The Role of Universities in Research for Developing Natural Products as Medicines

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Over past 25 years nearly half of the 1184 new chemical entities that have been marketed come from substances found in Nature.
Drugs from Nature—Penicillin

Penicillin G isolated from the mold *Penicillium notatum*

Drugs from Nature—Semi-Synthesis Penicillin

Oxacillin
Anticancer Agent: Drugs from Nature—Taxol
Anticancer Agent: Synthesis from pine needles of European Tree

10-Deacetylbaccatin

Taxol
Examples of Synthetic Drugs

Valium (Diazepam)

Viagra (Sildenafil Citrate)

Lipitor (Atorvastatin)
Reverse Transcriptase Inhibitors

- AZT
- Emtricitabine (Emtriva)
- Nevirapine

Protease Inhibitors:

- Saquinavir
Two Projects in our Laboratories

• Natural Product based Project

Tanzania: four plants used to prolong the life of people infected with HIV

What are the active ingredients?

*Prenacanthe kaurabassana* tuber
Extraction of natural (organic) products by following the bioactivity.

• How do you do this?

• What bioassay do you use?

• Use organic solvent (EtOAc). Extract showed moderate anti-HIV activity as HIV entry inhibitor assay by displaying full inhibition at 25 µg/mL.

• Could be wrong bioassay—might not be entry inhibitor!
Take crude organic solvent (EtOAc) that showed moderate anti-HIV activity and try to purify mixture.

\[\text{Chemical Structures} \]

- \( \text{CO}_2\text{H} \)
- \( \text{OH} \)
- \( \text{OMe} \)

\( R = \text{H} \)

\( R = \text{Me} \)
Table 4. HIV Screening Results of Xanthones 1 and 2 in the deCIPhR® Assay

IC$_{50}$ = 50% inhibitory concentration in anti-HIV assay; TC$_{50}$ = 50% inhibitory concentration in cytotoxicity assay

<table>
<thead>
<tr>
<th>Sample</th>
<th>IC$_{50}$</th>
<th>TC$_{50}$</th>
<th>SI</th>
<th>IC$_{90}$</th>
<th>TC$_{90}$</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthone 1</td>
<td>21</td>
<td>&gt;12.5</td>
<td>-</td>
<td>111</td>
<td>&gt;12.5</td>
<td>-</td>
</tr>
<tr>
<td>Xanthone 2</td>
<td>2</td>
<td>31</td>
<td>15.5</td>
<td>22</td>
<td>154</td>
<td>7</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>0.01</td>
<td>Not done</td>
<td>-</td>
<td>0.026</td>
<td>Not done</td>
<td>-</td>
</tr>
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(positive control)
NMR Spectroscopy Facility

R8 million
Needs liquid argon and nitrogen
Synthesis based Project
Synthesis based Project
Study their activity against diseases

Colon Cancer---Caco 2 and HT 29 cell lines

Work out their mechanism of action

Compounds were found to be very active against colon cancer and not toxic to white blood cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>HT-29 (µM)</th>
<th>Caco-2 (µM)</th>
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<tr>
<td>3</td>
<td>12.89 ± 2.41</td>
<td>11.91 ± 1.10</td>
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<td>4</td>
<td>6.57 ± 1.91</td>
<td>6.43 ± 1.01</td>
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<td>9.55 ± 2.21</td>
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<th>Compound</th>
<th>White Blood Cell Viability %</th>
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<tr>
<td>3</td>
<td>76.176 ± 0.567 %</td>
</tr>
<tr>
<td>4</td>
<td>88.943 ± 1.996 %</td>
</tr>
<tr>
<td>6</td>
<td>83.762 ± 1.389 %</td>
</tr>
<tr>
<td>7</td>
<td>93.834 ± 0.271 %</td>
</tr>
<tr>
<td>12</td>
<td>96.311 ± 5.023 %</td>
</tr>
<tr>
<td>13</td>
<td>97.479 ± 1.178 %</td>
</tr>
<tr>
<td>14</td>
<td>77.345 ± 1.005 %</td>
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<tr>
<td>Camptothecin</td>
<td>33.782 ± 2.031 %</td>
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Imidazo[1,2-a]pyridines

Caspase 8 activation

↓ mitochondrial transmembrane potential

Cytochrome c release

Caspase 3 activation

APOPTOSIS

Targets for Drugs often Enzymes/Proteins:

Lock and Key Analogy
- key = substrate
- lock = enzyme
- correct fit, will react
- incorrect substrate
- no reaction

Induced Fit Theory
- Substrate - Enzyme Complex
- Active Site

C. Ophardt, c. 2003
The X8 Diffractometer

- 80-500 K Oxford Cryostream Plus system
- 2.7 kW Microstar Cu rotating-anode generator
- λ = 1.54178 Å
- 4K Platinum 135 CCD detector
- Four-axis Kappa goniometer
- Montel optics
Anti-HIV drugs

Crystal structure of nevirapine inhibiting reverse transcriptase

Nevirapine (Viramune)
Anti-HIV drugs
Crystal structure of saquinavir inhibiting HIV protease

Saquinavir
(Invirase)
• Natural Products are important compounds for discovery of medicines

• Natural product isolation combined with synthesis allows for assembly of new biologically chemical entities

• Universities can do basic research such as isolation, synthesis, identifying biological targets, preliminary biological testing
Drug R&D in Review

Define Target  Find Lead  Choose candidate  File IND  First Human Dose  First Effective Dose  Product Decision  File NDA

Lead Identification  Lead Optimization  Pre-clinical development  Phase 1  Phase 2  Phase 3  FDA

300-600 days  450  450  500  800  400

$10-70M  $3-10M  $4-50M  $20-200M  $100-500M

2900-3200 Days or 8-9 Years

Good Idea  Drug Approved

$137-830M

Oh, and there is roughly a 4% chance of success

"Half of the modern drugs could well be thrown out of the window, except that the birds might eat them."

Martin Henry Fischer: