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Review Article

A REVIEW ON "CARBAZOLES": CHEMISTRY AND PHARMACOLOGICAL ACTIVITY

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For over half a century, the carbazole skeleton has been the key structural motif of many biologically active compounds including natural and synthetic products. Carbazoles have taken an important part in all the existing anti-cancer drugs because of their discovery from a large variety of organisms, including bacteria, fungi, plants, and animals. In this article, we specifically explored the literature from 2012 to 2018 on the anti-tumor activities reported to carbazole derivatives and we have critically collected the most significant data. The most described carbazole anti-tumour agents were classified according to their structure, starting from the tricyclic–carbazole motif to fused tetra-, penta-, hexa- and heptacyclic carbazoles. To date, three derivatives are available on the market and approved in cancer therapy.

Key Words: carbazole, derivatives , anti-cancer drugs, anti-tumor activities .

INTRODUCTION

Heterocyclic compound is defined as any organic compound where their molecules are characterized by rings containing at least one atom other than carbon. These compounds are structurally similar to cyclic organic hydrocarbons, but their properties can vary widely from those of their hydrocarbon counterparts and are largely governed by the identity, location and number of heteroatoms present in the molecule. It is this rich diversity of physical and biological properties that has led to intense study of heterocyclic compounds. It follows then that heterocyclic chemistry is the study of all aspects of heterocyclic compounds.[1]

Heterocyclic systems are ring compounds containing atoms of at least two different elements as ring members. Organic heterocyclic systems contain one or more "foreign" elements such as oxygen, sulphur or nitrogen in addition to T Meghani et al Asian Journal of Pharmaceutical Research and Development. 2020; 8(3): 152-161 ISSN: 2320-4850 [153] CODEN (USA): AJPRHS carbon; atoms of such elements conceptually replacing carbon in a ring system have long been called hetero atoms. In recent years, however, the meaning of the term heteroatom has been broadened to include atoms other than carbon occurring in chains as

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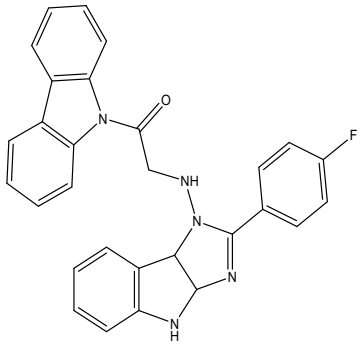
well as in rings. The general method of naming organic ring and chain systems based on the hetero atom concept is known as replacement nomenclature4 Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogues by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulphur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous. [2]

Pharmacological activity:

1. Anticancer activity:

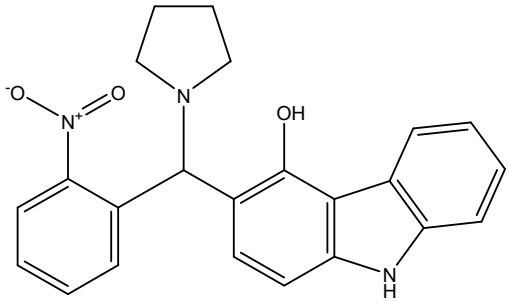
Devender Pathak etal. (2012) have been synthesized of some newer carbazole derivatives from a starting key product carbazole. carbazole on reacting with chloroacetyl chloride managed N9-(chloroacetyl)-carbazole. Condensation of with various aromatic aldehydes managed N9-(arylidene hydrazinoacetyl)-carbazoles 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, 1hand 1ishows the promising anticancer activity against the A549 cell lines, but a substituted fluoro group in compound 1don Para position it forms a significant anticancer active compound.



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

2. Antioxidant activity:

Pedavenkatagari Narayana Raddy etal(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 show a higher active radical- scavenging activities than ascorbic acid. But Compound 2c show the largest Antioxidant activity (IC50=16M) compare with their standard drug ascorbic acid



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

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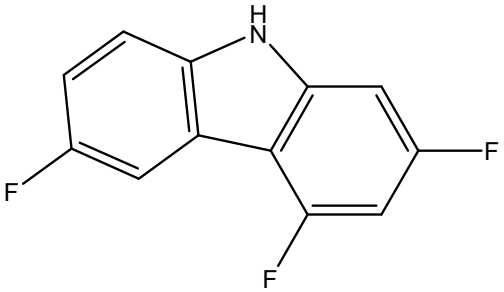
and rutin. The synthesized derivatives were characterized by use of IR, 1H NMR, and Mass spectroscopy and elemental analysis. Ascorbic acid and rutin use as a reference. [3-4]

3. Antibacterial activity:

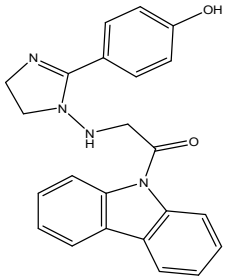
Sherg-liang Zhou et al. (2019) have synthesiszed a new fluorine-substituted carbazole series (1-8). All the compounds indicated possible activity against G-positive bacteria. Among the compound 1,2,4shows the good antibacterial activity but compound 2displays highly active antibacterial activity compare with their standard drug Meropenem. The structure was affirmed by IR, 1H & 13C NMR, MS. [5]



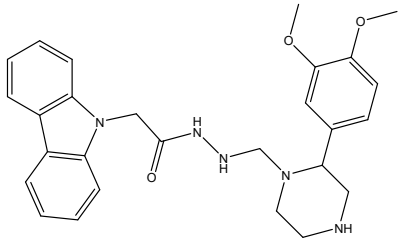
2,4,6-Trifluoro-9H-carbazole

4. Anticancer Activity:

Nitin kumar etal. (2016) have synthesized a series of novel carbazole based derivatives **(1a-1e)** (2a-2e). all recently synthesized structure simply described by utilizing an IR, 1H NMR, 13C 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 2ahaving hydroxyl and dimethoxy group as substituent respectively showed highest activity.[6]



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)

5. Antimicrobial activity:

Ling Zhanget 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*-alkyl carbazole aminothiazoles using Friedel craft reaction. All newly synthesized compound designed and characterized by using 1H NMR, 13C NMR, IR, MS and HRMS spectra. Compounds may synthesize were analyse for antimicrobial activities in vitro against Gram-positive bacteria (S. aureus ATCC25923, etc.), four Gram-negative bacteria (E. coli JM109, etc.) also five

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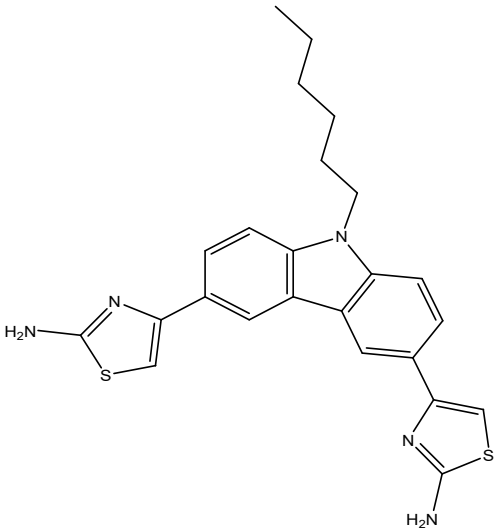
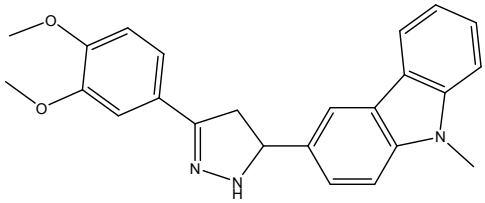
fungi (C. utilis ATCC9950, etc). carbazole aminothiazole 1f shows better inhibition activity against a MRSA (MIC = 4 µg/mL) Chloromycin & Norfloxacin as a reference drug.[7]



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

6. Anti-inflammatory activity:

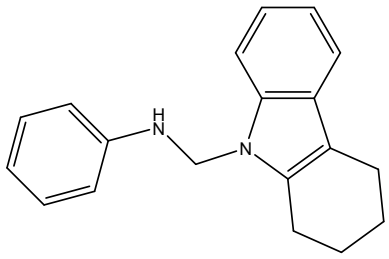
Babasaheb P. Bandgaret al.(2012) have synthesized a 3-(substituted)-aryl-5-(9-methyl-3-carbazole)-1H-2-pyrazolines series by using a Vilsmeier-Haack and Claisen schimdt condensation reaction starting key material a methylation of carbazole with methyl iodide give 9-methyl carbazole whi on Vilsmeier-Haack 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, 1H NMR and Mass spectroscopy and all compound analyze for *in vitro* &*in vivo* anti- inflammatory activity. Compound **1c** shows a potential anti-inflammatory activity against COX inhibitor compare with their refrence indomethacin drug.[8]



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

7. Antifungal activity

Periyasamy Parthiban etal. (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, 1H NMR, and MS. Its shows antifungal activity against C.albicans and



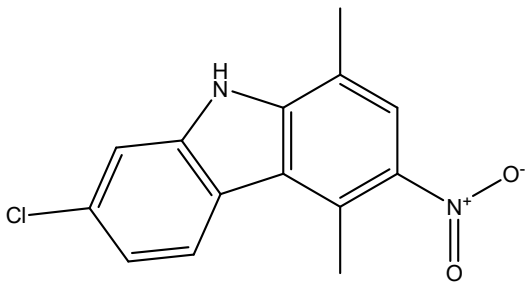
N-((5,6,7,8-tetrahydrocarbazol-9-yl) methyl) benzenamine

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.[9]

8. Anti-HIV Activity:

Fedora Grande etal(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) an indole reacts 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, 1H 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. [10-15]



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

9. 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 IC50 value from 0-48 to 1.03 m 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 1H and 13C 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. [16-17]

Conclusion:

Carbazole moiety is present in many compounds possessing various biomedical applications. Various synthetic drug molecules contain acarbazole nucleus as a part of their pharmacophore structure and it helps in affixing drugs to the residues of the binding site of desired targets.

Derivatives holding carbazole core exhibit different biological activities namely antidiabetic, anticancer, antimicrobial, anti-HIV, antiviral, anti-inflammatory, antioxidant, anticholinesterase, antitubercular, and antimalarial activities, etc. Due to these activities, carbazole has attracted the attention of researchers in the discovery of novel chemical entities. These chemical entities may be safer and effective drugs for various ailments. Summarizing the literature reports described above, we can say that carbazole

displays a diverse spectrum of biological activities. carbazole has an immense potential to be investigated for newer therapeutic possibilities. Chemistry of carbazole derivatives described in this review would help the researchers worldwide in the design and synthesis of novel drugs useful in the mitigation of various disorders.

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