The Role of Natural Products in Drug Discovery

For thousands of years medicine and natural products have been closely linked through the use of traditional medicines and natural poisons.

Which is the STATUS of NATURAL PRODUCTS in DRUG DISCOVERY today?

Table 1. Top 35 Worldwide Ethical Drug Sales for 2000, 2001, and 2002 with Natural Product-Derived Drugs in Blue, Biologically Derived Drugs in Magenta, and Synthetically Derived Drugs in Black

<table>
<thead>
<tr>
<th>Rank</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
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<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
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<td>2</td>
<td>Sertraline</td>
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<td>3</td>
<td>Lamotrigine</td>
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<td>4</td>
<td>Levetiracetam</td>
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<td>Haloperidol</td>
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<td>6</td>
<td>Citalopram</td>
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<td>Haloperidol</td>
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<td>Citalopram</td>
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<tr>
<td>35</td>
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</tbody>
</table>

* Top 35 worldwide ethical drug sales data supplied by Wad Markonie, Boston, MA. ‡ NP-derived indicates that the drug is either a NP, a semisynthetic derivative of a NP, or a synthetic drug that is modeled on a NP pharmacophore. § Biologically derived indicates that the drug is hormone or protein derived. † Erythropoietin is sold by both Johnson & Johnson (J&J) and Amgen, while prostaglandin is marketed in Japan by Sankyo and the United States by Bristol-Myers Squibb (BMS).

Butler, M. S. J. Nat. Prod. 2004 67 2141
Understanding the Cell-Cycle with Natural Products

Understanding Protein Function in Cells

- Genetic Approach: making mutations in genes that alter the function of the encoded protein
- Chemical Approach: to alter the function of the protein directly by using a cell-permeable ligand that binds to the protein in its intracellular environment

Small molecule natural products inhibit progression of the cell cycle by binding to a protein required for cell division, thus helping to determine the function of the protein.

NATURAL PRODUCTS CHEMISTRY → CELL BIOLOGY

An understanding of cell cycle events helps in understanding the mechanisms of action of many cell-cycle inhibitors.

Currently the most valuable collection of ligands for use in the study of protein function are NATURAL PRODUCTS or compounds that are closely related to a NATURAL PRODUCT.


Relative Timing of Arrest by Different Cell-Cycle Arrest Agents

EUKARYOTIC CELL CYCLE

M (mitosis)
G2 (Gap 2)
S phase (DNA synthesis)
G1 (Gap 1)
Cells that cease division

DICCIN
WORTMANNIN
OKADAIC ACID
APHIDOCOLIN
RAPAMYCIN
TUNICAMYCIN
The Viridin Family of Steroidal Antibiotic: The Furanosteroids


- Anti-inflammatory Activity
- Antibiotic Activity
- Potent and Specific Phosphatidylinositol 3'-kinase (PI 3K) Inhibitors

Furanosteroids: Proposed Biosynthesis

1. Squalene
2. Squalene 2,3-Epoxide
3. Lanosterol
4. Viridin
5. Wortmannin
Wortmannin Irreversible Inhibition of PI-3 Kinase

Wortmannin

\[
IC_{50} = 4.2 \text{nM}
\]

\[
IC_{50} = 4600 \text{nM}
\]

\[
IC_{50} > 32000 \text{nM}
\]

\[
IC_{50} = 16.7 \text{nM}
\]

\[
IC_{50} = 0.4 \text{nM}
\]

\[
IC_{50} > 500 \text{nM}
\]

\[
IC_{50} = 6.0 \text{nM}
\]

\[
IC_{50} = 271 \text{nM}
\]

Planar Polycyclics from the Marine Sponge Xestospongia

Planar Polycyclics from the Marine Sponge Xestospongia

Distribution of Marine Natural Products by Phylum

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Number of Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microrganisms</td>
<td>10%</td>
</tr>
<tr>
<td>Algae</td>
<td>15%</td>
</tr>
<tr>
<td>Coelenterates</td>
<td>35%</td>
</tr>
<tr>
<td>Echinoderms</td>
<td>5%</td>
</tr>
<tr>
<td>Red algae</td>
<td>5%</td>
</tr>
<tr>
<td>Green algae</td>
<td>2%</td>
</tr>
<tr>
<td>Brown algae</td>
<td>2%</td>
</tr>
<tr>
<td>Bryozoa</td>
<td>1%</td>
</tr>
</tbody>
</table>

Biogenetic Origins of Marine Natural Products

- T: monoterpene
- T: sesquiterpene
- T: diterpene
- T: sesterterpene
- T: triterpene/steroid
- T: monoterpenes
- A: polyketide
- A: 3-alkylpyridine
- A: shikimate
- A: tryptophan
- A: other
- PK: polyketide
- PK: fatty acid/esteramide
- PK: macrolide
- PK: peptide
- PK: peptide/desipeptide
Planar Polycyclics from the Marine Sponge Xestospongia

[+]-Xestooquinone  [+]-Halenaquinone  [+]-Halenaquinol

Isolated from Xestospongia Sayra in 1980  Isolated from Xestospongia Esigua in 1983

- Antibacterial Activity
- Cardiotoxic Properties
- Inhibition of pp60 Kinase
- Inhibition of EGFR Kinase
- Inhibition of the Dual Specificity Phosphatase Cdc25

Are These Compounds Triketides - Sesquiterpenes Hybrids?

<table>
<thead>
<tr>
<th>Triketide Unit</th>
<th>Sesquiterpene Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isozonarol</td>
<td>Halenaquinone</td>
</tr>
</tbody>
</table>

Protein Tyrosine Kinase (PTK) Inhibition

IC50 values against pp60

<table>
<thead>
<tr>
<th>[+]Xestooquinone</th>
<th>[+]Halenaquinone</th>
<th>[+]Halenaquinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 = 60 µM</td>
<td>IC50 = 1.5 µM</td>
<td>IC50 = 0.6 µM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wortmannin</th>
<th>Viridin</th>
<th>7-Methylviridin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 ≫ 200 µM</td>
<td>IC50 = 30 µM</td>
<td>IC50 = 27 µM</td>
</tr>
</tbody>
</table>

Synthetic Efforts Outline

- Halenaquinone
  - HARADA [Chiral building block]
  - RODRIGO [α-Benzoquinone monoketals Cascade Reactions]
  - SHIBASAKI [Catalytic Asymmetric Intramolecular Cascade Heck-Suzuki Couplings]

- Viridin
  - SORENSEN [Alkyne Trimerization and ρ Claisen Rearr.]

- Wortmännin
  - SHIBASAKI [Chiral building block]
  - SHIBASAKI [Diastereoselective Intramolecular Heck Couplings and Diophenol Claisen]

Synthesis of (±) - Halenaquinol [Rodrigo]


Synthesis of (+) - Halenaquinol [Shibasaki]

1. BBBr, DCM
2. BnBr, K$_2$CO$_3$
3. CrO$_3$
4. KHMDS, Mel
5. H$_2$, Pt/C

TBAF, 2,6-LutidineNaHMDS, MeOTf

1. T$_2$D Py

Viridin

23 steps
57%

PPTS, MeOH ( ) -


Synthesis of (+) - Halenaquinol [Shibasaki]

Tf$_2$O

Halenaquinol

21 steps
0.3%

1. CAN, MeOH - H$_2$O

99%

45%

58%


Synthesis of (±) - Viridin [Sorensen]

1. nBuLi / DMF
2. Zn, HgCl$_2$
3. K$_2$CO$_3$, MeOH

85% (4 diastereoisomers)

2. 0$_2$, KO$_2$, Bu

76%


[±] - Halenaquinol
21 steps
0.3%


[±] - Viridin
23 steps
5%
**[1] Synthesis of (±) - Wortmannin [Shibasaki]**

Hydrocortisone

1. 4 Steps 27%
   1. Br, OsO₄, NaOAc 39%
   2. DIBAL-H 96%
   3. TBSCI, Imid. 14%
   4. [DCC]₂, DMSO 44%
   5. K₂C₆O₆ 55%

α = 18:1


**[2] Synthesis of (±) - Wortmannin [Shibasaki]**

1. 41 Steps 0.04%
   1. Br, OsO₄, NaOAc 39%
   2. DIBAL-H 96%
   3. TBSCI, Imid. 14%
   4. [DCC]₂, DMSO 44%
   5. K₂C₆O₆ 55%

[TIPS]


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