ligands 3,6-di(2-pyridyl)-4,5-diphenyl-pyridazine and dppm was also prepared.

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Guest Article

Natural product driven drug discovery

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The success stories reveal that the world's biodiversity offer human society with various pharmaceuticals, agrochemicals and research biochemicals. Various methods such as isolation of compounds from plants, microorganisms and other sources; synthetic chemistry, combinatorial chemistry and molecular modeling are being used for obtaining compounds for drug discovery. According to the most recent review of Newman and Cragg natural product driven drug discovery is still alive and going well. For an example, in the area of cancer, out of the 175 small molecules approved as drugs during 1940-2014, 75 % are non-synthetics, of which 49% is either natural products or directly derived from natural products.

Although there are numerous success stories of natural product driven drug discovery, the process of drug development from natural products are faced with frequent challenges. The path to the success of drug discovery using natural products is through a lot of obstacles. While most of the drugs such as antibiotics become obsolete with time due to the resistivity developed by the pathogenic bacteria, the natural products scientists and pharmaceutical industries continuously need to look into lead substances with novel structures and novel mechanisms of action or improve the quality of the existing ones through modifications to suit the needs.

Drug discovery process consists of several steps (Figure 1) which expands for an average period of 10 years and the estimated cost per drug development in average will reach up to $800 million or more. The first step in the process, which is identifying a drug lead, is also a tedious course. From the step of identifying an active extract to activity guided isolation of bioactive compounds take a substantial time limit. In addition to lead identification, lead optimization which involves medicinal and combinatorial chemistry, lead development using pharmacology, toxicology, pharmacokinetics and drug delivery and finally clinical trials prolong the drug discovery process.

Active compound isolation procedures coupled with the bioassays take weeks or months. This is simply too sluggish to complete with the screening of pure compounds. Nevertheless, with only microgram quantities of the active compound being isolated is not sufficient to drive the meaningful biological evaluation or clinical trials. In such situations re-isolation of the active compounds, i.e. if it is from a microbial source re-culturing, extraction, and isolation need to be carried out which makes this time-consuming process. Unfortunately, during some of these occasions some microorganisms under long term storage and growing on artificial media may have stopped producing the bioactive compounds. This has become one of the major challenges in microbial natural product drug discovery route.

On the other hand, to collect the active compound sufficient for the structure elucidation process large biological samples (plant, animal or microorganism) need to be utilized. Obtaining large biological samples such as a plant or an animal draw various issues related to conservation and ethics. In contrast, obtaining large

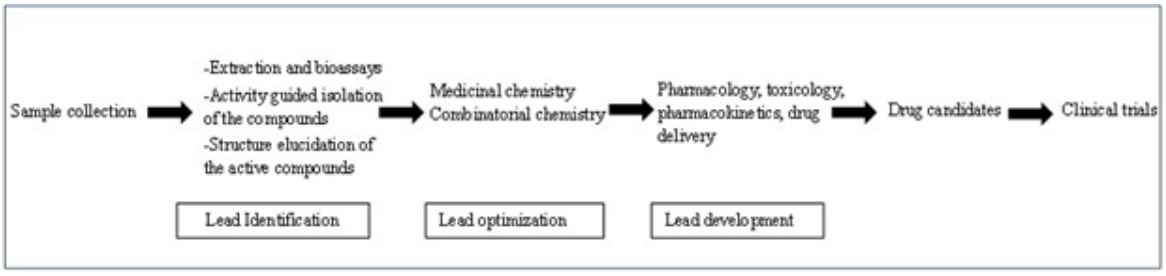

Figure 1: Drug discovery process
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microorganism cultures are less problematic although it utilizes a lot of man power, time and a high cost for artificial growth media.

Though there are highly sensitive Nuclear Magnetic Resonance (NMR) spectrometers available nowadays, structure elucidation of new and unprecedented carbon skeletons often requires several milligram quantities of the compounds and a considerable time period because the stereochemistry of the new structure also needs to confirmed. The issue of isolating low quantities of the active compounds can be overcome by exploring synthetic and medicinal approaches for semi or total synthesis of the active compounds. However due to the complexities of the structures of the natural products, synthesis or modification processes become frequently challenging. Similarly, preparation of natural product analogues is also difficult compared to the synthetic chemicals within the same time period.

Despite of all above, biological material collection process from nature also causes certain issues that need to be dealt according to the legislative requirements of the country. This would require researchers to seek permission from appropriate regulatory authorities prior to collecting biological materials. However, research may involve continuous collection of biological materials from time to time or from various locations thus making it impractical to seek permission each time, and this also extends the lead identification process. Most often after identifying an active plant extract, researcher needs to collect the plant again in bulk which may in turn exert a problem due to plants' threaten status and scattered distribution. At the same time improper authentication of biological material cause various issues when trying to re isolate the lead compound. Hence, preparation of voucher specimens including the location/ time/season/ geographical conditions of collection, and depositing them in a herbarium becomes important in case of repeated studies.

It is probable that unusual ecological niches in developing countries will yield novel microorganisms and novel natural products for drug discovery. Most of these niches have not yet been investigated by the natives due to lack of knowledge, skills or technical advances. However, developing countries are reluctant to allow the export of the biological materials for fear of losing control of their value. This limits scientists in the developed world to access and make immediate use of them in drug development. In such a situation for effective utilization of biological resources for the benefit of the world, countries should implement proper processes to sign agreements or memorandum of understanding for covering issues regard to genetic resources and intellectual property rights related to the discovery, or fare method of sharing of benefits in an event of a commercialization. However, legal requirements involved will be time-consuming while these will limit the academic researchers' activities in non-commercial studies such as ecology, taxonomy etc. Nevertheless, these provisions are essential to conduct the natural product research in an ethical manner.

High throughput screening (HTS) is a novel approach practiced these days in screening thousands of compounds/extracts for biological activities within like a week to speed up the drug discovery process. However, this approach is not successful other than for screening pure compound libraries. One reason is the complexities of natural product extracts which give rise to false positive readings. Secondly if an extract was identified as 'active' from HTS, then from the classical approach the active compound needs to be isolated basically through chromatographic techniques which will take weeks or months. As the HTS assays will be online only for a few weeks, the initially used assays may not be able to use to screen the purified fractions or isolated pure compounds with the extended times they take for the purification process. Thus, the design determination and implementation of appropriate, clinically relevant, high-throughput bioassays are difficult procedures for all drug discovery programmes.

Due to lack of efficient dereplication methodologies, rediscovery of the known compounds becomes a major issue in the field. Also, when the active compound becomes a known compound with a known activity it is not protectable from patents.

Currently there are financial pressures for pharmaceutical research and development in general and particularly in the USA. Therefore, the developing countries cannot rely on 'big pharma' to discover and develop their medicinal natural products. Thus, in developing nations this should be supported and carried out by smaller pharmaceutical companies and academic researchers. However, in Sri Lanka the pharmaceutical companies are not yet in a confident state to invest and initiate the drug development process using drug leads from nature other than using plant or herb extracts to formulate tablets, capsules or oral liquid preparations.

Sri Lanka, along with the Western Ghats of India is listed as one of the 35 biodiversity hotspots of the world. We are rich in our own flora with 4203 flowering plants in which 889 are endemics. Other than those there are around 35 Gymnosperms, 336 Pteridophytes, 560 mosses, 222 liverworts and 661 lichens. Despite having an exceptional level of biodiversity to drive the drug discovery process, Sri Lanka still spends a lot of revenue to import pharmaceuticals from elsewhere. As a nation, our researchers and pharmaceutical companies should unite to use our invaluable biological resources in drug discovery for the benefit of our country and for the human race as a whole, overcoming all the obstacles.

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Graduate Chemists Welfare Fund

This fund has been established with effect from 1-1-2012. The principal benefits towards CCS Graduate Chemists would be,

I. To provide partial assistance towards international travel of those proceeding abroad for PG degrees (once a life time). Assistance for
Active Graduate Chemists : Rs. 60,000 Passive Graduate Chemists: Rs. 30,000

ii. To provide partial assistance towards registration fees in respect of IChemC /CCS events such as international Conferences.

iii. To provide assistance towards registration fees for IChemC /CCS training seminars etc.

iv. To provide partial assistance towards activities of the Alumni Association.

Note:
Depending on the demand, Graduate Chemists who maintain positive contact and participate in IChemC/ Alumni activities will get preference for the above mentioned assistance scheme.

AUSTRALIAN NATIONAL CHEMISTRY QUIZ AWARD CEREMONY

The award ceremony of the Australian National Chemistry Quiz – 2017 was held on 4th April 2018 at the Institute premises. The Chief Guest of the occasion was **Dr. Janaka Dias**, a former Merit winner of ANCQ. Fifty three students received plaques and certificates for their performances at the competition. Eighteen coordinating teachers who served as Assistant Supervisors for more than 5 years were also awarded with plaques and certificates of appreciation.