Medicinal Chemistry: The art of drug discovery
Developing new drug

1. Identifying target and developing activity assays.
2. Screening for a compound or rational design of a molecule with desired activity i.e. enzyme inhibition, binding to receptor.
3. Identifying a “lead”.
4. Optimizing the lead based on various factors.

From organic chemistry point of view the synthesis needs to provide high diversity and cost is not important.

Development of “scaled –up” procedures to make kilogram quantities for clinical trials.

Development of commercially viable process.
Once a “lead” compound is identified

Identification of pharmacophore and changes of the molecular structure in a “feedback loop” based on in-vitro and in-vivo tests

- efficacy
- toxicology
- pharmacokinetics (absorption, distribution, metabolism, clearance)

Molecular modification
- Shorting / lengthening side chains
- Adding/changing heteroatoms
- Changing rings
(some modifications are dictated by synthetic accessibility)
From lab to the medicinal chest: Phases of drug development

**Preclinical Testing**
- 3.5 Y
- Laboratory and animal studies for assessing biological activity and safety

**Clinical Trials**

- **Phase I**
  - 1 Y
  - 20-80 healthy volunteers
  - Determine safety and dosage

- **Phase II**
  - 2 Y
  - 100-300 patient volunteers
  - Evaluating effectiveness and looking for side effects

- **Phase III**
  - 3 Y
  - 1000-3000 patient volunteers
  - Monitoring long term use

**FDA**
- 2.5 Y
- Review/approval

**FDA Review/approval**
- 5,000
- Preclinical testing
- Clinical testing
- FDA approval

12 Years !!!
According to the Tufts Center for the Study of Drug development:

1987  $ 231 million
2002  $ 801 million

Critics claim that the this is inflated number and the cost is $110
Relatively soon after the discovery of HIV, researchers were able to elucidate the genetic structure of the virus -- a process that identified an array of structural and regulatory gene products. Within the pol region of the virion's genetic structure researchers found codons for HIV protease, reverse transcriptase, and integrase.
HIV life cycle

- **envelope**
- **receptor binding proteins**
- **capsid**
- **reverse transcriptase**
- **two copies of single stranded RNA**

**loss of envelope and cell entry**

**loss of capsid**

**synthesis of DNA strand (RT)**

**highly spliced RNA**

**integration into host chromosome**

**transcription by host**

**translation by host**

**Tat**

**Rev**

**envelope proteins**

**capsid proteins**

**cleavage by protease**

**polypeptide**

**translation by host**

**reverse transcriptase**

**virus assembly**

**virus budding**

**NUCLEUS**
AZT-like Drugs Inhibit Reverse Transcription

- AZT was one of the first nucleoside analogs shown to have potent anti-HIV activity in-vitro.
- AZT enters cells by passive diffusion, and appears to be phosphorylated by the same enzymes that convert thymidine (dT) to dT-5' TP.
- AZT-triphosphate (AZT-TP) is the active species, acting as a chain terminating substrate for HIV reverse transcriptase (HIV-RT) during either first or second strand DNA synthesis.
HIV Protease

- When viral RNA is translated into a polypeptide sequence, that sequence is assembled in a long chain that includes several individual proteins (reverse transcriptase, protease, integrase). Before these enzymes become functional, they must be cut from the longer polypeptide chain. Viral protease cuts the long chain into its individual enzyme components which then facilitate the production of new viruses.
HIV Protease

HIV-1 protease, is essential for the maturation of new virus particles

Although the genetic sequence of the HIV protease enzyme was described soon after the discovery of the virus itself, the three-dimensional structure of the gene was not demonstrated until several years later, when the protease gene product was expressed and crystallized.

Once the structure had finally been identified, researchers were able to begin designing compounds that specifically targeted the active site of the HIV protease.
**HIV Protease inhibitors**

HIV-1 protease, is essential for the maturation of new virus particles

The enzyme is a homodimer (two identical subunits) with 100 amino acids per subunit. Two Asp residues (Asp 25 in both chains) are critical for activity

The enzyme cleaves peptide bonds between a bulky aromatic residue and a proline.

The 'normal' substrate for HIV-PR is the following:
**Mode of action**

The mechanism is general acid-base catalysis mediated by the two aspartate.

- Asp residue deprotonate water molecule to form a better nucleophile.
- The transition state is tetrahedral (sp3 carbon) were the negative charge is stabilized by the other Asp residue
**Transition state analogs**

Transition state analog mimic the structure of the transition state but are not cleaved by the enzyme. The analog should bind to the enzyme with higher affinity then the natural substrate.

For HIV protease:

- It has to have a tetrahedral center.
- It should contain OH that will be bound to the Asp.
- Resemble the overall structure of the substrate.
Chemical challenges

6 chiral centers therefore

64 possible stereoisomers!

Saquinavir

INVIRASE® (saquinavir mesylate)
Antidepressant drugs are medicines that relieve symptoms of depressive disorders.

Depressive disorders may be either unipolar (depression alone) or bipolar (depression alternating with periods of extreme excitation). The formal diagnosis requires a cluster of symptoms, lasting at least two weeks.

Antidepressant agents act by increasing the levels of excitatory neurotransmitters.

The main types of antidepressant drugs in use today are: tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and selective serotonin reuptake inhibitor (SSRIs or serotonin boosters).
Neurotransmitters
Serotonin (5-hydroxytryptamine, 5HT), a monoamine neurotransmitter, plays an important role in many behaviors including sleep, appetite, memory, sexual behavior, neuroendocrine function, and mood.

Serotonin is synthesized from the amino acid precursor tryptophan, packaged into vesicles, and released into the synapse following an action potential. Once in the synapse, serotonin can interact with both the pre- and postsynaptic receptors. However, immediately after reacting with the pre- and postsynaptic receptors, it is critically important that serotonin be removed from the synapse.

Re-uptake, the process of removing transmitters after release, determines the extent, duration, and spatial domain of receptor activation. Any transmitter not removed from the cleft prevents further signals from getting through. Active removal reduces the level of transmitter in the cleft faster than diffusion, constrains the effects of released transmitter to smaller areas, and allows at least part of the released chemical to be recycled for further use. Re-uptake is carried out by transporter proteins which bind to the released transmitter and carry it across the plasma membrane into the presynaptic neuron.
Serotonin activity

Serotonin containing vesicle
Serotonin transporter
Synaptic knob
SSRI
Synaptic gap
Receiving neuron
Serotonin receptors

Serotonin

Serotonin reuptake

HO

\[
\text{Serotonin} \\
\text{Reuptake}
\]
**Selective serotonin reuptake inhibitors (SSRIs)**

Selective serotonin reuptake inhibitors maintain levels of the excitatory neurohormone serotonin in the brain.

Because of increased selectivity as compared to previous drugs (such as tricyclics and non-selective MAO inhibitors which have affinity for amines, acetylcholine, and norepinephrine transporters), SSRIs produce significantly fewer unwelcome side effects because they work exclusively on serotonin pathways.

SSRIs include fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft)
**Fluoxetine (prozac)**

In 1970 diphenhydramine, an antihistamine, was found to inhibit monoamine uptake; analogs began being built from in the phenoxyphenylpropylamine series.

CF₃ at *para* position significantly reduces affinity for NE uptake sites. Blocking NE uptake sites was a major problem with MAO inhibitors. (When taking MAOI and certain foods induce the synthesis of NE (a vasoconstrictor) is triggered. MAO usually breaks down NE, but since it is inhibited, it cause hypertension and can cause death).

Fluoxetine blocks SERT activity immediately, however, therapeutic effects are seen only after 2-3 weeks of treatment. A patient given Prozac may experience greater depression before feeling better.
Synthesis of fluoxetine (Prozac)