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Editorial

Special Issue "Carbazole Derivatives: Latest Advances and Prospects"

Anna Caruso [1,2]

[1] Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Arcavacata di Rende, Italy; anna.caruso@unical.it or anna.caruso@unibas.it
[2] Department of Science, University of Basilicata, 85100 Potenza, Italy

1. Introduction

The academic community has extensively explored, over the years, heterocyclic compounds of the carbazolic motif. These extremely versatile molecules have found applications both in science materials and the pharmaceutical industry. In particular, it was shown that many carbazole derivatives possess a diversity of biological activities and could be used as anticancer, antimicrobial, anti-inflammatory, antioxidant, antiepileptic, antihistamine, antidiarrheal, analgesic, antidiabetic, and neuroprotective agents. Overall, the data reported in this Special Issue could constitute an important resource for the development of novel, efficient, and safe drugs for the treatment of various diseases.

2. The Present Issue

A study in this Special Issue reported the β1-blocking activity of 5,8-dimethyl-9*H*-carbazol-3-yl ethyl carbonate and its derivatives. In particular, two of these derivatives, 1-methyl-1*H*-indol-5-yl-but-2-ynoate and indol-5-yl-but-2-ynoate, emerged as potential counteracting agents against ISO-dependent in vitro cardiac hypertrophy. The data are promising as they were obtained using lower concentrations than those of the traditional β-AR antagonist propranolol. Following molecular docking studies, the authors tested these molecules by bioassays in H9c2 cardiomyocytes exposed to isoproterenol (ISO) to confirm their potential as β1-blocking agents and their activity at low doses, along with their limited side effects [1].

Some studies suggest that many carbazole derivatives could be promising anticancer agents. According to some studies, their effects could also be due to the involvement of the JAK/STAT pathway. According to literature data, some carbazoles could act by downregulating STAT proteins, mostly STAT-3, also affecting interleukins and *i*-NOS production. Several researchers have evaluated the STAT inhibitory activity of different carbazoles, such as carbamazepine, 2-hydroxycarbazole, mahanine, 7-hydroxy-1-methyl-9*H*-carbazol-2-yl 5-(dimethylamino)-naphthalene-1-sulfonate, EC-70124, Lestaurtinib, and some series of *N*-alkylcarbazoles, 1,4-dimethyl-carbazoles, 9*H*-carbazole-1-carboxamides, and carbazol carbonitriles, reporting promising results [2]. Other important work has reported the anticancer activity of a series of nitrocarbazoles. One of the latter compounds, namely 2-nitro-1,4-di-*p*-tolyl-9*H*-carbazole, exhibited good anticancer activity against two breast cancer cell lines, i.e., ER(+) MCF-7 and triple-negative MDA-MB-231, with IC_{50} values of 7 $\pm$ 1.0 and 11.6 $\pm$ 0.8 μM, respectively. Furthermore, this compound did not interfere with the growth of the normal cell line MCF-10A (human mammary epithelial cell line). In vitro immunofluorescence studies and docking simulations demonstrated the ability of the 2-nitrocarbazole derivative to interfere with tubulin organization, a feature that results in triggering MCF-7 cell death by apoptosis [3].

Several research groups have extensively studied the involvement of carbazole derivatives, of synthetic or natural origin, in diabetes pathways. From the analysis of these

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studies it was shown that *N*-substitution, on the carbazole scaffold, by triazinic-, as in 1-((5,6-di(furan-2-yl)-1,2,4-triazin-3-yl)thio)-3-(3,6-dibromo-9*H*-carbazol-9-yl)propan-2-ol, or triazolic moieties, as in 2-(4-((9*H*-carbazol-9-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-1-(3-bromo-4-hydroxyphenyl)ethanone, favors α-glucosidase inhibitory activity; the presence of cyclic sulfonamidic, as in 2-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)isothiazoline-1,1-dioxide, or cyclic urea groups, as in 1-(3-(3,6-difluoro-9*H*-carbazol-9-yl)-2-hydroxypropyl)imidazolidin-2-one, modulates cryptochrome activity; the presence of ethylphenoxy groups, as in Chiglitazar, improves insulin sensitivity; hydrogenation of a ring of the carbazole core promotes the hypoglycemic effect via the AMPK pathway, as in 6-(benzyloxy)-9-(4-chlorobenzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid, and the tetracyclic system, as in mahanine derivatives, is crucial in glucose uptake and translocation of glucose transporter GLUT4 in skeletal muscle and adipocyte cells. Furthermore, compounds with a high conjugation effect, such as bisgerayafoline D, show predominant antioxidant activity. The data reported could provide an important guide reference for the development of alternative and effective antidiabetic agents [4].

Lastly, considering the pandemic period that has affected everyone's life since 2020, some authors reported the latest carbazole therapeutic strategies for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. In particular, they reported the data of 14 drugs containing a carbazole structure, including Carprofen, Carvedilol, and five carbazole alkaloids obtained from *Murraya koenigii*, which were studied as SARS-CoV-2 M-pro inhibitors. Edotecarin, 7-hydroxystaurosporine, CIMSSNa, and 6-formylindolo(3,2-b)carbazole were reported as viral entry inhibitors targeting human ACE2, while 2-((2-(1-benzylpiperidin-4-yl)ethyl)amino)-*N*-(9*H*-carbazol-9-yl)acetamide was reported as an NPC1 inhibitor; 6-cyano-5-methoxy-12-methylindolo [2, 3A] carbazole was reported as antiviral against PLpro; and Ramatroban was reported as an immunotherapy treatment. The studies and observations which reported about carbazoles for the treatment of COVID-19 infection can signify potentially useful clinical applications. Moreover, some of these molecules can be used for designing new antivirals [5].

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