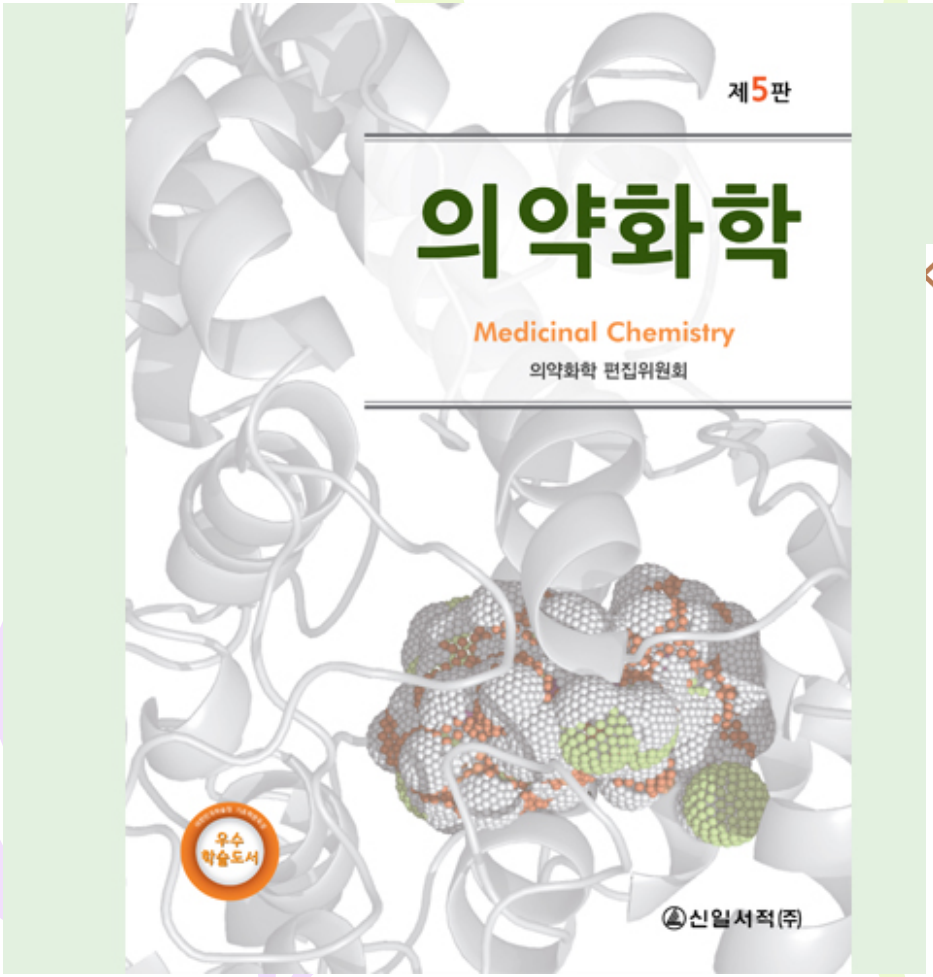
Medicinal Chemistry for

Drug Discovery & Drug Development

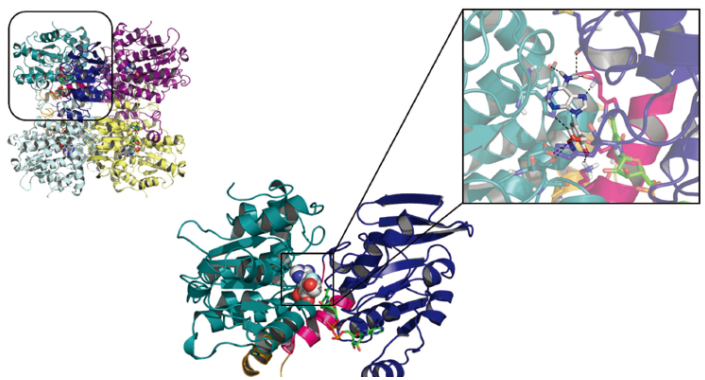


Chaper. 01

의약화학과 신약개발

Medicinal Chemistry and Drug Development

S-Adenosylhomocysteine hydrolase에 fluoroneplanocin A가 co-crystallized 된 complex (PDB ID: 3NJ4)



Medicinal Chemistry for

Drug Discovery & Drug Development

Drug discovery is the process by which new candidate medications are discovered.

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research, filing for regulatory status, such as via the United States FDA for an investigational new drug (IND) to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug.

신약개발과정

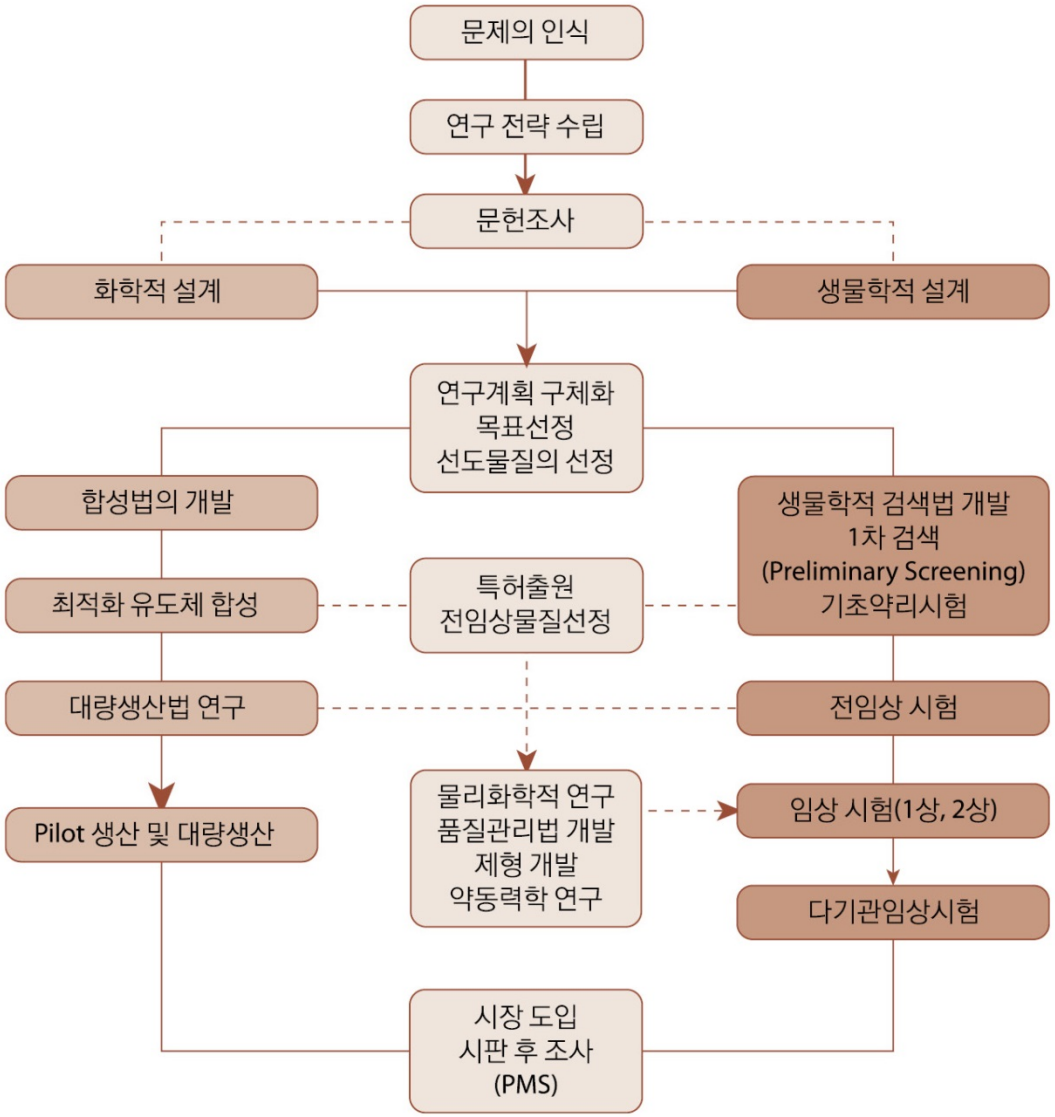


그림 1-1 신약개발 과정

신약개발과정 (미국 기준)

(new drug application, NDA)

신약허가 절차과정 (1년)

1,000-5,000명 환자를 대상으로 장기적 사용에 의한 효능 및 부작용을 확인함

임상3상 (3-4년)

100-500명의 환자를 대상으로 효능 및 부작용에 대한 평가가 수행됨

임상2상 (2년)

20-100명의 건강한 자원자를 대상으로 약물의 안정성 및 용량을 평가함

임상1상 (2년)

IND

Discovery (1-3년) 및 전임상 (3-5년)

수많은 화합물 중 2-3종의 신약후보물질이 선택, 동물모델에서의 안정성, 효능 및 제제연구가 수행됨

* 한 개의 신약의 개발을 위해 평균 15년 정도의 시간

신약 탄생 확률

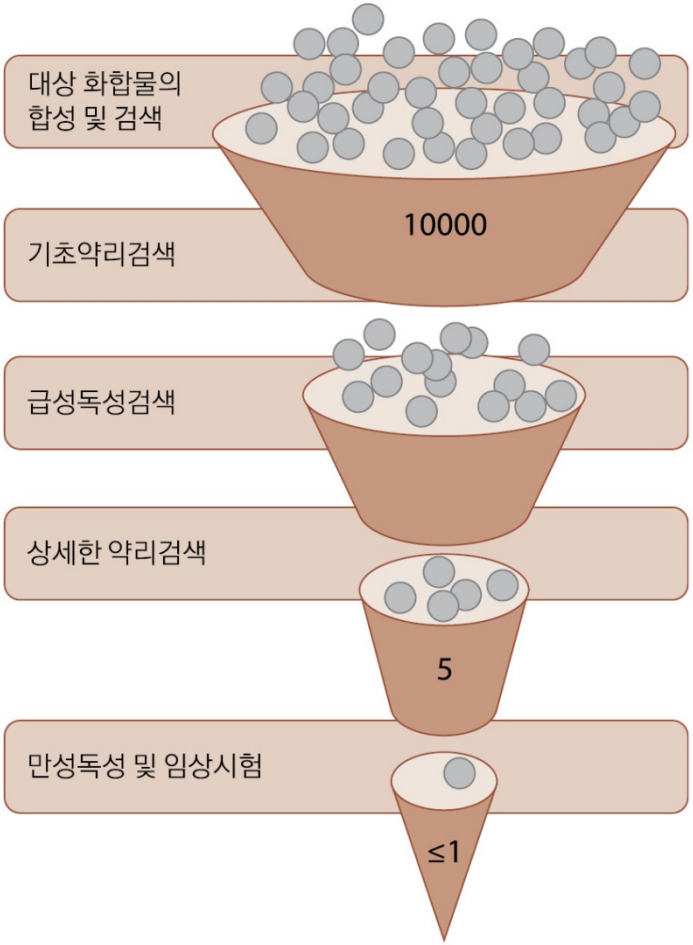


그림 1-2 신약의 탄생 확률

치료제에서 새로운 유용한 물질을 얻기 위해서는 합성하거나 천연물에서 추출하여 1980년대까지는 평균 8,000~10,000개의 화학 물질들을 검색하여야 하는 것으로 알려져 있다(그림 1-2). 그러나 최근에 들어서는 합리적 설계(rational design)가 발전함에 따라서 1000~2000개 정도의 화합물들의 합성으로도 유용한 화합물을 얻을 수 있게 되었다. 지난 50년 동안 신약의 90%가 회사에서 개발되었고, 9%가 대학이나 대학 부설 연구소에서 개발되었다. 그리고 1%가 정부연구기관에서 이루어졌다. 이것은 1950년대 대학교에서 50%가 이루어졌던 것과는 큰 변화이다. 이는 신약개발에 다양한 분야가 필요하고, 많은 연구비의 투자가 요구되기 때문이다.

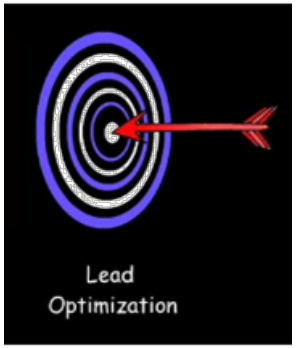
제약 기업들은 새로운 약의 연구와 개발에 예산의 10-15% 가량을 투자하고 있다. 이들의 연구에 대한 투자는

hit, lead, drug candidate ?

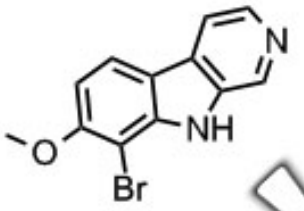
- **Hit compound (히트 화합물)**
  : compound with selective in vitro activity (usually $IC_{50} \leq 1uM$) against target whole organism and/or protein.

- **Lead compound (선도물질)**
  : compound with drug characteristics, and efficacious in disease animal model with no overt toxicity.

- **Drug candidate (신약 후보물질)**
  : optimized lead compound with in vitro and in vivo activity equivalent or better than drug standards, acceptable pharmacokinetic and toxicity profile, amenable to cost-effective scale-up.



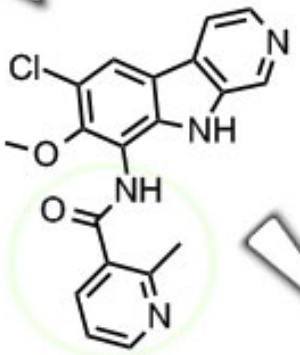
hit, lead, drug candidate ?



Screening hit

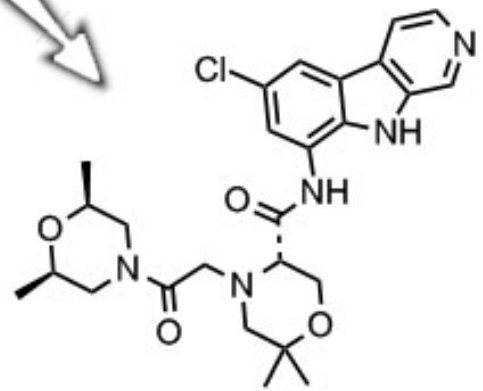
Lead identification

Lead:



선도물질 최적화
Lead optimization

Candidate:



Millenium's beta-carboline's

얼마나 많은 저분자유기화합물(Small Organic Molecules)이 존재 가능할까요?

Known Compounds (in Chemical Abstracts)

20,000,000

Theoretical Number of Small Organic Molecules
(Daylight Chemical Information Systems)

100,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000

1×10^{68}개

바닷가와 사막의 모래알 개수 7×10^{21}
별의 개수 7×10^{22}

- Dr. Simon Driver, of the Australian National University -

Hit or Lead discovery

Chaper. 01

의약화학과 신약개발

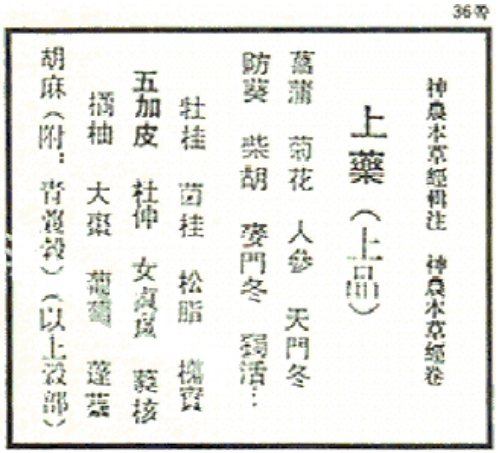
Medicinal Chemistry and Drug Development

약이 되는 물질을 찾아서…

고대 ~ 18세기 : 동식물의 추출물/혼합물, 광물질

BC 1552 : 이집트 Ebers Papyrus 고문서_ 700종 약품과 811종 처방전

Ad 250 (후한시대) : 신농본초경_ 365종 생약



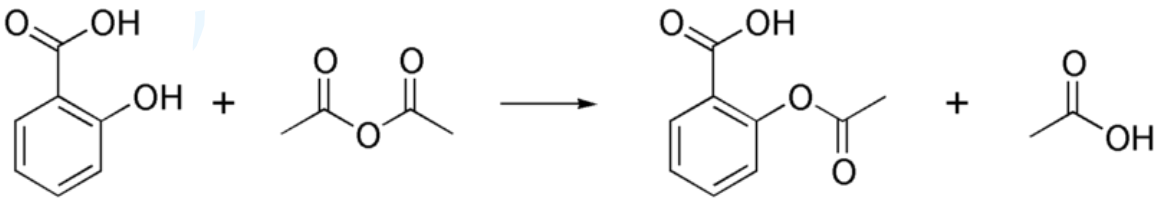
약이 되는 물질을 찾아서…

19세기 초반 : 생약에서 치료효과의 원인이 되는 약효성분 규명 시작

1806 : 아편에서 몰핀(morphine) 분리
1823 : 키나피에서 quinine 분리 _ 말라리아 치료제

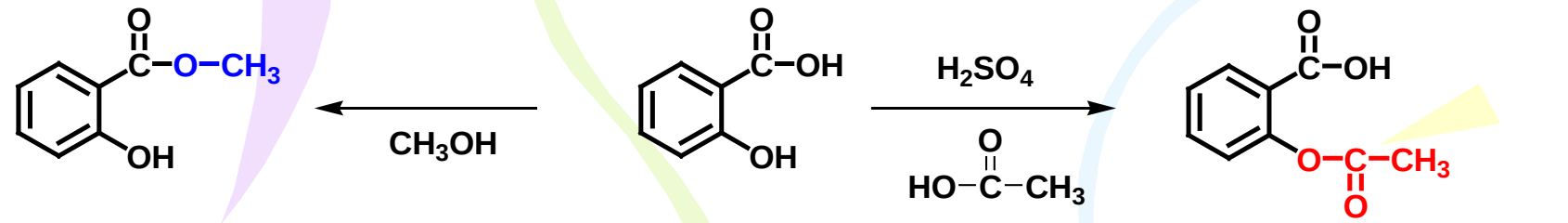
19세기 후반: 인공합성 화합물 사용 시작

1886 : 안티페브린 (acetanilide) 해열제 사용
1887 : 펜아세틴 (phenacetin)
1899 : 아스피린 사용 _ Bayer사의 Hoffmann 발명/발견?



유기 합성을 통한 화합물의 구조 변경으로 새로운 약물을 개발!

- 버드나무 껍질에서 추출
- 진통 해열작용이 있어 고대부터 약으로 이용됨
- 위벽을 자극하고 설사를 일으키는 부작용



Methyl Salicylate | **Salicylic acid** | **Acetyl-Salicylic acid** *(Aspirin)*

- 대표적인 진통 해열제
- 심혈관질환, 심장발작 예방제, 항암제

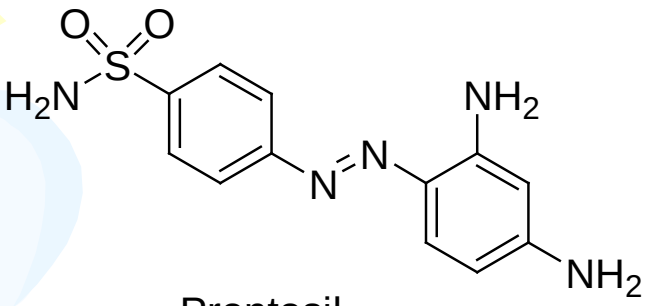
약이 되는 물질을 찾아서…

1900-1950 : 생약, 생체등에서 약효성분의 활발한 규명
: 유기화합물이 본격적으로 약품으로 사용

1911 : 비타민 규명 _ Funk
1929 : 페니실린 발견 _ Fleming; 항생제시대 열림
기타 : 인슐린, 아세틸콜린, 호르몬 …

1910 : 살바산 (Salvarsan; 606)_매독치료제 _ Paul Ehrlich
현대식 약물 발견의 효시
1932 : Prontosil 발견_ Domagk ; sulfa제 시대 개막_약물발견 방법의 전환

1932 : Prontosil 발견_ Domagk ; sulfa제 시대 개막_약물발견 방법의 전환

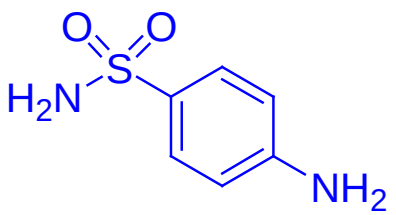


Prontosil

염료

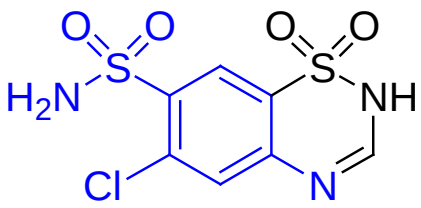
in vivo

Sulfa제의부작용: 혈당 감소, 이뇨

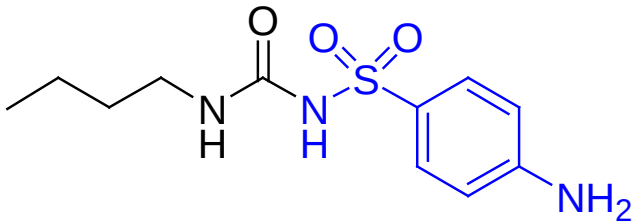


Sulfanilamide

화합물구조 변형



Chlorothiazide 이뇨제



Tolbutamide 혈당저하제

약이 되는 물질을 찾아서…

1950 이후 : 인접학문의 지식 도입하여 비약적 발전 시작

의약화학 (medicinal chemistry) : 학문분야로 정착

Medicinal Chemistry

- Discovery or Design of new therapeutic chemicals
- Development of such into useful medicines

Areas of Study

- synthesis of new compounds
- structure-activity relationships
- elucidating the mode of interaction with targets (receptors/enzymes/DNA)
- absorption, distribution, metabolism, and excretion (ADME)
- metabolic transformations
- pharmacogenetics

약이 되는 물질을 찾아서…

- 1960년대 이후
- 유기합성법의 괄목할 만한 발전 선도물질의 최적화 (lead optimization)을 이용한 신약의 발굴이 가능

- 1980년대 이후
- 질병의 원인을 규명할 수 있는 생물학의 발전과 컴퓨터의 발전으로 신약의 발견이 합리적 설계 (rational drug design)에 의한 기법으로 변형.

- 2000년 이후
- 최적화와 합리적 설계 기법과 더불어 적극적이고 합리적인 방법으로 lead identification을 수행하여 신약을 개발하는 방법으로 큰 변화
- 게놈시대가 열리게 됨에 따라 방대한 양의 유전정보로부터 나오는 functional genomics를 통해 그에 해당하는 단백질의 기능을 규명해서 질병치료에 가능성을 지닌 효소나 수용체를 찾아 화합물 라이브러리의 고효율 검색을 통하여 선도물질을 발굴하는 것이 가능해짐
- 컴퓨터 시뮬레이션을 이용한 가상검색 (virtual screening) 기법 도입.

선도물질 발굴 (Lead identification)

1. Serendipity and the Prepared Mind
2. Screening of Natural Products
3. Medical Folklore
4. Existing Drugs
5. Starting from the Natural Ligand or Modulator
6. Screening Synthetic Compound ‘Libraries’
7. Combinatorial Synthesis – Library
8. Computer-Aided Design (Rational Drug Design)
9. Computerized Searching of Structural Databases
   : Virtual Screening, 3D Pharmacophore Search

Etc.

Hit or Lead Compound을 찾는 법…

우연한 발견

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

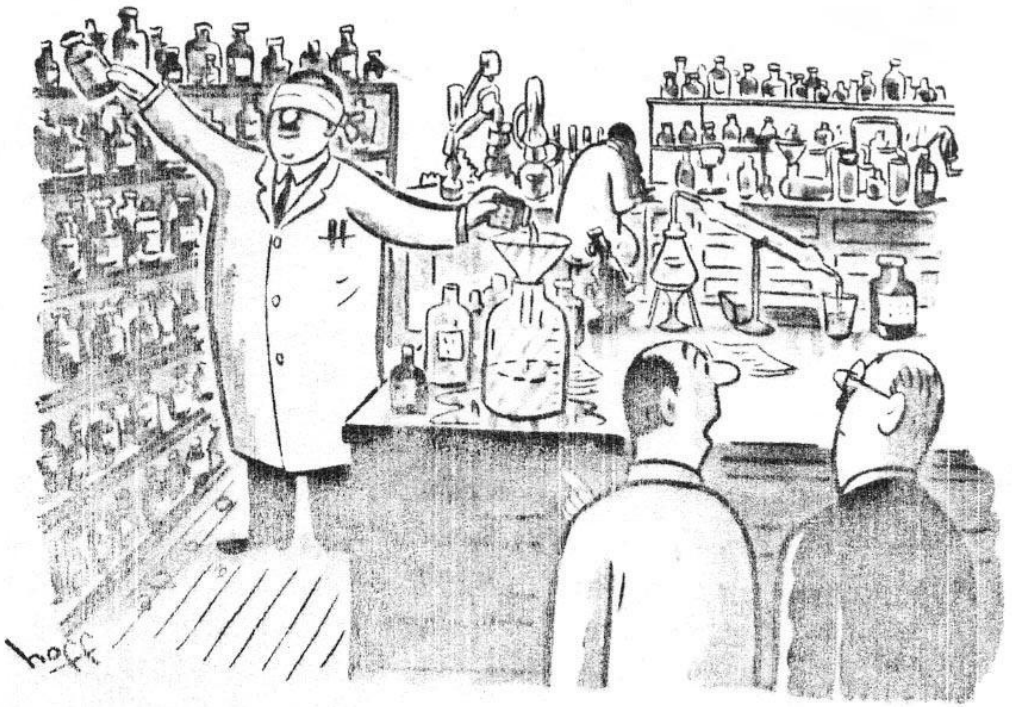
Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases



'That's Dr Arnold Moore. He's conducting an experiment to test the theory that most great scientific discoveries were hit on by accident.'

Drawing by Hoff; © 1957
The New Yorker Magazine, Inc.

Hit or Lead Compound을 찾는 법...

천연물과 전통약물로부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

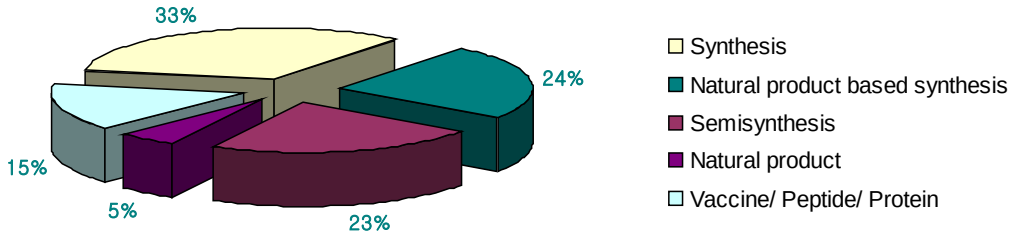
Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis – Library

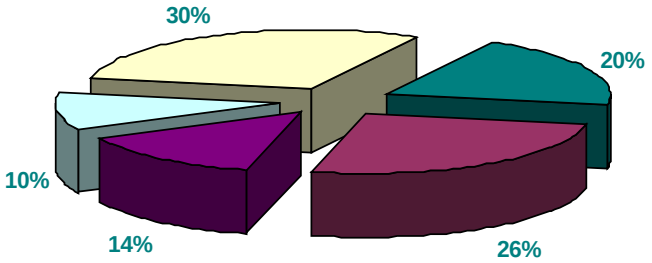
Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases

All new chemical entities, 1981-2002



All available anticancer drugs, 1981-2002



Hit or Lead Compound을 찾는 법…

기존약품으로부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

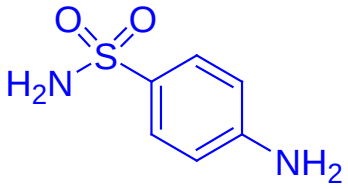
Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

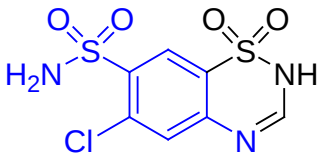
Computerized Searching of Structural dtabases

Sulfa제의부작용: 혈당 감소, 이뇨



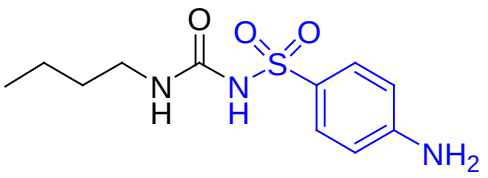
Sulfanilamide

화합물구조 변형



Chlorothiazide

이뇨제



Tolbutamide

혈당저하제

Hit or Lead Compound을 찾는 법…

기존약품으로부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis – Library

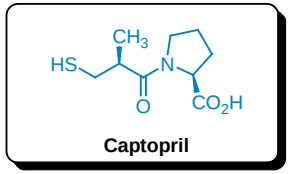
Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases

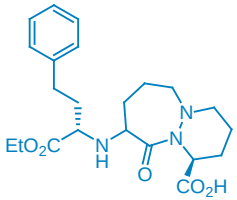
'Me too' drugs

: To modify the structure sufficiently such that it avoids patent restrictions, retain activity, and ideally has improved therapeutic properties.

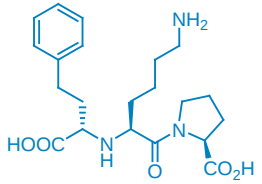
ex) captopril (antihypertensive drug) : used as a lead compound by various companies



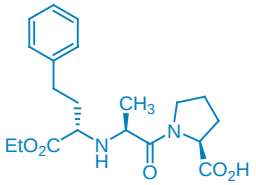
Captopril



Cilazapril
(Hoffmann-LaRoche)



Lisinopril
(Merck)



Enalapril
(Merck)

Hit or Lead Compound을 찾는 법…

생체내 존재하는 물질으로부터

- Natural ligands for receptors
- Natural substrates for enzymes
- Enzyme products as lead compounds
- Natural modulators as lead compounds

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

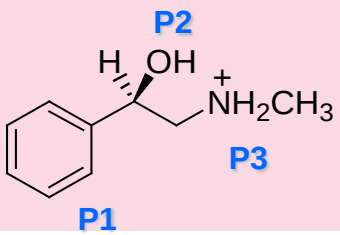
Screening Synthetic Compound 'Libraries'

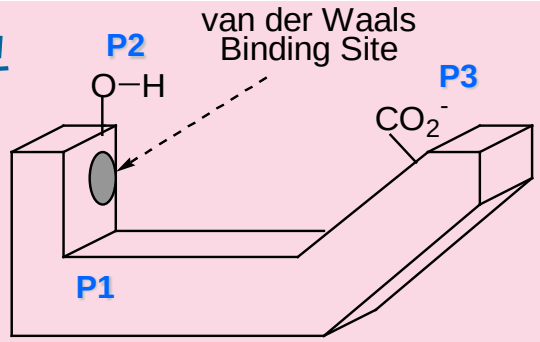
Combinatorial Synthesis – Library

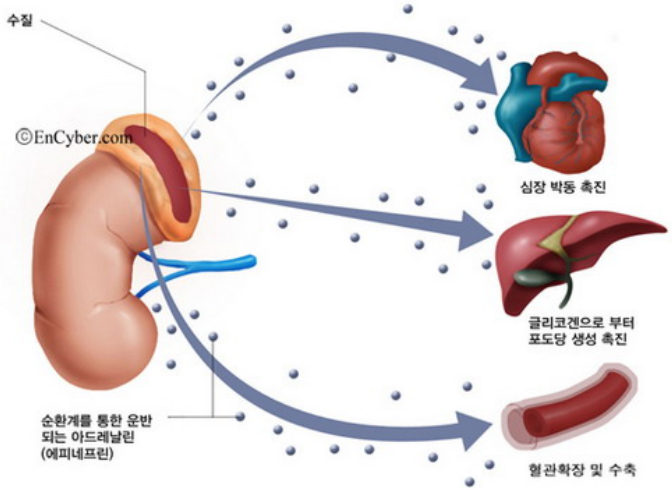
Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases

Epinephrine = 아드레날린







Hit or Lead Compound을 찾는 법...

생체내 존재하는 물질으로부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

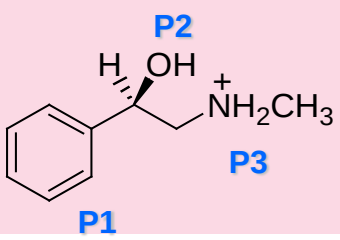
Screening Synthetic Compound 'Libraries'

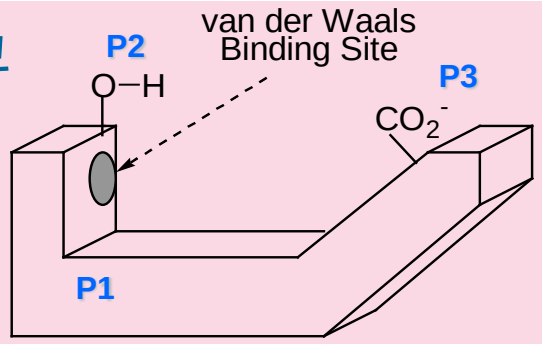
Combinatorial Synthesis – Library

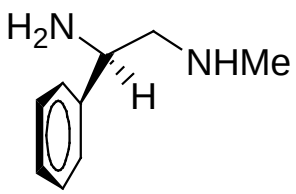
Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases

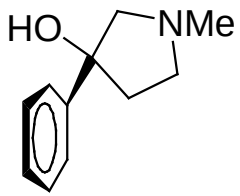
Epinephrine = 아드레날린



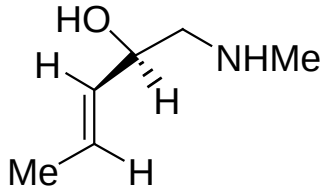




Isosteric substitution of hydroxyl



Conformational Constrained Analog



Isosteric substitution of phenyl

Hit or Lead Compound을 찾는 법...

(컴퓨터를 이용한) 합리적분자 설계

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis - Library

Computer-Aided Design

(Rational Drug Design)

Computerized Searching of Structural dtabases

합리적 약물 설계 (Rational drug design) :
논리적이고 이론적인 지식을 이용하여 새로운 약물의 구조를 설계하여 창조하는 것.

- 분자 또는 전자 수준에서 약리 기전과 작용 부위,
- 정성적이고 정량적인 구조와 활성의 관계,
- 약물 수용체와 약물 간의 3차원적인 모형도
- 약물과 수용체 결합의 형태,
- 약물의 특정 관능기의 약물학적인 효과,
- 약물과 관련된 물리화학적 변수와의 관계
- 화학적 또는 생화학적 반응 경로,
- 대사산물이나 세포 구성 물질의 생합성,
- 새로운 화학 요법제가 조사되는 과정에서 포유류와 기생충 사이의 차이점 등을 이용.

Hit or Lead Compound을 찾는 법…

(컴퓨터를 이용한) 합리적분자 설계

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modula

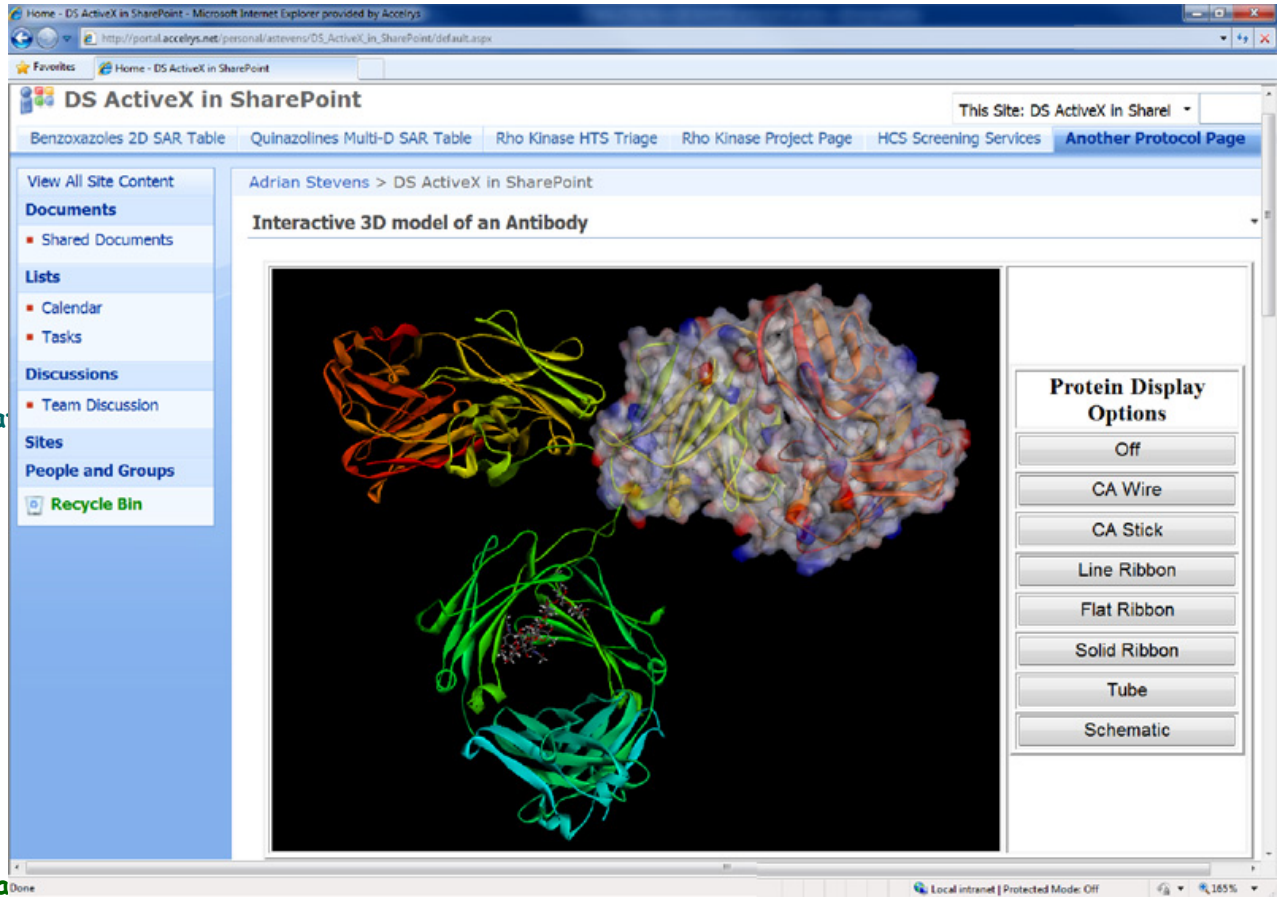
Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis – Library

Computer-Aided Design

(Rational Drug Design)

Computerized Searching of Structural dtaba



BIOVIA Discovery Studio

Hit or Lead Compound을 찾는 법...

(컴퓨터를 이용한) 합리적분자 설계

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

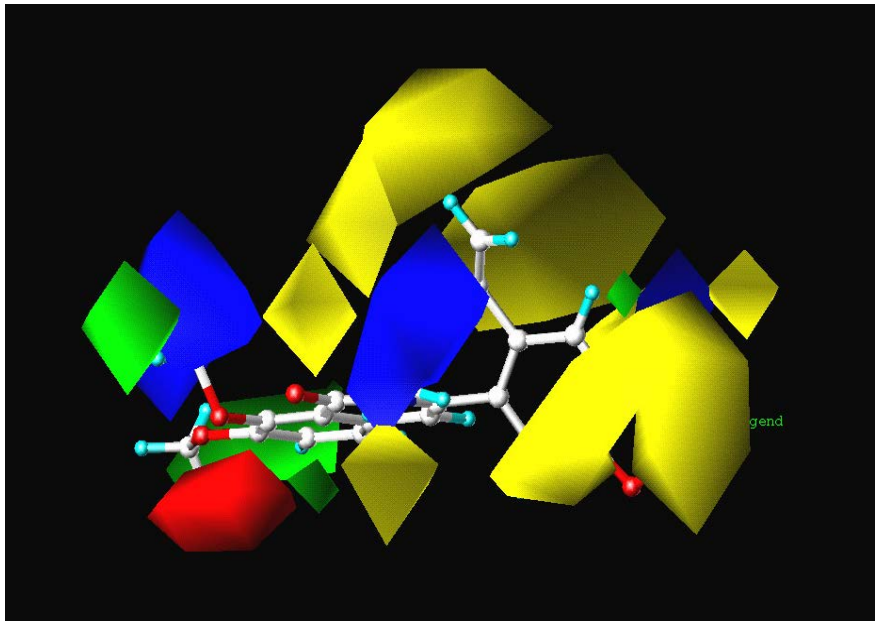
Combinatorial Synthesis - Library

Computer-Aided Design

(Rational Drug Design)

Computerized Searching of Structural dtabases

- 정성적이고 정량적인 구조와 활성의 관계,
- 약물과 관련된 물리화학적 변수와의 관계



Hit or Lead Compound을 찾는 법...

(컴퓨터를 이용한) 합리적분자 설계

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

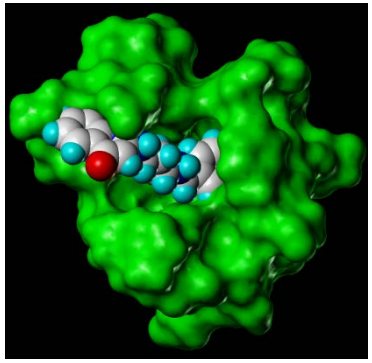
Combinatorial Synthesis - Library

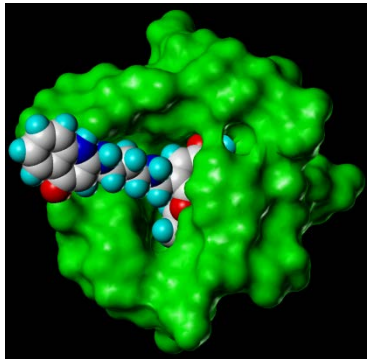
Computer-Aided Design

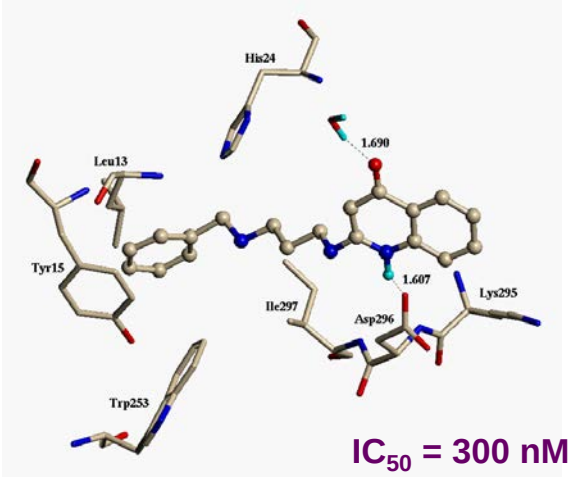
(Rational Drug Design)

Computerized Searching of Structural dtabases

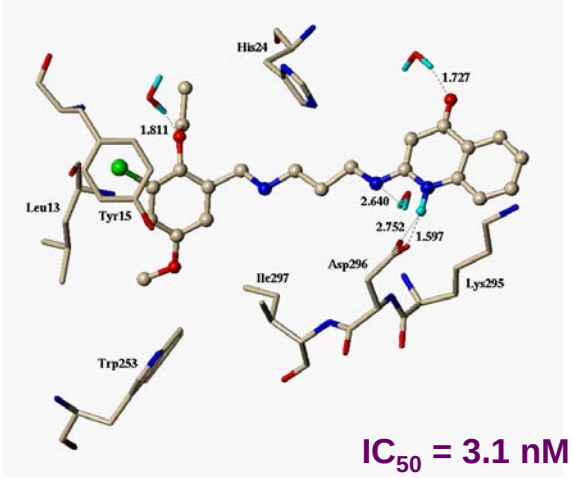
•약물 수용체와 약물 간의 3차원적인 모형도
•약물과 관련된 물리화학적 변수와의 관계







IC_{50} = 300 nM



IC_{50} = 3.1 nM

Hit or Lead Compound을 찾는 법…

(컴퓨터를 이용한) 합리적분자 설계

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

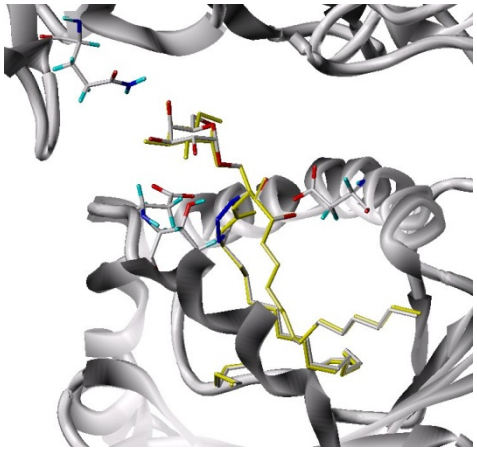
Combinatorial Synthesis – Library

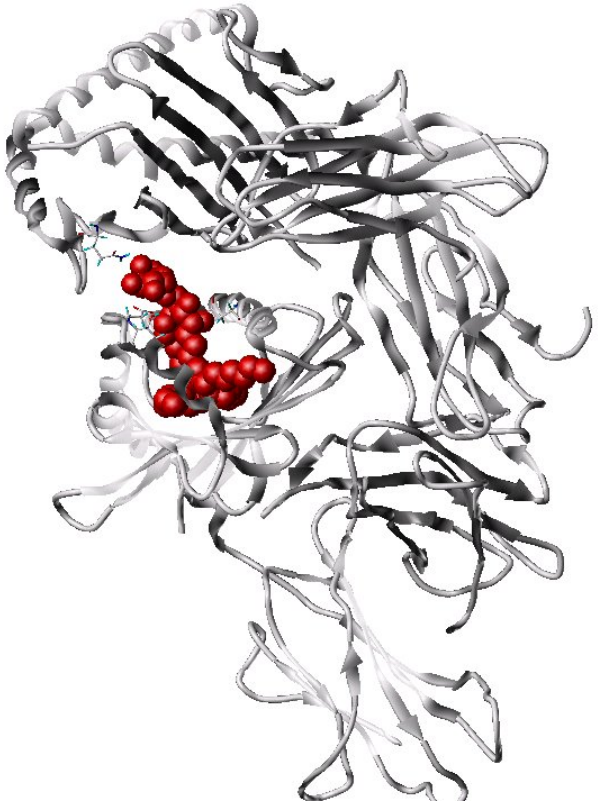
Computer-Aided Design

(Rational Drug Design)

Computerized Searching of Structural dtabases

•약물 수용체와 약물 간의 3차원적인 모형도





Hit or Lead Compound을 찾는 법…

(컴퓨터를 이용한) 약물 탐색

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

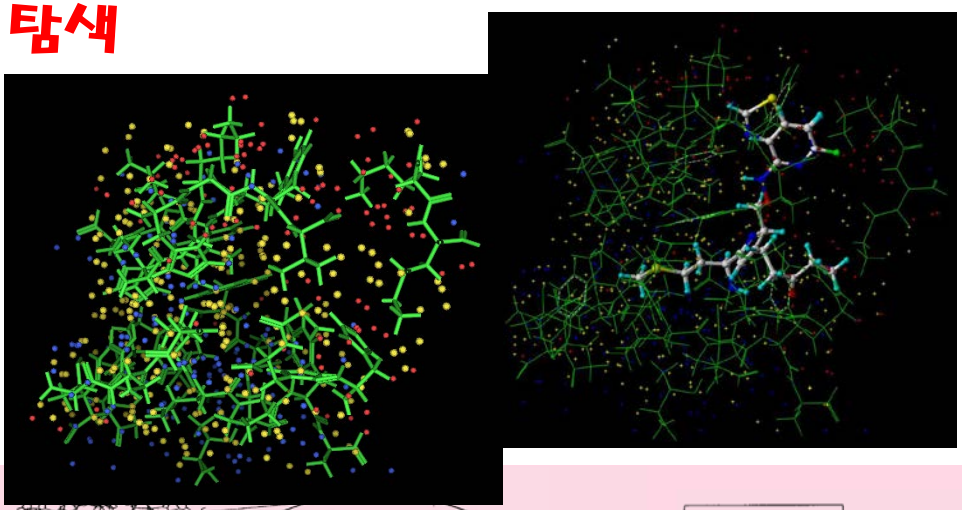
Screening Synthetic Compound 'Libraries'

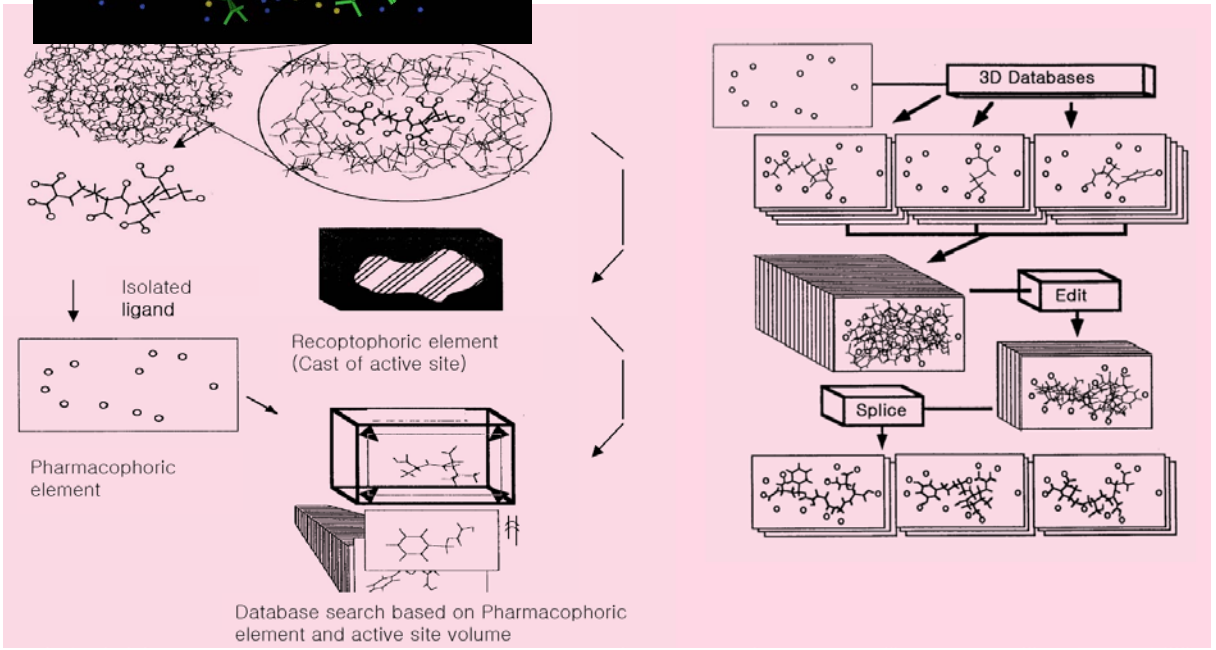
Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of

Structural databases





Hit or Lead Compound을 찾는 법…

(컴퓨터를 이용한) 약물 탐색

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Ma

Screening Synthetic Compound 'Libraries

Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of

Structural databases

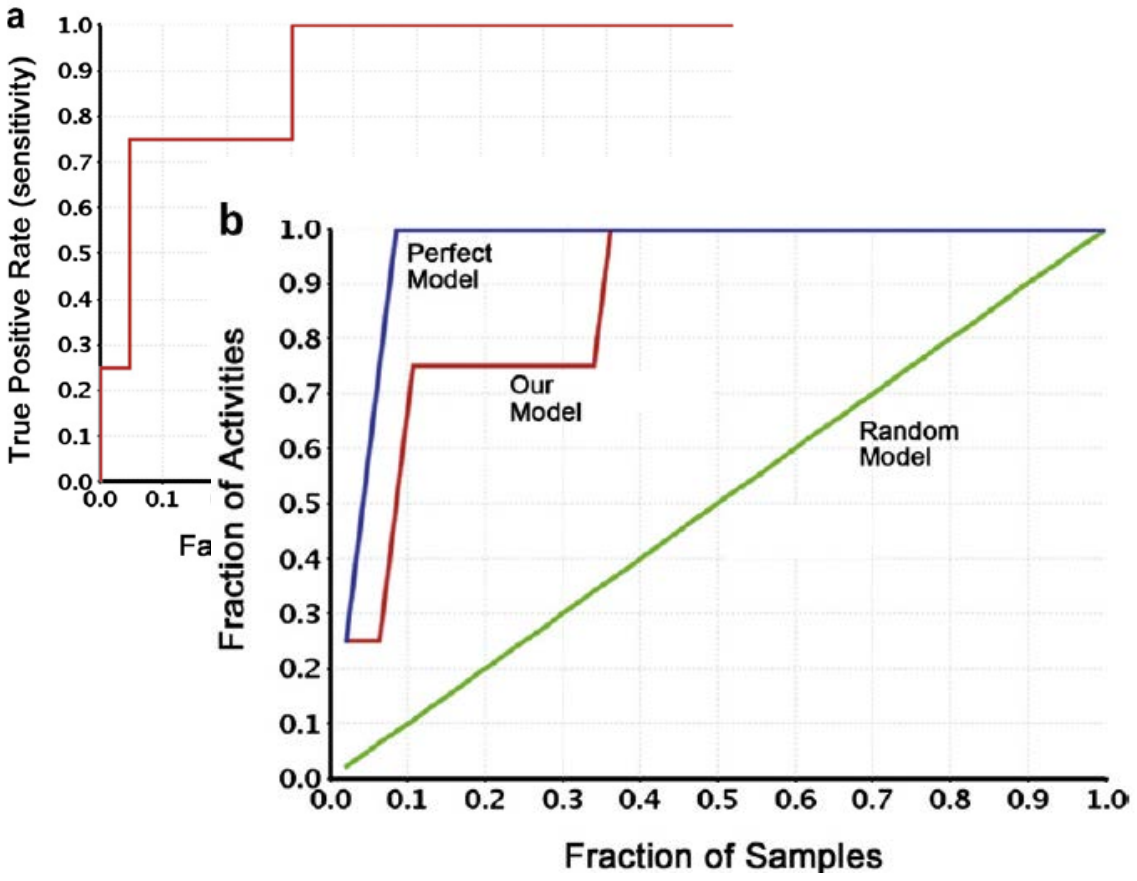


Figure 5. ROC and enrichment plots of the Laplacian-modified naïve Bayesian model for the test set.

Hit or Lead Compound을 찾는 법…

화합물 라이브러리 부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound

'Libraries'

Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases

A **chemical library** or compound library is a collection of stored chemicals usually used ultimately in high-throughput screening.

Hit or Lead Compound을 찾는 법…

화합물 라이브러리 부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound

'Libraries'

Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

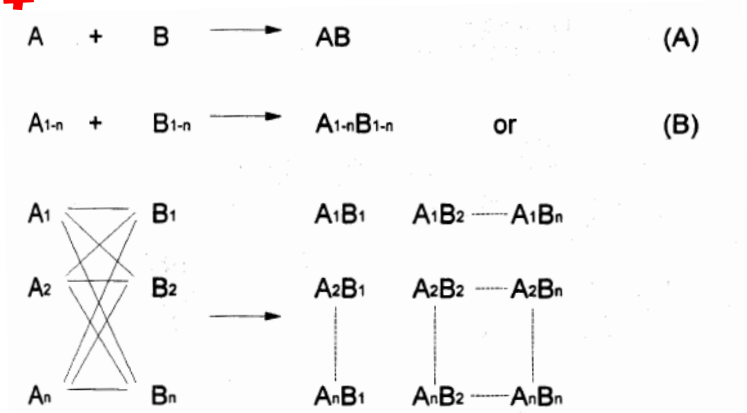
Computerized Searching of Structural dtabases

HTS (High-throughput screening)

Today's HTS rate; 10,000 of compounds per assay per day.

Hit or Lead Compound을 찾는 법...

조합화학을 이용한 화합물 라이브러리 부터



Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

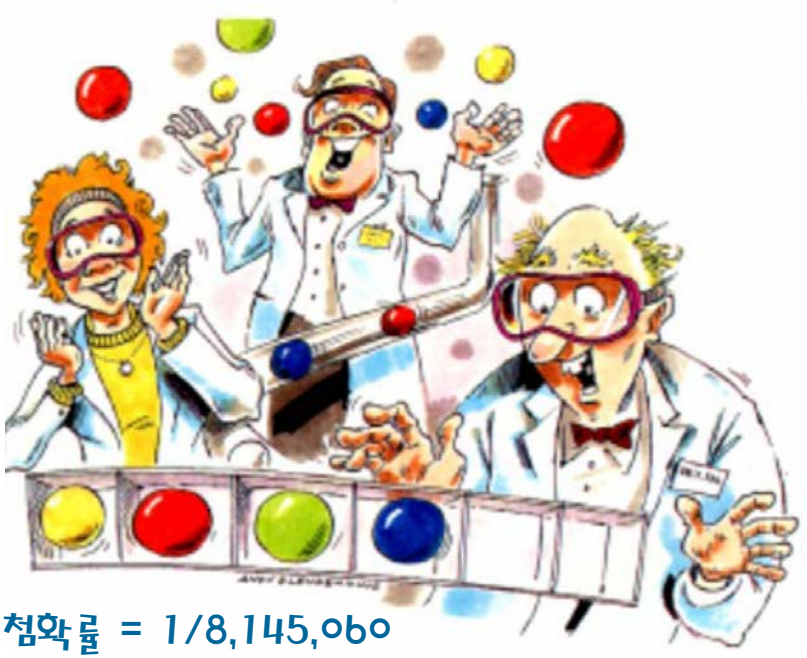
Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis - Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases



로또 1등 당첨확률 = 1/8,145,060

Hit or Lead Compound을 찾는 법...

조합화학을 이용한 화합물 라이브러리 부터

Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

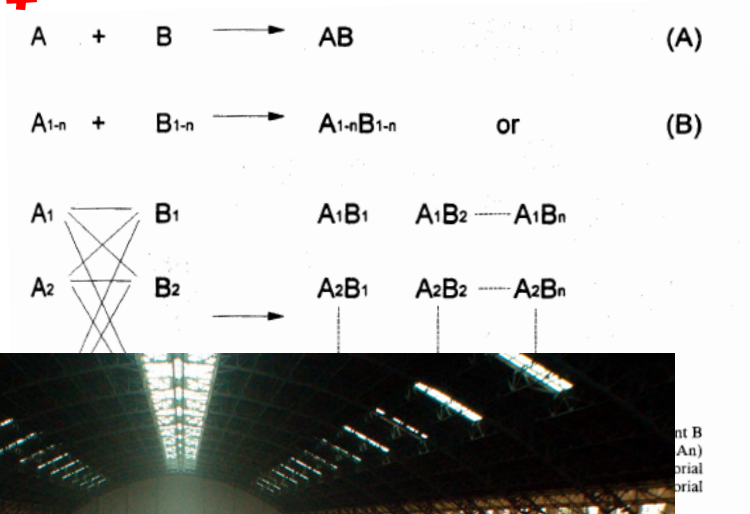
Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis - Library

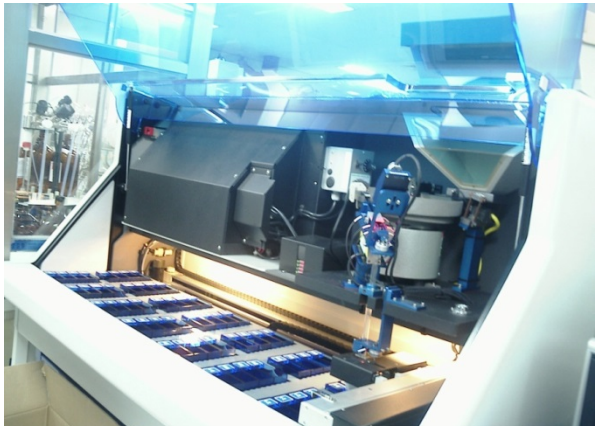
Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases



Hit or Lead Compound을 찾는 법…

조합화학을 이용한 화합물 라이브러리 부터



Serendipity and the Prepared Mind

Screening of Natural Products

Medical Folklore

Existing Drugs

biological testing → chemical synthesis

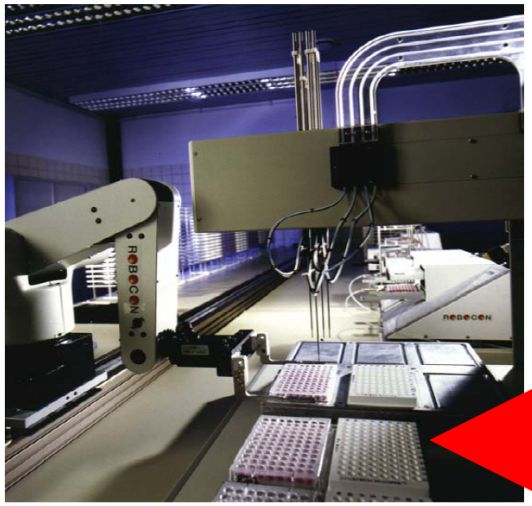
Starting from the Natural Ligand or Modulator

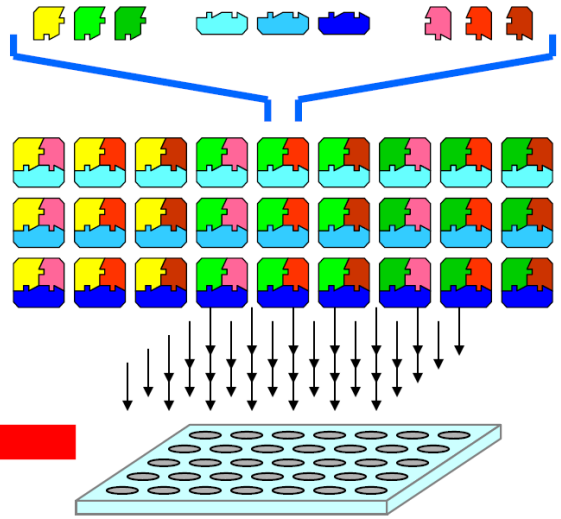
Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis – Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases





Hit or Lead Compound을 찾는 법...

Serendipity and the Prepared Mind

Screening of **Natural Products**

Medical Folklore

Existing Drugs

Starting from the Natural Ligand or Modulator

Screening Synthetic Compound 'Libraries'

Combinatorial Synthesis - Library

Computer-Aided Design (Rational Drug Design)

Computerized Searching of Structural dtabases

선도물질의 최적화 (Lead optimization)

- ✓ 기본적으로 이미 알려진 생물학적 활성을 가진 화학 물질을 선도 화합물 (lead compound)로 하여 구조적으로 유사한 화합물이나 유도체를 합성하여 보다 유용한 약효를 갖는 화합물을 찾는 것.
- ✓ 선도물질의 구조 변형을 이용한 신약 발견 발견이 오늘날 가장 유용한 방법으로 의약화학의 요체

구조 변형에 의한 신약의 발견 방법이 효율적인 이유 by Schueler

- 무작위로 선택되거나 합성된 화합물 보다는 선도 화합물과 유사한 동족체, 유도체 화합물이 유사한 약리학적 성질을 가질 가능성이 크다.
- 약리학적으로 더 우수한 화합물을 얻을 수 있는 가능성이 크다.
- 유사성으로 인하여 새로운 약물 발견이 경제적일 가능성이 높다.
- 선도 화합물과 유사한 화합물을 합성 함으로서 생산법의 개발이 용이하다.
- 구조 활성 관계를 명확히 할 수 있는 정보를 수집할 수 있다.
- 선도 화합물에 적용한 생물학적 시험법과 같은 시험 법을 사용할 수 있다.

구조의 최적화 또는 구조 변형의 목적/방법

- ✓ 선도 화합물의 효능, 독성, 선택성, 작용 시간, 투여, 취급, 안정성 및 생산가격 등에서 보다 더 바람직한 성질을 갖는 약물 획득하는 것.
- ✓ 구조활성 관계 (structure activity relationship)를 이해하여 약물이 약리학적 작용을 나타내기 위한 분자의 형태인 **필수적인 약리단 (pharmacophoric moiety)을 발견하여 이용.**

약리단 (pharmacophoric moiety) 발견

Identification of Pharmacophore

Need to established the relevant functional groups important for activity or interact with the target (enzyme, receptor, etc.)

Modifications to lead compound

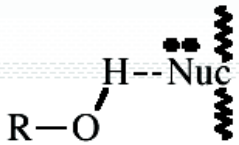
- remove structural feature
- exaggerate structural features
- block structural features

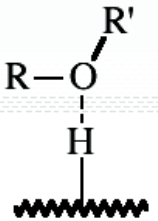
Functional groups most easily modified:

- Hydroxyl (-OH)
- Amino (-NH_2, -NH_R,-NR_2)
- Aromatic Rings
- Double Bonds

Hydroxyl Group

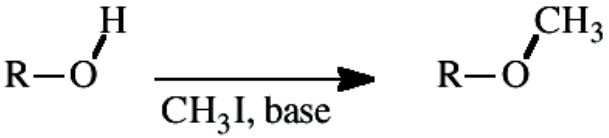
Potential H-Bond Interations (H-donor or H-acceptor)



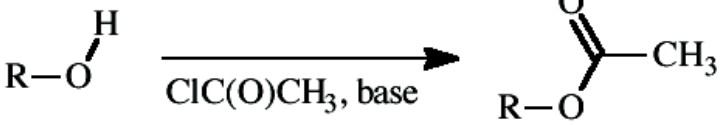


Modifications to destroy these interactions:

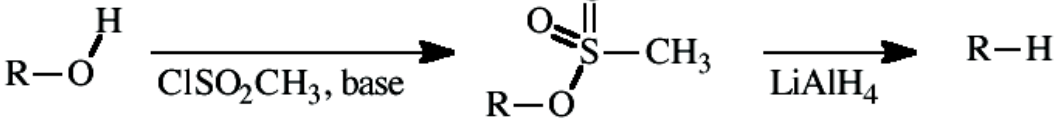
- Alkylation



- Acylation

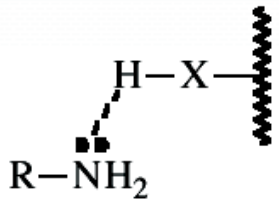


- Reduction

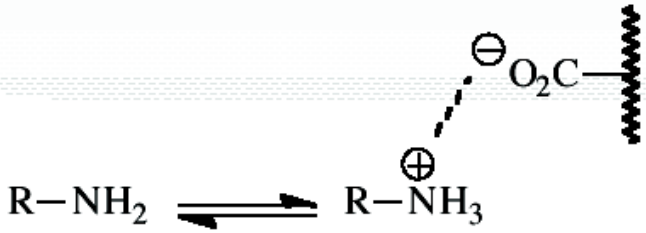


Amino Group

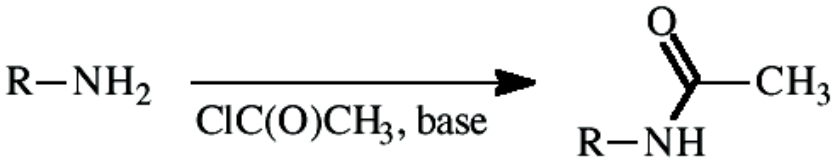
Potential H-Bond (H-acceptor)



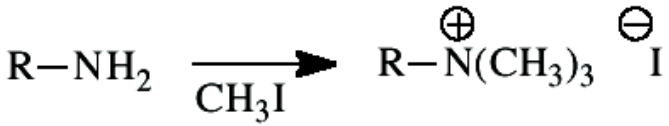
Possible Ionic interactions



- Acylation

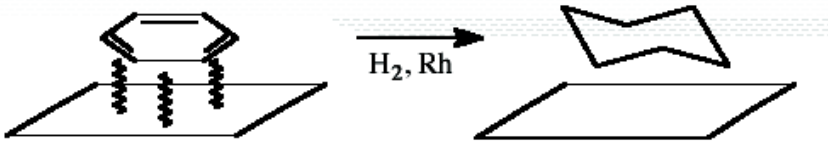


- Alkylation



Aromatic Rings

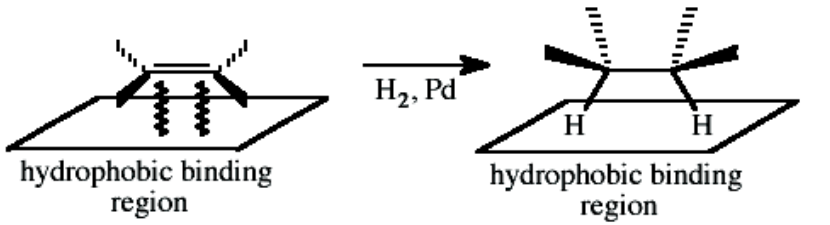
Involved in van der Waals interactions with “flat” hydrophobic regions in binding site.



(unfavorable interaction; sterics?)

Double Bonds

Similar to aromatic rings



(unfavorable interaction; sterics?)

What can we do for Lead optimization?

- Change substituents
- Extend structure
- Chain extension/contraction
- Ring extension/contraction
- Ring variations
- Isosteres
- Simplify structure
- Rigidification of structure

Chemical modifiaction changes the chemical or physical features such as

- Basicity
- Lipophilicity
- Electronic distribution
- Size steric bulk

Alkyl Substitutions

- easily attached to alcohol, amine, phenol
- vary chain length (bulk)
- change basicity of amine
- change lipophilicity
- change selectivity

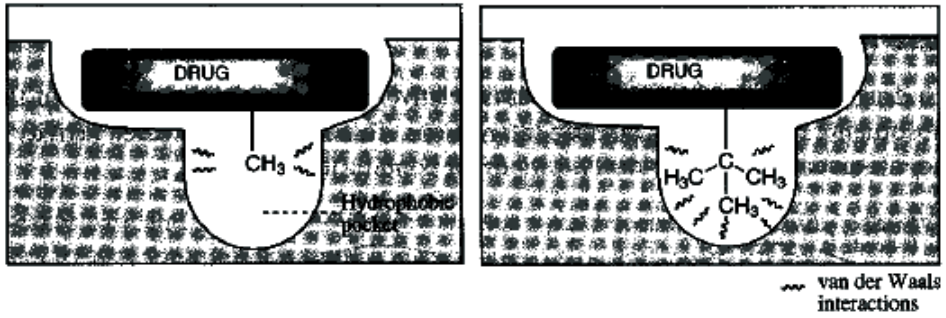


Fig. 9.2 Variation of alkyl chain to fill a hydrophobic pocket.

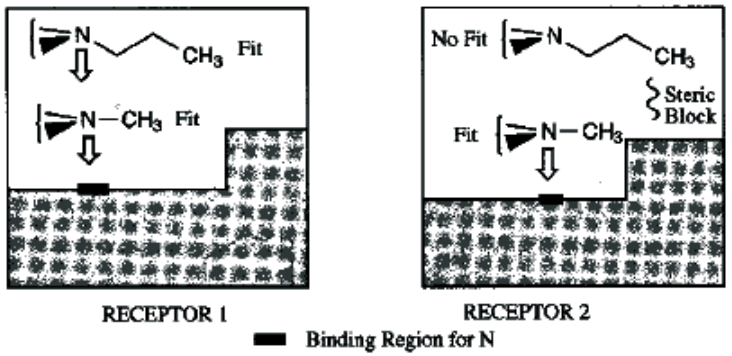


Fig. 9.3 Use of a larger alkyl group to confer selectivity on a drug.

Alkyl Substitutions

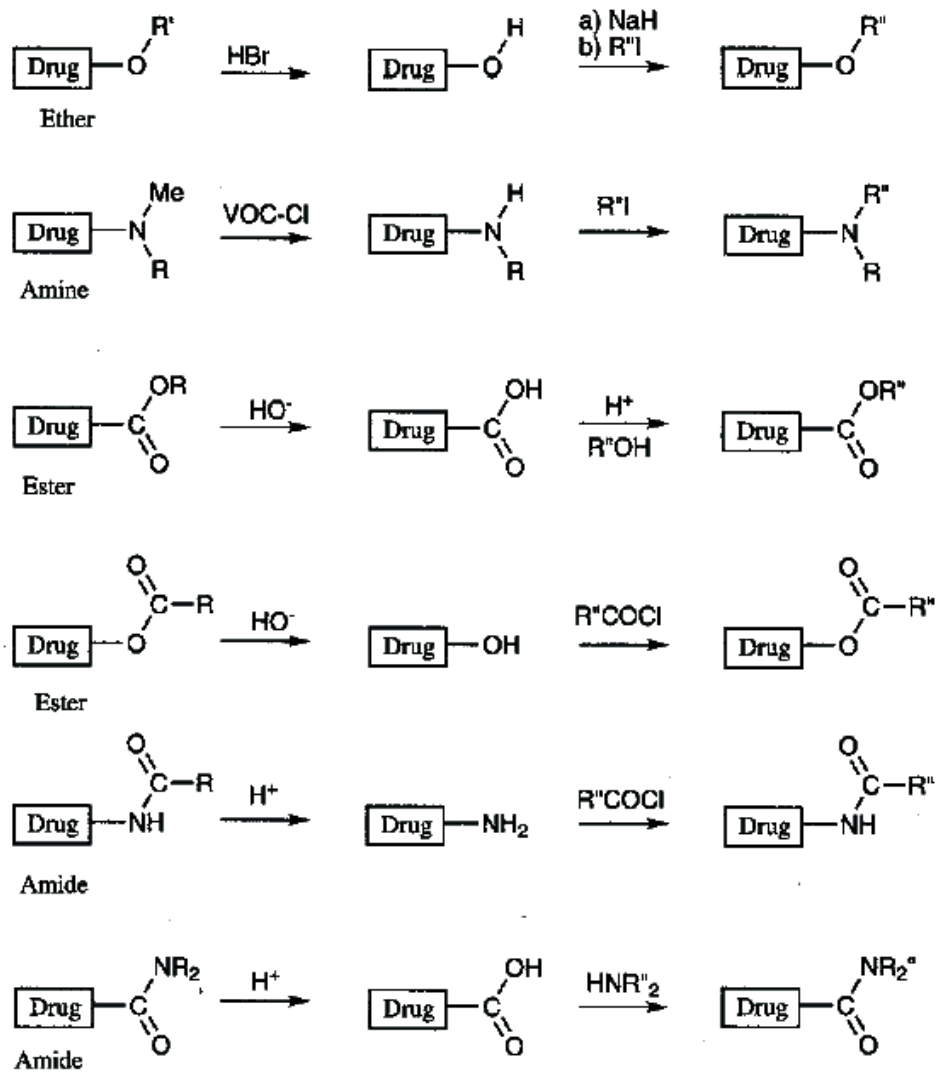


Fig. 9.1 Alkyl modifications.

Aromatic Substitutions

- change substituents on ring
- change substituent pattern

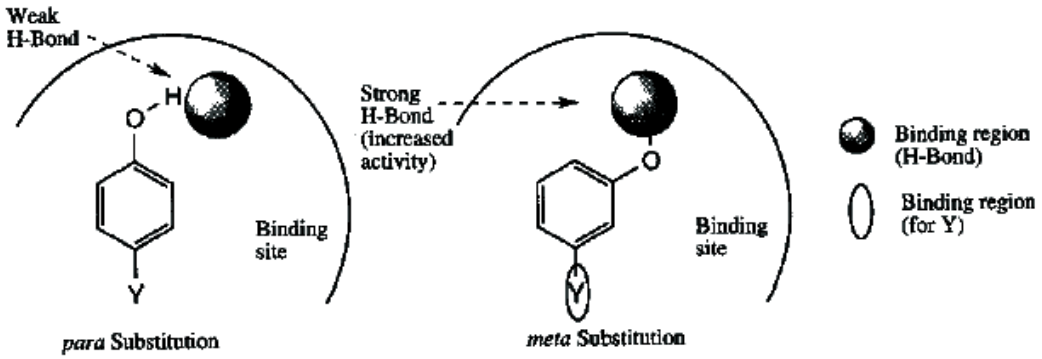


Fig. 9.5 Aromatic substitutions.

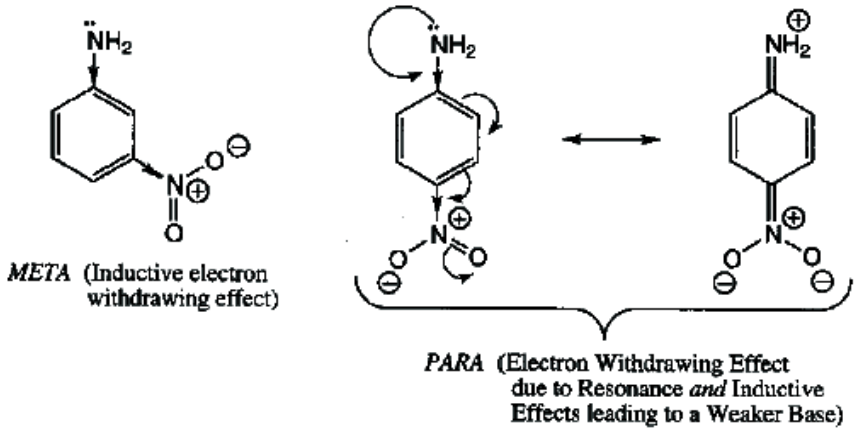


Fig. 9.7 Electronic effects of aromatic substitutions.

- **Extension of Structure**
- Add extra binding groups to search for nearby binding sites that may be used by the endogenous substrates. As a result, we may increase the interactions of the drug with binding site and thus increase activity. Alternatively, by increasing the interactions of the drug with binding site, we could prevent the natural substrate from binding (antagonist)

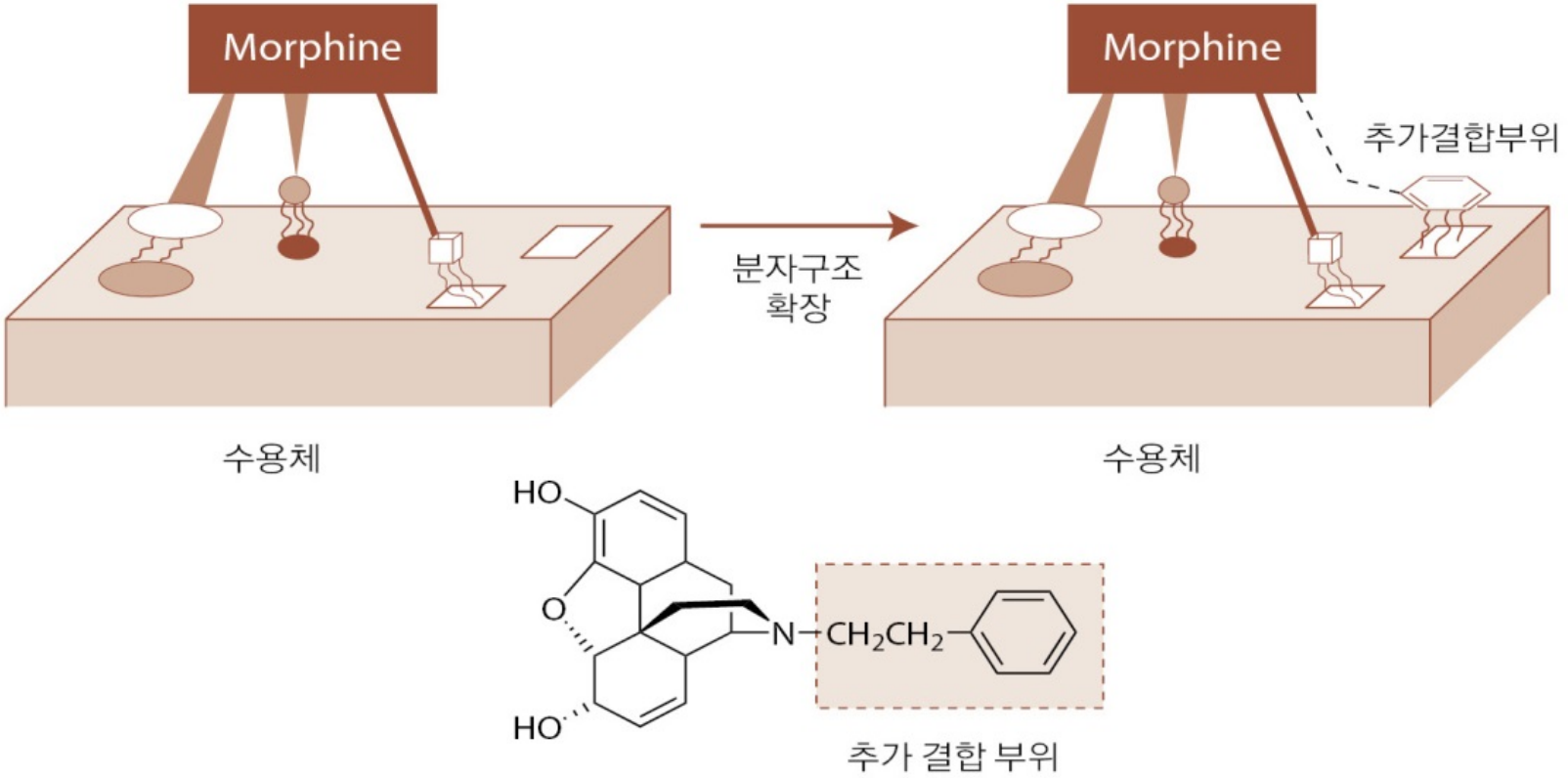


그림 1-14 Morphine 구조 확장

- **Extension of Structure**
- Add extra binding groups to search for nearby binding sites that may be used by the endogenous substrates. As a result, we may increase the interactions of the drug with binding site and thus increase activity. Alternatively, by increasing the interactions of the drug with binding site, we could prevent the natural substrate from binding (antagonist)

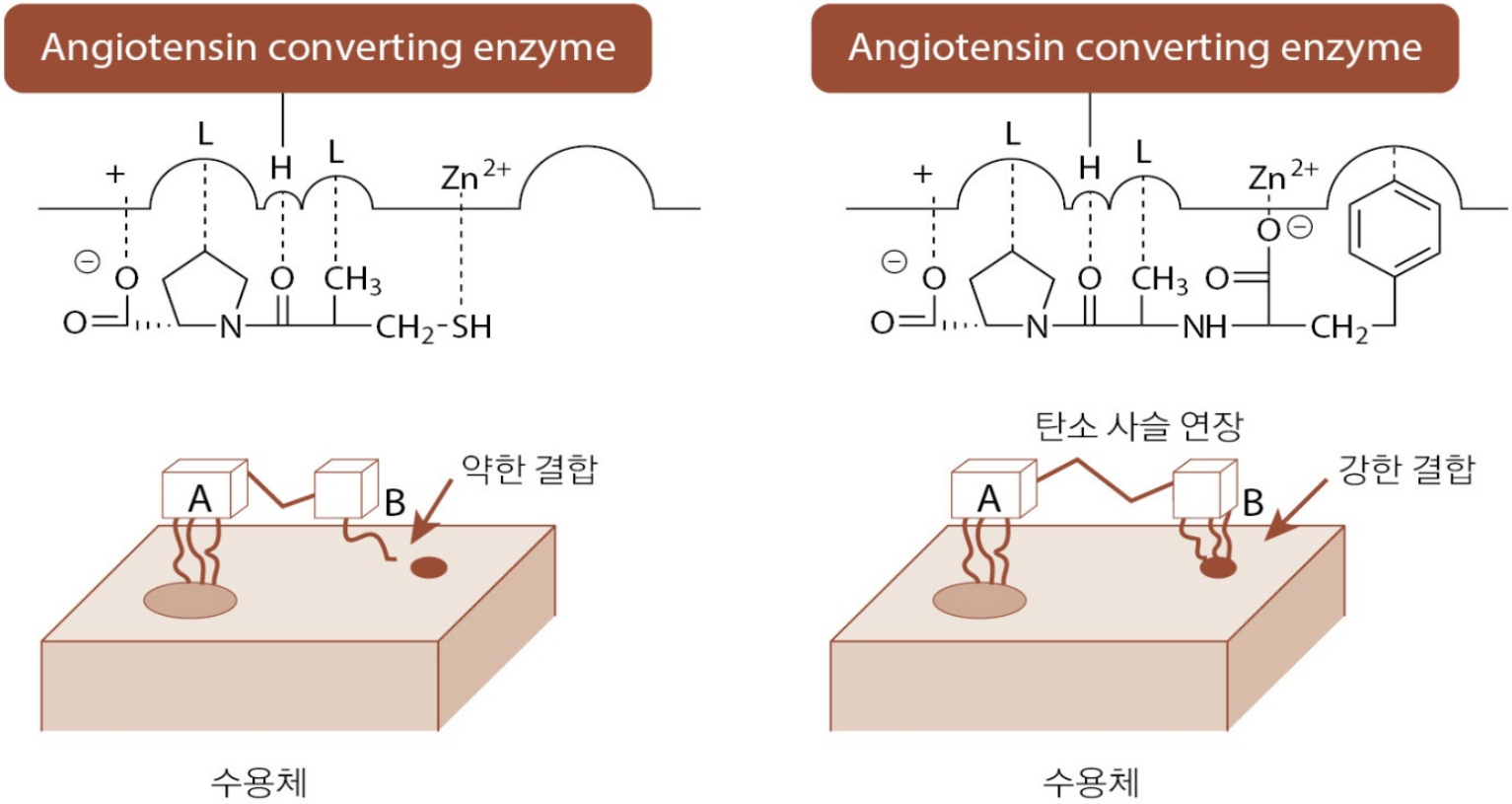
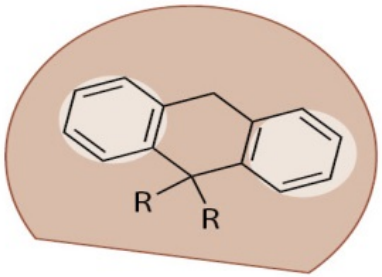


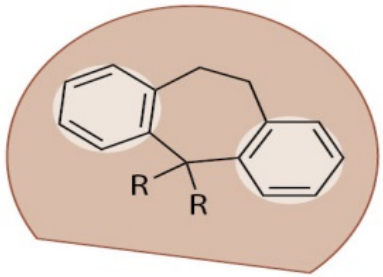
그림 1-15 ACE 억제제의 분자구조 확장

Ring Expansion/ Contraction

Similar to previous chain modifications.



6,6,6 고리 구조
수용체의 소수성 위치와 결합



6,7,6 고리 구조
수용체의 소수성 위치와 결합 최적화

그림 1-16 고리구조의 확장

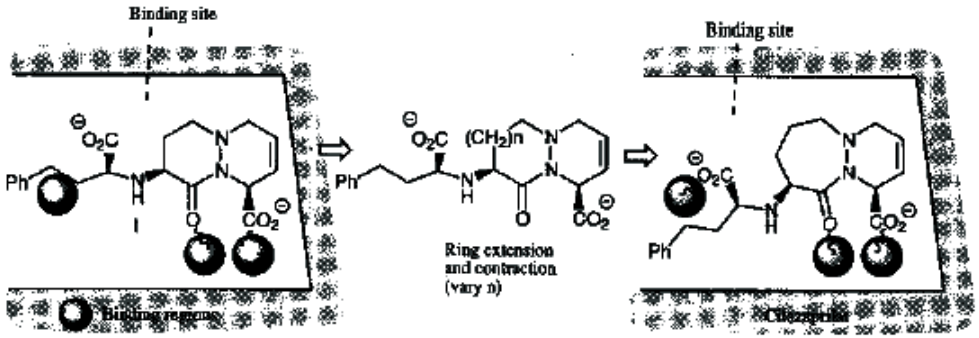


Fig. 9.12 Development of cilazaprilat.

Ring Variations

Change aromatic or heteroaromatic to:

- other heteroaromatic rings
- different size rings
- alter heteroatom positions

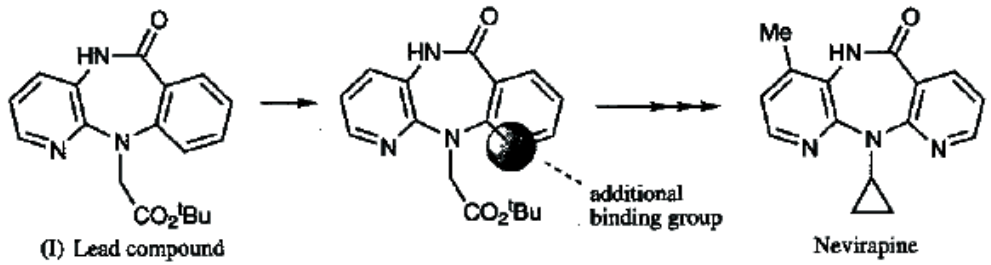


Fig. 9.15 Development of nevirapine

Ring Fusions

May change selectivity or increase interactions

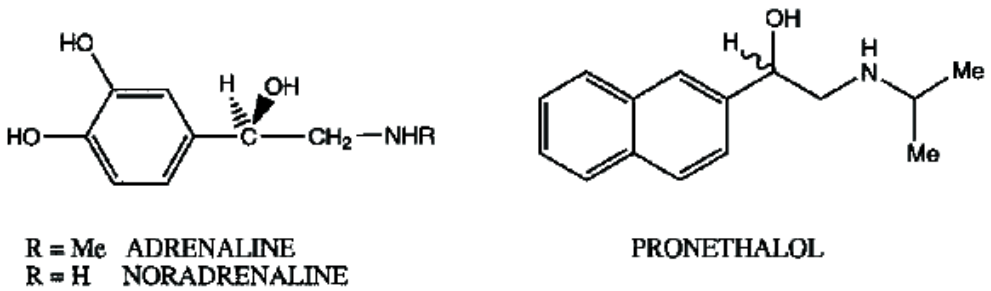


Fig. 9.16 Ring variation of adrenaline.

Isosteres or Bioisosteres

- Atoms (or groups of atoms) that have the same number of outer shell e⁻
- Useful for changing stability of Drug
- May alter electronic distribution, polarity, bonding, sterics
- Provide info on whether groups are involved in H-bonding.

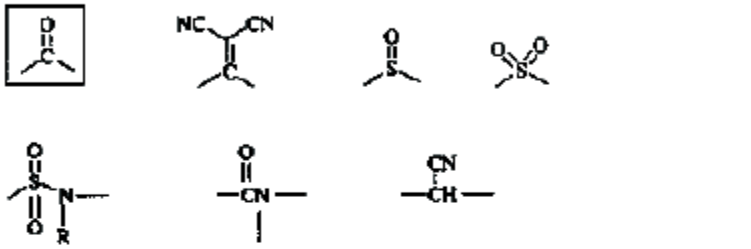
Table 2.2 Classical Isosteres[24,25]

1. Univalent atoms and groups					
a. CH_3	NH_2	OH	F	Cl	
b. Cl	PH_2	SH			
c. Br	*i*-Pr				
d. I	*t*-Bu				
2. Bivalent atoms and groups					
a. $-CH_2-$	$-NH-$	$-O-$	$-S-$	$-Se-$	
b. $-COCH_2R$	$-CONHR$	$-CO_2R$	$-COSR$		
3. Trivalent atoms and groups					
a. $-CH=$	$-N=$				
b. $-P=$	$-As=$				
4. Tetravalent atoms					
a. $-\overset{\vert}{\underset{\vert}{C}}-$	$-\overset{\vert}{\underset{\vert}{Si}}-$				
b. $=C=$	$=\overset{+}{N}=$	$=\overset{+}{P}=$			
5. Ring equivalents					
a. $-CH=CH-$	$-S-$	(e.g., benzene, thiophene)			
b. $-CH=$	$-N=$	(e.g., benzene, pyridine)			
c. $-O-$	$-S-$	$-CH_2-$	$-NH-$	(e.g., tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)	

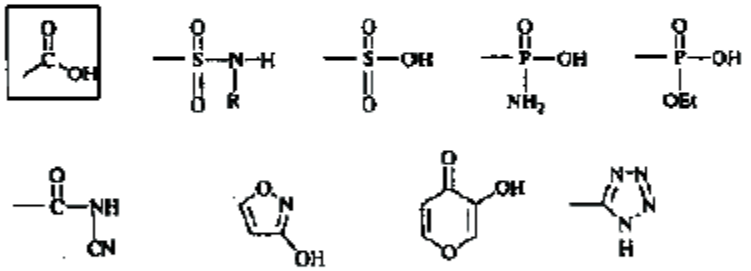
Nonclassical Bioisosteres

Table 2.3 Nonclassical Bioisosteres[23]

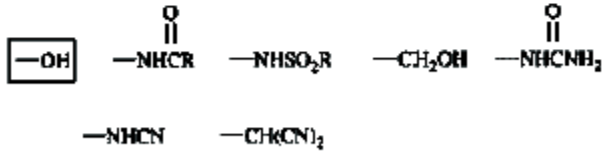
1. **Carbonyl group**



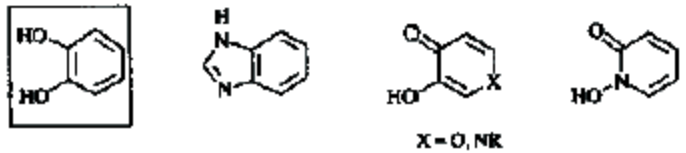
2. **Carboxylic acid group**



3. **Hydroxy group**



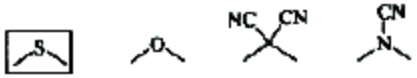
4. **Catechol**



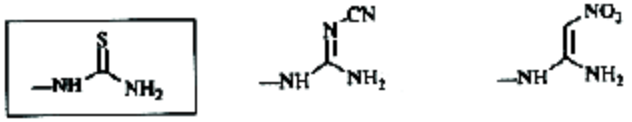
Nonclassical Bioisosteres

5. **Halogen**

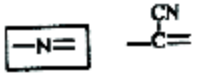
6. **Thioether**



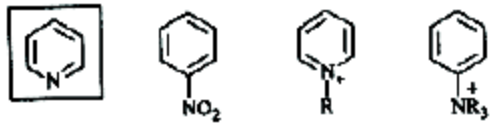
7. **Thiourea**



8. **Azomethine**



9. **Pyridine**



10. **Spacer group**

11. **Hydrogen**

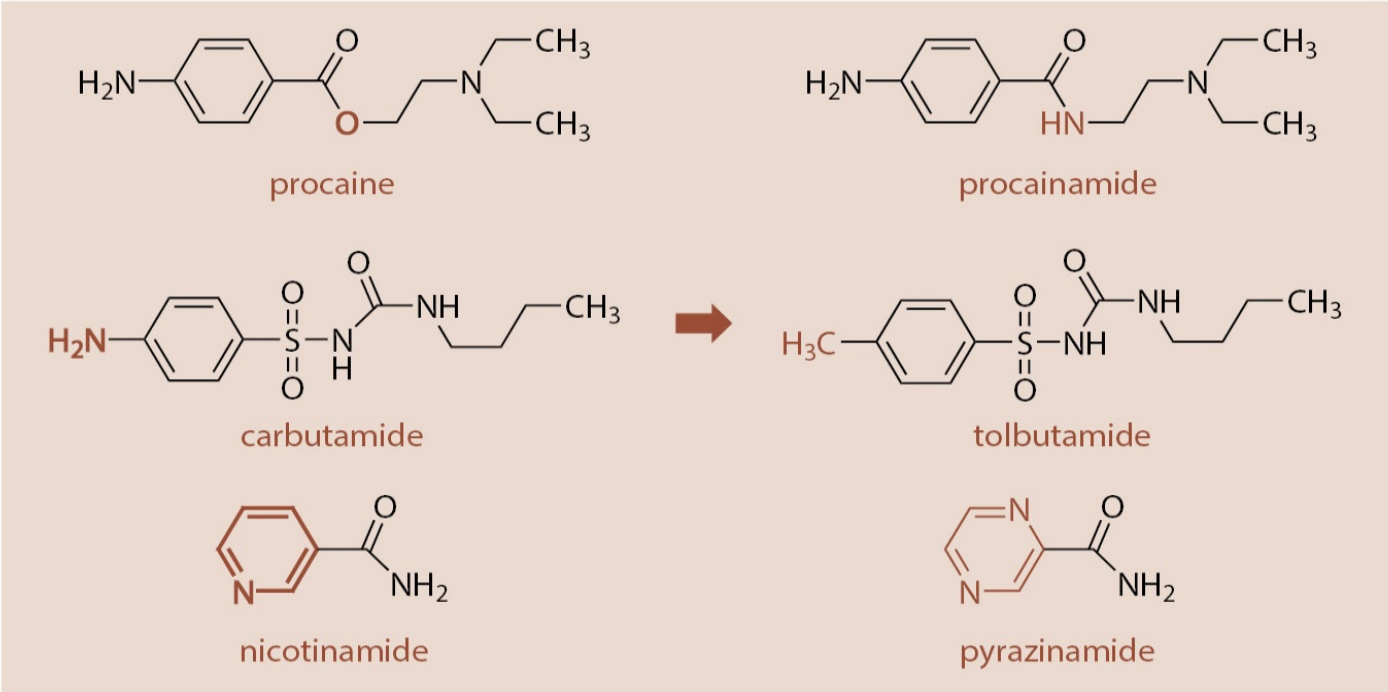


그림 1-18 동등체 치환을 이용한 구조변형

선도구조의 단순화(Simplification of lead structure)

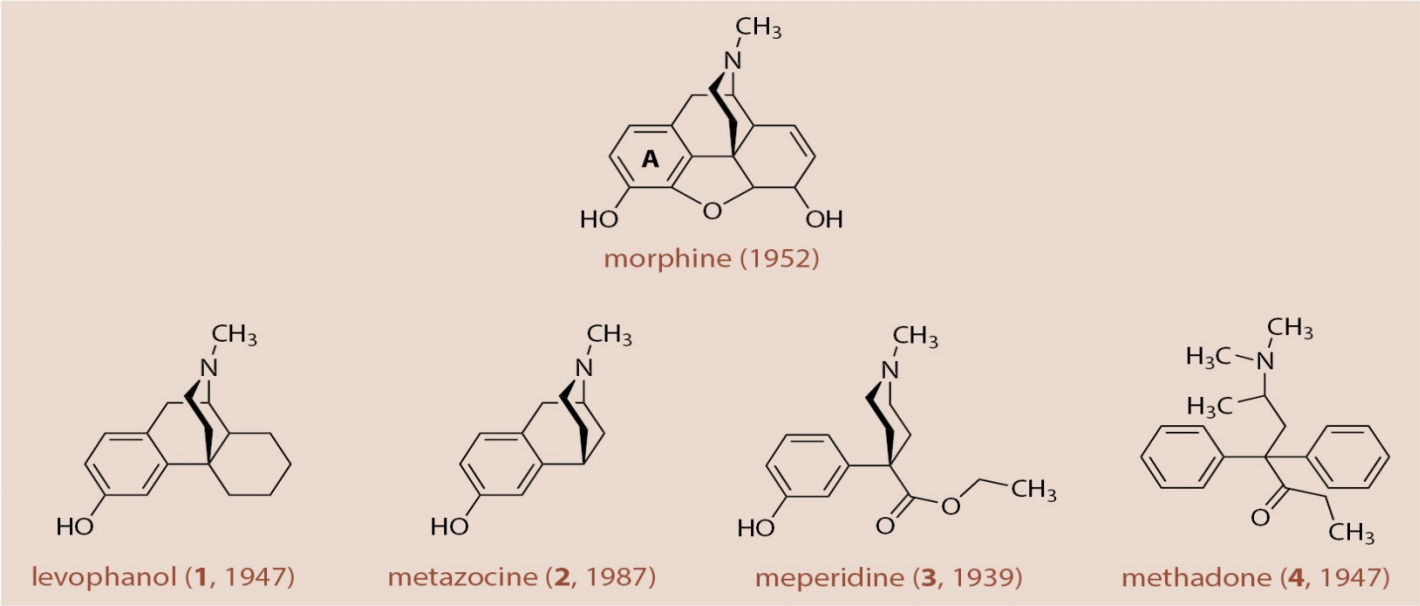


그림 1-20 Morphine 구조의 단순화

Rigidification of Structure

- may increase activity or decrease side effects.
- multiple conformations allow interactions with more than one receptor (especially true for neurotransmitters)
- restriction of rotations allow only conformations necessary for binding at receptor of interest and not receptors causing side effects.

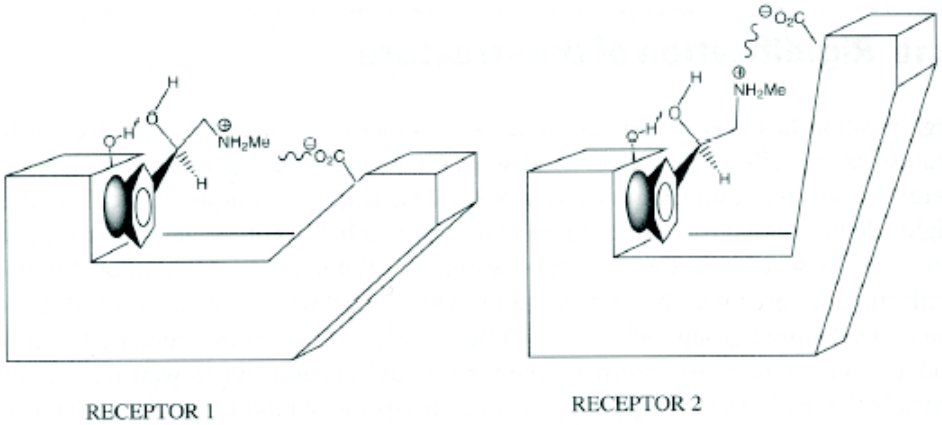


Fig. 9.21 Two conformations of a neurotransmitter which are capable of binding with different receptors.

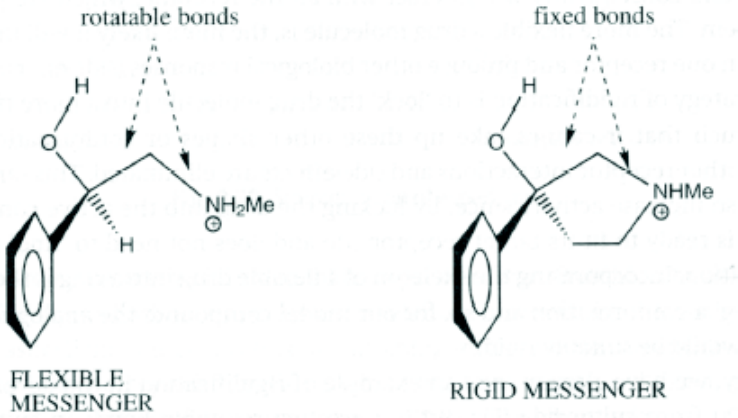


Fig. 9.22 Locked analogue.

- One receptor may cause the desired effect while interaction with the other may lead to undesired effects.

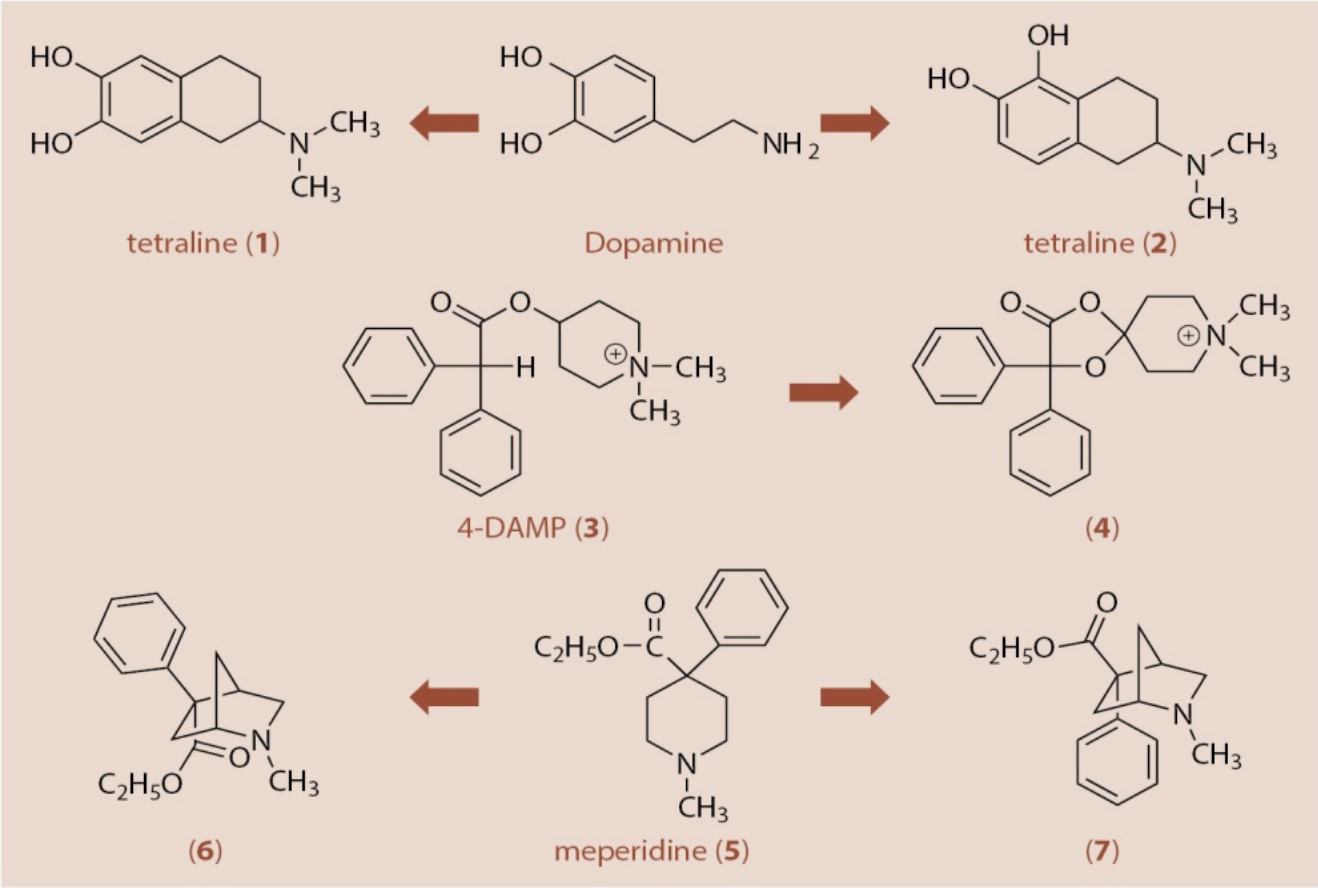


그림 1-22 Dopamine, 4-DMAP 및 meperidine의 강직화 구조

약리단 사이의 거리 변화 (Variation of interatomic distance)

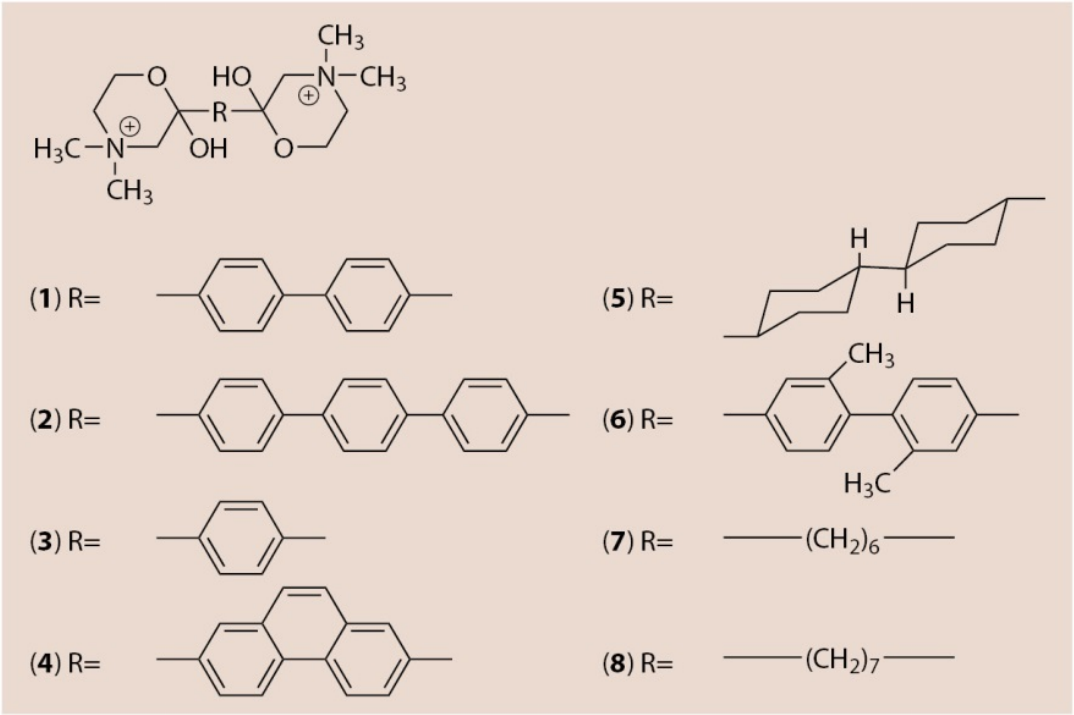


그림 1-23 Hemicholinium의 4급 ammonium간의 거리 변화

입체 화학 변경을 이용한 설계 (Alteration of stereochemistry)

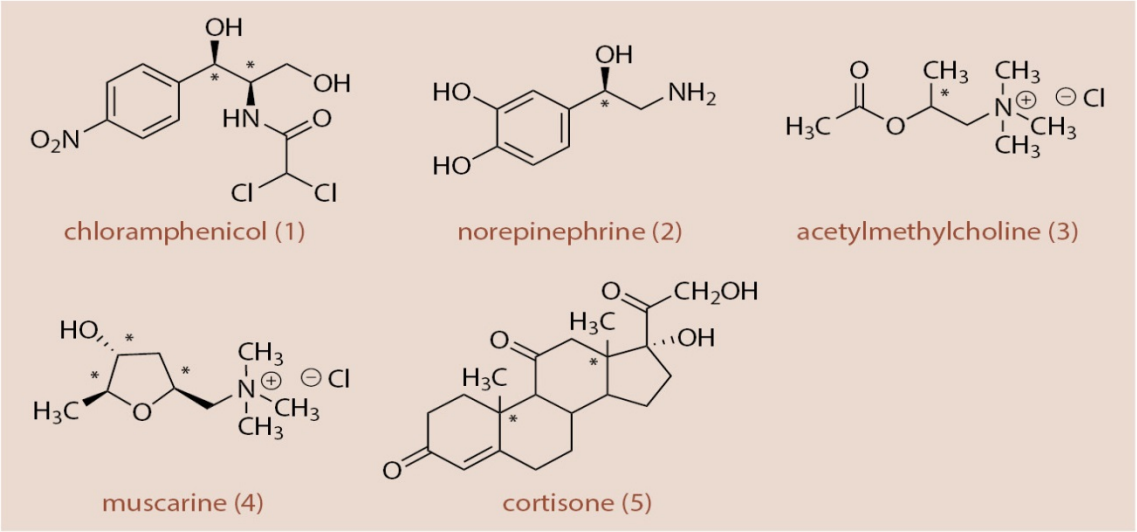


그림 1-25 입체 이성체의 효과 변화

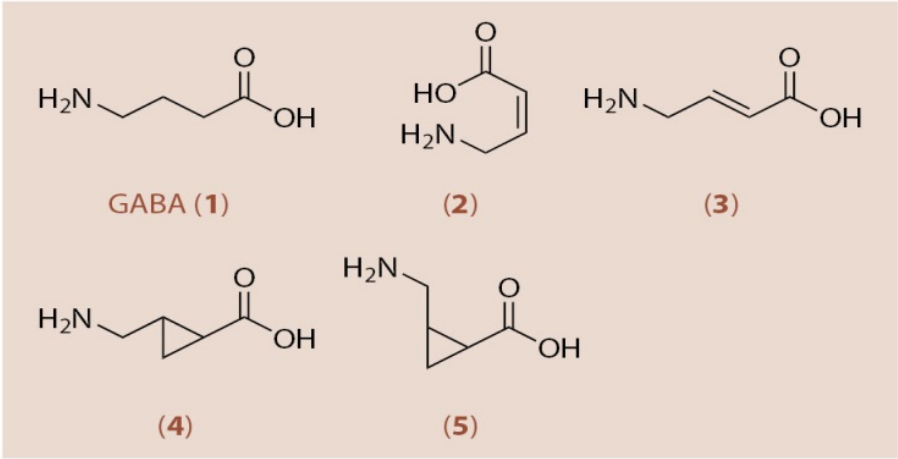


그림 1-26 γ-Aminobutyric acid(GABA)의 입체적 변화