Medicinal Chemistry: An Overview

Course Outline

Lecture	Date	Topic
1	2015/12/17	General Aspects of Medicinal Chemistry
2	2016/01/07	General Biochemistry
3	2016/01/21	Principles of Chemical Synthesis
4	2016/02/04	Chemical Synthesis of Small and Complex Molecules
5	2016/02/18	Chemical Synthesis of Peptides
6	2016/04/07	Strategies for Discovering Lead Compounds
7	2016/04/14	Structure Activity Relationship
8	2016/04/21	Spatial Organization, Receptor Mapping and Molecular Modeling
9	2016/04/28	Pharmacokinetic Properties
10	2016/05/12	Legal and Economic Aspects of Drug Development

Hits and Leads

A hit is an active substance that has a selective activity for target. The hit should:

1. have reproducible activity
2. identified structure and high purity
3. be specific for the target
4. has potential for novelty
5. molecules having a certain affinity for a target

Subsequent evaluation of the hit produces the lead.
Evaluation of the hit includes:

1. *in vitro* and *in vivo activity*
2. no human ether-a-go-go-related (hERG) toxicity
3. unambiguous structure-activity relationships (SAR) by analogs of the hit
4. investigation of the ADME and physiochemical properties of the hit series
5. absence of reactive functional groups
6. patentability

A brief toxicological study on the lead generates the “clinical drug candidate”.

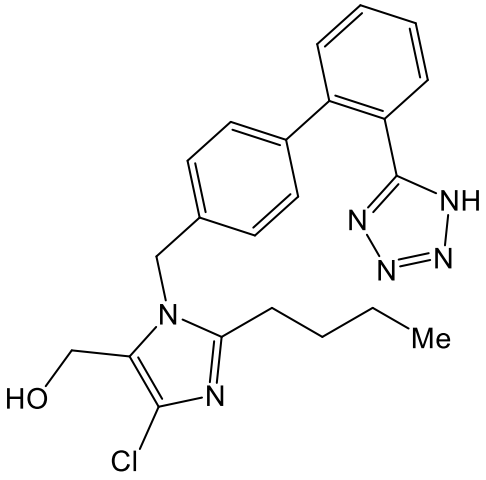
Main Hit or Lead Generating Strategies

1. Analog design
2. Systematic screening
3. Exploitation of biological information
4. Planned research and rational approaches
5. Application of biophysical and computational methods

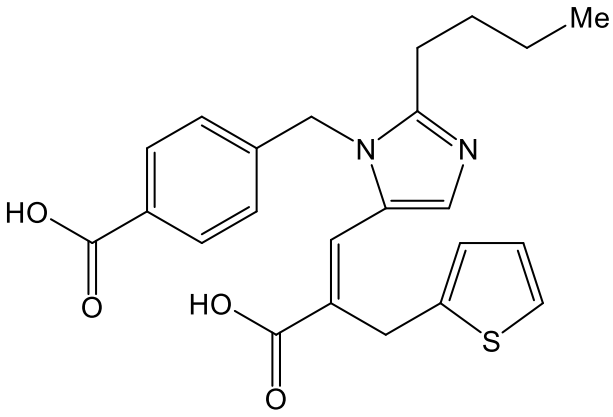
Analog Design

Analog design involves the synthesis of analogs of existing active molecules resulting in the generation of “follow-on” or “me-too compounds”, which are suppose to be more potent, more safe, more selective or easier to handle by physicians and nurses.

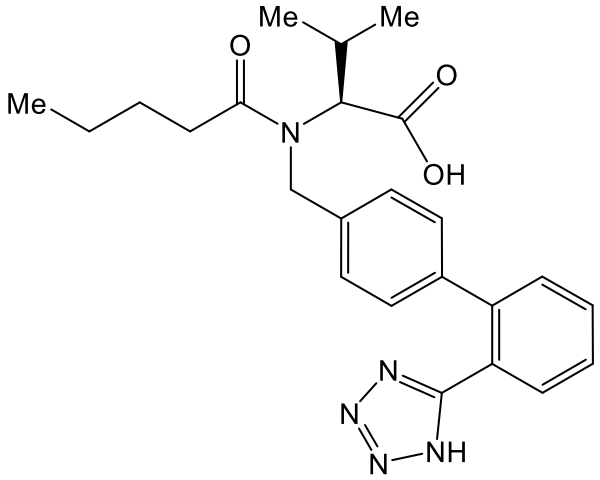
Angiotensin AT1 anatagonists derived from losartan.



Losartan
Dupont (1986/1994)



Eprosatan
SmithKline Beecham (1989/1997)



Valsartan
SmithKline Beecham (1990/1996)

While analog design guarantees an active drug, it lacks originality.

Systematic Screening

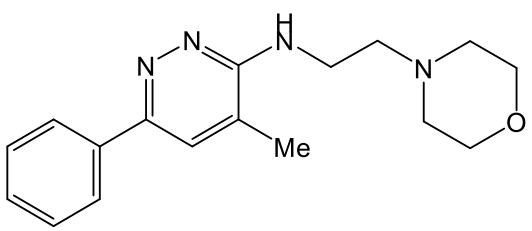
This involves the testing of compounds without having pharmacological or therapeutic potential of the compounds. The screening can either be random, extensive, or both as in the case of high-throughput screening (HTS).

Random screening involves the evaluation of several thousands of compounds in a limited number of experimental models. Extensive screening entails the evaluation of a limited number of molecules in many experimental models.

Screening of synthetic intermediates.

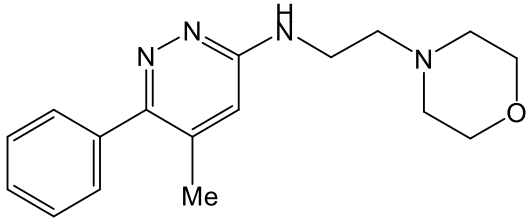
Selective optimization of side activities (SOSA). In this approach, well-known drugs are screened for new pharmacological targets.

Transformation of minaprine to a potent and selective muscarinic M1 agonist.

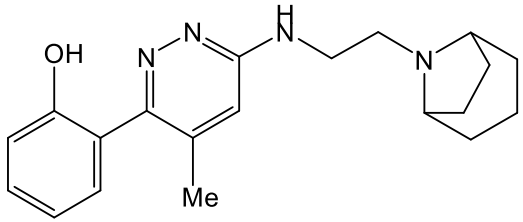


Minaprine

(an antidepressant with a weak affinity for muscarinic M_1 receptors: IC_{50} = 17,000 nM)



(IC_{50} = 550 nM)

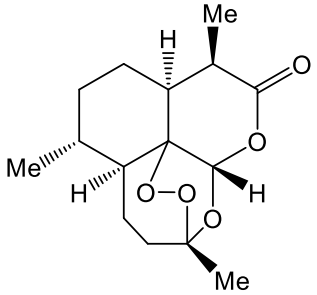


(IC_{50} = 3 nM)

Exploitation of Biological Information

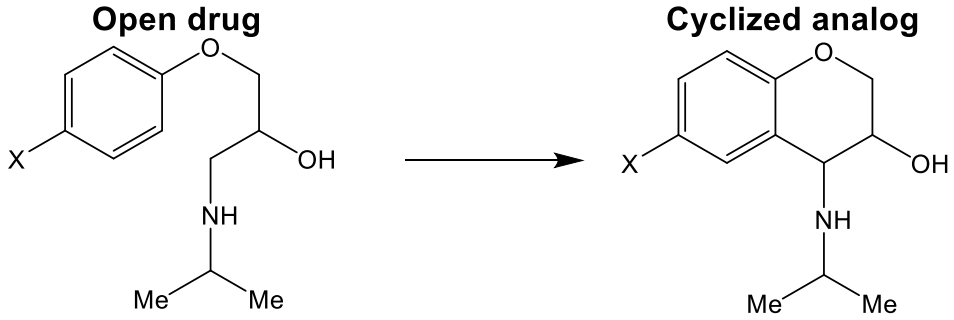
Utilization of observations made in humans, in animals, in the plant kingdom, and in microbiology.

1) Ethnopharmacolgy: study of indigenous medicines.



Artemisin (an antimalaria agent)

2) Observation of the side effects of medicines.



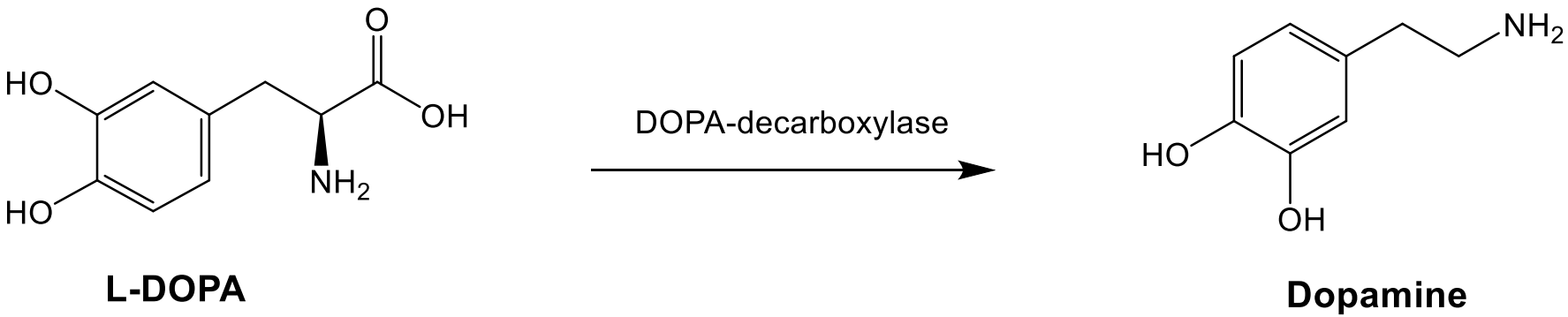
The "open" form has hypotensive and β-blocking properties while the cyclized analog is devoid of the β-blocking properties.

3) Repurposing of old drugs: the thalidomide story.

4) Accidental discovery of activities of industrial chemical products: the strong vasodilating properties of nitroglycerine in workers led to it use as a cerebral dilator.

Planned Research and Rational Approaches

L-DOPA and Parkinsonism



L-DOPA **Dopamine**

Compared to healthy people, parkinsonism patients have low levels of dopamine in the basal ganglions of the brain. Hence a rational therapy involving administration of L-DOPA, a BBB-penetrant molecule and precursor of dopamine, was invented. Decarboxylation of L-DOPA by brain DOPA-decarboxylase increases dopamine levels in the brain.

However, to increase the bioavailability by oral administration, a peripheral inhibitor of DOPA-decarboxylase is added to the treatment.

Application of Biophysical and Computational Methods

Availability of the three-dimensional structures of protein targets can accelerate drug discovery.

Biophysical Methods

- protein cystallization
- ligand-protein co-crystallization and soaking
- ligand-protein H^3 and N^{15}-NMR
- surface plasmon resonance
- differential scanning fluorimetry
- mass spectrometry

Computational Methods

- virtual screening
- computational drug repurposing
- scaffold hopping

Conclusion

The discovery of novel lead compounds is unpredictable. However, when a lead is found, its conversion into a drug should be done in a rational way.

Next Lecture (to be decided)

Structure Activity Relationship: tuning of the chemotype to get the desired phenotype.