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REVIEW

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Diverse pharmacological actions of potential carbazole derivatives by influencing various pathways of molecular signaling

Archita Tiwari[1] and Bharat Mishra[2*]

Abstract

Background Carbazoles are an important class of heterocyclic aromatic compounds that contain nitrogen atom in the ring. They have a large-conjugated system, attractive "electrical and charge-transport properties", and the ability to efficiently incorporate different functional groups into the structurally inflexible carbazolyl ring.

Main text Carbazole derivative ECCA acts as an anticancer agent by reactivating the P53 molecular signaling pathway; similarly, some other derivatives of carbazole show antifungal activity by acting on the RAS-MAPK pathway. Carbazole derivatives also show their effect on inflammation by inhibiting the p38 mitogen-activated protein kinase signaling pathway by stopping the conversion of DAXX protein into ASK-1. By modifying the AKT molecular signaling pathway through boosting protein phosphatase activity in the brain, they show anti-Alzheimer's activity and also by translocating the GLUT4 these are effective against diabetes.

Conclusion After exploring the literature on carbazole, it was found that carbazole has an immeasurably great potential for the treatment of various diseases as the carbazole nucleus leads to various synthesized derivatives which are used for their pharmacological activities. So there is a need to explore carbazole for some newer drugs.

Keywords Carbazole, Carbazole derivatives, Molecular signaling, Anticancer, Antidiabetic, Antifungal

Background

Heterocyclic compounds are composed of cyclic rings containing two or more different types of atoms [1, 2]. Throughout nature, heterocyclic compounds are very common and essential. In carbazole, two benzene rings with 6 carbon atoms are fused on either side of a five-membered heterocyclic ring with nitrogen atom showing vast delocalization of electrons [3].

Carbazole and its compounds are useful types of heterocyclic aromatic compounds that show desirable properties of transporting electrons and charges throughout the ring [4]. Also, many polyfunctional groups can be easily added into the carbazolyl ring for the formation of some other novel derivatives [5]. These properties of carbazole-based derivatives result in a wide range of potential applications in the chemistry field (dyes, photoelectrical materials, supramolecular recognition, etc.), and these derivatives also result in various pharmacological activities like antidiabetic [6, 7], antitumor [8–10], anticonvulsant [11], antimicrobial [12–14], antioxidative [15, 16], antifungal [17, 18] antihistaminic [19], anti-inflammatory [20, 21], antitubercular [22], antiviral [23], carbonic anhydrase enzyme activity [24], neuroprotective activity [25] and antidiarrhoel [26], etc.

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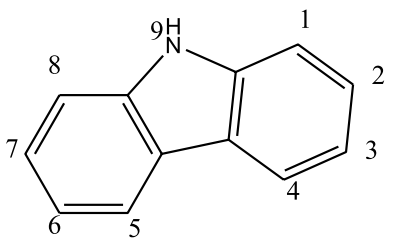


9*H*-carbazole

(1)

C-3 and C-6 positions in carbazoles have the highest electron density so in recent years the synthesis of some novel carbazoles has been done by modification in carbazole at C-3 and C-6, and 9th positions of N [27]. If there is no steric hindrance that occurs, the carbazoles along with unblocked 3rd and 6th positions of Carbon in the ring form at least a dimer upon oxidation. Carbazoles undergo electrophilic substitution reaction like sulfonation, nitration, Friedel–Crafts acylation and Friedel–Crafts alkylation forming different derivatives of carbazole. The problem with this substitution is that a mixture of ortho and para positions is obtained but due to high electron density at the 3rd and 6th carbon positions, 75% of the para product formed concerning C-1 and C-8 (ortho position). Formation of mono along with di-, tri-, and tetra-substituted carbazoles is possible due to the reactivity of carbon atoms to the imine group in carbazole. By using appropriate alkylating or acylating agents at room temperature, the N-9 substituted carbazole derivatives are also formed [4].

Main text

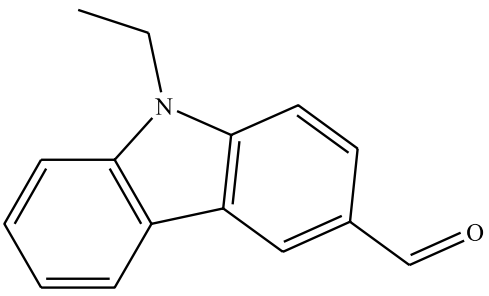
Diseases with neurodegeneration

Neurodegenerative diseases (NDs) are a group of disorders (multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, etc.) that cause loss of neuron's structure or function [28–33]. As a result of these changes in the brain anatomy, the logical or functional decline may result in protein misfolding, diminished mitochondrial functions, oxidative stress, impaired neuro-transmission, and loss of neurons which are just a few physiological indicators of NDs [34, 35].

Anticancer potential

Cancer is the major health problem in individuals. Every year approx 18 million peoples are diagnosed with cancer, and it is the prime cause of death worldwide. In developed countries, the age-standardized rate for diagnosis is 296 cases per 1000,000 peoples [36–40]. Cancer is a pathological condition of the body which is due to various genetic mutations which are characterized by uncontrolled proliferation and growth of cells [41–44]. Every cell of the body can become a cancer cell when a genetic mutation occurs [45]. Carcinogenesis process occurs in three stages; in the first stage alteration has already been identified so it is called the initiation stage, in the second promotion stage these altered cells are mutated and form malignant cells, and in the last stage of carcinogenesis which is continuation stage once the tumor has increased in size and cancer cells begin to split in an accelerated irreversible mode. And in the last stage the cells instead of growing locally start to disseminate to other body parts (metastasis) [46–48].

In human melanoma cells, the p53 pathway is reactivated by the anticancer effect of carbazole derivative ECCA, (9-ethyl-9*H*-carbazole-3-carbaldehyde). In melanoma therapy, about 84% of human melanomas harbor wild-type p53 is thought to be a supreme target for treating melanoma. Carbazole derivatives enhanced the phosphorylation of c-Jun N-terminal kinase (JNK) and p38-MAPK, and either a p38 mitogen-activated protein kinase or c-Jun N-terminal kinase inhibitor reassured cell proliferation inhibition produced by 9-ethyl-9-*H*-carbazole-3-carbaldehyde (ECCA), whose expression was dependent on p53 gene. Carbazole derivatives selectively and significantly depress the expansion of melanoma cells by persuading the programmed cell death of melanoma cells and senescence through p53 activation [49].

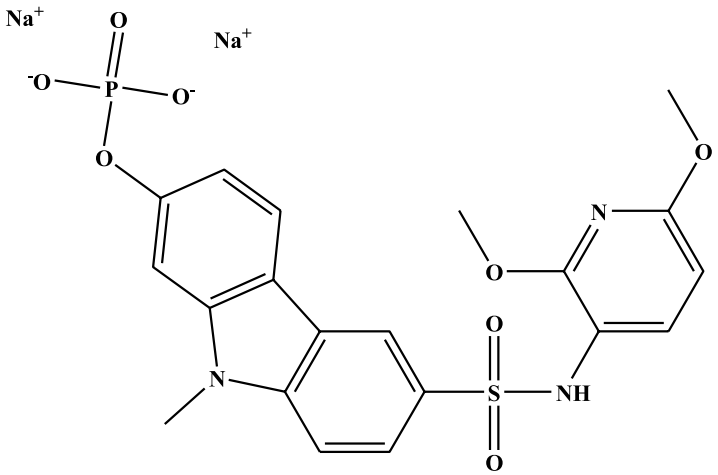


Compound ECCA: 9-ethyl-9*H*-carbazole-3-carbaldehyde

(2)

Yonghua et al. designated water-soluble carbazole and sulfonamide derivatives which are tested in vivo against human HepG2 (hepatoblastoma liver cancer cell line)

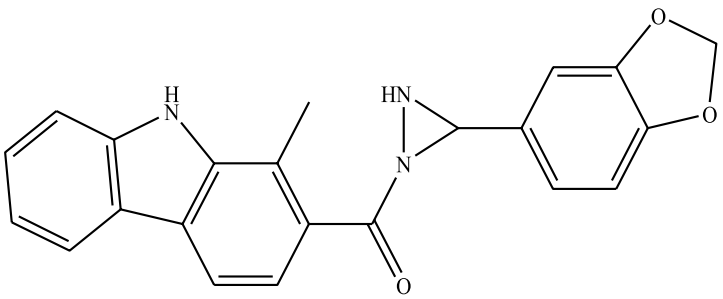
xenograft mouse tumor expansion and found that compound 4c (Sodium 6-(*N*-(2,6-dimethoxypyridin-3-yl) sulfamoyl)-9-methyl-9*H*-carbazol-2-yl phosphate) is the most effective tumor inhibitor [50–52].



Compound 4c: (Sodium 6-(N-(2,6-dimethoxypyridin-3-yl)sulfamoyl)-9-methyl-9H-carbazol-2-yl phosphate)

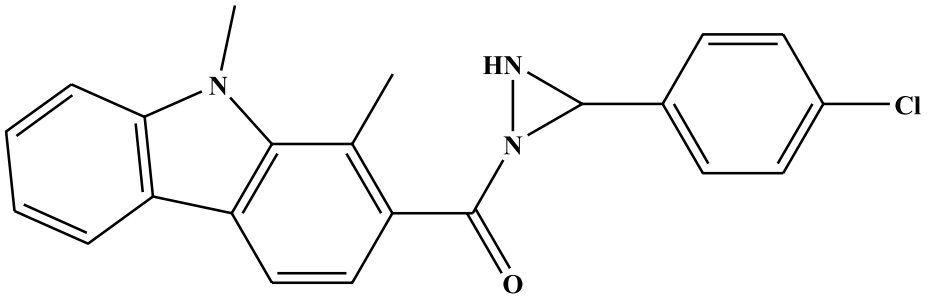
(3)

Huang shows the in vitro cytotoxic activity of different synthesized carbazole derivatives in which compound 7 g (*N*′-(Benzo[d](1,3) dioxol-5-ylmethylene)-1-methyl-9*H*-carbazole-2-carbohydrazide) and compound 7p (*N*′-(4-Chlorobenzylidene)-1,9-dimethyl-9*H*-carbazole-2-carbohydrazide) is the potent inhibitor of cancer cells but do not affect normal cells. 7g Carbazole derivative with acylhydrazone substituted with 1,3-benzodiooxozole displayed significant selective proliferation inhibition activity in vitro with ($IC_{50} < 12.24$ μM). For the in vitro investigation of cytotoxic activity three cell lines, human melanoma (A875), human hepatocellular liver carcinoma (HepG2), and a subclone of the African green monkey cell line (MARC145) were used [53].



Compound 7g: (3-(benzo[*d*][1,3]dioxol-5-yl)diaziridin-1-yl)(1-methyl-9*H*-carbazol-2-yl)methanone **(IC50 < 12.24 μM)**

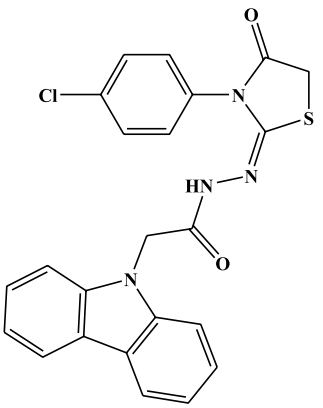
(4)



Compound 7p: (3-(4-chlorophenyl)diaziridin-1-yl)(1,9-dimethyl-9*H*-carbazol-2-yl)methanone

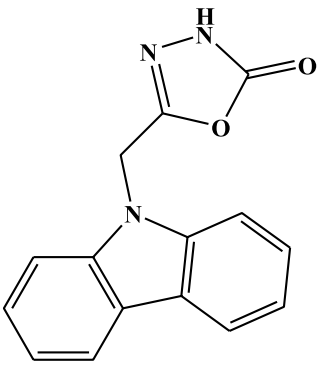
(5)

Capan, I et al. synthesized a sequence of carbazole derivatives. Result among all the synthesized derivatives showed that compound 9 [(*E*)-2-(9*H*-carbazol-9-yl)-*N*′-(3-(4-chlorophenyl)-4-oxothiazolidin-2-ylidene)acetohydrazide)] and compound 10 [5-((9*H*-carbazol-9-yl) methyl)-1,3,4-oxadiazol-2(3*H*)-one] are found most potent anticancer agent against HepG2, HeLa, and MCF-7 cancer cell lines with IC_{50} values of 7.68, 10.09 μM. Against HeLa, cancer cell lines found that compound 9 is the best antiproliferative agent [54].



Compound 9: (*E*)-2-(9*H*-carbazol-9-yl)-*N*′-(3-(4-chlorophenyl)-4-oxothiazolidin-2-ylidene)acetohydrazide (**IC50 values of 7.68 μM)**

(6)



Compound 10: (5-((9*H*-carbazol-9-yl)methyl)-1,3,4-oxadiazol-2(3*H*)-one) (**IC50 values of 10.09 μM)**

(7)

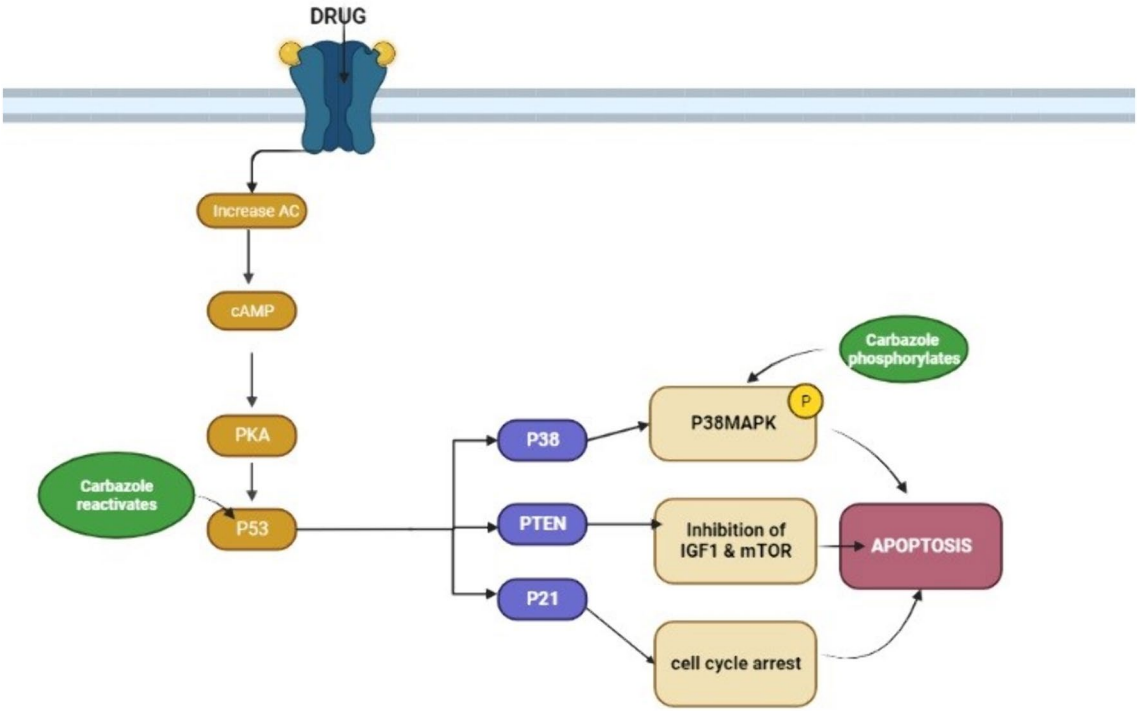
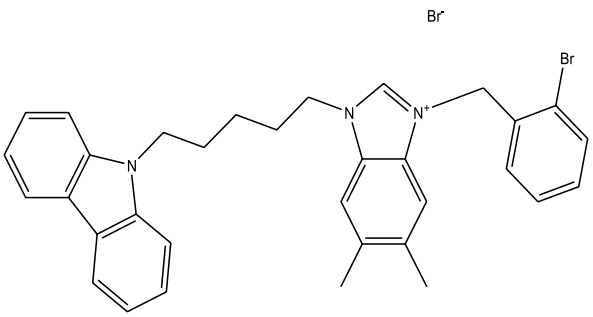


Fig. 1 Anticancer mechanism of carbazole derivatives. 9-Ethyl-9-*H*-carbazole-3-carbaldehyde (ECCA) re-activates P53 pathway and causes phosphorylation of P38MAPK

Leu et al. synthesized a novel series of carbazole derivatives that are synthesized by imidazole derivatives along with *N*-alkyl bromide substituted carbazole. Compound 61[1-(5-(9*H*-carbazol-9-yl)pentyl)-3-(2-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-3-ium bromide], which was bearing a 2-bromobenzyl substituent at position-3 of the 5,6-dimethyl-benzimidazole, showed powerful inhibitory activities and found to be more selective to human promyelocytic leukemia cell line (HL-60), human hepatocellular carcinoma cell line (SMMC-7721), breast cancer cell line (MCF-7) and human colon adenocarcinoma (SW480) cell lines with IC_{50} values 0.51–2.48 μM. The results of the research indicated that the presence of 5,6-dimethyl-benzimidazole ring and substitution of the imidazolyl-3-position with a 2-bromobenzyl group, as well as for the antitumor activity the length of alkyl chain between carbazole and imidazole ring were important [55] (Fig. 1).



Compound 61: [1-(5-(9H-carbazol-9-yl)pentyl)-3-(2-bromobenzyl)-5,6-dimethyl-1H-benzo[d]imidazol-3-ium bromide] (**IC50 values 0.51-2.48μM**)

(8)

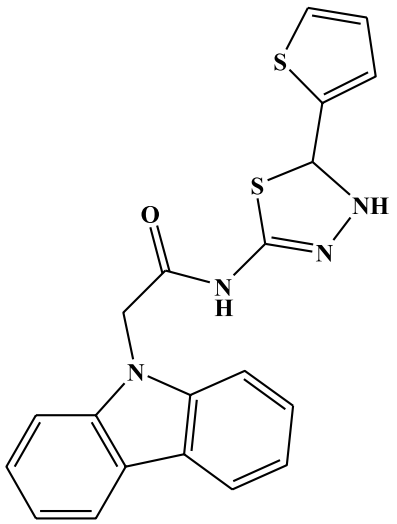
Breast and uterine *cancer*

The natural and synthetic carbazole derivatives represent an exciting heterocycle class that has shown several pharmaceutical properties and is also an excellent antitumor tool in preclinical experiments. The antibodies target several cellular key points, such as Topoisomerases I, II and DNA. Several efforts have been made to plan and synthesize some novel carbazole derivatives that have lesser side effects and good potency. The carbazole derivatives without affecting non-tumor cell lines possess antiproliferative activities against uterine and breast cancer cell lines. Carbazole derivatives through the inhibition of Topoisomerase II trigger cancer cells' intrinsic apoptotic pathway.

Antifungal potential

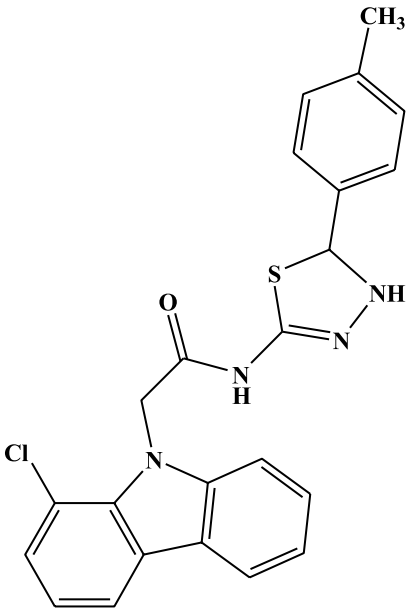
Fungal infections (mycosis) are increasing throughout the world. Although there are several reasons for this higher increase in mycosis, immune modulation of the host is one of the foremost risk factors for intrusive mycosis [56]. Humans suffer from most of the fungal infections due to the setting of iatrogenic immunosuppression. When these factors are absent fungi cause mild, self-limited mucocutaneous surface infections. When this infection develops in a normal host, it causes adaptive immune dysfunction because of genetic defects [56–58].

Tang et al. tested the antifungal activity of all the synthesized compounds against different fungal strains and found that compound 3f (2-(9*H*-carbazol-9-yl)-*N*-(4,5-dihydro-5-(thiophen-2-yl)-1,3,4-thiadiazol-2-yl) acetamide) and 3i (2-(1-chloro-9*H*-carbazol-9-yl)-*N*-(4,5-dihydro-5-*p*-tolyl-1,3,4-thiadiazol-2-yl)acetamide) exhibited the most potent inhibitory activity against *C.* wilt having inhibition rates 72.40% and 67.65% [59].



Compound 3f: 2-(9*H*-carbazol-9-yl)-*N*-(4,5-dihydro-5-(thiophen-2-yl)-1,3,4-thiadiazol-2-yl)acetamide

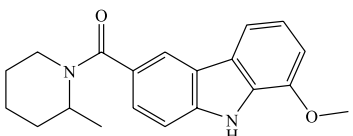
(9)



Compound 3i: 2-(1-chloro-9*H*-carbazol-9-yl)-*N*-(4,5-dihydro-5-*p*-tolyl-1,3,4-thiadiazol-2-yl)acetamide

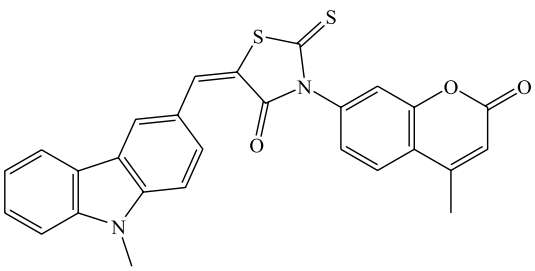
(10)

Shaikh et al. synthesized two series of carbazole analogues. The first one is 8-methoxy-*N*-substituted-9*H*-carbazole-3-carboxamides, and the second one is carbazolyl-substituted rhodanines. The final compounds were prepared from these two series and were tested for antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* [60–62] and antifungal activity against *Cryptococcus tropicalis*, *Aspergillus niger*, *Cryptococcus neoformans*, and *Candida albicans* [63–65]. Various substituents, nitrogen-containing heterocyclic systems like pyrimidinyl and piperidinyl on carbazole nucleus exerted a significant antifungal activity in the first series of compounds. 2-Methyl piperidinyl carboxamide derivative compound 6f (8-Methoxy-9*H*-carbazol-3-yl)(2-methylpiperidin-1-yl)methanone found as potent antifungal and antibacterial agent. In second series substitution at 3 positions of rhodanines which is conjugated to -methyl carbazole through an acrylidine linkage, the result showed the effect of bioisosteres coumarin present in compound 15i [(5*Z*)-3-(4-methyl-2-oxo-2*H*-chromen-7-yl)-5-((9-methyl-9*H*-carbazol-6-yl)methylene)-2-thioxothiazolidin-4-one] were shown potent inhibitory activity. It was concluded that electron donating groups such as hydroxy, alkoxy, and alkyl groups on the aromatic ring greatly contributed toward the antifungal and antibacterial activity [64].



Compound 6f: (8-Methoxy-9H-carbazol-3-yl)(2-methylpiperidin-1-yl)methanone

(11)



Compound 15i: (5*Z*)-3-(4-methyl-2-oxo-2H-chromen-7-yl)-5-((9-methyl-9H-carbazol-6-yl)methylene)-2-thioxothiazolidin-4-one

(12)

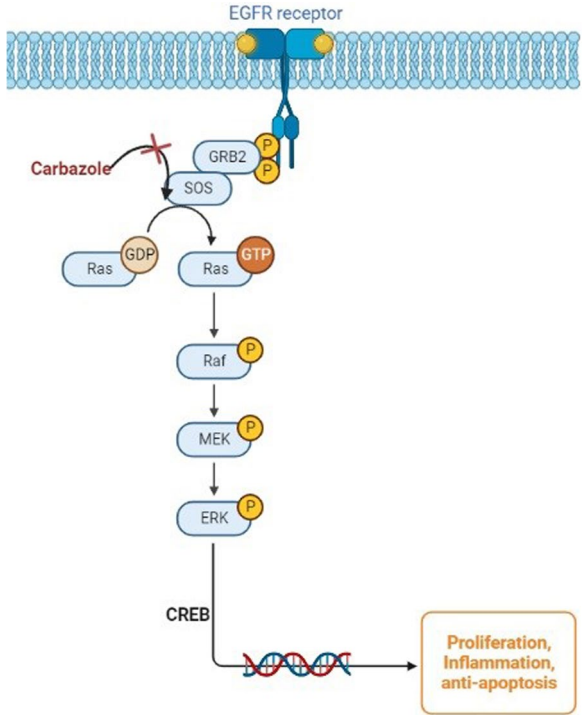


Fig. 2 Antifungal mechanism of carbazole derivatives. *N*-(4-methoxybenzyl)-3(9*H*-carbazol-9yl) propan 1-amine inhibits morphogenesis by suppressing protein and RNA levels of Ras/MAPK-related genes

The morphogenic process came up with the virulency of *Candida albicans*, an opportunistic human fungal pathogen. Ras1-MAPK pathways are crucial to *Candida albicans* virulence through controlling morphogenesis, cell growth, and biofilm formation.

Several carbazole-containing drugs have been prescribed for infections of *Candida albicans*, leading to the expansion of drug-resistant strains. For that reason, it is needed to properly treat fungal infections, and new compounds must be developed. By suppressing Ras/MAPK-related gene protein and RNA levels, carbazole derivatives prevent morphogenesis [66, 67] (Fig. 2).

Anti-psoriasis potential

Psoriasis is a chronic autoimmune disease that is associated with systemic manifestation and characterized by keratinocytes and hyperproliferation mediated by T-cells [68–70]. It is an autoimmune disease with a genetic predisposition. In the psoriatic lesions presence of dendritic cells, cytokines and T lymphocytes has prompted the development of biologic therapies [71, 72].

Carbazole present in coal tar is an active antiangiogenic compound along with that antiangiogenic effect carbazole also withdraws the formation of inflammatory IL-15 by human mononuclear cells. It is believed that IL-15, which is increased in psoriasis, contributes to the inflammation of psoriasis [29, 73]. Moreover, carbazole treatment reduced the activity of nitric oxide synthase (iNOS) (a pro-inflammatory enzyme), which is elevated in psoriasis patients. In a study on human psoriasis, carbazole was found to inhibit the activator of stat 3-mediated transcription, which is relevant to psoriasis. iNOS, IL-15, and stat3 activation rely on the small GTPase Rac for optimum activity. As a mechanism for inhibiting downstream inflammatory and angiogenic pathways, carbazole inhibits Rac activation [74]. The mechanism of action of carbazole could involve the inhibition of pro-inflammatory cytokine synthesis, inhibition of activator protein-1 (AP-1) activity, and inhibition of EGFR activation. Production of IL-15 by mononuclear cells is also inhibited by carbazole, a key cytokine in psoriasis [75–77] (Fig. 3).

Anti-Alzheimer potential

Generally, dementia is caused by Alzheimer's disease, the primary or cellular phase of Alzheimer's disease happens in parallel with accumulating amyloid β, inducing the spread of tau pathology [78]. Pathological characteristics in Alzheimer's disease (AD) are deposition of β-amyloid (Aβ) peptide and hyperphosphorylated tau in the brain, carbazole derivative (9c) *N*(6-(9*H*-carbazol-9-yl)-hexyl)-1benzylpiperidin-4-amine modulated AKT pathway and boosting protein phosphatase 2A activity in the brain. The compound 9c with (IC_{50} = 26.5 μM for AChE and IC_{50} = 0.18 μM for BuChE) results in the highest inhibitory activity against butyrylcholinesterase and acetylcholinesterase. Structure–activity relationship suggested that attachment to the 4-amino-*N*-benzylpiperidine fragment with C5 and C6 alkyl linkers in compound 9c results in the most potent compound among all [79].

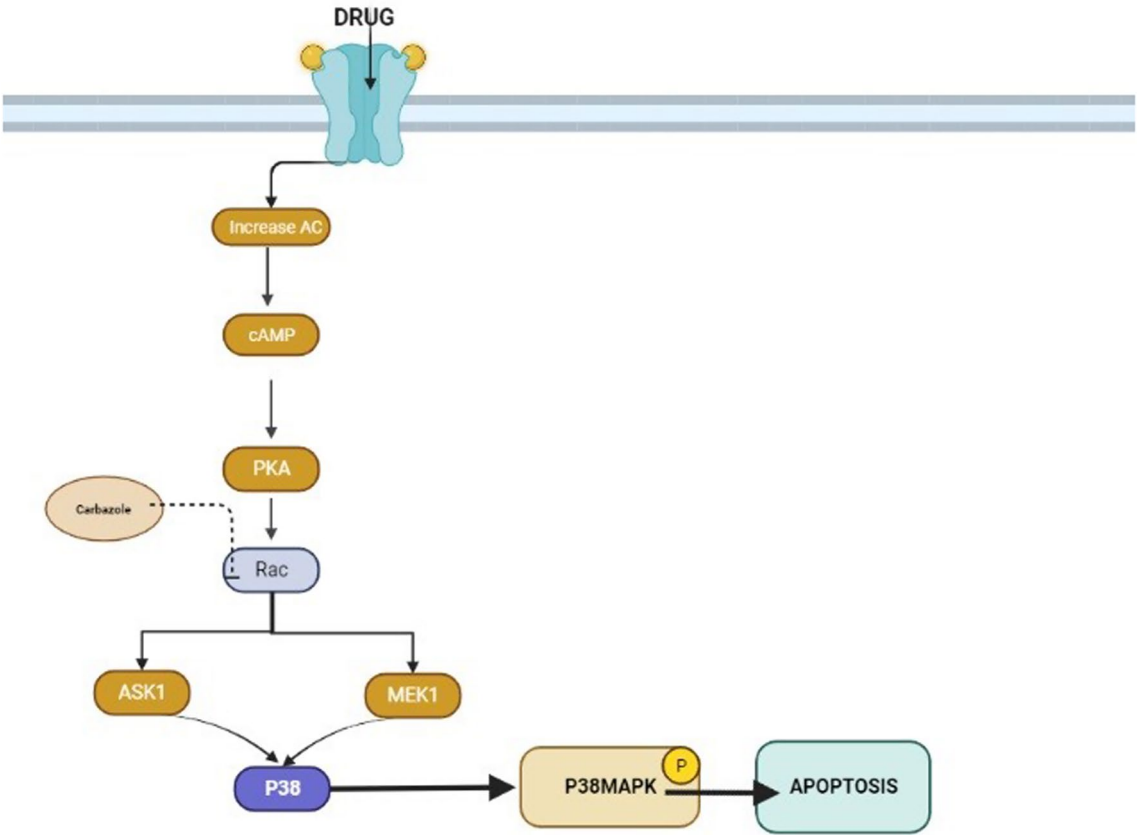
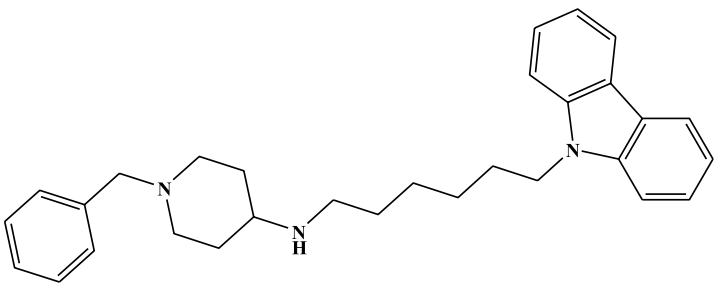


Fig. 3 Anti-psoriasis mechanism of carbazole derivatives. Carbazole present in coal tar inhibits the P38 signaling pathway by inactivation of Rac

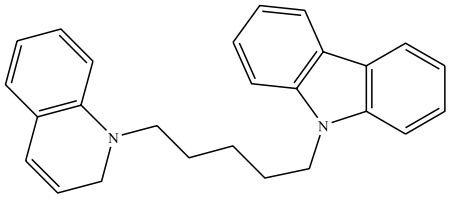


Compound 9c: N-(6-(9H-carbazol-9-yl)hexyl)-1-benzylpiperidin-4-amine **(IC50 = 26.5 µM for AChE and IC50 = 0.18 µM for BuChE)**

(13)

Choubdar et al. designated several carbazole derivatives by using some heterocyclic nucleus like quinoline, pyridine, piperidine, benzyl piperidine, and benzyl piperazine, etc., in which compound 3s (9-(5-(quinoline-1(2*H*)-yl)pentyl)-9*H*-carbazole) linked with quinoline found as the potent drug against BuChE and AChE and also showed the inhibitory activity for AChE induced β-amyloid (Aβ) aggregation. The most potent compound 3s with IC50 = 0.11 µM and 0.02 µM showed the best activity against AChE and BuChE, respectively.

The presence of quinoline moiety in compound 3s more actively inhibited Aβ self-aggregation. Docking studies suggested that compound 3s binds effectively to the PAS and anionic binding site of the enzyme with the assistance of π stacking and hydrophobic interactions [80].



Compound 3s: 9-(5-(quinolin-1(2*H*)-yl)pentyl)-9*H*-carbazole **(IC50 = 0.11 μM and 0.02 μM)**

(14)

Carbazole derivatives regulating Ca2+/CaMKII/CREB signaling pathway. The brain contains CaMKII (Calcium/Calmodulin-dependent Protein Kinase II) which is a specific protein kinase of serine/threonine, which is regulated by Ca2+/calmodulin [81].

Shaikh et al. synthesized a series of α-amino phosphonate-based carbazole derivatives that were in silico and in vitro tested for their cholinesterase activity. All the compounds present better AchE activity [0.475–7.781 μM] than BuChE (3.306–21.32 μM). Against AChE as well as BuChE compound 4j [Diethyl(9-ethyl-9*H*-carbazol-3-yl)amino) (3nhydroxyphenyl)methyl) phosphonate] was the most potent derivative with IC_{50}¼0.475 ± 0.12 mM and IC50¼3.306 ± 0.21 μM, respectively [82] (Fig. 4).

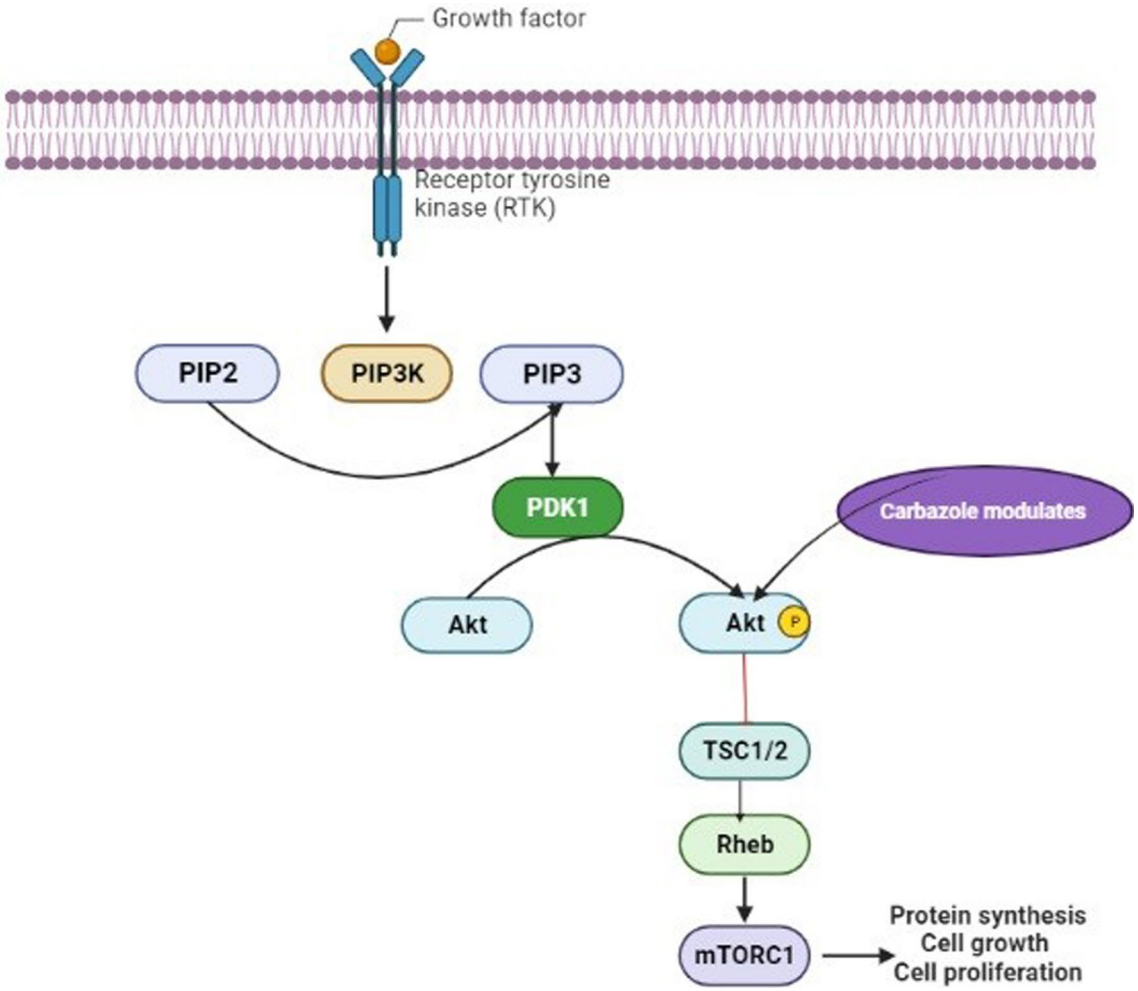
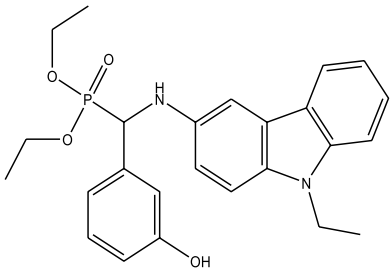


Fig. 4 Anti-Alzheimer mechanism of carbazole derivatives. AKT pathway regulation by carbazole derivative *N*-(6-(9-*H*-carbazol-9yl) hexyl)-1-benzylp iperidine-4-amine by boosting protein phosphatase activity in brain



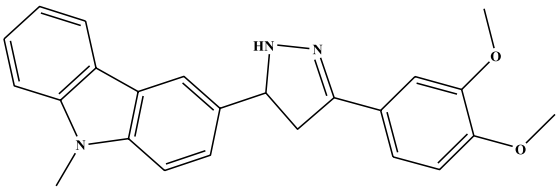
Compound 4j: Diethyl (((9-ethyl-9H-carbazol-3-yl)amino)(3-hydroxyphenyl)methyl)phosphonate(**IC50¼0.475 ± 0.12 μM and IC50¼3.306 ± 0.21 μM**)

(15)

Anti-inflammatory potential

Inflammation is a result of a complex biological response that includes inflammatory mediators, sensors, inflammation-inducing factors, and affected target tissues [83, 84]. Physical injuries, toxic chemicals, viruses, fungi, and bacteria are some harmful stimuli under inflammation-inducing factors. Pathogen-associated molecular patterns (PAMs) triggered the inflammatory response [85, 86]. Inflammatory pathways are mediated by some inflammatory mediators like cyclooxygenase (COX), chemokines, vasoactive amines nitric oxide (NO), etc. [87]. The inflammatory responses finally lead to symptoms like heat, pain, redness, and swelling, etc. [88, 89].

Bandgar et al. designated a novel series of carbazole(5a–o) which was tested against the anti-inflammatory activity. Compound 5c via hydrophobic interactions potently binds at the site of COX-II. The oxygen atom of the methoxy group on compound 5c formed two hydrogen bonds with the Asp B:225 and Nag C:671 and the nitrogen atom present in the pyrazoline ring on compound 5c formed two hydrogen bonds with the Leu A:131 [90].



Compound 5c: 3-(4,5-dihydro-3-(3,4-dimethoxyphenyl)-1*H*-pyrazol-5-yl)-9-methyl-9*H*-carbazole

(16)

Carbazole derivatives inhibit the lipopolysaccharide-induced inflammatory mediator production in macrophages via suppression of p38 MAPK (mitogen-activated protein kinase signaling pathway). Carbazole derivatives inhibit the formation of TNF-α (tumor necrosis factor α), PGE_2 (prostaglandin E_2), and nitric oxide (NO) induced by Lipopolysaccharide (LPS) [91–93] (Fig. 5).

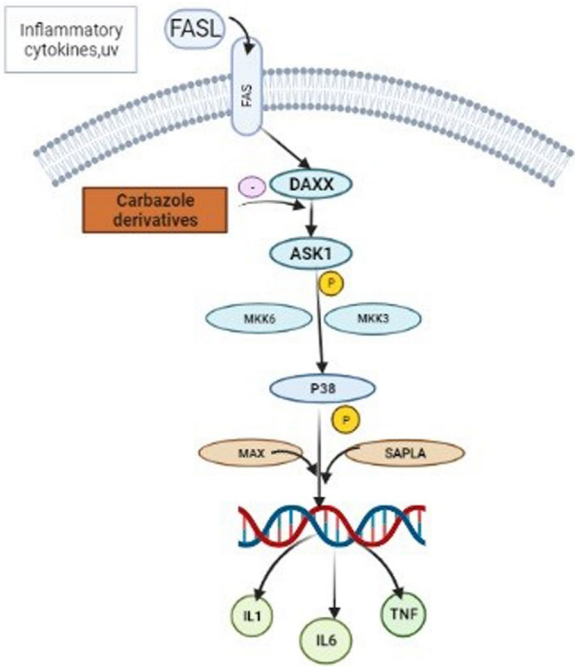
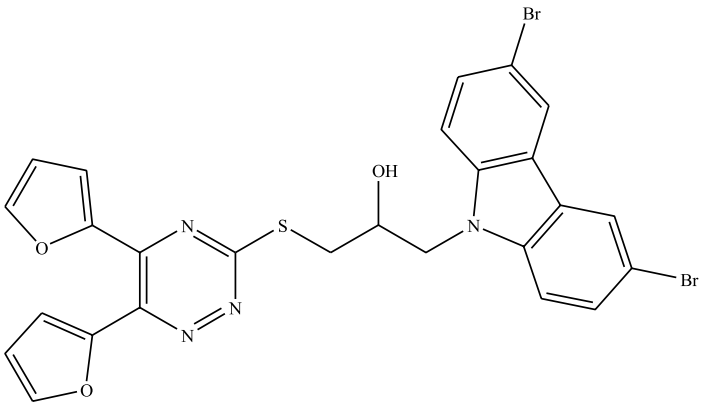


Fig. 5 Anti-inflammatory mechanism of carbazole derivatives. 3-(3-(2-Methoxy-5-methylphenoxy)-4 5-dihydro-1*H* pyrazole-5yl)-9*H*-Carbazole inhibits the p38 MAPK signaling pathway by stopping the conversion of DAXX protein into ASK-1

Antidiabetic potential

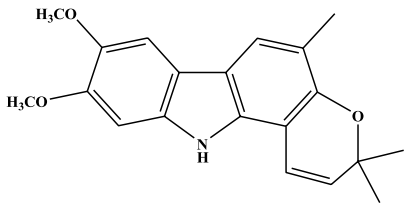
Diabetes is a condition in which due to autoimmune destruction pancreatic β cells slow down the production of insulin results hyperglycemia due to excess availability of glucose [94–98]. α-glucosidase inhibitory activity of compound 7k (1-(5,6-di(furan-2-yl)-1,2,4-triazin-3-ylthio)-3-(3,6-dibromo-9*H*-carbazol-9-yl) propan-2-ol)was found most effective and the result revealed that compound7k is the potent compound with h IC_{50} values of 4.27 ± 0.07 μM among all the synthesized compound by Wang et al. The potent compound with high-density van der Waals contact binds at the bottom of the α-glucosidase pocket, whereas near the entrance of the pocket, furan ring was positioned which made only a few contacts. Detailed analysis showed that the carbazole ring of the potent compound formed arene-cation interactions with Arg-439 and Arg-312 residues, respectively. Furan ring of a potent compound located at the hydrophobic pocket, surrounded by Leu-176, Phe-177, Phe-157, and Pro-240 residues. All these interactions helped 7k to anchor in the binding site of α-glucosidase [99].



Compound 7k: 1-(5,6-di(furan-2-yl)-1,2,4-triazin-3-ylthio)-3-(3,6-dibromo-9*H*-carbazol-9-yl)propan-2-ol **(IC50 values of 4.27 ± 0.07 μM)**

(17)

Carbazole derivative koenidine translocates the GLUT 4 which is mediated through the AKT-dependent signaling pathway (4) in L6-GLUT-4 myc myotubes [100].



Compound koenidine: 3,11-dihydro-8,9-dimethoxy-3,3,5-trimethylpyrano[3,2-*a*]carbazole

(18)

The in vitro testing of separated carbazole alkaloids on uptake of glucose and translocation of GLUT 4 in L6-GLUT-4 myc myotubes was done on streptozotocin-induced diabetic rats for their activities. Therefore, the in vitro study of the koenidine suggested that koenidine, a carbazole derivative, possesses a promising antidiabetic activity through managing diabetes and insulin resistance [6, 101] (Fig. 6).

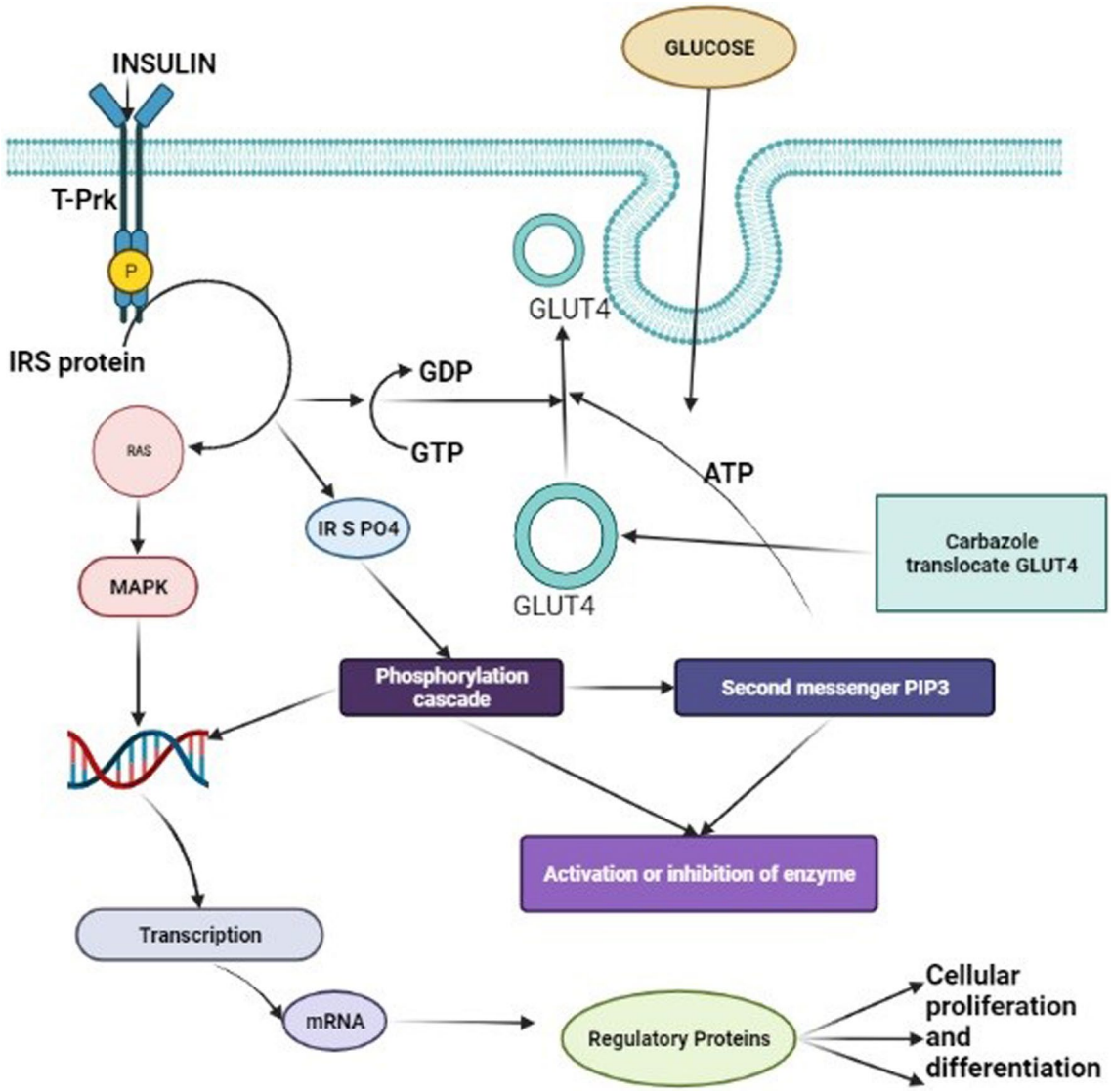


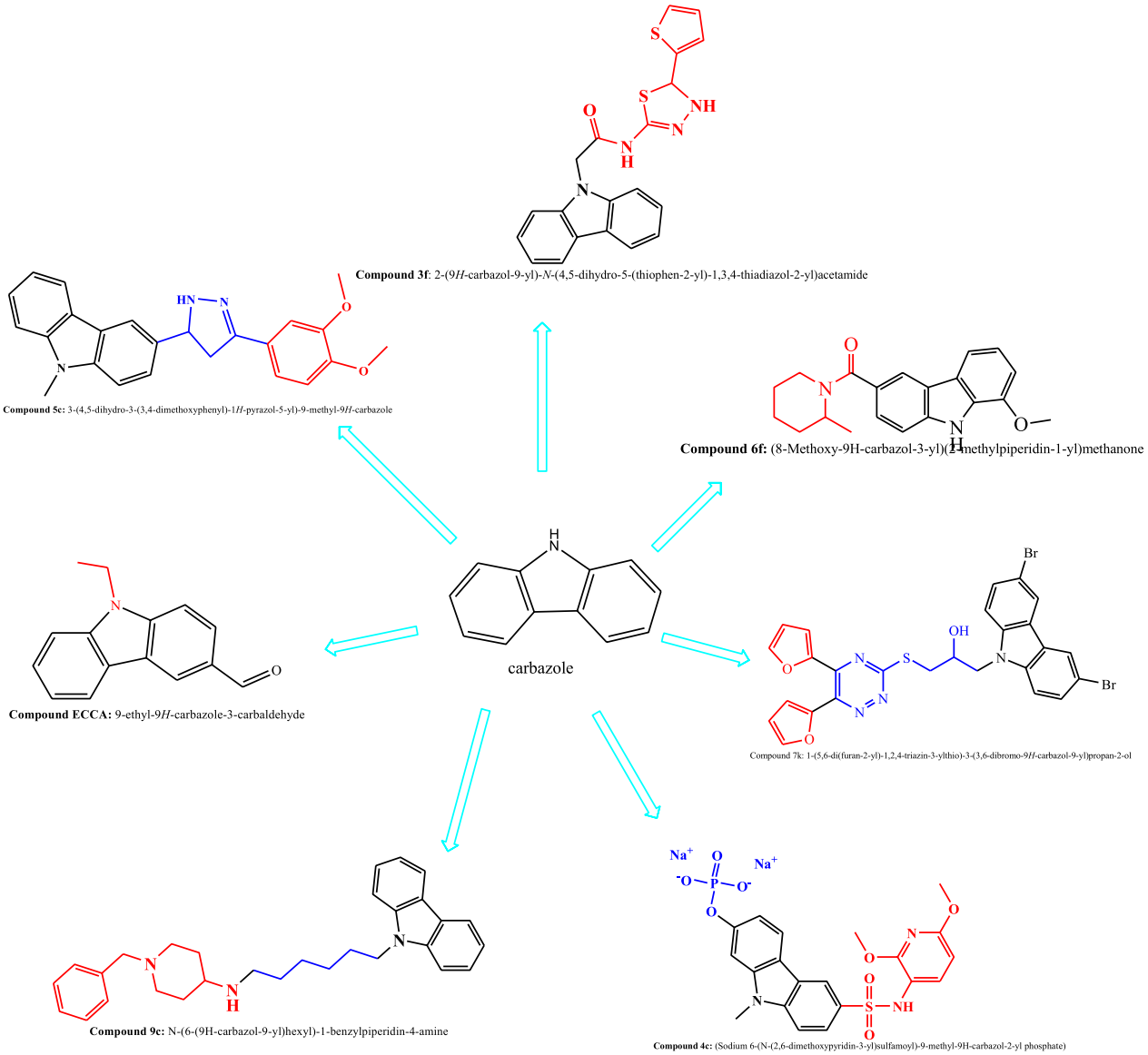
Fig. 6 Antidiabetic mechanism of carbazole derivatives. Koenidine 4 translocates GLUT 4 for antidiabetic activity

Conclusion

Carbazole moiety itself is responsible for various types of pharmacological activities; due to high electron delocalization, carbazole shows better physicochemical properties. Derivatives having carbazole pharmacophore are responsible for various therapeutic activities like anti-Alzheimer, antioxidant, antidiabetic, anticancer, anticonvulsant, antimicrobial, and anti-inflammatory, etc., by specifically acting on potential molecular level proteins and factors such as RAS-MAPK, DAXX, ASK-1, AKT, and JNK, either by inhibiting or by activating them by de-phosphorylation or phosphorylation (Fig. 7). Due to all these important activities, the carbazole nucleus has attracted the attention of researchers in the discovery of other novel derivatives of carbazole.

Fig. 7 Molecular mechanisms of carbazole derivatives for different pharmacological activities

Complete SAR of carbazole derivatives



Abbreviations

GLUT 4	Glucose transporter type 4
ASK-1	Apoptosis signal-regulating kinase 1
ECCA	9-Ethyl-9*H*-carbazole-3-carbaldehyde
RAS-MAPK	Ras/mitogen-activated protein kinase
DAXX	Death-domain-associated protein
AKT	Protein kinase B
JNK	Jun N-terminal kinase
MCF-7	Michigan Cancer Foundation
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
iNOS	Inducible nitric oxide synthase
IL-5	Interleukin-5
EGFR	Epidermal growth factor receptor
AChE	Acetylcholinesterase
BuChE	Butyrylcholinesterase
A875	Human melanoma
HepG2	Human hepatocellular liver carcinoma
MARC145	A subclone of the African green monkey cell line
HL-60	Human promyelocytic leukemia cell line
SMMC-7721	Human hepatocellular carcinoma cell line
MCF-7	Breast cancer cell line
SW480	Human colon adenocarcinoma cell lines

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Author contributions
AT has done various works on synthetic chemistry on carbazole derivatives and collected important information from her research and various literature for this review. BM has conceptualized the idea for this review, prepared the outlines and did the refinement of the paper.

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Ethics approval and consent to participate
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Competing interests
The authors declare that they have no competing interests.

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