Synthesis of natural products of therapeutic significance

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Annual meeting of the Indian Academy of Sciences, IISER, Pune 07 November 2015
Natural Products

Compounds derived from natural resources such as plants, animals or microorganisms

Generally derived from countless bio-synthetic pathways and numerous reactions and mechanisms involving the building blocks such as acetyl co-enzyme A, shikimic acid, mevalonic acid etc.

*Natural product space:*
*Dyes, pigments, therapeutics, pesticides etc.*

<10% of the world bio-diversity has been evaluated for the potential activity, while more natural products await the evaluation.
Molecules of therapeutic importance from Natural Products

Fractionation

Bio-activity assay
(anti-fungal, anti-microbial, anti-cancer, anti-bacterial)

Find the active fraction by Bio-activity assay

Purification of individual compound of active fraction.

Find the active compound by Bioactivity assay

Large scale Purification of Bioactive compound.

Chemical/ enzymatic modification for enhancement of bioactivity

Clinical trials

Pharmacological study in vitro, in vivo assays

Exploring Biosynthetic pathway

Chemical synthesis

Characterization
Mass, NMR, Crystallography.

Plant Sample
Structural and elemental diversity in therapeutics

Rings in Drugs
Miniperspective


Beyond C, H, O, and N! Analysis of the Elemental Composition of U.S. FDA Approved Drug Architectures
Miniperspective


Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals To Reveal Opportunities for Drug Design and Discovery
Miniperspective
**ABSTRACT:** We have analyzed the rings, ring systems, and frameworks in drugs listed in the FDA Orange Book to understand the frequency, timelines, molecular property space, and the application of these rings in different therapeutic areas and target classes. This analysis shows that there are only 351 ring systems and frameworks in drugs that came onto the market before 2013.
Natural products are unmatched for their diversity, structural variety and some of them are validated for their activity against various diseases, thus allowing entry into the drug discovery progression at an advanced stage.

Unusual, efficacious bioactivity profile
(Interceptors of key cellular pathways and specific inhibitors/promoters of key enzymes)
2010: DISTRIBUTION OF DRUGS APPROVED BY THE FDA BY CHEMICAL SPECIES

Out of total 21 drugs in 2010

- Protein: 6
- Synthetic small molecule: 5
- Natural product: 4
- Mab: 2
- Peptide: 1
- Amino acid: 1
- Steroid: 1
- Other: 1
Nature: The master craftsman with Diversity

- Acetylsalicylic acid
- Morphine
- Penicillin
- Quinine
- Pilocarpine
- Artemisinin
Styryllactones: Natural products from Annonaceae

More than 350 natural products isolated from various Annonaceae species

Used in folklore medicine: Proved for various ailments

Shown to exhibit cytotoxic activity

Some of the compounds are in phase II clinical trials

Biosynthetic pathway is believed to be Shikimic acid pathway
Styryllactones: Natural products from *Annonaceae*

- Goniotriol
- Cardiobutanolide
- 7-epi-Goniofurfurone
- Goniothalesdiol
- Goniofurfurone
- Gonioppyrpyrone
- Goniodiol
- Altholactone
- Etharvensin
Styryllactones: Natural products from *Annonaceae*

Abundant chiral pool compounds
Carbohydrates, amino acids etc

Modification of functional groups
Masked aldehyde
C₂ symmetric

both enantiomers are commercially available
Small molecule that activates mutant p53 to the active form

In collaboration With Prof. P. Kondaiah

ACS Chem. Bio, 2013, 8, 1429

Org. Lett. 2014, 16, 4001
Tetrahedron 2014, 70, 4552

J. Org. Chem. 2013, 78, 3313
ACS Chem. Bio, 2013, 8, 1429
Chem. – Asian. J. 2013, 8, 488
Tetrahedron, 2013, 69, 6512
Synthesis, 2013, 45, 785

Chem. Eur. – J. 2012, 18, 15202
J. Org. Chem. 2011, 76, 6889
J. Org. Chem. 2011, 76, 2029
Org. Lett. 2011, 13, 4252

Synthesis, 2010, 2521
Synlett, 2010, 1093
Tetrahedron: Asymmetry 2010, 21, 275
Synlett, 2009, 2593

J. Org. Chem. 2008, 73, 2916
J. Org. Chem. 2008, 73, 2
Palmerolide-A: Natural Product from Antarctica

palmerolide A, a 20-membered macrolactone from the marine tunicate Synoicum adareanum found in the Antarctic region.

Found to exhibit excellent antitumor activity against melanoma cancer cells, which is attributed to its potent inhibitory activity against vacuolar ATPase.

Treaty that prohibits commercial exploitation of Antarctic resources, the development of a synthetic strategy that allows the synthesis of palmerolide A and an array of its analogues is warranted.

Total synthesis of natural products accomplished in our laboratory.
Acknowledgements

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