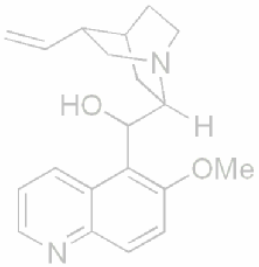
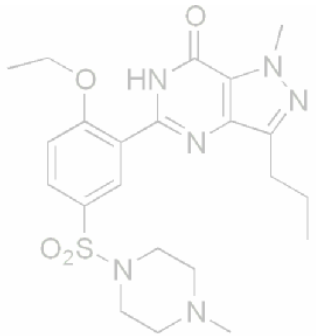
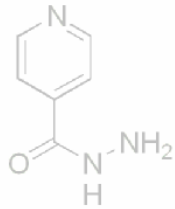
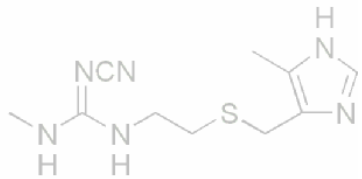
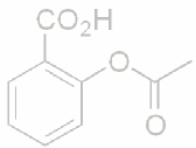
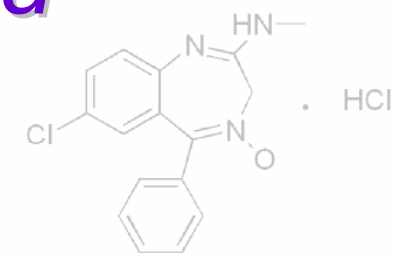
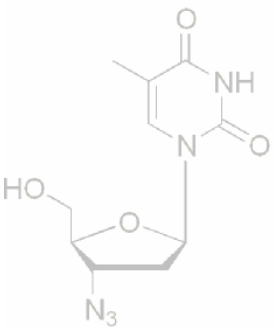
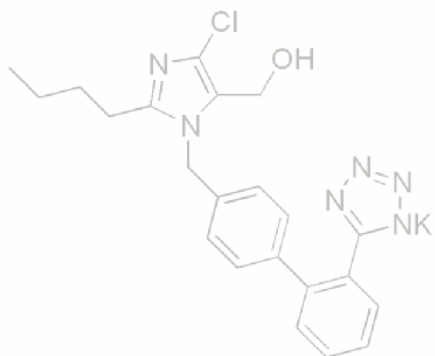
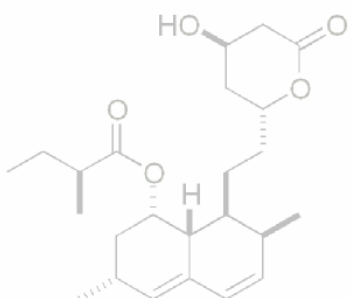
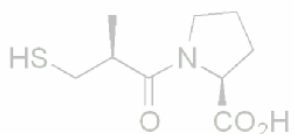





Medicinal Chemistry:
Blockbuster Drugs and How to Make Them

Dr. Paul A. Clarke

Room C170

Resources

‘Organic Chemistry’ by Clayden, Greeves, Warren and Wothers.

‘Top Drugs: Top Synthetic Routes’ by John Saunders. Oxford Primer

http://www.york.ac.uk/res/pac/teaching/medchem.html

Scope of the Course

In the limited time available we will look at how medicinal chemists have developed therapies for a number of human diseases. A brief introduction to the disease area and the biological target will be given. This will be followed by an analysis of the rational design and syntheses of a number drug molecules. Particular emphasis will be placed on the organic chemistry used in each synthesis.

Learning Objectives

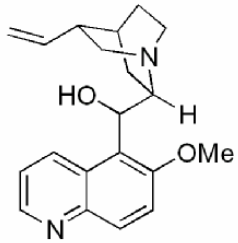
1) To appreciate the general strategies used by medicinal chemists for the synthesis/development of potential drug candidates.

2) To know the structures of the drug molecules discussed and to have a basic understanding of their mode of action.

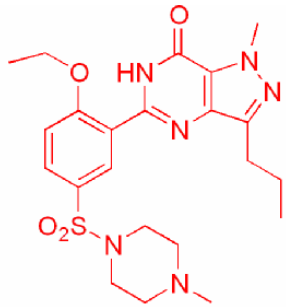
3) To gain a mechanistic understanding of the synthetic procedures utilised to prepare drugs discussed in this course.

4) Be able to identify good and bad points in the synthesis of a drug molecule.

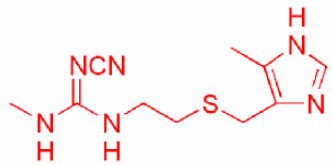
Examples of Pharmaceuticals



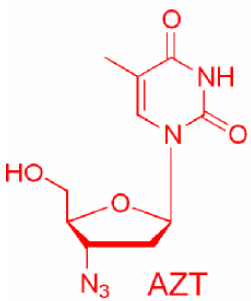
quinine
(anti-malaria in tonic water)



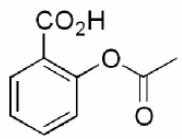
Viagra
(impotence treatment)



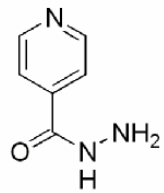
Tagamet (anti-ulcer drug)



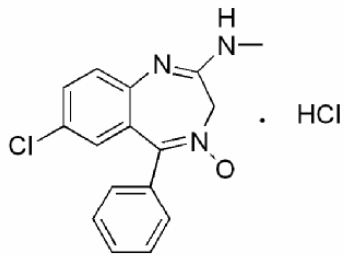
AZT
(HIV treatment)



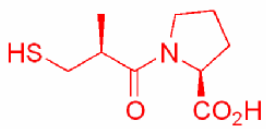
Asprin (analgesic)



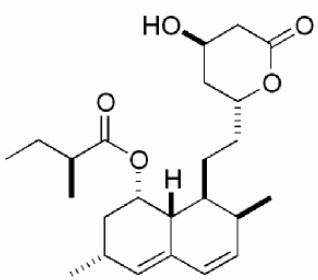
Isonazid
(anti-tuberculosis)



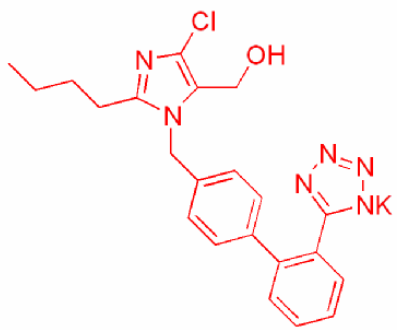
Librium (mood altering)



Captopril
(anti-hypertensive)



Lovastatin
(cholesterol lowering)



Losartan (anti-hypertensive)

Course Outline

Introduction to medicinal chemistry research.

Control of Blood Pressure:
ACE inhibitors: captopril
Blockade of Angiotensin-II receptors: losartan

Anti-ulcer remedies:
Antagonists of histamine: cimetidine, ranitidine

Erectile Disfunction:
Inhibitors of type-5 CGMP Phosphodiesterase: viagra

The future: natural products, chemical space and diversity

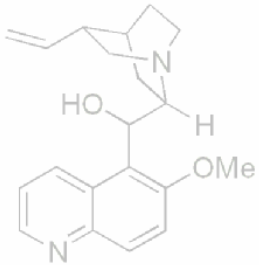
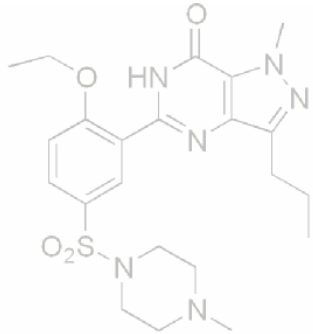
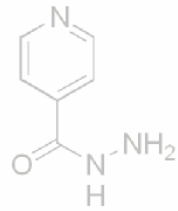
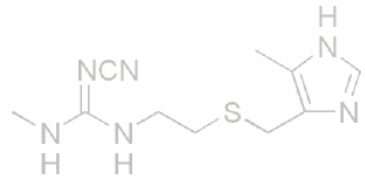
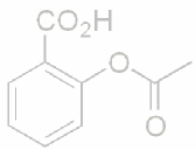
Introduction:
Medicinal Chemistry Research

Medicinal Chemists aim to synthesise small molecules which will interact with biological systems to produce an effect which will provide relief from or cure for a human disease or ailment.

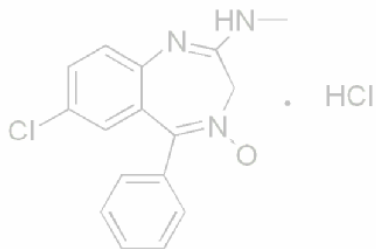
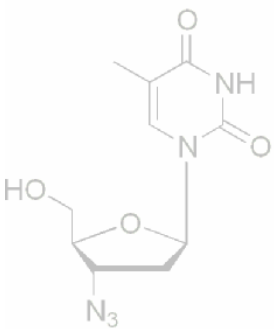
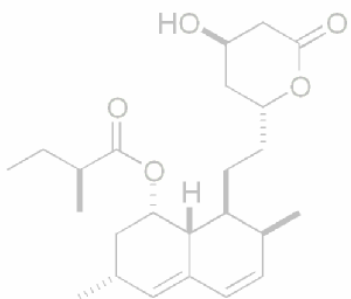
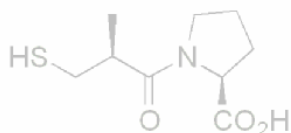
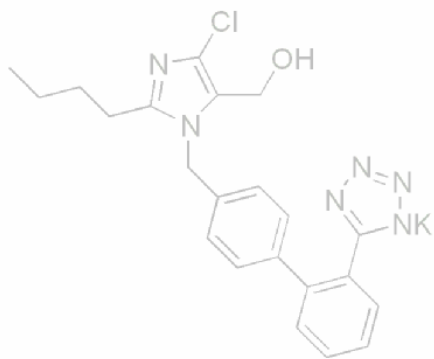
There are in general 3 strategies:

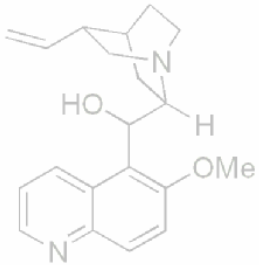
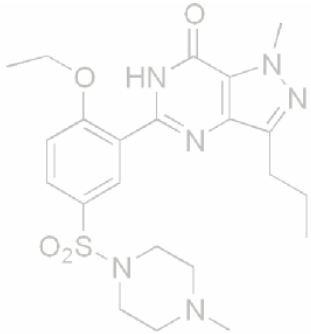
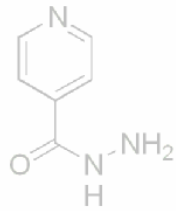
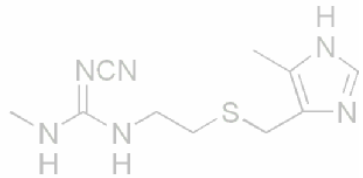
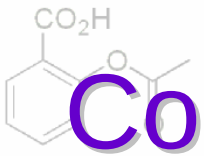
Most drug molecules synthesised conform to a set of emprical observations noted by Lipinski. This has since become known as Lipinski's Rule of Five. These are that, in general, an orally active drug has:

There are two typical misunderstandings with these rules.
1) Molecules that conform to this rule are not automatically drug-like.
2) This rule was derived for drugs and not for lead structures, which usually have a lower molecular weight, fewer rings, fewer rotatable bonds, and a lower lipophilicity. However, medicinal chemists are prone to forget this!

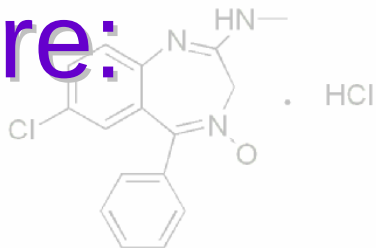
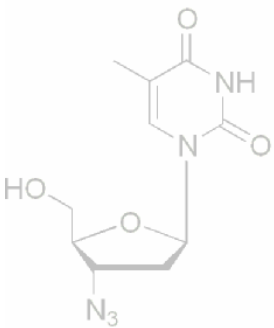
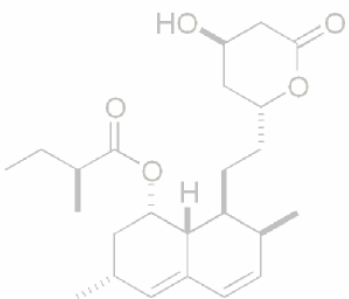
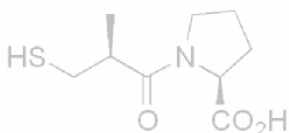
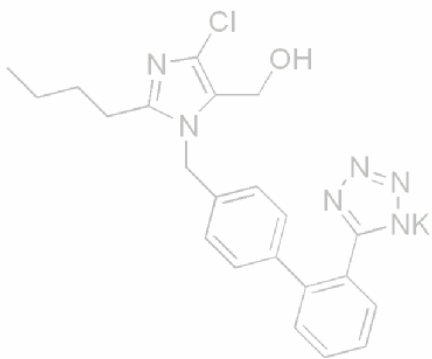






Case Studies

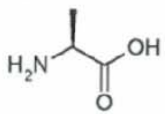






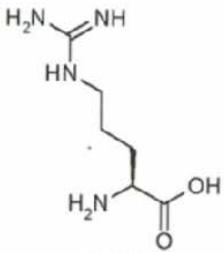






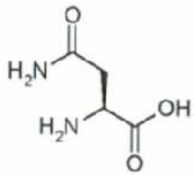
Control of Blood Pressure: ACE Inhibitors

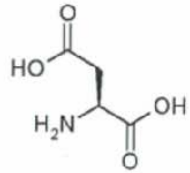






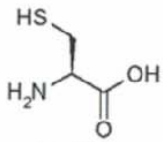
The Twenty Proteinogenic α-Amino Acids

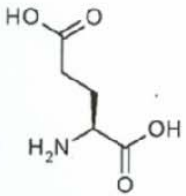

Alanine
(Ala, A)

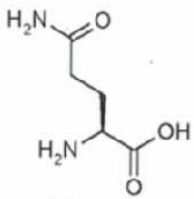

Arginine
(Arg, R)

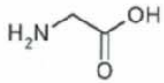

Asparagine
(Asn, N)

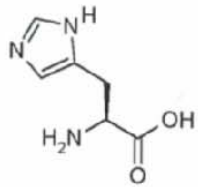

Aspartic acid
(Asp, D)

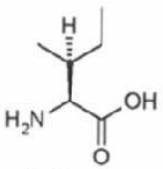

Cysteine
(Cys, C)

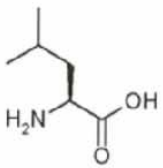

Glutamic acid
(Glu, E)

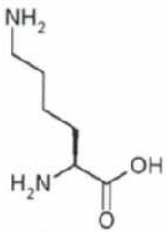

Glutamine
(Gln, Q)

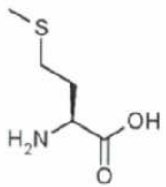

Glycine
(Gly, G)

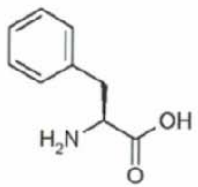

Histidine
(His, H)

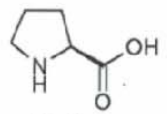

Isoleucine
(Ile, I)

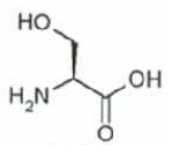

Leucine
(Leu, L)

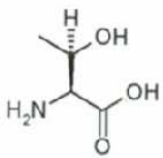

Lysine
(Lys, K)

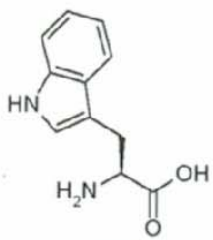

Methionine
(Met, M)

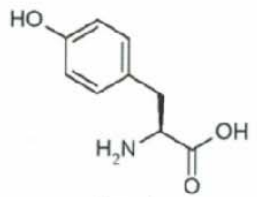

Phenylalanine
(Phe, F)

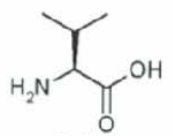

Proline
(Pro, P)


Serine
(Ser, S)


Threonine
(Thr, T)


Tryptophan
(Trp, W)

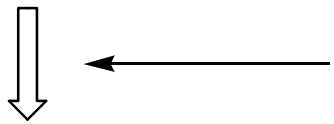

Tyrosine
(Tyr, Y)


Valine
(Val, V)

Biological Target

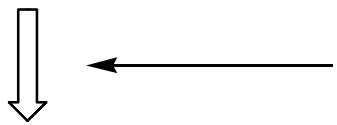
Angiotensinogen

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-Tyr-Ser-Protein



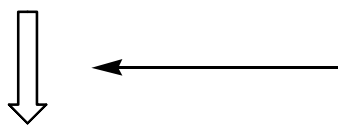
Angiotensin-I, A-I

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-OH

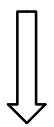


Angiotensin-II, A-II

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH



Activation of A-II receptors
Aldosterone Release and Sodium Reabsorption



Vasoconstriction
Water Retention

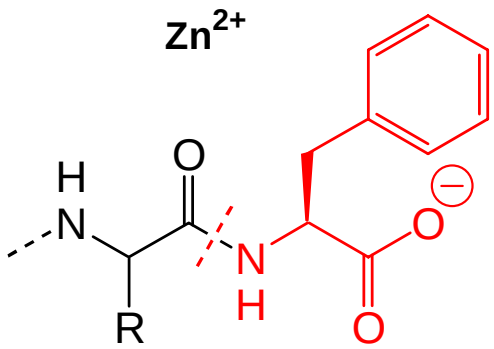
Angiotensin converting enzyme (ACE) controls the level of angiotensin II, a potent vasoconstrictor.

Aspartyl proteinase cleaves angiotensinogen at Leu^{10}-Val^{11} to produce A-I in the rate limiting step.

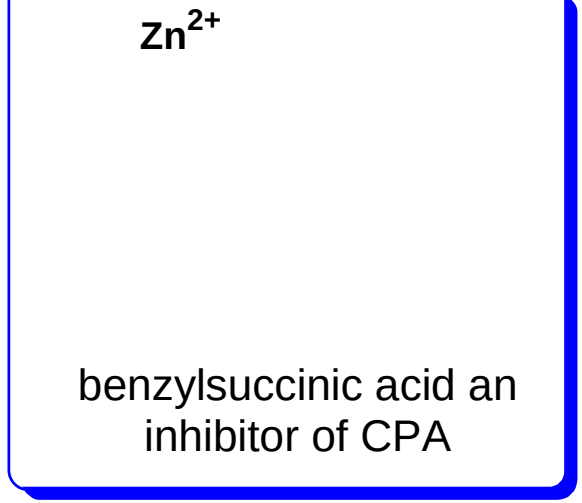
The resulting decapeptide is cleaved at Phe^{8}-His^{9} by ACE to generate A-II, which can raise blood pressure either by directly acting on the A-II receptors or indirectly by the release of aldosterone from the kidney.

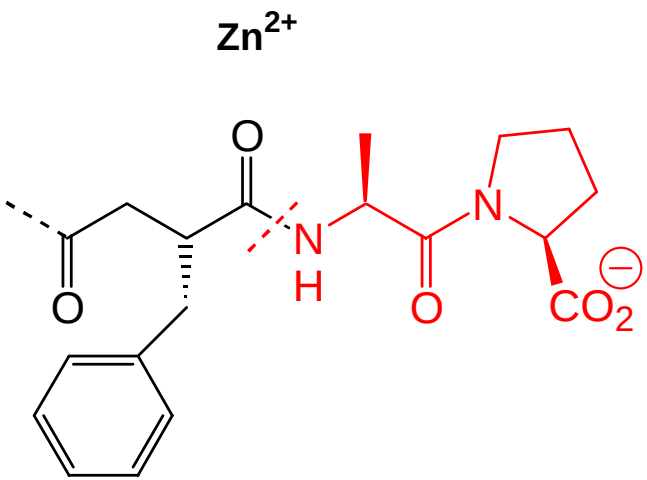
Intervention on the pathway at any point should result in reduced blood pressure in a hypertensive patient.

Mode of Action

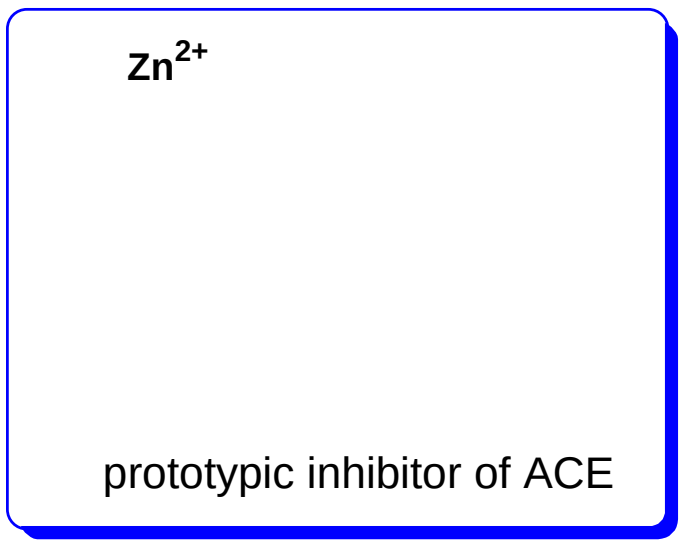


C-terminus of carboxypeptidase A (CPA) substrate with scissile amide bond aligned wit active site Zn





C-terminus of A-I the substrate for ACE



It was noted that the active site of ACE was similar to that of CPA, and that (*D*)-benzylsuccinic acid was a potent inhibitor of CPA.

It was postulated that the carboxylic acid entity of (*D*)-benzylsuccinic acid was interacting with the active site Zn and inhibiting CPA.

Extending the inhibitor by one amino acid residue and taking into account the substrate differences between the two enzymes may produce a potent ACE inhibitor.

Building on the logic that –SH has a greater affinity to Zn^{2+} than $–CO_2H$ led to the discovery of captopril.

Captopril

First Generation Synthesis of Captopril

DCCI coupling of 3-acetylthio-2-methylpropionic acid and *L*-proline *tert*-butyl ester generated a 1:1 mixture of diastereomers.

These were separated by crystallisation of the dicyclohexylamine salts, which afforded the (S,S) diastereomer, the (R,S) diastereomer was obtained from the mother liquors.

Thiol group unmasked with methanolic ammonia. Care was needed to exclude oxygen from this reaction to avoid disulfide formation.

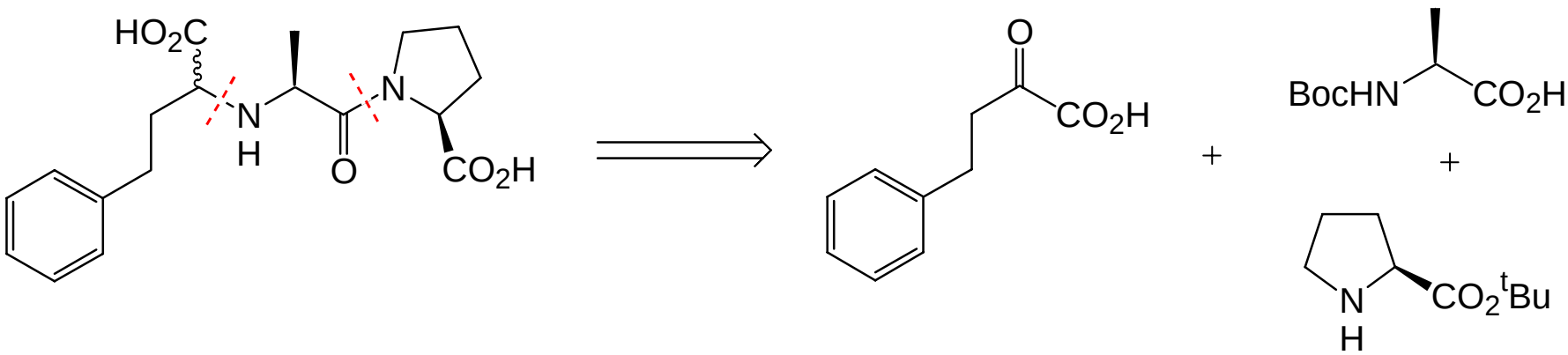
The (S,S) isomer is 100-fold more active than the (R,S) isomer

An Alternative Synthesis of Captopril

Microbiological mediated hydration is stereoselective and obviates the need to separate diastereomers.

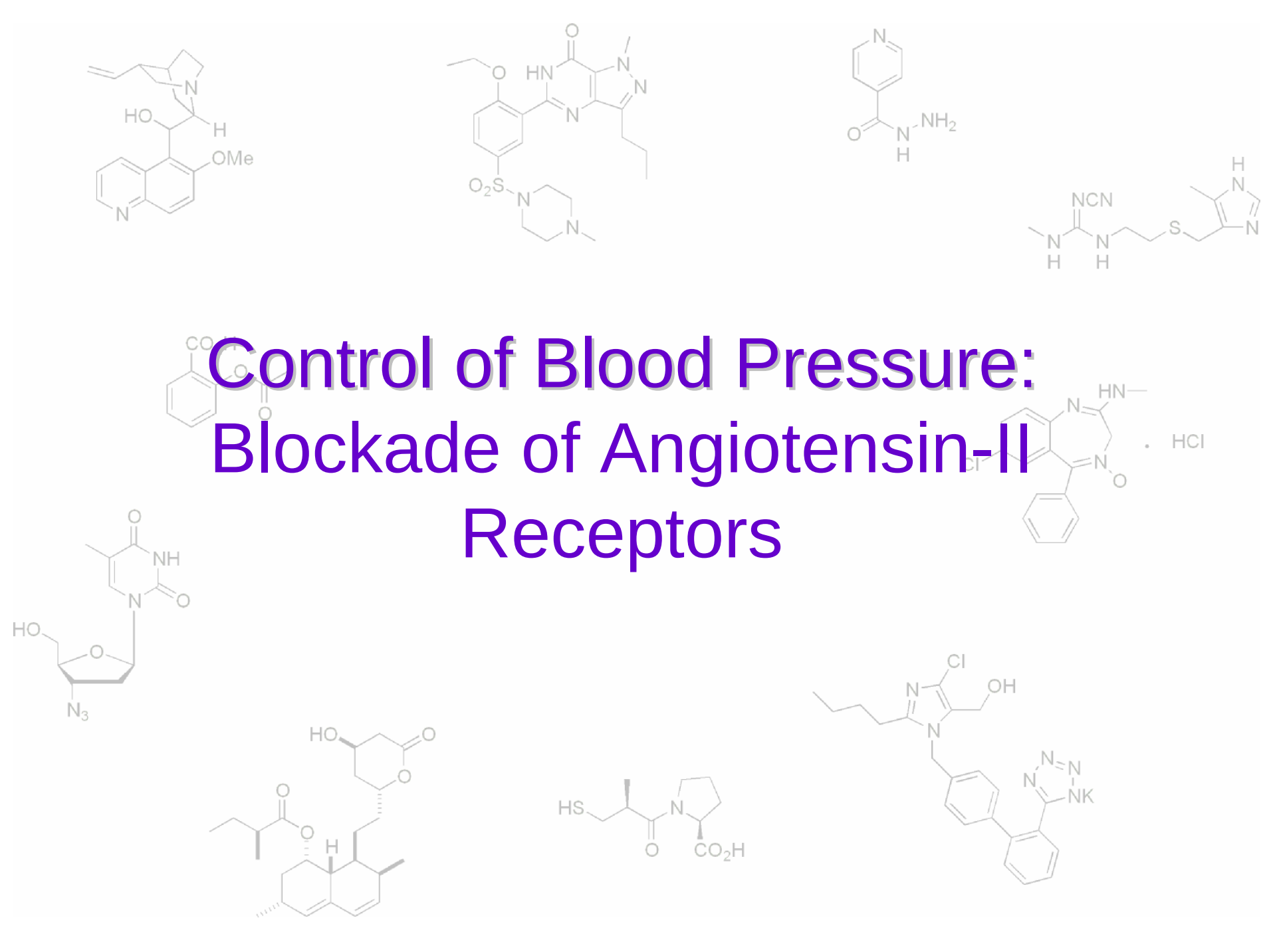
No need to protect the thiol group.

Enalaprilat



Suggest a synthesis for the ACE inhibitor enalaprilat from the starting materials shown.

Hint: the final transformation is a reductive amination.



Control of Blood Pressure: Blockade of Angiotensin-II Receptors

Biological Target

Angiotensinogen

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-Tyr-Ser-Protein

Renin Inhibitors

Angiotensin-I, A-I

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-OH

ACE Inhibitors

Angiotensin-II, A-II

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH

Angiotensin-II Antagonists

Activation of A-II receptors
Aldosterone Release and Sodium Reabsorption

Vasoconstriction
Water Retention

ELEVATED BLOOD PRESSURE

ACE inhibitors also interfere in the bradykinin pathway, which can lead to side effects in certain patient groups. Inhibition in the angiotensin cascade at a later point could be effective at reducing hypertension and remove some side effects asssociated with ACE inhibitors.

Angiotensin-II antagonists are one such treatment.

In 1982 the first non-selective, non-peptide inhibitor of angiotensin-II was discovered by a chance observation of the cardiovascular properties of a compound originally synthesised as an anti-inflammatory agent (**1**). This finding, coupled with ideas on the active site conformation of angiotensin-II derived from molecular modelling studies, led to the synthesis of losartan.

Losartan is as effective as some ACE inhibitors in reducing blood pressure in hypertensive patients. Interestingly, it has a longer duration of action, suggesting an active metabolite. It is likely that this metabolite is the carboxylic acid derived from liver induced oxidation of the primary alcohol.

Synthesis of Losartan

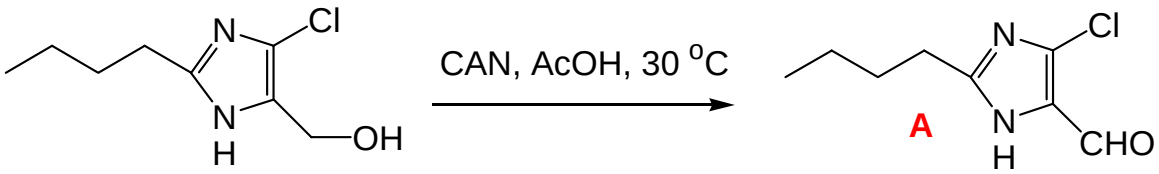
Imidazole formation and chlorination gave the first coupling partner in the synthesis. Ullmann biaryl synthesis followed by a radical bromination gave the biphenyl unit required.

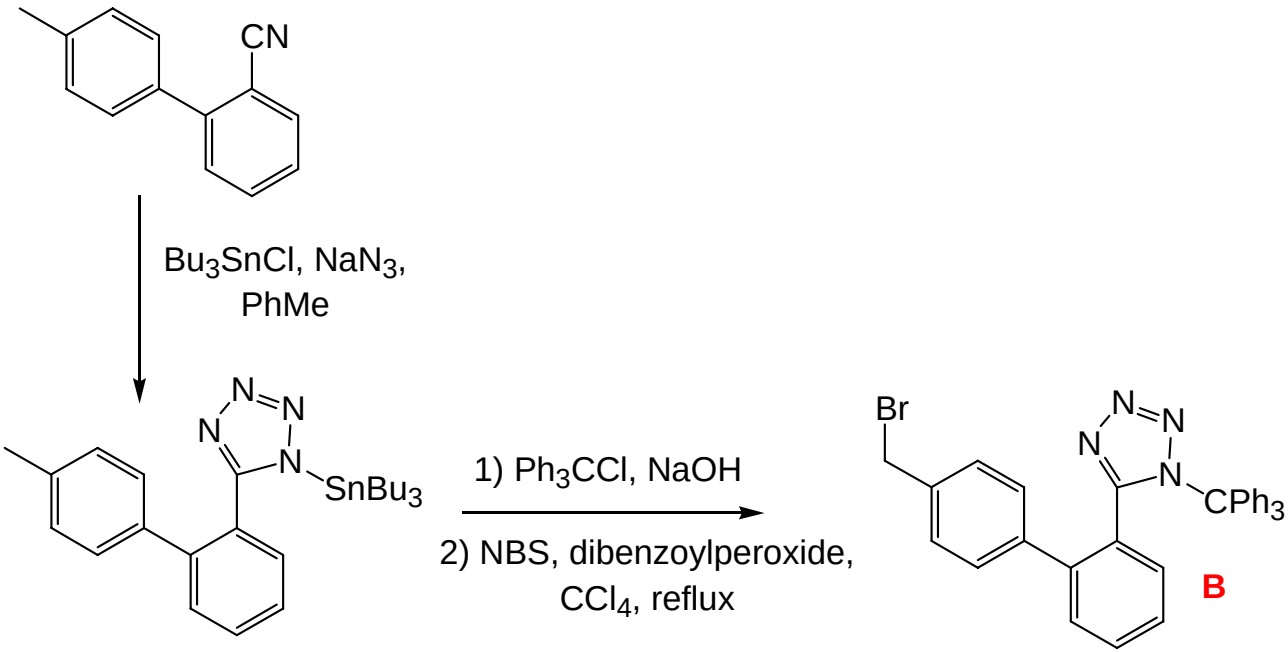
Synthesis of Losartan

Two major limitations of this synthesis.

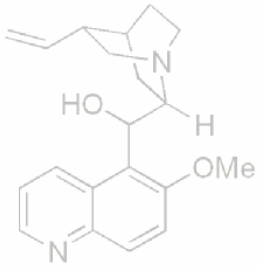
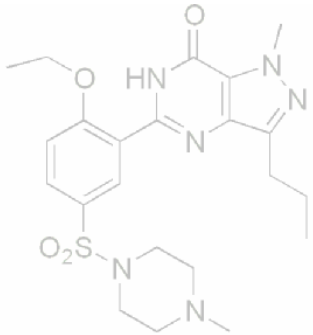
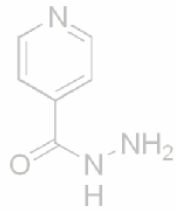
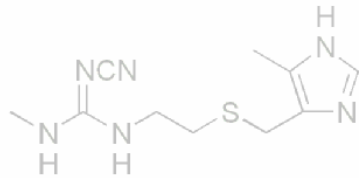
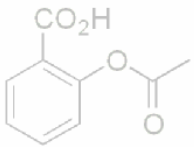
1) Alkylation of the imidazole resulted in both possible isomers which had to be separated by chromatography.
2) Tetrazole formation took 9 days and gave a low yield of product.

An Alternative Synthesis of Losartan

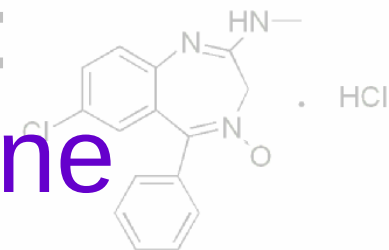
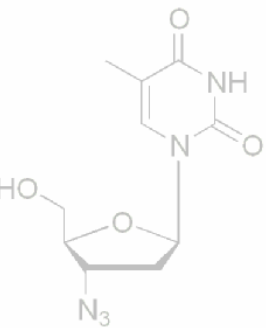
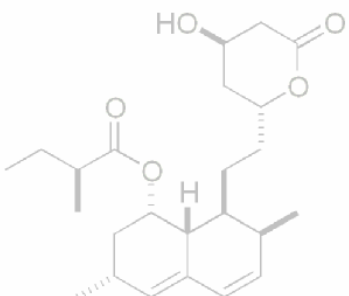
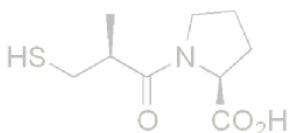
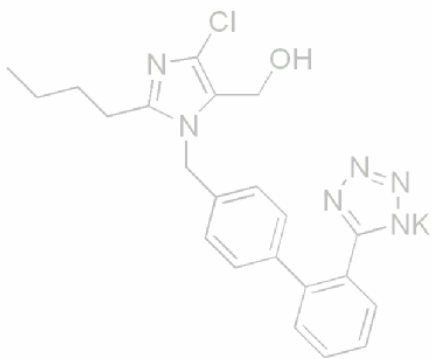




1. Higher yields in the tetrazole formation were achieved when tributyltin azide was used.
2. Alkylation using the imidazole 5-carboxaldehyde was regioselective for the desired isomer.
3. Sodium borohydride reduction of the aldehyde and removal of the trityl group revealed losartan.

Anti-ulcer remedies:
Antagonists of histamine

Introduction and Mode of Action

Histamine was known to stimulate the smooth muscle in the gastrointestinal tract and this action was specifically blocked by the drug mepyramine. However, there are also other actions of histamine which are mepyramine insensitive, such as stimulation of acid secretion in the stomach. To account for this observation the receptors were assumed to be different and were labeled H_1 and H_2 respectively.

It is now known that these receptors belong to a large gene superfamily of G-protein coupled receptors (GPCR's) thus called because agonist (histamine) occupation of the receptor leads to activation of the associated intracellular G-protein.

Introduction and Mode of Action

In this way an intracellular event, such as histamine binding may be transformed into an intracellular signal which forms the basis for a physiological response – release of H^+ from the parietal cells in the stomach. Since it is known that excess acid is responsible for pain associated with peptic ulcers, it was believed that specific H_2 antagonists would give relief to patients and also improve the chances of healing the lesion. These ideas gave rise to the most successful class of drugs to emerge out of medicinal chemistry research.

Synthesis of Cimetidine

A hypothesis was developed that the antagonist could resemble the endogenous ligand (*i.e.* histamine) and early studies focused on this approach.

Na and liq. NH_3 was the method of choice for reduction of the ester. Interestingly, over reduction to give Birch intermediates was not observed.

Alternative Synthesis of Cimetidine

Later diphenylcyanocarbonimidate was developed as a low cost alternative to *N*-cyanoguanidine. This also avoided the displacement of the toxic gaseous side product (MeSH).

Alternative Synthesis of Cimetidine

During a study 2-(*N*-cyanoimino)thiazolidine derivatives towards nucleophiles an interesting N to S transfer occurred, which was subsequently used in a new synthesis of cimetidine.

Sir James W. Black

In 1988, James Black was awarded the Nobel Prize for Medicine for his development of the H_2-receptor antagonist cimetidine and the development of the beta-blocker drug propranolol.

Born 1924

http://nobelprize.org/nobel_prizes/medicine/laureates/1988/index.html

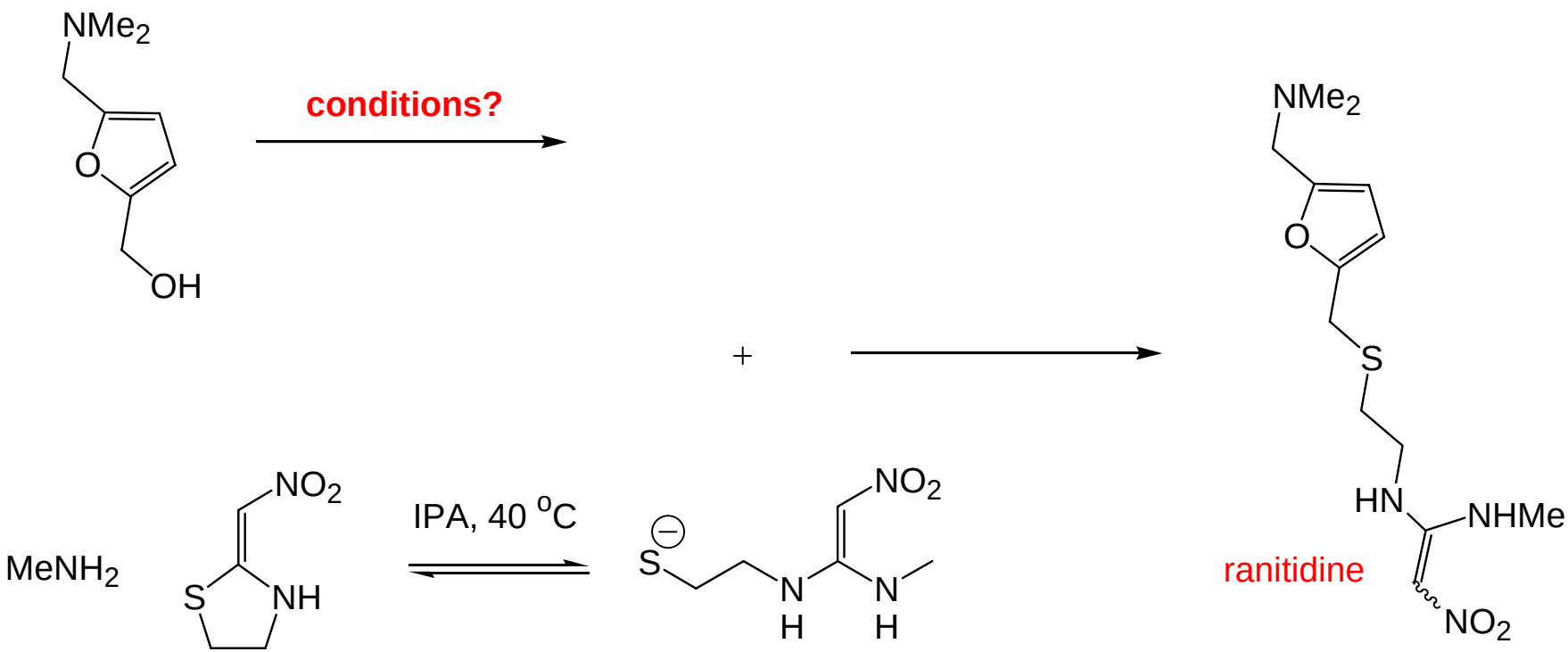
http://nobelprize.org/nobel_prizes/medicine/laureates/1988/black-lecture.pdf

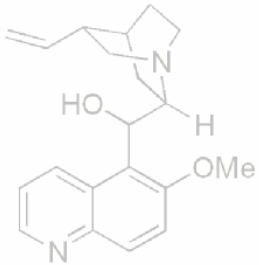
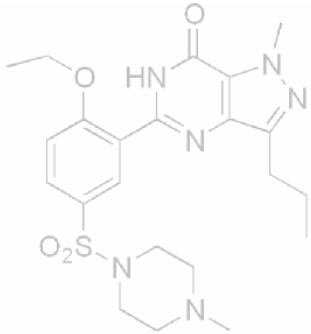
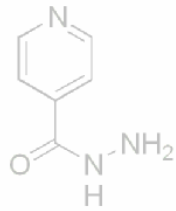
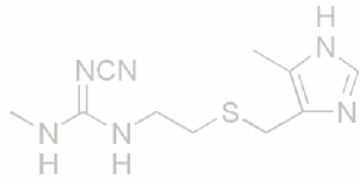
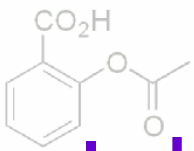
Ranitidine

Although the idea that the drugs must resemble histamine was successful, this dogma did mean that other heterocycles were not investigated by the original med chem team. The result was that the best selling drug of all time was discovered by a competitor. At its height ranitidine generated over $2 billion each year!

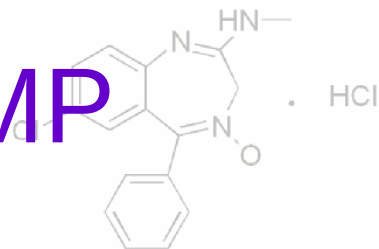
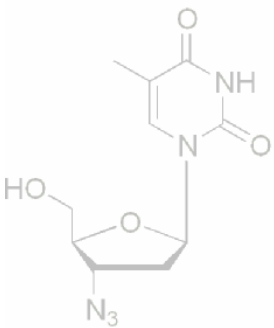
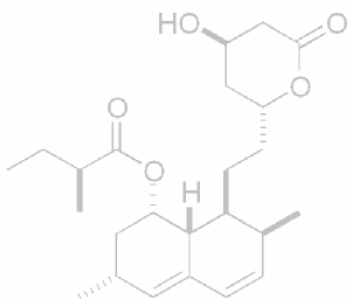
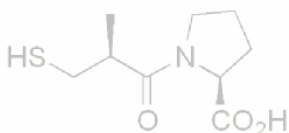
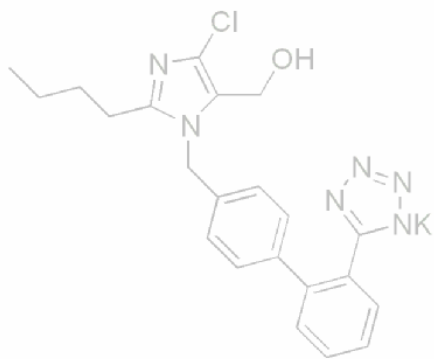
Shortest route to Ranitidine

Starting from the Mannich product is only 2 steps!



Erectile Disfunction:
Inhibitors of type-5 CGMP Phosphodiesterase

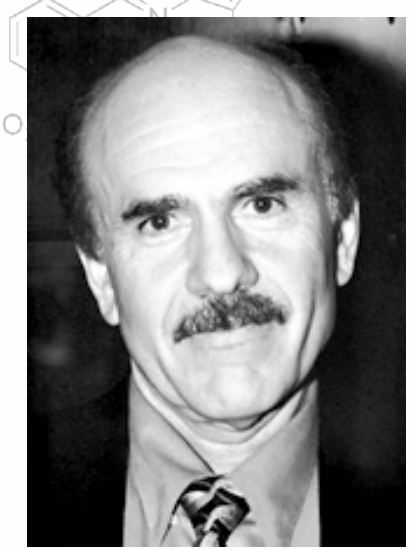
Introduction

It is estimated that 10% of men suffer from erectile dysfunction, and that this figure is as much as 52% for men between 40 and 70 years old!

Sildenafil was discovered by a research team at Pfizer in Kent. The Pfizer research team started working on the programme in 1985 with the aim of discovering antihypertensive and antianginal compounds. They were studying compounds which inhibit phosphodiesterase (PDE). At that point, the team had no idea that their research would lead them to discover an anti-impotence drug. In 1989 sildenafil had been synthesised. Clinical trials of sildenafil were started in July 1991. In 1992, it was realised that the drug was not as effective as they had hoped. However, they were surprised because many of the patients that had tried it were reluctant to stop the trial, and wanted to continue taking the drug. The researchers finally learnt from some of the patients that one of the side effects of the drug was that it helped erections.

Robert F. Furchgott, Louis J. Ignarro and Ferid Murad

b. 1916



b. 1941

b. 1936

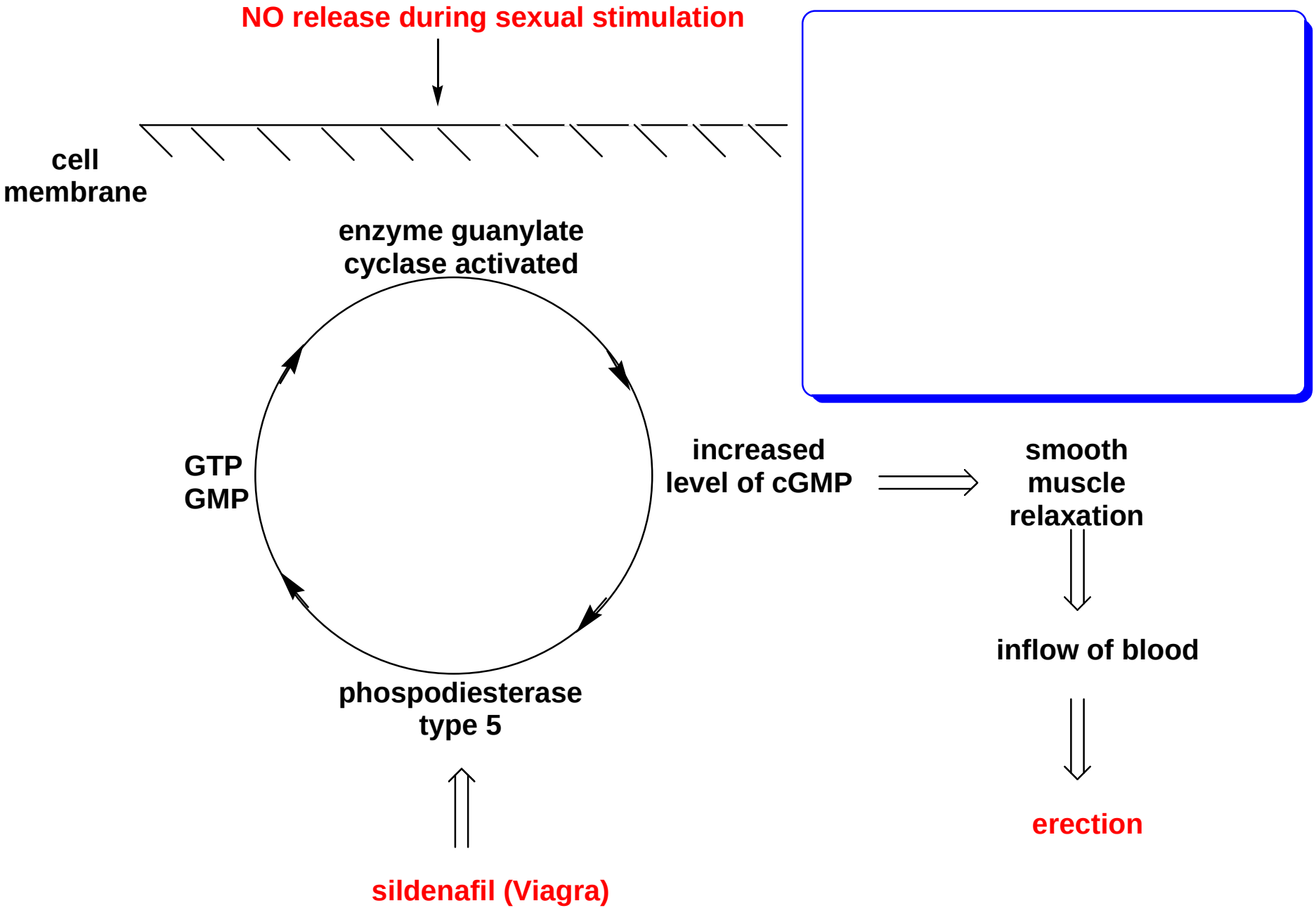
In 1998, Furcgott, Ignarro and Murad were awarded the Nobel Prize for Medicine for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system.

http://nobelprize.org/nobel_prizes/medicine/laureates/1998/

Mode of Action

Nitric Oxide (NO) is released with sexual stimulation from nerve endings and endothelial cells in the spongy erectile tissue, of the penis. The enzyme guanylate cyclase then converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP causes the smooth muscle to relax, which causes an inflow of blood which leads to an erection. cGMP is then hydrolysed back to the inactive GMP by phosphodiesteras type 5 (PDE5). The levels of cGMP are therefore controlled by the activation of cyclic nucleotide cyclase and the breakdown by PDE5. It is the latter that sildenafil acts upon.

Mode of Action

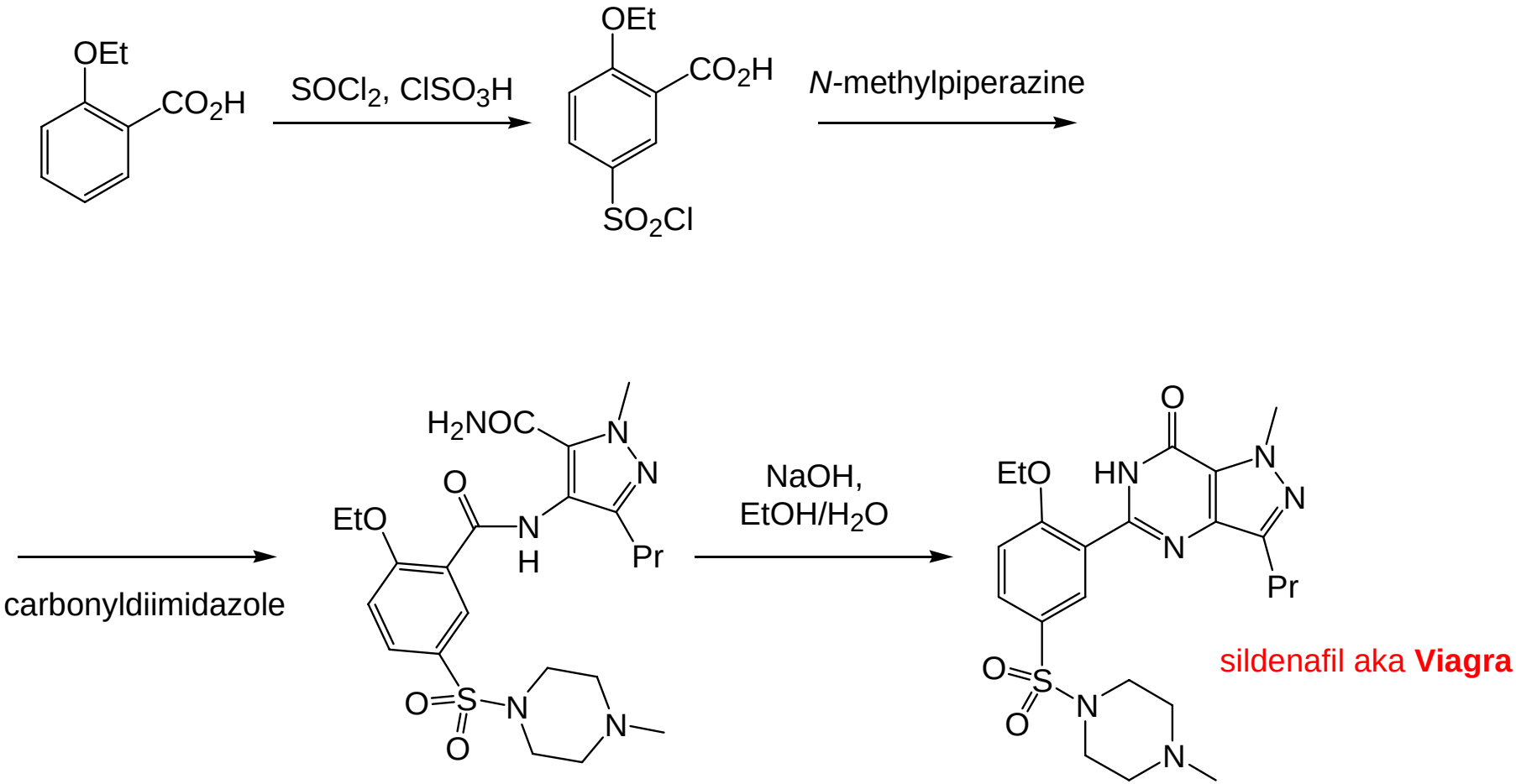


Mode of Action

Men who suffer from erectile dysfunction often produce too little amounts of NO. This means that the small amount of cGMP they produce is broken down at the same rate and therefore doesn't have the time to accumulate and cause a prolonged vasodilation effect.
Sildenafil works by inhibiting the enzyme PDE5 by occupying its active site. This means that cGMP is not hydrolysed as fast and this allows the smooth muscle to relax. Sildenafil is a potent and highly selective inhibitor of PDE5.

Synthesis of sildenafil

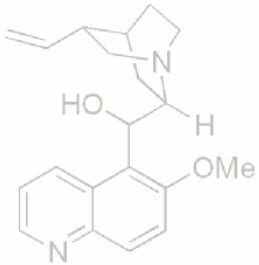
Alternative Synthesis of sildenafil

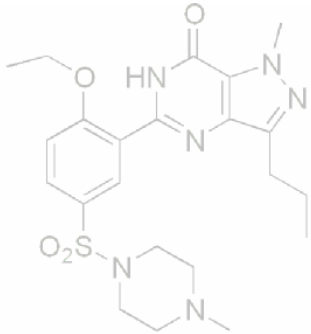


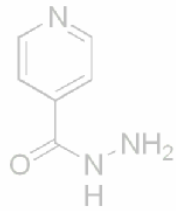
sildenafil aka **Viagra**

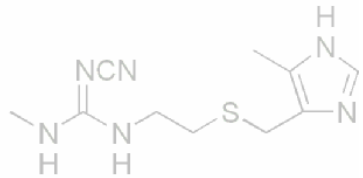
The overall yield of sildenafil *via* this second route can be as high as 52%, which compares favourably with the first route in which the overall yield is 28%. The actual commercial route used by Pfizer has not been published.

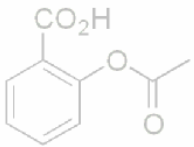
The Future:
A Change of Strategy?

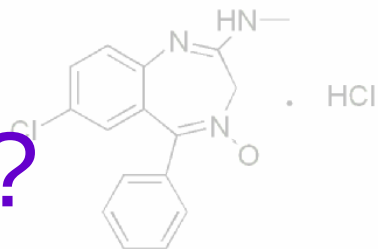


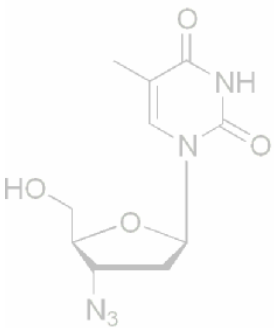


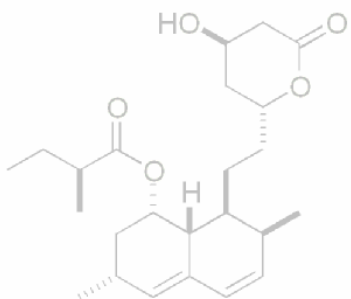


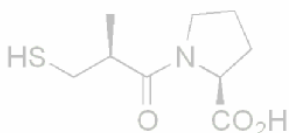


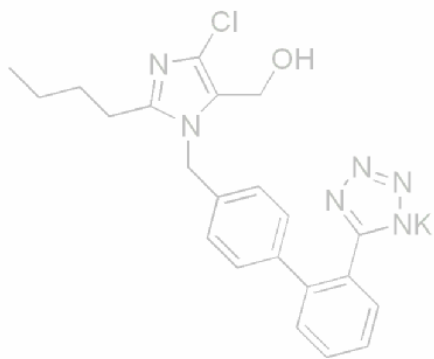










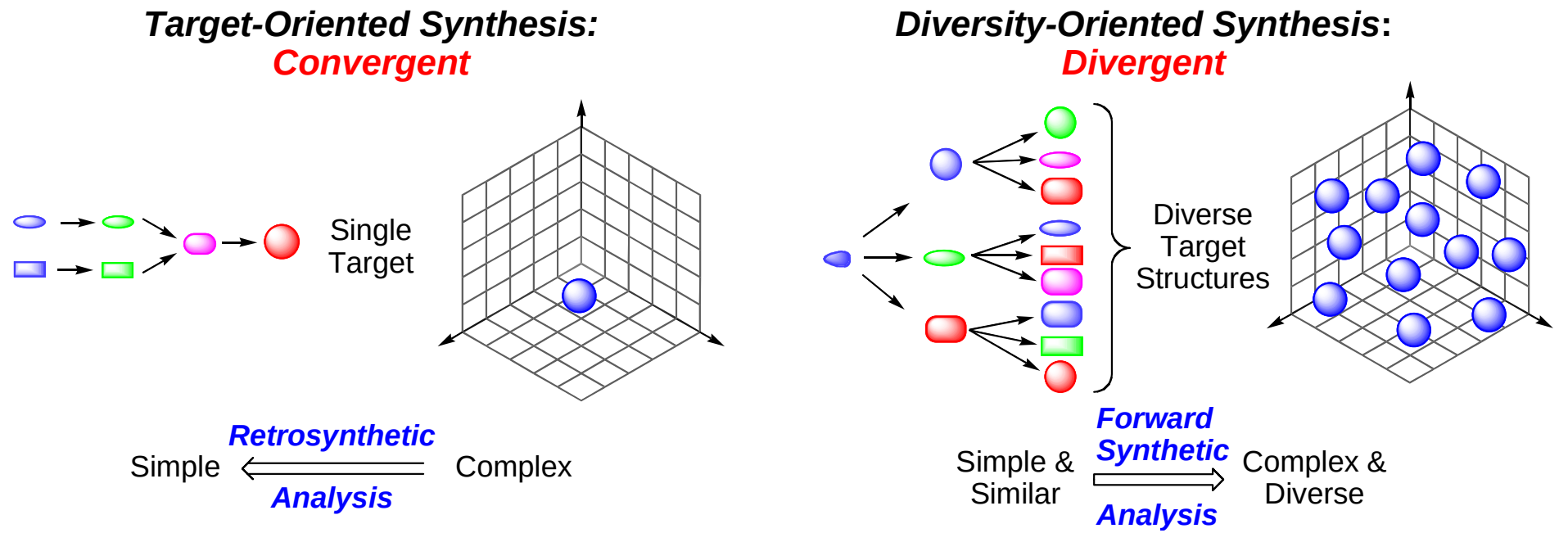


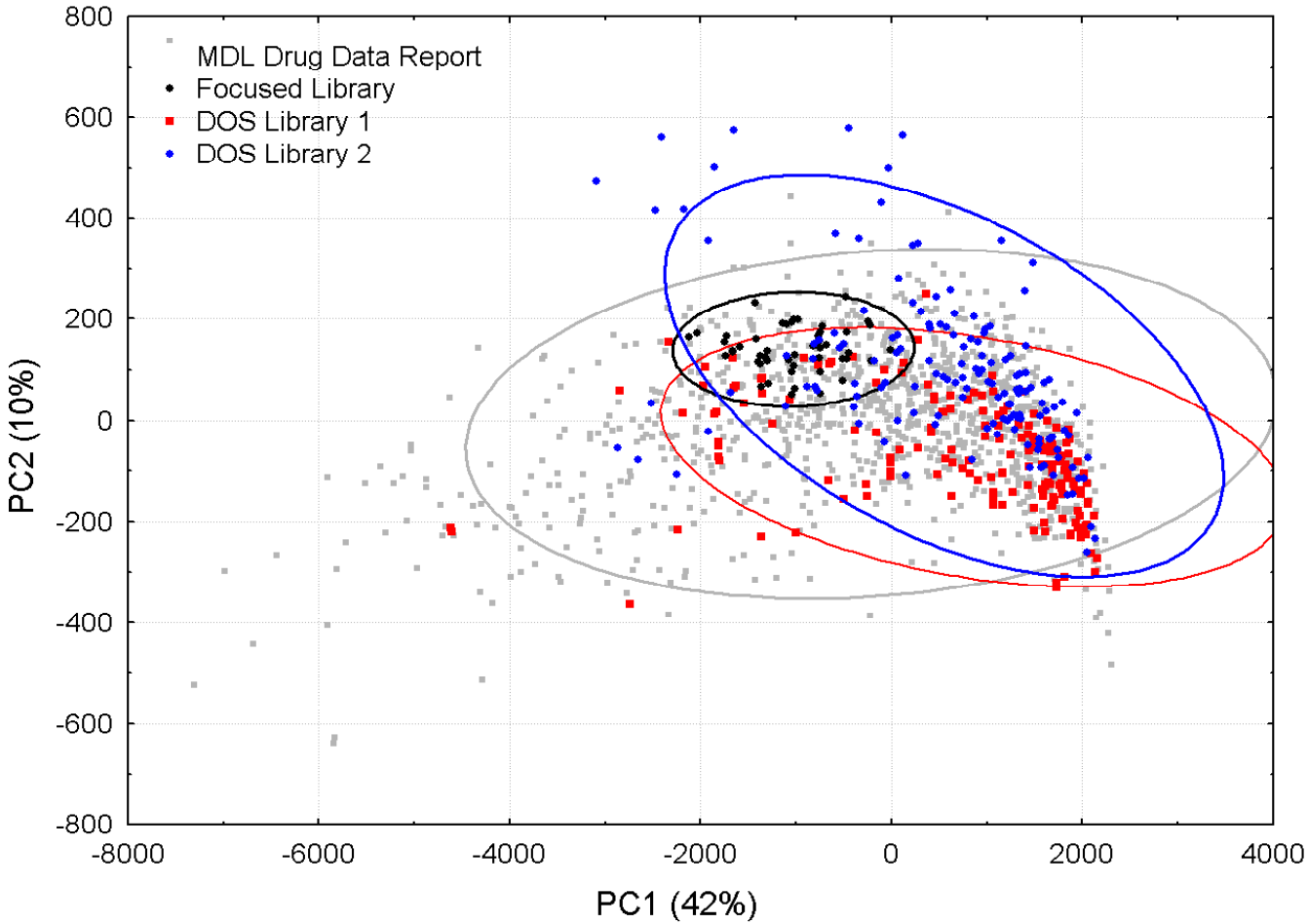
A recent review has highlighted the success and limitations of the current approach to the discovery of new drug molecules. The data was taken from the process groups of 3 of the major pharmaceutical companies in the UK. It was shown that:

As all 3 companies use the same types of reactions and adhere to the dogma of Lipinski's Rule of Five, it is unsurprising that they generate the same types of molecular structures as potential drugs and hence explore the same area of chemical space.

Diversity Oriented Synthesis

A strategy designed to explore greater areas of chemical space than those accessed by traditional med chem approaches is diversity oriented synthesis (DOS). A comparison of (DOS) with the more conventional target oriented synthesis (TOS) is given below.





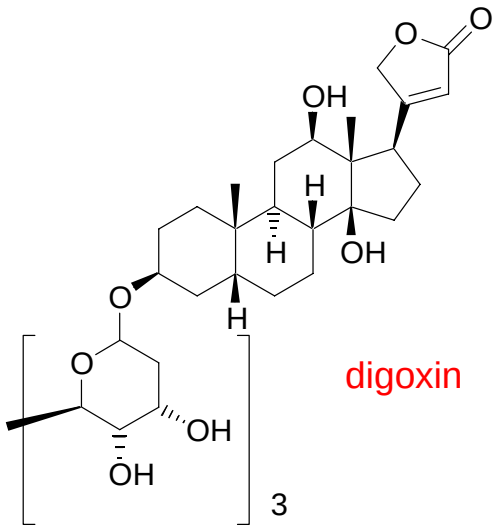
Library	STDDEV (PC1)	STDDEV (PC2)	STDDEV (PC3)	Average 'Chemical Space' occupied per compound
Focused	4.90	0.46	0.50	1.08
DOS 1	13.18	1.03	0.74	10.09
DOS 2	11.78	1.60	1.49	28.10
MDDR	17.31	1.44	1.15	28.09

Natural Products

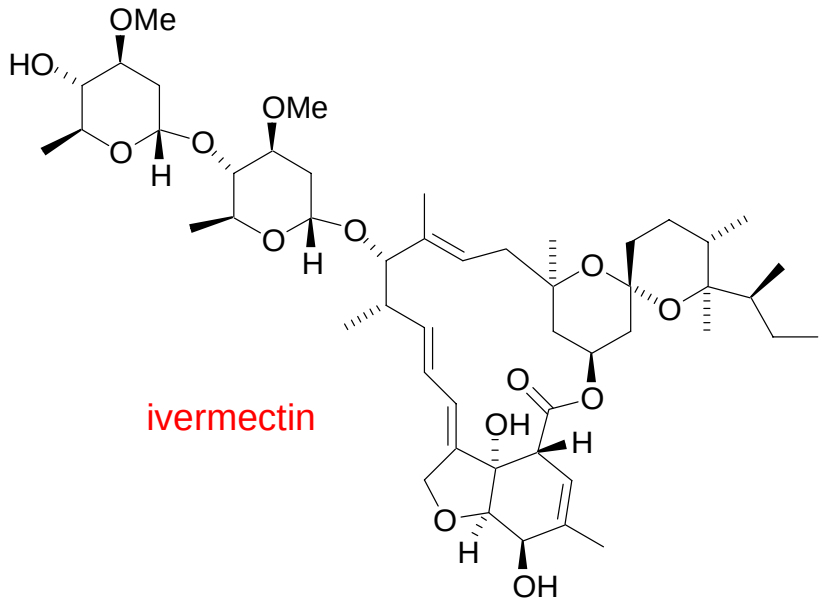
As well as DOS, the manipulation of chemical entities found in nature (natural products) can also provide diverse lead structures for investigation and evaluation as potential drug candidates.

For example drugs such as Taxol (anti cancer), cyclosporin A (immuno-suppressant), digoxin (heart failure), ivermectin (river blindness) and lovastatin (cholesterol lowering) are all natural products or derived from natural products. It is hard to see how these drugs would have been discovered *via* a Lipinski Rule of Five driven medicinal chemistry research project.

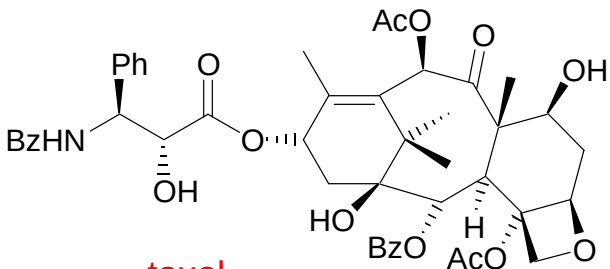
Natural Products



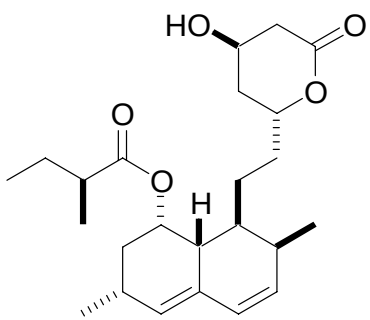
digoxin



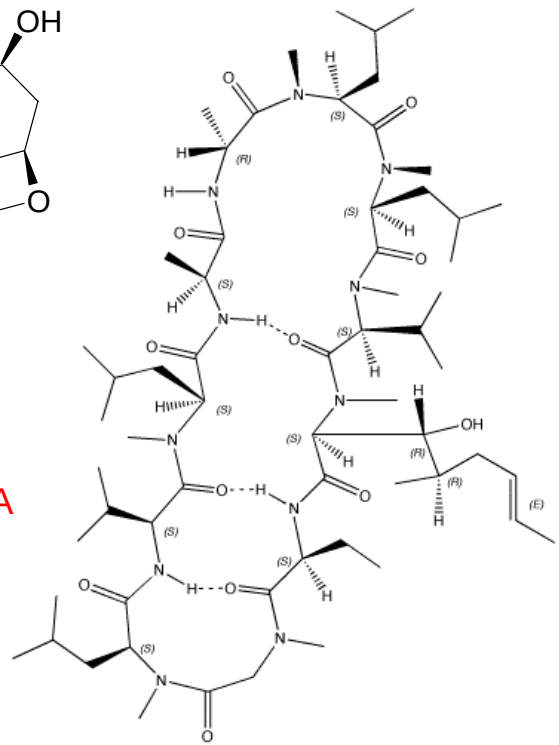
ivermectin



taxol



Lovastatin



cyclosporin A

End of the Course

You should have an appreciation of the types of molecules targeted by medicinal chemists and be able to discuss the pros and cons in the syntheses of a number of drug molecules. You should aim to familiarise yourselves with each chemical transformation discussed in the course and with the mechanisms of those highlighted. Some rudimentary understanding of the importance of each drug and its mode of action should have also been acquired.