Day Hikes for New Medicines
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Goals of the Presentation

- History of natural products drug discovery
- Why study fungi
- How do we search for new drug leads
- Example research project
Goals of the Presentation
Drugs Derived from Natural Products

All new approved drugs, 01/1981-2010, by source
(N = 1355)

All anticancer drugs, 1940s-2010, by source
(N = 175)

Taxol and Camptothecin from RTI

Historically Important Fungal Metabolites

Penicillins
Penicillium

Cephalosporins
Acremonium

Griseofulvin
Penicillium griseofulvum

Cyclosporin A
Tolypocladium inflatum

Lovastatin
Aspergillus terreus

Fingolimod
Isaria sinclairii
Fungi are Vastly Under Studied

Bioactivity-directed Fractionation

Prioritization

Medicinal Chemistry (camptothecin)

Source

Extract

Bioassay

Bioactivity-directed

Fractionate

Bioassay

Fractionation

Purify

Structure Elucidation

Lead

Mechanism of Action

Drug

Supply Issues (taxol)

Screening
Diverse Fungal Libraries
New Biodiversity, New Chemistry, New Ph.D.

New Biodiversity
**Table 6. Activities of Compounds 1–7, 9-11, and 13-14 Against Two Human Tumor Cell Lines**

<table>
<thead>
<tr>
<th>compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; values in µM&lt;sup&gt;b&lt;/sup&gt;</th>
<th>MDA–MB–435&lt;sup&gt;c&lt;/sup&gt;</th>
<th>HT–29&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.1</td>
<td>&gt;20</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14.1</td>
<td>&gt;20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.9</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>14.5</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>11.2</td>
<td>25.4</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Compounds 2, 3, 7, 9, 11, 13, 14 were inactive (IC<sub>50</sub> values >20 µM).

<sup>b</sup>IC<sub>50</sub> values were determined as the concentration required to inhibit growth to 50% of control with a 72 h incubation.

<sup>c</sup>Positive control was vinblastine tested at concentration of 1 nM in MDA–MB–435 cells and 10 nM in HT–29 cells, which had 21% and 44% viable cells, respectively.
Spectacular Investment in Research

El-Elimat et al. (2013) *J. Nat. Prod.* **76**: 1709-1716

Fungus Culture → Active Extract → Sample Preparation

ACD Labs Intellixtract Software → HRMS and MS/MS LTQ Orbitrap → UPLC-PDA Separation

15 min → 5 min → 10 min
Funded Research Collaborations

Biotechnology Research Grant (2011-BRG-1206)
Collaborative Funding Grant (2011-CFG-8008)