Natural product chemistry

Introduction Of Natural Product Chemistry

In the beginning of organic chemistry was natural products chemistry. For a long period, up to the 1960’s the structural studies of natural products served as the principle driving force for the discovery of new chemical reactivity. The introduction of spectroscopic techniques, however, removed much of the “ intellectual challenge” involved in structure elucidation. Furthermore, natural products chemistry suffered a dramatic decline from the mid 1990’s when major pharmaceutical companies disinvested in this area and switched to more “ rational” combi-chem approaches. Nevertheless, the improvements in spectroscopic methods have historically stimulated natural products chemistry and the efforts to examine new compounds from unusual organisms rapidly and systematically. Natural products chemistry survived and began to flourish again in recent years also through chemical biology and chemical genetics and the realization that natural product structures often explore structural space unavailable to combi-chem approaches. As a result, challenges for natural product chemists are not diminishing, they are just changing. Natural product chemistry turned to an interdisciplinary science, where the success of a chemist would only be possible in close collaboration with biologists, pharmacologists, and clinicists. Thus many novel biological activities – such as beta-tubulin assembly inhibitors for example, could only have emerged from the natural products arena.

Contents Of Natural Chemistry

Steroids.- Terpenoids.- Fatty Lipids and Prostaglandins.- Alkaloid.- Amino Acids and Proteins.- Nucleic Acids.- Carbohydrates.- Plant and Insect Growth

Regulators.- Phenolic Compounds and Natural Dyes.- Marine Natural Products.- Antibacterials.- Vitamins and Hormones.

Natural product

A natural product is a chemical compound or substance produced by a living organism – found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. A natural product can be considered as such even if it can be prepared by total synthesis.

These small molecules provide the source or inspiration for the majority of FDA-approved agents and continue to be one of the major sources of inspiration for drug discovery. In particular, these compounds are important in the treatment of life-threatening conditions.

Natural sources

Natural products may be extracted from tissues of terrestrial plants, marine organisms or microorganism fermentation broths. A crude (untreated) extract from any one of these sources typically contains novel, structurally diverse chemical compounds, which the natural environment is a rich source of.

Chemical diversity in nature is based on biological and geographical diversity, so researchers travel around the world obtaining samples to analyze and evaluate in drug discovery screens or bioassays. This effort to search for natural products is known as bioprospecting.

Animal sources

Animals can sometimes be a source of new lead compounds. For example, a series of antibiotic peptides were extracted from the skin of the African clawed frog and a potent analgesic compound called epibatidine was obtained from the skin extracts of the Ecuadorian poison frog.

Screening of natural products

Pharmacognosy provides the tools to identify, select and process natural products destined for medicinal use. Usually, the natural product compound has some form of biological activity and that compound is known as the active principle – such a structure can act as a lead compound (not to be confused with compounds containing the element lead). Many of today's medicines are obtained directly from a natural source.

On the other hand, some medicines are developed from a lead compound originally obtained from a natural source. This means the lead compound:

- can be produced by total synthesis, or
- can be a starting point (precursor) for a semisynthetic compound, or
- can act as a template for a structurally different total synthetic compound.

This is because most biologically active natural product compounds are secondary metabolites with very complex structures. This has an advantage in that they are extremely novel compounds but this complexity also makes many lead compounds' synthesis difficult and the compound usually has to be extracted from its natural source – a slow, expensive and inefficient

process. As a result, there is usually an advantage in designing simpler analogues.

The plant kingdom

Plants have always been a rich source of lead compounds (e. g. morphine, cocaine, digitalis, quinine, tubocurarine, nicotine, and muscarine). Many of these lead compounds are useful drugs in themselves (e. g. morphine and quinine), and others have been the basis for synthetic drugs (e. g. local anaesthetics developed from cocaine). Clinically useful drugs which have been recently isolated from plants include the anticancer agent paclitaxel (Taxol) from the yew tree, and the antimalarial agent artemisinin from Artemisia annua.

Plants provide a large bank of rich, complex and highly varied structures which are unlikely to be synthesized in laboratories. Furthermore, evolution has already carried out a screening process itself whereby plants are more likely to survive if they contain potent compounds which deter animals or insects from eating them. Even today, the number of plants that have been extensively studied is relatively very few and the vast majority have not been studied at all.

The marine world

In recent years, there has been a great interest in finding lead compounds from marine sources. Coral, sponges, fish, and marine microorganisms have a wealth of biologically potent chemicals with interesting inflammatory, antiviral, and anticancer activity. For example, curacin A is obtained from a marine cyanobacterium and shows potent antitumor activity. Other

antitumor agents derived from marine sources include eleutherobin, discodermolide, bryostatins, dolostatins, and cephalostatins.

The microbial world

Microorganisms such as bacteria and fungi have been invaluable for discovering drugs and lead compounds. These microorganisms produce a large variety of antimicrobial agents which have evolved to give their hosts an advantage over their competitors in the microbiological world.

The screening of microorganisms became highly popular after the discovery of penicillin. Soil and water samples were collected from all over the world in order to study new bacterial or fungal strains, leading to an impressive arsenal of antibacterial agents such as the cephalosporins, tetracyclines, aminoglycosides, rifamycins, and chloramphenicol.

Although most of the drugs derived from microorganisms are used in antibacterial therapy, some microbial metabolites have provided lead compounds in other fields of medicine. For example, asperlicin – isolated from Aspergillus alliaceus – is a novel antagonist of a peptide hormone called cholecystokinin (CCK) which is involved in the control of appetite. CCK also acts as a neurotransmitter in the brain and is thought to be involved in panic attacks. Analogues of asperlicin may therefore have potential in treating anxiety. Other examples include the fungal metabolite lovastatin, which was the lead compound for a series of drugs that lower cholesterol levels, and another fungal metabolite called ciclosporin which is used to suppress the immune response after transplantation operations.

Venoms and toxins

Venoms and toxins from animals, plants, snakes, spiders, scorpions, insects, and microorganisms are extremely potent because they often have very specific interactions with a macromolecular target in the body. As a result, they have proved important tools in studying receptors, ion channels, and enzymes. Many of these toxins are polypeptides (e. g. α-bungarotoxin from cobras). However, non-peptide toxins such as tetrodotoxin from the puffer fish are also extremely potent.

Venoms and toxins have been used as lead compounds in the development of novel drugs. For example, teprotide, a peptide isolated from the venom of the Brazilian viper, was the lead compound for the development of the antihypertensive agents cilazapril and captopril.

The neurotoxins from Clostridium botulinum are responsible for serious food poisoning (botulism), but they have a clinical use as well. They can be injected into specific muscles (such as those controlling the eyelid) to prevent muscle spasm. These toxins prevent cholinergic transmission and could well prove a lead for the development of novel anticholinergic drugs.

Traditional Medicine

In the past, traditional peoples or ancient civilizations depended greatly on local flora and fauna for their survival. They would experiment with various berries, leaves, roots, animal parts or minerals to find out what effects they had. As a result, many crude drugs were observed by the local healer or shaman to have some medical use. Although some preparations may have been dangerous, or worked by a ceremonial or placebo effect, traditional healing systems usually had a substantial active pharmacopoeia, and in fact

most western medicines up until the 1920s were developed this way. Some systems, like traditional Chinese medicine or Ayurveda were fully as sophisticated and as documented systems as western medicine, although they might use different paradigms. Many of these aqueous, ethanolic, distilled, condensed or dried extracts do indeed have a real and beneficial effect, and a study of ethnobotany can give clues as to which plants might be worth studying in more detail. Rhubarb root has been used as a purgative for many centuries. In China, it was called “ The General” because of its “ galloping charge” and was only used for one or two doses unless processed to reduce its purgative qualities. (Bulk laxatives would follow or be used on weaker patients according to the complex laxative protocols of the medical system.[2]) The most significant chemicals in rhubarb root are anthraquinones, which were used as the lead compounds in the design of the laxative dantron.

The extensive records of Chinese medicine about response to Artemisia preparations for malaria also provided the clue to the novel antimalarial drug artemisinin. The therapeutic properties of the opium poppy (active principle morphine) were known in Ancient Egypt, were those of the Solanaceae plants in ancient Greece (active principles atropine and hyoscine). The snakeroot plant was well regarded in India (active principle reserpine), and herbalists in medieval England used extracts from the willow tree(salicin) and foxglove (active principle digitalis – a mixture of compounds such as digitoxin, digitonin, digitalin). The Aztec and Mayan cultures of Mesoamerica used extracts from a variety of bushes and trees including the ipecacuanha

root (active principle emetine), coca bush (active principle cocaine), and cinchona bark (active principle quinine).

It can be challenging to obtain information from practitioners of traditional medicine unless a genuine long term relationship is made. Ethnobotanist Richard Schultes approached the Amazonian shamans with respect, dealing with them on their terms. He became a “ depswa” – medicine man – sharing their rituals while gaining knowledge. They responded to his inquiries in kind, leading to new medicines.[3] On the other hand Cherokee herbalist David Winston recounts how his uncle, a medicine priest, would habitually give misinformation to the visiting ethnobotanists. The acupuncturists who investigated Mayan medicine recounted in Wind in the Blood had something to share with the native healers and thus were able to find information not available to anthropologists.[4] The issue of rights to medicine derived from native plants used and frequently cultivated by native healers complicates this issue.

Isolation and purification

If the lead compound (or active principle) is present in a mixture of other compounds from a natural source, it has to be isolated and purified. The ease with which the active principle can be isolated and purified depends much on the structure, stability, and quantity of the compound. For example, Alexander Fleming recognized the antibiotic qualities of penicillin and its remarkable non-toxic nature to humans, but he disregarded it as a clinically useful drug because he was unable to purify it. He could isolate it in aqueous solution, but whenever he tried to remove the water, the drug was destroyed. It was not until the development of new experimental procedures

such as freeze drying and chromatography that the successful isolation and purification of penicillin and other natural products became feasible.

Synthesis

Not all natural products can be fully synthesized and many natural products have very complex structures that are too difficult and expensive to synthesize on an industrial scale. These include drugs such as penicillin, morphine, and paclitaxel (Taxol). Such compounds can only be harvested from their natural source – a process which can be tedious, time consuming, and expensive, as well as being wasteful on the natural resource. For example, one yew tree would have to be cut down to extract enough paclitaxel from its bark for a single dose. Furthermore, the number of structural analogues that can be obtained from harvesting is severely limited.

A further problem is that isolates often work differently than the original natural products which have synergies and may combine, say, antimicrobial compounds with compounds that stimulate various pathways of the immune system:

Many higher plants contain novel metabolites with antimicrobial and antiviral properties. However, in the developed world almost all clinically used chemotherapeutics have been produced by in vitro chemical synthesis. Exceptions, like taxol and vincristine, were structurally complex metabolites that were difficult to synthesize in vitro. Many non-natural, synthetic drugs cause severe side effects that were not acceptable except as treatments of last resort for terminal diseases such as cancer. The metabolites discovered

in medicinal plants may avoid the side effect of synthetic drugs, because they must accumulate within living cells.

Semisynthetic procedures can sometimes get around these problems. This often involves harvesting a biosynthetic intermediate from the natural source, rather than the final (lead) compound itself. The intermediate could then be converted to the final product by conventional synthesis. This approach can have two advantages. First, the intermediate may be more easily extracted in higher yield than the final product itself. Second, it may allow the possibility of synthesizing analogues of the final product. The semisynthetic penicillins are an illustration of this approach. Another recent example is that of paclitaxel. It is manufactured by extracting 10-deacetylbaccatin III from the needles of the yew tree, then carrying out a four-stage synthesis.

Use Of Natural Product

1. Ayurveda
2. Chinese medicine
3. Ethnobotany
4. Journal of Natural Products
5. Pharmacognosy
6. Phytotherapy
7. Secondary metabolite
8. During the last few decades, research into natural products has advanced tremendously thanks to contributions from the fields of chemistry, life sciences, food science and material sciences. Comparisons of natural products from microorganisms, lower

eukaryotes, animals, higher plants and marine organisms are now well documented. This book provides an easy-to-read overview of natural products. It includes twelve chapters covering most of the aspects of natural products chemistry. Each chapter covers general introduction, nomenclature, occurrence, isolation, detection, structure elucidation both by degradation and spectroscopic techniques, biosynthesis, synthesis, biological activity and commercial applications, if any, of the compounds mentioned in each topic. Therefore it will be useful for students, other researchers and industry. The introduction to each chapter is brief and attempts only to supply general knowledge in the particular field. Furthermore, at the end of each chapter there is a list of recommended books for additional study and a list of relevant questions for practice.

9. Combined with pharmacological screening, natural products chemistry has always provided highly useful leads for drug discovery. The searches for new biologically active compounds are most often based on hints coming from ethnobotany but there are still a huge number of unstudied plants, not to speak of mushrooms, marine organisms, insects, and microorganisms. There is a wealth of molecular diversity out there, waiting to be discovered and utilized. The central issue of such type of studies, structure elucidation, although often believed to be trivial, is still a process full of adventure, discovery, and even unavoidable pitfalls. Thus structure elucidation has still much to offer, especially when combined with biological tests. Chemistry Central Journal is waiting for your results to publish.

10. Besides the classic studies connected to pharmacological activities, new developments challenge natural products chemists, such as metabolomics, the large-scale phytochemical analysis in the functional genomics era. Metabolomic requires from a natural product chemist brilliant knowledge of modern analytical techniques and chemometry and close collaboration with biochemists and biologists. Chemical ecology, too, could not advance properly without natural product chemistry.
11. Approximately 60% of the world’s population relies almost entirely on plants for medication. However, if phytopharmaceuticals want to be regarded as rational drugs, they need to be standardized and pharmaceutical quality must be approved. For this reason, another important task for natural products chemistry is connected to standardization: to develop proper analytical methods of quality control, to make sure that medicines obtained from natural sources are safe and of reproducible efficacy.
12. The publication of natural product research results in an open access journal is of great importance with respect both to research activities and to effective use of natural resources, removing both price and permission barriers. It is also important to authors, giving them the opportunity to publish their results where they will be most easily accessed by those who mostly need them.

Natural Product Chemistry for Drug Discovery provides a comprehensive summary of where natural product chemistry is today in drug discovery. The book covers emerging technologies and case studies and is a source of up-

to-date information on the topical subject of natural products. The authors, all experts in their respective fields, provide compelling arguments as to why naturel products should be considered important tools in the drug discovery process. The book will appeal across the board from scientists to professionals, postgraduates and industrial chemists.

The case studies selected for inclusion highlight recently marketed drugs and development candidates that have been derived from natural products. These ‘ real-life’ examples show how new technologies, such as advances in screening, isolation, dereplication and prefractionation, have significantly enhanced the discovery process.

Introduction Of Synthetic Chemistry

In primitive societies, even today, clothes are cleaned by beating them on rocks near a stream. Certain plants, such as soapworts, have leaves that produce sapions, chemical compounds that give a soapy lather. These were probably the first detergents people used.

If you look up detergent in a dictionary it is simply defined as cleaning agent. During the last two to three decades, however, the word detergent has tended to imply synthetic detergent, or syndet for short, rather than the older soap. In fact, commercial formulations consist of a number of components, and we shall use the term surface-active agent, or it’s abbreviation surfactant, to describe the special active ingredients that give detergents their unusual properties.

Soap, by this definition, is a surfactant. In fact, it is the oldest one and has been in use for over 4500 years. Some soap manufacture took place in

Venice and Savona in the fifteenth century, and in Marseilles in the seventeenth century. By the eighteenth century, manufacture was widespread throughout Europe and North America, and by the nineteenth century the making of soap had become a major industry. As a matter of fact, soap became a detergent in 1907 when a German company put the product “ Persil” on the market. In addition to the carboxylic acid soap, “ Persil” contained sodium perborate, sodium silicate and sodium carbonate. Hence perborate + silicate = “ PERSIL”.

Synthetic Surfactant or Soap?

You may well ask why soap, which served well for so many years, was eventually displaced. Soaps are cheap and they are manufactured from a renewable source, whereas many of the synthetic detergents are made from petrochemicals. Soaps are also biodegradable; that is, they are readily broken down by bacteria, and thus they do not pollute rivers. However, due to their gelling properties, soaps do have a greater tendency to clog sewerage reticulation systems than synthetic detergents. The grease trap of a non-sewered house was often laden with soap. But the most important reason for the displacement of soap is the fact that, when a carboxylic acid soap is used in hard water, precipitation occurs. The calcium and magnesium ions, which give hardness to the water, form insoluble salts with the fatty acid in soap and a curd-like precipitate occurs and settles, of course, on what ever is being washed. By using a large excess of soap, it is possible to redisperse the precipitate, but it is extremely sticky and difficult to move. This problem with soap can be demonstrated by a simple experiment in which a concentrated solution of hard-water salts is added to a 0. 1%

solution of soap and also to a 0. 1% solution of synthetic surfactant. The soap precipitates, but the synthetic surfactant remains clear because it’s salts are water soluble.

You may live in an area where the water is extremely soft. But calcium and magnesium ions are present in the dirt that you wash out of your clothes, so that some precipitation still occurs if soap is used, and gradually deposits are built up in the fabric.

There are other disadvantages with soap; it deteriorates on storage, and it lacks cleaning power when compared with the modern synthetic surfactants, which can be designed to perform specialised cleaning tasks. Finally and very importantly from a domestic laundry point of view, soap does not rinse out; it tends to leave a residue behind in the fabric that is being washed. A residue gradually builds up and causes bad odour, deterioration of the fabric and other associated problems.

What’s the Difference?

What’s the difference between a surfactant and soap? In general terms, the difference can be likened to the difference between cotton and nylon. On the one hand, soap and cotton are produced from natural products by a relatively small modification. On the other hand, synthetic surfactants and nylon are produced entirely in a chemical factory. Synthetic surfactants are not very new, either. Back in 1834 the first forerunner of today’s synthetic surfactants was produced in the form of a sulfated castor oil, which was used in the textile industry.

The development of the first detergents in an effort to overcome the reaction of soaps with hard water provides a good illustration of one of the standard chemical approaches. If a useful substance has some undesirable property, an attempt is made to prepare an analogue, a near chemical relation, which will prove more satisfactory.

The petroleum industry had, as a waste product, the compound propylene, CH3-CH= CH2, which used to be burnt off. By joining four of these propylene molecules together and if benzene is attached at the double bond, the resulting compound reacts with sulphuric acid. Then sodium hydroxide is added to neutralise the sulfonic acid and a sodium salt is obtained. The new substance is closely related to an ordinary soap, and is an excellent detergent.

Detergent Foam Level

The relationship between foaming power and detergency has always been of interest, and foaming power has become associated in many consumers' minds with high detergent power. The first liquid detergent on the Australian market was " Trix". It was non-foaming, so was soon replaced because of consumer resistance. However, it is generally conceded by detergent technologists that foam height has no direct relationship to cleaning power in ordinary fabric washing systems.

In systems where the amount of washing fluid is low, foam may play an important role. The individual foam films tend to take up and hold particles of soil that have been removed from the item, preventing them from being re-deposited and allowing them to be washed or scraped away. Front loading

washing machines work by bashing clothes against the side of the tub – the high tech version of beating clothes on rocks. Front loaders clean clothes better than top loaders, but only if a low-suds detergent is used, because the suds cushion the impact and reduce the cleaning action.

Chemical Characteristics Of Synthetic Chemistry

Synthetic detergents dissolve or tend to dissolve in water or other solvents. To enable them to do this, they require distinct chemical characteristics. Hydrophilic (water loving) groupings in their molecular structure, and hydrophobic (water hating) groupings, help the detergent in it’s “ detergency” action.

This detergency depends on the balance of the molecular weight of the hydrophobic to the hydrophilic portion. This is called the HLB value, and can range from 1 upwards. HLB is Hydrophilic-Lypophilic Balance. As the 0HLB value increases, the product can tend towards being a paste or solid. The lower number HLB values tend to be less water soluble, and more oil soluble. The higher the HLB the more water soluble the product.

Mixtures of low and high HLB detergents produce good detergents to handle oil, fat and grease, the higher HLB detergent helps solubilise the less water soluble, low HLB detergent into an aqueous system.