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Srivari Chandrasekhar of CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad), who has made important contributions in the area of potential drug developments, has been awarded the Infosys Prize 2014 in the category of physical sciences. The award carries a purse of Rs 55 lakhs, a 22 carat gold medal along with a citation. He has been conferred the honour for his significant contributions in the field of organic and medicinal chemistry. Chandrasekhar obtained his Bachelor's and Master's degrees in 1982 and 1985 respectively, from Osmania University, Hyderabad and excelled in the same with distinction. He then joined A. V. Rama Rao's group at CSIR–IICT and earned his doctorate in 1991, also from Osmania University. Between 1991 and 1994 he was associated with J. R. Falck (University of Texas Southwestern Medical Center) as a postdoctoral student. In 1994, Chandrasekhar joined his parent institute (CSIR–IICT) as a scientist. His major contributions include synthesis of complex natural products, especially from marine sources which are screened for various biological activities such as anticancer, anti-arthritic, antifungal and anti-depressant, green chemistry and automation chemistry to make a large number of relevant new chemicals. More recently Chandrasekhar and his team have embarked on a prudent area of research wherein hybrid peptides (sugar-amino acid) are designed and oligomerized in various combinations to realize novel helices, tubes and sheets. He has published more than 250 papers in national and international journals. His work has fetched him several awards, including INSA medal for Young Scientists, CSIR Young Scientist, B. M. Birla Science Prize, AVRA Young Scientist, Andhra Pradesh Scientist Award, NASI Reliance Platinum Jubilee Award, Ranbaxy Research Award and FAPCCI award. Under his able guidance around 50 students have obtained their Ph Ds and over 20 students are currently being trained. He has blended academic research with application at the industrial and society level to make his research work relevant. In conversation with *Current Science*, he spoke on his research interests, his love for synthetic chemistry, the strength of organic chemists in translating biomedical research to clinical practice and also shared his thoughts on the importance of discipline and hard-work.

*Congratulations on winning the Infosys Prize 2014. Can you tell us about the current research work you are engaged with?*

Thank you for your wishes.

Research in my group focuses on the following areas:

- Synthesis of complex and scarcely available natural products having relevance to cure human diseases and libraries of compounds.
- Synthesis of unusual peptides and peptidomimetics.
- Development of patent onnon-infringing processes for drugs, which are going off-patent in the near future.
- Synthesis and application of new organocatalysts.
- Development of synthetic routes for compounds which are in clinical trials.
- Use of polyethelene glycol (PEG) as a solvent in an effort towards 'green chemistry and processes'.
- Synthesis of deuterated compounds (to treat or combine molecules with deuterium, to increase its half life).

*How do you pick what to synthesize (lead-oriented synthesis) or rather decide the genesis of molecules that can be successful as lead compounds?*

I am always fascinated by biological activity coupled with structural complexity of molecules and achieving their synthesis gives immense satisfaction. That is one of the driving forces for me to choose molecules for synthesis. A thorough reading of the latest trends in drug discovery helps me decide which compounds to select and chosen areas (anti-cancer, CNS-related, anti-coagulants, anti-infectives) help narrow down the search. My interaction with industry also gives pointers to hot topics and current trends. After successfully synthesizing ~30 complex molecules (lead oriented synthesis), I have recently started working in the area of lead generation. Three scaffolds were found to show anti-cancer activity through histone deacetylases (HDAC) inhibition and these compounds are going towards the process of drug discovery. Two compounds with activity in the nanomolar range have been identified for which PK and toxicity studies in mice and rat are underway. These compounds have selective HDAC inhibition and thus will decrease side-effects.

*Can you explain the importance of lead-oriented synthesis in the field of medicinal chemistry?*

Drug discovery is a costly and time-consuming process. As a result teams working in the area of drug discovery screen thousands of compounds to identify HITs followed by leads. Most of these compounds are synthesized following Lipinski's rule of five or through combinatorial chemistry. The drawback of these two methods is that molecules which are lipophilic and which have high molecular weight or complex structural features are eliminated. Lead-oriented synthesis (LOS) has been developed to target molecules which are complex in structure and polar in nature. A library of compounds is then synthesized from the lead molecule. LOS focuses on deliberate design and robust synthetic methods for the preparation of diverse scaffolds required for drug discovery. LOS works on the knowledge of the mechanism of biological activity, diversity of scaffolds, reactivity in biological systems, polarity of the selected scaffold and affordability of the synthetic route. It is emerging as a good addition in the field of drug discovery.

*Can you help us understand the principle of Lipinski's rule of five and its implications in the purview of drug design?*

Christopher Lipinski and his team studied ~2000 molecules in clinical trials

which observed that most of them were small molecules which exhibited lipophilicity. Based on these observations the rule was formulated, where the molecular weight of the scaffolds should be less than 500 Da, the molecule should have less than five hydrogen-bond donors (amino, hydroxyl or carboxylic acid groups) and less than 10 hydrogen-bond acceptors (nitrogen and oxygen atoms in the molecule) with a log *P* greater than 5. The rule is important as it describes the requirements for absorption, distribution, metabolism and excretion (ADME) properties of molecules, but cannot predict if the molecule can be biologically active. During the process of HIT and LOS, the rule of five is of immense help in adding or removing functionalities in the chosen molecule to make it more 'drug-like'. It has been observed that molecules which obey the rule of five have lower attrition rate in clinical trials.

Having said that, I would like to state that not all molecules that are drugs follow Lipinski's rule. There are several drugs which are exceptions to this rule. Many a times it has been observed that drugs are discovered with intuition and experience.

*Give us an insight on the importance of automation in drug discovery and the 'National MolBank' established at IICT*

Drug discovery requires screening of thousands of compounds in the initial stages to narrow down to a few scaffolds, which show desired activity. Generation of these thousands of compounds manually is a herculean task. Automation has made life easy for synthetic chemists as libraries of compounds in multiples of 96 (number of vials in a screening as well as synthesizing plate) can be prepared using a common starting material and varying the other reagents. The synthesized compounds can be purified by automated high-performance liquid chromatography (HPLC) system. Pure compounds are then stored in facilities such as National MolBank, which are totally automated. The next step in drug discovery, high throughput screening, also uses automation for its execution.

The National MolBank at CSIR-IICT is a unique facility which stores pure compounds at –20°C under inert atmosphere controlling the moisture and oxygen content of the chamber. The storage at low temperature under nitrogen atmosphere ensures the safekeeping of the samples for a long period of time. The samples are screened against disease targets and thus MolBank plays a major role in the process of drug discovery. As long life of the samples is assured, assays, which will be developed at a later stage, will be able to screen the compounds that are synthesized. In earlier cases when such sophisticated storage systems were not available, the chemists had to either resynthesize the scaffolds for new screens or many a times good scaffolds could not be screened for new assays due to decomposition of the stored samples.

*Can you tell us how marine ecology can help in the betterment of human health and the present challenges in the field?*

About 70% of the Earth is covered by oceans and they have remained mostly unexplored. Marine ecosystem is one of the most dynamic ecosystems, and flora and fauna thriving in it require special chemicals for survival. With advances such as scuba diving, more and more species are being explored for isolating new scaffolds. Of late, isolation and biological screening of these chemicals has gained importance with advances in isolation and structure characterization techniques. The first compounds isolated from marine sources and approved as drugs were cytarbine (anti-cancer, 1967) and vidarbine (anti-viral, 1976). After a lull of more than 20 years, ziconotide (management of severe chronic pain) was approved in 2004. This is the synthetic equivalent of cone snail *Conus magus* venom. During a search by NCI, USA, an extract from sea squirt *Ecteinascidia turbinate* was found to have anti-cancer activity. Separation of fractions and structure determination led to ecteinascisin 743 or trabectedin, which was approved in 2007 for treatment of patients with advanced soft tissue sarcoma. The latest drug to get approval is eribulin mesylate (Halaven®), a derivative of halochondrin isolated from marine sponge *Halichondria okadai*. Recently, scientists were able to isolate molecules which had incorporated arsenic in place of phosphorus into macromolecules. Thus, marine sources are revealing complex, site-specific and advanced cures for many human ailments.

A major challenge in acquiring compounds from marine resources is their quantity. The compounds are available in miniscule quantity and after structure determination hardly any compound is left for biological screening. Total synthesis, fermentation and biotechnological advances help in overcoming this hurdle.

*What are natural product hybrids?*

Natural product hybrids are molecules that incorporate frameworks of two or more molecules into one, where at least one molecule is known to show biological activity and at least one is a natural product. The hybrid natural product can target the same site or different sites based on the parent molecules. Many natural product hybrids are planned to overcome resistance developed by the administration of the parent molecules. I have published a review on hybrid natural products in collaboration with L. F. Tietze, which can be referred to for more details in this area (*Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3996–4028).

*Can you elaborate on the role of synthetic chemistry in anti-cancer drug development and also emphasize on its potential limitations?*

Synthetic organic chemistry plays a prominent role in drug discovery by synthesizing complex molecules and libraries thereof for finding a better drug. Anti-cancer drug discovery is no different from traditional drug discovery. Most of the drugs approved for cancer treatment are obtained by either semi-synthesis or total synthesis of HITs and leads. A latest example of this is the discovery of eribulin mesylate for metastatic breast cancer. Halichondrin was isolated from marine sponge, and Kishi *et al*. started a total synthesis of the same. During the course of synthesis, some of the advanced intermediates were screened for activity and it was realized that one of the intermediates was very potent. A slight tweaking of the original scaffold led to eribulin, which is a totally synthetic molecule, though based on a natural product scaffold.

The limitations are the number of synthetic steps involved to get complex skeletons and scalability of the target molecule.

*Give us an insight on eco-friendly solvents and their uses in synthetic chemistry*

Traditionally synthesis has been carried out in organic solvents, which creates

pollution and is an environmental hazard. A new trend has been the use of PEG and ionic liquids which can be reused and recycled effectively without any loss in the yield and composition of the molecules synthesized. My group has demonstrated successfully that metal catalysts can be used in PEG and both solvent and catalyst can be recycled. This reduces the cost of manufacture and decreases pollution. Ionic liquids are another area in which my group has carried out work, especially in the synthesis of prostaglandins.

*Can you talk about the concept of foldamers and their relevance in nanochemistry?*

Proteins fold naturally and thus create cavities which are responsible for the activity of a particular protein either by embedding the nucleoside, amino acid or drug molecule. Natural proteins are comprised of alpha amino acids and require 10-membered structures for $\beta$-turn. My group has worked on the synthesis of unusual $\beta$-amino acids and their incorporation has resulted in $\beta$-turn with tetra- and hexamers. These properties are useful in studying the cause of a disease and also in finding a cure for the disease. These unusual peptides developed by my group show distinct nano-structures and hence can be used for drug delivery to specific sites.

*Comment on the path to be traversed from laboratory to industry and to the marketplace*

The process of drug discovery is complex and requires time, manpower and finance to reach the goal. One more important factor in drug discovery is 'luck'. My work has been focused on innovative basic research with cost-effective processes, thereby making them less cumbersome. We have contributed in cost-reduction by developing new synthetic routes, or by using solvents such as PEG which can be reused several times over, or have developed new methodologies to achieve the synthetic target. We have also been collaborating with industry to discover a lead molecule from the scaffolds available in the CSIR–IICT-owned National MolBank.

*Can you elaborate on your statement 'importance of bringing discipline in research community'?*

I strongly believe that research has to be carried out with utmost discipline. It is like the religious rituals that we all follow meticulously. Hard work along with discipline is rewarded in the end. Of late, it is observed that researchers want to get quick recognition and follow short-cuts. This leads to sub-standard research and needs to be changed. Instead of trying 'me too' approaches, researchers should try and find a new path and embark on a road of enjoyable science.

*The first 'Eureka' moment in your scientific life*

'Eureka moment' is a big term to use and suits great scientists like Archimedes and Newton. But I had some instances in my scientific life which inspired me to progress in a new direction and thereby making me different from my peers. After a close interaction and a keen observation of my mentors, I decided that I will be working in the health sector, to find new drug molecules, to synthesize existing ones with lesser impact on the environment and with decrease in cost. Thus I have always focused on new scaffolds which can later become cures for human illnesses. One particular moment which stands out in my scientific life is when I decided to work on 'green solvents', particularly on PEG. I am thankful to a French student who was presenting his work on PEG-conjugated drug molecules and he had with him a bottle containing PEG. He was asking everyone to smell, touch and feel PEG as it is not hazardous, non-toxic and has good bio-compatibility. He was trying to convince that PEG-conjugated drugs will have better efficacy. This set my thought process working and I thought if PEG is stable, non-toxic, can be recycled easily and is bio-compatible, then why not try some reactions using this? I was the first to work in this area and even today this is an area of highest impact.

*What are the factors that groomed you to become a synthetic organic chemist?*

I am always fascinated by nature's unique skills to build complex materials with very simple raw materials. My first liking to synthetic organic chemistry goes back to my days of M Sc, where I had the great privilege to attend inspiring lectures in Osmania University under the Subbarao memorial lecture series. During this period the lectures delivered by Rama Rao and Goverdhan Mehta were so special to me, which have driven me to take up synthetic organic chemistry as a serious profession. The satisfaction, that a synthetic organic chemist derives when total synthesis of a natural product is achieved, is unmatched by any other accomplishment.

*Do you think India is producing sufficient Ph Ds and what is your take on quality versus quantity with respect to churning out Ph Ds from Indian academia?*

I believe in the management principle of demand and supply. The system takes care of this naturally. Keeping in view the vast size of the nation, both quantity and quality are of utmost importance. I am one of those believers; conscious quantity will lead to good quality output.

*Do you support the idea of students opting for industrial jobs or being entrepreneurs rather than pursuing academics after Ph D?*

This depends on the aptitude of the individual besides opportunities. I have come across students who were keen to come into academics, but due to non-availability of opportunity, they ended up in industrial jobs and also became entrepreneurs. They have adapted well and became successful individuals.

*How important was it to win the Infosys Prize?*

It is a great recognition to the community of organic chemists. I believe, I am only a medium. I owe a lot to my mentors, peers and students for what I am.

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