Frontiers in Natural Product Chemistry

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Frontiers in Natural Product Chemistry

(Volume 8)

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PREFACE

Frontiers in Natural Product Chemistry presents recent advances in the chemistry and biochemistry of naturally occurring compounds. It covers a range of topics, including important researches on natural substances. The book is a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information on bioactive natural products.

The chapters in this volume are written by eminent authorities in the field. Bose *et al.,* in chapter 1 of the volume, explain recent developments regarding antiviral agents from seaweeds and seagrass. Singh *et al.,* in chapter 2, present a comprehensive review of various quinolizidine and *bis*-1-oxaquinolizidine alkaloids isolated from marine organisms, presenting their chemical structures and reported biological properties. Ona and Bouso, in chapter 3 of the book, review the use of natural product mixtures instead of isolated compounds thereby combining two recent paradigms: psychedelic assisted therapy on the one side and polypharmacology on the other. Hussain *et al.,* in chapter 4 give a brief overview of the physiological activities of phenolic compounds along with their potential neuroprotective effects . Yeong and Chin discuss the neuroprotective effects and bioactive constituents of common herbs from the Lamiaceae family in chapter 5 of the book. Masoodi *et al.* review the coumarin derivatives as potential anti-inflammatory agents for drug development in chapter 6. In the last chapter of the book, *Eshghi et al.* discuss the recent progress in the synthesis and biological activity of chromene and its derivatives.

I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new and novel therapies against various diseases. I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), Mr. Obaid Sadiq (In-charge Books Department), and Miss Asma Ahmed (Senior Manager Publications) at Bentham Science Publishers.

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CHAPTER 1

Chemistry, Antiviral Properties and Clinical Relevance of Marine Macroalgae and Seagrass

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Abstract:

Background

Marine organisms are always considered as one of the richest sources of natural products. Historically, they are being used as medicines in diverse ailments. In recent years, researchers have reported several primary and secondary metabolites in marine organisms (few examples are macroalgae, sponges, seagrasses, bacteria, microalgae), which serve in numerous disorders, of which 20–25% have shown antiviral, antimicrobial, antifungal, anticancer or anti-inflammatory properties. According to the global pharmaceutical website, there are a total of nine approved pharmaceuticals from a marine source, and apart from this, thirty-one other compounds are currently in a clinical trial.

Objective

Discovery of potent antiviral drugs is required currently to mitigate life-threatening viruses. Considerable research exploring the bioactivity of marine macroalgae has been documented, highlighting the immense biochemical diversity of its primary and secondary metabolites with a novel mechanism of action, making them perfect sources for novel antiviral bioactive compounds of pharmaceutical interest.

Methods

Databases utilizing bibliographic databanks, such as PubMed, SpringerLink, Elsevier journal, Science Direct, Scopus databases, and Google search were surveyed using keywords anti-viral, seaweeds, antiviral drugs, seagrass, polyphenols, pharmacology, clinical trials.

Results

Marine phytoplanktons are found to be the major source of several key medicinal agents (polyphenols, phenolic compounds), which are largely obtained from seaweeds

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and seagrasses and have shown promising antiviral activity in cell culture studies. This review explains recent developments regarding antiviral agents from seaweeds and seagrass.

Keywords: Antiviral Drugs, Polyphenols, Seagrass, Seaweeds.

INTRODUCTION

Since the last 50 years, a huge number of novel compounds and their metabolites, with different biological properties ranging from anticancer to antiviral, have been procured from diverse marine organisms, some of which are presently in use [1]. Extreme rivalry, feeding pressure coupled with non-static marine environmental conditions lead to the generation of compounds with chemical and structural characteristics that are not commonly found in terrestrial plants [2]. It's this rare feature that renders the marine ecosystem a prolific storehouse of potential bioactive natural products to combat major diseases. Marine natural products are majorly secondary metabolites having no primary function related to the development, growth, or propagation of a species. Till 2008, around 68% of anti-infective agents (including antibacterial, antiviral, antiparasitic, and antifungal compounds) [3] were naturally derived. Over the last decades, there has been a surge in the demand for novel antivirals as different forms of infectious diseases caused by emerging or re-emerging viruses continue to pose a significant threat to humanity. In the light of the current pandemic situation due to the SARS-CoV2 virus, the market for antivirals is assumed to rise from $52.2 billion in 2019 to about $59.9 billion in 2020 [4], due to increasing demands for antiretroviral drugs utilized in the treatment of covid-19 patients along with potential antivirals, which could mitigate infection.

According to the global marine pharmaceutical website, there are currently 9 approved marine-derived pharmaceuticals [2] and an additional 31 compounds either in Phase I, II, and III of clinical pharmaceutical development [5]. Amongst them, Carragelose® and Vira-A® are antivirals approved for common cold/influenza-like infections and keratoconjunctivitis/keratitis due to herpes simplex virus (HSV), respectively. Despite a huge repertoire of antivirals approved for clinical use, insufficient drug efficacy, drug toxicity, along with the high cost of current antiviral drugs pose a challenge to the treatment.

Given the fact that there is interspecies variability in the life cycle of viruses, the six basic stages, *i.e*., attachment, penetration (also called virus entry), uncoating, replication, assembly, and release, are found to be the targets for antivirals [6]. Following the stage of viral entry, transcription and replication of virus-specific ribonucleic acids (RNAs) are carried out by a viral polymerase complex. Unlike

the polymerases of eukaryotic cells, viral polymerase lacks an error correction mechanism. Therefore, the frequency of mutations of the viral genome is 10^4 to 10^6 nucleotides per replication cycle according to various estimates. This is several orders of magnitude higher than the rate of mutation in bacteria and eukaryotes. As a result of the rapid rate of mutations, the virus escapes the immune response of the host. Thus, given the creation of an immune layer in the population due to vaccination and natural occurrence, annual epidemics occur. In addition, drug-resistant viral strains have grown as a result of the use of antiviral drugs, decrementing their efficacy [7].

Bioprospecting efforts since the last 40 years have led to over 20,000 compounds of marine origin. Based on the discovery of drugs from the natural origin such as, lovastatin and paclitaxel, it is speculated that the marine environment might yield more potent antiviral candidates with higher efficiency, better selectivity and lesser chances of resistance development. This situation warrants novel lead molecules from untapped natural resources to be investigated for the development of alternative therapy as nature generally create more refined and improved systems with a complex mode of action.

REASON OF SPECIAL INTEREST IN MACROALGAE AND SEAGRASS AS NOVEL ANTIVIRALS

Marine sponges, corals, and microorganisms form 70% of marine metabolites, whereas molluscs, ascidians, and algae metabolites are just a small proportion [2]. Of late, marine phytoplanktons, including macroalgae and seagrass, have attracted considerable attention due to promising antiviral activity. *Chlorella vulgaris*, an aquatic microalga, was first reported to have antibacterial activity [8], followed by antimicrobial properties of macroalgae/seaweed extracts in the coming two decades [9]. Micro and macroalgae were one of the primary sources of natural components exhibiting *in vitro* anti-human immunodeficiency virus (anti-HIV) activity [10]. Halitunal, a novel diterpenealdehyde isolated from marine algae *Halimeda tuna* showed *in vitro* antiviral effect against murine coronavirus [11], while *in vivo* protection against *Semeliki forest* virus was exhibited by sphingosine isolated by Indian green algae *Ulva fasciata* [12]. Sulphated flavones Thalassoilins A, B and C, isolated from sea grass *Thalassia testudinum* [13], were found to restrain HIV enzyme integrase *via* binding to the catalytic domain of HIV integrase.

Marine polysaccharides, as biological macromolecule, have been discovered to be of utmost significance among the enormous amount of marine extracts. Although they extensively exist in marine biodiversity, including animals [14, 15], plants and microorganisms [16, 17], seaweeds (macroalgae) have been reported to be the

CHAPTER 2

Quinolizidine Alkaloids from Marine Organisms: A Perspective on Chemical, Bioactivity and Synthesis

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Abstract: Marine organisms produce numerous secondary metabolites that exhibit a wide range of biological activities, which have applications in pharmaceutical research. Numerous secondary metabolites have been discovered from various marine organisms and studied for their chemical and biological properties. Among the secondary metabolites of marine organisms, alkaloids constitute a versatile group of bioactive natural products with promising bio-activities. Several alkaloids, such as pyridoacridines, pyrroles, bisindole, isoquinolines, quinolizidines and bromotyrosines, *etc*., to name a few, have been isolated from marine organisms. The chemical diversity and bio-activities of marine alkaloids are reported in several research and review articles. Quinolizidine alkaloids (QAs) are a group of compounds that possess either a quinolizidine ring or its derivatives. They are isolated from terrestrial plants, animals and also from numerous marine organisms, such as sponges, tunicates, fungus, *etc*. Biological activities exhibited by QAs include ichthyotoxicity, chemical defense, anti-microbial, antiviral, and inhibition of nicotinic acetylcholine receptors. In the past years, a few scattered reviews appeared on the isolation of QAs from natural sources, mostly from terrestrial sources, but the reports skipped several QAs of marine origin. This chapter presents a comprehensive review of various quinolizidine and *bis*-1-oxaquinolizidine alkaloids isolated from marine organisms, detailing their chemical structures and reported biological properties. Further, the chapter highlighted synthesis of some marine-derived QAs, namely, petrosins, xestospongins, clavepictines, pictamine, citrinadins A and B.

Keywords: 1-Oxa-Bisquinolizidine, Marine Organisms, Pictamine Alkaloid, Quinolizidine Alkaloids, Sonogoshira Coupling, Sponges, Synthesis, Tunicates.

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INTRODUCTION

Marine life represents highly prolific and rich biodiversity on the earth. It not only supports the livelihood of millions of people but also gives pharmacologically important bioactive compounds. Indeed, several biologically active compounds have been discovered from the marine environment, of which many of them are under clinical and preclinical trials, while a few candidates have already entered the market [1]. Numerous bioactive compounds have been isolated from marine organisms, which include alkaloids, terpenoids, sterols, pyrones and peptides, *etc*., to name a few. Alkaloids represent one of the most important bioactive compounds isolated from marine organisms [2]. The chemical and biological activities of alkaloids isolated from sponges [3], ascidians [4] and bacteria [5] have been well documented. Further, over the past years, alkaloids derived from marine organisms *viz.* pyrrole [6, 7], bromotyrosine [8], indole [9], pyridine [10], and pyridoacridine [11] have also been presented in several research and review articles. However, a review dedicated to marine-derived quinolizidine alkaloids, which are known for their diverse bioactivities, is so far lacking, although a few scattered reports are available in the literature [3, 4, 12].

QAs are a group of alkaloid family that contains a quinolizidine ring. Most of the QAs possess diverse biological activities, and they are known from both terrestrial plants as well as marine organisms [13 - 15]. They comprised more than 2% of all the alkaloids isolated from terrestrial plants. QAs can be grouped into eight structural types, namely, lupinine (**1**), sparteine (**2**), lupanine (**3**), anagyrine (**4**), tetrahydrorhobifoline (**5**), cytosine (**6**), matrine (**7**) and multiflorine (**8**) (Fig. **1**) [16]. In the marine environment, QAs have been isolated from various organisms, primarily from sponges, and a few are isolated from ascidian and fungi. QAs isolated from the marine environment are mostly lupinine type. Biological properties of marine-derived QAs include vasodilative [17], ichthyotoxicity [18], anticancer [19], anti-HIV [20], antimicrobial [21], cytotoxicity [22] and anti-malarial (Table **1**) [23].

Table 1. Selected quinolizidine alkaloids derived from marine organisms with their bioactivity.

Compounds	Source	Bioactivity	References
Petrosin (**9**)	**Sponge:** *Petrosia seriata*, *Oceanapia*sp., *Petrosia similis*	Ichthyotoxicity, antimicrobial, anti-HIV	[18, 20, 21, 25]
Petrosin A (**10**)	*Petrosia similis*	Anti-HIV	[20]
Araguspongine A (**26**)	*Xestospongia* sp.	NO inhibition	[33]

(Table 1) cont.....

Compounds	Source	Bioactivity	References
Araguspongines N-P (**37-39**) Araguspongins K **(30**) & L(**31**) Aragupetrosin A (**24**)	*Xestospongia muta* *Xestospongia exigua* *Xestospongia* sp.	NO inhibition Antimalarial Vasodilative	[17, 23, 41]
Xestospongin C (**14**)	*Oceanapia* sp., *Xestospongia exigua*	Antimicrobial	[21, 27]
Xestospongin D (**15**)	*Oceanapia* sp., *Xestospongia exigua, Niphates* sp.,	Antimicrobial, anticancer, vasodilative	[21, 27, 28]
Araguspongine C (**17**)	*Xestospongia* sp., *Xestospongia exigua, Xestospongia muta*	Anticancer, cytotoxic, vasodilative, antimalarial, antituberculosis, antifungal, antifouling	[19, 22, 23, 29, 36, 37, 41]
Araguspongines M (**32**), B (**13**) and D (**18**)	*Neopetrosia exigua*	Cytotoxic	[22]
Demethylxestospongin B (**25**)	*Xestospongia muta, Xestospongia* sp.	Cytotoxic antifungal activity	[34, 39]
Clavepictine A (**43**) and clavepictine B (**44**)	*Clauelina picta (Ascidian)*	Antitumor, antimicrobial	[45, 46]
citrinadin A (**46**)	*Actinotrichia fragilis, Penicillium citrinum*	Cytotoxicity	[48, 49]

This chapter presents a comprehensive review of the various quinolizidine and bis-1-oxaquinolizidine alkaloids isolated from marine organisms, namely, sponges, tunicates, fungus, *etc*., detailing their chemical structures and reported biological properties. Further, the chapter describes the total synthesis of marine-derived QAs *viz.*, petrosins, xestospongins, clavepictines, pictamine, and citrinadins A and B.

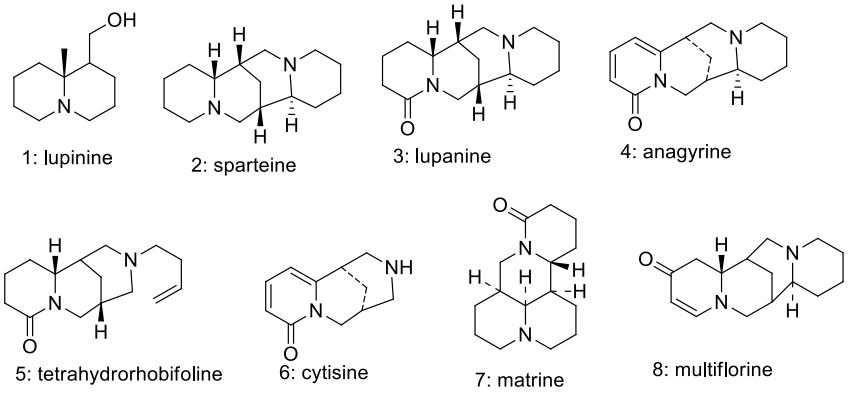

Fig. (1). Structural types of quinolizidine alkaloids.

CHAPTER 3

Towards the Use of Whole Natural Products in Psychedelic Research and Therapy: Synergy, Multi-Target Profiles, and Beyond

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Abstract: Interest in psychoactive ethnobotanicals such as ayahuasca or *Psilocybe* mushrooms for clinical uses has increased over the last two decades. While clinical and experimental approaches have focused on using isolated compounds of interest (such as psilocybin), an emerging trend in drug discovery involves a more comprehensive approach. The polypharmacology paradigm, as it has been named, suggests that promiscuous drugs could be safer and more effective than highly selective ones. This is especially relevant with regards to complex diseases, like most mental health problems and neurodegenerative diseases, and for natural products, including psychoactive ethnobotanicals. Natural products not only show a multi-target profile, but they also contain several compounds capable of interacting with one another and producing synergistic effects. In this chapter, the use of whole natural products instead of isolated compounds is suggested in support of combining two recent paradigms: psychedelic-assisted therapy on the one side and polypharmacology on the other.

Keywords: Natural products, Polypharmacology, Psychedelics, Synergy.

INTRODUCTION

Cultures around the world have long used psychoactive ethnobotanicals (PE) like *Tabernanthe iboga* and *Psilocybe cubensis*. Lesser-known or at least less-ritually-used PE in Western societies includes *Amanita muscaria* and some *Datura* species [1]. Despite this long-established tradition, it has only been in recent decades that researchers decided to elucidate the complex and unique effects

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produced by PE. These plants and fungi have challenged anthropologists, psychologists, pharmacologists, health professionals, and anyone else who approached them. Beyond the complexities easily found among natural products, PE are challenging because of their ability to induce altered states of consciousness that dramatically change how we see both the external and internal worlds. Both the pharmacological and the psychological effects of PE are pushing the limits of our knowledge, challenging us to develop new understandings that will eventually lead to innovative and effective ways to deal with physical and mental disorders.

One of these new understandings concerns how we use drugs for the treatment of diseases or their symptoms. The classical posology, in which one should take a pill every eight hours and expect symptom-relief effects, might be replaced by a limited number of sessions within a psychotherapeutic setting in which you take a PE, and your therapist guides you through a transformative psychological journey. However, another new understanding, the one this chapter focuses on, concerns how we develop new drugs. The approach on which pharmacology has been based during the last century consists of isolating active principles found in natural products and developing medications that are as selective as possible. This idea was elegantly suggested by Paul Ehrlich (1854-1915), Nobel Prize laureate, at the end of the 19th century, although similar ideas were proposed at the end of the 18th century by E.A. Nicolai. According to Ehrlich, the optimal agents for the treatment of infections (which he termed "magic bullets") would be the ones with a high affinity for the pathogen and low toxicity for the patient ("high parasitotropism with low organotropism," in his words) [2]. Notably, Ehrlich successfully developed a "magic bullet," arsphenamine, which was the first human-produced antibiotic [2, 3]. Although this approach was especially valid in the case of infections, it was also used as a model for general drug development until very recently, continuing the assumption that a selective ligand that does not interact with a high number of biological targets is always preferable. This paradigm's zenith was reached following the completion of the human genome-sequencing project in 2000 [4]. After 10 years of international collaboration, the human genome was finally revealed, further encouraging the identification of disease-causing genes for subsequent molecular interventions [5]. However, while Ehrlich's "magic bullets" were effective only when dealing with infections, genetically-developed "magic bullets" are effective in the few cases where diseases are caused by single genes. Unfortunately, the etiology of most of the central nervous system (CNS) disorders is unknown, often polygenic, and epigenetically modulated by several factors [6 - 9]. Moreover, the paradigm that conceives of diseases as a kind of house of cards, where if you take out one or two cards from the base, the entire structure will collapse, is progressively being substituted by a model in which diseases are considered systems sustained by

large and complex biological networks [10]. Natural products, including PE, offer us complex tools capable of dealing with those networks. Thus, in recent years, the use of multi-target ligands and whole natural products has been observed as potentially being more advantageous than highly selective ligands. This has led to a paradigm shift in drug discovery towards the polypharmacology approach that embraces the use of multi-target drugs. We believe that these advances should be applied to the clinical use of PE, as most of them are of a natural origin. This chapter provides a fertile background for effectively connecting psychedelic research with polypharmacology, two emerging, innovative, and promising paradigms.

In order to effectively use natural products in general and PE specifically, it is necessary to understand them and their mechanisms of action. Fortunately, major developments have recently occurred in the field of natural products research. This chapter's following sections will present the current knowledge on the topic, first introducing the concept of synergy and other interactions between the compounds in natural products; then, recent advances obtained in the field of psychedelic medicine focusing on PE *P. cubensis*, *T. iboga*, and ayahuasca will be outlined; reasons for using whole products rather than isolated compounds (*e.g.,* psilocybin in the case of *P. cubensis*) will be discussed; ethical concerns regarding sustainability and traditional knowledge will be considered; and lastly, future challenges and recommendations will briefly be suggested.

INTERACTIONS BETWEEN COMPOUNDS IN NATURAL PRODUCTS AND THEIR MULTI-TARGET EFFECTS

Plants have developed the ability to interact with their surroundings in various ways, either communicating with other plants [11] or attracting/repelling insects and herbivores [12, 13]. The production of flowers exemplifies the extent to which plants interact with other beings, as flowers were specifically developed when plant reproduction started to be in collaboration with insects, and therefore they had to attract them using different stimuli (colours, odours, nectar, *etc.*).

Plants' defence strategies have attracted remarkable attention, and there are currently several hypotheses regarding why they exist [14]. The defence process is highly complex and involves both direct and indirect actions. Chemicals produced by plants play a vital role in those actions. In order to carry out not only defence mechanisms but also several other complex processes, plants have developed different classes of chemicals (*e.g.,* flavonoids, alkaloids, terpenoids, and fatty acids, among others). Some of them are known as secondary metabolites, which is to say, compounds not directly linked to the basic processes of the plant (feeding, growth) but associated with the enhancement of survival. Among the direct

CHAPTER 4

Neuroprotective Effects of Polyphenols

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Abstract: Phenolic compounds, the bioactive phytochemicals, are abundantly found in a huge variety of food items, including fruits, vegetables, cereals, legumes, and herbs. Phenolic compounds are often called phenols, phenolics, and polyphenols. They are secondary metabolites of plants and are considered an integral part of both animal and human diet. Natural phenolic compounds have acquired increasing attention in the last few years because of their countless health-related therapeutic interventions. Biological activities of phenolic compounds include anti-oxidative, anti-inflammatory, anti-allergic, and anti-hypertensive are found to play their role in neuroprotection. All of these above mentioned properties of different phenolic compounds play a critical and central role in preventing the progression of neurodegenerative, neurological disorders and brain injuries. A list of phenolic compounds including resveratrol, quercetin, rutin, curcumin, baiclein, luteolin, and (-) Epigallocatechin-3-gallateon have been discussed in detail in the context of their neuroprotective action. The present chapter describes a brief and comprehensive overview of the physiological activities of phenolic compounds along with their potential neuroprotective approach.

Keywords: Antioxidants, Cognitive Functions, Neurodegenerative Diseases, Neuronal Survival, Neuroprotection, Phenolic Compounds.

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INTRODUCTION

Polyphenol compounds, sometimes called phenolics and phenols, are an extensive class of chemical compounds containing a hydroxyl group (-OH). Phenolic compounds are the secondary metabolites which are classified based on the number of phenol units present in one molecule [1, 2]. Phenolic compounds (PCs) are not only produced by various species of microorganisms and plants but are also synthesized industrially [3]. These substances contain a variety of compounds such as complex and simple flavonoids, phenolic acids, coumarins, phenylpropanoids, stilbenoids, phenols, lignans, and xanthones [4]. These compounds are potentially involved in maintaining human health *via* acting as anti-inflammatory, anti-aging, anti-proliferative and anti-oxidative agents [5]. Several studies reported that phenols are beneficial in some neuropsychiatric disorders, neurodegenerative diseases, and brain injuries [6]. In this regard, the potential therapeutic and neuroprotective approaches of different phenolic compounds are illustrated in the next sections of this chapter.

CLASSIFICATION

Phenolic compounds are classified into different classes based on the number and location of the hydroxyl group. Among the natural phenols, the most important and vast class is flavonoids, which contain flavones, flavanones, isoflavonoids and anthocyanins. However, a detailed classification of phenolic compounds is well presented in Fig. (**1**) below.

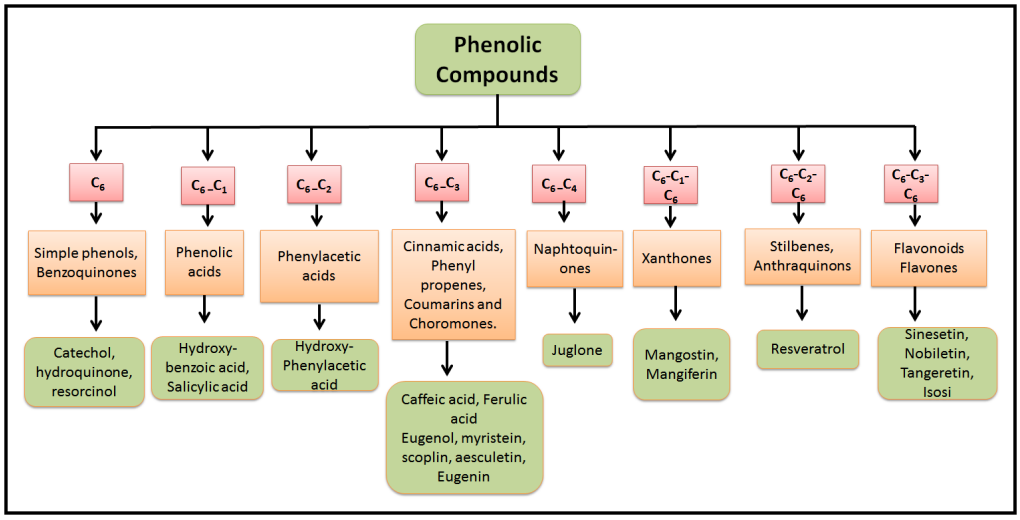

Fig. (1). Classification of phenolic compounds and their examples.

CHEMICAL CHARACTERISTICS

Principally, phenolic compounds as a diverse group of phytochemicals are involved in the modulation of various physiological processes of the living system [7, 8]. Because of the chemical characteristics of these compounds, it is worthy to state that these compounds exist in both volatile and soluble forms. However, the majority of these compounds are soluble. The structures of these phenolic compounds with their major classes are illustrated below in Fig. (**2**).

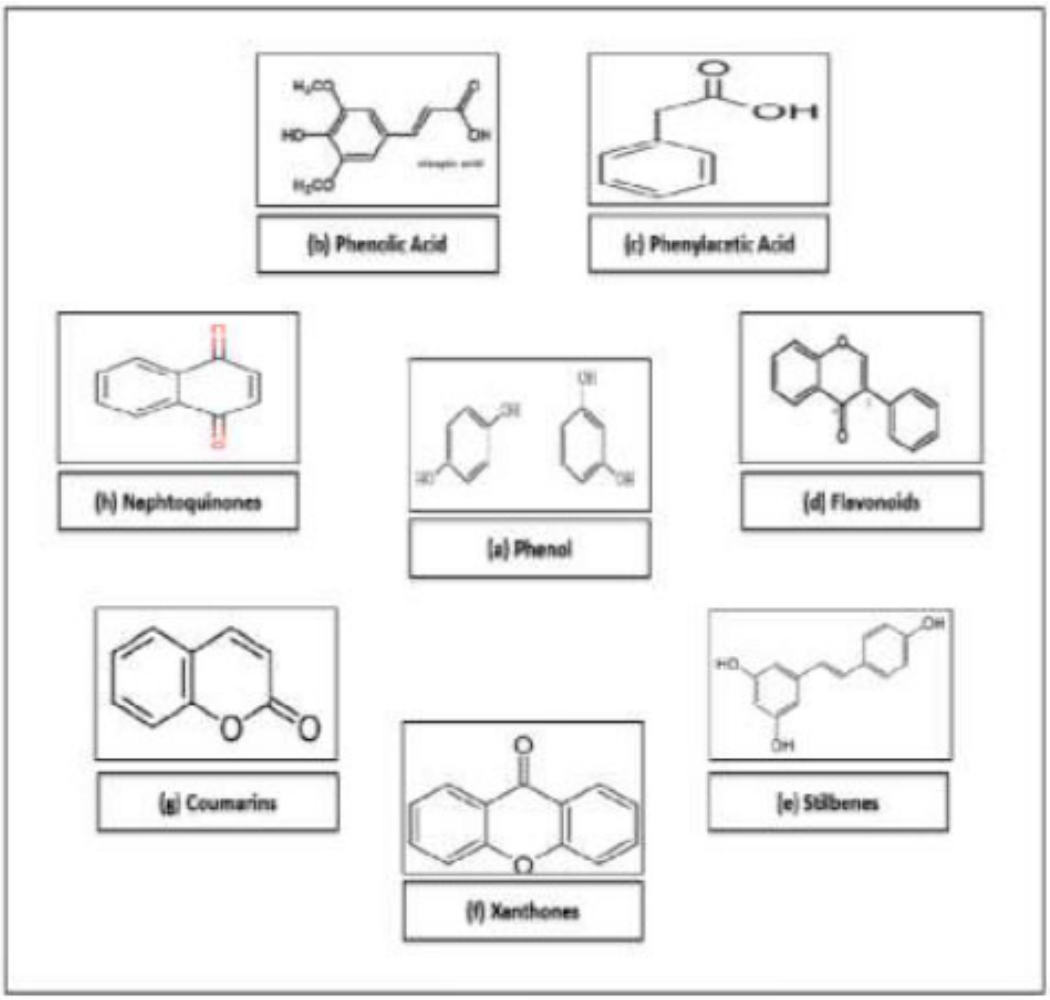

Fig. (2). Structures of main classes of phenolic compounds.

CHAPTER 5

Neuroprotection with the Functional Herbs from the Lamiaceae Family

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Abstract: The growth of the average lifespan of the global population is accompanied by a progressive increase in the prevalence of neurodegenerative disease (NDD). Common NDDs such as Alzheimer's, Parkinson's, Huntington's diseases, and others are known to be strongly related to aging. The prevalence of NDD is expected to increase steeply with the increment in life expectancy. The currently available therapeutic interventions are mainly symptomatic, and most have failed to reverse or slow down the disease progression. Hence, new treatments and preventive measures are urgently needed. Plants from the Lamiaceae family have reported several neuroprotective effects attributed to the abundance of secondary metabolites that could target multiple pathways of the cellular death mechanism. Owing to the multifactorial nature of NDDs, the abundance of secondary metabolites in plants has attracted the attention of researchersto the neuroprotective potentials of natural products. The neuroprotective effects and bioactive constituents of common herbs such as *Perilla frutescens* (Perilla), *Sideritis scardica* (Ironwort), *Ocimum sanctum* (Holy basil), *Origanum syriacum* (Lebanese oregano), *Satureja bachtiarica* (Bakhtiari savory), *Orthosiphon stamineus* (Cat whisker), *Prunella vulgaris* (Prunella), *Pogostemon cablin* (Patchouli) and *Stachys sieboldii* (Japanese artichoke) from the Lamiaceae family are discussed in this chapter. The neuroprotective property of these herbs relied **on** their ability to target the underlying mechanisms of neuronal cell death, such as aberrant protein aggregation, excessive oxidative stress, neurotransmission system dysfunction, neuroinflammation, and others. The multi-targeting ability of these plants is attributed to their complex chemical compositions with different bioactive compounds. Thus, the incorporation of these plants and herbs into the management of NDD should be further explored. Their role as dietary supplements to preserve the function of the nervous system is also strongly advocate.

Keywords: Lamiaceae, Neurodegenerative disease, Neuroprotective, Ocimum sanctum, Origanum syriacum, *Orthosiphon stamineus*, *Perilla frutescens*, *Pogostemon cablin*, Satureja bachtiarica, *Sideritis scardica*, *Stachys sieboldii*.

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Atta-ur-Rahman, *FRS* (Ed.)

INTRODUCTION

Background and Disease Pathogenesis

The nervous system is one of the most crucial systems in humans as it is responsible for the coordination and regulation of communication and process within the human body to maintain homeostasis and adaptation to the continually changing environment. Neurodegenerative disease (NDD) represents a group of disorders characterised by the irreversible loss of neurons and functions of the nervous system. The most common NDDs are Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease (HD). Patients afflicted with NDD usually suffer from a spectrum of disabilities such as cognitive and behavioural changes, mental disorders, and loss of motor control. Despite different clinical manifestations, the majority of the NDDs shared mutual pathogenesis of cell death. Established cell death pathogenesis includes the accumulation of aberrant protein, oxidative stress, neuroinflammation, excitotoxicity, synaptic dysfunction, neurotrophic factors deficiency, cellular protein degradation system dysfunction, and cellular apoptosis Interrelation of these activities are shown in Fig. (**1**).

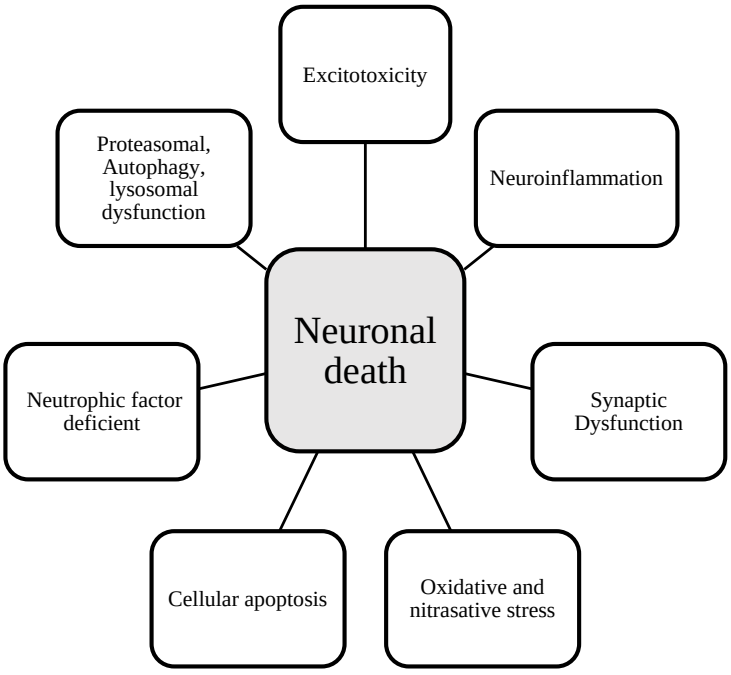

Fig. (1). An overview of the causes of neuronal death.

As the global population starts to age, the incidence rate of NDDs is expected to rise exponentially, as the majority of them are classified as age-associated disorders. According to the World Alzheimer Report 2018, the number of people with dementia worldwide is likely to increase to 152 million by 2050 [1]. The prevalence of AD, the most frequently diagnosed NDD, increases exponentially above 65 years of age. In addition, the associated costs of care are expected to exceed over 1 trillion USD. This will impose a massive burden on the individual, society, and economy of a country. Unfortunately, most if not all of the current NDD treatments are mainly symptomatic treatments, and the efficacy is rather short-term with associated side effects. The low efficacy of most current therapies has led to an interest in finding alternative options to treat NDDs. Nevertheless, the complexity of NDDs makes it very difficult to pinpoint the exact cause of these disorders. Several hypotheses have been put forward over the years. First of all, the most common pathogenic factor of cellular death is the accumulation of aberrant proteins or commonly known as proteinopathies. For example, the deposition of amyloid-beta (Aβ) peptide and hyperphosphorylated tau (τ) protein in the form of neurofibrillary tangles in AD, aggregation of alpha-synuclein (α-synuclein) proteins in the form of Lewy bodies in PD and Huntingtin proteins in HD [2]. These proteins could impair the structure of neuronal cells in the brain by forming calcium ion (Ca^{2+})-permeable pores on the plasma membrane leading to dysregulation of calcium ion homeostasis (excitotoxicity) and disrupting cellular signalling pathways leads to detrimental effects on the brain [3]. Under normal conditions, the protein aggregates are removed by the intracellular ubiquitin-proteasome-autophagy system in order to restore protein dynamics. However, impairment of this system is found in many NDDs [4]. As a consequence, the misfolded protein accumulates and elicits toxic effects on the neuronal cells. In addition, the involvement of neuroinflammatory cascade was also a common feature of NDDs [5]. Neuroinflammation can either protect the brain from injury or infection by initiating tissue repair and removing cellular debris or amplify the damaging effect of the insult. The imbalance between pro-and anti-inflammatory pathways is associated with the persistent inflammatory response in the aging brain or diseased brain [6]. Pro-inflammatory cytokines such as interleukin (IL)-1β and tumour necrosis factor (TNF)-α produced by activated microglial are essential in the modulation of inflammatory response to remove invaders or harmful substances. The injurious manner of inflammation is partially attributed to the secondary consequences originating from the pro-inflammatory cytokine in non-resolving inflammations. For instance, IL-1β and IL-6 were reported to promote iron accumulation through alteration in iron transporter expression within the neuronal cell [7]. The altered iron homeostatic balance then leads to subsequent events such as reactive oxygen species (ROS) production, impaired mitochondrial functions, and increased pro-inflammatory activity [8]. The

CHAPTER 6

Coumarin Derivatives as Potential Anti-inflammatory Agents for Drug Development

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Abstract: The search for anti-inflammatory drugs is still challenging, even though recent advances in modern medicine have provided some relief. Coumarins, well known secondary metabolites widely distributed in plant kingdom, have successfully documented their candidature in the development of anti-inflammatory agents. Natural coumarins, including esculetin, umbelliferone, scopoletin and marmin showed potent anti-inflammatory activity through various targets, including COX-2, LOX, iNOS TNF-α, TXB2. Over the past decade, various synthetic modifications have been carried out on the scaffold of these natural products. The current review focuses on various synthetic and semi-synthetic modifications carried out on the coumarin nucleus with a primary focus on the evaluation of anti-inflammatory activity along with structure-activity relationship study.

Keywords: Anti-Inflammatory agents, Cox-2, Natural Coumarins, SAR, Synthetic Analogs.

INTRODUCTION

Inflammation is the first step of the body's immune reaction against disruption to its cells or tissue by any stimulus, *viz.* infection, bacteria or adverse stimuli. Our

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# These Authors Contributed equally

immune system acts in response to these infections and initiates a healing mechanism called inflammation. Inflammation is, thus, simply a type of defensive process which is required by our body to reduce infection or damage [1]. Generation of pro-inflammatory factors, innate immune cell infiltration, and tissue destruction are implicated in inflammation. The four key symptoms of inflammation are redness, heat, pain, and swelling [2]. The response of immune system to destructive factors, *viz.* bacteria, toxic compounds, infected cells, is inflammation, which works by eliminating and activating the repairing mechanism by removing injurious stimuli. Therefore, inflammation is a protective process that is significant for our wellbeing. Typically, in the case of inflammatory reactions of acute nature, molecular and cellular process interactions mitigate acute risk effectively. This prevention process leads to the regeneration of the tissue's homeostasis, thus resolving inflammation of acute nature. Unregulated acute inflammation, however, can become chronic, leading to a number of inflammatory disorders of chronic nature [3]. Several forms of microcirculatory activities that alter during inflammation are vascular permeability, mobilization of white blood cells and their aggregation, and release of inflammatory mediators [4, 5]. Inflammation can be chronic or acute and is made up of several mechanisms. Our body seeks to maintain tissue homeostasis in the case of acute inflammation and if acute inflammation turns to be extreme, it may cause chronic inflammation [6]. Tissue damage caused by different pathogenic agents can trigger inflammation. The etiology of inflammation may be contagious or non-infectious. The body starts a chemical signaling pathway in response to tissue injury, which induces responses directed at repairing injured tissues. Such signals activate the leukocyte chemotaxis from the general circulation to sites of injury. Cytokines formed by these activated leukocytes induce inflammatory responses [7]. The organized incitement of signaling pathways in resident tissue cells and inflammatory cells recruited from the blood is an inflammatory response controls inflammatory mediator levels [8]. The prevailing pathogenesis of most chronic disorders is inflammation, including coronary and gastrointestinal diseases, arthritis, asthma and cancer. While inflammatory response mechanism depend on the exact nature of the initial stimuli and its position in the body, they all share a similar pathway that can categorized as **(a)** cell surface pattern receptors identify harmful stimuli **(b)** trigger inflammatory cascade **(c)** release mediators of inflammation and **(d)** recruit inflammatory cells [9].

Inflammatory reaction may be regulated by removing inducers, blocking sensors, inhibiting markers, else acting straight on target tissues [10]. Removal of inducers, in specific ailing conditions, can require longer duration drug therapy; subsequently, in such situations, the regulation of inflammation through the optimum usage of anti-inflammatory drugs is necessary to avoid remodeling of

tissue [11]. Inflammatory mediators such as arachidonic acid metabolites (such as leukotrienes and PGE_2), cytokines, histamine, plasma proteases, serotonin, chemokines, nitric oxide, and colony-stimulating factors are the most commonly researched inflammatory regulation targets. Various pathways, including cyclooxygenases, kinases and caspases (such as cyclin-dependent kinases, Janus kinases, serine threonine kinases, mitogen-activated protein kinases/extracellular signal-regulated kinases, mitogen-activated protein kinases 38, c-jun N-terminal kinases, NF-kβ, and lymphocyte-specific kinases are used to produce these mediators. It is stated that the inflammatory mechanism is inhibited at one stage or another by a wide variety of chemicals obtained from a complex population of heterocyclic nuclei [12, 13]. A significant class of anti-inflammatory molecules comprises coumarin analogs. Several researchers have documented that several variants of coumarin at different steps inhibit inflammation [14].

COUMARINS

Coumarins form an exclusive community of compounds in nature that inhibit a special location. Coumarins, along with a number of other chemicals, are pharmacologically flavonoids. A number of biological and pharmacological behaviors have been found to be exhibited by coumarins. Coumarins and their derivatives have gathered significant concern because of their possible useful outcomes on human health [15 - 17]. As a consequence, coumarins and their derivatives have been studied in detail. The basic capacity of certain coumarin derivatives is affecting free radical damage and scavenging of reactive oxygen species. They were also shown to inhibit the peroxidation of lipids and exhibit anti-inflammatory activity. In addition, coumarin and associated derivatives have been used as an inhibitor of arachidonic acid synthesis pathways for lipoxygenase (LOX) and cyclooxygenase (COX) [18]. Coumarin, naturally found in many plants, is an aromatic chemical. Coumarins are especially found in cinnamon and tonka beans in foodstuffs. Many medicines have used the bioactivity of coumarins [19]. Coumarins have also demonstrated useful outcomes in decreasing the incidence of certain malignancies, coronary and brain diseases [20]. However, these are considered to show hepatotoxicity at higher doses [21]. Few coumarin derivatives have shown beneficial parasitic effects and act as phytoalexins that can rapidly accumulate when parasitic infections occur. Psoralen (a furanocoumarin) has anti-arthritic, anti-inflammatory, and anti-microbial properties [22]. While esculetin has been documented in shielding single-cell DNA from various oxidative attacks. Esculetin facilitates the regulation of vasoconstriction, overpowers the transcription factor of Sp1 and gets attached to β-catenin proteins by reducing the release of nitric oxide, resulting in suppression of the signaling process of β-catenin-Tcf gastrointestinal tumorigenesis and also

CHAPTER 7

Recent Progress in the Synthesis and Biological Activity of Chromene and Its Derivatives

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Abstract: Heterocycles have a crucial role in the design and discovery of active pharmaceutical ingredients. Chromenes are heterocycles containing oxygen that are abundantly found in nature and have attracted much attention because of their interesting drug activities. Chromene and its derivatives cover an extensive range of biological properties such as antibacterial, anti-inflammatory, anti-HIV, anti-cancer, anti-oxidant and antimicrobial properties. Regarding the numerous investigations conducted on these valuable compounds during the past few years, we have also pointed to the advances of the last five years in the field of the synthetic and biological importance of these compounds. Concerning the high importance of synthesis of chromene and its derivatives by synthesis methods of 2H-chromenes, 4H-chromenes, benzochromenes, benzopyrans and fused-chromenes, we mentioned that this issue includes the necessity of using various catalysts in mild conditions and/or in microwave conditions. In the following, concerning the very high biological importance of chromenes, we implied some biological properties, including anti-cancer, anti-inflammatory, anti-oxidant and antimicrobial activities, which indicated that the considered results could be promising and effective for the use of chromene derivatives in the field of drug design. Ultimately, we mentioned several vital methods and strategies include green synthesis and multi-component reactions in various categories for the general synthesis of various types of chromene derivatives. In economical, efficient, green and mild conditions, the above-said methods can synthesize high-efficiency products of chromene and its derivatives in a short period of time.

Keywords: Anti-Cancer Drug Activities, Anti-HIV, Anti-Oxidant, Antibacterial, Active Pharmaceutical, Biological Properties, Chromenes, Heterocycles, Nature.

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INTRODUCTION

The oxygen-containing heterocycles [1 - 8] are among important compounds, which are found in natural products and have interesting biological activities [9 - 12]. Over the past few years, chromene [13 - 17] and its derivatives have been significantly considered due to the wide range of biological properties [18 - 26]. These compounds are found in the structure of natural products and also have extensive medicinal properties with wide applications in synthesis of organic compounds. Chromenes are important compounds in oxygen-containing heterocycles. The chromene ring contains a benzene ring welded to the pyran ring. Chromenes play an important role in medicinal chemistry. The high drug potential and the fact that these compounds are low in toxicity have led to a great deal of interest in the synthesis of chromene derivatives in recent years. These compounds play an important role in the design of pharmaceutically and biologically active compounds. The two isomers of chromene are shown in the Fig. (**1**), which according to IUPAC rules [27] are scored from the side of the ring with heteroatom. The great importance of these compounds in the field of medicine, biology and the synthesis of organic compounds has led us to mention the synthesis strategies of a number of important chromene derivatives and their biological properties.

Fig. (1). The two isomers of chromene.

SYNTHESIS OF CHROMENE DERIVATIVES

Synthesis of 2H-Chromenes

2H-chromenes are important compounds which have shown biological activities. Because of their importance, some trustworthy methods for the synthesis of 2H-chromene derivatives have been developed [28 - 35].

kamazani's group used mesoporous Cu-SBA-15 as nanocatalyst for synthesis of 2H-chromene dyes by reacting 5-phenylazo-salicylaldehyde with acetylacetone in CH_2Cl_2/EtOH; 2:1 in high yields (Fig. **2**) [36].

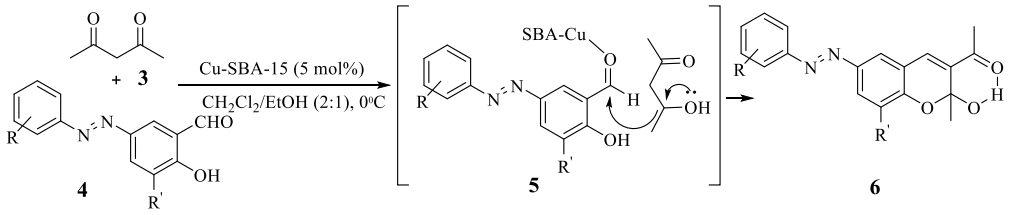

Fig. (2). The synthesis of azo-chromene dyes.

Li *et al.* demonstrated that different 2H-chromenes were synthesized in one step by carbene insertion reaction of aryldiazoacetates and (E)-2-hydroxy cinnamaldehydes by using $Rh_2(esp)_2$ with Na_2CO_3 as additive in the presence of CH_2Cl_2 at room temperature in good yields (Fig. **3**) [23].

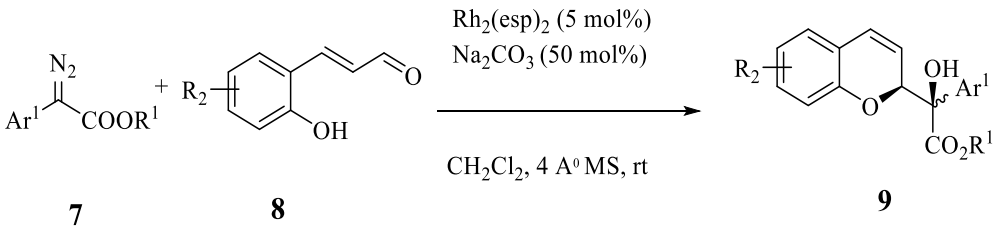

Fig. (3). The synthesis of 2H-chromenes.

In 2018, Asheri and co-workers reported the reaction of diethyl acetylenedicarboxylate, triphenylphosphine and 5-bromo-2-hydroxybenzaldehyde acid in the presence of dichloromethane at room temperature (Fig. **4**) [37].

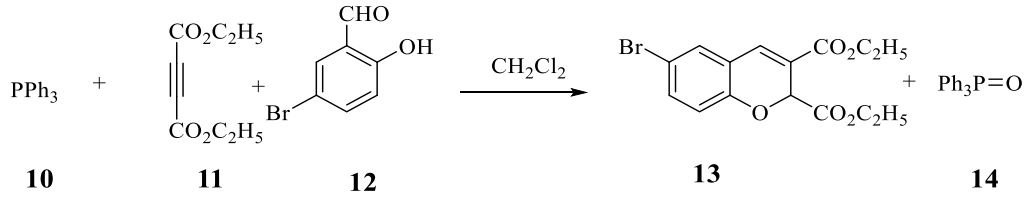

Fig. (4). The synthesis of diethyl 6-bromo-2H-chromene-2,3-dicarboxylate.

Synthesis of 4H-Chromenes

4H-chromenes are found in several natural compounds that have displayed numerous medical activities [38]. Many researchers are interested in the synthesis of 4H-chromenes derivatives [39 - 64].

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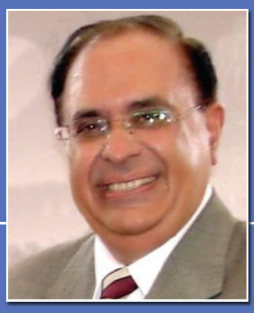

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.