Bio-Organic Chemistry of Natural Enediyne Anticancer Antibiotics - Web course

COURSE OUTLINE

Ever since the discovery of the enediyne anticancer antibiotics in the late 1980s, it has got tremendous research interest by scientist from various disciplines because of their novel molecular architecture, remarkable biological activity, and fascinating mode of action, and potential medical applications. Synthetic chemists and molecular designers have been engaged to synthesize these molecules and to model their unique molecular architecture. Considerable efforts have also been paid by chemists, biologists and medicinal chemists to understand the mechanism of action and DNA cleavage properties associated with these natural products. The study of biosyntheses of their unique molecular scaffolds and unprecedented modes of self-resistance property would also uncover novel mechanistic enzymology and may provide opportunity to the rational biosynthetic modification of enediyne architecture for the development of new drug candidates.

Therefore, in this course the basics of enediyne class of natural and designed antitumor antibiotics, their history of discovery, novel biological activity, and their medicinal application will be focused. In a truly interdisciplinary way enediyne natural products attract the attentions of organic/bioorganic chemists, biochemists, and medicinal chemists.

This course will describe the history of discovery of enediyne class of natural products, their molecular architechture, mode of biological action and the key chemistry behind their potent DNA cleaving activity. Slowly it will provide an overview the chemical synthesis as well as biosynthesis of enediyne scaffolds, various design and synthesis of model enediynes and elucidation their potent biological activity. At last, this course will emphasize on the recent clinical advancement to the application of enediyne as clinically approved anticancer agent.

Thus, this course will be an appetizer for all students of chemistry and biotechnology at almost any institution who want to continue their study at the interface of chemistry and biology. This new curriculum thus, will find more usefulness and relevance to the majority of our audience to improve the education at the interface of chemistry and biology.

A Web course shall contain 40 or more 1 hour lecture equivalents

Module No	Module Topic	No. of Hours
1	**Introduction to Enediyne Class of Natural Products**	10
2	**Synthesis/Biosynthesis of Enediynes Class of Natural Products**	16
3	**Designed Enediyne Model Systems**	17
4	**Applications of Enediyne Antitumor Antibiotics**	8
	Total	51

Course Details

Module 1: Introduction to Enediyne Class of Natural Products: History of Discovery of Enediynes; Isolation of Enediynes; Molecular Structures of Enediynes; Biological Properties and Mechanisms of Action of Naturally Occurring Enediynes; The Bergman Cyclisation Reaction; The Myers-Saito Cyclisation Reaction. (**10 lectures**)

Module 2: Synthesis/Biosynthesis of Enediynes Class of Natural Products: Classifications of Natural Enediynes-Calicheamicins/ Esperamicins class of enediynes (Class I), The Dynemicins class of enediynes (Class II), and The Chromoprotein class of enediynes (Class III)**;** Mechanism of DNA Cleavage by Each Class; Chemical Synthesis of a Few Members of Enediynes Natural Products**;** Biosynthesis of a Few Members of Natural Enediynes. **(16 Lectures)**

NP-TEL

NPTEL

http://nptel.iitm.ac.in

Chemistry and Biochemistry

Pre-requisites:

- Organic Chemistry background specially, preliminary knowledge of organic reaction mechanisms, reactive intermediates, organic transformations, and stereochemistry. Basic knowledge of nucleic acids. Most of the topics including “Bioorganic Chemistry” will be found in the NPTEL site.

Additional Reading:

1. Nicolaou, K. C., S. A. Snyder, A. G. Meyers, and S. J. Danishefsky. "Dynemicin A." Classics in Total Synthesis II: More Targets, Strategies, Methods. Weinheim: Wiley-VCH, 2003. 75-107.
2. Schulz-Aellen, Marie-Franoise. "Cancer Drugs." Aging and Human Longevity. Boston: Birkhuser, 1997. 203-04
3. Silverman, Richard B. "Dynemicin A." The Organic Chemistry of Drug Design and Drug Action. Amsterdam: Elsevier Academic, 2004. 381-85
4. Nicolaou, K. C.; Smith, A. L. Modern Acetylene Chemistry (Eds. Stang, P. J.; Diederich, F.), VCH, Weinheim 1995, 203.
5. Basak, A.; Mandal, S.; Bag, S. S. Chem. Rev. 2003, 103, 4077.
6. Bergman, R. G. Acc. Chem. Res. 1973, 6, 25.
7. Van Lanen, S. G.; Shen, B. Curr. Top. Med. Chem. 2008, 8, 448.
8. Shao, R.-G. Curr. Mol. Pharmacol. 2008, 1, 50.
9. Liang, Z.-X. Nat. Prod. Rep. 2010, 27, 499.

Hyperlinks:

1. For Bergman cyclisation see: http://www.organic-chemistry.org/namedreactions/bergman-cyclization.shtm
2. For enediyne see: en.wikipedia.org/wiki/Enediyne
3. For Dynemycin enediyne see: http://www.columbia.edu/cu/chemistry/groups/synth-lit/MIR2009/2009_06_12-AElsohly-Dynemycin.pdf

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Module 3: Designed Enediyne Model Systems: Introduction to Structural Features of Enedynes; Factors Affecting the Reactivity of Enediynes; Molecular Design of Enediyne Models; Various Synthetic Approaches to Acyclic/Cyclic Enediynes; Various Synthetic Aprroaches to Cyclic Enediynes; Synthesis of Dienediyne Core of NCS chromophore; β-Lactam as a Molecular Lock of Enediyne: Synthesis of β-Lactam Fused Enediynes; Enediynes with pH-Based Triggering Devices; Photoswitchable Enediynes; Biological Actions of Some Synthetic Models; Enediyne as a Scaffold for Peptidomimetics; Enediyne as Peptide Cleaving Agent. **(17 Lectures)**

Module 4: Applications of Enediyne Antitumor Antibiotics: Defining Cancer and Its Various Type; Cancer-Treatment of Choice; Cancer-Combination Therapies; Therapeutic Applications of Enediyne Antitumor Antibiotics; The Approved Enediynes for Use as Anticancer Drugs; Enediynes Under Clinical Investigation; Immunoconjugates; Antibody –Drug Conjugates; Targeted Chemotherapy; Antibody-Enediyne Conjugate under Clinical Investigation Future Prospect and recent advances in Enediyne Research. **(8 Lectures)**

Module wise

Sl. No.	Lecture No.	Lecture Titles	No. of Hours
1	**Module 1: Introduction to Enediyne Class of Natural Products (10 Lectures)**		**10 hrs**
	1	**History of Discovery of Enediynes and History of Cancer**	1 hr
	2	**Microbial Drug Discovery and Isolation of Enediynes**	1 hr
	3	**Molecular Structures of Enediynes**	1 hr
	4	**Biological Properties and Mechanisms of Action of Naturally Occurring Enediynes**	1 hr
	5	**The Bergman Cyclisation Reaction-Part-1**	1 hr
	6	**The Bergman Cyclisation Reaction-Part-2**	1 hr
	7	**The Bergman Cyclisation Reaction-Part-3**	1 hr
	8	**The Bergman Cyclisation Reaction-Part-4**	1 hr
	9	**The Myers-Saito Cyclisation Reaction-Part-1**	1 hr
	10	**The Myers-Saito Cyclisation Reaction-Part-2**	1 hr
	Module 2: Synthesis/Biosynthesis of Enediynes Class of Natural Products (16 lectures)		**16 hrs**
	1	**Classifications of Natural Enediynes**	1 hr
	2	**Mechanism of DNA Cleavage by Each Class**	1 hr
	3	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of Neocarzinostatin)-Part-1**	1 hr
	4	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of Calicheamicin)-Part-2**	1 hr

	5	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of Calicheamicin)-Part-3**	1 hr	
	6	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of Dynemicin A)-Part-4**	1 hr	
	7	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of N1999A2)-Part-5**	1 hr	
	8	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of Kedarcidin Chromophore-Hirama's Approach)-Part-6**	1 hr	
2	9	**Chemical Synthesis of a Few Members of Enediynes Natural Products (Synthesis of Kedarcidin Chromophore-Myers' Approach)-Part-7**	1 hr	
	10	**Biosynthesis of a Few Members of Natural Enediynes (Synthesis of Maduropeptin)-Part-8**	1 hr	
	11	**Biosynthesis of a Few Members of Natural Enediynes-Part-1**	1 hr	
	12	**Biosynthesis of a Few Members of Natural Enediynes (General Biosynthesis)-Part-2**	1 hr	
	13	**Biosynthesis of a Few Members of Natural Enediynes (Biosynthesis of C-1027)-Part-3**	1 hr	
	14	**Biosynthesis of a Few Members of Natural Enediynes (Biosynthesis of Neocarzinostatin)-Part-4**	1 hr	
	15	**Biosynthesis of a Few Members of Natural Enediynes (Biosynthesis of Maduropeptin)-Part-5**	1 hr	
	16	**Biosynthesis of a Few Members of Natural Enediynes (Biosynthesis of 10-Membered Enediynes , Calicheamicin g1I)-Part-6**	1 hr	
	Module 3: Designed Enediyne Model Systems (17 lectures)		**17 hrs**	
	1	**Introduction to Structural Features of Enedynes and Factors Affecting the Reactivity of Enediynes**	1 hr	
	2	**Molecular Design of Enediyne Models (Acyclic Enediynes- Structural Representation) Part-1**	1 hr	
	3	**Molecular Design of Enediyne Models (Acyclic Enediynes-Representative Examples)-Part-2**	1 hr	
	4	**Molecular Design of Enediyne Models (Cyclic Enediynes- Structural Representation)-Part-3**	1 hr	
	5	**Molecular Design of Enediyne Models (Cyclic Enediynes-Representative Examples)-Part-4**	1 hr	
	6	**Various Synthetic Approaches to Acyclic/Cyclic**	1 hr	

		Enediynes	
3	**7**	**Various Synthetic Aprroaches to Cyclic Enediynes-Part-1**	1 hr
	8	**Various Synthetic Aprroaches to Cyclic Enediynes-Part-2**	1 hr
	9	**Synthesis of Dienediyne Core of NCS chromophore**	1 hr
	10	**β-Lactam as a Molecular Lock of Enediyne: Synthesis of β-Lactam Fused Enediynes**	1 hr
	11	**Enediynes with pH-Based Triggering Devices (Category 1-3)-Part-1**	1 hr
	12	**Enediynes with pH-Based Triggering Devices (Category 4-5)-Part-2**	1 hr
	13	**Photoswitchable Enediynes (Category 1-2)-Part-1**	1 hr
	14	**Photoswitchable Enediynes (Category 3-6)-Part-2**	1 hr
	15	**Biological Actions of Some Synthetic Models**	1 hr
	16	**Enediyne as a Scaffold for Peptidomimetics**	1 hr
	17	**Enediyne as Peptide Cleaving Agent**	1 hr

4	**Module 4: Applications of Enediyne Antitumor Antibiotics (8 Lectures)**		**8 hrs**
	1	**Defining Cancer and Its Various Type-Part-1**	1 hr
	2	**Defining Cancer and Its Various Type- Part-2 and Cancer-Combination Therapies**	1 hr
	3	**Therapeutic Applications of Enediyne Antitumor Antibiotics**	1 hr
	4	**The Approved Enediynes for Use as Anticancer Drugs**	1 hr
	5	**Enediynes Under Clinical Investigation and Immunoconjugates**	1 hr
	6	**Antibody–Drug Conjugates**	1 hr
	7	**Targeted Chemotherapy**	1 hr
	8	**Antibody-Enediyne Conjugate under Clinical Investigation and Future Prospect and Recent Advances in Enediyne Research**	1 hr

References:

1. Biochemistry, 5th Ed. (Hardcover) by Lubert Stryer, Jeremy M. Berg, and John L. Tymoczko.
2. Enediyne Antibiotics as Antitumor Agents; Borders, D. B., Doyle, T. W., Eds.; Marcel Dekker: New York, 1995.
3. Meunier, B. Ed. DNA and RNA Cleavers and Chemotherapy of Cancer and Viral Diseases, Kluwer Publishers, Dordrecht, 1996, p1;
4. Xi, Z.; Goldberg, I. H. Comprehensive Natural Product Chemistry (Eds. Barton, D. H. R.; Nakanishi, K. Pergamon, Oxford, 1999, 7, 553.
5. Schor, NF. The Enediynes. In: Teicher, BA., editor. Cancer Therapeutics: Experimental and Clinical Agents;. Humana Press Inc; Totowa, NJ: 1997. p. 229-239.
6. Xi, Z.; Goldberg, IH. DNA-Damaging Enediyne Compounds. In: Kool, ET., editor. Comprehensive Natural Products Chemistry. Vol. 7. Elsevier; New York: 1999. p. 533.
7. In: Li, J. J., author. Name Reactions-A Collection of Detailed Reaction Mechanisms and Synthetic Applications. Springer Berlin Heidelberg; 4th expanded ed., 2009, XXII, 621 p. 6 illus.