Study of Lead compound or Lead

Course: Drug Design
Course code: 0510412

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Learning Outcomes

At the end of this lesson students will be able to

- Outline the entire process involved in the lead discovery.
- Explain various sources of lead molecules in the lead discovery process with examples.
- Define and describe bioassay or screening process in lead identification and discovery.
- Explain 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

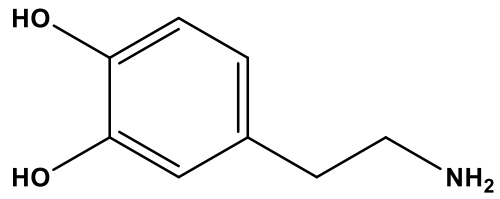
1. Endogenous or natural ligands
2. Agonists for receptors
3. Marketed drugs
4. Metabolites
5. Compounds used in clinical trials
6. Screening for lead compounds or bioassay
7. Random screening
8. Non random screening or targeted screening or focussed screening
9. Computational approaches

Sources of Lead Compounds

1. Endogenous or natural ligands:

Substrates for transporters and enzymes

Ex-1: Dopamine (a neurotransmitter) for Rotigotine



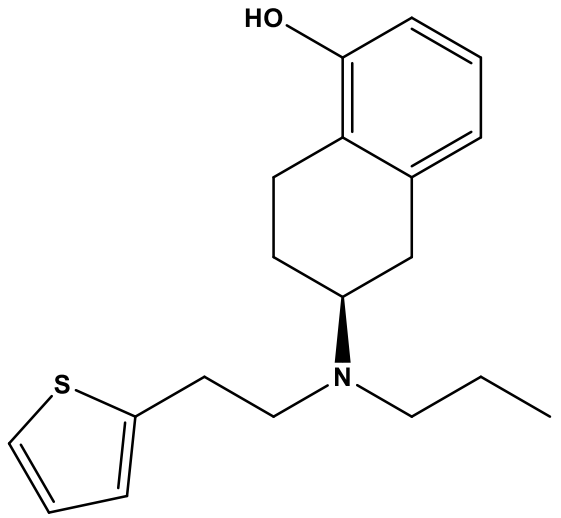
Dopamine (neurotransmitter; source)

Dopamine is not administered directly to treat Parkinson's Disease.

Reason:-

Highly polar due to the presence of polar functional groups (OH, NH_2).

So it cannot cross Blood Brain Barrier.

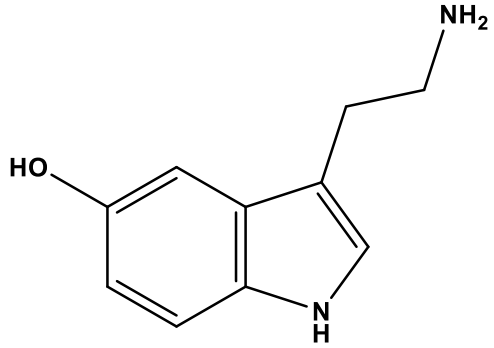


Rotigotine (Antiparkinsonism agent;lead)

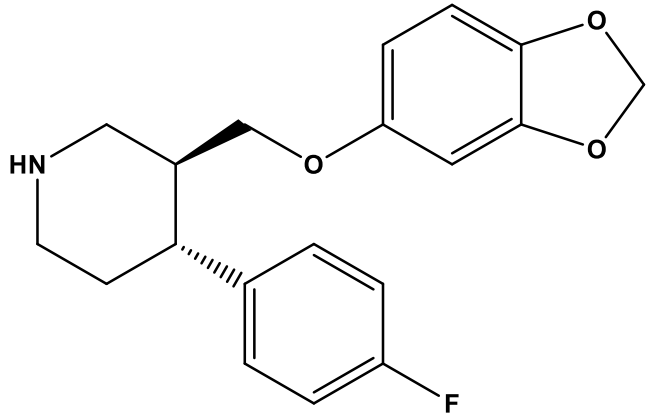
Rotigotine is an agonist for dopaminergic receptors. It is more lipophilic than Dopamine. So it can cross BBB and increases the dopamine level by activating Dopaminergic receptors.

Sources of Lead Compounds

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

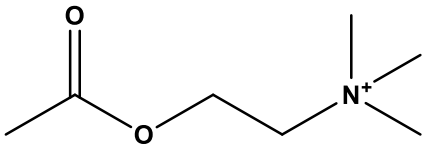


Serotonin (Neurotransmitter; Source)

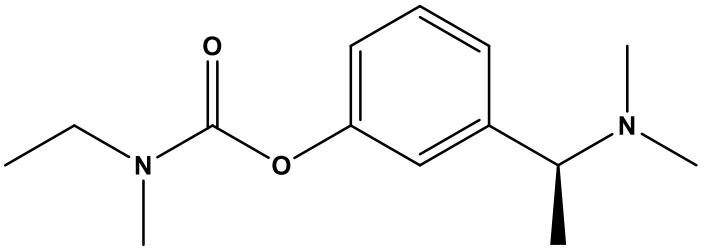


Paroxetine (antidepressant; lead)

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



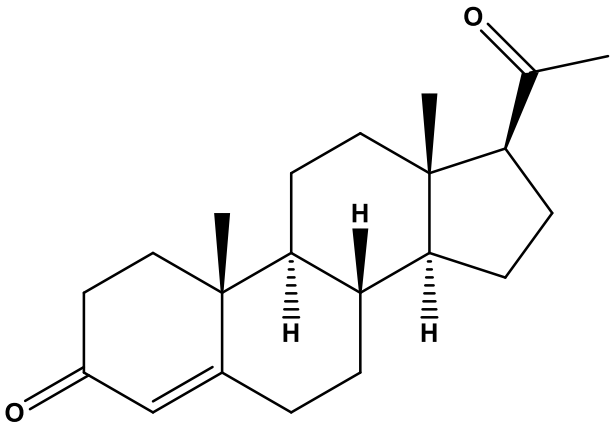
Acetyl choline (neurotransmitter; source)



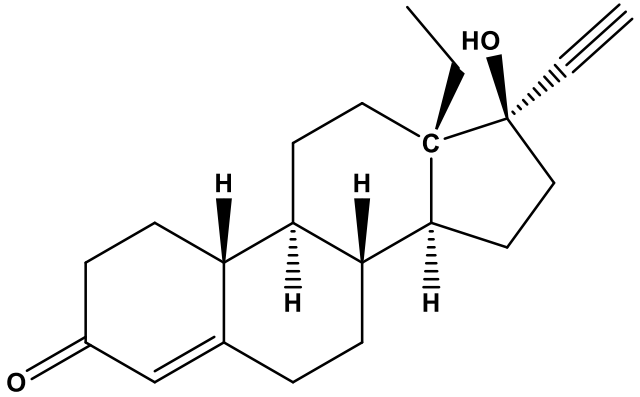
Rivastigmine (treatment of dementia; lead)

Sources of Lead Compounds

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



Progesterone (endogenous steroid; source)



(+)-norgestrel (hormonal contraceptive; lead)

2. Agonists for receptors

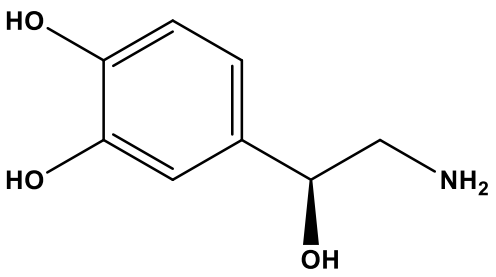
Agonist? A chemical that binds to a receptor and activates the receptor to produce a biological response.

Receptor? A receptor is a protein-molecule that recognizes and responds to endogenous chemical signals.

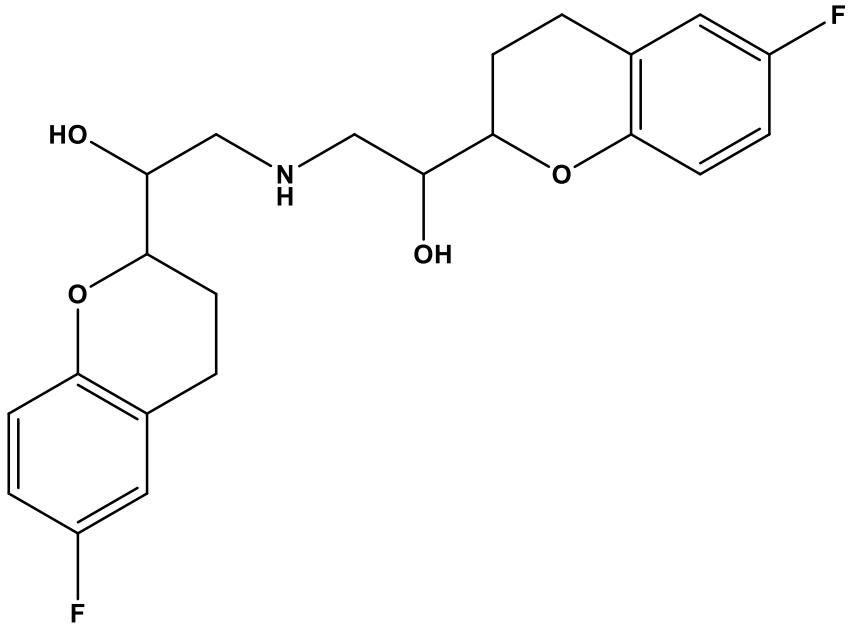
Sources of Lead Compounds

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

Adrenergic receptor ligand



Norepinephrine (neurotransmitter/hormone)

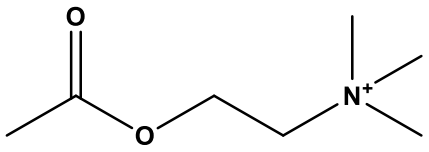


Nebivolol (Antihypertensive agent; lead)

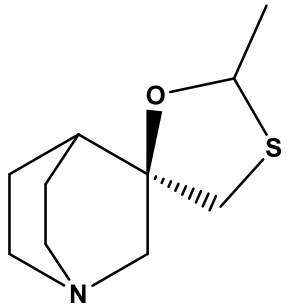
Sources of Lead Compounds

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)

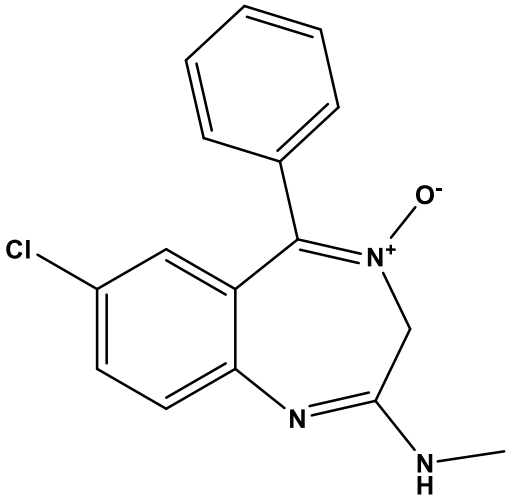


Cevemaline (treatment of dry mouth; lead)

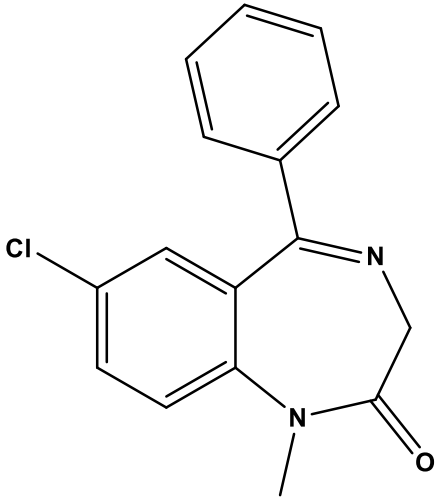
Sources of Lead Compounds

3. Marketed drugs

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



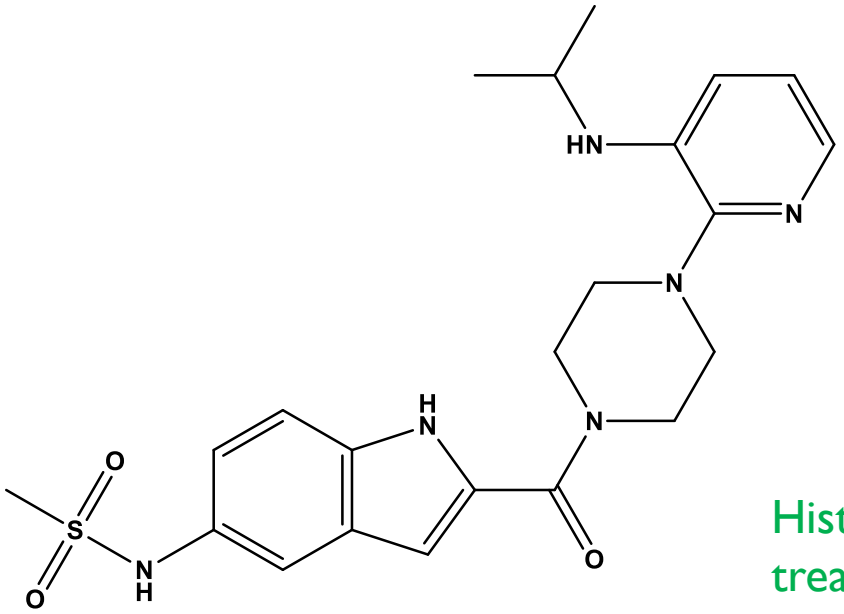
Chlordiazepoxide (sedative/hypnotic; source)



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



Delavirdine

A reverse transcriptase inhibitor;
Anti-HIV agent

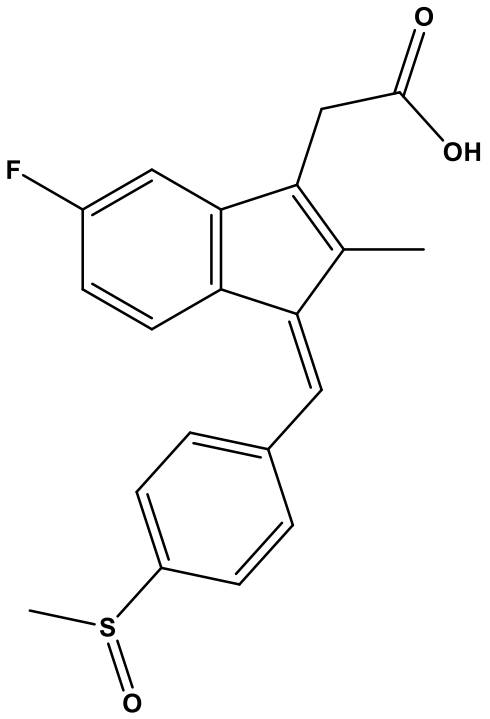
Histamine H_4 receptor antagonist for the treatment of asthma and allergies

Sources of Lead Compounds

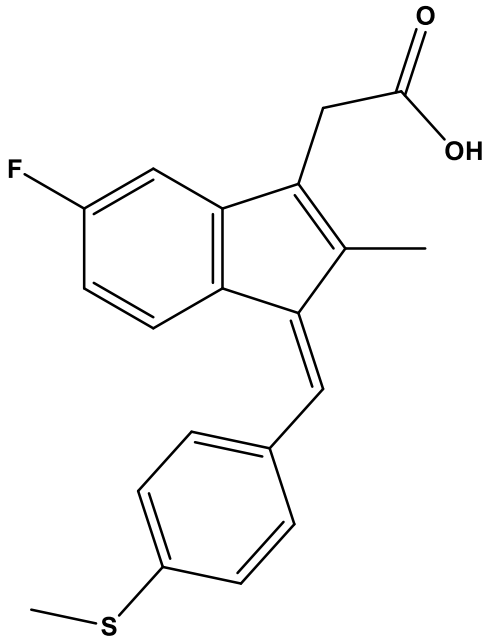
4. Metabolites

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



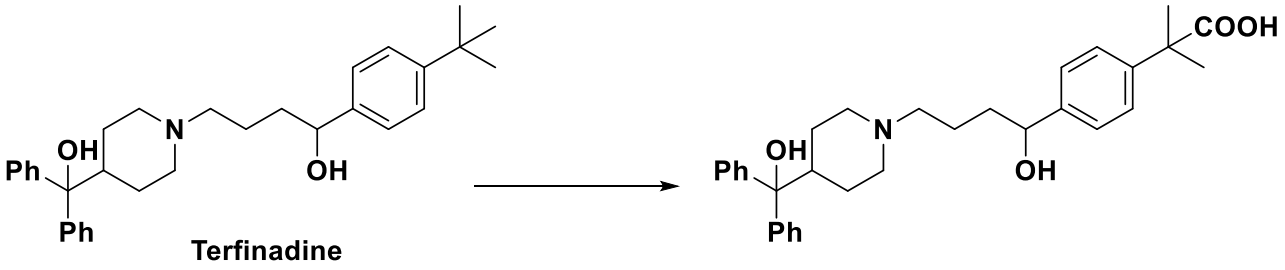
Sulindac (antiinflammatory agent; less potent)



Metabolite of Sulindac (antiinflammatory agent; more potent)

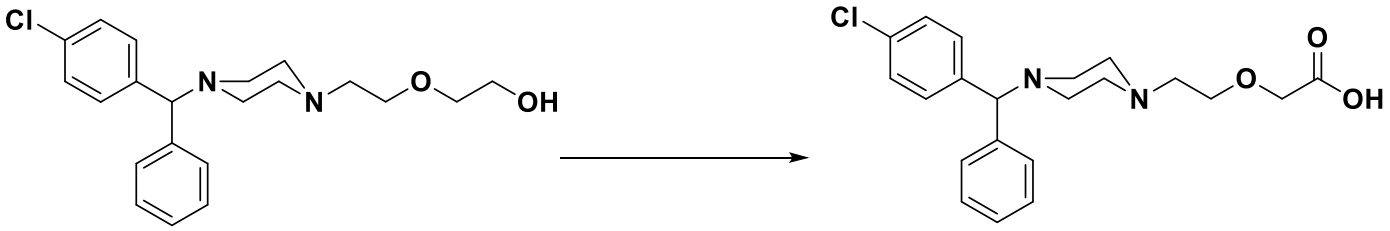
Sources of Lead Compounds

Ex-2: Nonsedating antihistamine terfenadine produces abnormal heart rhythym in patients taking antifungal drugs which metabolizes terfenadine. But fexofenadine (a metabolite of terfenadine) is not affected by the antifungal drugs.



Terfinadine

Fexofinadine (metabolite)
more active
Less sedating antihistaminic agent



Hydroxyzine

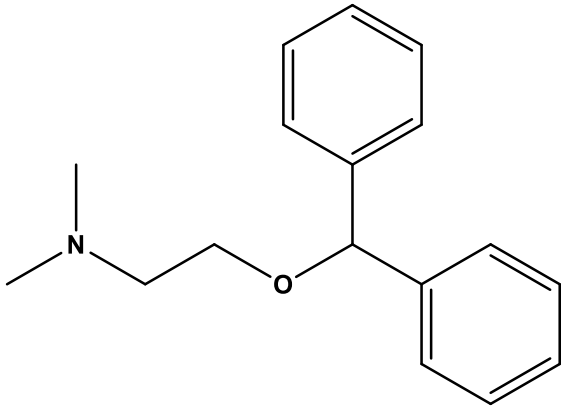
Cetirizine (metabolite)
Antiallergic

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

Car sickness

Sea sickness

Air sickness

All forms of motion 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

Time period	Number of compounds screened per year
Early 1990's	200,000
Mid 1990's	5 to 6 million
Late 990's	> 50 million
In 2010	10 million assay reactions per hour

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

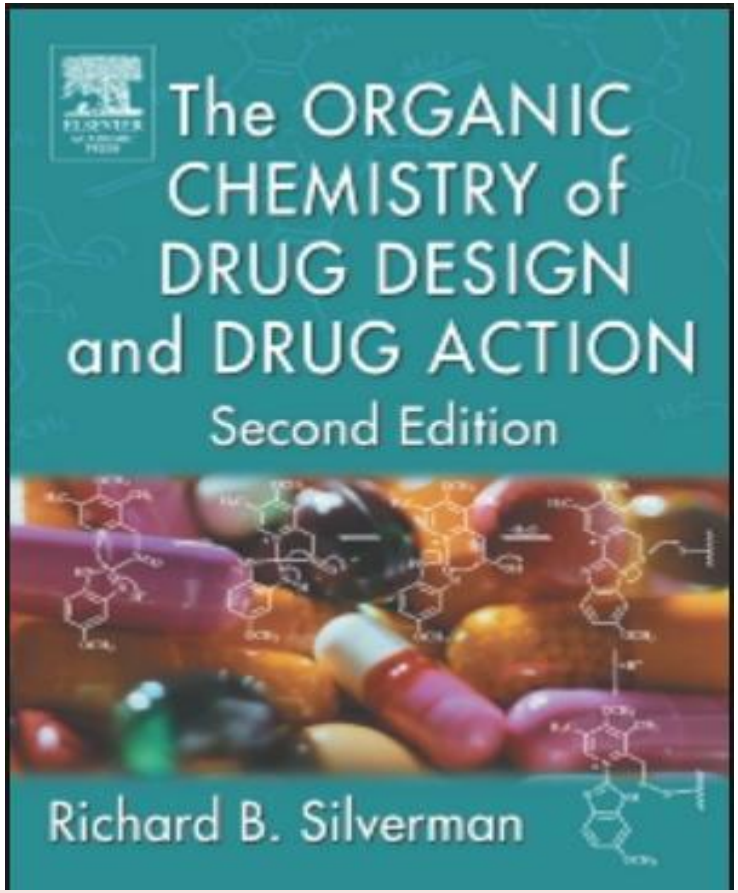
In this approach, the compounds having some structural similarity to a weakly active agents or compounds having different functional groups than the lead compounds are tested selectively.

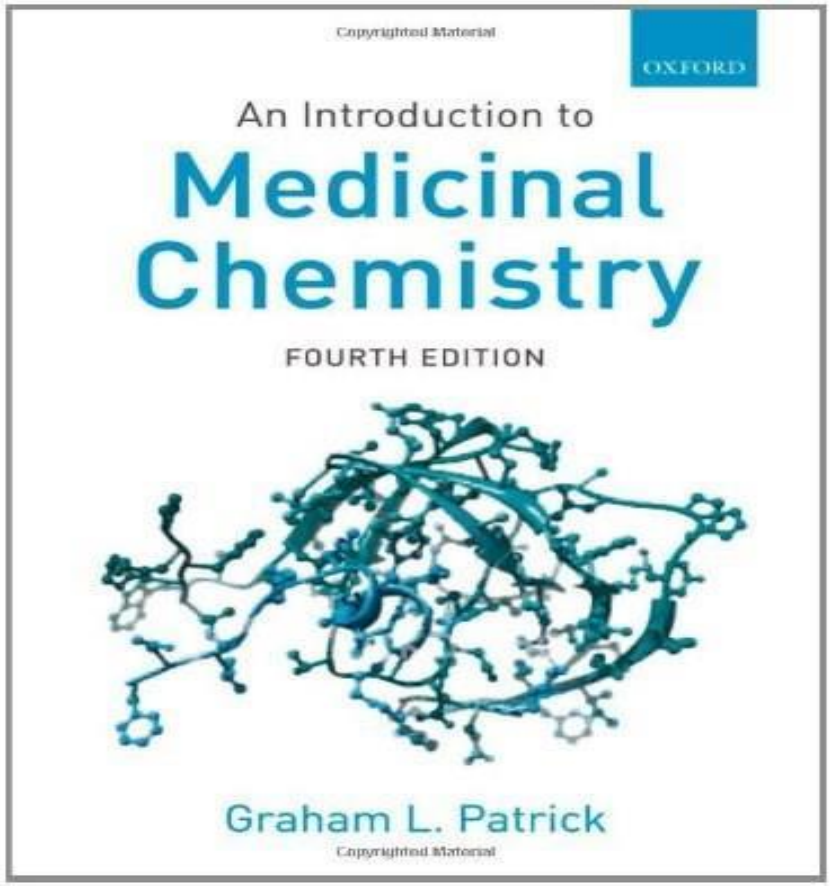
9. Computational approaches

In this approach, through the X-ray crystallography, knowledge of the binding site on the target is gained and utilized for the identification of lead compounds.

Also, using the chemical structures of the standard ligands, new lead compounds can be identified.

Recommended Books





1. The organic chemistry of drug design by Richard B. Silverman. Second edition, Elsevier, 2004.

2. An introduction to Medicinal Chemistry by Graham L. Patrick. Fourth edition, Oxford, 2009.


Thank
You