Biochemistry Research Trends

Bioactive Heterocycles

Synthesis and Biological Evaluation

K. L. Ameta
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Editors

NOVA

BIOCHEMISTRY RESEARCH TRENDS

BIOACTIVE HETEROCYCLES

SYNTHESIS AND BIOLOGICAL EVALUATION

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Preface

The majority of pharmaceuticals and biologically active agrochemicals are heterocycles while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural feature inherent to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three-dimensional representations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

They have been immensely conducive to the development of society from a biological and industrial point of view as well as to the understanding of life processes and the efforts to improve the quality of life. Amongst approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half of them are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is widely known and recognized. However, specifically, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis.

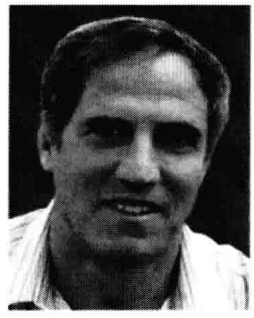
Nevertheless, heterocycles with other heteroatom such as oxygen, phosphorus and selenium also appear on the scene. Many natural drugs such as papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate fall under the same name. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. Thus, the purpose behind writing this book is to provide a succinct summary of methods for the synthesis and biological activities of various different sized bioactive heterocycles apart from highlighting anticancer, antifungal, antibacterial, antiHIV, anti-inflammatory, antioxidant and many more biological activities of heterocyclic compound.

The Editors

About the Editors

Dr. K. L. Ameta received his doctorate degree in Organic Chemistry from M. L. Sukhadia University, Udaipur, India in the year 2002. Presently, he is working as Assistant Professor of Chemistry, Faculty of Arts, Science and Commerce, Mody Institute of Technology and Science (Deemed University) Lakshmangarh, Rajasthan, India. He has vast experience of teaching both graduate and postgraduate level students. His research area involves synthesis, characterization and biological evaluation of different sized bioactive heterocyclic systems. In addition, to this he has keen interests in photocatalysis. He has published a number of research articles in various journal of national and international repute.

Dr. R. P. Pawar is serving as a Head and Associate Professor in Deogiri College, Aurangabad, Maharashtra, India. He completed his doctorate degree in Organic Chemistry from Swami Ramanand Teerth Marathwada University, Nanded, India in the year 1998. He did his postdoctoral training at Department of Medicine, The Hebrew University, Jerusalem, Israel. He has immense experience of graduate and postgraduate level teaching. His research area involves Synthetic Organic Chemistry, Synthesis and Biological evaluation of novel bioactive heterocyclic systems, Green Chemistry Approches. He has published a number of research articles in National and International reputed journals.



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Contents

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Chapter 1

Multipotent 1,8-Naphthyridines, as New Tacrine Analogues, for the Treatment of Alzheimer's Disease

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Abstract

The synthesis and biological evaluation of 1,8-naphthyridines, new tacrine analogues, as acetylcholinesterase and butyrylcholinesterase inhibitors, as well as voltage-dependent Ca^{2+} channels modulators is reviewed. These compounds are hybrids from tacrine and 1,4-dihydropyridines, well-known Ca^{2+}-antagonists. They were synthesized from conveniently substituted and functionalized 2-amino-3-cyano substituted heterocycles *via* Friedlander-type reaction with diverse cycloalkanones. These compounds are moderate and selective AChE inhibitors, as well as Ca^{2+} channels antagonists. As the regulation of Ca^{2+} entry to cells has been described to play a key role in the cell apoptosis process, some of them were studied as neuroprotective agents against different toxic agents.

Keywords: Acetylcholinesterase; Butyrylcholinesterase; Friedländer reaction; Tacrine; 1,8-Naphthyridines; 1,4-Dihydropyridines; Voltage-dependent calcium channels; Neurodegenerative diseases; Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative, irreversible disorder clinically characterized by abnormal memory loss along with deterioration of other cognitive abilities as well as motor capacities [1]. Although the etiology of AD is still poorly understood, amyloid β (Aβ) deposits [2], τ-protein aggregation [3], oxidative stress [4] or low levels of acetylcholine (ACh) are of paramount importance in the progress of the disease [5-6]. Based on the cholinergic hypothesis, cholinesterase inhibitors (ChEI) such as rivastigmine, donepezil, and galanthamine [7,8] are currently used for the treatment of AD. ChEI, by inhibiting acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), prevent the hydrolysis of ACh at the synaptic cleft [9], enhancing the central cholinergic deficit, thus alleviating its symptomatology [10].

A renewed interest in AChEI [11, 12] emerged when beneficial effects, which were not directly linked to cholinergic neurotransmission, were demonstrated for some of them [13-17]. In this regard, galanthamine has been described to protect human neuroblastoma cells and cortical neurons against Aβ-induced neurotoxicity [18-19]. Furthermore, donepezil was confirmed to reduce τ-phosphorylation by inhibition of glycogen synthase kinase 3β [20-22]. In addition, AChE seems to accelerate Aβ fibril aggregation in the brain [23], an activity located in the peripheral anionic site (PAS) of AChE [24, 25]. *In vivo* studies of some AChEI-antiaggregating drugs showed reversion of the cognitive impairment due to scopolamine in the MWM (Morris Water Maze) test, as well as reduction of plaque load in the brains of human amyloid precursor protein (APP) transgenic mice [26].

The multifactorial profile of AD has prompted the search for multipotent drugs able to interact simultaneously in two or more targets [27]. The multitarget approach [28] has driven to hybrids of tacrine-donepezil [29, 30], tacrine-melatonin [31, 32], tacrine/8-hydroxyquinolein [33], coumarins that inhibit both MAO and the AChE enzyme [34, 35], and highly potent neuroprotective rasagiline-rivastigmine hybrids [36].

Since 1996 the group led by Marco-Contelles and colleagues has been investigating new multipotent drugs able to target the cell Ca^{2+} signal [37, 38] along with a good inhibitory activity of ChE enzymes [39-41].

Though Ca^{2+} overload is the main factor that triggers processes leading to cell death, the Ca^{2+} dyshomeostasis has been a poorly investigated target in order to develop new drugs for the treatment of AD [42]. The Ca^{2+} hypothesis of ageing [43], supported by the fact that sustained changes in the regulation of $[Ca^{2+}]_i$ are due to age-dependent alterations in the cellular mechanisms of Ca^{2+} homeostasis, has shown that calcium dysfunction can increase Aβ formation and τau hyperphosphorylation [44, 45]. More recently, some authors reported that the P86L-mutated channel CALHM1 generates both mitochondrial ($[Ca^{2+}]_m$) and cytosolic ($[Ca^{2+}]_c$) Ca^{2+} signal with a transient pattern, but Ca^{2+} entry through P86L-CALHM1 generates a plateau of sustained and prolonged in time $[Ca^{2+}]_m$, which could be relevant in the context of mitochondrial Ca^{2+} overload, neuronal death, and the association between P86L-CALHM1 and the risk of AD [46, 47]. Calcium entry through L-type Ca^{2+} channels causes both calcium overload and mitochondrial disruption, which leads to activation of the apoptotic cascade and cell death [48]. Hence, blocking the entrance of Ca^{2+} through this specific subtype of Ca^{2+} channel could be valuable to prevent cell death. This is