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A REVIEW ON VARIOUS PHARMACOLOGICAL ACTIVITY OF NEWLY SYNTHESIZED CARBAZOLE MOIETIES

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ABSTRACT

Carbazole is an heterocyclic compound comprise of two- six member ring that it can be merge on both side of five membered ring hold nitrogen atom. The carbazole nucleus plays a important role in medicinal chemistry to synthesized a series of multiple biological active derivatives are anti-inflammatory, Anti-proliferative, Anti-bacterial, Antidiabetic, Antioxidant, Antifungal, Anticancer. All the carbazole derivatives and substituents are mention in article. These derivative of carbazole are tested for varying pharmacological activities. The main motive of the review article to describe their pharmacological action and activities against different type of bacteria using different type of models(in vitro assay, in vivo assay etc). Different types methods for synthesizing carbazole derivatives and pharmacological action are discussed.

KEYWORDS: Carbazole, Anti-cancer, Antibacterial activity, Antimicrobial, Antifungal, Anti-HIV activity.

INTRODUCTION HETEROCYCLIC COMPOUND

Carbocyclic compound are a cyclic compound having carbon atom in ring establishment. A heteroatoms are other than carbon. “Heteros”, it means “different” word derive by a greek. These hetro molecule are mostly Nitrogen, oxygen, and sulphur. Elements like P, B, Si, Sn, Al, As, Cu are also occasionally incorporated in the ring. Epoxides(e.g., ethylene oxide) and

lactones (e.g., γ-butyrolactone) are generally excluded due to the relative instability of their ring systems.

They are organize in aromatic and aliphatic. The aliphatic heterocyclics are amines, ether, thioethers, amide, etc. consist of 3-and 4-membered and 5to7 membered ring. Aromatic heterocyclic compounds are those compounds having a heteroatom in the ring and behave similar to benzene with few properties. It follow general rule introduced by Huckel. According to Huckel rule cyclic conjugated and planar systems having (4n+2) π electrons are acquire in aromaticity.

Heterocyclic ring may be saturated or unsaturated consist of three or more atoms. Also the ring may be similar or dissimilar containing more than one hetero atom.

The heterocyclic compound are aliphatic and aromatic compound having great interest in theoretical and practical standard. Heterocyclic compounds occour widely in nature and in a variety of non-naturally occurring compounds. heterocyclic compounds important to life compounds :- alkaloids, amino acids, haemoglobin, vitamins, hormones etc. and synthetic drugs and dyes having hetrocyclic ring systems. In biosynthesis and drug metabolism a heterocyclic chemistry are beneficial.

Carbazole profile

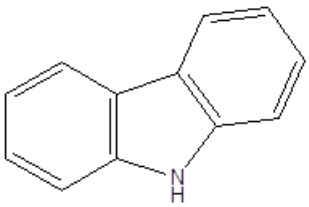
Carbazole is a heterocyclic compound having a two – six member benzene rings that can be merge on both side of a nitrogen containing five membered ring, nitrogen show vast electron delocalization. The molecular formula of carbazole is C_{12} H_9N.

It is structurally depend on the indole structure, second benzene ring is attach at 2-3 position five-membered ring of indole.

Carbazole used for making a chemical reagents, insecticides, lubricants, antioxidant etc. and use as analytical reagents and also organic synthesis.

Borsche-Drechsel cyclization is a classical laboratory organic chemistry of carbazole.

Carbazole is an constitute of tobacco smoke. The carbazole chemistry is similarly to indole.

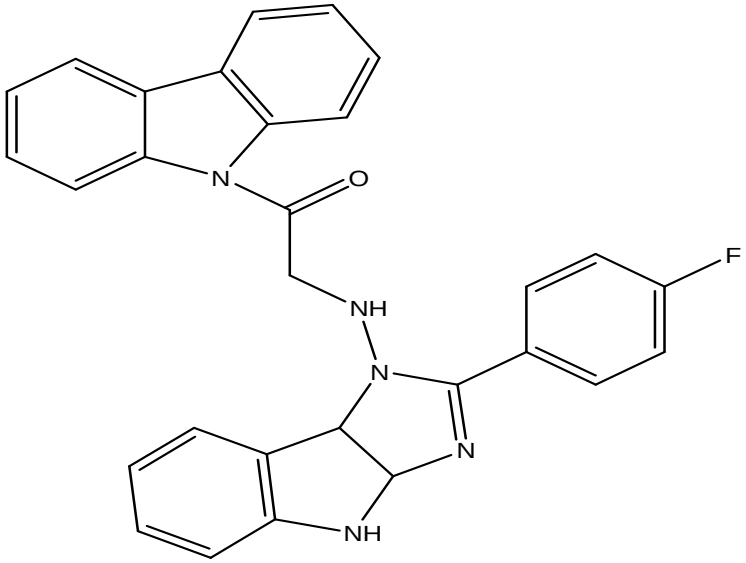


Structure of Carbazole

In 1872 the Graebe and Glazer first reported a chemistry of carbazole isolated from the anthracene distillate of coal tar and also Bhattacharya et al. from Glycosmis pentaphylla plant isolate a carbazole. Carbazole have fluorescent properties and also basic in nature .Carbazole having pi-electrons used in luminescence chemistry as a photosensitizing agent. In the synthesis of pharmaceuticals , agrochemicals , and other organic compounds carbaole and their derivatives used a intermediary . when a structure of carbazole change in pharmaceuticals such as carvediol and carazolol useded in the treatment of high blood pressure and tonprevent cardiac arrhymias and angina. The carbazole is the main part of some alkaloids. Furukawa et al reported 3-formylcarbazole separate from the root bark of M.euchrestifolia.

1. Anticancer activity.

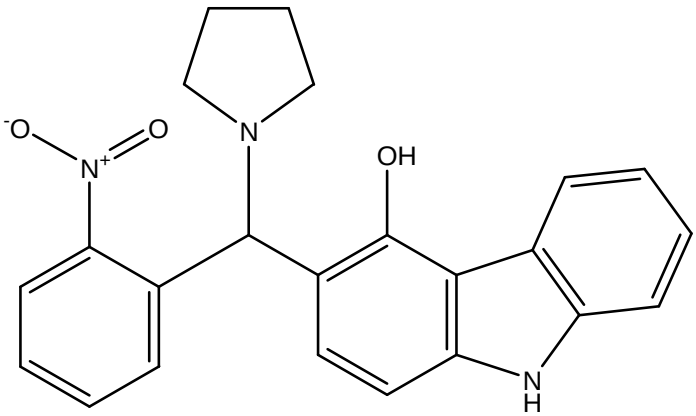
Devender Pathak *et al*. (2012) have been synthesized of some newer carbazole derivatives from a starting key product carbazole. carbazole on reacting with chloroacetyl chloride managed N^9-(chloroacetyl)-carbazole. Condensation of with various aromatic aldehydes managed N^9-(arylidene hydrazinoacetyl)-carbazoles followed by cycloaddition reaction to give the final product. All the synthesized compounds (**1a-1k**) structure characterization by applying FT-IR, MS, ^{1}H NMR, and elemental analysis. After structure confirmation goes for their pharmacological activity in SRB assay compare with their standard drug such as Adriamycin compounds **1a, 1d, 1h** and **1i** shows the promising anticancer activity against the *A549 cell lines*, but a substituted fluoro group in compound **1d** on Para position it forms a significant anticancer active compound**.**



2-(2-(4-fluorophenyl)-3a,4-dihydroimidazo[4,5-*b*]indol-1(8b*H*)-ylamino)-1-(9*H*-carbazol-9-yl)ethanone

2. Antioxidant activity

Pedavenkatagari Narayana Raddy *et al* (2017) newly synthesize a carbazole derivatives from (2a-2n) by Mannich bases using 4-hydroxycarbazole as starting material and evaluated for their antioxidant activity. Mostly newly synthesized compounds shows a higher active radical- scavenging activities than ascorbic acid. But Compound 2c show the largest Antioxidant activity (IC_{50}=16μM) compare with their standard drug ascorbic acid and rutin. The synthesized derivatives was characterized by use of IR, ^{1}H NMR, and Mass spectroscopy and elemental analysis. Ascorbic acid and rutin use as a reference.

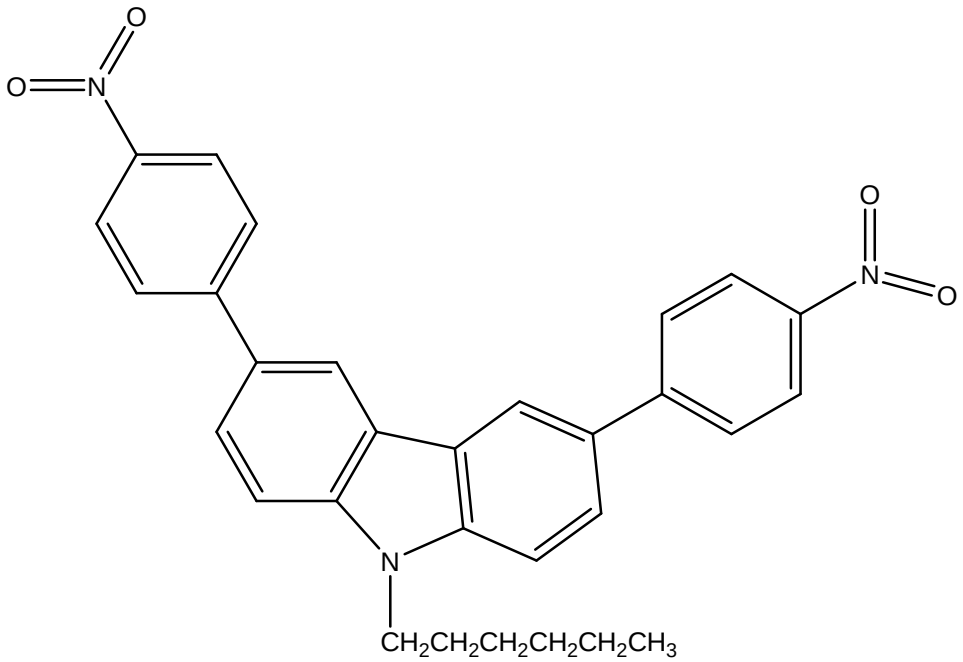


3-((2-nitrophenyl)(pyrrolidin-1-yl)methyl)-9*H*-carbazol-4-ol

3. Novel Scorpion –Like Carbazole derivatives shows Aggregation-Induced emission.

Sheng Hua Liu *et al* (2018) have synthesized a nitrophenyl substituted carbazole subordinates series(1-6) have carrying a D-π-A systems were readied and its photophysical

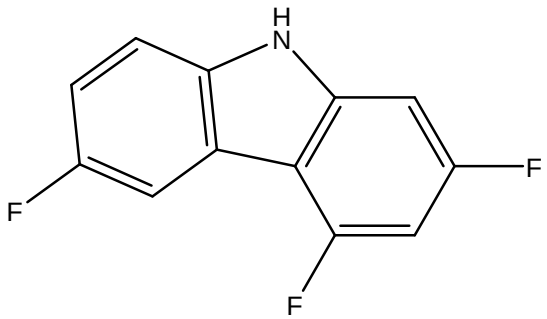
properties were examined nearly and deliberately. Compound 1,2,5 and 6 displayed Properties of AIE in mixture of DMF/Water ,and it forms a bright luminescence. The taget active compound may be structurally identify by NMR, ^{13}C NMR, and EI-MS. Compound 6 exhibit a mechanochromic property. It can be synthesized through a **pd catalyzed Suzuki coupling reaction** between the precursor 2a-5a and 4-nitrophenylbronic acid pinacol ester.



9-hexyl-3,6-bis(4-nitrophenyl)-9*H*-carbazole

4. Antibacterial activity.

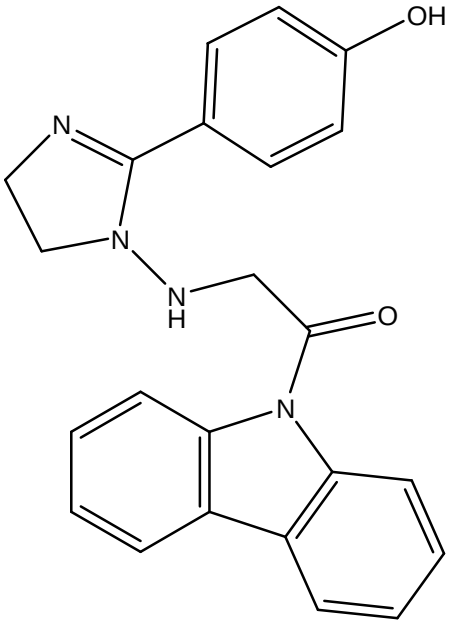
Sherg-liang Zhou et al. (2019) have synthesiszed a new fluorine-substituted carbazole series (1-8). All the compounds indicated possible activity against G-positive bacteria. Among the compound **1,2,4** shows the good antibacterial activity but compound **2** displays highly active antibacterial activity compare with their standard drug Meropenem. The structure were affirmed by IR, ^{1}H & ^{13}C NMR, MS.



2,4,6-Trifluoro-9H-carbazole

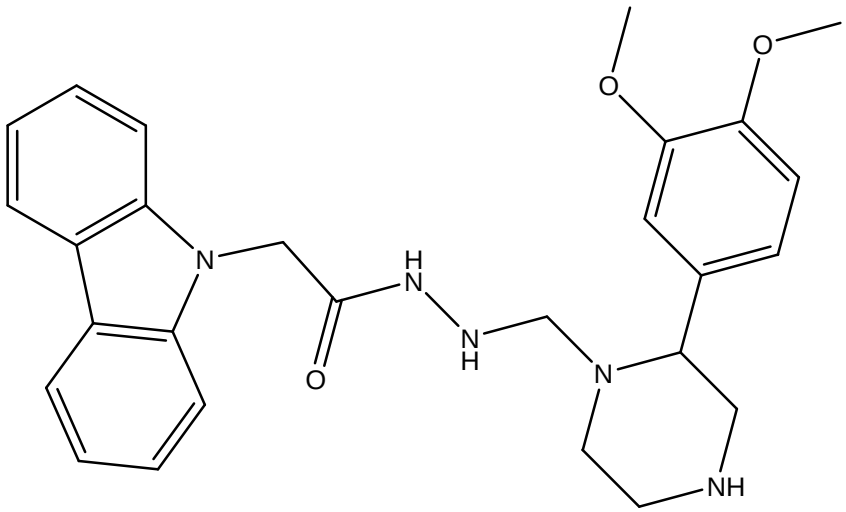
5. Anticancer Activity.

Nitin kumar *et al*. (2016) have synthesized a series of novel carbazole based derivatives **(1a-1e)** (**2a-2e**). all recently synthesized structure simply described by utilizing an IR, ^{1}H NMR, ^{13}C NMR, MS and elemental investigation. And tested *in-vitro* anticancer activity against human breast cancer cell using assay method of sulphorodamine B. Rebeccamycin used as a standard drug. Compound **1c and 2a** having hydroxyl and dimethoxy group as substituent respectively showed highest activity.



2-[4,5-dihydro-2-(4-hydroxyphenyl)imidazol-1-ylamino]-1-(9H-carbazol-9-yl)ethanone

(1c)

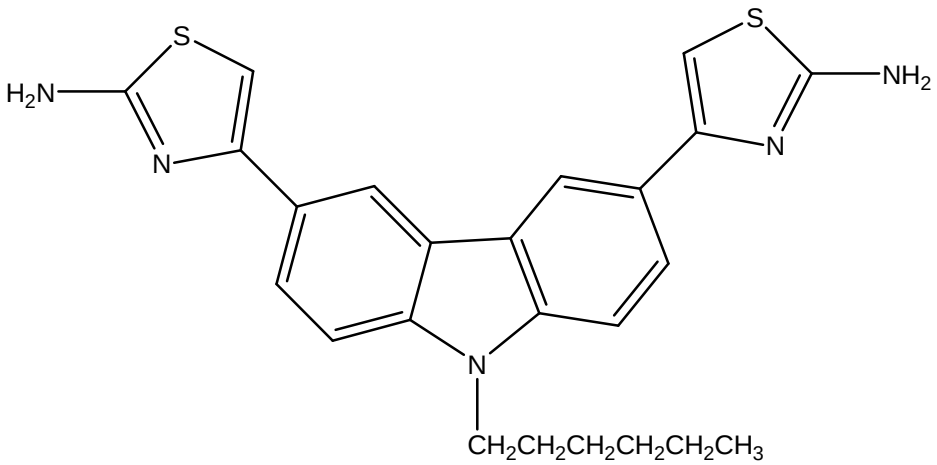


2-(9H-carbazol-9-yl)-N'-[{(3,4-dimethoxyphenyl)(piperazin-1-yl)}methyl]acetohydrazide

(2a)

6. Antimicrobial activity.

Ling Zhang *et al.* **(2016)** have synthesized a novel carbazole aminothiazoles series as a antimicrobial derivative (1a-j) were synthesized by involving a Friedel-crafts reaction a starting key a carbazole react with a alkyl bromides in a nitrogen atmosphere and follow friedel-crafts reaction and then compounds treat with thiourea reflux absolute ethanol gave a *N*-alkylcarbazole aminothiazoles using friedel craft reaction. All newly synthesized compound designed and characterized by using ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS spectra. Compounds may synthesized were enalyze for antimicrobial activities in vitro against Gram-positive bacteria (S. aureus ATCC25923,etc.), four Gram-negative bacteria (E. coli JM109, etc.) also five fungi (C. utilis ATCC9950,etc). carbazole aminothiazole 1f shows better inhibition activity against a MRSA (MIC = 4 µg/mL) Chloromycin & Norfloxacin as a reference drug.

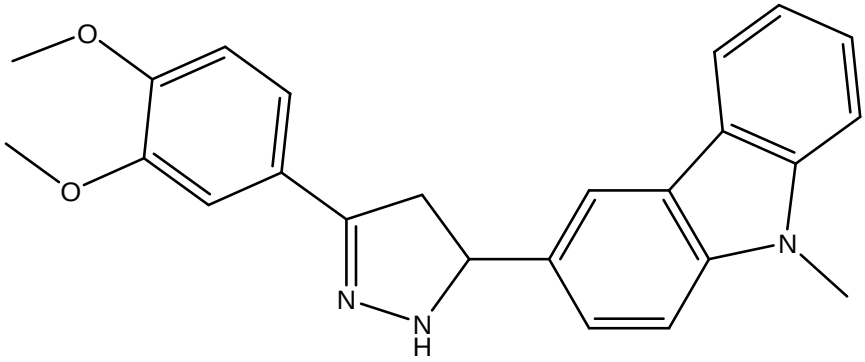


4-(3-(2-aminothiazol-4-yl)-9-hexyl-9*H*-carbazol-6-yl)thiazol-2-amine

7. Anti-inflammatory activity.

Babasaheb P. Bandgar *et al.* (2012) have synthesized a 3-(substituted)-aryl-5-(9-methyl-3-carbazole)-1H-2-pyrazolines series by using a Vilsmeier-Haack and Claisen schimdt condensation reaction starting key material a methylation of carbazole with methyl iodide give 9-methyl carbazole whi on Vilsmeier-Haack formylation and then Claisen schimdt condensation with avarious aromatic acetophenone and hetroaromatic acetophenone in sodium hydroxide and then compound further ethanol in hydrazine hydrate treated and it gave a final target compound (1a-o). All synthesized compound were descrived by IR, ^{1}H NMR and Mass spectroscopy and all compound analyze for *in vitro* & *in vivo* anti-

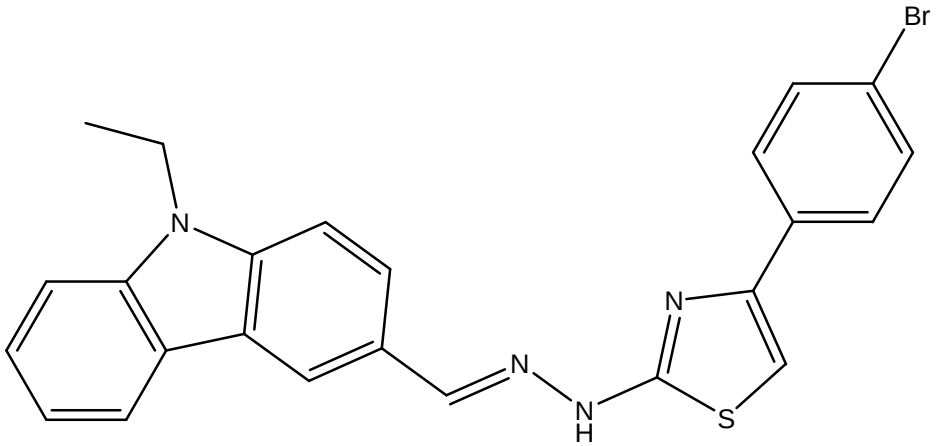
inflammatory activity. Compound **1c** shows a potential anti-inflammatory activities against COX inhibitor compare with their refrence indomethacin drug.



3-(3-(3,4-Dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)-9-methyl-9H-carbazole

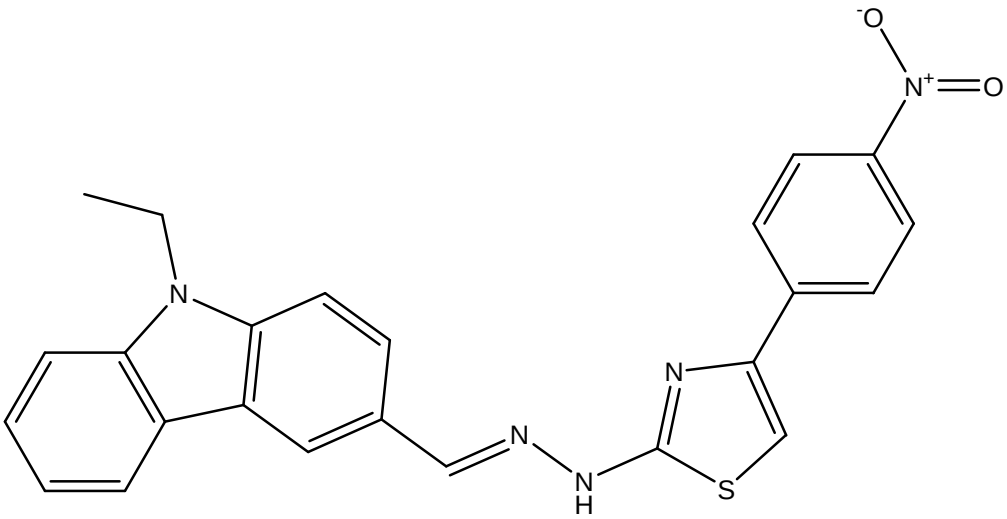
8. Anticancer activity

Soonheum Park *et al* (2015) have synthesized and characterized a novel series of (3a-3j) carbazole-based thiazole derivatives(3a-j). These newly synyhesized structure were described by IR, ^{1}H,^{13}C NMR and Mass spectroscopy. The compound (3f) and (3g) shows important or remarkable cytotoxicity against a three cancer cell lines A549, MCF-7 and HT29 by a MTT assay.



4-(4-bromophenyl)-2-(2-((9-ethyl-9H-carbazol-3-yl)methylene)hydrazinyl)thiazole

(3f)



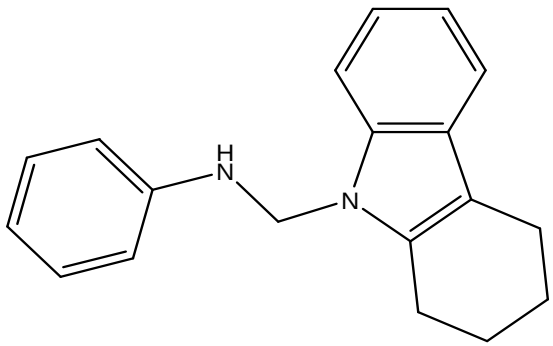
2-(2-((9-ethyl-9H-carbazol-3-yl)methylene)hydrazinyl)-4-(4-nitrophenyl)thiazole

(3g)

9. Antifungal activity

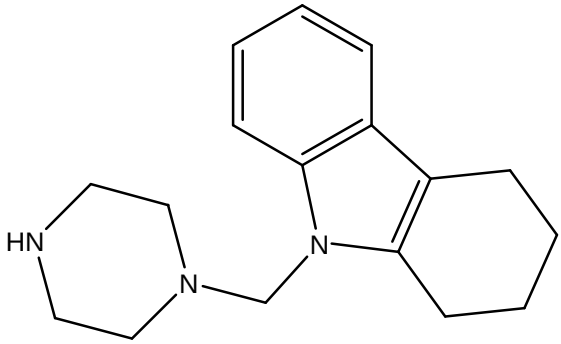
Periyasamy Parthiban *et al.*(2014) have synthesized a novel series of N-((5,6,7,8-tetrahydro carbazol-9-yl)methyl)substituted amines(PM1-PM5) derivatives follow mannich reaction. First step condensation of cyclohexanone, phenyl hydrazine, and glacial acetic acid yield 1,2,3,4,-tetrahydro carbazole mix with formaldehyde and with aromatic amine by mannich base reaction obtain final yield compound. The synthesized compound, characterized by IR, ^{1}H NMR, and MS. Its shows antifungal activity against C.albicans and A. niger at 50 and 100 µg/ml level, griseofulvin use as a standard drug. Compounds PM1 and PM5 shows a better antifungal against 100 µg/ml concentration.

[PM1]



N-((5,6,7,8-tetrahydrocarbazol-9-yl)methyl)benzenamine

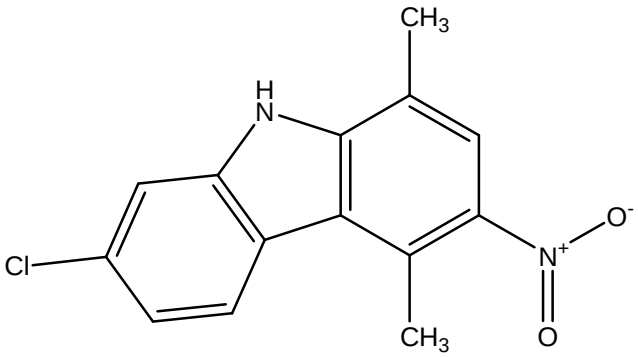
[PM3]



6,7,8,9-tetrahydro-9-((piperazin-1-yl)methyl)-5*H*-carbazole

10. Anti-HIV Activity

Fedora Grande *et al* (2018) have synthesized novel chain of carbazole 3-Nitro-1,4-dimethyl-9H-carbazole from a starting reaction 6-chloro-1.4-dimethyl-9H-carazoles(2a,b-4a,b) a indole react with a carbazole by a Cranwell and Saxton method yield 3-amino-1,4-dimethyl-9H-carbazole added to a solution of 1,4-dimethyl-9H-carbazole in dichloromethane added in acetic anhydride and nitric acid then obtain pure yield product. In all compounds the compound (3b) shows a potent activity. All synthesized compound were distinguished by Infrared, ^{1}H Nuclear magnetic resonance, and elemental analysis and a column chromatography. All compound Testing in luciferase and Escherichia coli β-galactosidase expressing CCR5+, CXCR4+, CD4+, TZM-bl cells .Maraviroc used as standard drug.

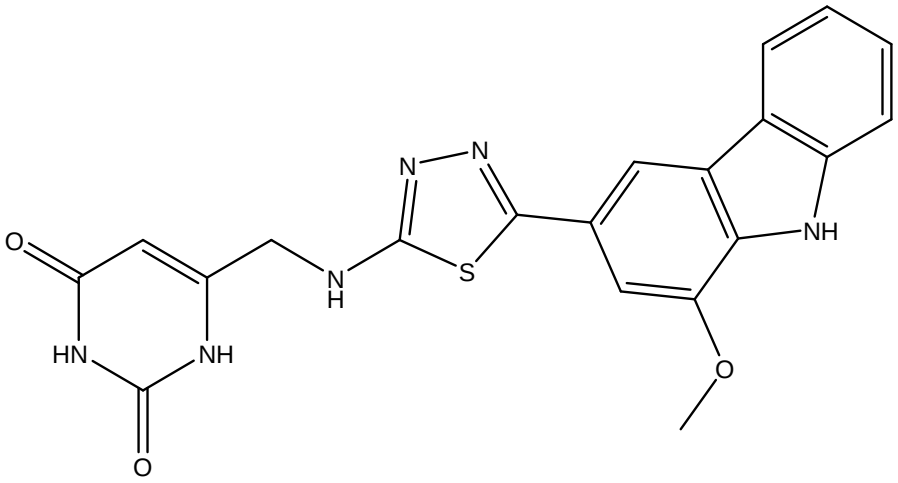


7-chloro-1,4-dimethyl-3-nitro-9*H*-carbazole

11. Anti-inflammatory Activity

Debarshi Kar Mahapatra *et al* (2018) have synthesized murrayanine-1,3,4-thiazole-uracil and the starting material reaction 5-(1-methoxy-9H-carbazol-3-yl)-1,3,4-thiadiazol-2-amine and 6-(chloromethyl)pyrimidine-2,4(1H,3H)dione triethylamine in ethanol to give the final compound. The synthetic compound 6-(((5-(1-methoxy-9H-carbazol-3-yl)-1,3,4thiadiazol-2-

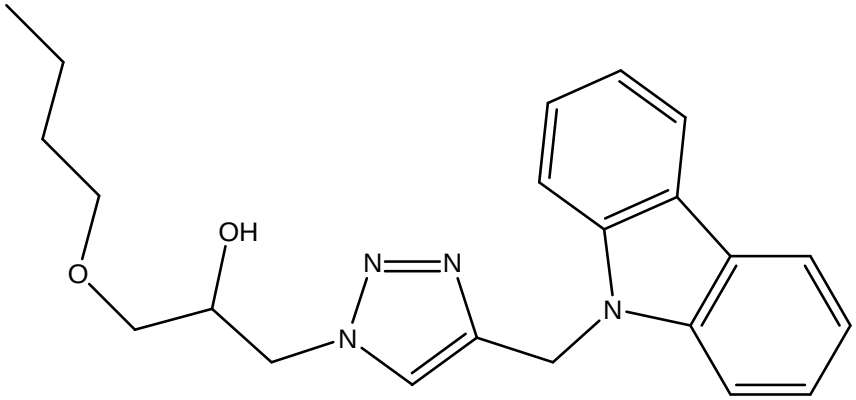
yl)amino)methyl)pyrimidine2,4(1H,3H)-dione shows potent anti-inflammatory activity. All synthesized compound structurally distinguish by FT-IR, ^{1}H NMR, MS, and elemental analysis. Indomethacin used as a standard drug for the activity may be in *in-vivo* using Carragenan-induced-paw edema. Murrayanine-1,3,4-thiazole has shows better anti-inflammatory activity.



6-((5-(1-methoxy-9*H*-carbazol-3-yl)-1,3,4-thiadiazol-2-ylamino)methyl)pyrimidine-2,4(1*H*,3*H*)-dione

12. Antifungal activity

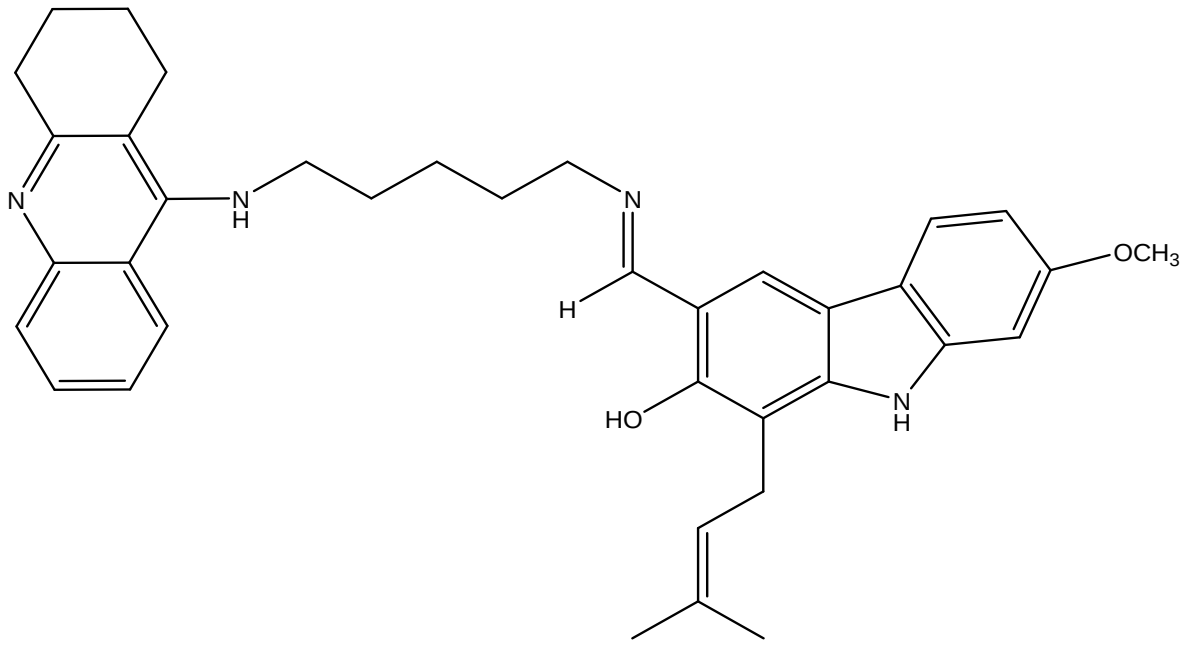
Mohammad Navid Soltani Rad et al (2016) have newly, synthesis, design and characterized some novel seires of 1,2,3-triazolyl β-hydroxy alkyl/carbazole hybrid molecule (10a-10n), followed by Huisgen condensation and cycloaddition reaction. There newly synthesized derivatives was distinguish by ^{1}H and ^{13}C NMR and IR. In biological screening mostly compounds are active against pathogenic fungi comprise *Trichophyton Rubrum, Candida albicans, Aspergillus niger,* and *Candida krusei* and also tested for Gram-positive bacteria included *Staphylococus aureus* and *Escherichia coli*. The active compound (10e) having better antifungal activity similar with Fluconazole & clotrimazole used as a standard drugs. DMSO as a solvent used to determine 10a-10n MIC_{50} value.



1-(4-((9*H*-carbazol-9-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-3-butoxypropan-2-ol

13. Alzheimer disease activity.

Chantana Boonyarat et al (2014) have discovered a new tacrine-carbazole hybrid as a anti-alzheimer agents for their cholinesterase inhibitory activities. These developing derivatives having high inhibitory activity against acetylcholinesterase with IC_{50} value from 0-48 to 1.03μm range. The compounds (S1-S3) were synthesized by reaction of antioxidant moiety with alkylenediamine it gave a target compound. The synthesize derivatives are distinguished by IR, MS, and ^{1}H and ^{13}C NMR. Compound **S1** having high potency for AChE inhibitory and radical scavenging activity also S1 improve memory defect in mice by reference scopolamine. At last Tacrine-carbazole derivatives as a potent pharmacological development in Alzheimer's disease.



N^{1}-(7-methoxyheptaphilline)-N^{6}-(1,2,3,4-tetrahydroacridine-9-yl)Pentane-1,5-diamie

CONCLUSION

The moiety carbazole and their its derivatives previously studied and gave better pharmacological and pathological condition it can be also briefly mention in the article. The article may be focused on their various derivatives such as 2-(2-fluoro-3a,4-dihydroimidazo[4,5-b]indol-1(8bH)-yl amino-1-(9H-carbazol-9-yl)ethanone shows better anticancer activity against A549 cell. Next compound 4-(3-(2-aminothiazol-4yl)-9-ethyl-9H-carbazol-6-yl)thiazol-2-amino shows antimicrobial activity against gram-positive and gram-negative bacteria and fungi 950, C.mycoderma ATCC9888 etc. Next compound 7-chloro-1,4-dimethyl-3-nitro-9H-carbazole shows anti-HIV activity against Luciferase and Eschericha coli β-galactosidase shows CCR5+, TZM-bl, CD4+, CXCR4+ cells and some other activities such as anticancer, anti-inflammatory, anti-proliferative, anti-microbial anti helminitic etc. are studied and also mention in the article. All carbazole derivatives shows different activity studied in previous years and also further still used in future to discover a new drug against many pharmacological and pathological activity.

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