Steroid Spiroketal Peptide: Triple Hybrid Constructs

Abhisek Banerjee
Research Topic Seminar
19-Feb-2008
Where Do We Stand.....

**Combinatorial Compounds**

**Natural Products**

**Drugs**

Natural Products in Drug Discovery

All New Chemical Entities (NCEs) 1981-2006

B: Biological;  N: Natural Product;  ND: Derived from N;
S: Totally synthetic drug;  V: Vaccine;  NM: N Mimic
S*: Synthetic but Pharmacophore is/was from N;

Worldwide Pharmaceutical Natural Product Patents

More Natural Product Like………..

Function-Oriented Synthesis

Designing One’s Own Target:

Bryostatin $K_i = 1.4 \text{ nM} > 70 \text{ steps}$

Lead Analog $K_i = 0.3 \text{ nM} 29 \text{ steps}$
Hybrid Molecules: Dream or Reality?

Bleomycin: Three structural entities with three different biological roles

Meunier B. *Acc. Chem. Res.* **2008**, *41*, 69
Steroid-Spiroketal Nucleus in Natural Products

Ritterazone B
Cytotoxic agent

Cephalostatin 1
Cytotoxic agent

Dioscin and Polyphyllin D
Exhibit Cardiovascular, Cytotoxic, Antifungal, Antitumor, Hemostatic activity
IC$_{50}$ (HeLa Cell): 3.8 and 1.1 μM

Desgalactotigonin

Steroid Peptide Natural Conjugates

Bufetoxin
Isolated from Chinese Hoptoad

Triseramide
Isolated from Starfish

X: CO₂H, Cholyl glycine
X: SO₃H, Cholyl taurine

Carolisterol C
Isolated from Starfish


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Steroid Peptide Conjugates

Cholic acid conjugate
HIV Protease Inhibitor

Insulin-Deoxycholic acid derivative

Cationic Steroid Antibiotics


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Arginine-Glycine-Aspartic Acid (RGD) Tripeptide

Most of the integrin superfamily members especially $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$, recognize Arg-Gly-Asp (RGD) sequence, an epitope shared by a variety of extracellular ligands including vitronectin, fibronectin, osteopontin, bone sialoprotein and fibrinogen.

Pioneer: Erkki Ruoslahti, Burnham Institute of Medical Research

*Nature* 1984, 309, 30 and *Science* 1987, 238, 491

A Generic Field of Research
Integrins

Integrins are a large family of heterodimeric non-covalent proteins expressed on cell surface.

- Consists of two different chains α and β which associates to provide $\alpha_x\beta_y$ receptors
- 18 α and 8 β subunits are known which produces 26 different heterodimers
- Large N-terminal extracellular domain
- Transmembrane domain
- Short C-terminal intracellular tail

Therapeutic targets due to cell adhesion


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2/16/2008
αvβ3 Integrin

- Expressed on the cell surface of a variety of cell types such as Platelets, Endothelial cells, Vascular muscle cells, Osteoclasts and Tumor cells.

- Plays key role in Physiological processes such as angiogenesis, apoptosis.

- Expected to have major impact on the treatment of Osteoporosis, Rheumatoid arthritis, and Cancer.

- For drug development it is desirable to obtain antagonists selective to αvβ3.

Chapleur Y. et al. Mini Reviews in Medicinal Chemistry 2002, 2, 531
Towards More Active and Selective RGD Mimetics

**Essential Parts of Pharmacophore**

- Carboxylate Group
- Guanidinium moiety
- Hydrophobic group

**Some Key Features**

- Shorter distance between guanidinium and carboxylate group (< 6.7Å).
- Conformational constrains with rigid cores, cyclic structures, turn inducers.

Spiroketalts via Oxidative Enol Ether Rearrangement

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Acknowledgments

Prof. Peter Wipf
David Waller
Stephanie Nicolay
Pete Chambers
Adam Hoye
Shuli Mao
Amol Kulkarni
Wipf Group Members