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Review Article

Recent advancement of carbazole hybrid: a privileged scaffold in new drug discovery.

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ABSTRACT

Carbazole comprises an important class of heterocycles. Carbazole is a tricyclic molecule having a coal tar carbon backbone, and also it has the structural properties of numerous compounds used in electronics for the manufacturing of polymers or dyes and electroluminescent materials, owing to its luminous quality. It has been reported that diverse biological activities include anti-cytotoxicity, bacteria-related problems, neurological problems, etc. Some carbazole derivatives were created such carbazoles with N-substitution, benzocarbazoles, furocarbazoles, pyrrolo-carbazoles, imidazo-carbazoles, etc. N-substitution derivatives have gained interest from researchers because of their active participation in neuro-related disorders and cell stimulation.

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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 [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 [7,8] and murrayafoline A [9]. Series of carbazole derivatives and N-substituted carbazoles have been synthesized (oxazinocarbazoles, isoxazolocarbazolequinone, pyrido-carbazolequinone [10], tetrahydro carbazoles [11], benzocarbazoles [12] furo-carbazoles [13] pyridocarbazoles 1[4], pyrrolo-carbazoles [15,16]. indolocarbazoles [17] oxazolinyl carbazoles [18]

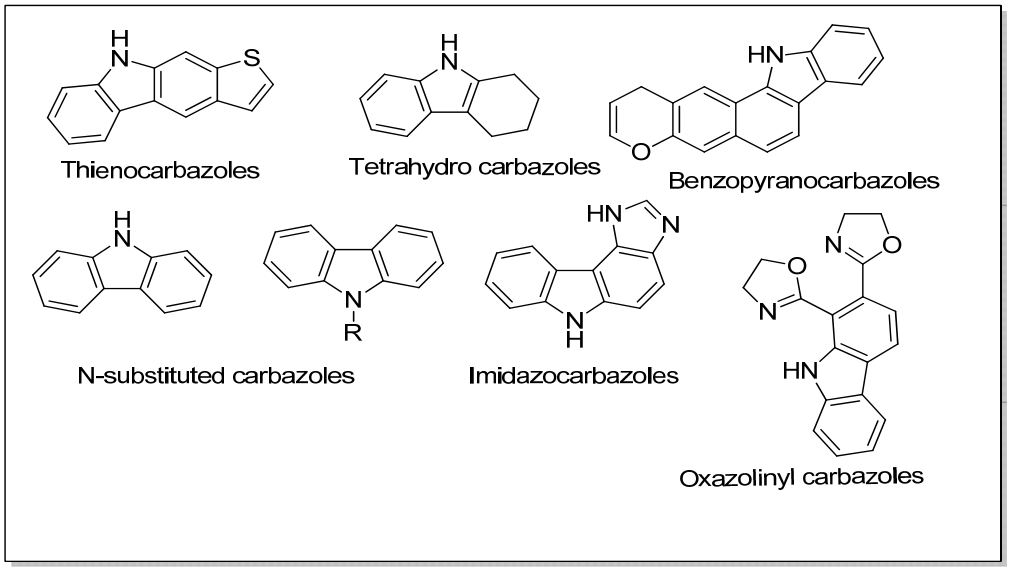

Figure 1. Structures of various classes of carbazoles.

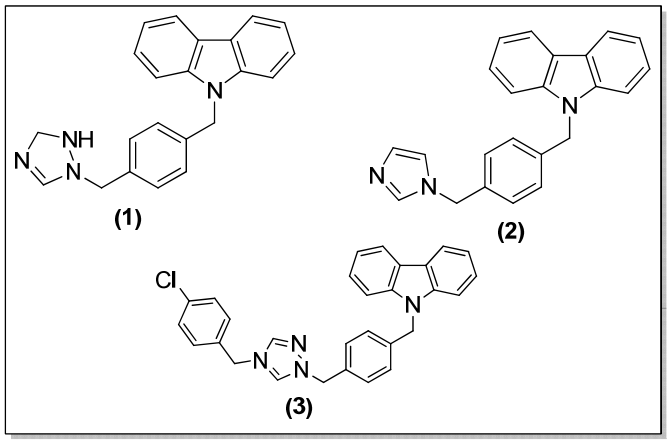

Figure 2. Structures of imidazole and triazole carbazoles 1–3.

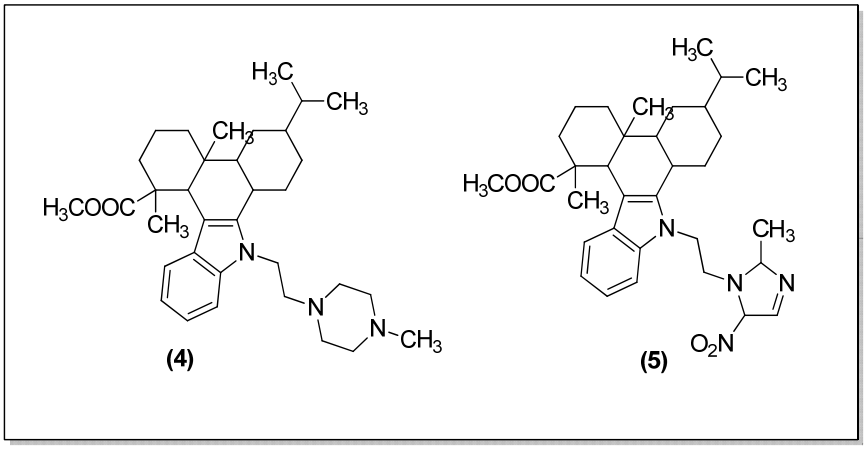

Figure 3. Structures of acetylenic amine and dibenzo-]carbazoles 4–6.

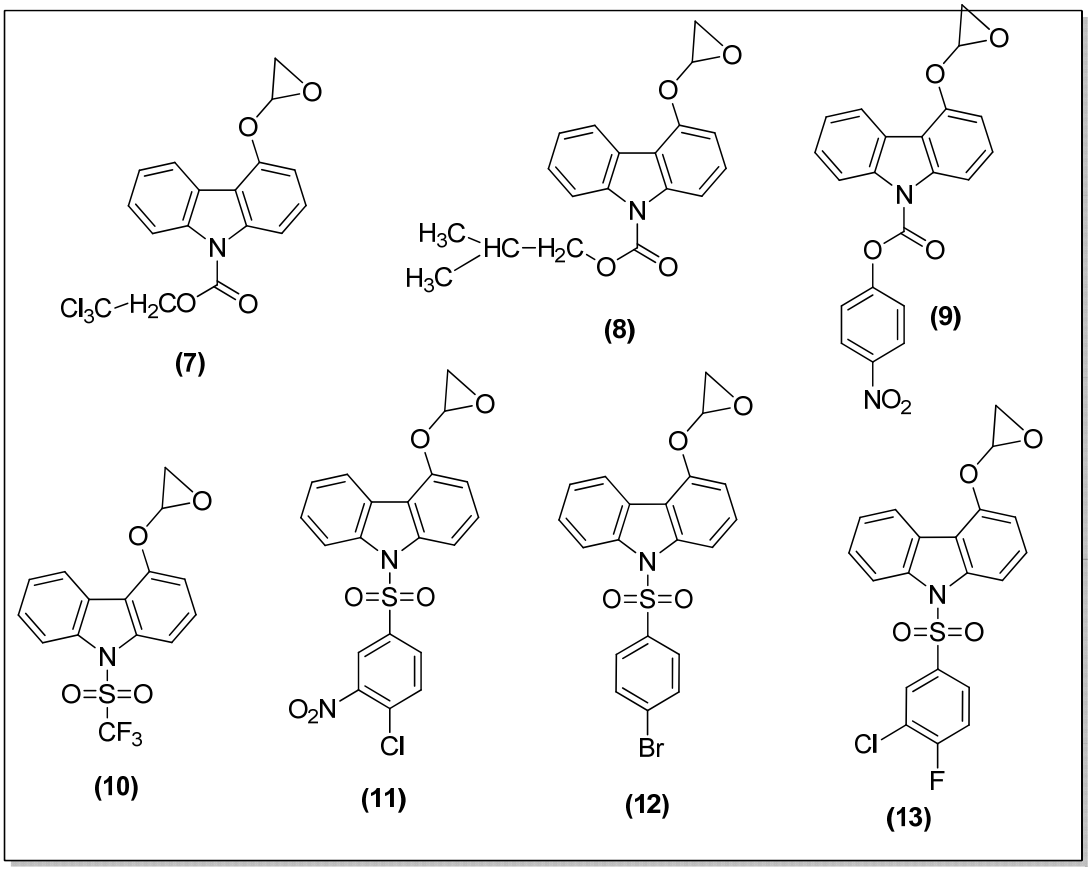

Figure 4. Structures of carbamate carbazoles 7–9 and sulphonamide carbazoles 11–13.

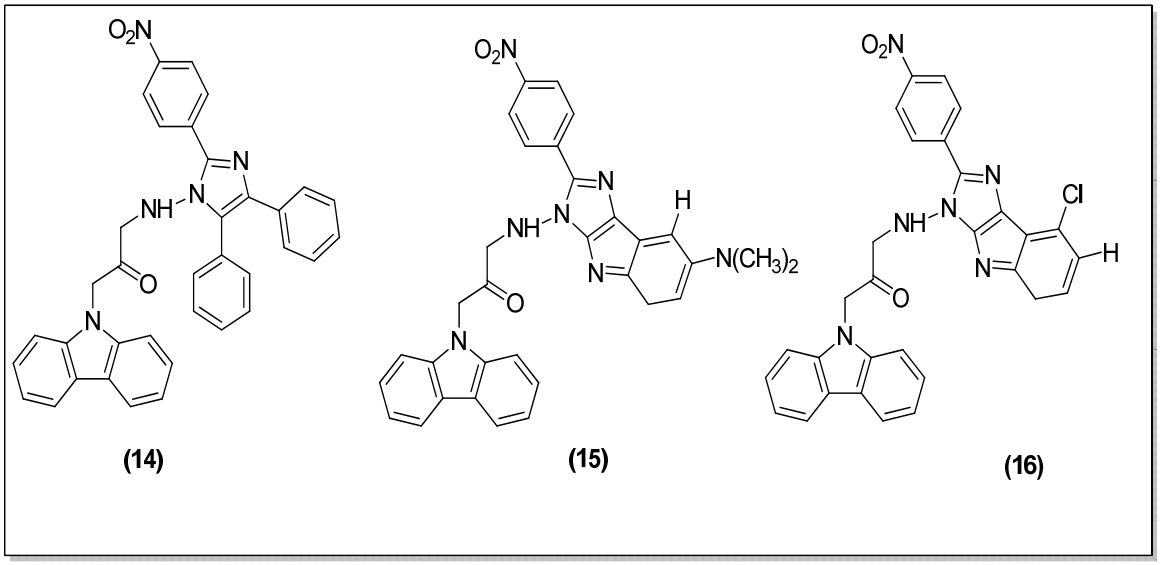

Figure 5. Structures of hydrazinoacetyl carbazoles 14–16.

thienocarbazoles [19], imidazocarbazoles [20], thiazolocarbazoles [21], benzopyrano-carbazoles [22], benzofurano-carbazoles [23] and are well known for their various therapeutical actions [24] such as antioxidant [25], anti-inflammatory [26], antibacterial [27], antitumor [28, 29], anticonvulsant 30, antipsychotic [31], antidiabetic [32], larvicidal [33] properties, etc. The current study focuses on the pharmacological activities of carbazole and conceptualizes the potency of N-substituted carbazole.

Biological Activities of N-Substituted Carbazoles.

Antimicrobial Activity

Bacteria that have developed resistance showed a lower efficiency against numerous bactericidal agents [34,] while various infections which are mainly caused by fungus have also expanded drastically in the vaccine-compromised population during the last several decades [35,36]. Carbazoles are a major class of antimicrobials [37,38]. A study reported a sequence of N-substituted carbazoles [39]. The insertion of the 1,2,4-triazole moiety to carbazoles (chemical 1) enhances its capacity to kill fungus like Candida albicans at a fixed inhibitory dose of 2–4 g / mL. (Minimum Inhibition Concentration). The inclusion of an imidazole moiety (compound 2) improves antibacterial effectiveness against different bacteria like S. Aurores, (1–8g / mL MIC). The quaternization product of triazole, carbazole thiazolium, had remarkable activities against different bacteria and fungi with Minimum Inhibition Concentration (ranging from 1.0 to 64g / mL) (Figure 2).

Gu et al. (2010) developed a variety of new N-substituted carbazole derivatives [40]. These newly produced antibacterial substances have been evaluated. N-ethyl-N-methyl-piperazinyl 4 was shown to be antimicrobial to the advantage of B. Leader, S. M. Hears, and G. E. Antifungal activity against E. coli, Penicillium fluorescent, and Candida albicans, A. Albania Niger has a MIC range of 1.9 to 7.8 g / mL. 5-derivative of N-ethyl imidazole 2-methyl-5-nitro was shown to be antibacterial against B. Subtilis (MIC 0.9 g / mL), which was comparable to the reference medicine (amikacin). Kaissy et al. [41] devised an effective synthesis technique for N-acetylenic aminocarbazol derivatives. The N-1-buto-2y-nyl-4(N all-N to methyl-Phenyl) carbazole exhibited a significantly different action against Escheria coli, which is a gram-negative bacteria that showed a 25 mm diameter inhibition zone at a conc. of 800 μg / mL (6). (Figure 3).

Reddy et al. [42] produced and evaluated the antibacterial activity of N-substituted carbamates at the inhibitory concentration.

The compounds 7, 9, 10, and 13 demonstrated superior antibacterial action against S. Core, M. Melancholy, E. coli, and A. Bordeaux, and Albicans. At a conc. of 100 g / mL, zones of inhibition ranging in diameter from 12.6–22.3 mm were discovered. (Figure 4).

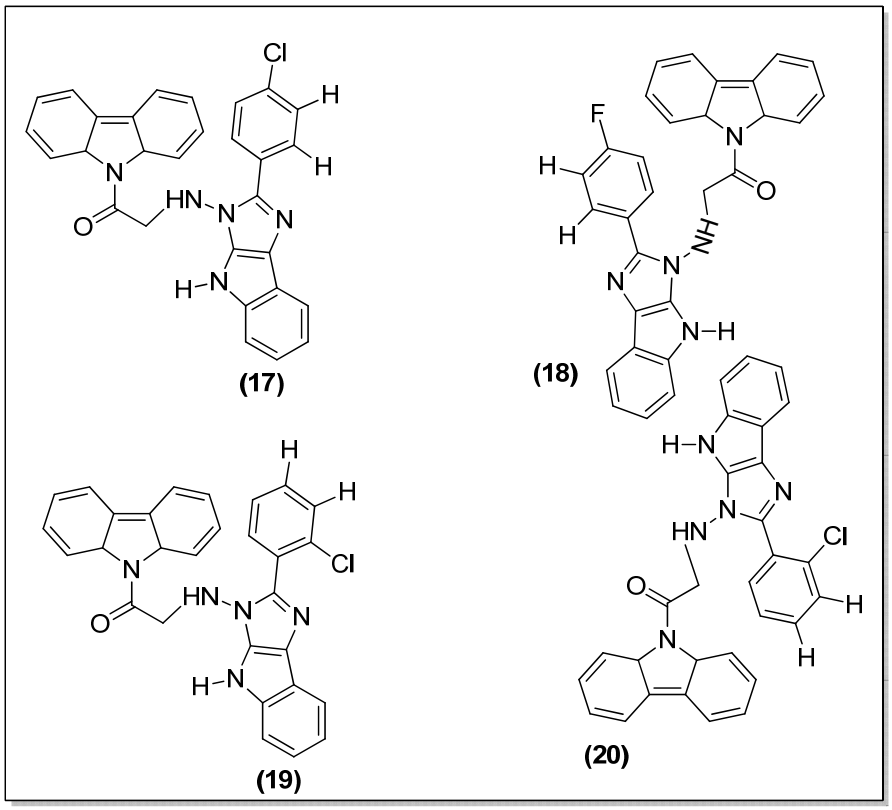

Figure 6. Structures of imidazo-indole carbazoles 17–19.

Kumar et al. [43] discussed the method of preparation of nine N-(hydrazinoacetyl)-carbazoles and their promising activity against different microbes. With the insertion of imidazole and indole-imidazole moieties, the derivatives (15 and 16) were shown more efficacy against B. Muzzle, S. Core, E. Coli, and M. and K. Pneumoniae, with inhibitory zones measuring 10.3–15.4 mm in diameter and Minimum inhibition conc. (from 6.2 to 50 g / mL.(Figure 5).

Bioassays were conducted to determine the antibacterial activity of 1-carbazole-9-yl-2-(substituted phenyl)-1,4-dihydroimidazo-4,5 against S.aureus. -indole-carbazole derivatives 17–21, which were produced by Kaushik et al. [44]. The 18 and 20 compounds can show bactericidal action against all bacterial species, with inhibition zones measuring 16.82–26.08 mm in diameter at 50 g / mL, whereas the 17–21 compounds exhibited potent antifungal activity against *Candida albicans A. niger,* with inhibitory zones measuring 7.91–16.8 mm in diameter at 50 g / mL (Figure 6).

A study demonstrated that n-alkylated carbazoles include compound (22) and wiskostatin (23). MIC albicans < 11 μM and MIC albicans 100 μM (Figure 7) [45]. Wiskostatin was found as an antifungal drug because it inhibits Wiskott-Aldrich neuronal protein syndrome (N-WASP)-mediated actin polymerization in vitro relative to WASP [46].

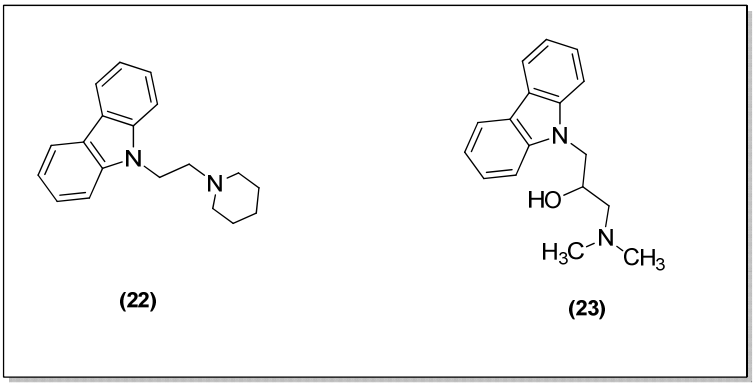

Figure 7. Structures of piperidinyl carbazole 22 an wiskostatin 23.

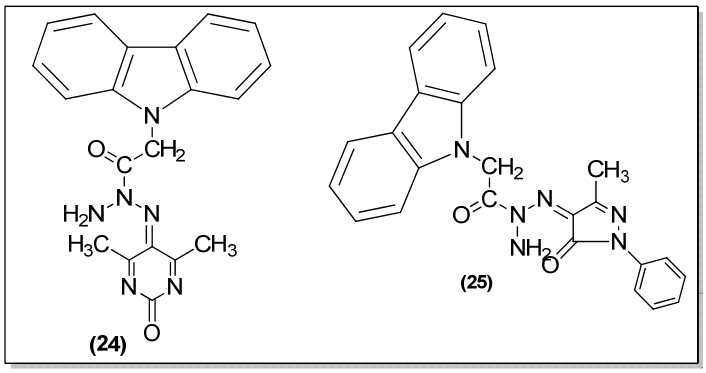

Figure 8. Structures of pyrimidine carbazole 24 and 25 pyrazole carbazole.

Two N-substituted carbazoles, 5-3-(9H-carbazol-9-ylacetyl) triazanylidene-4,6-dimethylpyrimidine-2(5H)-one (24) and 4-3-(9H-carbazol-9-yl acetyl)-triazanylidene-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (25), were developed by Salih et al [47]. (Figure 8).

They exhibited effective anti-fungal action against Candida albicans with Minimum Inhibition concentration values from 8.7 to 10.8 g / mL and bactericidal action against S. Aurores, B. Subtle, and Escheria coli with Minimum Inhibition Concertation (1.1 to 10.3 g / mL). The lipophilic nature of these chemicals may facilitate microorganisms' passage of biological membranes, hence inhibiting their development [48].

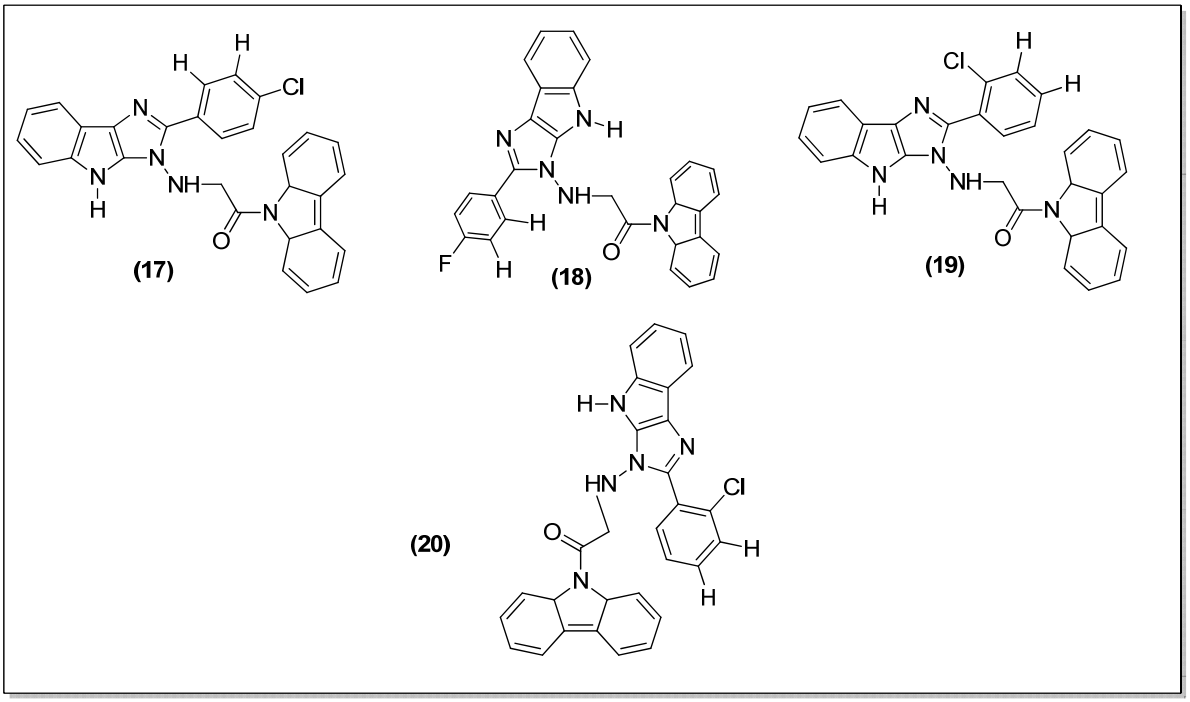

Figure 9. Structures of piperazinyl-oxadiazole carbazoles 26–28.

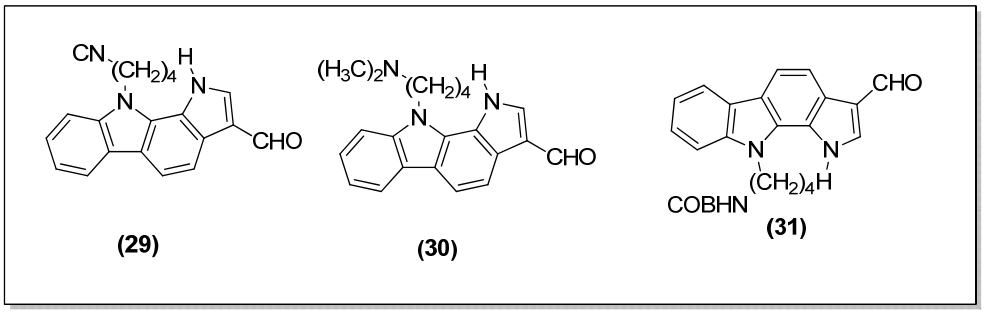

Figure 10. Structures of pyrrolo-carbazoles 29–31.

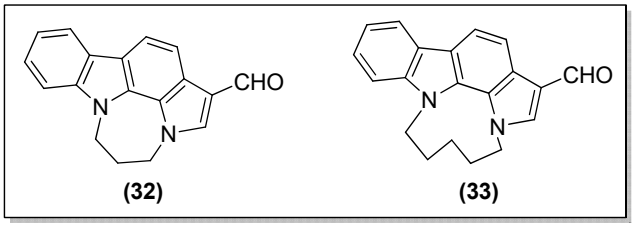

Figure 11. Structures of N1-N10 bridged pyrrolo-carbazoles 32 and 33.

Anticancer Activity

Cancer has become one of the world's most distressing illnesses in recent decades. It is a multifaceted illness in which aberrant cells multiply and invade uncontrollably, resulting in the creation of tumors [49]. 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. [50] produced pyrrolo-carbazoles derivatives. The capacity of these drugs to suppress pim-kinases has been determined. The chemicals (32) and (33) 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 11).

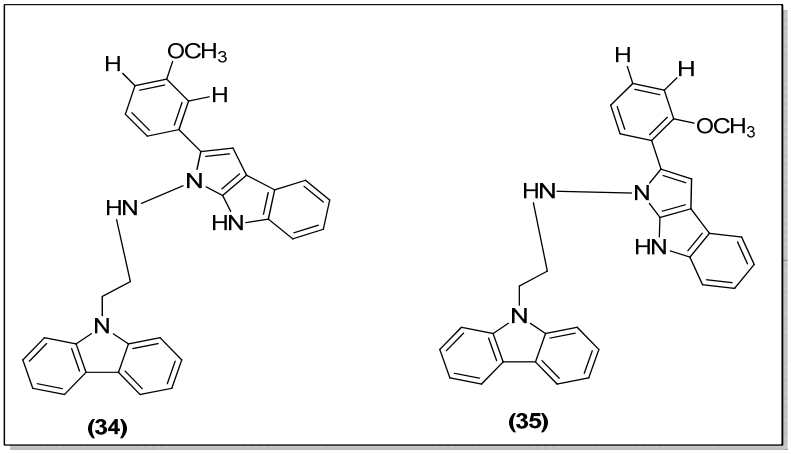

Figure 12. Structures of hydrazinoacetyl carbazoles 34 and 35.

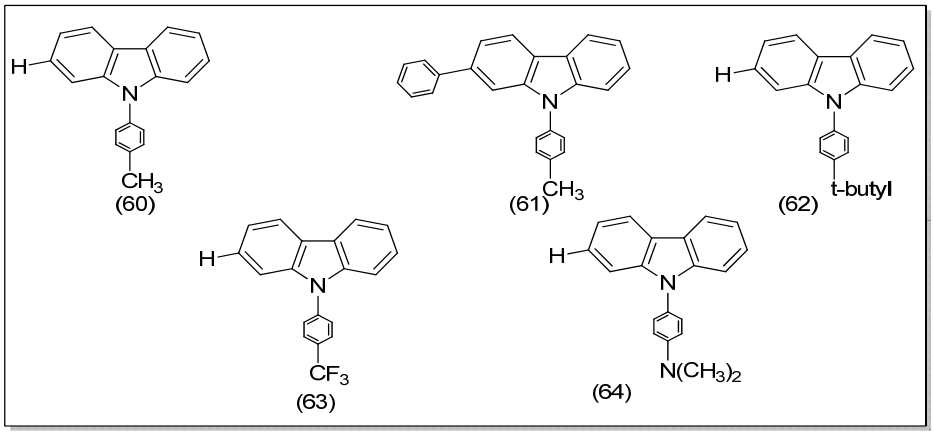

Figure 13. Structures of phenyl-carbazoles 60–64.

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 disease (PD). Dose-response studies show 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 [51]. In-vivo screening assay also protect 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 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) [52].

The anticancer activity of Compound (34, 35) produced by Kumar et al.43 was evaluated in cell laryngeal lines (HEP2) and Ehrlich's Ascites Carcinoma (EAC) cells. The chemicals 15, 34, and 35 were discovered to be effective against tumor cell lines (Figure 12). The reason behind this can be linked with EDG which enhances the fundamental properties of the molecule.

Neuroprotective Activity

Neuroprotection encompasses both acute (e.g., stroke or trauma) and chronic neurodegenerative disease (chronic neurodegenerative disease) techniques, as well as related processes, capable of inhibiting the central nervous system (CNS). An elevated level of OS has been implicated in several neuro-related illnesses, including AD, PD and stroke [44,45].

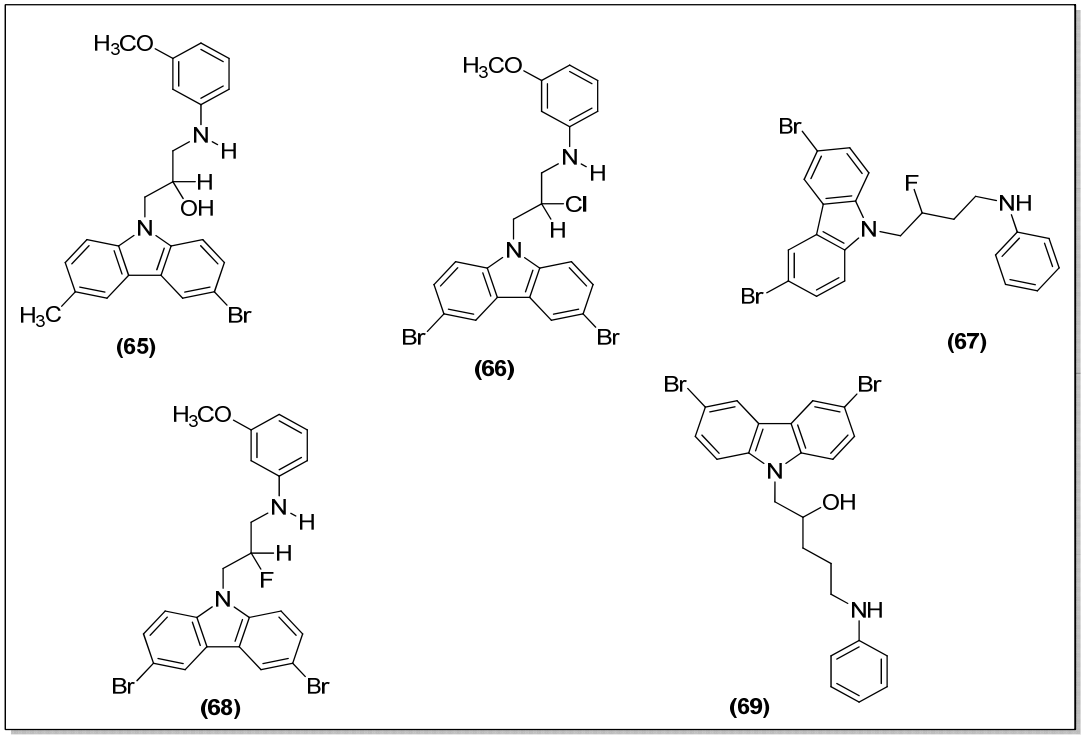

Figure 14. Structure of advantageous carbazole 65- 69.

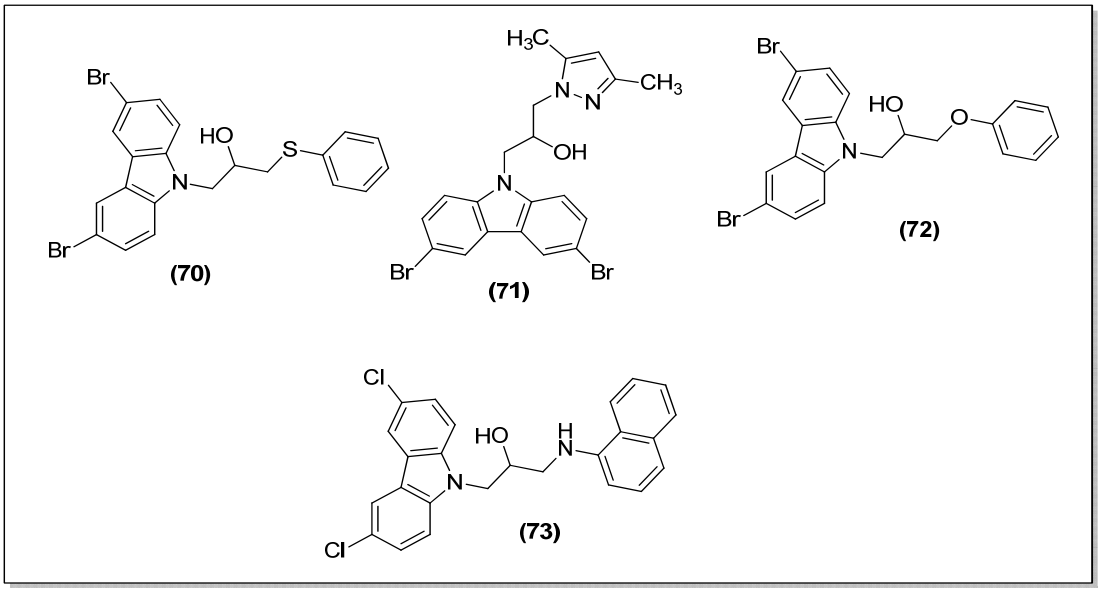

Figure 15. Structures of P7C3 derivatives 70–73.

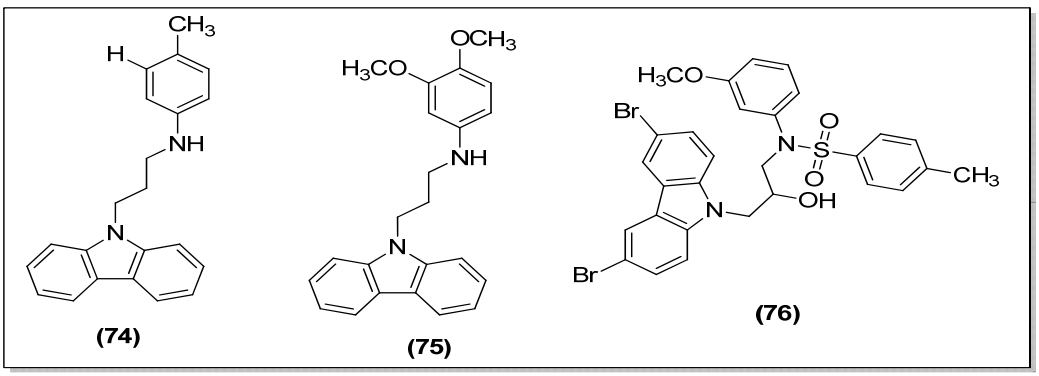

Figure 16. Structures of amino propyl-carbazoles 74–76.

At a conc. of 30 M, compounds substituted with bulky groups such as methoxy-phenyl (compound 61), t-butyl-phenyl (62), trifluoro-phenyl (46) and N, N-dimethyl-phenyl (47) exhibited considerable neuroprotective effects as well. It was discovered that carbazole's neuroprotective effect is dependent on the presence of a substituent at the N-position (Figure 13).

MacMillan et al. [46] synthesized a series of P7C3 derivatives and compounds, one of which, 65-69, was discovered to be more efficacious than the existing molecule. (Figure 14).

It has been observed that an amino propyl-carbazole (P7C3) inhibits the apoptosis of dopaminergic neurons in PD. A recent study evaluated the efficacy of P7C3 analogs against neuro-related disorders. In an experiment, the compounds P7C3-S7 (70), P7C3-S25 (71) and the (S)-enantiomer of P7C3-S41 (72) were proven more effective. P7C3-S184 (73), a -secretase antagonist that inhibited the synthesis of A-peptide from amyloid precursor protein, has been presented as a possible treatment method for AD (Figure 15) [47].

Yoon et al. synthesized and evaluated twenty-five aminopropyl-carbazole compounds for their ability to stimulate neurogenesis in cultured neural stem cells. Between these variants, compounds 79–81 exhibited superior pro-neurogenic and neuroprotective efficacy while exhibiting no obvious toxicity. (Figure 16).

CONCLUSIONS

Carbazole is a unique structure that has a variety of biological actions. They are of major significance to the scientific establishment as carbazole derivatives, particularly N-substituted carbazoles, exhibit complex and useful biological characteristics. These chemicals' antibacterial, anticancer, and antinociceptive properties make them appealing candidates for a variety of additional ailments, including neurological illness and epilepsy. This study conducted a descriptive investigation of the biological activity of reported active N-substituted carbazoles. Additional study is necessary to determine their therapeutic potential for a variety of additional disorders, including HIV, and many more.

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CONFLICT OF INTEREST

None declared.

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