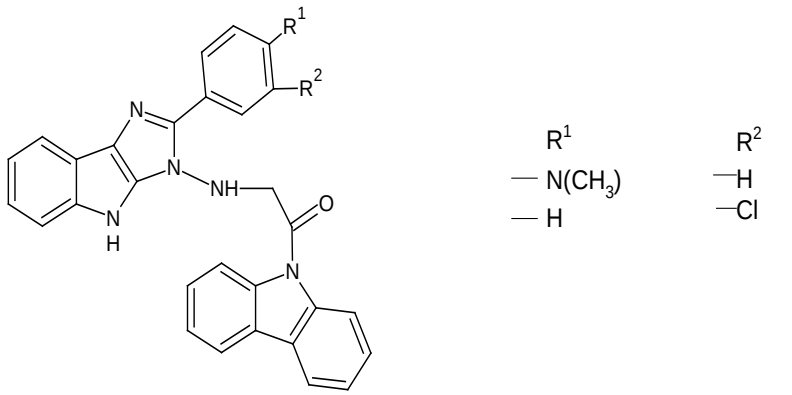


Figure 5. Structures of hydrazinoacetyl carbazoles

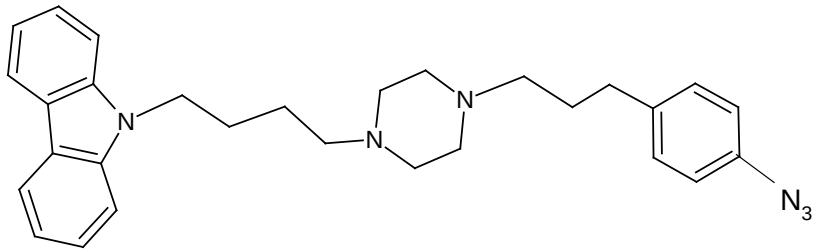


Figure 6. Structure of Incentrom A

N^9-(hydrazinoacetyl)-carbazoles which have been synthesized and evaluated for the potential antimicrobial activity. The carbazole derivatives containing imidazole and indole-imidazole moieties such as 1-carbazole-9-yl-2-(4-nitro-phenyl)-4,5 diphenyl-1*H*-1-yl-amino)- ethanone and 1-carbazole-9-yl-2-(substituted phenyl)-1,4-dihydroimidazo[4,5-*b*] indol-1-yl-amino)- ethanones were found to be the most potent against *B. subtilis*, *S. aureus*, *E. coli* and *K.pneumoniae* with zones of inhibition of 10.4–15.3 mm in diameter at MIC values ranging from 6.2 to 50 µg/mL.[5]

Incentrom A is a compound that could be useful in diagnosis of yeast-specific growth inhibitors providing opportunities to develop novel antifungal drugs . The mechanism of action is based on the process of chromosome segregation, which is done by specialized chromosomal structures called the centromeres (DNAregion) and the kinetochore (protein assembly).[1]

One of the most dangerous parasitic diseases to this day remains malaria (about one million deaths per year) caused by parasites of the Plasmodium species. However, the Plasmodium falciparum strains are the most deadly. Some crude root extracts of the *Clausena harmandiana* show antiplasmodial activity against these strains due to presence of carbazole compounds.

2. Neurological disorders

Neural stem cells (NSCs) are characterized by multipotency, which means that they can differentiate into all the cells of the nervous system, the neurons and glial cells. NSCs are a source of nutrients and protection for dysfunctional or damaged cells, they have the ability to migrate to distant sites of injury secretion and stimulate higher levels of SDF-1 by endothelial cells and astrocytes in the injured tissues. Mammals possess little capacity to regenerate and repair the central nervoussystem. In adult mammalian neurogenesis in vivo occurs in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles of the brain. Because neurogenesis occurs continually throughout the adult's life, NSCs hold great promise for treating neurological disorders including multiple sclerosis, Parkinson's disease and Alzheimer's disease. Still, clinical applications of NSCs have not been successful.

An alternative is the activation of endogenous neurogenesis and neuroprotection by chemical or genetic modification. Small molecules that can retard neuronal death or induce neurogenesis and neuroprotection are particularly interesting not only because of their therapeutic implications as novel therapeutic agents, but also because they can be used as an inestimable tool to study the mechanisms of neurogenesis.

One of the neurological disorder is Alzheimer's disease (AD), a progressive, degenerative disease of the central nervous system characterized by the existence of dementia, progressive deficits in cognitive functions and severe behavioral abnormalities, related to the disappearance of cerebral cortex. To date, there are no drugs retracting or stopping the progression of the disease. Pharmacological treatment consists of symptomatic treatment of memory disorders and cognitive functions. Currently, AD is increasing in people aged 65 years or elder and affects over 35 million people worldwide. The pathogenesis of AD has been found to be associated with numerous pathways including deficit in cholinergic functions , incorrect beta amyloid protein metabolism and tau protein phosphorylation , and the connection inflammatory pathwayand oxidative stress. One of the widely accepted theories says that beta-amyloid (Ab)

peptides of 40 and 42 residues formed from the cleavage of amyloid precursor protein play a key role in AD pathogenesis. The aggregation of monomeric Ab peptides to insoluble plaque also known as senile plaques may lead to the death of neuronal cells (on microscopic level plaques accumulate on the walls of blood vessels). The Ab peptides are generated by sequential processing of the amyloid precursor protein (APP) by b- and g-secretase. The g-secretase complex catalyzes the most important step in the liberation of these Ab isoforms, and this can be a promising target for prevention of AD .

In recent years effective fibril inhibitors and b-sheet breakers that can prevent the aggregation of Ab monomers into oligomeric and fibrillar conformations have been developed. The tested compounds must show blood brain barrier (BBB) permeability, low neurotoxicity and high in vivo stability to be clinically useful. One of the tested inhibitors of Alzheimer b-amyloid fibril formation was the derivative of carbazole. [1]

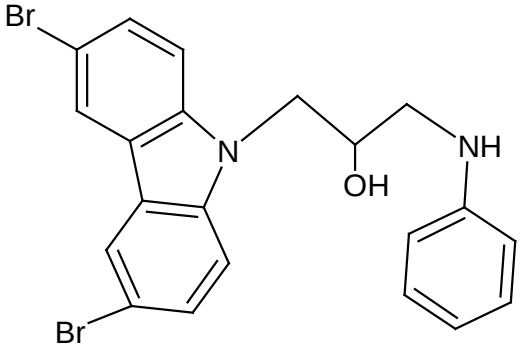


Figure 7. Structure of aminopropyl carbazole P7C3

3. Anti-Epileptic and Antinociceptive Activities

Epilepsy is the most frequent neurologic infection characterized by excessive temporary neuronal discharge . The overall prevalence of the disease is 1.0% of the population and up to 50 million people worldwide. Recent studies showed that a significant percent of individuals using anti-epileptic drugs are resistant to the currently used therapeutic agents. Therefore researchers are trying to find more active and less toxic compounds to control the seizures and produce a more comfortable life for the patients. The *N*-substituted carbazoles have been introduced by and were screened for their anticonvulsive and analgesic activities . Compound showed highly significant anti-epileptic potential at a concentration of 20 mg/kg. This may be due to the substituent 2-(2,-3-dimethyl-phenyl)-amino-benzoic acid. The compounds have been reported to possess analgesic potential.[6]

4. Anticancer activity

Cancer has emerged as one of the most startled disease in the last few decades throughout the world. It is a disease that contributes towards uncontrolled growth and invasion of abnormal cells leading to the formation of tumors. Pim (proviral integration site for moloney murine leukemia virus)-kinases control various proteins involved in significant biological processes such as cell cycle progression and apoptosis which is a form of programmed cell death that occurs in multicellular organisms. Over expression of pim-kinases have been observed in human leukaemia and lymphoma, prostate, pancreatic and colon cancer contributed to tumorigenesis. For these reasons, pim-kinases are considered as important targets for the development of new anticancer drugs.[7]

A series of *N*-substituted carbazoles have been studied for their antiproliferative activity. These pyrrolocarbazoles which is N- substitutedwere found to be most potent inhibitors for pim-kinase activity with IC50(the concentration of a drug that is required for 50% inhibition in vitro) in the nanomolar range (46–75 nM) and have demonstrated antiproliferative activities or which suppresses the cell growth against three human cancer cell lines, PA1 (ovarian carcinoma) ,PC3 and DU145 (prostatic carcinoma) with MIC values in the range of 8–20 μM.[8]

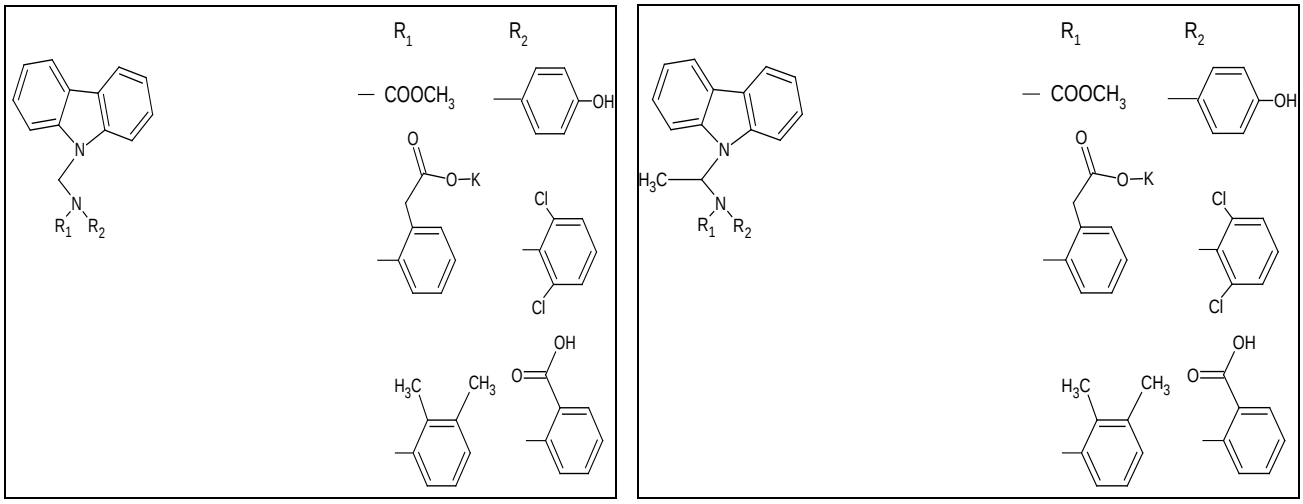


Figure 8. Structures of *N*-alkyl-carbazoles

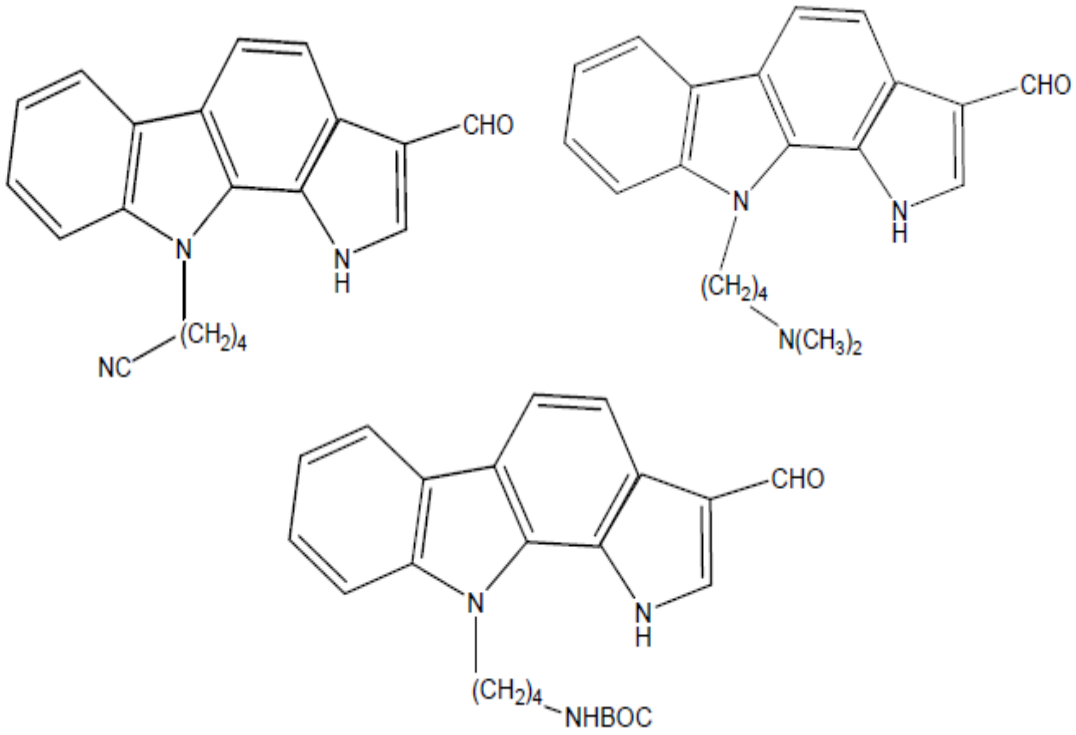


Figure 9. Structures of pyrrolo-carbazoles

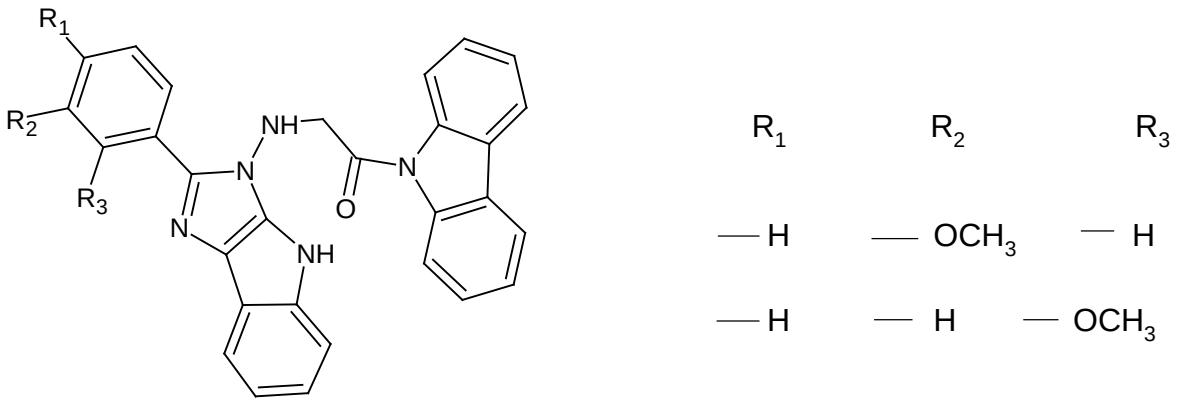


Figure 10. Structures of hydrazinoacetyl carbazoles

Various derivatives of 1-carbazole-9-yl-2-(substituted phenyl)-1,4-dihydroimidazo-4,5-indole-1-yl-amino-ethanones have been synthesized and evaluated for antitumour potential for laryngeal cancercell lines HEP2 (Human Epithelial Type 2) and Ehrlich's Ascites Carcinoma (EAC) cells. The compounds found to be active against tumor cell lines. The activity may be attributed due to the presence of electron donor group which may increase the basicity and reduce the acidity of the compound.[5]

A study was carried on A549 cell lines in order to explore the anti-tumorpotential of *N*-substituted carbazoles and compounds were found to be active. A fluoro group at *para*-position in compound makes its anticancer activity more significant.[9]

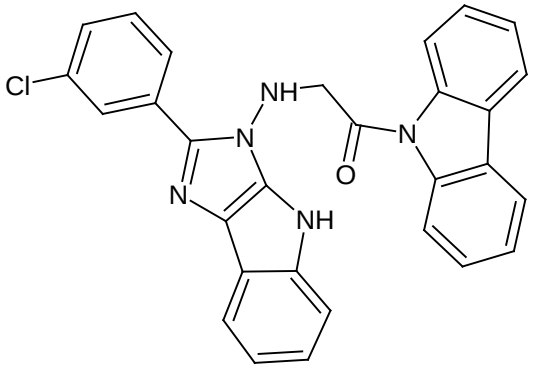


Figure 11. Structure of imidazo-indole carbazole

N-substituted carbazoles, have been synthesized and screened for their antitumor activity. The derivatives of 5-[(9*H*-carbazol-9-yl)-methyl]-*N*-[(substituted phenyl)(piperazin-1-yl)methyl]-1,3,4-oxadiazol-2-amines were found to be effective against human breast carcinoma cell lineswhich contains progesterone, estrogen and glucocorticoid receptors(MCF-7)[10].

Several pyridocarbazole derivatives have been reported to exhibit anti-cancer and anti-human immunodeficiency virus (HIV) activities. In particular, ellipticine and its regioisomeric annulated indol and carbazole derivatives with pyrido[4,3-b]carbazole framework constitute an interesting class of antitumor activity drugs. Many experimental studies indicated that the size, shape, and planarity of the ellipticine and derivatives are important factors for their mechanism of cytotoxicity and antitumor activity. Furthermore, it appears that positions 9 and N-2 are crucial for activity whereas the positions 1 and 11 are relatively tolerant and some variations into the scaffold of the molecule are allowed .For example, the 9-methoxyellipticine shows activity against a variety of human tumor cell lines, especially against leukaemia, whereas the quaternary pyridinium salt ellipticinium acetate was developed against metastatic breast cancer.[11]

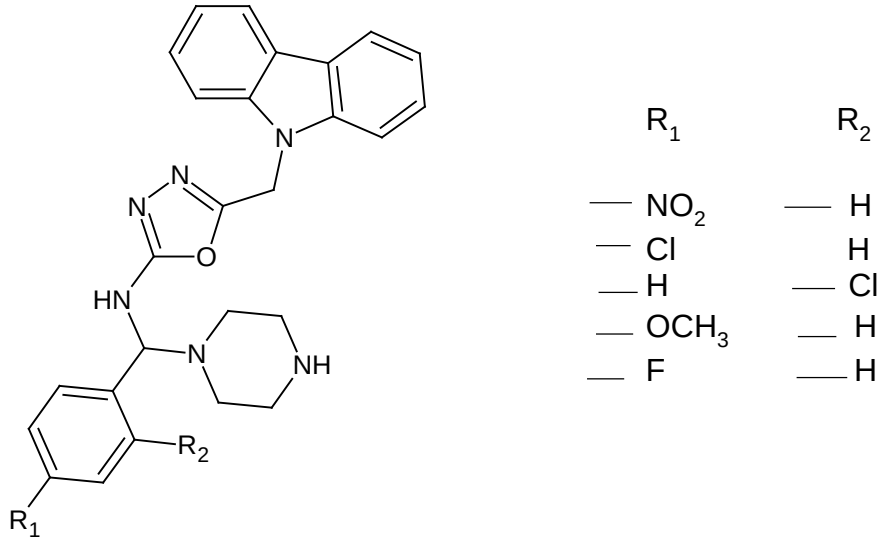
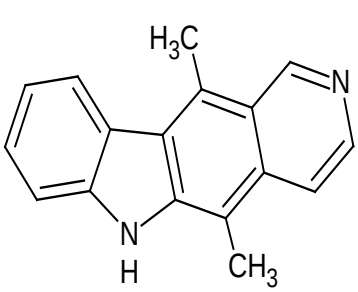
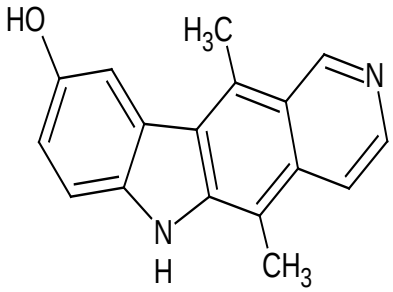


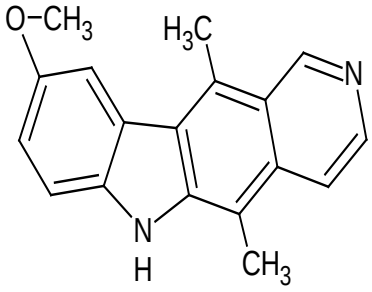
Figure 12. Structures of piperazinyl-oxadiazole carbazoles



Ellipticine



9-Hydroxyellipticine



9-Methoxyellipticine

Figure 13. Structures of ellipticine and its derivatives

CONCLUSION:

According to the research works, Carbazoles have been reported to possess, anticonvulsant, antimicrobial, antitumor, analgesics, anti-inflammatory and other anticipated activities. It can be concluded that carbazoles have great potential for synthesizing of novel drugs because of the strong pharmacophoric group and ring position present in the carbazole nucleus. The substitution of various functional groups in the carbazole rings leads to various novel carbazole derivatives with diverse biological activities. It is a promising lead molecule for the design and development of new drugs.

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