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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. Also, it has the structural properties of numerous compounds used in electronics for manufacturing 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-carbazols, *etc*. Researchers have gained interest in N-substitution derivatives because of their active participation in neuro-related disorders and cell stimulation.

INTRODUCTION: The heterocycles are inextricably tied to the periods of life [1]. The role of heterocycles in producing molecules or drugs is a critical area of medicinal chemistry/Pharmaceutical chemistry [2]. Several heterocyclic compounds have 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 often found in nature [5].

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Fig. 1 illustrates the numerous carbazole groups found in a range of naturally occurring medicinal active compounds [6]. *e.g.*, carbazomycins [7, 8] and murrayafoline [9].

A Series of carbazole derivativesand N-substituted carbazoles have been synthesized (oxazino-carbazoles, isoxazolocarbazolequinone, pyrido-carbazolequinone [10], tetrahydro carbazoles [11], benzocarbazoles [12] furo-carbazoles [13] pyrido-carbazoles [14], pyrrolo-carbazoles [15, 16].

Indolocarbazoles [17] oxazolinyl carbazoles [18] thieno-carbazoles [19], imidazocarbazoles [20], thiazolo-carbazoles [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 conceptualizesthe potency of N-substituted carbazole.

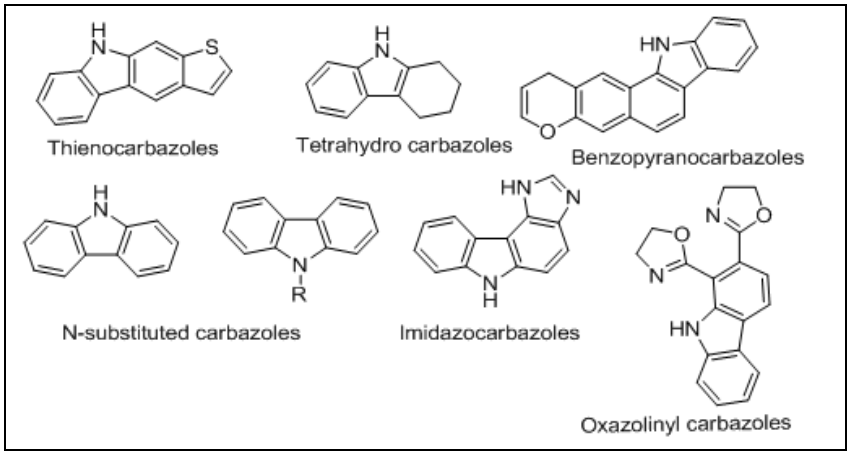

FIG. 1: STRUCTURES OF VARIOUS CLASSES OF CARBAZOLES

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]. Zhang *et al.* [39] reported a sequence of *N-substituted carbazoles*. The insertion of the 1,2,4-triazole moiety to carbazoles (chemical 1) enhances its capacity to kill fungi 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) **Fig. 2.**

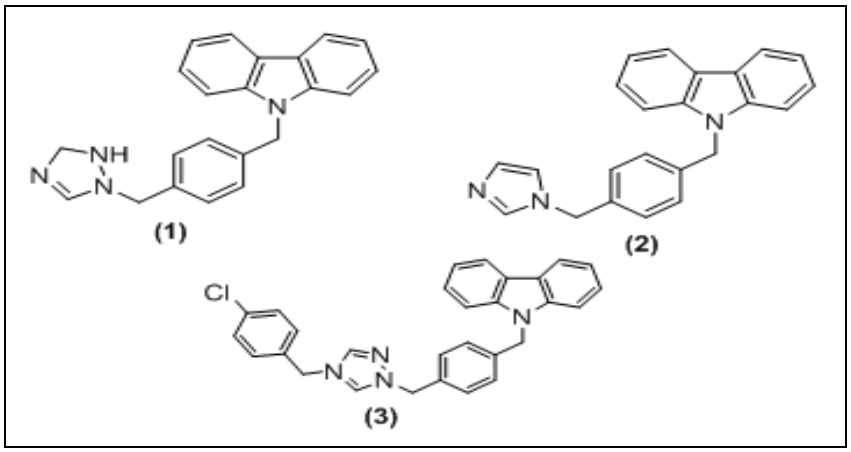

FIG. 2: STRUCTURES OF IMIDAZOLE AND TRIAZOLE CARBAZOLES 1–3

Gu *et al.* 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 800µg / mL(6) **Fig. 3.**

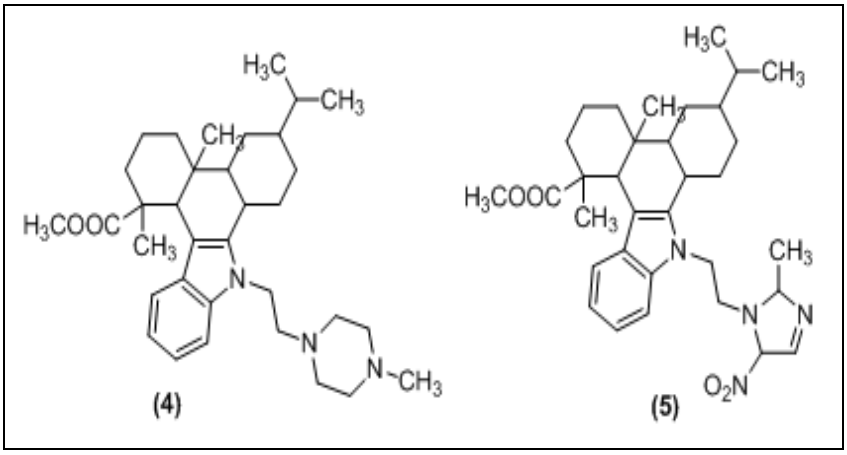

FIG. 3: STRUCTURES OF ACETYLENIC AMINE AND DIBENZO-CARBAZOLES 4–6

Reddy *et al.* [42] produced and evaluated the antibacterial activity of N-substituted carbamates at the inhibitory concentration. 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 in **Fig. 4.**

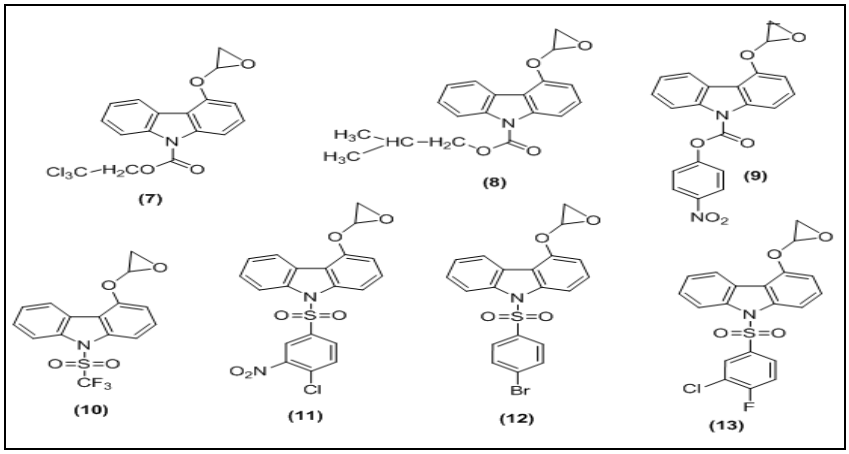

FIG. 4: STRUCTURES OF CARBAMATE CARBAZOLES 7–9 AND SULPHONAMIDE CARBAZOLES 11–13

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 to have 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 **Fig. 5.**

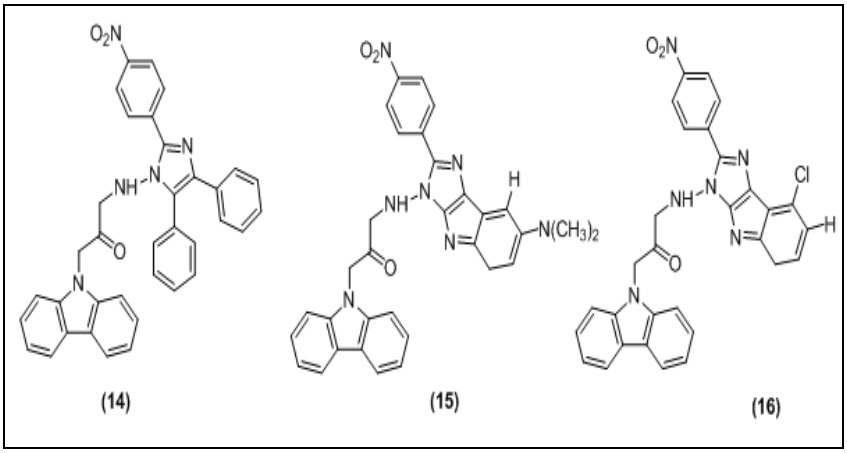

FIG. 5: STRUCTURES OF HYDRAZINOACETYL CARBAZOLES 14–16

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 **Fig. 6.**

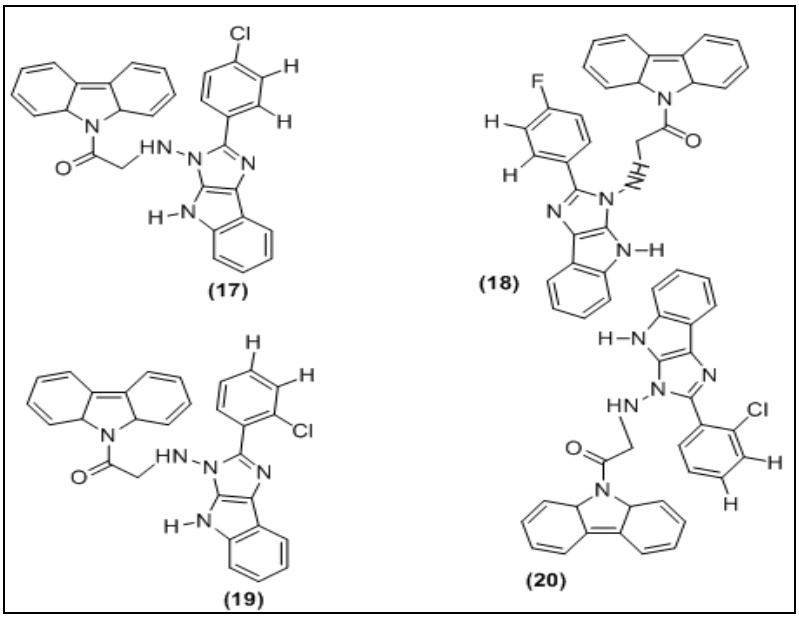

FIG. 6: STRUCTURES OF IMIDAZO-INDOLE CARBAZOLES 17–19

Segall and associates [45] demonstrated that n-alkylated carbazoles include compound (22) and wiskostatin (23). MIC albicans < 11 μM and MIC albicans 100 μM **Fig. 7**. 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].

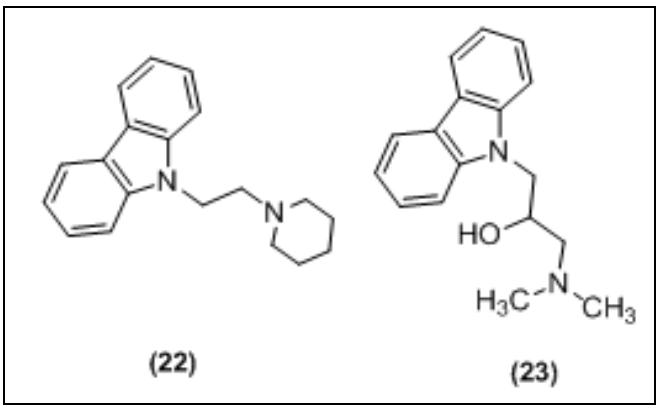

FIG. 7: STRUCTURES OF PIPERIDINYL CARBAZOLE 22 ANWISKOSTATIN 23

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] **Fig. 8.**

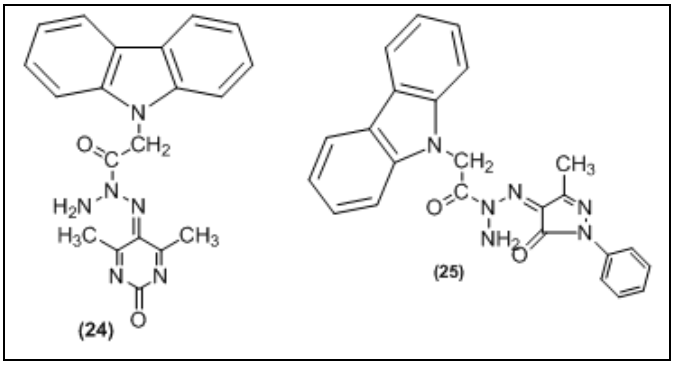

FIG. 8: STRUCTURES OF PYRIMIDINE CARBAZOLE 24 AND 25 PYRAZOLE CARBAZOLE

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. A series of N-substituted carbazoles prepared by Sharma *et al.*[48] were evaluated for their antibacterial activity.

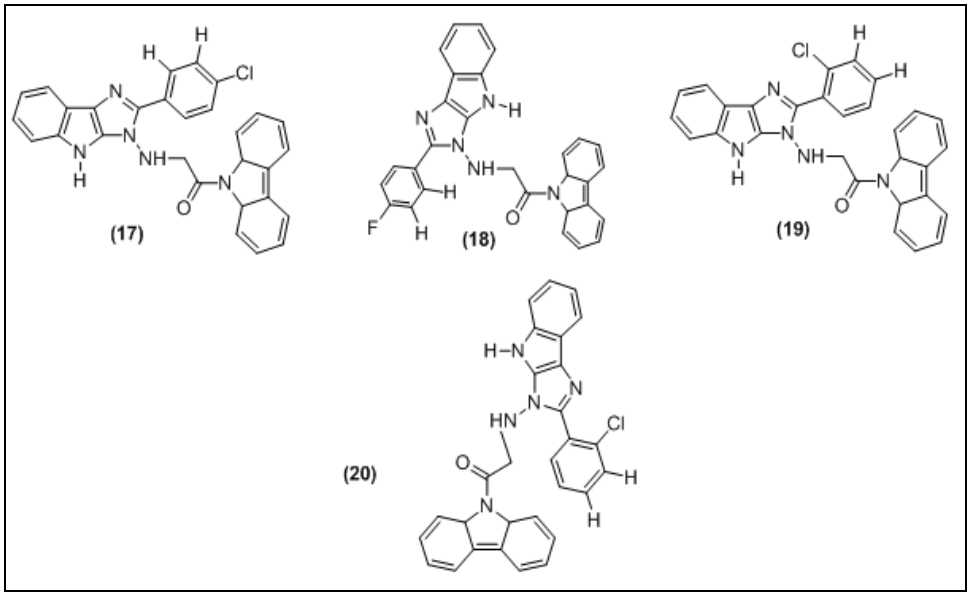

FIG. 9: STRUCTURES OF PIPERAZINYL-OXADIAZOLE CARBAZOLES 26–28

Anti-Cancer 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, creating tumors [49]. Pim-kinases assay various proteins involved in critical biological processes such as cell cycle progression and apoptosis. It has been shown that over-expression 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.

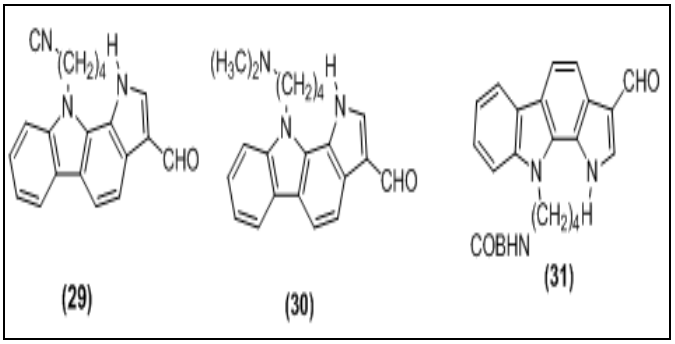

FIG. 10: STRUCTURES OF PYRROLO-CARBAZOLES 29–31

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 **Fig. 11.**

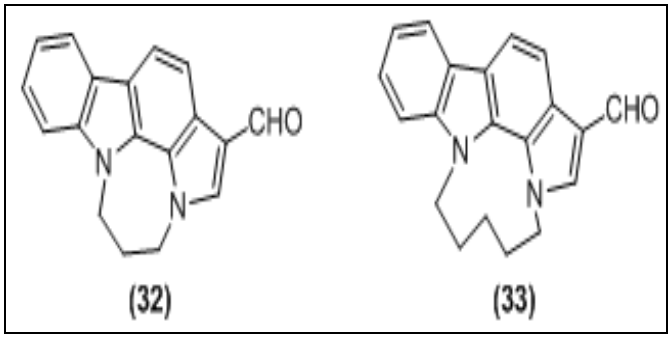

FIG. 11: STRUCTURES OF N1-N10 BRIDGED PYRROLO-CARBAZOLES 32 AND 33

The anticancer activity of compound (34, 35) produced by Kumar *et al.*[43] was evaluated in laryngeal cell lines (HEP2) and Ehrlich's Ascites Carcinoma (EAC) cells.

The chemicals 15, 34, and 35 were discovered to be effective against tumor cell lines **Fig. 12.** The reason behind this can be linked to EDG, which enhances the fundamental properties of the molecule.

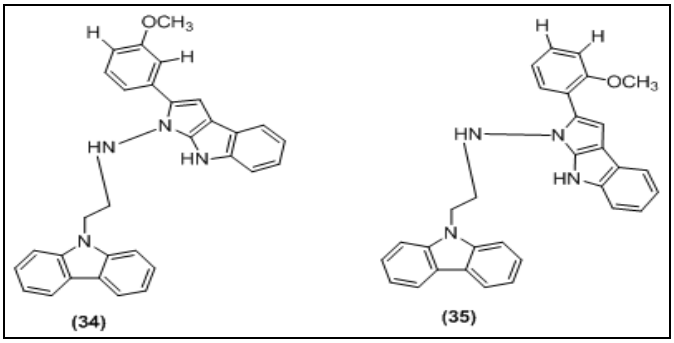

FIG. 12: STRUCTURES OF HYDRAZINOACETYL CARBAZOLES 34 AND 35

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].

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 **Fig. 13.**

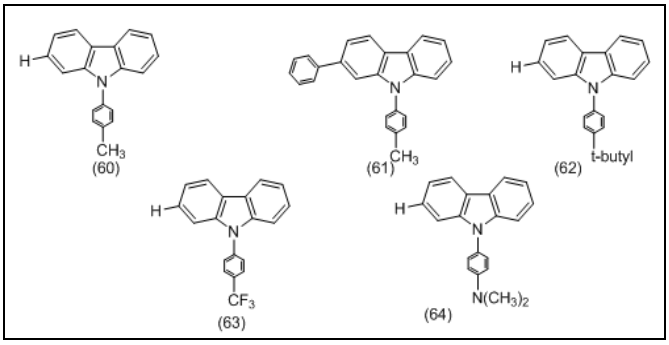

FIG. 13: STRUCTURES OF PHENYL-CARBAZOLES 60–64

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

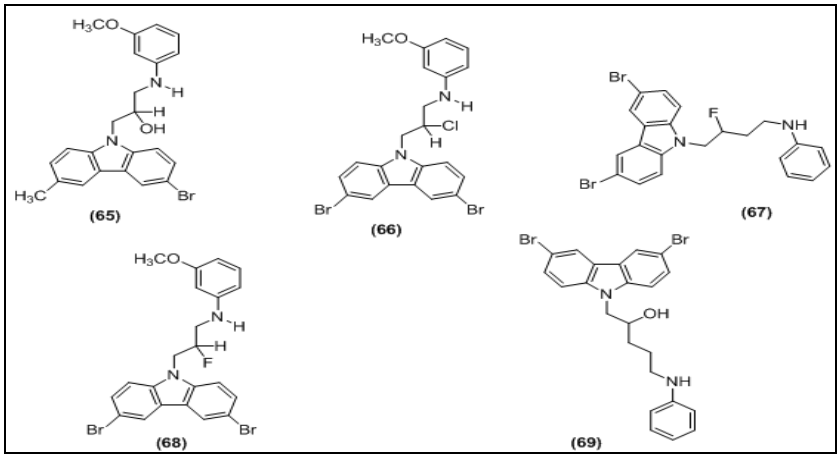

FIG. 14: STRUCTURE OF ADVANTAGEOUS CARBAZOLE 65- 69

It has been observed that an amino propyl-carbazole (P7C3) inhibits the apoptosis of dopaminergic neurons in PD. Cortes *et al.* [47] 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 **Fig. 15.**

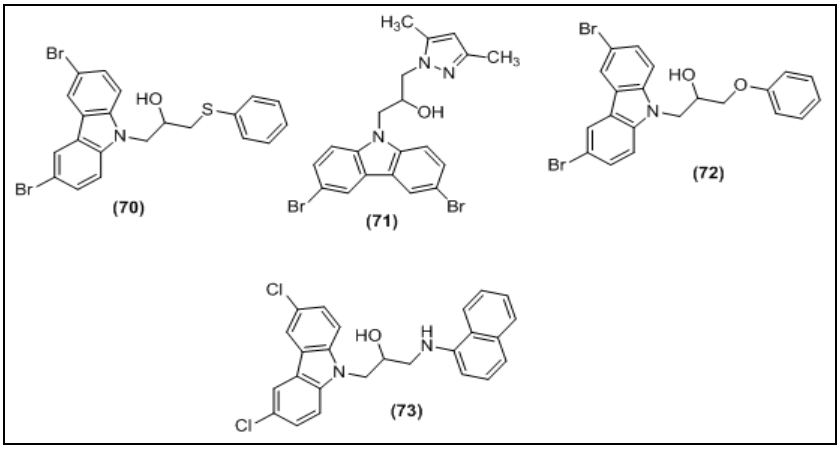

FIG. 15: STRUCTURES OF P7C3 DERIVATIVES 70–73

Yoon *et al.* [53] 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 **Fig. 16.**

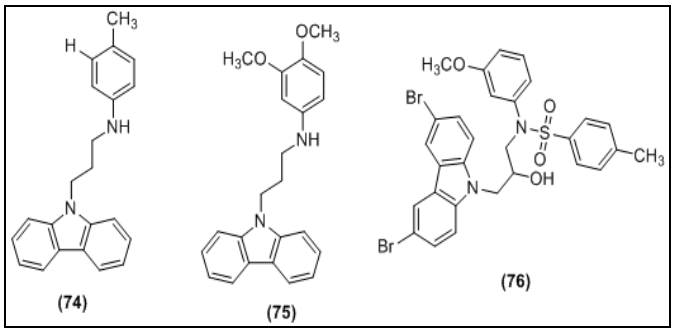

FIG. 16: STRUCTURES OF AMINO PROPYL-CARBAZOLES 74–76

CONCLUSIONS: Carbazole is a unique structure with various 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 various 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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