CARBAZOLE DERIVATIVES IN CANCER TREATMENT- A REVIEW

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ABSTRACT
Cancer is genetic irregularity of immortal cells which aggravates various metabolic disorders that can be fatal and also untreatable. Every year it causes millions of death and therefore notoriously ranked on the second place in the category of deadly diseases. Present circumstances pose a serious threat to the current anticancer chemotherapy and are mainly governed by poor selectivity, high toxicity and increased incidences of resistance. Therefore there is prerequisite need of the new alternative scaffold which can become a lead molecule to eradicate the cancer anomalies. Carbazoles represent an important class of heterocycles. These have been reported to exhibit diverse biological activities such as antimicrobial, antitumor, antiepileptic, antihistaminic, antioxidant, anti-inflammatory, antidiarrhoeal, analgesic, neuroprotective and pancreatic lipase inhibition properties. The carbazole derivatives have gained the attention of researchers due to their therapeutic potential against neurological disorders and cell proliferation. Here in an attempt is made to review the medicinal importance of recently synthesized carbazole derivatives.

KEYWORDS: Carbazoles, heterocycles, antidiarrhoeal, analgesic, neuroprotective.

INTRODUCTION
Heterocycles are inextricably woven into the life processes. The importance of heterocycles in drug discovery is one of the major areas in medicinal chemistry. There are a vast number of pharmacologically active heterocyclic compounds, many of which are being used clinically. Carbazole is an aromatic heterocyclic organic compound. It has a tricyclic
structure, consisting of two six membered benzene ring fused on either side with a five membered nitrogen-containing ring. Carbazole and its derivatives are an important type of nitrogen containing heterocyclic compounds that are widespread in nature. carbazole derivatives are well known for their pharmacological activities such as anti-inflammatory[1], analgesic[2], antiepileptic[3], antidiabetic[4], neuronal protecting[5], antimicrobial[6], antispasmodial[7], anti-bio film activity[8], antioxidant[9], antibacterial[10], immunological activity[11], anti HIV[12], anticonvulsant[13], antitumor[14], properties, etc. Keeping in view the so vast therapeutical potential of carbazoles, this review will summarize Antimicrobial and anticancer activities so far reported for the carbazoles derivatives.

**Anticancer activity**

1. A number of new 1-substituted-6H-pyrido[4,3-b]carbazole derivatives have been synthesized by Beata Tylinska et al and the compounds were subjected to preliminary in vitro cytostatic activity screening against murine leukemia (L1210), human lung cancer (A549) and human colon cancer (HT29) cell lines. One particular compound 6f exhibited over 20 times better activity against L1210 tumor cell line than the reference ellipticine.[15]

![Chemical structure of 6f](attachment:structure.png)

2. Kumar N, Sharma GK and Pathak D worked on the Microwave Assisted and Parallel Synthesis of Novel Substituted Carbazole Derivatives. The synthesized compounds were evaluated for their antibacterial and anticancer activity. Some of the synthesized carbazole derivatives exhibited significant cytotoxic activity against Ehrlich’s Ascites Carcinoma (EAC) and HEP2 cell lines.[16]

![Chemical structure of synthetic compounds](attachment:structure.png)
3. Mahadevan et al., Synthesized the 2, 3-Dimethylindoles and Tetrahydrocarbazoles via Fisher indole synthesis and evaluation of their the anticancer properties. The differently substituted 2,3-dimethylindoles and tetrahydrocarbazoles have reported to possess significant activity.\[^{17}\]

\[
\begin{align*}
R_1 &= H, F, CH_3, OCH_3 \\
R_2 &= H, F \\
R_3 &= H, F \\
R_4 &= H, CH_3, Ph, PhCN
\end{align*}
\]

4. L. Nagarapu et al., carried out the Synthesis and cytotoxicity evaluation of 1-[3-(9H-carbazol-4-yloxy)-2-hydroxypropyl]-3-aryl-1H-pyrazole-5-carboxylic acid derivatives. The cytotoxicity of synthesized compounds was evaluated by a SRB (sulforhodamine B) assay against cancer cell such as SKeNeSH human neuroblastoma (NB), human A549 lung carcinoma, human breast cancer MCF-7 cell lines. The results showed that seven compounds can suppress SKeNeSH tumor cancer cell growth. Among them, compound 3d was the most effective small molecule in inhibiting SKeNeSH cell growth.\[^{18}\]

\[
\begin{align*}
R, a &= 4-OCH_3 \\
b &= 3-OCH_3 \\
c &= 4-CH_3 \\
d &= 3-CH_3 \\
e &= 4-NO_2 \\
f &= 3-NO_2 \\
g &= 2-NO_2
\end{align*}
\]

5. Parita B. Shah et al worked on the Design, Synthesis and Anticancer Evaluation of Carbazole Comprised With 1,3,4-Thiadiazole Derivative; All the synthesized compounds are evaluated for their anticancer activity by MTT assay and compared with standard drugs. The test compounds showed significant anticancer activity.\[^{19}\]

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\text{Ar} = \text{Phenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-chlorophenyl, 4-chlorophenyl, (2-hydroxyphenyl, furan-2-yl)
\]

6. Norbert Haider et al carried out the Electrophilic Substitution of Dimethyl 1-Methylcarbazole-2,3-dicarboxylate: Synthesis of New b-Fused Carbazoles. Antiproliferative activity of compounds was assessed using an XTT assay method.\[^{20}\]
7. Tran Thi Thu Thuy et al carried out the Synthesis of novel derivatives of murrayafoline A and their inhibitory effect on LPS-stimulated production of proinflammatory cytokines in bone marrow-derived dendritic cells. Results indicated that murrayafoline A derivatives containing 1,2,3-triazole nucleus potentially possessed anti-inflammatory action through inhibiting production of IL-6, IL-12 p40 and TNF-α.[21]

8. Prudent et al. worked on the Antitumor Activity of Pyridocarbazole and Benzopyridoindole Derivatives that Inhibit Protein Kinase CK2 activity associated with cell cycle arrest and apoptosis in human cancer cells. Further, in vivo assays demonstrate antitumor activity in a mouse xenograft model of human glioblastoma.[22]

9. Devender Pathak et al synthesized some newer carbazole derivatives. All the synthesized compounds were evaluated for their antibacterial, antifungal and anticancer activity. The synthesized compounds were also evaluated for their anticancer activity by SRB assay method on A549 cell lines. All the newly synthesized substituted carbazoles have shown moderate to good antibacterial, antifungal and anticancer activity.[23]
10. E. Lampropoulou et al worked on the Pyrrolo[2,3-a]carbazole derivatives as topoisomerase I inhibitors that affect viability of glioma and endothelial cells in vitro and angiogenesis in vivo. All the tested compounds significantly decreased topoisomerase I activity in a concentration dependent manner. Finally, all the tested compounds inhibited angiogenesis in the chicken embryo chorioallantoic membrane in a significant and dose dependent manner, with the most effective inhibitor being compound 1d.\textsuperscript{[24]}

11. Chen et al worked on the BC3EE2, 9B (bis (carbazole-2, 9N-benzyl)-3-ethyl ethanoate), a synthetic carbazole derivative, upregulates autophagy and synergistically sensitizes human GBM8901 glioblastoma cells to temozolomide. In this study, anti-glioblastoma profiles of a series of synthetic carbazole derivatives were evaluated \textit{in vitro}. The most promising derivative in this series was BC3EE2, 9B, which showed significant anti-proliferative effects in GBM8401 and GBM8901 cells.\textsuperscript{[25]}

12. Molatlhegi RP, Phulukdaree A, Anand K, Gengan RM, Tiloke C, Chuturgoon AA; studied the Cytotoxic Effect of a Novel Synthesized Carbazole Compound on A549 Lung Cancer Cell Line. The study results the anticancer potential of ECAP on lung cancer.\textsuperscript{[26]}
13. Charles S. Vairappan worked on the Biological Activity of Carbazole Alkaloids and Essential Oil of Murraya koenigii Against Antibiotic Resistant Microbes and Cancer Cell Lines. The findings from this investigation are the first report of carbazole alkaloids’ potential against antibiotic resistant clinical bacteria, MCF-7 and P388 cell lines. [27]

14. Uraiwan Songsiang studied the Antioxidant activity and cytotoxicity against cholangiocarcinoma of carbazoles and coumarins from Clausena harmandiana. These compounds were evaluated for antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and lipid peroxidation assay and cytotoxicity against cholangiocarcinoma, KKU-OCA17 and KKU-214 cell lines. The two compounds exhibited strong cytotoxicity against KKU-OCA17 (IC50=88.7 and 46.1 μM, respectively) and KKU-214 (IC50=43.7 and 39.1 μM, respectively) cell lines. [28]

15. Lan-Xiang Liu synthesized novel N-substituted carbazole imidazolium salt derivatives and evaluated for the antitumor activity against five human tumor cell lines by MTS assay. [29]
CONCLUSION
The different type of carbazole derivatives were shown a wide spectrum of biological activities. The plethora of research described in this review indicates the wide spectrum of anticancer activities exhibited by carbazole derivatives. The biological profiles of these new generations of carbazole would represent a fruitful matrix for further development of carbazole nucleus, which can be a lead nucleus for future developments to get safer and effective anticancer therapeutic agents.

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