Topic 7 Drug Discovery and design Pt. 1

Chapter 9 Patrick

Contents

Part 1: Sections 9.1-9.3

DRUG DESIGN AND DEVELOPMENT

Stages

1) Identify target disease
2) Identify drug target
3) Establish testing procedures
4) Find a lead compound
5) Structure Activity Relationships (SAR)
6) Identify a pharmacophore
7) Drug design- optimising target interactions
8) Drug design - optimising pharmacokinetic properties
9) Toxicological and safety tests
10) Chemical development and production
11) Patenting and regulatory affairs
12) Clinical trials

1. TARGET DISEASE

Priority for the Pharmaceutical Industry

- **Can the profits from marketing a new drug outweigh the cost of developing and testing that drug?**

Questions to be addressed

- **Is the disease widespread?**
  (e.g. cardiovascular disease, ulcers, malaria)
- **Does the disease affect the first world?**
  (e.g. cardiovascular disease, ulcers)
- **Are there drugs already on the market?**
- **If so, what are there advantages and disadvantages?**
  (e.g. side effects)
- **Can one identify a market advantage for a new therapy?**

2. DRUG TARGETS-Remember?

A) LIPIDS

Cell Membrane Lipids

B) PROTEINS

Receptors
Enzymes
Carrier Proteins
Structural Proteins (tubulin)

C) NUCLEIC ACIDS

DNA
RNA

D) CARBOHYDRATES

Cell surface carbohydrates
Antigens and recognition molecules

2. DRUG TARGETS

TARGET SELECTIVITY

Between species

- **Antibacterial and antiviral agents**
- **Identify targets which are unique to the invading pathogen**
- **Identify targets which are shared but which are significantly different in structure**

Within the body

- **Selectivity between different enzymes, receptors etc.**
- **Selectivity between receptor types and subtypes**
- **Selectivity between isozymes**
- **Organ selectivity**

3. TESTING DRUGS

- **Tests are required in order to find lead compounds and for drug optimisation**
- **Tests can be *in vivo* or *in vitro***
- **A combination of tests is often used in research programs**

3.1 *in vivo* Tests

- **Carried out on live animals or humans**
- **Measure an observed physiological effect**
- **Measure a drug's ability to interact with its target and its ability to reach that target**
- **Can identify possible side effects**
- **Rationalization may be difficult due to the number of factors involved**
- **Transgenic animals - genetically modified animals**
- **Drug potency - concentration of drug required to produce 50% of the maximum possible effect**
- **Therapeutic ratio/index - compares the dose level of a drug required to produce a desired effect in 50% of the test sample (ED_{50}) versus the dose level that is lethal to 50% of the sample (LD_{50})**

3.2 *in vitro* Tests-See drug binding supplement

- **Tests not carried out on animals/humans**

  Target molecules (e.g. isolated enzymes or receptors)
  Cells (e.g. cloned cells)
  Tissues (e.g. muscle tissue)
  Organs
  Micro-organisms (for antibacterial agents)
- **More suitable for routine testing**
- **Used in high throughput screening**
- **Measure the interaction of a drug with the target but not the ability of the drug to reach the target**
- **Results are easier to rationalize - less factors involved**
- **Does not demonstrate a physiological or clinical effect**
- **Does not identify possible side effects**
- **Does not identify effective prodrugs**

3.2.1 Enzyme Inhibition Tests

- **Identify competitive or non competitive inhibition**
- **Strength of inhibition measured as IC_{50}**
- **IC_{50} = concentration of inhibitor required to reduce enzyme activity by 50%**

3.2.2 Testing with Receptors

- **Not easy to isolate membrane bound receptors**
- **Carried out on whole cells, tissue cultures, or isolated organs**
- **Affinity - strength with which compounds bind to a receptor**
- **Efficacy - measure of maximum biochemical effect resulting from binding of a compound to a receptor.**
- **Potency - concentration of an agonist required to produce 50% of the maximum possible effect.**

Contents

Part 2: Section 9.4 Lead compounds from the natural world

4 The Lead Compound

Introduction

Def: A compound demonstrating a property likely to be therapeutically useful

- The level of activity and target selectivity are not crucial
- Used as the starting point for drug design and development
- Found by design (molecular modelling or NMR) or by screening compounds (natural or synthetic)
- Need to identify a suitable test in order to find a lead compound
- Active Principle - a compound that is isolated from a natural extract and which is principally responsible for the extract's pharmacological activity. Often used as a lead compound.

4.1 Sources of Lead Compounds

A) The Natural World

Plantlife (flowers, trees, bushes)
Micro-organisms (bacteria, fungi)
Animal life (frogs, snakes, scorpions)
Biochemicals (Neurotransmitters, hormones)
Marine chemistry (corals, bacteria, fish etc)

B) The Synthetic World

Chemical synthesis (traditional)
Combinatorial synthesis

C) The Virtual World

Computer aided drug design

4.2 Identification of Lead Compounds

A) Isolation and purification

solvent-solvent extraction
chromatography
crystallization
distillation

B) Structure determination

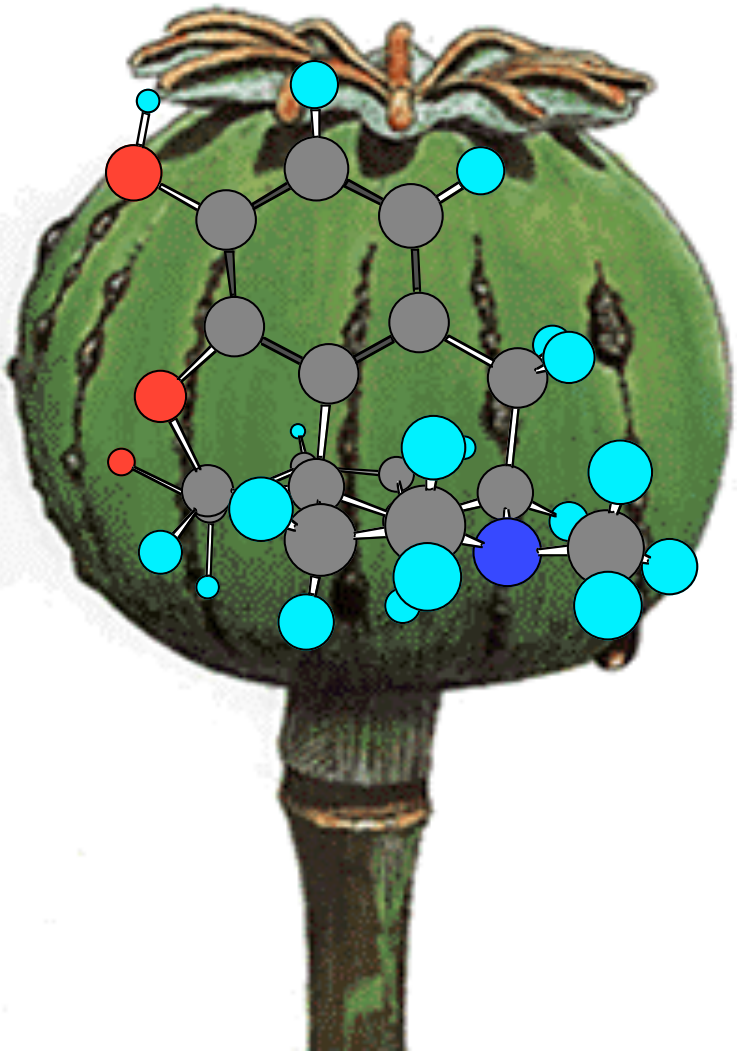
elemental analysis
molecular weight
mass spectrum
infrared
ultraviolet
nmr (^{1}H, ^{13}C, ^{2}D)
X-ray crystallography

4.3 Lead Compounds from the Natural World

PLANT EXTRACTS

4.3 Lead Compounds from the Natural World

PLANT EXTRACTS



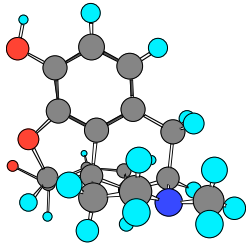
POPPY CAPSULE

MORPHINE

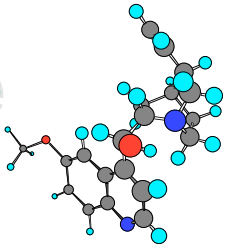
4.3 Lead Compounds from the Natural World

PLANT EXTRACTS

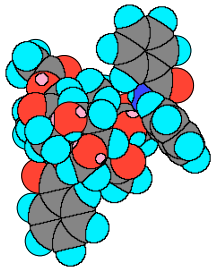
- OPIUM - Morphine



- CINCHONA BARK - Quinine



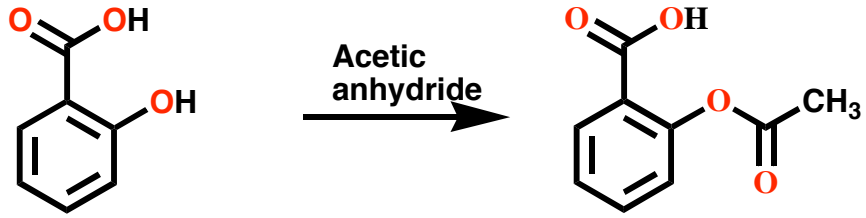
- YEW TREE - Taxol



4.3 Lead Compounds from the Natural World

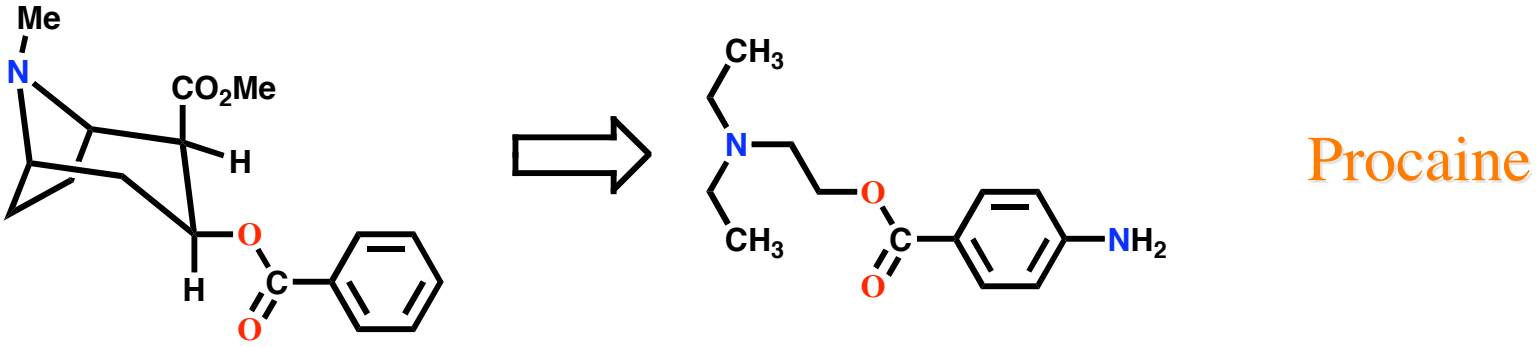
PLANT EXTRACTS

WILLOW TREE - SALICYLIC ACID



Aspirin

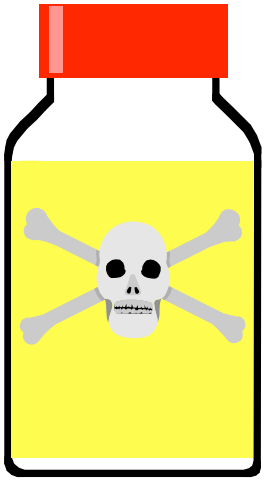
COCA BUSH - COCAINE



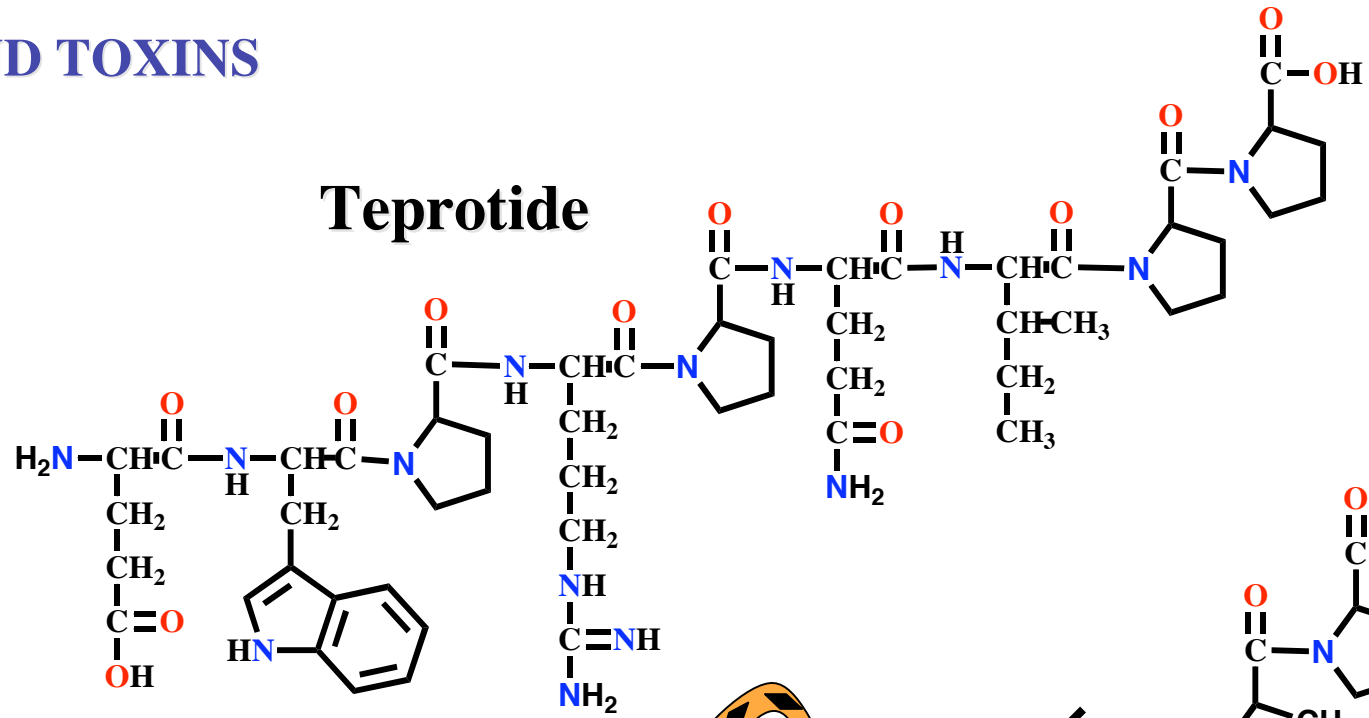
Procaine

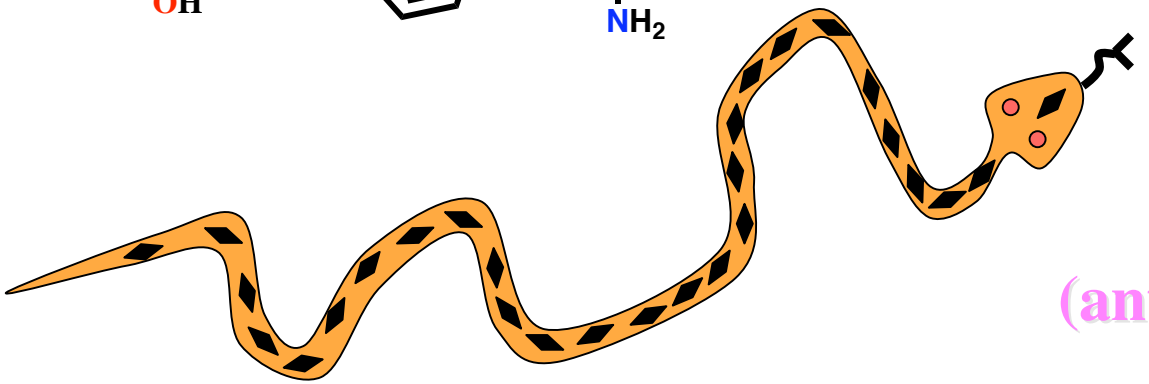
4.3 Lead Compounds from the Natural World

VENOMS AND TOXINS



Teprotide





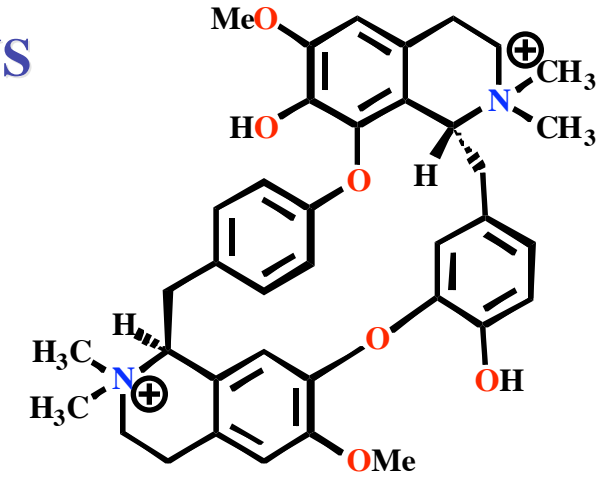
Captopril
(anti-hypertensive)

4.3 Lead Compounds from the Natural World

BUT WAIT….why do plants make these things???!!!

4.3 Lead Compounds from the Natural World

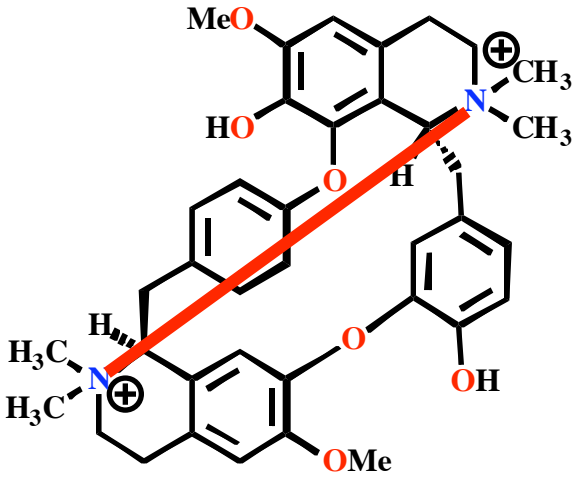
VENOMS AND TOXINS



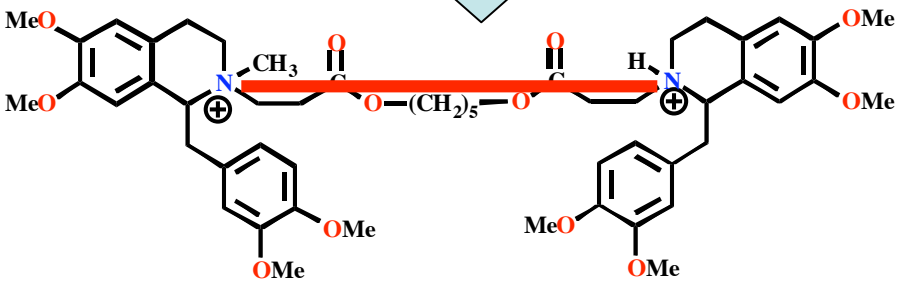
Tubocurarine
(from curare)

4.3 Lead Compounds from the Natural World

VENOMS AND TOXINS



Tubocurarine
(from curare)

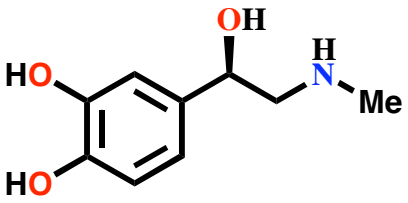


Atracurium
(Neuromuscular blocker)

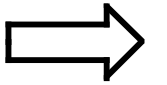
4.3 Lead Compounds from the Natural World

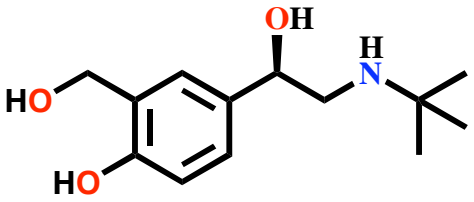
ENDOGENOUS COMPOUNDS: found in YOU

NATURAL LIGANDS FOR RECEPTORS



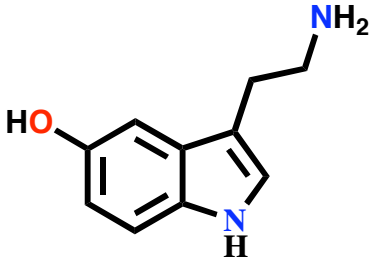
ADRENALINE



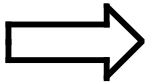


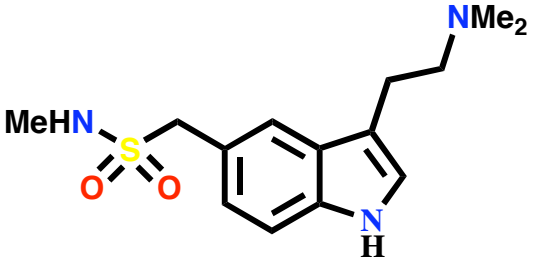
SALBUTAMOL

Agonist



5-HYDROXYTRYPTAMINE





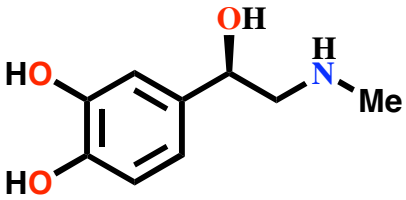
SUMATRIPTAN

Agonist

4.3 Lead Compounds from the Natural World

ENDOGENOUS COMPOUNDS

NATURAL LIGANDS FOR RECEPTORS



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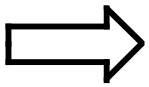
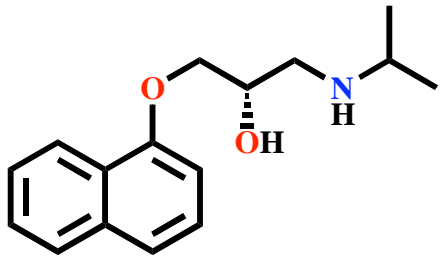
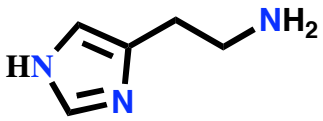


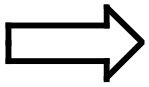


PROPRANOLOL

Antagonist



HISTAMINE



CIMETIDINE

Antagonist

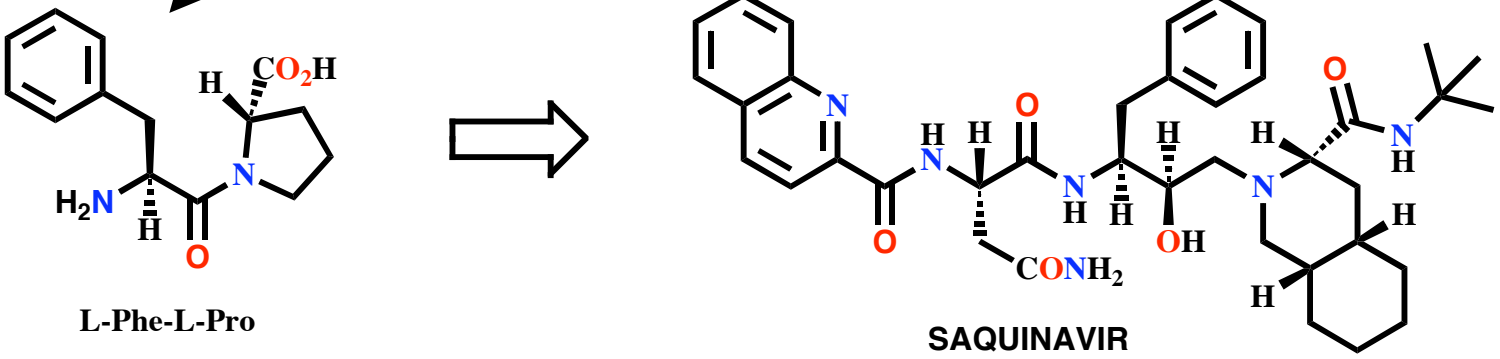
4.3 Lead Compounds from the Natural World

ENDOGENOUS COMPOUNDS

NATURAL SUBSTRATES FOR ENZYMES

Enkephalins ⇒ **Enkephalinase inhibitors**

HIV Peptides ⇒ **HIV Protease inhibitors**



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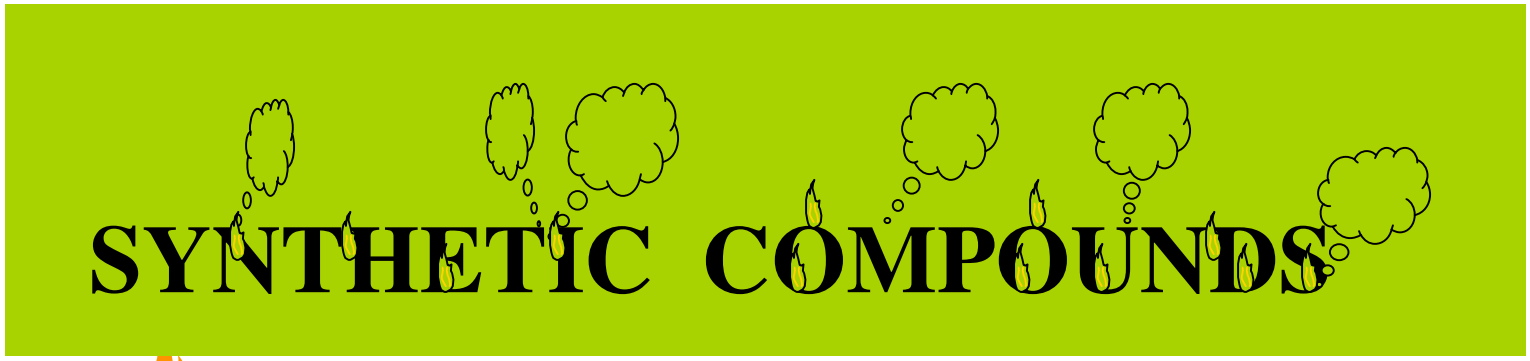
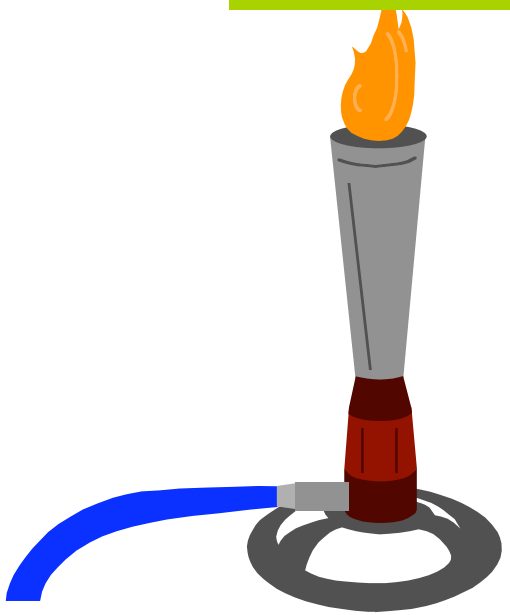
Part 3: Section 9.4 - Lead compounds from the synthetic world

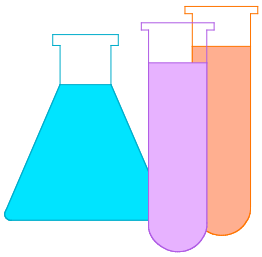
4.4. Lead Compounds from the Synthetic World

- Organic Synthesis
- Combinatorial Synthesis
- Combinatorial Synthesis - Peptide Synthesis
- Combinatorial Synthesis - Heterocyclic Synthesis

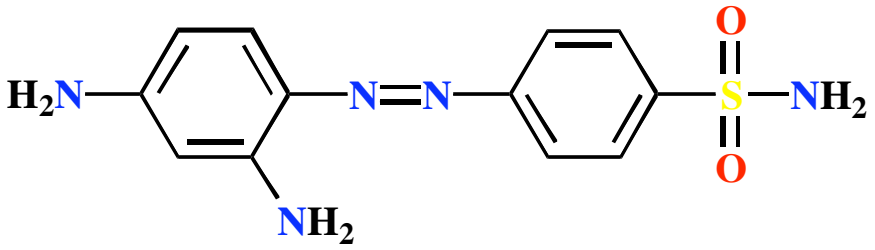
4.4 Lead Compounds from the Synthetic World



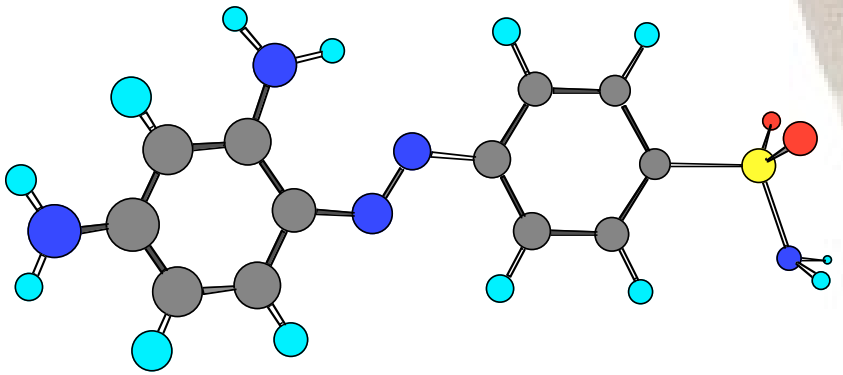




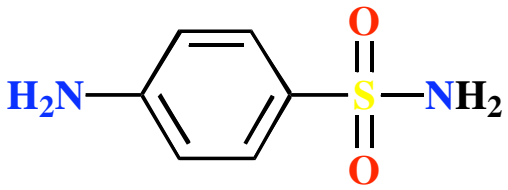
4.4 Lead Compounds from the Synthetic World

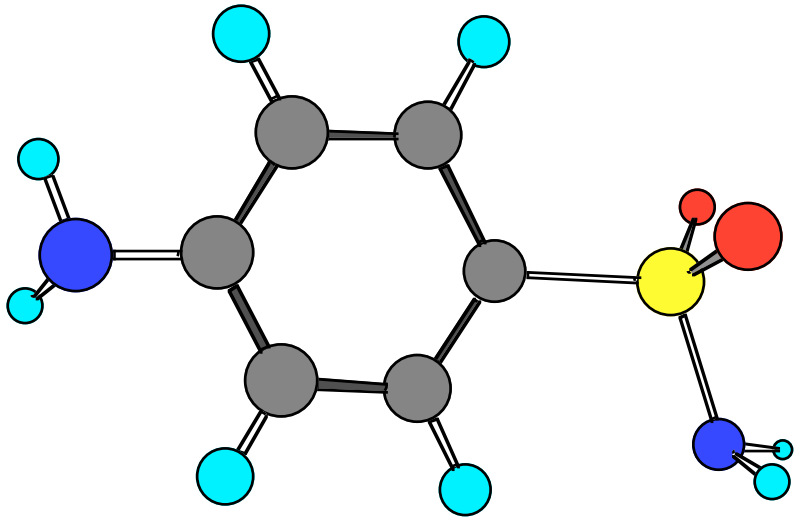


PRONTOSIL: a dye



4.4 Lead Compounds from the Synthetic World

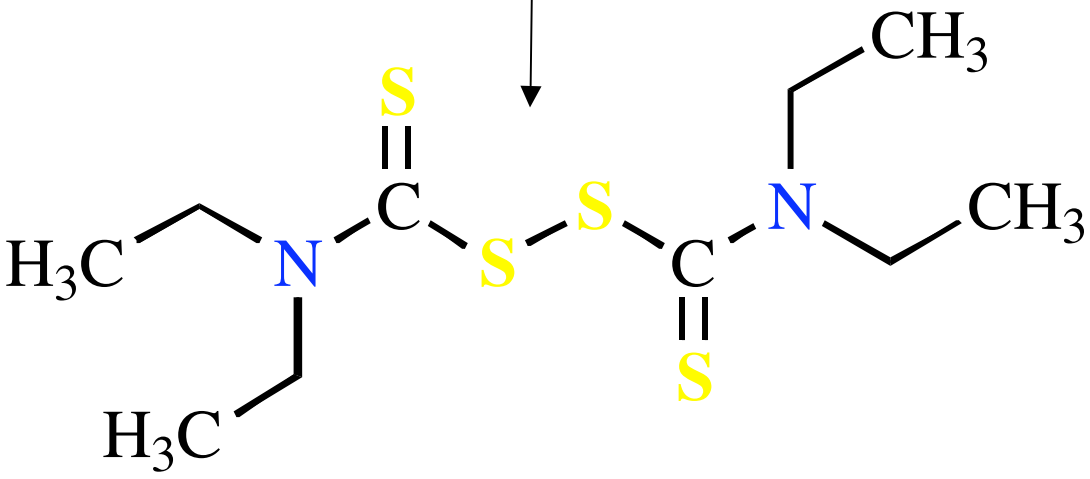




SULFANILAMIDE: not RED

4.4 Lead Compounds from the Synthetic World

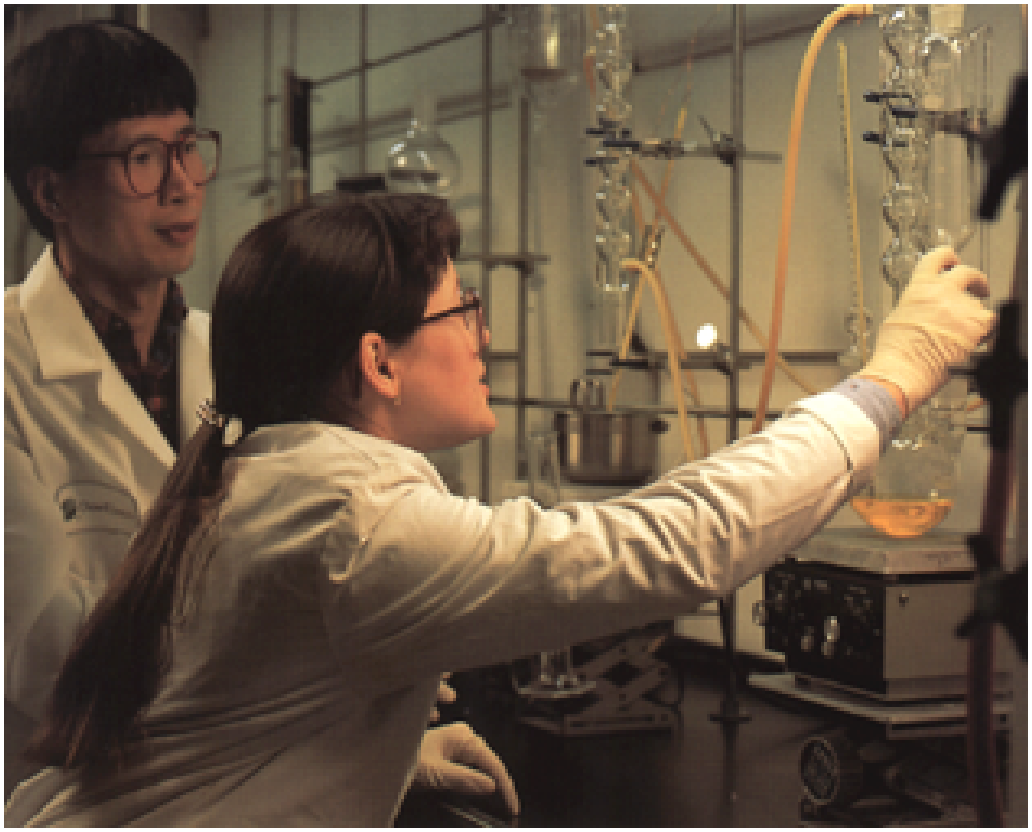
RUBBER INDUSTRY



ANTABUSE

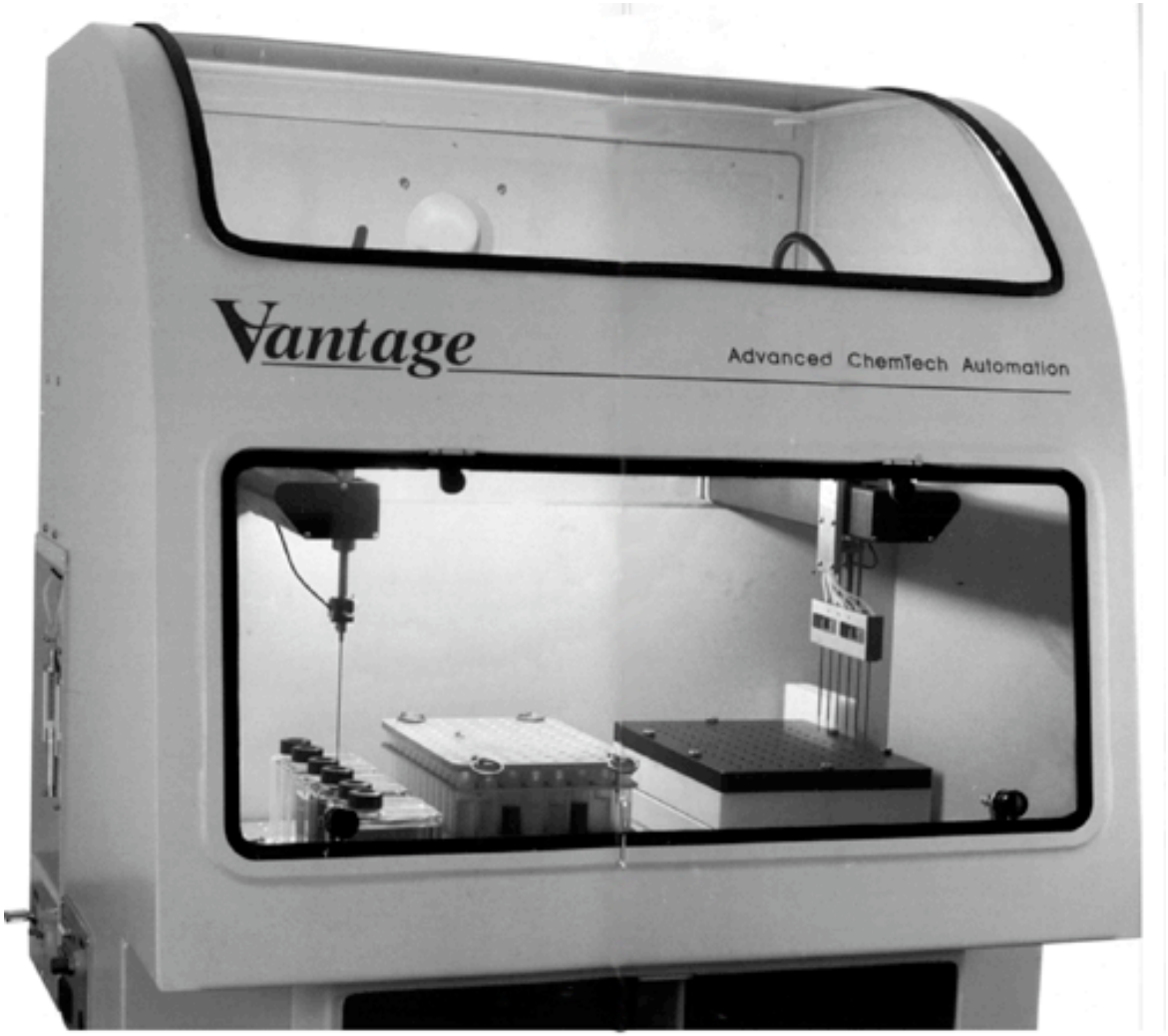
4.4 Lead Compounds from the Synthetic World

ORGANIC SYNTHESIS



4.4 Lead Compounds from the Synthetic World

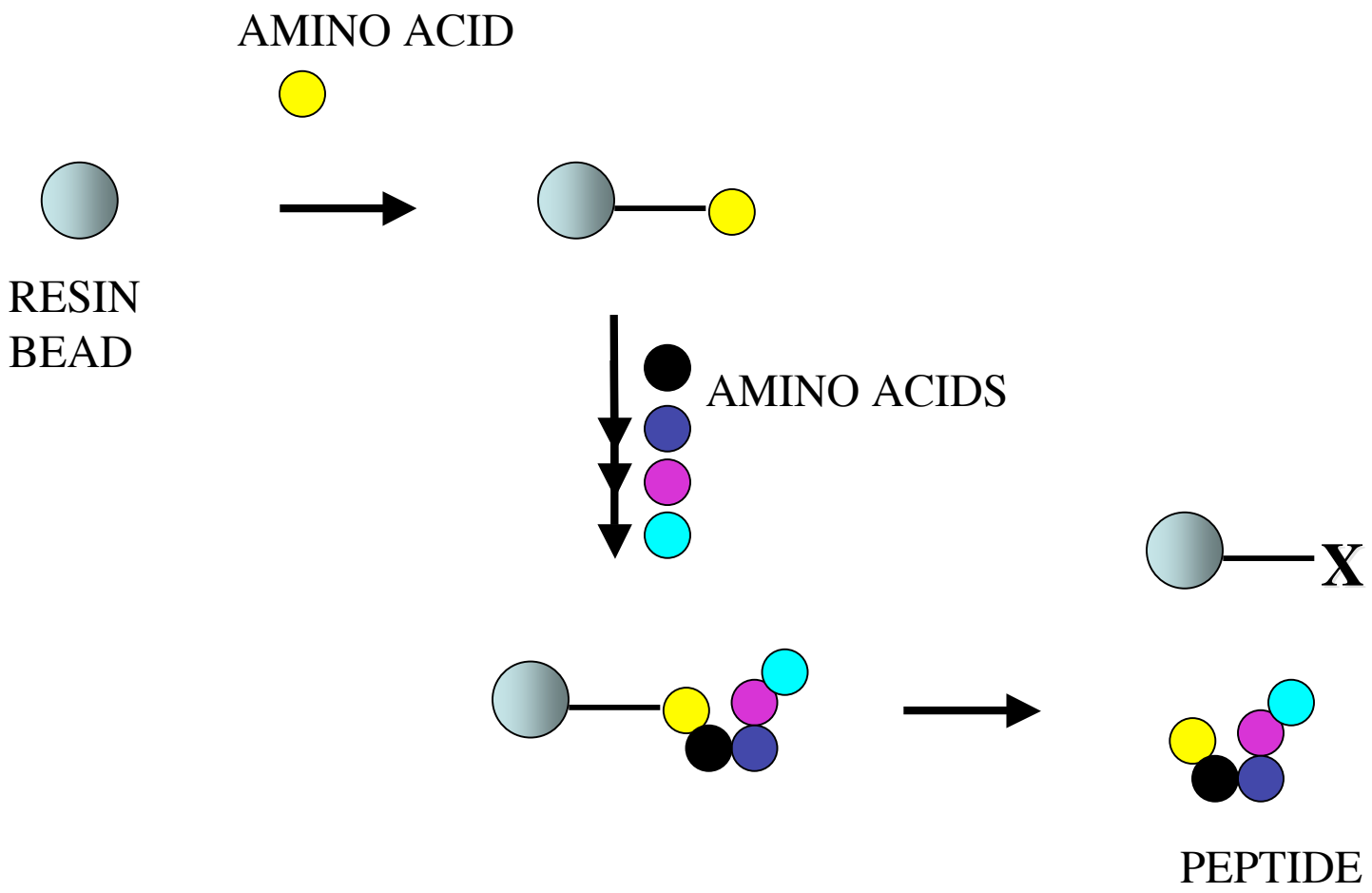
COMBINATORIAL SYNTHESIS



AUTOMATED SYNTHETIC MACHINES

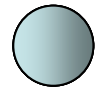
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - PEPTIDE SYNTHESIS

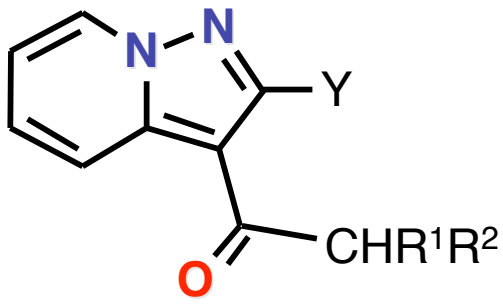


4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS

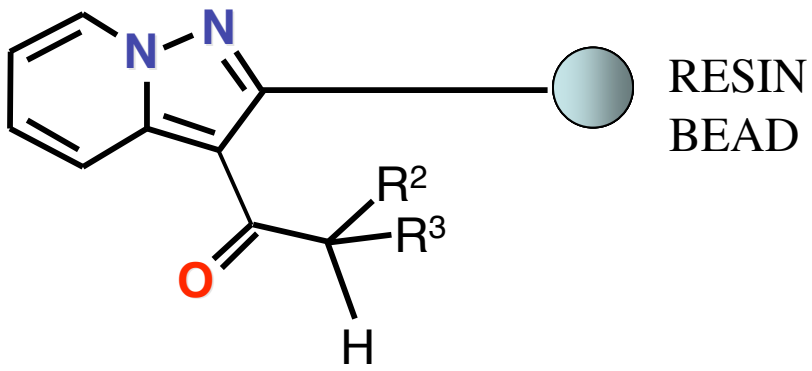


RESIN
BEAD



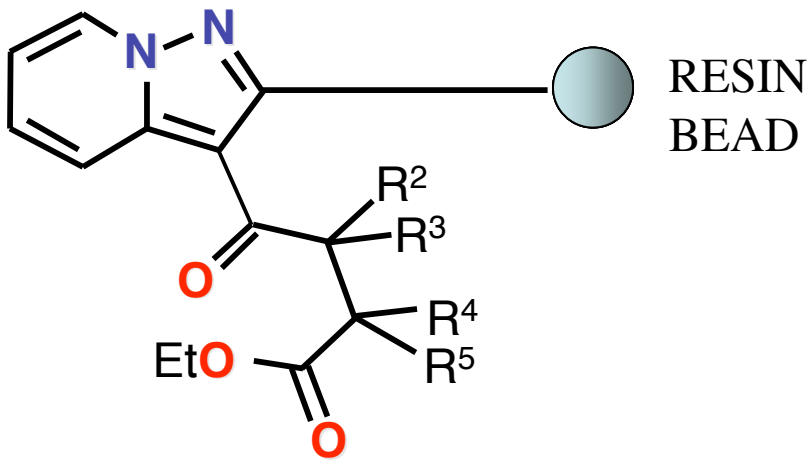
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS



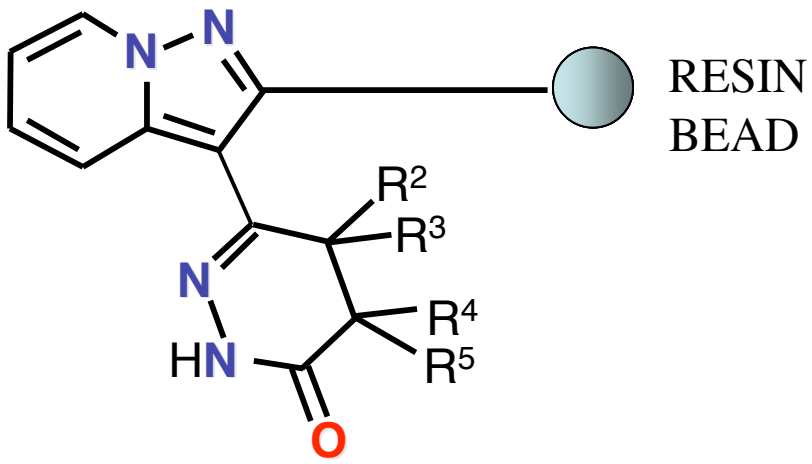
4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS



4.4 Lead Compounds from the Synthetic World

COMBINATORIAL SYNTHESIS - HETEROCYCLIC SYNTHESIS



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Part 4: Lead compounds - Impact of the human genome project

4.5 Lead Compounds
- Impact of the human genome project

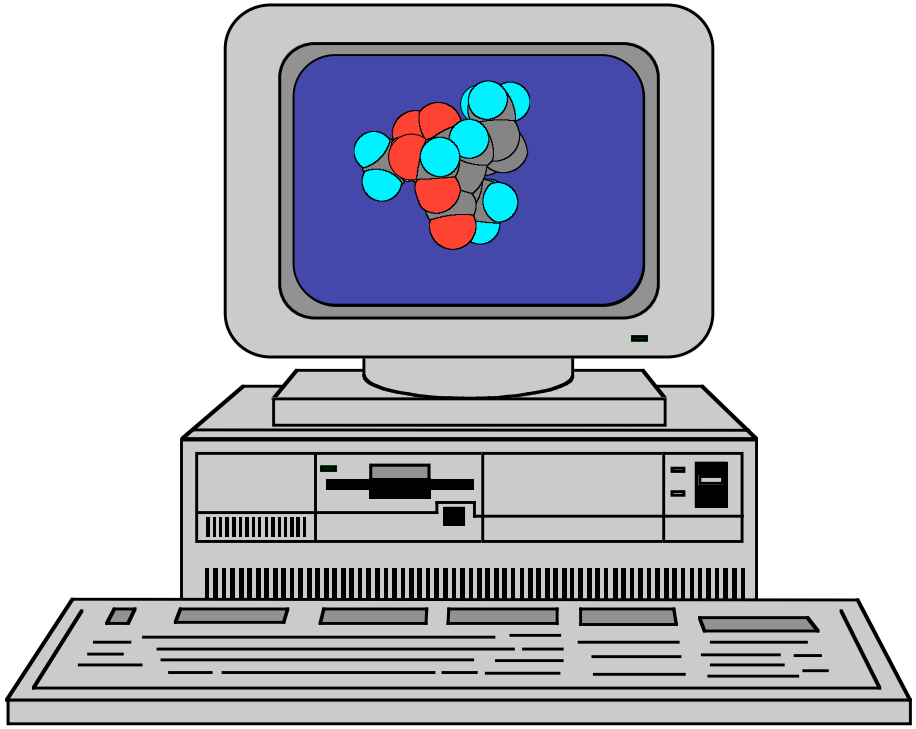
The Past

Lead Compound → Targets

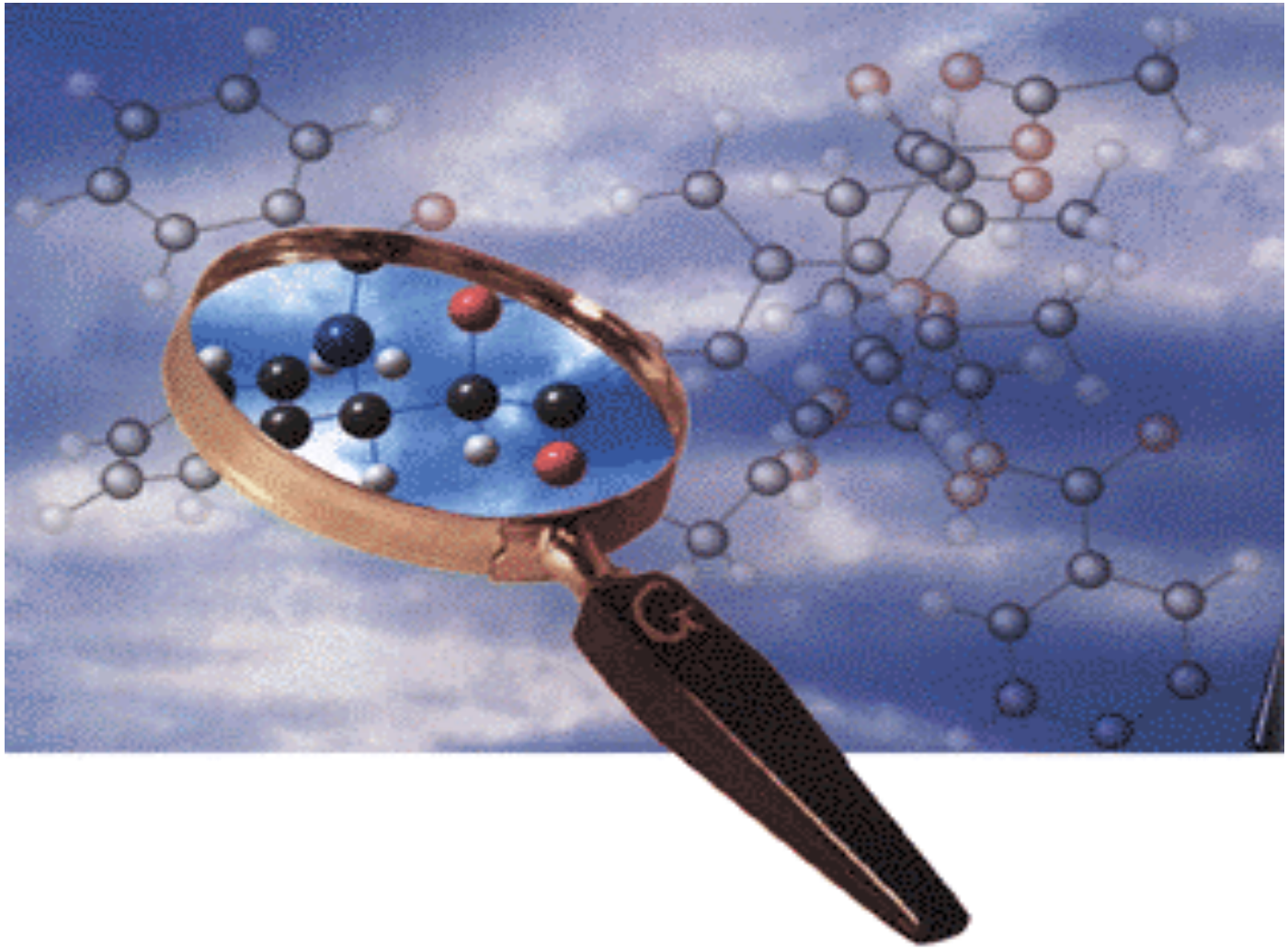
The Future

Targets → Lead compounds

4.6 Lead Compounds - *de novo* design

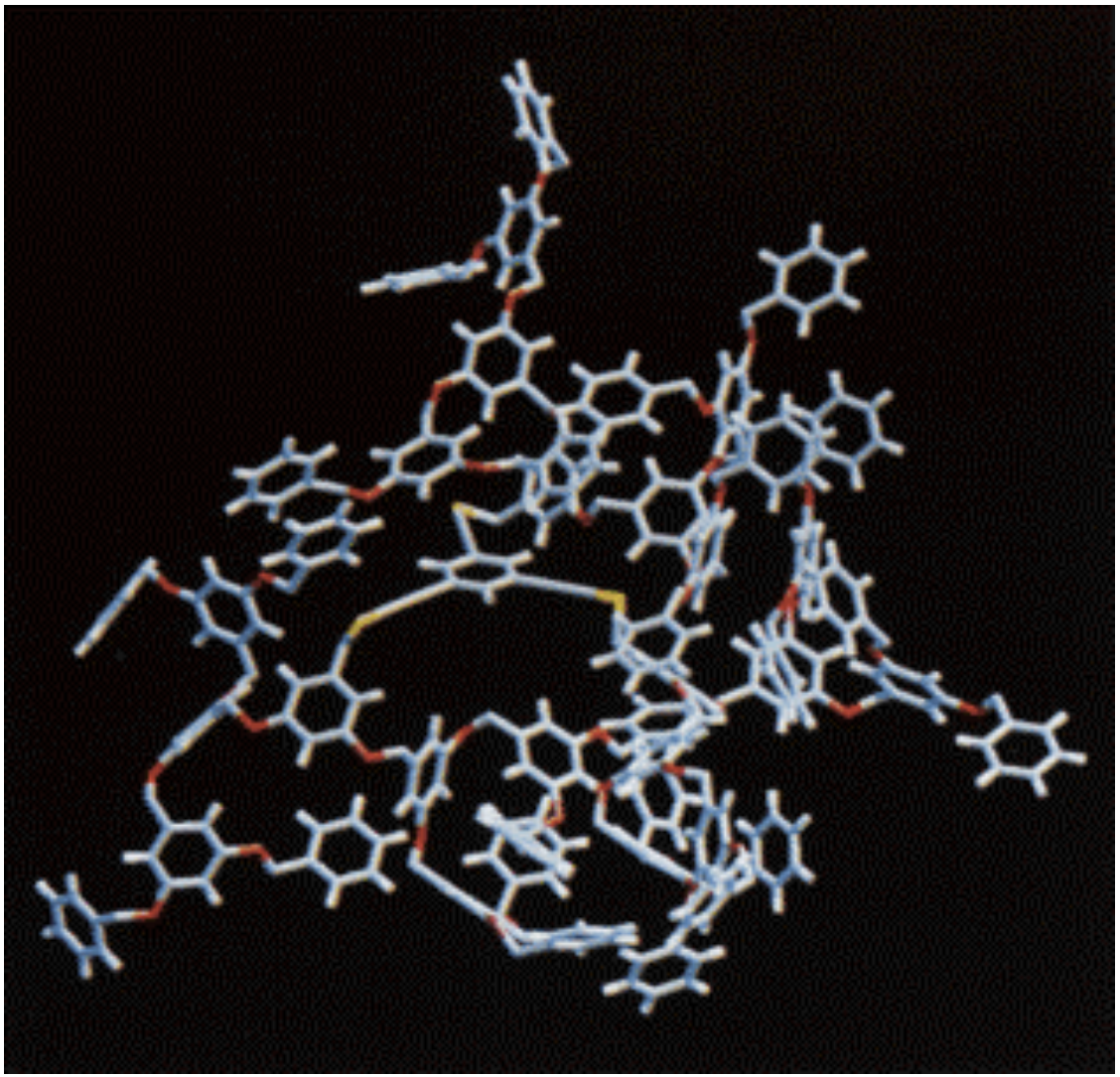


4.6 Lead Compounds - *de novo* design



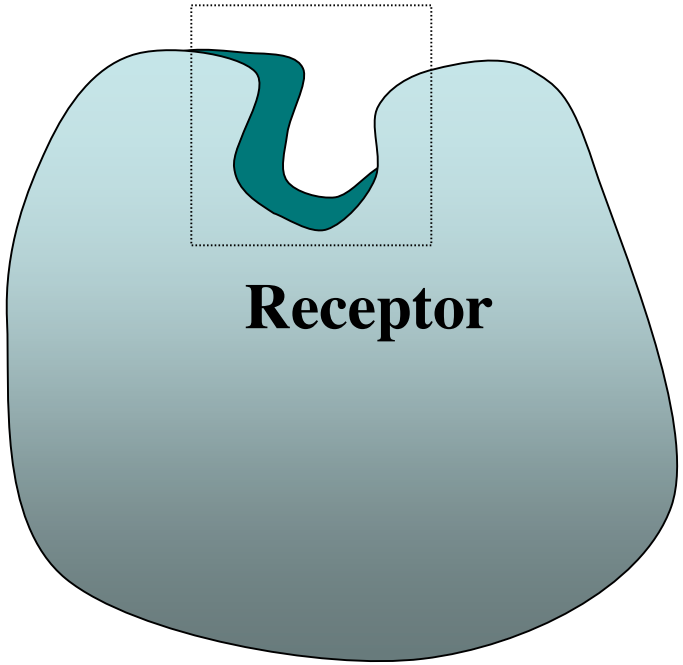
X-RAY CRYSTALLOGRAPHY

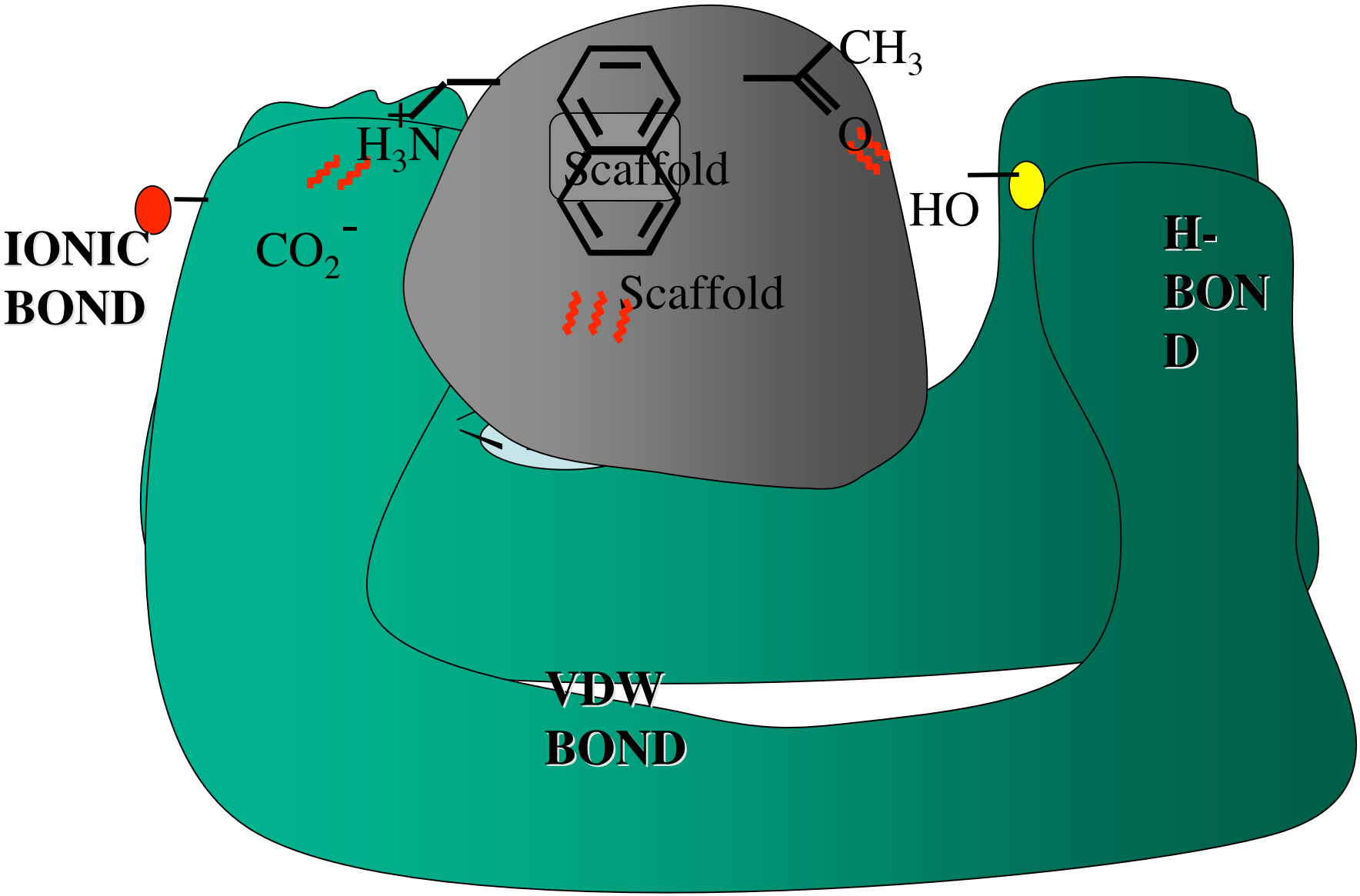
4.6 Lead Compounds - *de novo* design



PROTEIN STRUCTURE

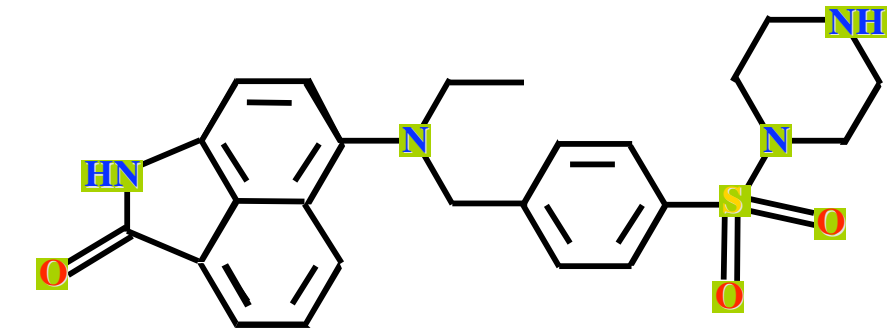
4.6 Lead Compounds - *de novo* design




CH3
H3N
O
Scaffold
HO
IONIC BOND
CO2-
Scaffold
H-BOND
VDW BOND

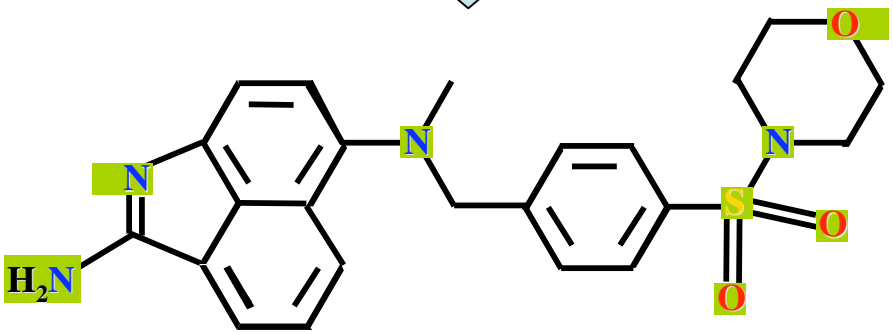
4.6 Lead Compounds - *de novo* design

THYMIDYLATE KINASE INHIBITOR



LEAD COMPOUND

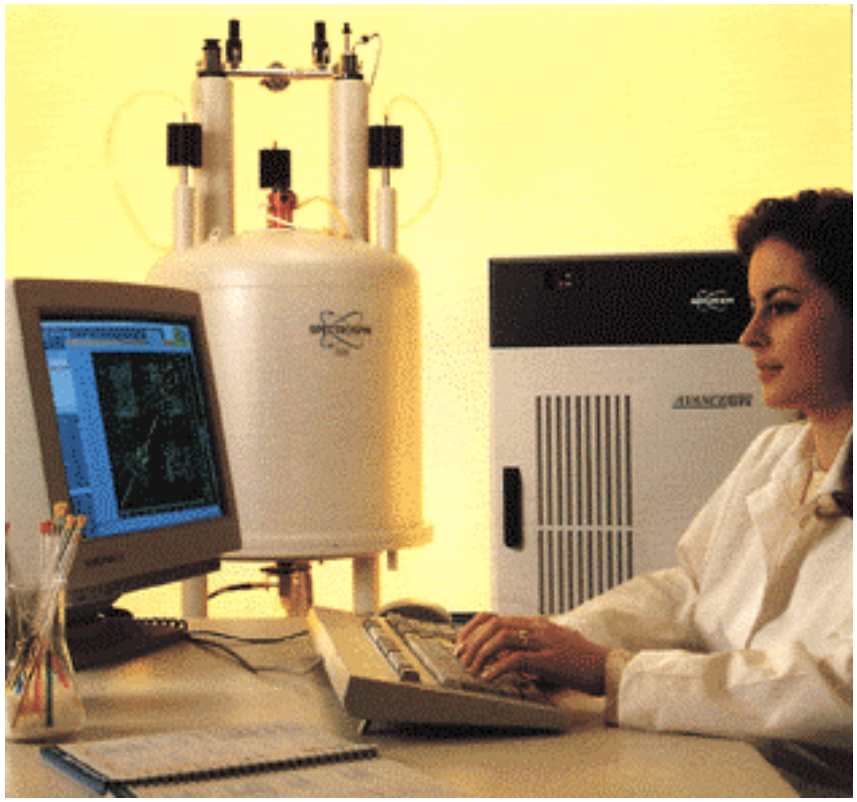
Optimisation



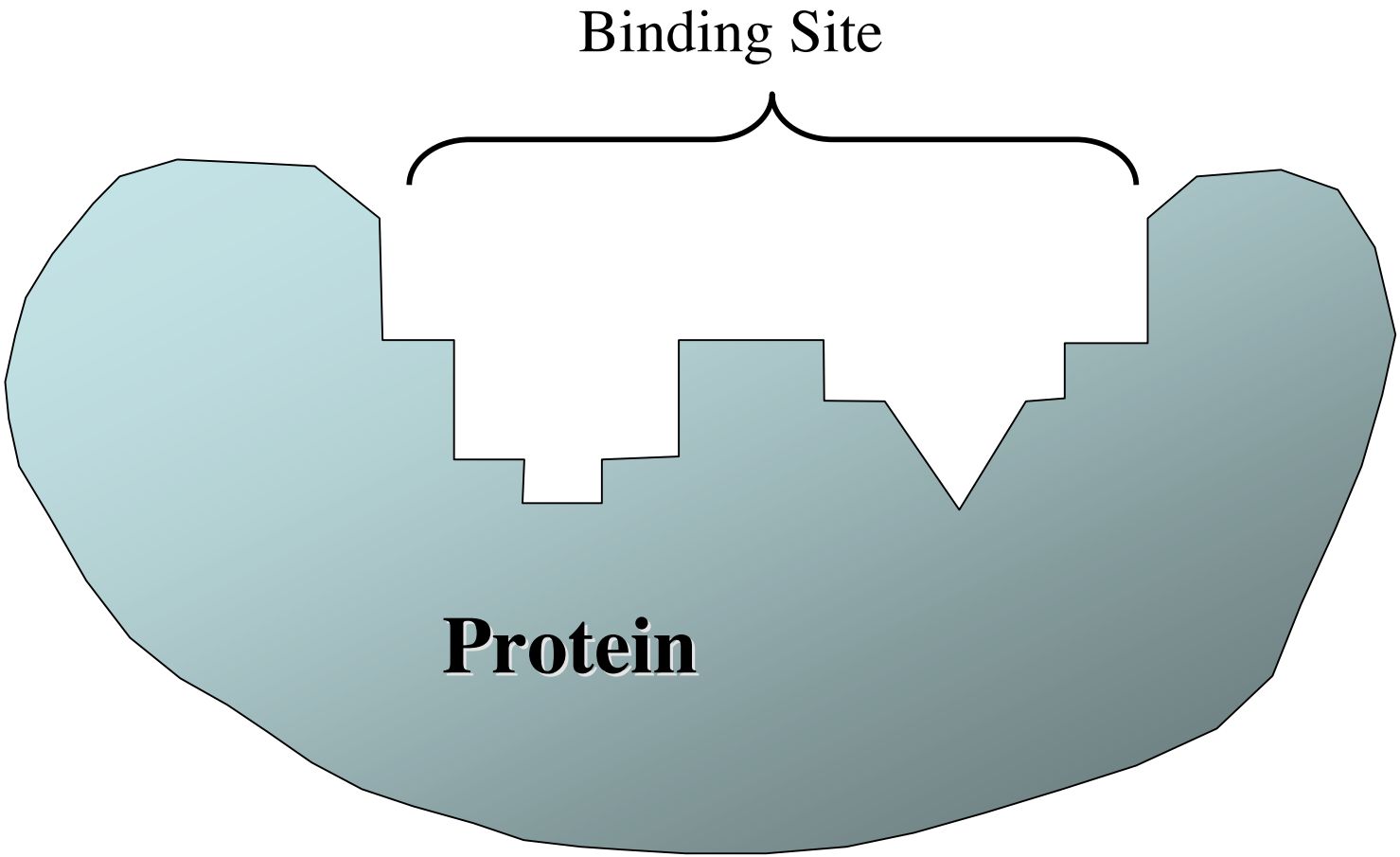
ANTICANCER AGENT

4.7 Design of Lead Compounds using NMR Spectroscopy

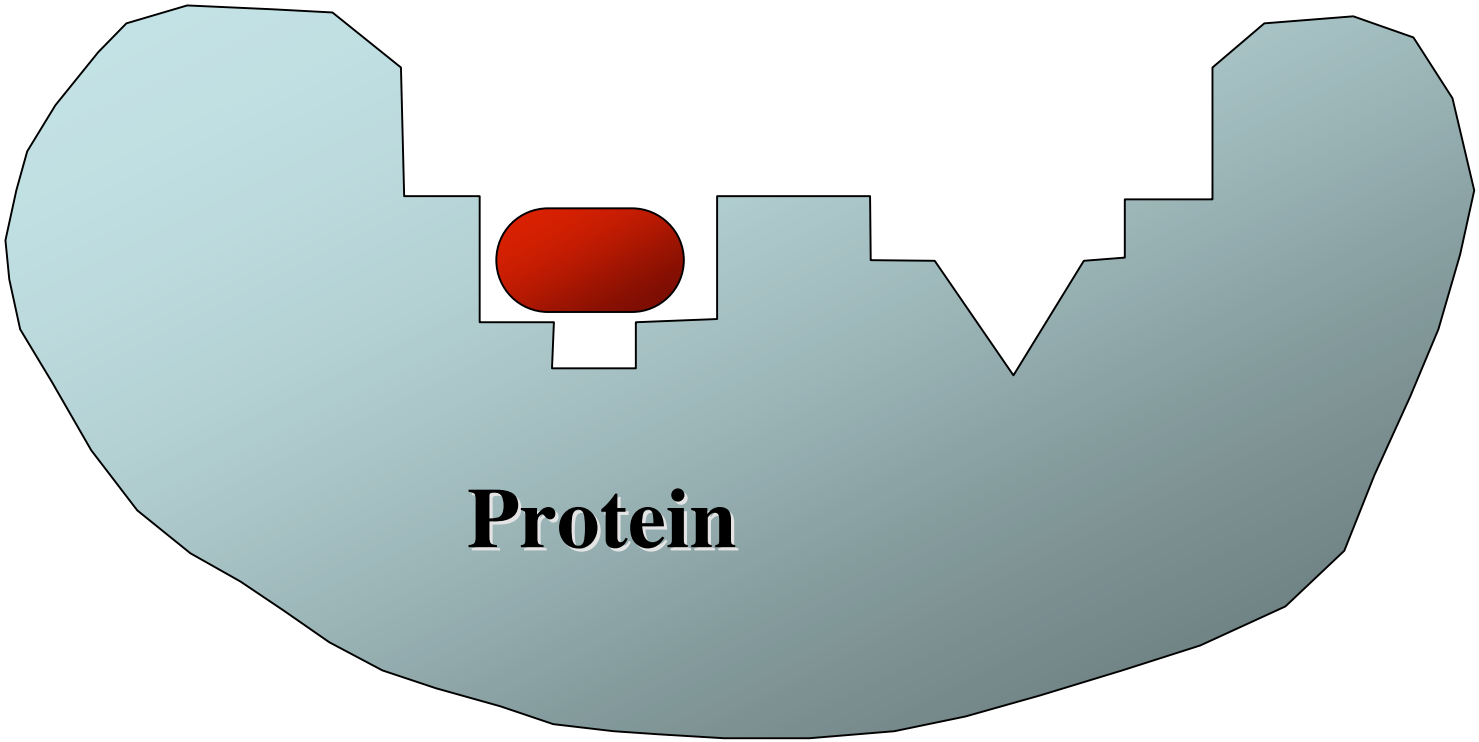
NMR SPECTROSCOPY



4.7 Design of Lead Compounds using NMR Spectroscopy

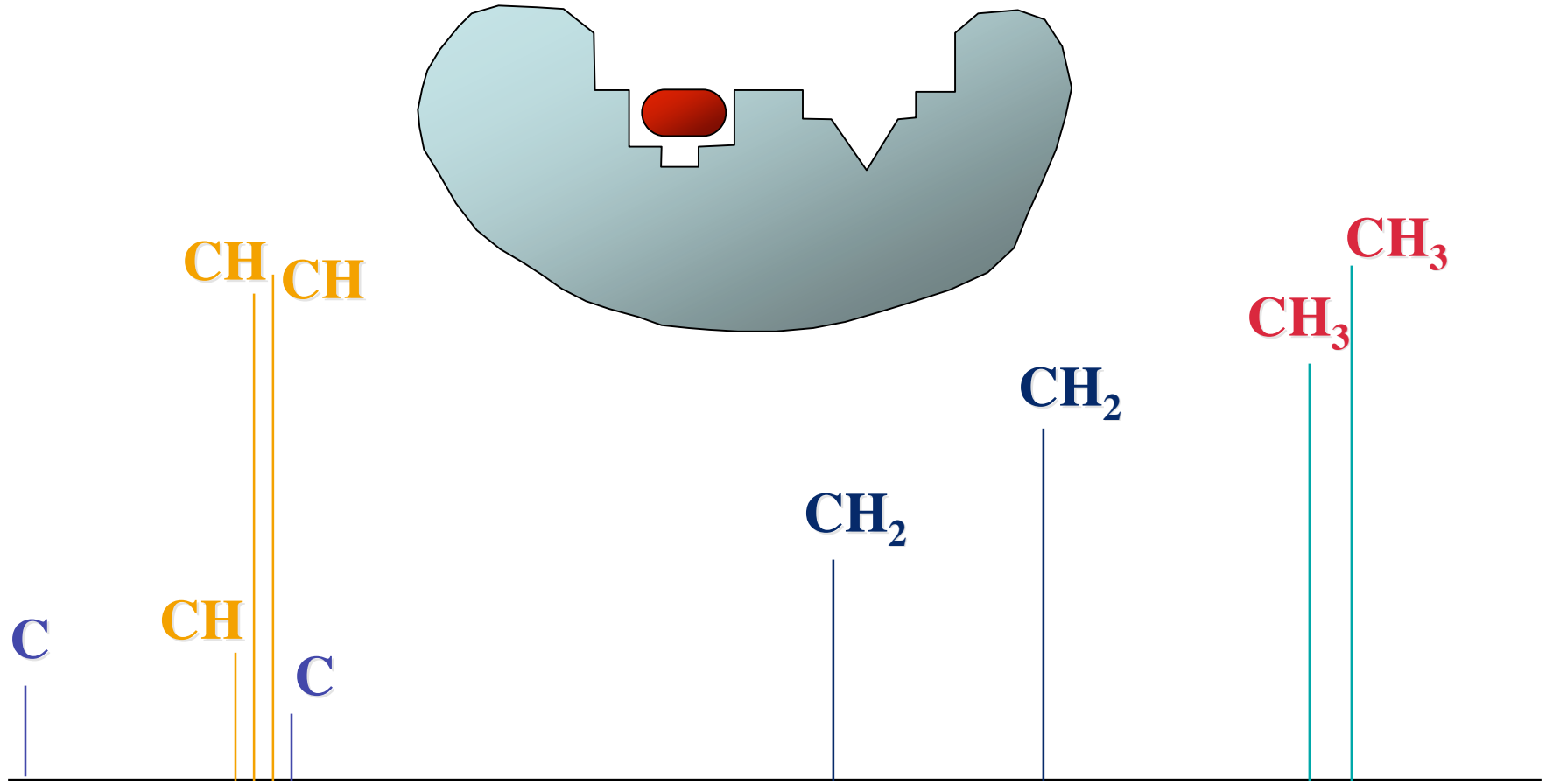


4.7 Design of Lead Compounds using NMR Spectroscopy



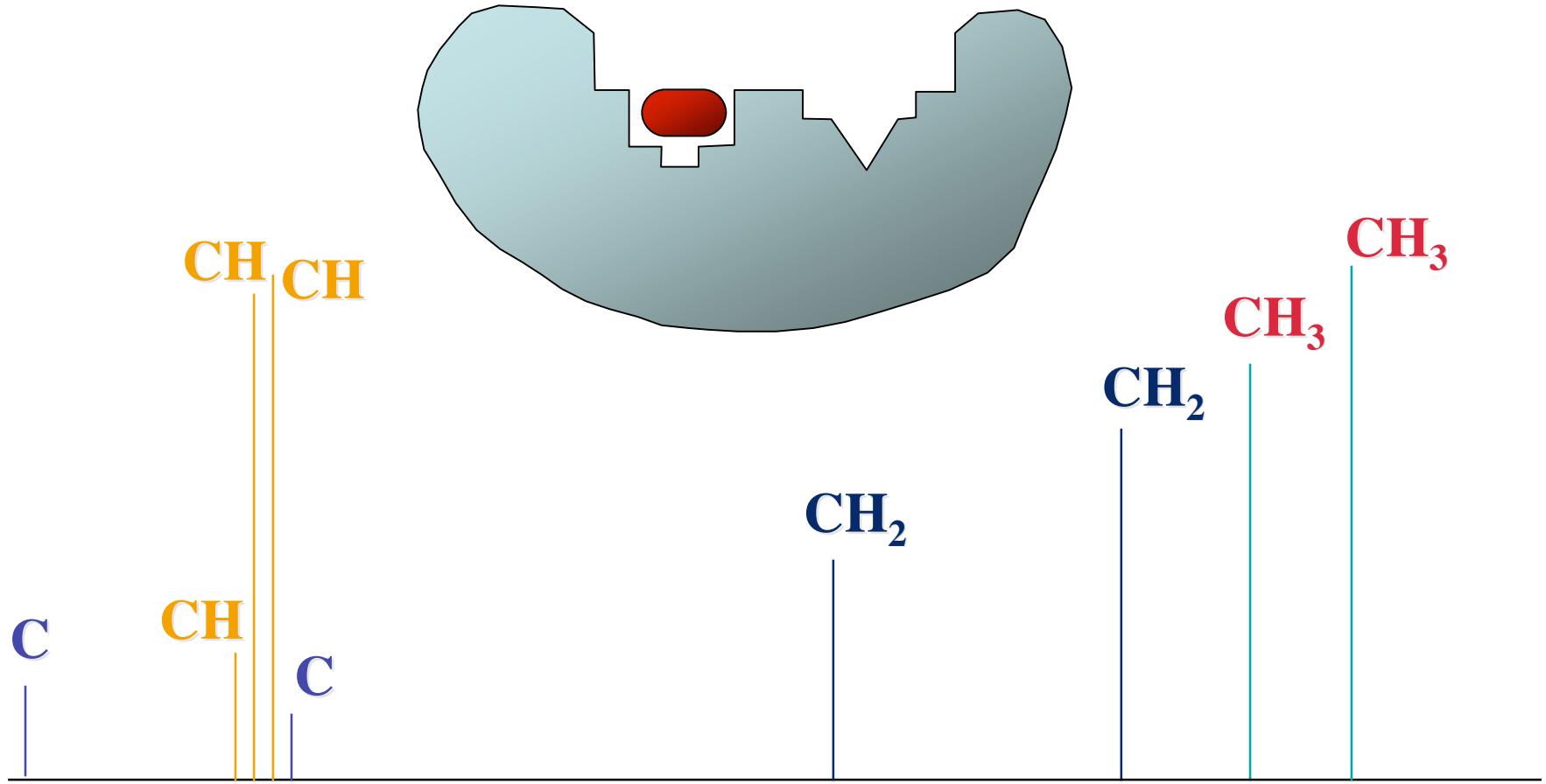
NO OBSERVABLE BIOLOGICAL EFFECT

4.7 Design of Lead Compounds using NMR Spectroscopy



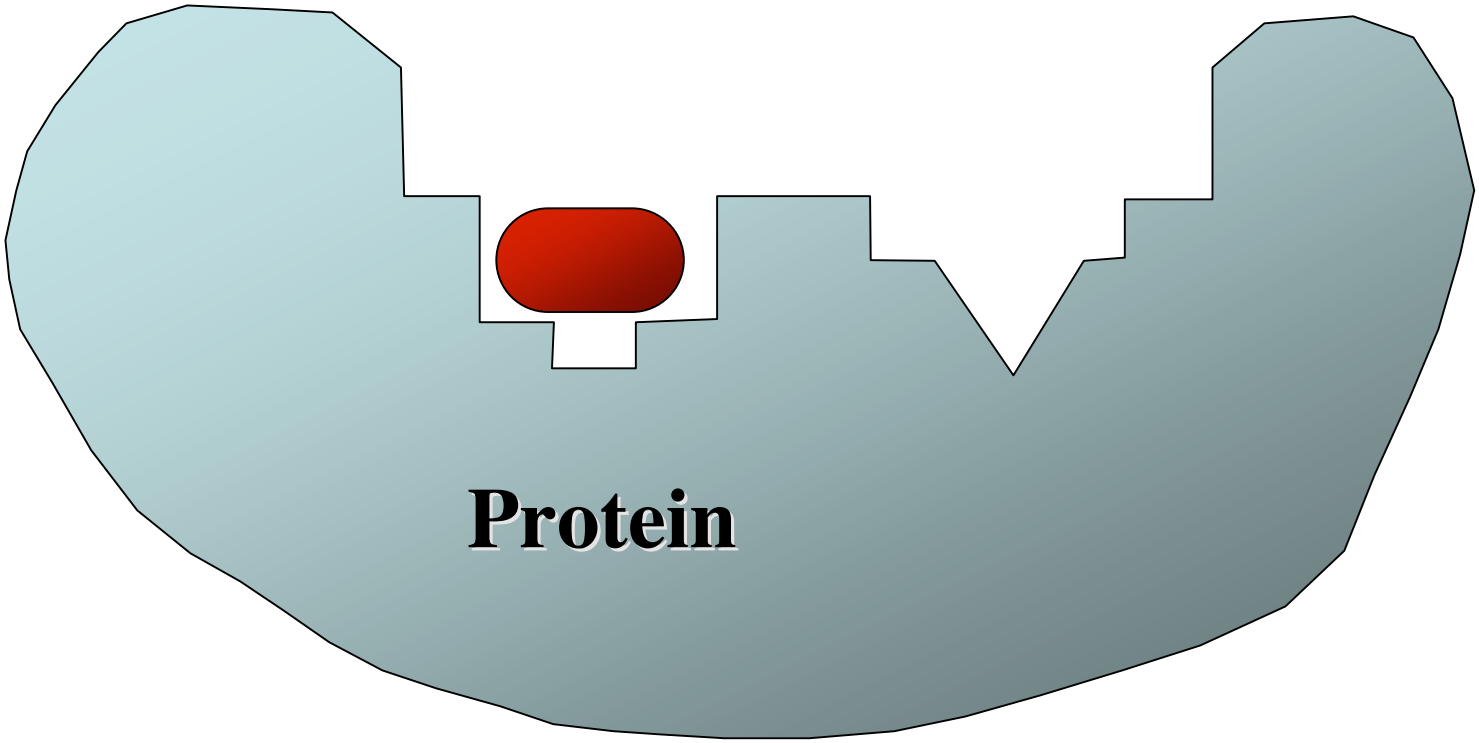
^{13}C NMR

4.7 Design of Lead Compounds using NMR Spectroscopy



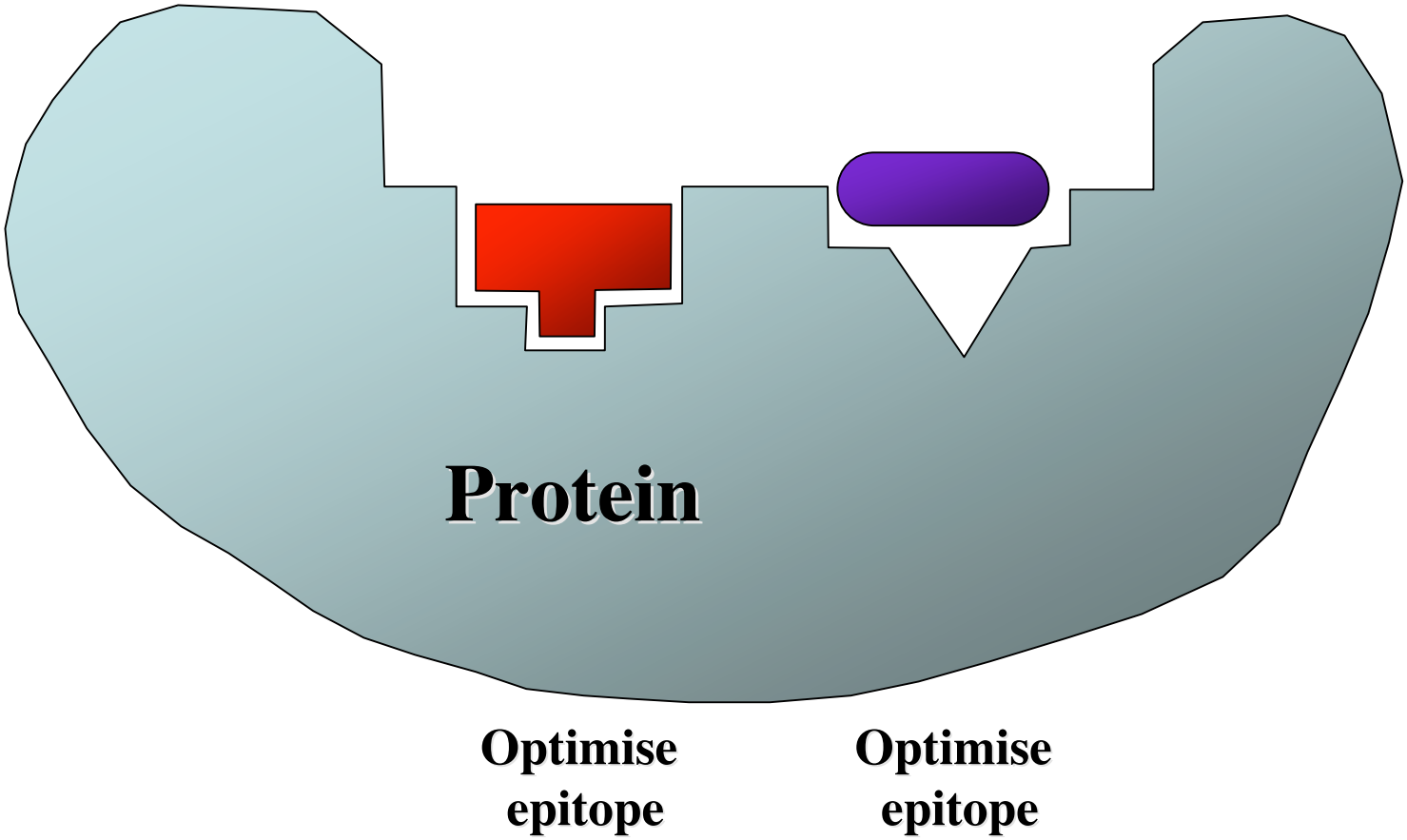
^{13}C NMR

4.7 Design of Lead Compounds using NMR Spectroscopy

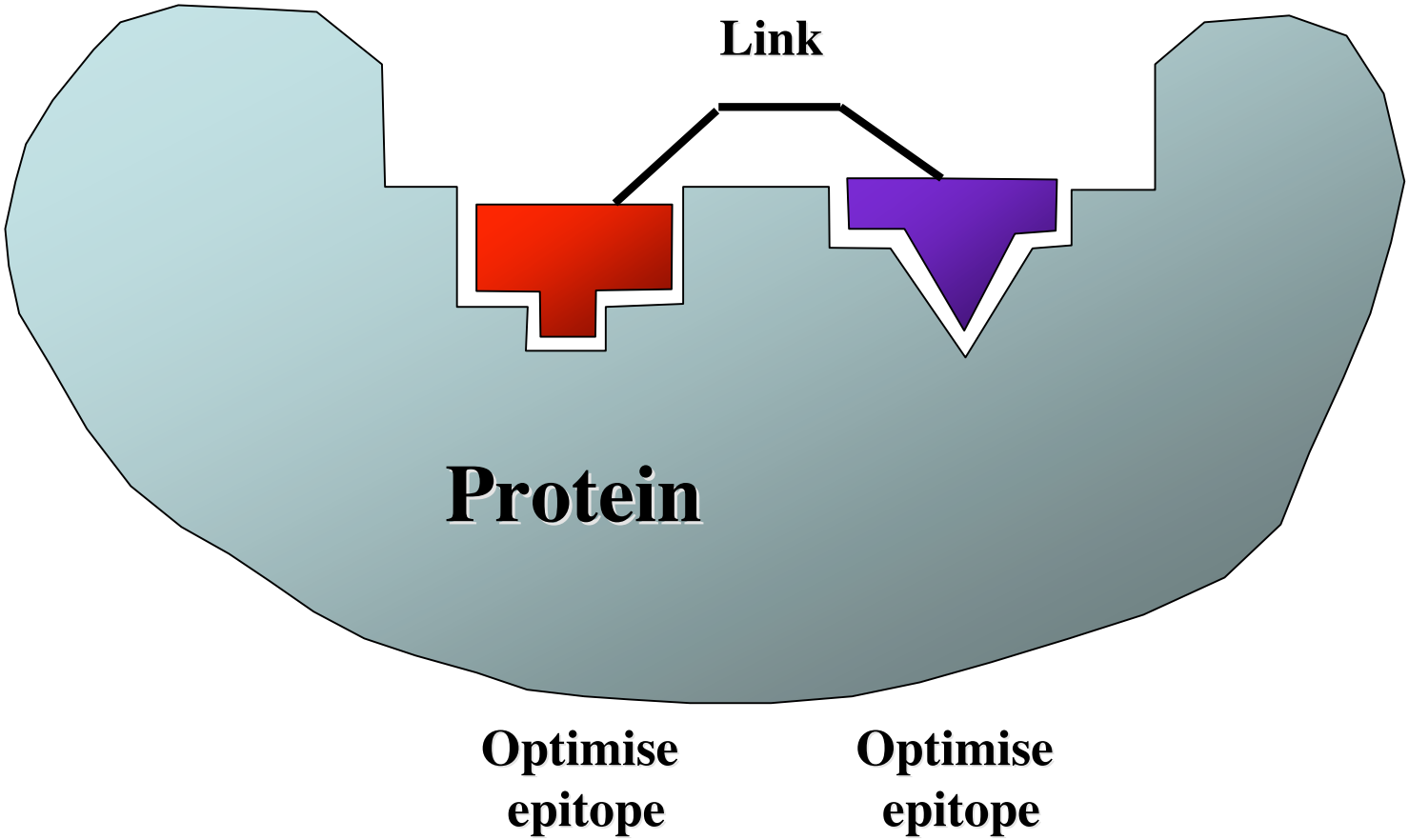


Optimise epitope

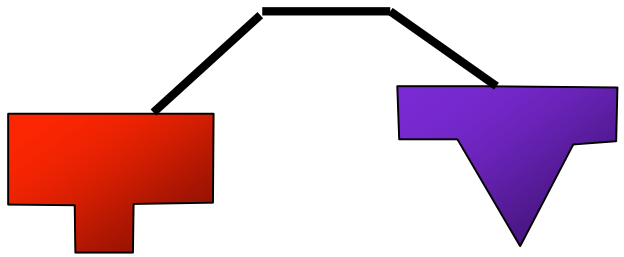
4.7 Design of Lead Compounds using NMR Spectroscopy



4.7 Design of Lead Compounds using NMR Spectroscopy



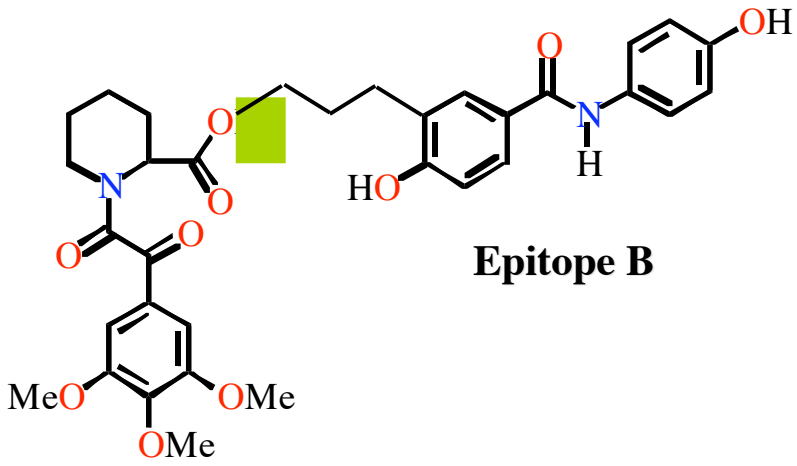
4.7 Design of Lead Compounds using NMR Spectroscopy



LEAD COMPOUND

4.7 Design of Lead Compounds using NMR Spectroscopy

Design of a lead compound as an immunosuppressant

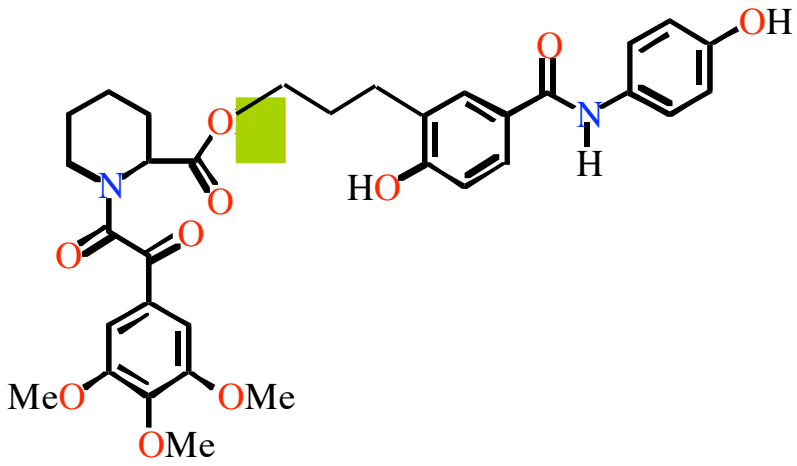


Epitope B

Epitope A

4.7 Design of Lead Compounds using NMR Spectroscopy

Design of a lead compound as an immunosuppressant



Lead compound