

A Comprehensive Review of Carbazole Based Heterocyclic Hybrids in Multi Target Drug Design

Anusree V S ¹ || Dr. Hima C S ² | Dr. S M Sandhya ³ | Dr. Shaiju S Dharan ⁴

¹ Student Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram.

² Professor, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram.

³ HOD, Professor, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram.

⁴ Principal, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram.

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ABSTRACT

The growing prevalence of multifactorial diseases such as Alzheimer's disease, cancer, diabetes, microbial infections and inflammatory disorders has highlighted the limitations of the conventional one drug one target therapeutic approach. As a result, multi target directed ligands (MTDL) have become a viable tactic for concurrently modifying several pathogenic pathways implicated in development of disease. Because of the tricyclic aromatic structure, favourable lipophilicity, ease of functionalization and variety of pharmacological actions, carbazole has gained significant attention among the several heterocyclic scaffolds investigated in medicinal chemistry. The carbazole nucleus is a desirable platform for hybrid drug discovery because of its exceptional neuroprotective, antioxidant, anticancer, antibacterial, anti-inflammatory and antidiabetic properties. This review highlights recent advances in the development of carbazole based heterocyclic hybrids as multifunctional therapeutic agents. Various molecular hybridization strategies involving carbazole conjugation with pharmacologically relevant scaffolds such as tacrine, stilbene, quinolinium, chromene, indole, pyridine, triazole, quinoline and pyrazoline are discussed. The influence of linker architecture, electronic modifications and substitution pattern on biological activity is also examined. The findings demonstrate that carbazole-based hybrid design can effectively interact with multiple biological targets and offering enhanced efficacy, reduced toxicity and improved pharmacological profiles. Overall, carbazole based heterocyclic scaffold represent a versatile and promising class of compounds for the development of next generation therapeutics aimed at the management of complex diseases.

Keywords: Carbazole, MTDL, Alzheimer's disease, Anticancer, Anti-inflammatory

INTRODUCTION

A major obstacle in the field of drug discovery and development is the ongoing growth of complicated and multifactorial disorders.¹ Disorders such as Alzheimer's disease, cancer, diabetes, inflammation and microbial infection involve multiple pathological pathways and molecular targets that contribute simultaneously to disease progression.² Because modulation of a single biological target is insufficient for controlling the complex network of pathogenic processes, conventional therapeutic techniques focussed on the one drug one target approach frequently fail to produce full clinical benefits.^{3,4} As a result, the focus of contemporary medicinal chemistry has switched to the creation of medicinal compounds with the ability to interact multiple biological targets at once. This innovative strategy, multitarget directed ligand (MTDL) has gained a lot of attention in now a day since it enhances therapeutic efficacy and reduces adverse effects and drug resistance.⁵

The goal of multitarget drug design is to incorporate several pharmacological actions into a single chemical structure. Multi target-directed ligands have the advantages of simpler pharmacokinetics, better patient compliance, less drug-drug interactions and more therapeutic synergy when compared with the combination therapy, which administers numerous medication individually.⁶ The multi target approach is useful when an ailment combines oxidative damage, inflammation, protein aggregation mitochondrial failure and neurotransmitter imbalance. Thus, in contemporary pharmacological research, the designing of multifunctional compounds that may modulate many pathogenic processes has emerging as an appealing approach.⁷

Because of their remarkable structural diversity and broad spectrum of pharmacological activities, heterocyclic compounds have gained significant attention in hybrid drug design. Heterocyclic rings are occurred in many therapeutically significant compounds, underscoring their importance in medicinal chemistry. Among these scholars have concentrated especially on nitrogen containing heterocycles because of their impressive pharmacological potential and the fact that many clinically effective medications contain them.⁸

Carbazoles are aromatic heterocyclic molecules that contain nitrogen. Its structure is made up of a five membered ring that contain nitrogen and two benzene rings joined on either side. The distinctive electrical and charge- transport capabilities of the carbazole nucleus are attributed to its stiff tricyclic structure and extended π conjugated system. Furthermore, the carbazoyl ring is a flexible scaffold for structural alteration and drug design since it makes it simple to introduce a wide array of functional groups in different positions.⁹

The favourable lipophilic nature of carbazole derivatives and their exceptional capacity to permeate biological membranes, particularly the blood-brain barrier are two of their main advantages. Because of this characteristic, carbazole compounds are very useful in treating illness of CNS disorders, according to several studies. Acetylcholinesterase enzyme inhibition, mitochondrial function stabilization and neuronal cell apoptosis protection are all possible with carbazole derivatives.¹⁰

The vast variety of biomedical properties of compounds generated from carbazole have been extensively described in scientific literature. Neuroprotective, antioxidant, anticancer, antidiabetic and pancreatic lipase inhibitory qualities are among them. This broad-spectrum action emphasizes the carbazole scaffold's medicinal significance.¹¹

Chemistry of Carbazole

Carbazole is a prominent nitrogen containing heteroaromatic molecule that has gained substantial interest across the various field of medicinal chemistry, organic synthesis and material science. Its unique tricyclic structure composed of two benzene rings fused to a central pyrrole ring, provide rigidity and highly conjugated aromatic framework that brings to its unique biochemical and biological triats. Carbazole has become a crucial core element in the designing of novel medicinal compounds and functional materials because of its structural adaptability and advantageous physicochemical properties.¹²

A dibenzopyrrole system with the chemical formula $C_{12}H_8N$ makes up the molecular structure of carbazole. The electronic properties of the molecule are mostly determined by the nitrogen atom contained in the centre ring. The nitrogen lone pair's involvement in the aromatic conjugation influences the carbazole nucleus's reactivity toward several chemical transformations while also improving its stability.¹³ The electron-rich and planar shape of the scaffold encourages intermolecular interactions like π - π stacking and bonding of hydrogen, which are essential both biological activities and material applications.¹⁴

From a synthetic perspective, carbazole can go through a range of functionalization processes and shows significant chemical flexibility. Because of very high electron density at the C-3 and C-6 locations, electrophilic substitution reactions frequently take place there. To produce structurally varied carbazole derivatives, reactions like halogenation, nitration, sulfonation, and acylation have been widely used.

Furthermore, the nitrogen atom provides a handy location for N-functionalization by acylation, alkylation, and other derivatization techniques. These changes allow carbazole-based molecules' physicochemical and pharmacological characteristics to be adjusted, increasing the range of possible uses for them.¹⁵

Species of plants especially those that belonging to the genus *Murraya*, have been discovered to contain carbazole alkaloids that exit naturally.¹⁶ Numerous biological actions, including as antioxidant, antibacterial, anti-inflammatory, anticancer, and neuroprotective properties, have been established by these naturally occurring chemicals. Extensive study into the synthesis and biological assessment of novel carbazole analogues and hybrid compounds has been prompted by the discovery of these bioactive natural chemicals.¹⁷

Carbazole is well known in medicinal chemistry as a special framework that communicates with various types of biological targets. There is evidence of significant pharmacological action for a number of carbazole derivatives through mechanisms such DNA binding, kinase inhibition, receptor modulation, and enzyme inhibition.^[14] The scaffold has been especially beneficial in the synthesis of multitarget-directed ligands for complicated disorders due to its structural rigidity, aromaticity, and ability to accommodate an array of substitution patterns. As a result, carbazole-based hybrid compounds have been most commonly studied for potential application in the treatment of infectious diseases, cancer, neurological conditions, and inflammatory diseases.¹⁸

Carbazole has made a contribution in the field of innovative materials outside of pharmaceutical research. Its excellent thermal stability, electron-donating ability, and charge-transport characteristics have led to its widespread use in organic electronic devices.¹⁹ Carbazole-containing materials have been employed in organic light-emitting diodes, photovoltaic cells, photorefractive systems, photoconductors, and fluorescent sensors. The extended π -conjugated system of carbazole facilitates efficient electronic communication, making it an attractive building block for the design of high-performance optoelectronic materials.²⁰

Overall, the carbazole nucleus is a very important and adaptable heterocyclic framework whose special blend of chemical stability, synthetic accessibility, and biological significance continues to spur innovation in materials research and drug discovery.²¹ A large range of molecules with improved pharmacological and functional qualities have been developed thanks to the carbazole scaffold's ability to be modified through different structural transformations, underscoring its ongoing significance in modern scientific study.²²

Design Strategies for Carbazole Hybrids

The design of carbazole-based heterocyclic hybrids is an important and rapidly advancing approach in multitarget drug discovery. By integrating the pharmacological properties of two or more physiologically active scaffolds into a single molecular framework, hybrid design aims to provide multifunctional therapeutic medications with improved efficacy, selectivity, and reduced toxicity. The rigid, planar, aromatic structure, electron-rich nitrogen atom, favourable lipophilicity, and wide varieties of biological activities, including antioxidant, anticancer, antimicrobial, anti-inflammatory, and neuroprotective effects, make the carbazole nucleus an ideal pharmacophore for hybridization.²³

Molecular hybridization, which links the carbazole scaffold to another physiologically active heterocyclic molecule like tacrine, triazole, pyridine, pyrimidine, quinoline, indole, benzothiazole, coumarin, chalcone, or imidazolidin-4-one, is also one of the main design strategies. The idea behind this strategy is to combine various pharmacological actions into a single molecule with the ability to interact with multiple disease-related sites at once. When treating multifactorial diseases that include numerous pathogenic pathways, like cancer, Alzheimer's disease, and inflammatory disorders, this approach is very helpful.²⁴

Biological activity, molecular flexibility, target engagement, and pharmacokinetic behaviour are all significantly influenced by the linker that joins the carbazole nucleus to another pharmacophore. Relying on the intended biological activity and therapeutic target, a wide variety of linkers such as alkyl chains, amide bonds, ether linkages, triazole rings, and hydrazone groups, are frequently used. The orientation of

pharmacophoric groups and their capacity to successfully interact with biological receptors or enzymes are strongly influenced by the length and flexibility of the linker.²⁵

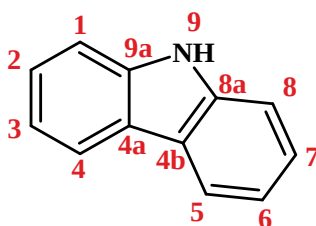
Electronic modification is also an essential strategy used in carbazole hybrid development. Introduction of electron-donating or electron-withdrawing substituents at different positions of the carbazole nucleus can greatly affect lipophilicity, binding affinity, antioxidant activity, and overall pharmacological properties. While electron-withdrawing groups like halogens and nitro groups may boost anticancer and antibacterial properties, electron-donating groups like methoxy and amino substituents frequently increase antioxidant and neuroprotective actions. Therefore, structural changes are carefully planned to maximize treatment efficacy and target selectivity²⁶.

When designing carbazole hybrids, planarity and aromaticity are also taken into account. Carbazole's planar aromatic structure enables it to communicate with biological macromolecules, including DNA and β -amyloid clumps through π - π stacking. This property is particularly important in anticancer and anti-Alzheimer drug development. Hybridization with aromatic heterocyclic systems further enhances these interactions and improves biological activity. In neuroprotective drug design, carbazole hybrids are often developed to simultaneously inhibit acetylcholinesterase, reduce oxidative stress, and prevent β -amyloid aggregation through multifunctional molecular interaction.

Lipophilicity and blood-brain barrier permeability are also critical parameters in the design of carbazole hybrids intended for central nervous system disorders. The carbazole nucleus has favourable lipophilic characteristics by nature, which make it easier to pass through biological membranes, such as the blood-brain barrier. Therefore, structural changes are selected to minimize toxicity, increase aqueous solubility, and preserve sufficient lipophilicity. Incorporation of cationic groups or hydrophilic substituents is sometimes employed to balance membrane permeability and pharmacokinetic properties.²⁷

Structure-Activity Relationship (SAR)

Because of its stiff planar aromatic structure and electron-rich nitrogen atom, the carbazole nucleus itself has a major role in biological activity in carbazole hybrids. While the planar aromatic system encourages π - π stacking interactions with proteins, enzymes, DNA, and β -amyloid clumps, the nitrogen atom improves connections with biological targets through hydrogen bonding. According to SAR research, pharmacological action is significantly influenced by replacement at various carbazole ring locations. In determining antioxidant, anticancer, antibacterial, and neuroprotective activities, changes at the third, sixth, and ninth positions are especially significant.²⁸ The rigid, planar carbazole ring provides a privileged structure for binding to multiple AD-relevant targets due to its aromaticity and ability to accommodate various substituents at multiple positions. N-alkylation or N-substitution increases the lipophilicity, BBB penetration and enhances the binding affinity for amyloid peptides and cholinesterase enzyme. Substituents at the 3rd position or other positions can increase the planarity or provide hydrogen bonding capability can disrupt amyloid beta assembly and aggregation, stabilizing soluble forms and reducing toxicity.



Carbazole Nucleus

Electron-donating substituents such as methoxy, methyl, and amino groups typically enhance antioxidant and neuroprotective activities by increasing electron density within the aromatic system and improving the capacity to scavenge free radical. These substitutions also contribute to enhanced interaction with acetylcholinesterase and other neurological targets. On the other hand, by increasing lipophilicity and

strengthening contact with enzyme active sites and cellular membranes, electron-withdrawing groups such as halogens, cyano, and nitro substituents frequently boost anticancer and antimicrobial activity.²⁹

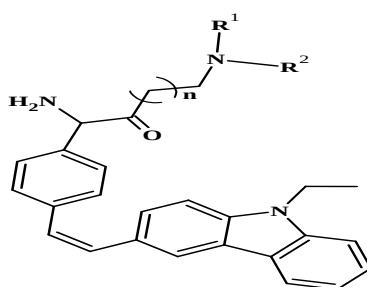
MTDL Strategies for Alzheimer's Disease

Alzheimer's disease is the most frequent cause of dementia and is a progressive neurological condition characterized by aberrant behaviour, cognitive deterioration, and memory loss and difficulty performing daily activities^{30,31}. Numerous pathogenic pathways, including the development of β -amyloid plaque, hyperphosphorylation of tau protein, cholinergic dysfunction, oxidative stress, neuroinflammation, and neuronal death, are linked to the condition.^{32,33} Drugs that are currently on the market, like as memantine and donepezil, simply relieve symptoms; they do not effectively halt the progression of the disease. Due to the multifaceted character of Alzheimer's disease and the limited effectiveness of the traditional single-target method, Multitarget-Directed Ligands (MTDLs) have emerged as a possible therapeutic option.^{34,35} Acetylcholinesterase inhibition, β -amyloid aggregation inhibition, antioxidant activity, metal chelation, and neuroprotection are few of the biological targets that MTDLs are intended to interact with concurrently.³⁶ This strategy has the potential to halt the progression of the disease, improve therapeutic efficacy, and minimize adverse effects. The creation of efficient multitarget treatments for Alzheimer's disease has showed great promise in recent research on hybrid compounds comprising carbazole, tacrine, quinoline, and imidazolidinone scaffolds.^{37,38}

Carbazole-Stilbene Hybrid Design

When creating multi-target-directed ligands for complicated illnesses like Alzheimer's disease, hybridization techniques has proven to be a successful method. In this regard, a lot of carbazole-stilbene hybrids have been developed, synthesized, and described by Patel V. and his associates as multifunctional medications for the therapy of Alzheimer's disease. Carbazole and stilbene, two biologically relevant scaffolds, were combined into a solitary molecular framework as part of their design strategy to provide a range of therapeutic effects.³⁹

The stilbene moiety brings antioxidant and anti-amyloid capabilities, while the carbazole nucleus offers a planar aromatic structure that is favourable for enzyme binding and π - π interactions. The formed substances were analysed for evaluating their ability to block butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE). Compound 50 showed an IC₅₀ value of 2.64 μ M against AChE and BuChE, which renders it the most promising derivative among them.⁴⁰



Carbazole-stilbene hybrid

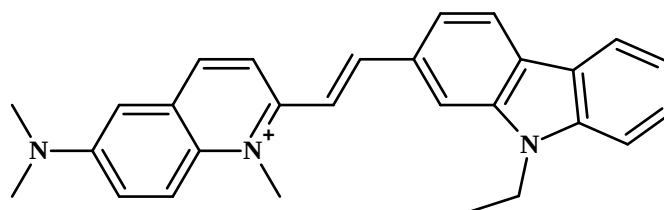
Because of the existence of a thiourea functional group, the lead compound also showed selective copper-chelating activity. This property enhances its therapeutic potential because copper and other metal are implicated in accelerating oxidative stress and amyloid aggregation.

Quinolinium-Carbazole Hybrid design

Quinolinium-carbazole conjugates were created by Xie and colleagues as targeted theranostic medications for the treatment of Alzheimer's disease. Their approach to molecular design involved combining a

quinolinium acceptor unit with a carbazole core to create a donor π acceptor framework that could be utilized for both photooxidative treatment and amyloid imaging.

The carbazole moiety serves as an electron donating unit and provides a rigid, planar aromatic structure that facilitates strong π - π interactions with β - amyloid aggregates. In contrast, the quinolinium fragment functions as an electron accepting group that will enhance the intramolecular charge transfer, improving water solubility through its cationic nature and encouraging negatively charged electrostatic contacts of amyloid species. This strategic combination enables fluorescence activation upon amyloid binding and efficient reactive oxygen species (ROS) generation under light irradiation.⁴¹



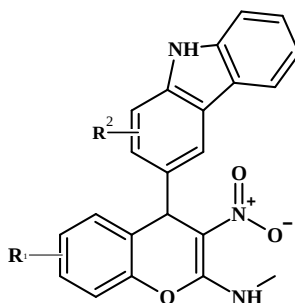
Quinolinium-Carbazole Hybrid

Carbazole- Chromene Hybrid Design

Another noteworthy strategy was the invention and synthesis of a number of unique 9H-carbazole-4H-chromene hybrids by Nissi Sharon and colleagues as possible dual cholinesterase inhibitors for the therapy of Alzheimer's disease. In order to improve therapeutic efficacy, their design also concentrated on integrating chromene and carbazole, two biologically active scaffolds, into a solitary molecular structure.

Strong π - π interactions in the cholinesterase enzymes' active areas were made possible by the incorporation of the carbazole moiety as a stiff, planar aromatic system. This structural characteristic greatly enhances the biological action and is recognized for increase binding affinity. Conversely, the chromene scaffold was created because of its well-known pharmacological characteristics, namely its function in enzyme blocking and neuroprotective benefits.⁴²

The authors used a one-pot, three-component synthesis method with salicylaldehydes, hydroxy carbazole, and N-methyl-1-(methylthio)-2-nitroethenamine in the presence of triethylamine as a catalyst to effectively create these hybrids. This technique offered benefits including gentle reaction conditions by enabling the simultaneous creation of many bonds in a single phase. Additionally, the synthetic compounds' biological examination showed encouraging dual inhibitory action against the enzymes butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE).^{43,44}

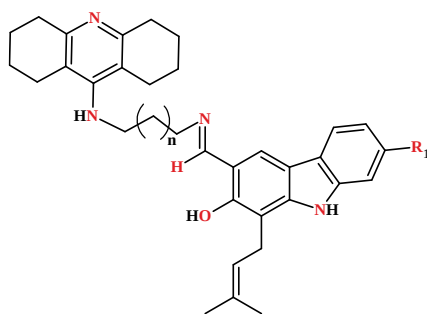


Carbazole- Chromene Hybrid

Carbazole-Tacrine Hybrid Design

In another significant study, the researchers also designed the tacrine-carbazole hybrids by combining the strong acetylcholinesterase inhibitory activity of tacrine with the antioxidant and neuroprotective property of

the carbazole nucleus, aiming to develop multifunctional compounds have the capability of acting on different pathological mechanisms involved in Alzheimer's disease.



Carbazole-Tacrine Hybrid

Tacrine is a well-known acetylcholinesterase (AChE) inhibitor that enhances cholinergic neurotransmission by preventing the breakdown of acetylcholine. However, its clinical use is limited because of hepatotoxicity and poor selectivity. On the other hand, carbazole derivatives possess several biological activities including antioxidant, neuroprotective, and anti-amyloid properties. By merging these two scaffolds, the authors aimed to develop multifunctional compounds with improved efficacy and reduced toxicity.

A methodical synthetic approach utilizing suitable linkers and substitution patterns was used to create the tacrine-carbazole hybrids. The produced compounds displayed high inhibitory action against acetylcholinesterase (AChE), with IC_{50} values ranging between 0.48 and 1.03 μ M, while also demonstrating significant selectivity toward AChE over butyrylcholinesterase (BuChE).^{45,46}

MTDL Strategies for Anticancer Activity

Uncontrolled cell proliferation, invasion, metastasis, and resistance to apoptosis are all hallmarks of cancer, a complicated and multifaceted illness brought on by changes in several cellular signalling pathways.^{47,48} Drug resistance, toxicity, and limited therapeutic efficacy can result from conventional anticancer therapy' frequent focus on a single biochemical pathway.^{49,50} As a result, the idea of Multitarget-Directed Ligands (MTDLs) has become a viable approach to the development of anticancer drugs.

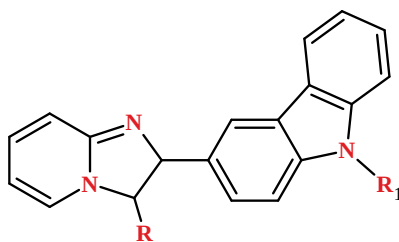
Cell cycle regulation, angiogenesis, apoptosis, kinase signalling, oxidative stress, and DNA replication are only a small portion of the biological targets that MTDLs can concurrently modulate.⁵¹ Increased therapeutic efficacy, decreased medication resistance, fewer side effects, and better patient compliance are some benefits of this strategy.^{52,53} The creation of hybrid compounds with pharmacologically active scaffolds including carbazole, quinoline, indole, and imidazolidinone derivatives—which have shown considerable anticancer promise through multitarget mechanisms—has been the focus of recent study. As a result, MTDL techniques offer a novel and successful method for creating anticancer drugs of the future.⁵⁵

Imidazopyridine-Carbazole Hybrid Compounds

The emergence of molecular hybrids as possible anticancer medicines that can bind with a svarious biological target has been highlighted by recent developments in medicinal chemistry. In this regard, a novel family of imidazopyridine-quinoline/carbazole hybrid compounds with strong antiproliferative potential were designed and synthesized by Sangeetha Meenakshisundaram, Manoj Manickam, and Venkateswaran Vinayagam.

In order to create multifunctional molecules with increased anticancer activity, the physiologically active imidazopyridine scaffold was integrated with quinoline and carbazole pharmacophores using a molecular hybridization technique.⁵⁶ The well-established pharmacological importance of these heterocyclic nuclei, which are known to display a wide variety of biological actions like DNA intercalation, kinase inhibition,

induction of apoptosis, and blocking of tumour cell proliferation, served as the justification for this design approach.

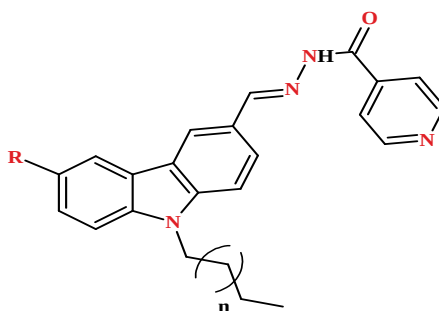


Imidazopyridine–Carbazole Hybrid

HeLa, MDA-MB-231, ACHN, and HCT-15 cancer cell lines were employed to evaluate the synthetic imidazopyridine–quinoline/carbazole hybrid compound's *invitro* anticancer activities. 2-chloro-6-methoxy-3-(3-(4-methylbenzyl) imidazo[1,2-a]pyridine-2-yl)quinoline had the highest cytotoxic activity among quinoline hybrids, suggesting that the 4-methylbenzyl substituent increased anticancer potency. 3-(3-benzylimidazo[1,2-a]pyridine-2-yl)-9-ethyl-9H-carbazole demonstrated higher antiproliferative action in the carbazole series, underscoring the significance of the carbazole nucleus. Hydrophobic aromatic groups and electron-donating substituents enhanced biological activity, according to structure–activity relationship studies, supporting imidazopyridine hybrid scaffolds as potential multitarget anticancer medicines.⁵⁷

Carbazole–Pyridine Hybrid

The combined pharmacological relevance of carbazole and pyridine moieties was reflected in an appearance of carbazole–pyridine hybrids as promising anticancer scaffolds. Breast, liver, pancreatic, melanoma, lung, and oesophageal cancers were among the many cancer cell lines against which a number of derivatives shown strong antiproliferative activity. Numerous hybrids showed excellent *in vivo* tumour suppression with favourable pharmacokinetic profiles and minimal toxicity. These substances function through a variety of mechanisms, including induction of apoptosis, suppression of Rac1 activation, and inhibition of microtubule assembly, according to mechanistic studies. Studies on the structure–activity relationship revealed that the anticancer potency is greatly influenced by suitable replacements on the carbazole nucleus. All things considered, carbazole–pyridine hybrids are useful lead compounds for the creation of innovative multitarget anticancer drugs.^{58,59}

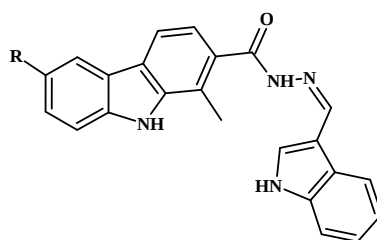


Carbazole–Pyridine Hybrid

Carbazole–Indole Hybrid

The indole nucleus is considered as one of the most extensively explored heterocyclic moiety in medicinal chemistry and it is widely present in both naturally occurring and synthetic bioactive compounds. Indole derivatives exhibit remarkable anticancer potential through multiple mechanisms of action, including inhibition of aromatase, kinases, tubulin polymerization, microtubule dynamics, PI3K/Akt/NF-κB/mTOR signalling pathways, and histone deacetylase (HDAC) activity. Several indole-containing anticancer agents, such as Midostaurin and Anlotinib, have already reached clinical application or clinical evaluation for the management of various malignancies. As a result, the molecular hybridization of indole and carbazole

pharmacophores has become a desirable approach for the creation of new anticancer drugs with enhanced therapeutic efficacy.^{60,61,62}



Carbazole–Indole Hybrid

A promising method for increasing anticancer activity and overcoming drug resistance is the hybridization of carbazole with indole. Racemosin B, a naturally occurring indolo[3,2-a]carbazole derived from *Caulerpa racemosa*, initially exhibited modest cytotoxicity; however, structural alteration (ester to amide conversion) greatly increased activity against breast cancer cell lines.^{63,64}

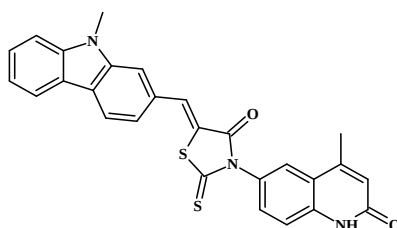
MTDL Strategies for Antimicrobial Activity

Infectious illnesses brought on by fungus and bacteria, viruses, and parasites are prevented and treated in large part by antimicrobial agents. Antimicrobial resistance has become a major worldwide health concern because to its rapid growth, which greatly lowers the effectiveness of traditional medicines⁶⁵. Target alteration, enzymatic drug degradation, efflux pump overexpression, and biofilm formation are few of the ways that microorganisms frequently acquire resistance.⁶⁶ The limitations of the conventional "one drug–one target" approach have been brought to light by these intricate resistance mechanisms, underscoring the necessity for novel therapeutic approaches. In this sense, the creation of multitarget-directed ligands has attracted a lot of interest as a potentially successful tactic to combat microbial infections by simultaneously altering multiple biological targets crucial to germ survival and resistance.⁶⁷

The sensible mixing of two or more pharmacologically active molecular fragments inside a single chemical entity is the fundamental basis of the notion of multitarget-directed ligands (MTDLs) in antimicrobial drug discovery. One of the most efficient methods for creating antimicrobial MTDLs is molecular hybridization, especially when heterocyclic scaffolds experiencing an extensive range of natural products.⁶⁸ Because of its planar aromatic structure, membrane permeability, and capacity to bind with an array of biological targets, carbazole has become the more appealing heterocyclic frameworks. Carbazole and other antimicrobial pharmacophores has been combined by researchers to create hybrid compounds with numerous modes of action.⁶⁹

Carbazole–Quinoline Hybrids

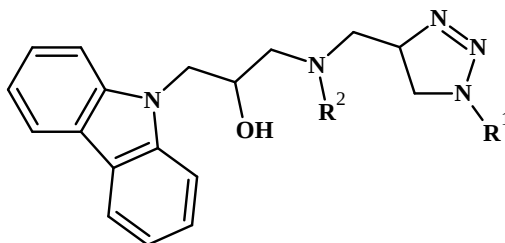
Carbazole–quinoline hybrids have been developed to simultaneously disrupt microbial DNA replication and membrane function. In these molecules, the quinoline moiety contributes DNA intercalation and enzyme inhibition properties, whereas the carbazole nucleus enhances lipophilicity and facilitates interactions with nucleic acids. The resulting hybrids often display superior antimicrobial activity compared with their parent compounds.



Carbazole–quinoline hybrids

Carbazole–Triazole Hybrids

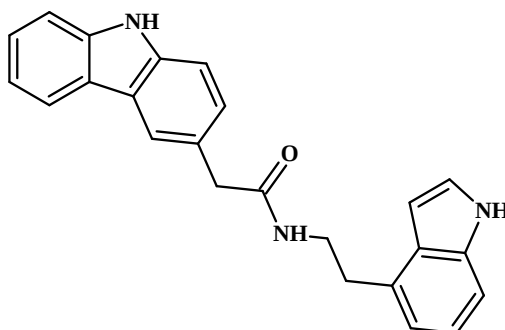
The designing of carbazole–triazole hybrids is another extensively studied approach. Because it inhibits enzymes involved in sterol production and microbial metabolism, the triazole ring is renowned for having antifungal and antibacterial qualities. The resultant hybrid moiety can bind with multiple intracellular targets while retaining advantageous physicochemical properties when attached to a carbazole scaffold. These substances have shown potential effectiveness against pathogenic fungus and strains of bacteria that are both Gram-positive and Gram-negative.⁷⁰



Carbazole–triazole hybrids

Carbazole–Indole Hybrids

Carbazole–indole hybrids represent another important class of antimicrobial MTDLs. The indole nucleus is recognized for its ability to interfere with quorum sensing, biofilm formation, and bacterial signalling pathways. Hybridization of carbazole with indole combines DNA-binding capability with inhibition of microbial communication systems. Consequently, these molecules can suppress bacterial growth while simultaneously preventing biofilm development, a major contributor to antimicrobial resistance and chronic infections.⁷¹



Carbazole–indole hybrids

There has also been a lot of interest in the coupling of carbazole with pharmacophores that contain pyridines. Numerous microbial enzymes involved in vital metabolic processes are known to be targeted by pyridine derivatives. The carbazole moiety frequently facilitates hydrophobic interactions and membrane penetration in carbazole–pyridine hybrids, whereas the pyridine ring improves binding to enzyme sites. By concurrently influencing several biological processes, these dual-action compounds have shown beneficial effectiveness against resistant bacterial strains.

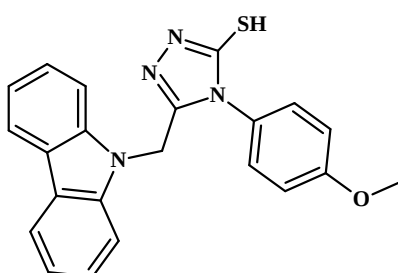
Additionally, Carbazole and benzimidazole hybrids have also been studied as multifunctional antibacterial agents. Derivatives of benzimidazole have the ability to bind with microbial DNA and block essential enzymes needed for cell division and replication. When benzimidazole and carbazole are combined, compounds that can target nucleic acid synthesis and interfere with membrane-associated activities are produced. Improved antibacterial efficacy and decreased resistance susceptibility are two benefits of this dual-target strategy. This dual-target mechanism contributes to improved antimicrobial potency and reduced susceptibility to resistance mechanisms.⁷²

MTDL Strategies for Antidiabetic Activity

Persistent hyperglycaemia brought on by decreased insulin secretion, action, or both is a hallmark of diabetes mellitus, a chronic metabolic disease. The illness is connected to several pathogenic factors, including insulin resistance, β -cell dysfunctioning, oxidative stressful condition, chronic inflammatory condition and altered glucose and lipid metabolism.⁷³ Effective long-term care of blood sugar level is still difficult despite the availability of various antidiabetic medications because of the complexity of the condition, the gradual loss of glycaemic control, and the emergence of various comorbidities. The evolution of multitarget treatment strategies that can concurrently modulate many pathways implicated in the evolution of diabetes is therefore gaining attention. Multitarget-directed ligands (MTDLs), which have the potential to increase therapeutic efficacy while lowering costs, have become a viable approach for the development of antidiabetic drugs. With the potential to increase therapeutic efficacy while lowering the requirement for combination therapy, multitarget-directed ligands (MTDLs) have emerged as a viable approach for antidiabetic drug discovery.⁷⁴

Carbazole-Triazole Hybrid

In order to overcome the shortcomings of the present antidiabetic treatments, which frequently fail to return blood glucose levels to normal in a sizable percentage of patients, a series of carbazole-1,2,4-triazole-thione derivatives were created. In addition to cytotoxicity evaluation and in vivo antidiabetic validation, the study concentrated on evaluating their inhibitory potency against important carbohydrate-hydrolysing enzymes, specifically α -amylase and α -glucosidase.⁷⁵



Carbazole-Triazole Hybrid

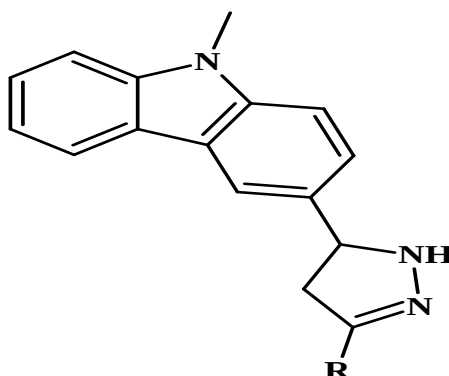
The majority of chemicals were non-toxic at 100 μ M, according to safety profile using typical hepatic stellate cells in humans (LX-2). When compared with the positive control 5-fluorouracil, C5o and C5s demonstrated noticeably less cytotoxicity, indicating a favourable safety profile. Strong binding contacts of active chemicals within the active sites of enzymes were further validated by molecular docking and chemoinformatic studies, underscoring the critical significance of both the carbazole and 1,2,4-triazole-3-thione scaffolds.⁷⁴

MTDL Strategies for Anti-Inflammatory Activity

A basic physiological reaction, inflammation is brought on by infections, injuries, or immune system disruptions. Prolonged or unchecked inflammation can cause the onset and progression of numerous chronic illnesses, including Inflammatory bowel disease and Rheumatoid arthritis, Cardiovascular disorders, Neurodegenerative conditions, and various types of cancer, even though this process is necessary for tissue protection and healing.^{75,76,77} Numerous molecular mediators and signalling pathways, including cyclooxygenases (COX), lipoxygenases (LOX), pro-inflammatory cytokines, reactive oxygen species (ROS), and transcription factors like nuclear factor-kappa B (NF- κ B), control the inflammatory response.^{78,79} Therapeutic medicines targeted at a single target frequently fail to produce maximum clinical benefits due to the involvement of many linked pathways and may cause undesired side effects. As a result, the idea of multitarget-directed ligands (MTDLs), which allow for the simultaneous control of multiple important inflammatory pathways, has become a viable strategy for the treatment of inflammatory illnesses.^{80,81} Among the several heterocyclic frameworks explored in medicinal chemistry, carbazole has

attracted a lot of attention due to its various biological processes, especially its immunoregulatory, anti-inflammatory, and antioxidant qualities. Because the carbazole scaffold's structural flexibility makes it easier to incorporate it into multifunctional molecular hybrids that can interact with a variety of biological targets, carbazole-based MTDLs are promising candidates for the designing of next-generation anti-inflammatory treatments.⁸²

A wide range of carbazole–pyrazoline hybrids were created by Bandgar and colleagues as multitarget-directed ligands (MTDLs) with possible anti-inflammatory and antioxidant properties. The pyrazoline pharmacophore, which is linked to cyclooxygenase (COX) inhibition, was molecularly hybridized with the carbazole scaffold, which is recognized for its anti-inflammatory and antioxidant qualities.⁸³



Carbazole–pyrazoline hybrid

Invitro, invivo, and molecular docking experiments were employed for evaluating the produced compounds. Several substances demonstrated strong anti-inflammatory properties, and some of their derivatives selectively inhibited COX-2, a crucial enzyme in the inflammatory process. One lead chemical showed strong anti-inflammatory activity among the investigated compounds by significantly reducing carrageenan-induced paw oedema in rats. Furthermore, by efficiently scavenging DPPH, superoxide, and hydroxyl radicals, the majority of derivatives demonstrated significant antioxidant activity. Furthermore, molecular docking investigations demonstrated favourable interactions between the active chemicals and the COX-2 binding site, supporting the observed biological activities. These carbazole–pyrazoline hybrids' concurrent anti-inflammatory and antioxidant properties demonstrate the efficacy of the MTDL strategy, which modulates several disease-related pathways with a single molecule. This study shows that carbazole-based molecular hybrids have the potential to be effective treatment options for oxidative stress-related inflammatory diseases.

Comparative Analysis of Partner Scaffolds Used in Carbazole-Based Multi-Target-Directed Ligands (MTDLs)

SCAFFOLD	TARGET DISEASE	PRIMARY BIOLOGICAL TARGETS	MAJOR ADVANTAGES
Carbazole-Tacrine	Alzheimer's disease	AChE, BuChE, BACE1	Improved cholinesterase inhibition and BBB penetration
Carbazole-Stilbene	Alzheimer's disease	A β aggregation, ROS	Antioxidant and anti-amyloid effects
Carbazole-Chromene	Alzheimer's disease	AChE, BuChE, Tubulin	Improved cholinesterase inhibition and BBB penetration
Carbazole-Quinolinium	Alzheimer's disease	AChE, BuChE	Improved cholinesterase inhibition and BBB penetration
Carbazole-Pyridine	Cancer	DNA gyrase, DNA intercalation	Broad-spectrum activity
Carbazole-Indole	Cancer	DNA gyrase, DNA	Broad-spectrum activity

		intercalation	
Carbazole-Triazole	Diabetes	α -Glucosidase, CYP51	Improved metabolic stability
Carbazole-Quinoline	Antimicrobial	DNA gyrase, DNA intercalation	Broad-spectrum activity
Carbazole-Pyrazoline	Inflammation	COX-2, ROS	Dual anti-inflammatory and antioxidant activity

CONCLUSION

An important family of multitarget-directed ligands (MTDLs) with substantial potential for the treatment of complicated and multifactorial disorders is carbazole-based heterocyclic hybrids. The carbazole scaffold's distinctive structural characteristics, such as its planar aromatic framework, favourable lipophilicity, and ease of functionalization, make it a desirable platform for the creation of therapeutic medicines with many functions. Carbazole has been hybridized with a variety of pharmacologically active heterocycles to produce molecules that can concurrently modulate several biological targets implicated in the course of disease.

The research covered in this study shows that carbazole hybrids have excellent therapeutic promise against a variety of illnesses, such as diabetes, cancer, Alzheimer's disease, microbial infections, and inflammatory diseases. These substances work through a variety of ways, including signalling regulation, antioxidant action, and enzyme inhibition. Additionally, research on the relationship between structure and function has shown that proper substitution patterns and linker changes are essential for improving biological activity and target selectivity.

Overall, the pharmacological adaptability of the carbazole nucleus in conjunction with the multitarget approach presents a viable method for getting beyond the drawbacks of traditional single-target treatments. Ongoing advancements in molecular hybridization, computational drug design, and biological evaluation are expected to expand the therapeutic applications of carbazole-based MTDLs and aid in the creation of safer and more potent medication choices to treat complicated illnesses.

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