A Review on Biological Activity of Heterocyclic Nucleus Carbazole

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Abstract

In this article we aimed to review existing literature and relevant websites regarding to heterocyclic nucleus such as carbazole and discussed about its biological activity. Carbazole contain most of the biological activities such as anti-inflammatory, antihypertensive, antianginal, antiarrhythmic etc. In this article we also discussed about the various carbazole containing drugs and there uses, IUPAC name and synthesis of carbazole nucleus.

Key words: Carbazole, antiarrhythmic, antianginal

Introduction

The history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. Some noteworthy developments were: Brugnatelli isolated alloxan from uric acid (1818), Dobereiner produced furfural (a furan) by treating starch with sulphuric acid (1832), Runge obtained pyrrole (“fiery oil”) by dry distillation of bones (1834), Friedlander synthesized indigo dye, allowing synthetic chemistry to displace a large agricultural industry (1906), Treibs isolated chlorophyl derivatives from crude oil, explaining the biological origin of petroleum (1936), Chargaff’s rules were described, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code (1951)1.

Heterocyclic chemistry has its origin in organic synthesis, natural products chemistry and medicinal chemistry. Indeed most any heterocyclic chemist will also consider themselves organic chemists and many will consider themselves to be natural products chemists and medicinal chemists as well. This relationship between disciplines arises because heterocyclic molecules are fundamental building blocks of biological systems. In addition to its importance to biology, heterocyclic chemistry has seen intense study in diverse areas such as dyes, photosensitizers, coordination compounds, polymeric materials and many other fields2.

Heterocyclic compounds

A 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 compounds3.

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
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 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.

Carbazole and its derivatives are an important type of nitrogen containing aromatic heterocyclic compounds, possess desirable electronic and charge-transport properties, as well as large π-conjugated system, and the various functional groups are easily introduced into the structurally rigid carbazolyl ring. These characteristics result in the extensive potential applications of carbazole based derivatives in the field of chemistry (photoelectrical materials, dyes, supramolecular recognition etc.) and medicinal chemistry (antitumor, antimicrobial, anticonvulsant, antihistaminic, anti-oxidative, anti-inflammatory, anti-diabetic, psychotropic agents, etc.).Carbazole alkaloids constitute an important class of naturally occurring heterocycles. A rough division of the carbazole alkaloids into three groups can be made. By far the largest group comprises alkaloids isolated from the Rutaceaefamily (=the Citrus family). The second group contains alkaloids of the hyellazole / carbazomycin, and the third group comprises of alkaloids that does not fall into the above two categories.

Carbazole alkaloids are of significant synthetic interest due to their range of biological activities. Carbazole rings are

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**CARBAZOLE**

| Abbreviation: | CARBAZOL |
|--------------|----------|
| IUPAC name:  | 9H-Carbazole |
| Synonyms:    | 9-Azafluorene |
|              | Dibenzo[b,d]pyrrole |
|              | Diphenylenimide |
|              | Diphenylenimine |

Carbazole is an aromatic heterocyclic organic compound. It has a tricyclic structure, consisting of two six-membered benzene ring fused on either side of a five-membered nitrogen-containing ring (Pyrrole).

The structure of compound is based on the indole structure but in which a second benzene ring is fused onto the five-membered ring at the 2-3 position of indole (equivalent to the 4a-9a double bond in carbazole)⁶.
present in a variety of naturally occurring medicinally active substances. For example, the carbazomycins are an unprecedented class of antibiotics with a carbazole framework. Carbazomycins A and B inhibit the growth of Phytopathogenic fungi and have antibacterial and anti-yeast activities. Many derivatives of the naturally occurring alkaloids elipticine and 9-methoxyelipticine which contain carbazole ring in their structure have been developed and tested for their anticancer activity. Carbazole is one of the most predominant tricyclic aromatic N-heterocyclic compounds in coal tar creosote and crude oil. It is used as a chemical raw material for the production of dyes, medicines, and plastics. By the virtue of their widespread occurrence in both important natural products (e.g. Alkaloids) and unnatural synthetic materials, as well as the broad spectrum of biological activity associated with these compounds, carbazole derivatives have received considerable attention in the literature, particularly in terms of their synthetic methodology. It is well-known that azole moieties such as oxadiazole, thiadiazole, imidazole, triazole nucleus as important pharmacophore appear extensively in various types of pharmaceutical agents, widely implicate in biochemical processes and display diversity of pharmacological activities.

SYNTHESIS OF CARBAZOLE NUCLEUS AND DERIVATIVES

A. Borsche-Drechsel Cyclization

\[
\text{2-Cyclohexylidene-1-phenylhydrazine} \xrightarrow{\text{HCl}} \text{Tetrahydrocarbazole} \xrightarrow{\text{Red lead}} \text{Carbazole}
\]

B. Bucherer Carbazole Synthesis

\[
\text{Naphthalen-1-ol} + \text{1-Phenylhydrazine} \xrightarrow{\text{NaHSO}_3} \text{7H-Benzol[c]carbazole}
\]

C. Pschorr Reaction

\[
\text{Carbazole}
\]
D. Various carbazoles can be synthesized from substituted biarylazides at 60°C using Rh$_2$(OCOC$_3$F$_7$)$_4$ or Rh$_2$(OCOC$_7$H$_5$)$_4$ as catalysts$^9$

![Substituted biaryl azide to substituted carbazole](image)

E. Synthesis of Carbazole from cyclization of 2-nitrobiphenyls.

![2-Nitrobiphenyls to Carbazole](image)

1.2 Marketed Drugs Containing Carbazole Moiety

![Carprofen](image)

**Figure: 5 Carprofen**

**IUPAC name:** 6-Chloro-α-methyl-9H-carbazole-2-acetic acid.

**Category:** Anti-inflammatory

![Figure: 6 Carvedilol](image)

**IUPAC name:** 1-([9H-Carbazole-4-yloxy]-3-[(2-(2-methoxy-phenoxy) ethyl]-2-propanol.

**Category:** Antihypertensive
Figure: 7 Carbazolol

IUPAC name: 1-(9H-Carbazol-4-yloxy)-3-[1-methyl-ethyl]amino]-2-propanol.

Category: Antihypertensive, Antianginal, Antiarrhythmic

Figure: 8 Carbazoleacetic acid

IUPAC name: Carbazyl-N-acetic acid

Category: In the detection of nitrates

Figure: 9 Cacotheline

IUPAC Name: 2,3-Dihydro-4-nitro-2,3-dioxo-9,10-secostrychnidin-10-oic-acid

Category: Muscle relaxant

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REVIEW OF LITERATURE

Anti-microbial activity

Salih N. et al. (2016) synthesized a series of 9H-carbazole derivatives. The synthesized compounds were tested for in vitro antibacterial activity against gram positive bacteria [Staphylococcus aureus (ATCC 6538), Bacillus subtilis (NRRL B-14819) and Micrococcus luteus (ATCC 21881)] and gram negative bacteria [Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853)] and Klebsiella pneumonia (clinical isolate)] by disk diffusion method by using Ampicillin trihydrate as standard drug. Compounds were also evaluated for in-vitro anti-fungal activity against fungi (Candida albicans, Candida tropicalis and Candida krusei) and moulds (Aspergillusniger, Aspergillusfumigatus and Tricophytonrubrum) by the serial plate dilution method using Clotrimazole and Miconazole as standard drugs. The result showed that Compound 12a and 12b has maximum antimicrobial activity.

Ahmad H. Abdullah et al. (2016) synthesized a selected set of N1-(4-chloro-9-ethylcarbazol-yl) amidrazones by reacting the respective hydrazonoyl chloride derived from 3-amino-9-ethylcarbazole, with an appropriate secyclicamine in ethanol in the presence of triethylamine. The compounds were evaluated for in-vitro antibacterial activity against Gram-positive [S. aureus (ATCC 25923), S. aureus (MRSA), B. cereus (ATCC 14579), C. xerosis (ATCC 00000)] . Gram-negative bacteria [Salmonella typhimurium (ATCC 14028), Klebsiellapneumoniae (ATCC 700603), and K. pneumonia and Shigellasonnei (ATCC 9290)], and fungus [Candida albicans] by standard broth dilution assay by using gentamycin as standard drug. The result showed that the compounds 13aaand 13bb exhibit the highest activity against MRSA and B. cereus, respectively.

L. V. Éktova et al. (2016) synthesized a indole [2,3-a]pyrrolo[3,4-c]carbazole-5,6-dione, the synthesized compound were evaluated for in-vitro anticancer activity against the different cell lines i.e. Leukemia (K-562, MOLT-4), Non-small cell lung cancer (NCI-H322M, NCI-H522), CNS tumors (SF-539, SNB-75), Melanoma (M14, SK-MEL-2), Ovarian tumors (OVCAR-4, SK-OV-3), Renal tumors (A498, SN12C), Breast tumors (MCF-7, HS 578T), Colon tumors (HCT-116, COLO205) by using the standard MTT test using the MTT reagent 2,4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide. The result shows the all compounds exhibit the high level of anticancer activity (IC₅₀= 10 6 – 108 M).

Chavanet al. (2019) synthesized a series of spirochromenocarbazole tethered 1,2,3-triazoles derivatives by one-pot, five component condensation reaction. The synthesized compounds tested for in-vitro anticancer activity against a panel of six human cancer cells namely MCF-7 and MDA-MB-231 (Breast Carcinoma), HeLa (Cervical Carcinoma), PANC-1 (Pancreas Carcinoma), A-549 (Lung Carcinoma) and THP-1 (acute monocytic leukemia) by MIT assay by using standard drug Paclitaxel and Doxorubicin. The result shows that compounds, 6f, 6k, 6g, 6s and 6u showed excellent activity towards MCF-7, MDAMB - 231 and HeLa cancer cell lines. The compound 6j was shows the good activity for all three cancer cell lines.
Peng-Hui Li et al. (2018) synthesized a series of carbazole derivatives containing chalcone analogs (CDCAs). The compounds were evaluated for in-vitro antiproliferative activity against four human cancer cell lines, including HeLa (human cervical cancer cell line), HL-60 (human acute leukemia cell line), A549 (adenocarcinomic human alveolar basal epithelial cancer cell line), and PC-3 (human prostate cancer cell line), by using the MTT (3-(4,5dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) assay by using standard drug Etoposide. The result shows that Compound 14a showed the most potent Topo II inhibitory activity15.

Gang Li et al. (2019) synthesized a methylene-bridged bis-carbazole. The compound were evaluated for in-vitro anticancer activity against four human tumor cell lines (human breast cancer cell), HepG2 (human liver carcinoma cell), HT29 (human colon cancer cell) and A375 (human malignant melanoma cell) by MTT assay by using standard drugs 5-Fluorouracil, Doxorubicin, Paclitaxel. The result shows that compound 15a exhibited the best anti-proliferative activities against HT-29, HepG2, A375 as well as MCF-7 cell due possibly to its selective G4-DNA binding nature16.

KarunanidhiMurali et al. (2017) synthesized a 2-amino-4-(3-bromo-4-methoxyphenyl)-8-chloro-11H-pyrimido[4,5-a]carbazole. The compounds were evaluated for in-vitro antitumor activities against two different cancer cell lines were utilized: MCF-7 (breast cancer) and A-549 (lung cancer) by MTT assay by using standard drug Cisplatin (IC50 =18±1.5).The result shows that Compound 16a exhibited significant activity against MCF-717.

Takashi Nishiyama et al. (2016) synthesized a carbazole-1,4-quinones derivatives. The compound were evaluated for in-vitro anti-proliferative activity against HCT-116 and HL-60 cell lines by MTT assay by using camptothecin as standard drug. The result shows monosubstituted derivatives were possess good anti-proliferative activity19.

PerumalSathiyachandran et al. (2018) synthesized a pyrrolo[2,3-a]carbazoles: 7-Chloro-2-oxo-3a-(2'-oxo-2',3'-dihydro-1'H-indol-3'-yl)-2,3,3a,4,5,10-hexahydro-pyrrolo[3,2-a]carbazole-1-carbonitrile derivative. The compound were evaluated for in-vitro anticancer activity against colon cancer cell lines (HCT-15 cells) by MTT assay for 24 hrs. by using Cisplatin as standard drug. The result shows that Compound 17a showed better anticancer activity20.
Lianqi Sun et al. (2016) synthesized a Carbazole Sulfonamide Derivatives. The compound were evaluated for in-vitro antitumour activity against different cell lines HepG2 cells (hepatoma cancer), MCF-7 (breast cancer), MIA PaCa-2 (pancreatic cancer), and Bel-7402 (hepatoma/liver cancer) by MTT assay using podophyllotoxin as standard drug. The result shows that new compounds 13f and 13i as potential potent antitumor activity.

Antidiabetic activity
ShaziaIqbal et al. (2017) synthesized a series of Newcarbazole linked 1,2,3-triazoles derivatives. The compounds were evaluated for in-vivo anti-diabetic activity by using α-glycosidase inhibition assay & acarbose used as standard drug. The compound were also tested for in-vitro cytotoxic activity against 3T3 (Mouse fibroblast) cell lines by MTT assay using cycloheximide as standard drug. The results shows that Compounds 7, 9, 10, 19, 20, and 23–26, showed a better activity than the standard α-glycosidase inhibitory drug, acarbose.. Compounds 18a (IC50 = 1.0 ± 0.057 lM) and 18b (IC50 = 0.8 ± 0.01 lM) were found to be most active among the series All the compounds 2–27 were found inactive, when tested for cytotoxicity against 3T3 cell lines, except a subset of four compounds (6, and 14–16).

Antituberculosis activity:
CarstenBörger et al. (2017) synthesized a series of 49 oxygenated tricyclic carbazole derivatives. The compounds were tested for in-vitro anti-tuberculosis activity against Mycobacterium tuberculosis strain H37Rv by the Micro plateAlomar Blue Assay (MABA) & Isoniazid and rifampicin (rifampin) used as standard drugs. The results shows that the compound 19a exhibit the anti-TB activity.

Antiviral activity:
Gerasimos Rassias et.al. (2019) synthesized carbazole derivatives. The compounds were tested for in-vitro antiviral activity against ZIKV NS3pro by inhibition assay using.
Neuroprotective activity:
Roshanak Ghobadian, et al. (2018) synthesized tetrahydrocarbazole benzyl pyridine hybrids. The compounds were tested for in-vitro neuroprotective activity against Butyryl cholinesterase (BuChE) inhibitors by Ellman’s method using Donepezil as a standard drug. The result shows that compound 20a (IC50 = 0.088±0.0009μM) exhibit the most potent BuChE inhibitor.

![Figure 18 Compound 20a](image)

Antiplasmodial and antischistosomal activities:
Weisi Wang et al. (2017) synthesized carizole amino alcohols derivatives. The compounds were tested for in-vitro anti-plasmodial and antischistosomal activity against Plasmodium falciparum 3D7 and Dd2 strains and adult and juvenile Schistosoma japonicum by P. falciparum whole cell assay using Chloroquine and dihydroartemisinin as standard drugs. The result shows that the compound 21a exhibit the most potent dual anti-parasitic activities.

![Figure 19 Compound 21a](image)

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