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Frontiers in Natural Product Chemistry

Editor:
Atta-ur-Rahman, *FRS*

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Frontiers in Natural Product Chemistry

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Edited by

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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 of plants, microbes and animals. The book is a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information in natural product chemistry. The chapters are written by authorities in the field. The contents of the present volume represent exciting recent researches on structure elucidation, biological activity, and synthesis of natural products as well as developments of new methods. I hope that the readers will find these reviews valuable and thought provoking so that they may trigger further research in the quest for the 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), and Mr. Shehzad Naqvi (Senior Manager Publications) at Bentham Science Publishers.

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CHAPTER 1

Microbial Involvement in the Production of Natural Products by Plants, Marine Invertebrates and Other Organisms

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Abstract: In the early 1980s, there were occasional reports of natural products isolated from marine invertebrates that were either identical to compounds from terrestrial sources, or were close chemical relatives. Since that time period it has become evident that microbes, whether they can currently be fermented under "normal conditions" or require genetic analyses and subsequent elaboration in surrogate hosts *etc*., are very heavily involved in the production of marine invertebrate secondary metabolites.

In the last few years, the situation with plant-derived natural products is very reminiscent of the early 1980s / marine invertebrate stories, as there are now significant numbers of reports invoking microbes (usually endophytic fungi), in the production of nominally plant-derived natural products. In one particular case, that of maytansine, the production by epiphytic root bacteria in the nominal producing plant is definitive.

Each issue of current journals covering genetic analyses of plants or marine invertebrates, often contains at least one article (basic science or review), that furthers the potential involvement of microbes in the production of even well-known molecules such as taxol, vinca alkaloids, homoharringtonine on the plant side and pederin-related (*e.g.* onnamide) derivatives on the marine side. We will also give information on bacterial, fungal and algal interactions that together lead to the production of natural products, though the exact involvement may not yet be known. We will broadly discuss the current situation and then hone in on areas where microbial involvement is definitive, and give the evidence for areas where it is still circumstantial.

Keywords: Biosynthesis, Biosynthetic gene clusters, Bioactive agents, Co-culture, Endophyte, Microbial interactions, Natural products, Sequencing, Symbiont, Unculturable.

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1. INTRODUCTION

Since Alexander Fleming's serendipitous discovery of penicillin from the fungus *Penicillium notatum* in 1928, microbe-derived natural products have been a prolific source of clinically-approved drugs. The clinical use of penicillin marked the beginning of the "Golden Age of Antibiotics" in the 1940s, resulting in the extensive investigation of microorganisms as sources of new therapeutics. Major breakthroughs were made in the area of drug discovery, including the development of blockbuster drug classes, such as the penicillins, cephalosporins, aminoglycosides, tetracyclines, cyclosporines, erythromycins, ivermectins, rapamycins, and cholesterol-lowering statins [1]. However, in the late 1970s, the frequency of finding structurally novel compounds decreased, as chemists had already exploited easily accessible microbes from terrestrial environments.

In the 1980s, pharmaceutical companies began to refocus their drug discovery efforts toward developing synthetic drugs using combinatorial chemistry. Unfortunately, this shift did not lead to a significant increase in the number of clinically-approved small molecule drugs. As a matter-of-fact, from 1981 to 2014, over 50% of all small molecule new chemical entities were classified as natural products, (semi)synthetic derivatives, or based on natural product pharmacophores [2], demonstrating the constancy of the number of natural product-inspired drugs in the clinical pipeline, though during this time frame, pharmaceutical companies were abandoning natural products altogether. Not surprisingly, the structural complexity and diversity, high selectivity, and biological activity of these molecules from marine or terrestrial microbes, plants, and other organisms make them invaluable pharmaceuticals. Researchers now have an even stronger argument for revisiting natural products for drug discovery.

Interestingly, microbes from all three domains of life, *Archaea*, *Prokarya*, and *Eukarya*, have been either identified as the producer of natural products or speculated to be involved in their production *via* symbiotic associations. Over the past twenty or so years, evidence of microbes from all sources being involved in the production of bioactive agents, has grown from being a slight possibility, to now at least in the area of marine natural products, being a major productive source(s) of bioactive agents reported from *Porifera* and perhaps other marine invertebrates. Confirmation of the "true producer" of these invertebrate-linked molecules has been rather difficult, because <1% of microbes that can be visualized in seawater and invertebrates / sediments by direct staining, could be cultivated under standard laboratory conditions. We should point out at this stage that the methodologies often used in past studies, were based on media that were "just too rich in carbon-containing components" when compared to the levels in seawater. However, advances in culture-dependent and -independent techniques,

such as (meta)-genomic and single cell sequencing, cell sorting, and other molecular approaches, have provided insight into genomes and microbiomes, enabling researchers to track, isolate, and validate the true producer(s) of these metabolites. We are now realizing the nominal "*i.e.,* collected source" of marine natural products may not necessarily be the producing organism.

In the case of plant-derived bioactive compounds, more reports of production by mainly epi- and endophytic microbes, usually fungi and actinobacteria have surfaced, though in some cases, production may possibly be due to horizontal gene transfer or genetic recombination occurring between plants and associated symbionts. These reports demonstrated that microbes can produce low levels of a "plant metabolite" upon fermentation but upon subsequent sub-culturing, the microbe was reported to lose its ability to produce this metabolite. However, in the last few years, academic researchers have started to use (rediscovered?) techniques that were commonly used in the pharmaceutical industry to find antibiotic producers but never formally published. For example, the supplementation of fermentation broths with extracts of parts of the "nominal producing source" can be used to induce or maintain the production of metabolites of interest.

In recent years, there have been reports of new bioactive compounds produced by microbial consortia, which contain specialized mutualistic and / or parasitic relationships. In mutualism, the interactions between two or more species are beneficial to all parties (*e.g.*, nutrition or protection), whereas microbes exploit each other in parasitism (*e.g.*, competition for resources). These interactions are mediated by chemical signals transmitted between the host and its microbiome. Researchers have been accustomed to the idea of a single microbe producing a given compound, when in reality microbes in nature rarely grow under axenic conditions. There are an infinite number of complex microbial interactions found in nature, and now mixed cultures are being recognized for playing a role in the "production" of new secondary metabolites, usually *via* silencing or activating the expression of biosynthetic gene clusters (BGCs) in one or more of organisms.

In this chapter, we describe the isolation and characterization of bioactive compounds in which the host was thought to be the producing organism, plus compounds found from mutual interactions between microbes in or around a host or hosts. Identification of the true producers of bioactive natural products, may ultimately aid in the production of these agents by use of techniques such as controllable activators of BGCs in surrogate hosts. These examples are chosen to demonstrate the metabolic and chemical diversity that arises from the unique environments created from microbial interactions with other organisms, and suggest ways in which these rich sources can be used in the future.

CHAPTER 2

The Chemical Biology of Natural Product Biosynthesis: Chemical Tools for the Proteomic Analysis of Nonribosomal Peptide Synthetases

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Abstract: Nonribosomal peptides display a broad range of biological activities, including antimicrobial, antitumor and immunosuppressive agents, as well as signaling molecules and virulence factors. Many of these nonribosomal peptides are biosynthesized by large, highly versatile multifunctional proteins known as nonribosomal peptide synthetases (NRPSs). The results of genetic, biochemical, and bioinformatic investigations over the past three decades have offered a profound understanding of the functional characteristics and molecular basis underpinning the enzymology of nonribosomal peptide biosynthesis; however, studies at the proteomic level are limited. This chapter will focus on tools recently developed not only for studies aimed at visualizing, monitoring and tracking NRPS proteins but also for rapid labeling, isolation, identification and enzymatic characterization of NRPS family members as required for proteomics in natural product biosynthesis.

Keywords: Activity-based protein profiling (ABPP), Adenylation domains, Chemical proteomic probes, Chemoproteomics, Competitive ABPP, Nonribosomal peptide synthetases, 5′-*O*-(*N*-aminoacyl)-sulfamoyladenosine.

INTRODUCTION

Nonribosomal peptide natural products are structurally diverse and complex secondary metabolites found in nature, and include a broad range of important medicinal agents such as the calcium-dependent daptomycin, the glycopeptide

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antibiotic vancomycin, the antitumor bleomycin A_2 and the immunosuppressant cyclosporin A (Fig. **1**) [1]. In light of their wide range of therapeutic potential, nonribosomal peptide natural products have gained considerable interest in the field of drug discovery and development [2]. These nonribosomal peptide natural products are biosynthesized by multifunctional nonribosomal peptide synthetase (NRPS) enzymes [3].

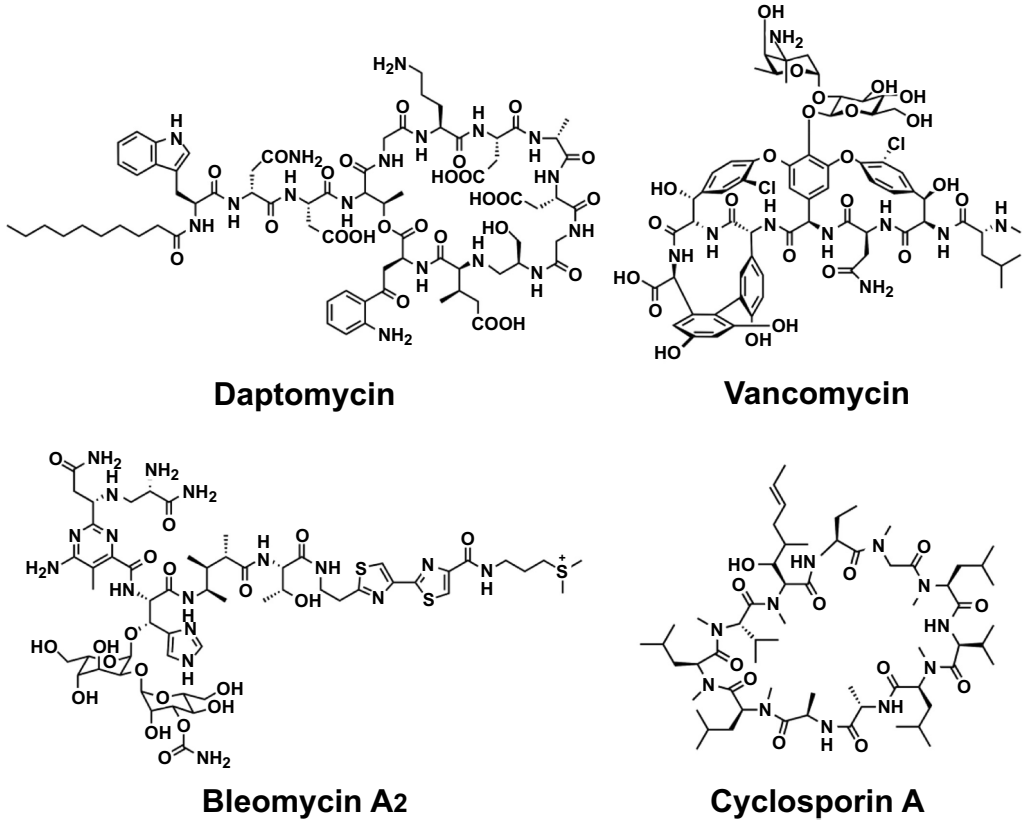

Fig. (1). A variety of nonribosomal peptide natural products.

Progress in genetic, biochemical, structural and bioinformatic investigations over the past three decades has greatly accelerated a detailed molecular understanding of the enzymology of nonribosomal peptide synthesis. Despite significant progress at the genetic and protein levels, our understanding of NRPS enzymes at the proteomic level remains limited. Very little is known regarding the post-translational events, transcriptional regulation, activity dynamics and degradation processes of NRPS enzymes in natural product producer organisms. Analogous to the importance of examining the human proteome encoded by the genome,

proteomic investigations of natural product producer organisms provide significant biological information that cannot be addressed by conventional genetic techniques [4]. In addition, some of these NRPS proteins are particularly resistant to cloning, expression and biochemical investigations as whole recombinant proteins. This is partly because these NRPS enzymes are large molecular weight proteins ranging on average between 300 and 800 kDa, and because of the intractability of the natural product producer organisms and/or heterologous protein expression. In addition, the complicated ensembles of symbiont microorganisms are not compatible with most genetic techniques on the basis of pure and isolated strains. One such example is the complex symbiotic relationships in toxic marine dinoflagellates [5]. Profiling of NRPS enzyme family members in diverse microorganisms should provide highly complementary genetic techniques by allowing us not only to understand the post-translational events, activity, transcriptional regulation and degradation processes, but also to accelerate the identification, isolation and functional characterization of NRPS enzymes in native proteomic environments. We have recently developed chemical proteomic strategies consisting of activity-based probes not only to visualize, monitor, track and analyze NRPS enzymatic activities, but also to isolate, enrich and identify NRPS enzyme family members in proteomic samples, as required for proteomics in natural product biosynthesis [6 - 9].

In this perspective, we describe chemical biology techniques toward NRPS biosynthetic enzymes. We have placed particular emphasis on chemical proteomics strategies, which use small-molecule probes for adenylation (A) domains in NRPS enzymes. To enrich this discussion, we provide a brief introduction to the general NRPS biosynthetic system, a detailed description of A-domain enzymology, conventional strategies to evaluate A-domain activities and chemical proteomics strategies for the study of NRPS biosynthetic enzymes.

Nonribosomal Peptide Synthetase Biosynthetic Enzymes

Nonribosomal peptide natural products are synthesized by large, highly versatile multimodular megaenzymes known as nonribosomal peptide synthetases (Fig. **2a**) (NRPSs) [3]. A minimal NRPS module contains carrier protein (CP), such as the peptidyl carrier protein (PCP) also known as the thiolation (T), adenylation (A), and condensation (C) domains. A NRPS module (C-A-T) is responsible for the incorporation of an amino acid building block into nonribosomal peptide natural products. The C domains catalyze peptide-bond formation reactions between two aminoacyl-S-T substrates in adjacent NRPS modules (Fig. **2b**) [10]. In addition to the C domains, A and T domains constitute the essential catalytic components of NRPS enzymes. The A-domains select the cognate amino acid building blocks from a much larger monomer pool and convert them to aminoacyl adenosine

CHAPTER 3

Current Knowledge and Future Perspectives of Oligosaccharides Research

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Abstract: Oligosaccharides are low molecular weight carbohydrates with a degree of polymerisation ranging from 3 to 10 sugar residues. These compounds have attracted an increasing attention because of their functional effects on human health, as well as their physicochemical properties, which are of interest for various applications in food technology. The functionality of oligosaccharide depends on its chemical structure, which relies on the nature of the building sugar residues, the linkage type, and the degree of polymerisation. Oligosaccharides can be found naturally in foods (from plants and animals) or are produced by the synthesis from disaccharide substrates or by the hydrolysis of polysaccharides (physical, chemical and/or biotechnological process). Certain oligosaccharides present important beneficial properties for consumers, including anti-carcinogenic effect, low caloric value and prebiotic properties. Prebiotics are selectively fermented ingredients that allow specific changes in the composition and/or activity of the gastrointestinal microbiota, which provides health benefits and well-being to the consumer. In the food industries, the oligosaccharides have been applied as dietary fiber, sweetener, and weight control agent, and as a humectant in confectioneries, bakeries and breweries. Thus, oligosaccharides are natural compounds that have been widely studied and used in science and industry. This chapter reviews (i) the chemical structure, (ii) emerging trends in production, (iii) applications in science and technology, as well as (iv) the beneficial health of oligosaccharides. In general, this chapter is useful for teachers, students and researchers seeking to understand the chemistry and the future research of oligosaccharides

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Keywords: Applications, Biological properties, Biotechnological production, Carbohydrate chemistry, Chemical synthesis, Classification, Health benefits, Hydrolysis of polysaccharides, Physicochemical properties, Prebiotic properties.

INTRODUCTION

Carbohydrates are one of the most diverse and important classes of biomolecules on the earth with functions ranging from the fundamental building block of RNA (ribose) to the most important energy store of the human bodies (glucose) [1]. Chemically, carbohydrates are polyhydroxy aldehydes (aldoses) or polyhydroxy ketones (ketoses), such as glucose and fructose, respectively. The general carbohydrate formula is $C_n(H_2O)_n$ and the simplest carbohydrates are monosaccharides, which cannot be divided into more simple sugars by hydrolysis. The monomeric units are joined by glycosidic linkages to form larger structures, for example, oligosaccharides (*e.g.,* 1-kestose) and polysaccharides (*e.g.*, fructan). The polyhydroxyl nature of carbohydrates increases the number of possibilities in monomeric unit combinations. Furthermore, the anomeric carbon (α or β glycoside linkage) and chirality centres of sugars (stereoisomerism) contribute to the diversity of carbohydrates structures found in nature [2]. Therefore, these compounds show several and interesting applications in different sectors of science and industry.

Carbohydrates can be classified according to their degree of polymerisation, following as disaccharides (2 monomer units), oligosaccharides (3 to 10 monomer units) and polysaccharides (>10 monomer units). Oligosaccharides play a fundamental role in many important biological processes and are commonly found in nature as glycoconjugates (glycoproteins or glycolipids) [3]. Oligosaccharides found on the surface of cells as part of glycoproteins and glycolipids play key roles in the control of various normal and pathological processes in living organisms, such as protein folding, cell–cell communication, bacterial adhesion, viral infection, masking of immunological epitopes, fertilization, embryogenesis, neural development and cell proliferation and organization into specific tissues [4].

Non-digestible carbohydrates such as dietary fibers, oligosaccharides, and resistant starch play critical physiological functions and their effects in well-being, in improving health and in the decrease of diseases have been well-documented. Among these compounds, the functional oligosaccharides show important physicochemical and physiological properties to consumer health and, for this reason, their use as food ingredient have grown quickly [5]. Oligosaccharides can be found naturally in foods (from plants and animals) or are produced by the synthesis from simple sugars substrates (mono- and disaccharides) or by the controlled hydrolysis of polysaccharides [6].

Oligosaccharides have been used extensively in the food, packaging, cosmetic and animal feed industries, besides the applications in medicine, pharmacology, agriculture, and others. Clearly, oligosaccharides are natural compounds that have been widely studied and used in science and industry.

This chapter aims to cover an extensive review about the classes and chemical structure of the oligosaccharides and the emerging trends in their production. Furthermore, the health benefits, as well as the general applications of oligosaccharides are described.

OLIGOSACCHARIDES: DEFINITION, PHYSICOCHEMICAL AND TECHNOLOGICAL PROPERTIES

According to the International Union of Pure and Applied Chemistry (IUPAC), oligosaccharides are compounds whose monosaccharide units are joined by glycosidic linkages, which may be classified as di-, tri-, tetra-, pentasaccharides, etc., according to the number of monomer units. The difference between oligo- and polysaccharides cannot be accurately described; however, the term "oligosaccharide" is commonly used to refer to a defined structure, whereas "polysaccharide" refers to a polymer of unspecified size [7].

Some researchers define oligosaccharides as low molecular weight carbohydrates with a degree of polymerisation (number of combined monosaccharide units) ranging between 3 and 10 [8]. In contrast, other researchers often consider that these compounds may exhibit degree of polymerisation of up to 20-25 [9].

Oligosaccharides are water soluble carbohydrates and moderately sweet (30-60% compared to the sweetness of sucrose), and its sweetness is dependent on the chemical structure and the degree of polymerisation (the longer the length of the oligosaccharide chain the lower the intensity of the sweetness). The relatively low sweetness makes them very useful in various types of food in which the use of sucrose is restricted due to its high sweetness or when it is desirable to add a stabilizing agent with reduced sweetness to improve the taste of food. Furthermore, they present low caloric content (1.5-2.0 kcal/g, about 40-50% compared to sucrose) and may be used together with artificial sweeteners such as aspartame and sucralose, with the advantage of masking residual flavours produced by some of these sweeteners [10,11]. Due to the higher molecular weight than mono- and disaccharides, oligosaccharides provide a higher viscosity by promoting improvement in the body and palatability of the food [11].

This class of carbohydrates can also be used to alter food-freezing temperature, control browning intensity in thermally processed products due to Maillard reactions and as fat substitutes for its binding properties to water and gelification.

CHAPTER 4

The Treatment of Pain with Topical Sesquiterpenes

James D. Adams*, Ian S. Haworth, Adriana Coricello, Filomena Perri, Christopher Nguyen, Francesca Aiello, Travis J. Williams and **Eric J. Lien**

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Abstract: The best and safest treatment for pain is with topical treatments on the skin. This is most evident with acupuncture that occurs in the skin, is safe and effective. Even broken bones, post-operative pain, replaced hips, replaced knees, cancer pain and other severe pain can be treated effectively and safely with topical medicines. A liniment is available that has been used in many acute and chronic pain patients with success as will be discussed. Cyclooxygenase-2 is found in the skin and is induced in chronic pain conditions. Oral medications do not reach high enough concentrations in the skin to inhibit the enzyme. Instead, oral nonsteroidal anti-inflammatory medications poison the body and are toxic to the stomach and kidneys. These oral medications cause at least 10,000 ulcer deaths yearly in the USA. They also cause clotting problems that lead to heart attacks and strokes. Pain is sensed in the skin at sensory afferent neurons. The activities of pain sensing transient receptor potential cation channels in these neurons are increased by prostaglandins made by cyclooxygenase-2. Pain is best treated with topical preparations that penetrate the skin in small amounts, inhibit cyclooxygenase-2 and are not poisonous to the body. Sesquiterpenes are 15 carbon compounds found in plants and can penetrate the skin. These compounds down regulate the transcription of cyclooxygenase-2 through an NF-kB mediated mechanism and may also inhibit cyclooxygenase-2 and other targets directly. This review is a discussion of the medicinal chemistry and pharmacology of sesquiterpenes that permits these molecules to relieve severe and chronic pain.

Keywords: Cyclooxygenase-2, Pain, Chronic pain, Sesquiterpene.

INTRODUCTION

Pain is a major medical problem and can be acute or chronic. The cost of health care for pain in 2010 was about $300 million in the US [1]. After including time lost from work and productivity, the total cost to society was about $600 million. According to a report in a British newspaper, people in the US consume over 80 percent of the world's supply of pain killing medications [2]. The American Academy of Pain Medicine reports that pain is responsible for 13% of the total

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days of work lost, with headache accounting for 5.4% of the days lost, back pain 3.2%, arthritis pain 2%, and musculoskeletal pain 2%. More than 100 million people in the US suffer from pain [1].

The causes of pain are frequently physical, such as over stretching or over working a muscle or joint. This leads to strains and sprains. Trauma causes pain, such as from compression injuries. Arthritis causes inflammation and degradation of cartilage and bone that causes pain. Burns, infections, and injuries produce inflammation and edema that is painful. Cancer causes pain through compression, inflammation and other mechanisms. Damage to nerves leads to pain during repair and recovery. Nerves are damaged by type 2 diabetes, HIV, herpes and other conditions. Headaches have many causes including: wine, stress, food, lack of sleep, concussion, dehydration, many diseases and inflammatory conditions of the brain. A cause of pain that is frequently overlooked is that many people in the US population are not physically fit to perform certain tasks, which leads to sports related and on the job injuries. All of these types of pain can be treated with the right topical medicine [3, 4].

The causes of chronic pain are less well understood. Chronic pain starts with acute pain that becomes chronic. In the skin, keratinocytes, fibroblasts, dendritic cells, endothelial cells and other cells secrete chemokines as the result of acute pain or inflammation [5]. It is possible that neurons in the skin may also secrete chemokines [6]. Chemokines are small proteins stabilized by cystine bonds that promote the chemotaxis of inflammatory cells from the blood and lymph. Monocytes infiltrate the skin and become macrophages that express COX2. Chemokine receptors are found on sensory neurons [7]. Activation of these receptors causes hypersensitivity and hyperexcitability that increase pain Fig. (**1**).

Neuropathic pain is caused by initial damage to a nerve that results in chronic pain during and after the healing process [8]. The initial damage causes damaged neurons to secrete chemokines [6] that attract monocytes. When the monocytes become macrophages, they express COX2 that makes prostaglandins. The prostaglandins stimulate the production of more chemokines in the skin. This establishes a chronic pain cycle in the skin. Neuropathic pain can be successfully treated with topical preparations [8].

The Carpenter Approach to Pain

Currently in the US, pain is treated with the carpenter approach. If the hammer is not big enough, get a bigger hammer. Patients are usually started on oral aspirin, naproxen or some other nonsteroidal anti-inflammatory drug (NSAID). When pain control proves inadequate, patients are quickly switched to oral opioids such as hydrocodone and oxycodone. The fentanyl patch is added for many patients.

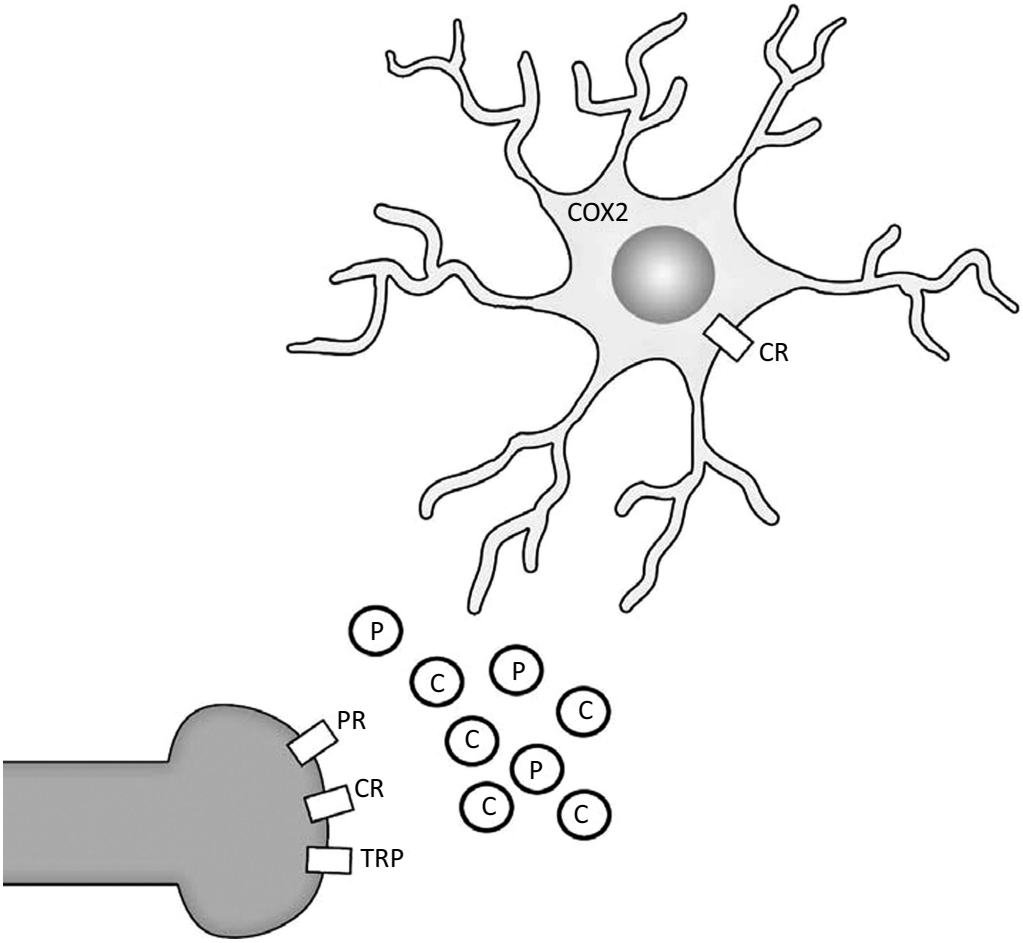

Fig. (1). Chemokines (labeled C) are secreted by skin neurons (such as CCL20 and CCL21) and macrophages (including CX3CL1, CCL13 and CCL22) in response to injury and inflammation [6, 73]. Neuronal chemokines bind to their specific G protein coupled receptors (CR) on macrophages, which activates macrophages and may induce COX2 [62]. Macrophage chemokines bind to their specific receptors on sensory neurons (CR) and increase cytoplasmic calcium and sodium levels resulting in the transactivation of TRP channels, which enhances pain [7]. Prostaglandins (P including PGI2 and PGE2) are secreted by macrophages and other cells, interact with prostaglandin receptors (PR such as EP2 and IP) on sensory neurons causing pain, and increase the activation of TRP channels enhancing pain. Opioid peptides secreted in the skin induce the production of chemokines and their receptors [13]. Other extracellular molecules involved in chronic pain including: bradykinin, histamine, nerve growth factor, IL-1β, tumor necrosis factor, 4-hydroxynonenal, ATP, 5,6-epoxyeicosatrienoic acid, 5-hydroxyeicosa-tetraenoic acid, calcitonin gene-related peptide, high mobility group protein B1. All of these factors are released following damage, pain and inflammation. This can establish chronic pain in the skin.

NSAIDs inhibit cyclooxygenase-1 (COX1) and COX2. A selective COX2 inhibitor, celecoxib, is also available. Acetaminophen selectively inhibits COX2

CHAPTER 5

The Biological Activities and Synthesis of 2,6-Disubstituted Piperidinols

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Abstract: 2,6-Disubstituted piperidinols are one of the most investigated groups of compounds owing to their potential therapeutic use and unique structures. They show a wide variety of biological activities, including inhibition of superoxide anion production, influence on the central nervous system, antibacterial, and plant growth inhibition. For these reasons, 2,6-disubstituted piperidinols have attracted attention from medicinal, phyto-, and synthetic organic chemists. In this review, the biological profile and chemistry of 2,6-disubstituted piperidinols are described. Recent developments in synthetic methods for 2,6-disubstituted piperidinols are also discussed.

Keywords: 2,6-Disubstituted piperidinols, Antibacterial, Antiparasitic, Bioactive compounds, DNA-damaging, inhibitor, Fucosidase, Nervous system, Synthesis, Plant growth.

INTRODUCTION

Heterocycles are generally considered the most promising class of compounds for pharmaceuticals owing to their interactions with biomolecules [1]. Alkaloids, a huge class of heterocycles, have been used as therapeutic agents in modern medicine as well as toxins and traditional medicine [2]. Piperidine alkaloids, which have a saturated six-membered ring containing one nitrogen atom, have attracted much attention in medicinal chemistry owing to their wide variety of biological activities [3 - 9].

Numerous 2,6-disubstituted piperidin-3-ols have already been isolated, mostly from *Cassia* and *Prosopis*. These species have been used as food plants and

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traditional medicines since ancient times. 2,6-Disubstituted piperidin-3-ols possess two alkyl groups at the C-2 and C-6 positions and one hydroxy group at the C-3 position on the piperidine ring (Fig. **1**).

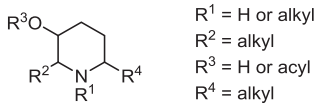

Fig. (1). Common structure of 2,6-disubstituted piperidin-3-ols.

They show a wide variety of biological activities, including anesthetic, antiparasitic, antibiotic, and DNA-damaging, and so on [3 - 7].

Much attention has been paid to these compounds by medicinal and synthetic organic chemists owing to their unique structures and biological features. Research into the biological activity of 2,6-disubstituted piperidin-3-ols has mostly focused on natural and semi-synthetic products. The synthesis of 2,6-disubstituted piperidin-3-ols involves the construction of three chiral centers on the piperidine ring, at the C-2, C-3, and C-6 positions. These carbon skeletons have been constructed by strategies including diastereoselective cyclization, reductive amination, and optical resolution [8 - 11].

In this review, we introduce the recently studied biological profiles and chemistry of 2,6-disubstituted piperidin-3-ols, with several examples, including synthetic methods for the construction of the carbon skeleton.

BIOLOGICAL ACTIVITIES OF 2,6-DISUBSTITUTED PIPERIDINOLS

1. Inhibition of Superoxide Anion Production

Scavenging of over-produced superoxide anions ($O_2^{\cdot -}$) is important for maintaining a healthy physiological state, because $O_2^{\cdot -}$ causes oxidative stress-related diseases such as inflammation, cancer, and hypertension [12]. There have been numerous studies of free radical scavengers, such as flavonoids and polyphenols [13]. However, only two alkaloids, spectamine A and B, have been reported as inhibitors of $O_2^{\cdot -}$ production [14]. Spectamine A (**1**) and B (**2**) were isolated from *Cassia spectabilis* by Kamo and co-workers (Fig. **2**). The absolute configuration of **1** and **2** was determined by converting to *iso*-6-cassine (**3**), followed by a modified Mosher's method, respectively [15, 16].

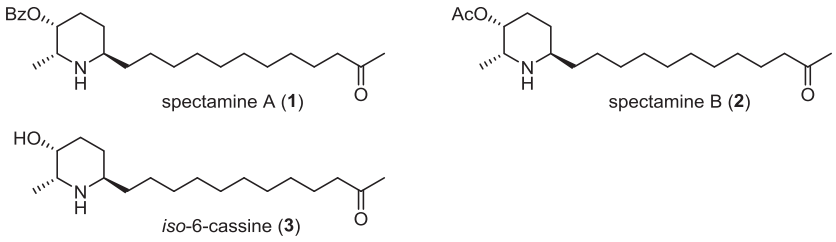

Fig. (2). Structures of spectamine A (**1**), spectamine B (**2**), and *iso*-6-cassine (**3**).

They evaluated inhibitory activity of **1**–**3** against superoxide production using both the xanthine oxidase (XOD) and macrophage test. In the XOD test, compounds **1**–**3** showed no inhibitory activity even at 125 μmol/L. In the macrophage test, while **1** showed 46.7 ± 13.2% inhibitory activity at 25 μmol/L, **2** and **3** showed 5.0 ± 9.9% and 7.0 ± 5.4% at the same concentration, respectively. This indicated that compound **1**, which possesses a benzoate group at C-3 position, might inhibit the superoxide production of macrophages.

2. Anticonvulsant Activity

Freitas *et al*. evaluated the anticonvulsant activity of *iso*-6-cassine (**3**) and *iso*-6-spectaline (**4**) from *Senna spectabilis* (Fig. **3**) [17, 18]. They confirmed the structures of isolated compounds by comparison of their reported spectral data [15, 19]. Compound **4** (0.1, 0.5 and 1.0 mg/kg) was administered by the oral route and showed significant inhibitory activity against pentylenetetrazole (PTZ)- and picrotoxin (PIC)-induced convulsions in mice at a dose of 1.0 mg/kg. The levels of inhibition were 80% for PTZ-induced convulsion and 50% for PIC-induced convulsion. Although **3** gave almost the same result, the required dose level was slightly higher (1.5 mg/kg). In these studies, the effect of **3** and **4** on locomotor activity was also separately investigated [17, 18]. Compounds **3** and **4** caused substantial decrease in ambulation at doses of 1.5 mg/kg and 1.0 mg/kg, respectively.

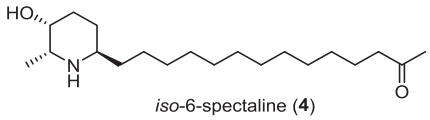

Fig. (3). Structure of *iso*-6-spectaline (**4**).

3. DNA-Damaging Activity

Several species of *Cassia* have attracted much attention because they are widely used in traditional medicine [20]. Consequently, significant efforts have been

CHAPTER 6

Plant Isoflavones, their Impact on Life Sciences, Medicine and Industry

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Abstract: Isoflavones are a relatively small, structurally well defined, group of plant secondary metabolites (natural products), which are of particular interest as biologically active, non-nutrient constituents of animal feed and human food. Chronologically, they were noticed at the beginning of XIXth century phytochemical studies as a class of plant pigments of considerable practical importance, but gained more significance after discovery of their estrogenic activity and interference with hormonal homeostasis of sheep, during 1940s. Contemporary studies of isoflavones are inseparably connected with soy, which is not only one of the principal agricultural crops of global significance, but also the richest source of genistein, daidzein and glycitein, which can occur as glycosides, aglycones or partly acylated glycosides. The presence of isoflavones in food products, which are derived from processing of soybean are generally considerd safe and beneficial for human health. Relatively recently, sufficiently selective and accurate analytical methods have been developed. These techniques have enabled the study of metabolic fates of isoflavones in experimental animals, as well as human patients, at the nanomolar levels which result from soy products ingestion or administration of pure isoflavones preparations. Although isoflavones share many physicochemical and biochemical characteristics with more numerous groups of natural products: flavonoids and polyphenolics (which are recognized as antioxidants, scavengers of the reactive oxygen species and anti-inflammatory agents), they also feature some selective activities, like estrogenicity or multitarget and pluripotent anticancer action. The large amount of isoflavone pharmacological data accumulated tend to become less consistent as we advance from molecular level, through animal models, to human clinical trials, which indicates shortcomings of traditional approaches and the need for including systems biology methods and interpretations. Natural isoflavones remain interesting molecular probes, and lead compounds for several therapeutic directions; their presence in certain food products and variety of dietary supplements seems to be generally accepted, but it becomes evident that prospective drug development must take into account considerable differences in individual metabolism, which results in large part from very different microbiota which harbors in human intestines. On the other hand, synthetic chemistry of phenylpropanoids in general, and isoflavones in particular, is well developed and capable of delivering modified structures in both: form of structurally

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diverse dedicated libraries, and also in form of a scalable process for manufacturing of an active pharmaceutical ingredient featuring selected structure.

Keywords: Isoflavones, secondary metabolites, natural products, plant polyphenolics, flavonoids, isoflavone biosynthesis, isoflavone metabolism, soy isoflavones, phytoestrogens, genistein, daidzein, equol, puerarin, isoflavone glycosides, synthesis of isoflavones.

INTRODUCTION

Approximately 200 years ago pharmacognosy emerged as a new discipline of modern science, devoted to the knowledge of drugs which originate from natural sources such as medicinal plants. Its principal ideology was then formulated by Viennese physician Johann Adam Schmidt (1759-1809) in a hand-written *Lehrbuch der Materia Medica* (1811), and in German pharmacists C. A. Seydler's short pamphlet *Analecta Pharmacognostica* (1815). Remarkably, German "pharmakognosie" started as a subject of studies even before the great boom of pure organic substances with strong biological activity, such as alkaloids, erupted [1 - 3]. Although herbal drugs were in use since the dawn of humanity, only united interdisciplinary approach of 19th century scientists - experts of the time in botany, chemistry, pharmacy and medicine, allowed isolation of the first individual pure chemicals from complex mixtures of biological origin (organic acids, alkaloids, glycosides). Around the same period modern organic chemistry started reaching operational efficiency and soon exploded with multitude of synthetic methods based on coal derived materials, which allowed easier preparation of substances known from plant sources, and also of their numerous mimics. Modern pharmacy was born by the application of synthetic chemistry to the materials isolated from plants, in an attempt to improve their efficacy, and as a result refined semi-synthetic drugs such as acetylsalicylic acid, in place of willow extracts, or codeine instead of opium, began to be manufactured in chemical factories [2 - 5].

During the eons of life evolution, plants have developed complex and effective strategies of chemical communication and defense, based on constitutive, as well as inducible biosynthesis of secondary metabolite (SM) molecules, sometimes also called phytochemicals. Natural products classified as SMs, feature great variety of basic structural scaffolds and immense diversity of the end use chemical structures, although they all stem from relatively few enzymatic cluster assembly lines, using limited number of small molecular weight precursors, present in biochemical cycles of the basic (primary) metabolism [6, 7]. Similarly, functional differentiation of secondary metabolites is immense; they serve as semiotic compounds in allelopathic and environmental communication, as

attractants facilitating root nodulation or flower pollination, deterrents against herbivores and phytoalexins against pathogenic bacteria and fungi. There are some problems with adequate definition of secondary metabolism, and ideas concerning SM and why they accumulate in plants changed dramatically after approximately a century of their investigation [8, 9]. Although current opinions tend to stress that SM are not necessary for a host survival, we prefer to employ the definition given by R. Verpoorte: "Secondary metabolites are compounds with a restricted occurrence in taxonomic groups, that are not necessary for a cell (organism) to live, but play a role in the interaction of the cell (organism) with its environment, ensuring the survival of the organism in its ecosystem" [9, 10]. It seems right to stress, that contrary to the old perception of SMs as ballast substances or waste molecules, their active role in interaction of a plant with its environment is essential for their existence. In summary, contemporary plant biochemistry endorsed the idea that SM can engage in environmental interactions, including: plant-plant, plant-vertebrate, plant-insect, and plant-microorganism signaling long before modern metabolomics could support it with solid evidence. Natural product chemistry was overviewed and summarized for the end of the century in a monumental nine volume edition, with numerous references to phenolics, flavonoids and isoflavonoids, particularly in vol. 1 [11].

Today we still rely to a large extent, in medicine and pharmacy, on the substances known as natural products (NPs). Modern life sciences continuously deliver evidence that each category of NPs deserve attention since they provide inspiration for design of new materials with interesting prospects of application in protection of human health and betterment of its quality [12 - 18]. Modern science is capable of creating a seemingly unlimited number of new materials by combining classical and modern synthetic chemistry with surface physicochemistry and nanostructure compositions. There exists a concept of chemical space, which accommodates all formally allowed individual chemicals, and this universe of tridimensional molecules is believed to contain at least 10^{60} small molecules (< 500 Da) and an unimaginable 10^{200} if all structures are considered. It must contain all compounds created by Nature and including also badly needed today, drugs of the future, both natural and synthetic, hopefully capable of curing presently unmanageable ailments. However, the rules of navigation for such a vast space, in order to locate clusters of compounds with desirable properties (expressed as some collection of molecular descriptors), are hard to find [19, 20]. In contrast, the realm of plant biochemistry looks like a more easily attainable rich source of diverse structures, to be used directly for medicinal purposes or to inspire new drugs design supported by rational arguments. Here, we also start with relatively large numbers: there are approximately 300 – 350 terrestrial vascular plant families, accommodating 300 000 – 500 000 species and a somewhat difficult to estimate number of biological

CHAPTER 7

Natural Benzophenones from Clusiaceae Family: Structural Diversity and Biological Activities

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Abstract: It is described in this book chapter structural features of natural benzophenones and an overview of their various biological activities. These compounds have been isolated mainly from plant species belonging to the Clusiaceae family. Biosynthetic processes involved in their formation are also presented.

Keywords: Benzophenones, Clusiaceae Family, Prenylated benzophenones.

1. INTRODUCTION

Nature has always aroused the curiosity of chemists. Through the investigation of plants, animals, and micro-organisms, chemists have found many interesting and useful substances, with such activity being denominated Chemistry of Natural Products [1].

The study of bioactive compounds extracted from natural sources is considered an important approach in the search for new pharmaceuticals. Besides being used as medication, natural products also provide useful structural information, leading to new bioactive compounds presenting the necessary requirements regarding drug activity, selectivity and toxicity [2].

Natural products have been exploited since the early days of medicine for the treatment of various diseases affecting humans [3 - 5]. Thus, the use of plants is one of the earliest forms of using natural products in the search for the cure of diseases [4]. Nowadays, continuous progress in chemistry and related fields has allowed the identification of an increasing number of natural substances with important therapeutic properties [6, 7].

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Phenolic compounds are secondary metabolites occurring widely in plants [8] and consumed by humans in their diet. They exhibit a broad spectrum of bioactivities that may be beneficial to human health [9].

However, despite the fact that a large amount of phenolic compounds has been isolated and characterized, some still need to be studied in detail. Among these compounds, benzophenones and their derivatives have attracted the attention of several research groups because of their various bioactivities and structural diversity [10 - 13]. It is estimated that more than 300 natural benzophenones [14] have been isolated and characterized.

Benzophenones have been isolated mainly from different parts of plants belonging to the Clusiaceae family, with important medicinal properties being described [15 - 19]. Aspects related to the structural diversity and bioactivities of some natural benzophenones, isolated mainly from species of the Clusiaceae family, are herein described, based on their broad chemical diversity and biological importance. It must be emphasized that, in view of the high number of natural benzophenones isolated and characterized to date, an exhaustive discussion of this class of compounds will not be presented. Thus, we have selected benzophenones that have received a greater attention in the literature and others that have recently been described.

2. STRUCTURAL DIVERSITY OF BENZOPHENONES EXTRACTED FROM NATURAL SOURCES

Benzophenones are structurally characterized in their most basic form by two aromatic rings (1 and 2) linked to a carbonyl group Fig. (**1**), and may present different substituents that modify their structural characteristics and biological properties [13].

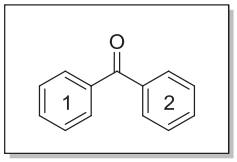
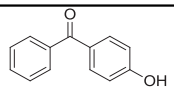
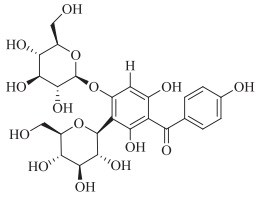
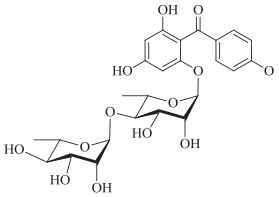
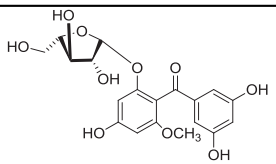
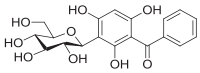
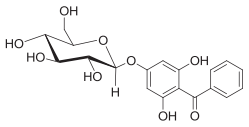
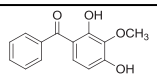
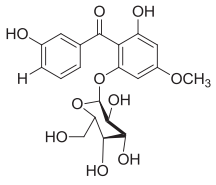


Fig. (1). Basic structure of benzophenones.

These substances have been isolated from distinct plant families, namely Clusiaceae, Hypericaceae, Fabaceae, Myrtaceae, Polygalaceae, Rosaceae, Gentianaceae, Magnoliaceae, Olacaceae, Thymelaceae, Moraceae, *etc*. [15, 16]. Among these families, Clusiaceae stands out as the most disseminated and largest source of benzophenone derivatives. Although they are mainly isolated from

plants, benzophenones have also been isolated from fungi [20, 21] and propolis [22]. Table **1** presents examples of benzophenones isolated from several sources.

Table 1. Benzophenones isolated from different natural sources.

Compound	Structure	Species	Family	Ref.
4-hydroxybenzophenone		*Talauma mexicana*	Magnoliaceae	[16]
3-*C*-*β*-D-glucopyranosyl-4-*O*-*β*--glucopyranosyliriflophenone		*Cyclopia genistoides*	Fabaceae	[23]
Aquilarinenside A		*Aquilaria sinensis*	Thymelaeaceae	[24]
3',4,5'-trihydroxy-6-methoxy-2-O-*α*-arabinosilbenzophenone		*Hypericum thasium* Griseb.	Hypericaceae	[25]
Malaferin A		*Malania oleifera*	Olacaceae	[26]
2,6-dihydroxy-4-*O*-*β*--glucopyranosylbenzophenone		*Psidium guajava* L.	Myrtaceae	[27]
2,4-dihydroxy-3-methoxybenzophenone		*Securidaca diversifolia*	Polygalaceae	[28]
2,3'-dihydroxy-4-methoxy-benzophenone-6-*O*-*β*-glucopyranoside		*Gentiana verna subsp. pontica*	Gentianaceae	[29]

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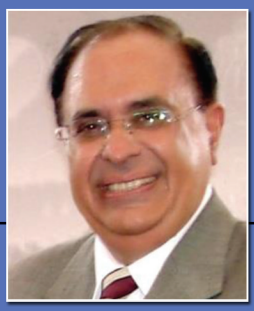

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1080 international publications in several fields of organic chemistry including 751 research publications, 37 international patents, 69 chapters in books and 221 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 54 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.