Int. J. Pharm. Investigation, 2022; 12(2) : 117-122 Review Article

Biological Potentials of Dibenzopyrrole Scaffolds: A Review

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ABSTRACT
Numerous bioactive heterocyclic products containing carbazole nucleus showed pharmacological and biological significance. Carbazole have been found in several of significant drug like fragments which provided a precious indication for action and in emerging new valuable derivatives. Carbazole possess several biological activities, i.e., action against viral infection, inflammation, cancer, HIV, microbial infection, tubercular infection, diabetes mellitus, malarial parasite infection, cholinesterase related disorders, etc. which made attention among research scholars to produce variety of carbazole molecules. This review revealed that carbazole molecules have different pharmacological actions and have a vast possible to be discovered for therapeutic potentials.

Keywords: Anticancer activities, Antimicrobial activities, Antifungal activities, Carbazole, Dibenzopyrrole, Tetrahydrocarbazole.

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INTRODUCTION

9H-Carbazole (Figure 1) was first discovered in the fraction of crude anthracene of cool tar during 1827, which also called as dibenzopyrrole which comprises dibenzenoid nucleus and has 14 pi-electrons out of which nitrogen offers lone pair of electrons and conjugated bonds offer 12 electrons which creates aromatic environment.

The molecular formula of carbazole is found to be $C_{12}H_9N$, and have a mass of 167.20 g/mol.[1] Melting point of carbazole is reported 243°C-246°C, affords water solubility of 1.1 mg/ml and log-p value is of 3.72. It is one of the electrons rich heterocyclic compound is white solid powder at room temperature.[2] Nitrogen containing heterocyclic molecule is a vital one in anthracene fraction of coal tar and derived oil after pyrolysis and also originate from the smoke produced from tar and incineration of wood. Carbazole is also a significant heterocyclic structure that offers the vital features to vincristine and vinblastine of vinca alkaloids obtained from the periwinkle plant and also too many other medicinally active molecules. Several carbazole systems have been synthesized and are widely recognized for their pharmacological actions, viz: benzo-carbazoles, oxazino-carbazoles, tetrahydro-carbazoles, furo-carbazoles, pyrido-carbazoles, pyrrolo-carbazoles, indolo-carbazoles, oxazolinyl-carbazoles and thienocarbazole.[3-4] Here, we have also tried to summarize the structures (Figure 2-9) of available Potential Active Pharmaceutical Ingredients of Carbazole available in Market.[5-12]

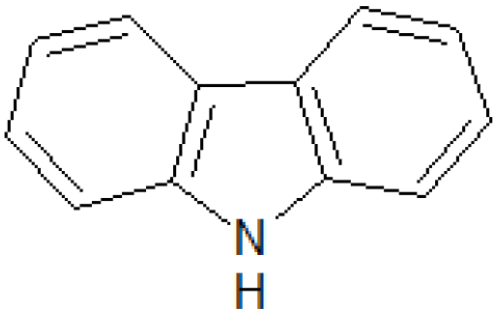

Figure 1: 9H-carbazole.

DIFFERENT REACTIONS INVOLVED IN THE SYNTHESIS OF CARBAZOLE

Cyclization of Diphenylamine's

As represented in Figure 10, here palladium acetate as a catalyst in presence of minute excess amount of glacial acetic acid cyclizes the diphenylamine and their derivatives into carbazole derivatives. In this reaction palladium acetate acts as productive catalyst in the course of cyclization.[13]

Condensation

Refluxing mixture of para-nitro-aniline and para-benzoquinone in presence of glacial acetic acid for four hours, up-on loss of water molecule affords 3-nitro-6-hydroxycarbazole which is represented in the Figure 11.[14]

Cyclization and Dehydrogenation

According to the Borsche-Synthesis carbazole synthesized by treating phenylhydrazine and cyclohexanone to yield hydrazine which cyclizes to form tetrahydrocarbazole in presence of dilute sulfuric acid and further the obtained tetrahydrocarbazole dehydrogenated in presence of lead oxide yields Carbazole which is illustrated in the Figure 12.[15]

Pyrolysis of Benzotriazole

The Graebe-Ullman Synthesis reported that, the cyclization reaction of diazonium salt of 2-aminodiphenylamine yields benzotriazole further upon pyrolysis produces carbazole with loss of nitrogen as represented in the Figure 13.[16]

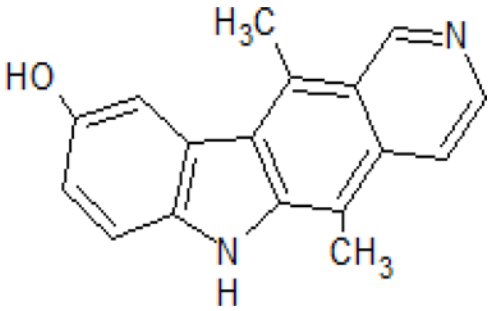

Figure 2: 9-Hydroxy ellipticine.

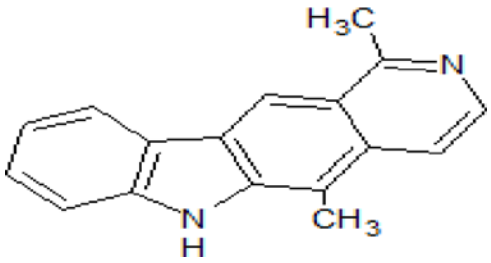

Figure 3: Olivacine.

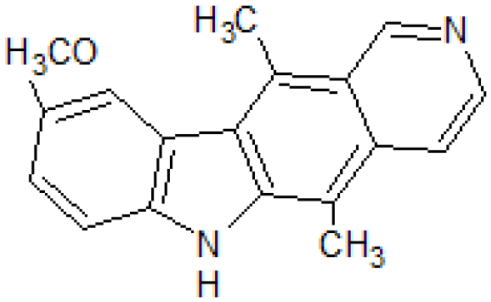

Figure 4: 9-Methoxyellipticine.

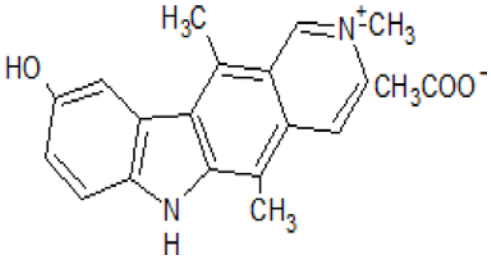

Figure 5: Celliptium.

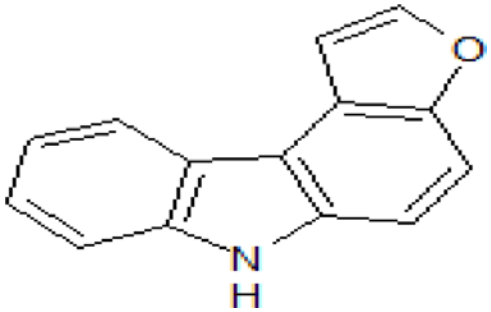

Figure 6: Eustifoline-D.

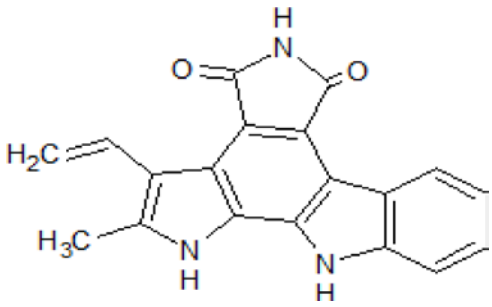

Figure 7: Arcyriaflavin.

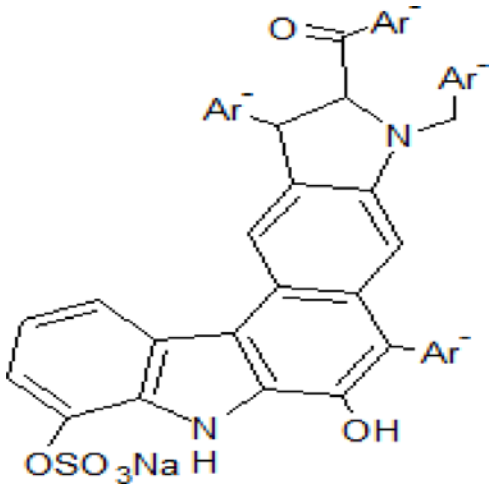

Figure 8: Dictyodendrin Ar= C6H5(4-OH).

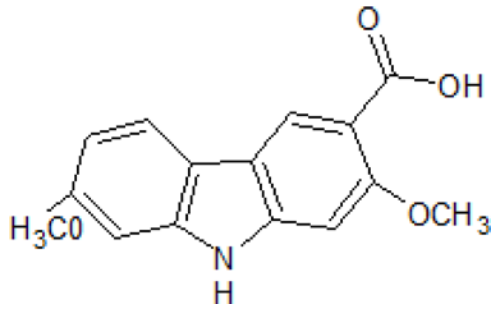

Figure 9: Clausine K.

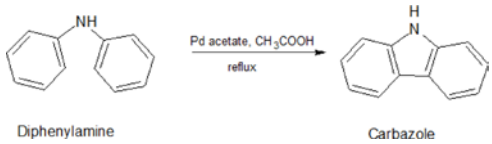

Figure 10: Cyclization of Diphenylamine's.

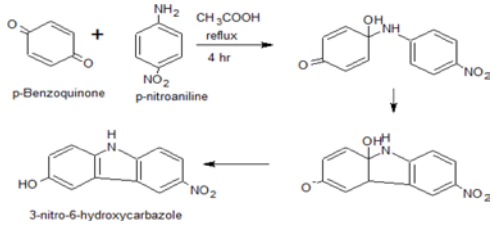

Figure 11: Condensation of p-Benzoquinone and p-Nitroaniline.

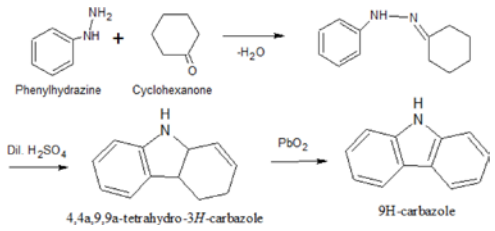

Figure 12: Cyclization of Tetrahydrocarbazole.

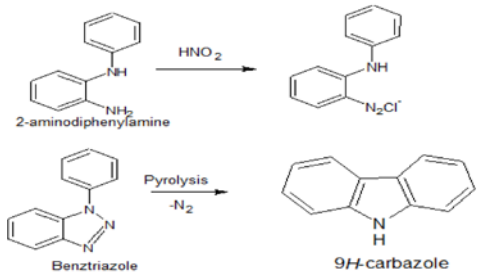

Figure 13: Pyrolysis of Benzotriazole.

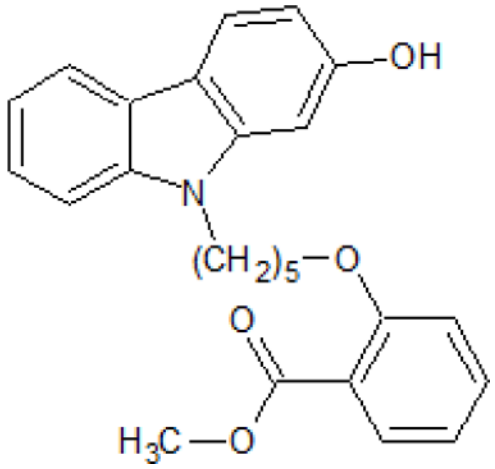

Figure 14: Structure of 2OH Carb 6B.

BIOLOGICAL ACTIVITIES

Alzheimer's

N-alkyl carbazole derivatives were synthesized and screened using AβX-40 and AβX-42 enzyme linked immune sorbent assay and the levels of alpha-beta peptides were screened according to the usual curvatures prepared successfully on the similar cups. Results indicated that, the two compounds show promising results such as 2-OH CARB 6-B (Figure 14) and 6-MeO CARB 5-B sal (Figure 15). These results are encouraging that N-alkyl-carbazole molecules might also inspire resulting forthcoming revisions desirable for increasing the acquaintance almost all the Alzheimer's disease methods.[17]

Sequence of ferulic carbazole molecules were synthesized and investigated *in-vitro* studies for various activities includes amalgamation of cholinesterase inhibition, anti-oxidant and neuro-protection as poly-functional anti-Alzheimer drug like agents by Lei *et al.*, with the IC_{50} value of 1.9 micro molar carbazole compound (Figure 16) showing its potency as anti-alzheimer agents which is five folds highly dynamic than that of standard galantamine.[18]

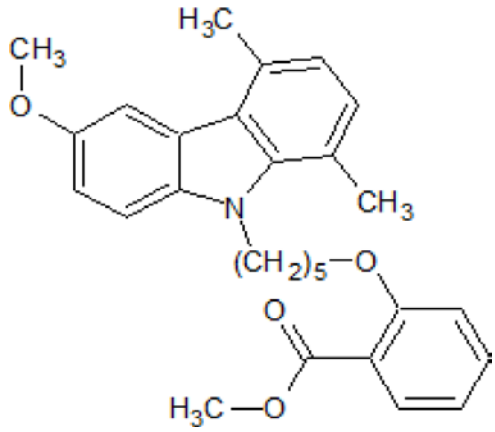

Figure 15: Structure of 6MeO Carb 5B Sal.

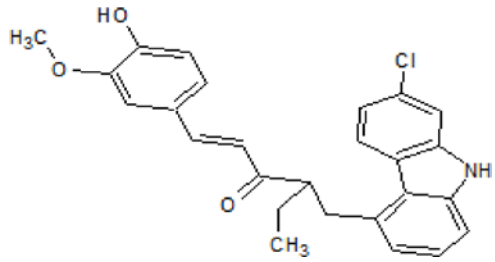

Figure 16: N-Ethyl-3-(4-hydroxy-3-methoxyphenyl)-N-((7-Chloro-9H-Carbazol-4-yl)methyl)acrylamide/ (Carbazole compound).

Antimicrobial

Sulfonamide and carbamate compounds based on carbazole were designed, synthesized and tested for antimicrobial and antioxidant activity. Compounds 4-(Oxiran-yl-methoxy)-9-(trifluoro-methyl-sulfonyl)-H-9-carbazole, 4-(oxiran-2-yl-methoxy)carbazole-9-(4-Chloro-3-fluorophenylsulfonyl), 2,2,2-Trichloroethyl 4-(oxiran-2-ylmethoxy)-9H-carbazole-9-carboxylate and 4-Nitrophenyl4-(oxiran-2-ylmethoxy)-carbazole-9-carboxylate seemed to have exceptional action against several strains of bacteria and fungus with MIC at lower concentrations, while compound 9-(4-Bromophenyl-sulfonyl)-4-(oxiran-2-yl-methoxy) carbazole seemed to have great activity against *Escherichia coli* strain, compound Isobutyl-4-(oxiran-2-yl-methoxy)carbazole-9-carboxylate have potent activity against *Bacillus subtilis*. These research findings may lay the groundwork for various potential lead compounds to also be explored in the study of antimicrobials activity.[19]

Carbazole derivatives (Figure 17) were prepared and subjected for antibacterial activity by considering chloramphenicol compound as standard against *Escherichia coli* and *Staphylococcus aureus*. Minimum inhibitory concentration of compounds found in the range of 100-400µg/ml. on other hand compounds 2-(4-methyl[1-2-4]triazol-3-yl)sulfanyl(9-Ethyl-carbazol)acetamido and 2-(1-methyl-H-tetrazol) sulfanyl-(9-Ethyl-carbazol)-acetamido showed similar activity compared to that of standard ketoconazole with MIC value 4µg/ml against *Candida albicans*.[20]

Yaqub G *et al.*, explored many Novel Pyridazino Carbazole derivatives. Compounds 9-(dimethyl-amino)-2, 3-dihydro-2-phenyl-pyridazino[4,5-b]carbazole-[1,4]-dione was effectively active against *Salmonella typhi* bacteria which is responsible for typhoid fever and compounds 2,3-Dihydro-9-nitro-2-phenyl-pyridazino[4-5b]carbazole [1-4]-dione, 9-(N-methyl-N-(2(methyl-amino)ethyl-amino)2,3-dihydro-

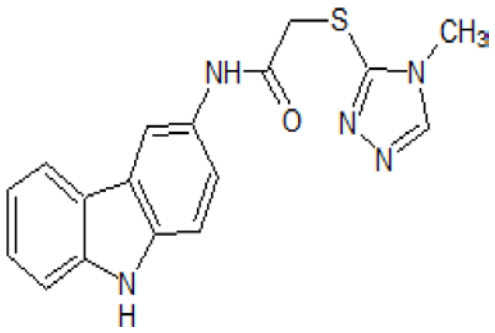

Figure 17: N-(9H-carbazol-3-yl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl] acetamide/ (Carbazole derivative).

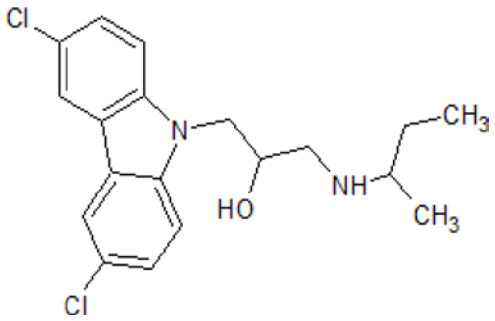

Figure 18: 1-(butan-2-ylamino)-3-(3,6-dichloro-9H-carbazol-9-yl)propan-2-ol.

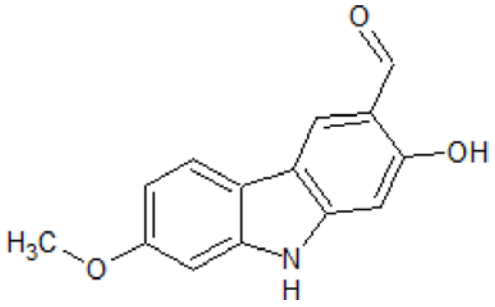

Figure 19: 2-hydroxy-7-methoxy-9H-Carbazole-3-carbaldehyde.

2-phenyl-pyridazino[4-5,b]carbazole[1,4]dione, 2-3-di-hydro8-9-dimethyl-2-phenyl-pyridazino[4-5,b]carbazole[1-4]dione and Pyridazino carbazole were remarkably active against *Candida albicans* with the IC_{50} value range of 16-32µg/ml.[21]

Thevissen K *et al.* screened various novel carbazole molecules for antifungal activity against different Candida species. Further they also performed anti-Candida biofilm activity for N-alkylated-[3,6]-dihalogeno-carbazoles and in specific compound 1-(butan-2-yl-amino)3-(3,6-dichloro-9-H-carbazol-9-yl)propan-2-ol (Figure 18), on other side molecules with effective fungicidal activity in contradiction of *Candida albicans* in micro molar concentrations of compound 2-hydroxy-7-methoxy-carbazole-3-carb-aldehyde (Figure 19), The above mentioned compounds are characterized by minimum inhibitory concentration less than 16 µm against *Candida albicans*.[22]

The carbazole compounds were prepared and tested against four fungal strains such as *Candida albicans, Cryptococcus neoformans*, *tropicalis*, and *Aspergillus niger* followed by other four bacterial strains such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis*. Compounds from series-1 (8-Methoxy-9-Hcarbazol-3-yl)(4-methylpiperidin-1yl)methanone, (8-Methoxy-9-Hcarbazol-3-yl) (3-methyl-piperidin-1-yl)methan-one, and (8-Methoxy-9H-carbazol) (2-methylpiperidin)methan-one were found to have potential activity against several fungal and bacterial strains, particularly against *Cryptococcus neoformans* and *Staphylococcus aureus.* Additionally 8-Methoxy-(carbazol)-2-methyl-piperidin-1-yl-methanone showed antibacterial action against proven isolates of *Candida albicans* (MIC: 12.5 g/mL) and *Candida neoformans* (MIC: 6.25 g/mL). Compounds from series-2 exhibited significant activity against fungal and bacterial strains, particularly against *Candida neoforman* and Sta*phylococcus aureus*.[23]

Anticancer Activities

Kumar N *et al.*, synthesized and characterized the compounds which are obtained through the condensation of 2-(9Hcarbazole-9-yl)aceto-hydrazide with several aromatic aldehydes and piperazine in acid medium produce compounds of 2(9H-carbazol-9-yl)N-substituted-phenyl) (piperazin1-yl)methyl)aceto-hydrazide. Further newly prepared molecules screened for anticancer activity in contradiction of breast cancer cell line MCF-7 by Sulphorodamine-B assay technique by relating standard *Adriamycin*. Results of study revealed that the evaluated compounds 2[2-4(dimethylamino)phenyl4-5-dihydroimidaz-ol-1ylamino]-1-(carbazol)ethanone, 2[4-5-dihydro2(4methoxy-phenyl)imidazole-amino]-1-(carbazol)ethanone, 2(9-H-carbazol-9-yl)-N-[{(4hydroxyphenyl) (piperazin)]methyl}aceto-hydrazid, 2-[4,5-dihydro-2-(4-methoxyphenyl) imidazol-1-ylamino]-1-(9H-carbazol-9-yl)ethanone and 2(carbazol) N[{[(3-methoxy-phenyl-piperazin)}methyl]aceto-hydrazide are as good as to the standard with the value of growth inhibition 50 < 10µg / ml.[24]

Tomoki T *et al.*, Synthesized and explored the structure activity relationship of novel Carbazole and Carboline molecules. These studies indicated that the co-planar conformations of biphenyl entities contribute to powerful K-S-P stops. The carbazole molecules fused to a 6-elemented lactam ring on the second and third sites showed the powerful K-S-P A-T-P-ase inhibition activity and consequential cyto-toxicity by actual cycle of cell stops in the Meta-phase. That was also confirmed from the bio-chemical assay and selectivity forms for numerous kinesins that the carbolines and carbazoles molecules work by way of A-T-P-modest K-S-P inhibition molecules by likely binding in same position to the one for the biphenyl derivatives. In this investigation they showed that similar fused indole scaffolds might offer two unique K-S-P inhibitors such as 7-(trifluoromethyl)-9*H*-β-carboline (Figure 20) and 2-(trifluoromethyl)-9*H*-carbazole-piperidin-2-one (Figure 21).[25]

Antidiabetic Activity

Humphries P.S *et al.* synthesized novel compounds of carbazole-containing sulfonamides and sulfamides and also summarized that the compounds shows good amount of potency as cryptochrome modulators. Further structure activity relationship studies revealed many potent molecules with enhanced lipophilic effects. 1-(9*H*-carbazol-9yl)-3-(1,1-dioxido-1,2-thiazolidin-2-yl)propan-2-ol (Figure 22) reported as drug

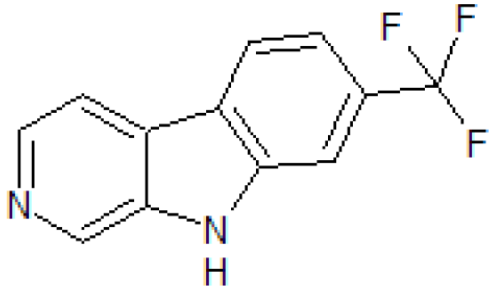

Figure 20: 7-(trifluoromethyl)-9H-b-Carboline.

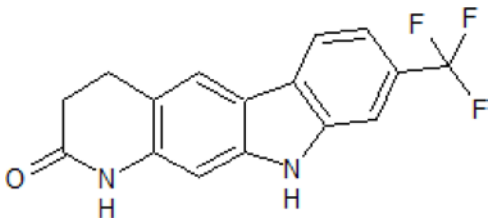

Figure 21: 2-(trifluoromethyl)-9H-carbzole-piperidin-2-one.

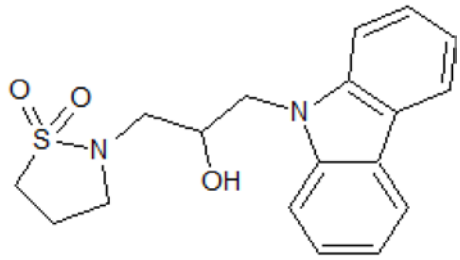

Figure 22: 1-(9H-carbazol-9-yl)-3-(1,1-dioxido-1,2-thiazolidin-2-yl)propan-2-ol.

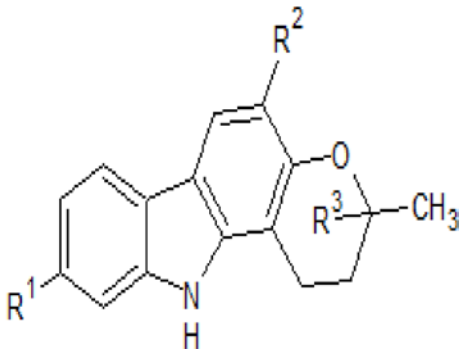

Figure 23: Mahanimbine: R1=H, R2=CH3, R3= -(CH2)2CH=C(CH3)2 Girinimbine: R1=H, R2=R3=CH3, Murrayacine: R1=H, R2=CHO, R3=CH3

like compound cryptochrome modulator nearly show oral effectiveness in animal model of type two-diabetes mellitus.[26]

Antiviral Activity

Murraya koenigii subjected for successive extraction for the following parts includes stem, bark, roots and leaves of with variety of solvents such as hexane, chloroform and methanol. Further followed by fractionation of these crude extracts by column chromatography separation to affords various carbazole which are characterized and recognized as mahanimbine, girinimbine, murrayacine (Figure 23) and 3-ethylcarbazole composed with beta-sitosterol showed robust activity against of Mosquito Larvae of *Aedes aegypti* through LC_{50} value of < 3 µg / mL.[27]

CONCLUSION

Several compounds of Carbazole were being prepared by synthetic routes and those molecules are showing good Pharmacological activities. Molecular property of carbazole as an important heterocyclic compound shows various significant activities specifically against diabetes, cancer, microbial and viral infections, inflammation, tuberculosis and malarial. Because of these broad ranges of activities, carbazole has fascinated the thoughtfulness of research scholars in findings of unique biological molecules. This review concludes that carbazole shows different spectrum of biological actions and also have huge possible to be studied for new beneficial abilities and the synthetic accessibility of carbazole molecules defined in this review would support chemists in planning and synthesizing of unique drug like agents in the treatment of several illness and syndromes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MIC: Minimum inhibitory concentration; **IC_{50}:** Half-maximal inhibitory concentration; **LC_{50}:** Lethal concentration 50.

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