Study of Lead compound or Lead

Course: Drug Design
Course code: 0510412

Dr. Balakumar Chandrasekaran
Dr. Bilal Al-Jaidi
Assistant Professors,
Pharmaceutical Medicinal Chemistry,
Faculty of Pharmacy,
Philadelphia University-Jordan
Learning Outcomes

At the end of this lesson students will be able to

- Outline the entire process involved in the lead discovery.
- Understand the basic requirements for the lead discovery.
- Gain the knowledge of sources of lead molecules in the lead discovery process with examples.
- Understand the bioassay or screening process in lead identification and discovery.
- Understand rational approaches in lead discovery.
Study of Lead compound or Lead

The lead is a prototype compound that has a number of attractive characteristics, including the desired biological or pharmacological activity.

Undesirable characteristics of lead are:
- High toxicity
- Other biological activities
- Absorption difficulties
- Solubility problems
- Metabolism problems

The lead optimization is to modify the chemical structure of the lead compound in order to improve the desired properties and trying to minimize the unwanted ones.
Lead Discovery

Lead identification is the starting point of lead optimization.

Requirements for lead identification:

- Well established bioassay to study potency and efficacy.
- High throughput screening (HTS) and ultra high throughput screening (UHTS).
- Instrumental analysis: Mass spectrometry and NMR spectroscopy.
Sources of Lead Compounds

1. Endogenous or natural ligands
2. Agonists for receptors
3. Marketed drugs
4. Metabolites
5. Compounds used in clinical trials
6. Screening for lead compounds or bioassay
7. Random screening
8. Non random screening or targeted screening or focussed screening
Sources of Lead Compounds

1. Endogenous or natural ligands:

Substrates for transporters and enzymes

Ex-1: Dopamine (a neurotransmitter) for Rotigotine
Sources of Lead Compounds

Ex-2: Serotonin (neurotransmitter) for Paroxetine (antidepressant)

Serotonin (Neurotransmitter; Source)

Paroxetine (antidepressant; lead)

Ex-3: Acetyl choline (acetyl choline esterase enzyme) for Rivastigmine (treatment of dementia)

Acetyl choline (neurotransmitter; source)

Rivastigmine (treatment of dementia; lead)
Sources of Lead Compounds

Ex-4: Progesterone (endogenous steroid) for (+)-norgestrel (contraceptive)

2. Agonists for receptors

Agonist? A chemical that binds to a receptor and activates the receptor to produce a biological response.

Receptor? A receptor is a protein-molecule that recognizes and responds to endogenous chemical signals
Sources of Lead Compounds

Ex-1: Norepineprine (a ligand for adrenergic receptors); Also a neurotransmitter or hormone act as a source for Nebivolol (Antihypertensive agent)

Adrenergic receptor ligand

Norepinephrine (neurotransmitter/hormone)

Nebivolol (Antihypertensive agent; lead)
Sources of Lead Compounds

Ex-2: Acetyl choline (a ligand for cholinergic receptors); Also a neurotransmitter act as a source for Cevemaline (treatment of dry mouth).

Cholinergic receptors ligand

Acetyl choline (neurotransmitter; source)  Cevemaline (treatment of dry mouth; lead)
Sources of Lead Compounds

3. Marketed drugs

Ex-1: Chlordiazepoxide (sedative and hypnotic) for diazepam (sedative and hypnotic) that is 10 times more potent

Chlordiazepoxide (sedative/hypnotic; source)  Diazepam (sedative/hypnotic; lead; 10 times more potent)
Sources of Lead Compounds

Ex-2: Delavirdine (a reverse transcriptase inhibitor; anti-HIV) for histamine H$_4$ receptor antagonist for the treatment of asthma and allergies
Sources of Lead Compounds

4. Metabolites

Drug degradation products generated in vivo from drug metabolism.

Ex-1: Sulindac, anti-inflammatory drug (less active) for converted to its metabolite (more active) after reduction.

![Sulindac structure](image1)

Sulindac (antiinflammatory agent; less potent)

![Metabolite structure](image2)

Metabolite of Sulindac (antiinflammatory agent; more potent)
Ex-2: Nonsedating antihistamine terfenadine affected by co-administration of antifungal drugs. But fexofenadine (a metabolite of terfenadine) is not affected by the co-administration of antifungal drugs.
Sources of Lead Compounds

5. Compounds used in clinical trials

Sometimes a drug candidate during clinical trials will exhibit more than one pharmacological activity.

Ex-1: In 1947, an antihistamine, dimenhydrinate used in allergy clinic at Johns Hopkins University, USA

Dimenhydrinate

All forms of motion sickness

Car sickness

Sea sickness

Air sickness
Sources of Lead Compounds

Ex-2: Sildenafil initially designed as **Antiangina/antihypertensive-agent** (blocking enzyme phosphodiesterase-5)

- **Phase I trials (1991)**
- **Phase II trials (failure)**
- **Treatment of erectile dysfunction**
Sources of Lead Compounds

6. Screening for lead compounds or bioassay

- **Bioassay** (or screen): determining in a biological system, relative to a control compound, if a compound has the desired activity, and if so, what is the relative potency of compound?

- **Activity**: biological or pharmacological effect; **Potency**: Strength of that effect.

**Screening techniques/methods**

- 1980s many screening efforts were conducted using whole animals or whole organisms.
- Electrospray ionization mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy.
- *High-throughput screening* (HTS)- rapid and sensitive in vitro screens by robotics.
### Sources of Lead Compounds

<table>
<thead>
<tr>
<th>Time period</th>
<th>Number of compounds screened per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 1990’s</td>
<td>200,000</td>
</tr>
<tr>
<td>Mid 1990’s</td>
<td>5 to 6 million</td>
</tr>
<tr>
<td>Late 990’s</td>
<td>&gt; 50 million</td>
</tr>
<tr>
<td>In 2010</td>
<td>10 million assay reactions per hour</td>
</tr>
</tbody>
</table>

#### 7. Random screening

This approach is used if we do not have known drugs and other compounds with desired activity.

Examples:

- Sulfa drug: sulfanilamide as a lead for the development of many sulfa drugs.
- Aminoglycosides and tetracyclines were discovered after random screening of soil samples on different bacterial strains.
Sources of Lead Compounds

8. Non random Screening or targeted screening or focussed screening

In this approach, the test compounds having some structural similarity to a weakly active agents.

Rational approaches to lead discovery

Identify the cause for the disease state

Natural ligands/enzyme substrates

Lead molecule