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Pharmaceutical organic analysis of certain drug active constituent in medicinal chemistry

A Final Thesis Presented to
The Academic Department
Of the School of science
In Partial Fulfillment of the Requirements
For the Degree of Master in chemistry

ATLANTIC INTERNATIONAL UNIVERSITY

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: Abstract

The main part of the thesis is the relation between the previous 8 courses in practical manner that enable me to use my practical knowledge and experience to reach my goals in synthesis, design and analysis of the drug. (Certain drug).

So we consider that all the following act as an introduction and important subjects to learn how to work practically in the thesis:

- **Introduction to medicinal chemistry and its applications in the pharmaceutical field**
- **Stereochemistry in pharmaceutical organic chemistry and its applications in medicinal chemistry and pharmaceutical analysis**
- **Organic chemistry reactions and its application in synthesis in medicinal chemistry**
- **Pharmaceutical analytical chemistry and its applications in medicinal chemistry and pharmaceutical analysis**
- **Drug design in pharmaceutical organic chemistry and its applications in medicinal chemistry and pharmaceutical analysis.**
- **Spectroscopy in pharmaceutical organic chemistry and its applications in medicinal chemistry and pharmaceutical analysis**
- **Fundamentals of math**
- **Statistics**

We mean that all the previous 8 courses are the basic of the thesis work as without appropriate knowledge and practical experience, it is nearly impossible to reach a novel discovery.

In other word „My thesis is divided mainly into two parts :

1-Theoritical part:

That is mainly consisting of the previous 8 courses and how to use them in practical part.

2-Practical Part:

After mention of all the previous work of certain drug and after of the full details about spectroscopy of the drug and all structural information from spectroscopy practical work (U.V. „„I.R.„„NMR„„MASS) and also from different text books and finally using many programs that will be listed at the bibliography :

All the previous work that the others had studies and modified , I mentioned it as it is „„and accurately I selected each reference , each website , and each book , and each other previous practical work…

And My novel work on the following drugs as after practical spectroscopy study and work , I could use novel techniques for drug design and drug discovery using many programs as drug design programs especially for DOCKING and MODIFICATIONS and CALCULATIONS and SCORES and COMPARISON BETWEEN MY NEW NOVEL AND THE PREVIOUS DRUGS USING COMPUTER PROGRAMS and COMPARISON OF THE SPECTROSCOPY IN DIFFERENT APPLICATIONS
And mainly I used the following programs :

- **Accelrys DS visualiser.**
- **Chem3D Ultra.**
- **Chemdraw Ultra.**
- **LigandScout for pharmacophore .**
- **Molebro docker,pdb:1uzf,synthesis is from grahampatric,modified interaction on DS**

And I worked hardly on the following drugs in the following cases :

Case 1 :

Beta one agonist drugs

1-Atenolol

2-Ceuticolol

Case 2 :

ACE inhibitors

1-Captopril
2-Zofenopril
3-Enalapril
4-Ramipril
5-Lisinopril
6-Benazepril
7-Fosinopril

Case 3 :
Beta-cryptogein inhibitor as anti fungal

Case 4 : TA-2005 beta two adrenergic agonist

Case 5 :beta two agonist of expected bronchodilator activity
1-Adrenaline
2-Isoprenaline
3-Salbutamol

Case 6 : Anti coagulant
1-coumarin derivatives
2-1,3 phenindiones
3-warfarin
4-coumarin
5-acenocomarol
6-phenoprocoumon
7-Dicomarol

Case 7 : HIV protease Inhibitors
1-Indinavir sulfate
2-Nelfinavir mesylate
3-Ritonavir
4-Saquinavir mesylate
5-Amprenavir

Case 8 :
Propranolol

So after the study of the previous 27 drugs in the previous 8 cases , now it is easy for any research worker on one of these drugs to use my study and my Docking and my calculations and comparison of scores of the drugs to start or finish his research also he can make use of the proposed novel methods of synthesis …and that is my THESIS

Chapter 1 :

General Introduction :

In order to develop our countries , There are many strategies that we should follow but from my point of view if our people is healthy , they can develop and build and start to think in their selves and their countries because when the human suffer from a disease it will be his first priority and he work and ask every day to overcome this disease .

so the public health is the key of success and so all the medicinal professionals should take in consideration that if they improved their work and their medical care , all the community will harvest the results and will be honored with them .

So the most novel doctorate degree programs all over the world discuss mainly either pharmaceutical synthesis or pharmaceutical analysis of novel drug and not the drug itself as Presence of drug is not a problem but the complicated problem is how to synthesize and how to analyze this drug by a selective accurate method that is suitable for all qualifications and

aspects that is certified by quality control assurance.

Chapter 2: Definition of the : (Investigation (or Issue

Computers in medicinal chemistry as one of the most recently methods in drug discovery is using the computer for simulating and imitate the drug and its receptors in the human body so we can predict the changes and chain reactions that the drug can undergo after invading our bodies . Also we can use computers for analysis as there are many new technologies in this issue that can help for accurate and precise analysis.

Drug design in medicinal chemistry has many applications but the main target of drug design is drug discovery as drug discovery has created many opportunities to accelerate drug discovery process and to give alternative for every drug and has generated new approaches to the design of drugs and also supposed many methods of analysis of the novel drugs depending on their structure.

This rise in the use of technology and new methods has increased the dependency of the medicinal chemist on new knowledge, new analytical procedures and theoretical skills as

drug design required the novel thing either synthesis or analysis of drug.

Drug discovery is one of the challenging subjects from the beginning of humanity as always there is a disease that we may fail to treat with or may be fatal or serious disease that we still did not discover any treatment for it but with drug design this is different now as we can predict the drug according to information about the disease .

In the previous few years , it was really technological mutation in most of fields in chemistry , one of the most important mutations is how to synthesize the drug using recent methods and new methods are available to protect the environment as green chemistry and drug design plays the most important role in this aspect as it can modify either drug itself or the novel methods to synthesize this drug .

Combinatorial synthesis as one of the most important applications in synthesis as we can obtain different products from different reactants at the same time .

There are many applications in medicinal chemistry that use combinatorial chemistry to produce drugs or different drugs at the same time so improve qualifications and reduce time required and eliminate many precautions .

As a novel method in drug synthesis to use many reactants and to produce many products in different reaction vessels at the same time . and there is many novel applications as Preparation of water – soluble compounds by covalent attachment of solubilizing moieties which is considered one of the most important applications in synthesis as mainly molecules either water soluble or lipid soluble .

So learn to modify water solubility or preparation of water soluble molecule or water insoluble is an important aspect for drug discovery and synthesis in medicinal chemistry also in gene therapy that is considered one of the most important aspects in novel drug therapy all over the world as gene therapy is promising to treat the most serious diseases as cancer and AIDS .

Chapter 3: Dynamics of the :Anticipated Solution

Spectroscopy :

Spectroscopy is considered as the main artery of medicinal chemistry as it provides the structure identification that is almost every thing as if we now know the structure , we can apply drug design to give alternatives or to make modifications but with the same pharmacophore .

Spectroscopy is considered one of the most important and complicated aspects in medicinal chemistry as it can predict and deduce the structure of the organic material that will be useful in medicinal chemistry as drug discovery .

Spectroscopy is branched science with different categories and it is divided mainly into 4 categories (the most important)

1- ultraviolet spectroscopy that is mainly depends on electronic transition

2- Infrared spectroscopy that is mainly depends on molecular vibration

3- NMR (nuclear magnetic resonance) that is mainly depends on magnetic resonance

4- Mass spectroscopy that is mainly depends on acceleration of molecules and then determination of its molecular weight

- # Drug synthesis and its relation with spectroscopy :

For (Kneipp, 2007)and* (*K.Feinstein., 1995):
There is a strong and efficient relation as after identification of the structure using the 4 following methods of identification we can predict the structure and so we can predict its synthesis ,,, as mentioned in the third chapter of the book *new Approaches in biomedical spectroscopy* and introductory to spectro in the book *Guide to Spectroscopic identification of organic compounds*

1 - ultraviolet spectroscopy that is mainly depends on electronic transition can predict stereochemistry of the organic molecule :

2 - Infrared spectroscopy that is mainly depends on molecular vibration can predict stereochemistry of the organic molecule :

3 - NMR (nuclear magnetic resonance) that is mainly depends on magnetic resonance can predict stereochemistry of the organic molecule :

4 - mass spectroscopy that is mainly depends on acceleration of molecules and then determination of its molecular weight can predict stereochemistry of the organic molecule

- # ULTRAVIOLET SPECTROSCOPY :

After using of ultraviolet and applying of it through the organic molecule , the molecule will undergo electronic transition that the electrons will migrate from HOMO to LUMO ,,, mean that electrons will migrate from the highest occupied molecular orbital to the lowest Unoccupied molecular orbital.

Each organic molecule has its specific energy and its certain difference between its energy levels so the migration or excitation from HOMO to LUMO will be different in each organic molecule that enable us to use this technology to differentiate between organic molecules .

There is an important concept in ultraviolet spectroscopy that take in consideration blue shift and red shift as type of the transition affect highly the result as if the type of transition was sigma and sigma it will differ than sigma and non-bonding .

Infrared spectroscopy :

Infrared spectroscopy that is mainly depends on molecular vibration as after vibration of organic molecule , the spectra will appear . each organic molecule will required different amounts of energy to be vibrated .

From my point of view to understand the concept of infra red spectroscopy imagine that we now vibrate a small car , of course it is different when we vibrate a large bus . organic molecules

are the same . it is different when we vibrate a small carbon atom than the vibration of large sulfur atom .

Vibration cause either bending or stretching and to understand the meaning of bending is to bend or to to flexible to certain limit and the meaning of stretching in to elongate to certain limit .

One of the most important applications in medicinal chemistry is to obtain identification of the function group using IR SPECTROSCOPY as each function group has its own energy required to be vibrated so we can not only to differentiate between reactants and products but also to identification and know the function group itself as it is tedious and time consuming to use any other technology to determinate the function group .

NMR SPECTROSCOPY :

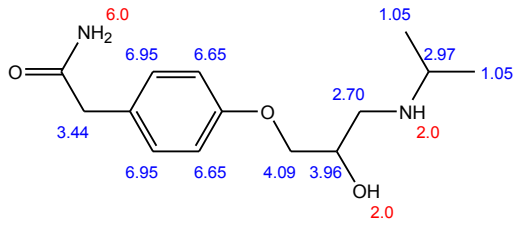
NMR has several advantages and characteristic features that make it particularly effective in drug discovery . It provides structural information about the binding mode of a ligand in solution and also the structure of many other important molecules in organic chemistry , the possibility of carrying out screening in the presence or absence of a cofactor , different protein activation states or environmental conditions.

And using NMR in the following 11 drugs as the first will be H.NMR and the second will be C.NMR as from the chemistry Program chemdraw ultra

And the following 11 drugs study of their NMR will be useful in determination of possible modifications of the drugs and so will give different docking on the other programs and the names of drugs are :

1- Atenolol
2- Enalapril
3- Ramipril
4- Lisinopril
5- Benazepril
6- Fosinopril
7- Adrenaline
8- Isoprenaline
9- Salbutamol
10-Coumarin
11-Warfarin

ChemNMR H-1 Estimation



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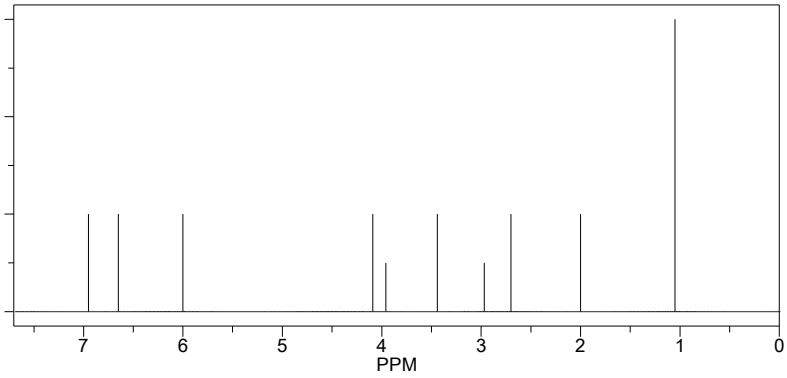
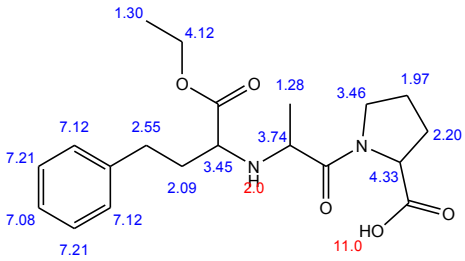


Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
NH2	6.0	6.00	prim. amide
CH2	3.44	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		0.85	1 alpha -C(=O)N
CH	6.95	7.26	1-benzene
		-0.20	1 -C
		-0.11	1 -O-C
CH	6.65	7.26	1-benzene
		-0.12	1 -C
		-0.49	1 -O-C
CH2	4.09	1.37	methylene
		2.61	1 alpha -O-1:C*C*C*C*C*C*1
		0.15	1 beta -O
		-0.04	1 beta -C
CH	3.96	1.50	methine
		1.73	1 alpha -O
		0.50	1 beta -O-1:C*C*C*C*C*C*1
		0.23	1 beta -N
OH	2.0	2.00	alcohol
CH2	2.70	1.37	methylene
		1.22	1 alpha -N-C
		0.15	1 beta -O
		-0.04	1 beta -C
NH	2.0	2.00	amine
CH	2.97	1.50	methine
		0.34	2 alpha -C
		1.13	1 alpha -N
CH3	1.05	0.86	methyl
		0.14	1 beta -N
		0.05	1 beta -C
CH3	1.05	0.86	methyl
		0.14	1 beta -N
		0.05	1 beta -C
CH	6.65	7.26	1-benzene
		-0.12	1 -C
		-0.49	1 -O-C
CH	6.95	7.26	1-benzene
		-0.20	1 -C
		-0.11	1 -O-C

ChemNMR H-1 Estimation



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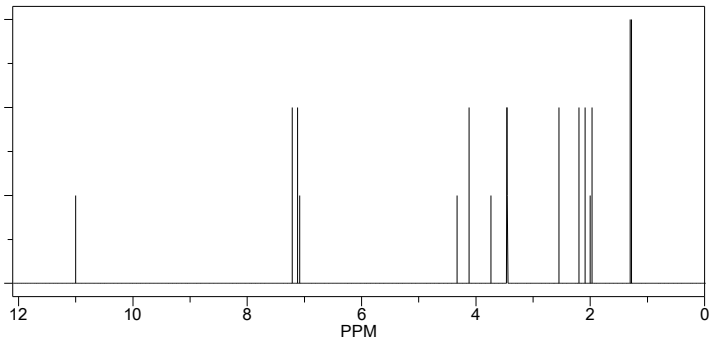
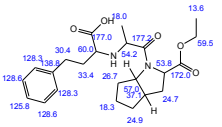


Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
OH	11.0	11.00	carboxylic acid
CH	4.33	2.75	pyrrolidine
		0.87	1 alpha -C(=O)O from methine
		0.71	1 -C(=O)C
CH	3.74	1.50	methine
		0.17	1 alpha -C
		1.13	1 alpha -N
		0.94	1 alpha -C(=O)N
CH3	1.28	0.86	methyl
		0.14	1 beta -N
		0.28	1 beta -C(=O)N
NH	2.0	2.00	amine
CH	3.45	1.50	methine
		1.13	1 alpha -N
		0.83	1 alpha -C(=O)OR
		-0.01	1 beta -C
CH2	4.12	1.37	methylene
		0.00	1 alpha -C
		2.75	1 alpha -OC(=O)-C
CH3	1.30	0.86	methyl
		0.44	1 beta -OC(=O)C
CH2	2.09	1.37	methylene
		0.08	1 beta -N-C
		0.35	1 beta -C(=O)O-C
		0.29	1 beta -1:C*C*C*C*C*C*1
CH2	2.55	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		-0.04	1 beta -C
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.08	7.26	1-benzene
		-0.18	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH2	3.46	2.75	pyrrolidine
		0.71	1 -C(=O)C
CH2	1.97	1.59	pyrrolidine
		0.38	1 -C(=O)C
CH2	2.20	1.59	pyrrolidine
		0.23	1 beta -C(=O)O from methylene
		0.38	1 -C(=O)C

ChemNMR C-13 Estimation



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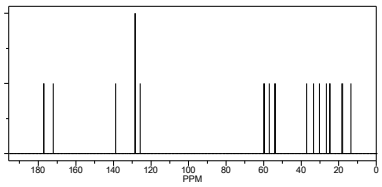
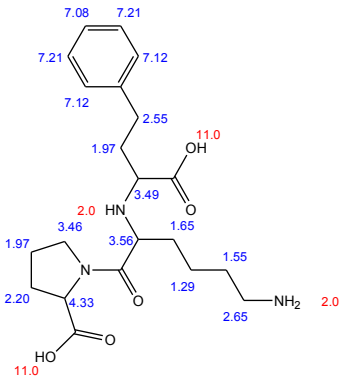


Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	172.0	166.0	1-carboxyl
		11.0	1 -C-C-C
		-5.0	1 -C from O-carboxyl
CH	53.8	-9.1	pyrrolidine
		21.8	1 alpha -C(=O)-O from aliphatic
		9.1	1 alpha -C from aliphatic
		28.3	1 alpha -N from aliphatic
		0.5	1 beta -C(=O)-C from aliphatic
		18.8	2 beta -C from aliphatic
		-7.5	3 gamma -C from aliphatic
		0.9	3 delta -C from aliphatic
		0.0	1 delta -N from aliphatic
		-9.0	steric corrections from aliphatic
CH2	24.7	-13.2	pyrrolidine
		18.2	2 alpha -C from aliphatic
		2.0	1 beta -C(=O)-O from aliphatic
		18.8	2 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
		-5.0	2 gamma -C from aliphatic
		0.3	1 delta -C from aliphatic
		-5.0	steric corrections from aliphatic
CH	37.1	-13.2	pyrrolidine
		27.3	3 alpha -C from aliphatic
		28.2	3 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.8	1 gamma -C(=O)-O from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
		-11.0	steric corrections from aliphatic
CH2	24.9	-11.4	cyclopentane
		18.2	2 alpha -C from aliphatic
		28.2	3 beta -C from aliphatic
		-2.5	1 gamma -C from aliphatic
		-5.1	1 gamma -N from aliphatic
		0.0	1 delta -C(=O)-O from aliphatic
		0.0	1 delta -C(=O)-C from aliphatic
		-2.5	steric corrections from aliphatic
CH2	18.3	-11.4	cyclopentane
		18.2	2 alpha -C from aliphatic
		18.8	2 beta -C from aliphatic
		-2.5	1 gamma -C from aliphatic
		-5.1	1 gamma -N from aliphatic
		0.0	1 delta -C(=O)-C from aliphatic
		0.3	1 delta -C from aliphatic
CH2	26.7	-11.4	cyclopentane
		18.2	2 alpha -C from aliphatic
		18.8	2 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
		-5.0	2 gamma -C from aliphatic
		0.0	1 delta -C(=O)-O from aliphatic
		-2.5	steric corrections from aliphatic
CH	57.0	-9.1	pyrrolidine
		18.2	2 alpha -C from aliphatic
		28.3	1 alpha -N from aliphatic
		0.5	1 beta -C(=O)-C from aliphatic
		37.6	4 beta -C from aliphatic
		-2.8	1 gamma -C(=O)-O from aliphatic
		0.3	1 delta -C from aliphatic
		0.0	1 delta -N from aliphatic
		-16.0	steric corrections from aliphatic
C	177.2	165.0	1-amide
		12.2	1 -C-C
CH	54.2	-2.3	aliphatic
		22.5	1 alpha -C(=O)-N
		9.1	1 alpha -C
		28.3	1 alpha -N
		9.4	1 beta -C
		-2.8	1 gamma -C(=O)-O
		-7.5	3 gamma -C
		0.0	1 delta -C(=O)-O
		1.2	4 delta -C
		-3.7	steric corrections
CH3	18.0	-2.3	aliphatic
		9.1	1 alpha -C
		2.6	1 beta -C(=O)-N
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.0	1 delta -C(=O)-O
		0.9	3 delta -C
		-1.1	steric corrections
CH	60.0	-2.3	aliphatic
		21.8	1 alpha -C(=O)-O
		9.1	1 alpha -C
		28.3	1 alpha -N
		18.8	2 beta -C
		-2.6	1 gamma -1:C*C*C*C*C*C*1
		-3.2	1 gamma -C(=O)-N
		-2.5	1 gamma -C
		-7.4	steric corrections
C	177.0	166.0	1-carboxyl
		11.0	1 -C-C-C
CH2	33.4	-2.3	aliphatic
		18.2	2 alpha -C
		9.3	1 beta -1:C*C*C*C*C*C*1
		2.0	1 beta -C(=O)-O
		11.3	1 beta -N
		-2.5	1 gamma -C
		-0.4	1 delta -C(=O)-N
		0.3	1 delta -C
		-2.5	steric corrections
CH2	30.4	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		9.4	1 beta -C
		-2.8	1 gamma -C(=O)-O
		-5.1	1 gamma -N
		0.3	1 delta -C
		-2.5	steric corrections
C	138.8	128.5	1-benzene
		10.3	1 -CCC
CH	128.3	128.5	1-benzene
		-0.2	1 -CCC
CH	128.6	128.5	1-benzene
		0.1	1 -CCC
CH	125.8	128.5	1-benzene
		-2.7	1 -CCC
CH	128.6	128.5	1-benzene
		0.1	1 -CCC
CH	128.3	128.5	1-benzene
		-0.2	1 -CCC
CH2	59.5	-2.3	aliphatic
		9.1	1 alpha -C
		54.9	1 alpha -O-C=O
		-2.5	1 gamma -C
		0.3	1 delta -C
		0.0	1 delta -N
CH3	13.6	-2.3	aliphatic
		9.1	1 alpha -C
		6.5	1 beta -O-C=O
		0.3	1 delta -C

ChemNMR H-1 Estimation



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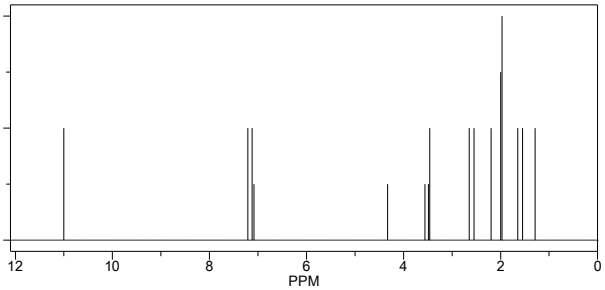

Protocol of the H-1 NMR Prediction:

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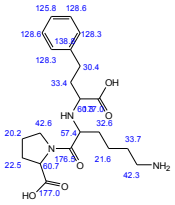
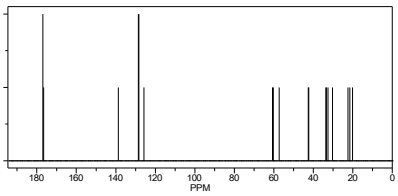
OH	11.0	11.00	carboxylic acid
CH	4.33	2.75	pyrrolidine
		0.87	1 alpha -C(=O)O from methine
		0.71	1 -C(=O)C
CH	3.56	1.50	methine
		1.13	1 alpha -N
		0.94	1 alpha -C(=O)N
		-0.01	1 beta -C
CH2	1.65	1.37	methylene
		0.08	1 beta -N-C
		0.24	1 beta -C(=O)N
		-0.04	1 beta -C
CH2	1.29	1.37	methylene
		-0.04	1 beta -C
		-0.04	1 beta -C
CH2	1.55	1.37	methylene
		-0.04	1 beta -C
		0.22	1 beta -N
CH2	2.65	1.37	methylene
		1.32	1 alpha -N
		-0.04	1 beta -C
NH2	2.0	2.00	amine
NH	2.0	2.00	amine
CH	3.49	1.50	methine
		1.13	1 alpha -N
		0.87	1 alpha -C(=O)O
		-0.01	1 beta -C
OH	11.0	11.00	carboxylic acid
CH2	1.97	1.37	methylene
		0.08	1 beta -N-C
		0.23	1 beta -C(=O)O
		0.29	1 beta -1:C*C*C*C*C*C*1
CH2	2.55	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		-0.04	1 beta -C
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.08	7.26	1-benzene
		-0.18	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH2	3.46	2.75	pyrrolidine
		0.71	1 -C(=O)C
CH2	1.97	1.59	pyrrolidine
		0.38	1 -C(=O)C
CH2	2.20	1.59	pyrrolidine
		0.23	1 beta -C(=O)O from methylene
		0.38	1 -C(=O)C

ChemNMR C-13 Estimation



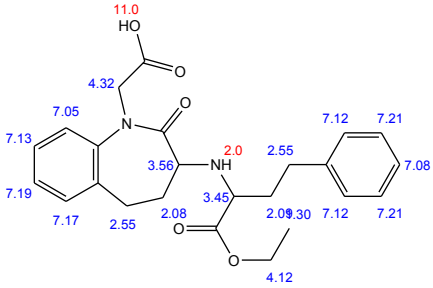
Estimation Quality: blue = good, magenta = medium, red = rough



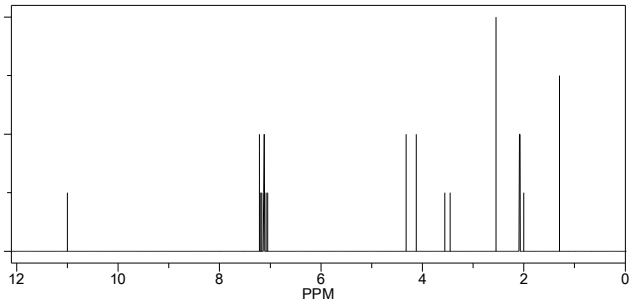
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	177.0	166.0	1-carboxyl
		11.0	1 -C-C-C
CH	60.7	-9.1	pyrrolidine
		21.8	1 alpha -C(=O)-O from aliphatic
		9.1	1 alpha -C from aliphatic
		28.3	1 alpha -N from aliphatic
		0.5	1 beta -C(=O)-C from aliphatic
		18.8	2 beta -C from aliphatic
		0.3	1 delta -C from aliphatic
		0.0	1 delta -N from aliphatic
		-9.0	steric corrections from aliphatic
C	176.5	165.0	1-amide
		11.5	1 -C-C-C
CH	57.4	-2.3	aliphatic
		22.5	1 alpha -C(=O)-N
		9.1	1 alpha -C
		28.3	1 alpha -N
		18.8	2 beta -C
		-2.8	1 gamma -C(=O)-O
		-10.0	4 gamma -C
		0.0	1 delta -C(=O)-O
		1.2	4 delta -C
		-7.4	steric corrections
CH2	32.6	-2.3	aliphatic
		18.2	2 alpha -C
		2.6	1 beta -C(=O)-N
		9.4	1 beta -C
		11.3	1 beta -N
		-5.0	2 gamma -C
		0.0	1 delta -C(=O)-O
		0.9	3 delta -C
		0.0	1 delta -N
		-2.5	steric corrections
CH2	21.6	-2.3	aliphatic
		18.2	2 alpha -C
		18.8	2 beta -C
		-3.2	1 gamma -C(=O)-N
		-10.2	2 gamma -N
		0.3	1 delta -C
CH2	33.7	-2.3	aliphatic
		18.2	2 alpha -C
		9.4	1 beta -C
		11.3	1 beta -N
		-2.5	1 gamma -C
		-0.4	1 delta -C(=O)-N
		0.0	1 delta -N
CH2	42.3	-2.3	aliphatic
		9.1	1 alpha -C
		28.3	1 alpha -N
		9.4	1 beta -C
		-2.5	1 gamma -C
		0.3	1 delta -C
CH	60.3	-2.3	aliphatic
		21.8	1 alpha -C(=O)-O
		9.1	1 alpha -C
		28.3	1 alpha -N
		18.8	2 beta -C
		-2.6	1 gamma -1:C*C*C*C*C*C*1
		-3.2	1 gamma -C(=O)-N
		-2.5	1 gamma -C
		0.3	1 delta -C
		-7.4	steric corrections
C	177.0	166.0	1-carboxyl
		11.0	1 -C-C-C
CH2	33.4	-2.3	aliphatic
		18.2	2 alpha -C
		9.3	1 beta -1:C*C*C*C*C*C*1
		2.0	1 beta -C(=O)-O
		11.3	1 beta -N
		-2.5	1 gamma -C
		-0.4	1 delta -C(=O)-N
		0.3	1 delta -C
		-2.5	steric corrections
CH2	30.4	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		9.4	1 beta -C
		-2.8	1 gamma -C(=O)-O
		-5.1	1 gamma -N
		0.3	1 delta -C
		-2.5	steric corrections
C	138.8	128.5	1-benzene
		10.3	1 -CCC
CH	128.3	128.5	1-benzene
		-0.2	1 -CCC
CH	128.6	128.5	1-benzene
		0.1	1 -CCC
CH	125.8	128.5	1-benzene
		-2.7	1 -CCC
CH	128.6	128.5	1-benzene
		0.1	1 -CCC
CH	128.3	128.5	1-benzene
		-0.2	1 -CCC
CH2	42.6	-9.1	pyrrolidine
		9.1	1 alpha -C from aliphatic
		28.3	1 alpha -N from aliphatic
		0.5	1 beta -C(=O)-C from aliphatic
		18.8	2 beta -C from aliphatic
		-2.8	1 gamma -C(=O)-O from aliphatic
		0.3	1 delta -C from aliphatic
		0.0	1 delta -N from aliphatic
		-2.5	steric corrections from aliphatic
CH2	20.2	-13.2	pyrrolidine
		18.2	2 alpha -C from aliphatic
		9.4	1 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.8	1 gamma -C(=O)-O from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
CH2	22.5	-13.2	pyrrolidine
		18.2	2 alpha -C from aliphatic
		2.0	1 beta -C(=O)-O from aliphatic
		9.4	1 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
		-2.5	steric corrections from aliphatic

ChemNMR H-1 Estimation



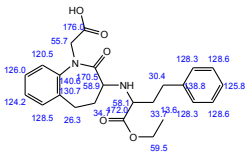
Estimation Quality: blue = good, magenta = medium, red = rough



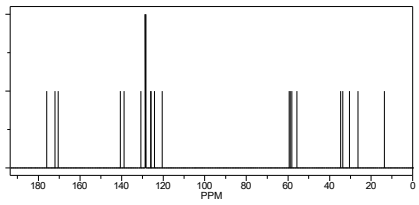
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
OH	11.0	11.00	carboxylic acid
CH2	4.32	1.37	methylene
		2.05	1 alpha -N(C*C)C(=O)C
		0.90	1 alpha -C(=O)O
CH	3.56	1.50	methine
		1.13	1 alpha -N
		0.94	1 alpha -C(=O)N
		-0.01	1 beta -C
NH	2.0	2.00	amine
CH	3.45	1.50	methine
		1.13	1 alpha -N
		0.83	1 alpha -C(=O)OR
		-0.01	1 beta -C
CH2	4.12	1.37	methylene
		0.00	1 alpha -C
		2.75	1 alpha -OC(=O)-C
CH3	1.30	0.86	methyl
		0.44	1 beta -OC(=O)C
CH2	2.09	1.37	methylene
		0.08	1 beta -N-C
		0.35	1 beta -C(=O)O-C
		0.29	1 beta -1:C*C*C*C*C*C*1
CH2	2.55	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		-0.04	1 beta -C
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.08	7.26	1-benzene
		-0.18	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH2	2.08	1.37	methylene
		0.08	1 beta -N-C
		0.34	1 beta -C(=O)N-1:C*C*C*C*C*C*1
		0.29	1 beta -1:C*C*C*C*C*C*1
CH2	2.55	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		-0.04	1 beta -C
CH	7.17	7.26	1-benzene
		-0.14	1 -CC
		0.05	1 -N(C)C(=O)C
CH	7.19	7.26	1-benzene
		-0.05	1 -CC
		-0.02	1 -N(C)C(=O)C
CH	7.13	7.26	1-benzene
		-0.18	1 -CC
		0.05	1 -N(C)C(=O)C
CH	7.05	7.26	1-benzene
		-0.05	1 -CC
		-0.16	1 -N(C)C(=O)C

ChemNMR C-13 Estimation



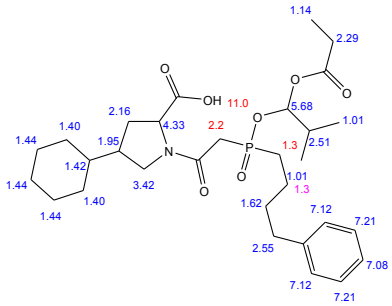
Estimation Quality: blue = good, magenta = medium, red = rough



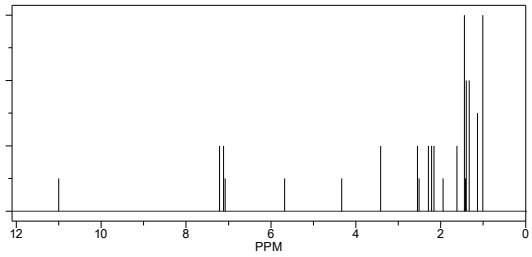
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	176.0	166.0	1-carboxyl
		10.0	1 -C
CH2	55.7	-2.3	aliphatic
		21.8	1 alpha -C(=O)-O
		28.3	1 alpha -N
		9.3	1 beta -1:C*C*C*C*C*C*1
		0.5	1 beta -C(=O)-C
		0.6	2 delta -C
		0.0	1 delta -N
		-2.5	steric corrections
C	170.5	165.0	1-amide
		11.5	1 -C-C-C
		-4.5	1 -1:C*C*C*C*C*C*1 from N-amide
		-1.5	1 -C from N-amide
CH	58.9	-2.3	aliphatic
		22.5	1 alpha -C(=O)-N
		9.1	1 alpha -C
		28.3	1 alpha -N
		18.8	2 beta -C
		-2.6	1 gamma -1:C*C*C*C*C*C*1
		-2.8	1 gamma -C(=O)-O
		-5.0	2 gamma -C
		0.0	1 delta -C(=O)-O
		0.3	1 delta -C
		-7.4	steric corrections
CH	58.1	-2.3	aliphatic
		21.8	1 alpha -C(=O)-O
		9.1	1 alpha -C
		28.3	1 alpha -N
		18.8	2 beta -C
		-2.6	1 gamma -1:C*C*C*C*C*C*1
		-3.2	1 gamma -C(=O)-N
		-5.0	2 gamma -C
		0.6	2 delta -C
		-7.4	steric corrections
C	172.0	166.0	1-carboxyl
		11.0	1 -C-C-C
		-5.0	1 -C from O-carboxyl
CH2	59.5	-2.3	aliphatic
		9.1	1 alpha -C
		54.9	1 alpha -O-C=O
		-2.5	1 gamma -C
		0.3	1 delta -C
		0.0	1 delta -N
CH3	13.6	-2.3	aliphatic
		9.1	1 alpha -C
		6.5	1 beta -O-C=O
		0.3	1 delta -C
CH2	33.7	-2.3	aliphatic
		18.2	2 alpha -C
		9.3	1 beta -1:C*C*C*C*C*C*1
		2.0	1 beta -C(=O)-O
		11.3	1 beta -N
		-2.5	1 gamma -C
		-0.4	1 delta -C(=O)-N
		0.6	2 delta -C
		-2.5	steric corrections
CH2	30.4	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		9.4	1 beta -C
		-2.8	1 gamma -C(=O)-O
		-5.1	1 gamma -N
		0.3	1 delta -C
		-2.5	steric corrections
C	138.8	128.5	1-benzene
		10.3	1 -CCC
CH	128.3	128.5	1-benzene
		-0.2	1 -CCC
CH	128.6	128.5	1-benzene
		0.1	1 -CCC
CH	125.8	128.5	1-benzene
		-2.7	1 -CCC
CH	128.6	128.5	1-benzene
		0.1	1 -CCC
CH	128.3	128.5	1-benzene
		-0.2	1 -CCC
CH2	34.7	-2.3	aliphatic
		18.2	2 alpha -C
		9.3	1 beta -1:C*C*C*C*C*C*1
		2.6	1 beta -C(=O)-N
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.0	1 delta -C(=O)-O
		0.6	2 delta -C
		-2.5	steric corrections
CH2	26.3	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		9.4	1 beta -C
		-3.2	1 gamma -C(=O)-N
		-5.1	1 gamma -N
		0.6	2 delta -C
		-2.5	steric corrections
		-4.0	gamma corrections
C	130.7	128.5	1-benzene
		10.3	1 -CCC
		-8.1	1 -N-C(=O)-C
CH	128.5	128.5	1-benzene
		-0.2	1 -CCC
		0.2	1 -N-C(=O)-C
CH	124.2	128.5	1-benzene
		0.1	1 -CCC
		-4.4	1 -N-C(=O)-C
CH	126.0	128.5	1-benzene
		-2.7	1 -CCC
		0.2	1 -N-C(=O)-C
CH	120.5	128.5	1-benzene
		0.1	1 -CCC
		-8.1	1 -N-C(=O)-C
C	140.6	128.5	1-benzene
		-0.2	1 -CCC
		12.3	1 -N-C(=O)-C

ChemNMR H-1 Estimation



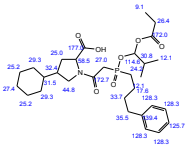
Estimation Quality: blue = good, magenta = medium, red = rough



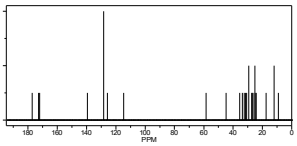
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
OH	11.0	11.00	carboxylic acid
CH	4.33	2.75	pyrrolidine
		0.87	1 alpha -C(=O)O from methine
		0.71	1 -C(=O)C
CH2	2.2	1.37	methylene
		0.85	1 alpha -C(=O)N
		?	1 unknown alpha substituent(s)
			-> 1 increment(s) not found
CH2	1.3	1.37	methylene
		?	1 unknown alpha substituent(s)
		-0.04	1 beta -C
			-> 1 increment(s) not found
CH2	1.3	1.37	methylene
		?	1 unknown beta substituent(s)
		-0.04	1 beta -C
			-> 1 increment(s) not found
CH2	1.62	1.37	methylene
		-0.04	1 beta -C
		0.29	1 beta -1:C*C*C*C*C*C*1
CH2	2.55	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		-0.04	1 beta -C
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.08	7.26	1-benzene
		-0.18	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH	5.68	1.50	methine
		2.47	1 alpha -O-C=O
		1.73	1 alpha -O
		-0.02	2 beta -C
CH2	2.29	1.37	methylene
		0.00	1 alpha -C
		0.92	1 alpha -C(=O)O-C
CH3	1.14	0.86	methyl
		0.28	1 beta -C(=O)OC
CH	2.51	1.50	methine
		0.34	2 alpha -C
		0.59	1 beta -O-C=O
		0.08	1 beta -O
CH3	1.01	0.86	methyl
		0.10	1 beta -C-R
		0.05	1 beta -C
CH3	1.01	0.86	methyl
		0.10	1 beta -C-R
		0.05	1 beta -C
CH2	3.42	2.75	pyrrolidine
		-0.04	1 beta -C from methylene
		0.71	1 -C(=O)C
CH	1.95	1.59	pyrrolidine
		-0.02	2 beta -C from methine
		0.38	1 -C(=O)C
CH	1.42	1.44	cyclohexane
		-0.02	2 beta -C from methine
CH2	1.40	1.44	cyclohexane
		-0.04	1 beta -C from methylene
CH2	1.44	1.44	cyclohexane
CH2	1.44	1.44	cyclohexane
CH2	1.44	1.44	cyclohexane
CH2	1.40	1.44	cyclohexane
		-0.04	1 beta -C from methylene
CH2	2.16	1.59	pyrrolidine
		-0.04	1 beta -C from methylene
		0.23	1 beta -C(=O)O from methylene
		0.38	1 -C(=O)C

ChemNMR C-13 Estimation



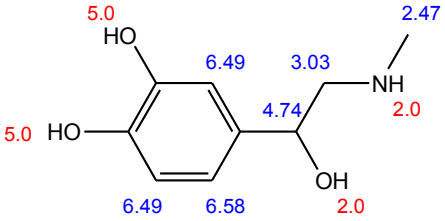
Estimation Quality: blue = good, magenta = medium, red = rough



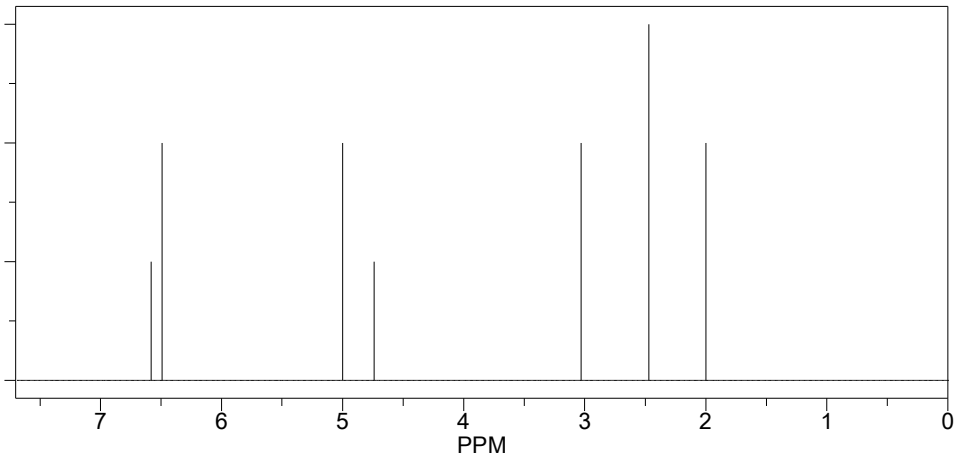
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	177.0	166.0	1-carboxyl
		11.0	1 -C-C-C
CH	58.5	-9.1	pyrrolidine
		21.8	1 alpha -C(=O)-O from aliphatic
		9.1	1 alpha -C from aliphatic
		28.3	1 alpha -N from aliphatic
		0.5	1 beta -C(=O)-C from aliphatic
		18.8	2 beta -C from aliphatic
		-2.5	1 gamma -C from aliphatic
		0.6	2 delta -C from aliphatic
		0.0	1 delta -P=O from aliphatic
		-9.0	steric corrections from aliphatic
C	172.7	165.0	1-amide
		7.7	1 -C
CH2	27.0	-2.3	aliphatic
		22.5	1 alpha -C(=O)-N
		2.1	1 alpha -P=O
		9.4	1 beta -C
		10.1	1 beta -O
		-10.0	4 gamma -C
		0.0	1 delta -C(=O)-O
		1.0	4 delta -C
		0.0	1 delta -O-C=O
		-6.0	steric corrections
CH2	24.2	-2.3	aliphatic
		9.1	1 alpha -C
		2.1	1 alpha -P=O
		18.8	2 beta -C
		10.1	1 beta -O
		-3.2	1 gamma -C(=O)-N
		-5.0	2 gamma -C
		0.3	1 delta -1:C*C*C*C*C*C*1
		0.3	1 delta -C
		0.0	1 delta -O-C=O
		-6.0	steric corrections
CH2	17.6	-2.3	aliphatic
		18.2	2 alpha -C
		9.4	1 beta -C
		3.7	1 beta -P=O
		-2.6	1 gamma -1:C*C*C*C*C*C*1
		-2.5	1 gamma -C
		-6.2	1 gamma -O
		-0.4	1 delta -C(=O)-N
		0.3	1 delta -C
CH2	33.7	-2.3	aliphatic
		18.2	2 alpha -C
		9.3	1 beta -1:C*C*C*C*C*C*1
		9.4	1 beta -C
		-1.5	1 gamma -P=O
		0.3	1 delta -C
		0.3	1 delta -O
CH2	35.5	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		9.4	1 beta -C
		-2.5	1 gamma -C
		0.0	1 delta -P=O
		-2.5	steric corrections
C	139.4	128.5	1-benzene
		10.9	1 -C-C-C-C
CH	128.3	128.5	1-benzene
		-0.2	1 -C-C-C-C
CH	128.3	128.5	1-benzene
		-0.2	1 -C-C-C-C
CH	125.7	128.5	1-benzene
		-2.8	1 -C-C-C-C
CH	128.3	128.5	1-benzene
		-0.2	1 -C-C-C-C
CH	128.3	128.5	1-benzene
		-0.2	1 -C-C-C-C
CH	114.6	-2.3	aliphatic
		9.1	1 alpha -C
		63.6	1 alpha -O-P(=O)
		54.9	1 alpha -O-C=O
		18.8	2 beta -C
		-7.5	3 gamma -C
		-0.4	1 delta -C(=O)-N
		0.6	2 delta -C
		-8.5	steric corrections
		-13.7	OO alpha corrections
C	172.0	166.0	1-carboxyl
		11.0	1 -C-C
CH2	26.4	-5.0	1 -C from O-carboxyl
		-2.3	aliphatic
		21.8	1 alpha -C(=O)-O
		9.1	1 alpha -C
		-2.5	1 gamma -C
		0.3	1 delta -C
		0.0	1 delta -O-P(=O)
CH3	9.1	+2.3	aliphatic
		9.1	1 alpha -C
		2.0	1 beta -C(=O)-O
		0.3	1 delta -C
CH	30.8	+2.3	aliphatic
		27.3	3 alpha -C
		6.9	1 beta -O-P(=O)
		6.5	1 beta -O-C=O
		0.9	3 delta -C
		-8.5	steric corrections
CH3	12.1	-2.3	aliphatic
		9.1	1 alpha -C
		18.8	2 beta -C
		-6.4	1 gamma -O-P(=O)
		-6.0	1 gamma -O-C=O
		+1.1	steric corrections
CH3	12.1	-2.3	aliphatic
		9.1	1 alpha -C
		18.8	2 beta -C
		-6.4	1 gamma -O-P(=O)
		-6.0	1 gamma -O-C=O
		-1.1	steric corrections
CH2	44.8	-9.1	pyrrolidine
		9.1	1 alpha -C from aliphatic
		28.3	1 alpha -N from aliphatic
		0.5	1 beta -C(=O)-C from aliphatic
		28.2	3 beta -C from aliphatic
		-2.8	1 gamma -C(=O)-O from aliphatic
		+5.0	2 gamma -C from aliphatic
		0.6	2 delta -C from aliphatic
		0.0	1 delta -P=O from aliphatic
		+5.0	steric corrections from aliphatic
CH	32.4	-13.2	pyrrolidine
		27.3	3 alpha -C from aliphatic
		28.2	3 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.8	1 gamma -C(=O)-O from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
		+5.0	2 gamma -C from aliphatic
		0.3	1 delta -C from aliphatic
		-11.0	steric corrections from aliphatic
CH	31.5	+7.4	cyclohexane
		27.3	3 alpha -C from aliphatic
		37.6	4 beta -C from aliphatic
		-5.0	2 gamma -C from aliphatic
		-5.1	1 gamma -N from aliphatic
		0.0	1 delta -C(=O)-O from aliphatic
		0.0	1 delta -C(=O)-C from aliphatic
		-15.9	steric corrections from aliphatic
CH2	29.3	+7.4	cyclohexane
		18.2	2 alpha -C from aliphatic
		28.2	3 beta -C from aliphatic
		-7.5	3 gamma -C from aliphatic
		0.3	1 delta -C from aliphatic
		0.0	1 delta -N from aliphatic
		-2.5	steric corrections from aliphatic
CH2	25.2	+7.4	cyclohexane
		18.2	2 alpha -C from aliphatic
		18.8	2 beta -C from aliphatic
		-5.0	2 gamma -C from aliphatic
		0.6	2 delta -C from aliphatic
CH2	27.4	+7.4	cyclohexane
		18.2	2 alpha -C from aliphatic
		18.8	2 beta -C from aliphatic
		-2.5	1 gamma -C from aliphatic
		0.3	1 delta -C from aliphatic
CH2	25.2	+7.4	cyclohexane
		18.2	2 alpha -C from aliphatic
		18.8	2 beta -C from aliphatic
		+5.0	2 gamma -C from aliphatic
		0.6	2 delta -C from aliphatic
CH2	29.3	+7.4	cyclohexane
		18.2	2 alpha -C from aliphatic
		28.2	3 beta -C from aliphatic
		-7.5	3 gamma -C from aliphatic
		0.3	1 delta -C from aliphatic
		0.0	1 delta -N from aliphatic
		-2.5	steric corrections from aliphatic
CH2	25.0	-13.2	pyrrolidine
		18.2	2 alpha -C from aliphatic
		2.0	1 beta -C(=O)-C from aliphatic
		18.8	2 beta -C from aliphatic
		11.3	1 beta -N from aliphatic
		-2.7	1 gamma -C(=O)-C from aliphatic
		+5.0	2 gamma -C from aliphatic
		0.6	2 delta -C from aliphatic
		+5.0	steric corrections from aliphatic

ChemNMR H-1 Estimation



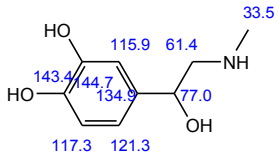
Estimation Quality: blue = good, magenta = medium, red = rough



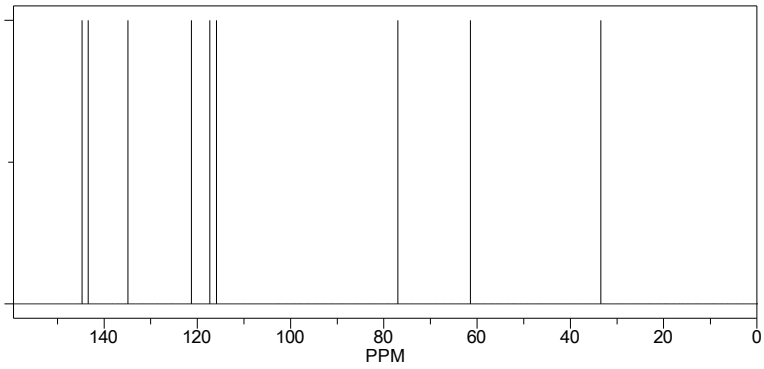
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
OH	5.0	5.00	aromatic C-OH
CH	6.49	7.26	1-benzene
		-0.53	1 -O
		-0.07	1 -C-O
		-0.17	1 -O
CH	4.74	1.50	methine
		1.28	1 alpha -1:C*C*C*C*C*C*1
		1.73	1 alpha -O
		0.23	1 beta -N
OH	2.0	2.00	alcohol
CH2	3.03	1.37	methylene
		1.22	1 alpha -N-C
		0.29	1 beta -1:C*C*C*C*C*C*1
		0.15	1 beta -O
NH	2.0	2.00	amine
CH3	2.47	0.86	methyl
		1.61	1 alpha -N
CH	6.58	7.26	1-benzene
		-0.44	1 -O
		-0.07	1 -C-O
		-0.17	1 -O
CH	6.49	7.26	1-benzene
		-0.17	1 -O
		-0.07	1 -C-O
		-0.53	1 -O
OH	5.0	5.00	aromatic C-OH

ChemNMR C-13 Estimation



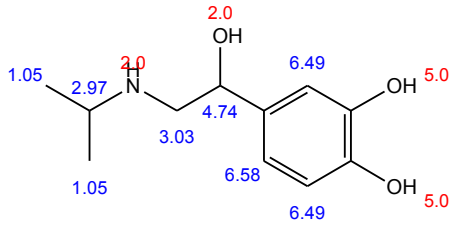
Estimation Quality: blue = good, magenta = medium, red = rough



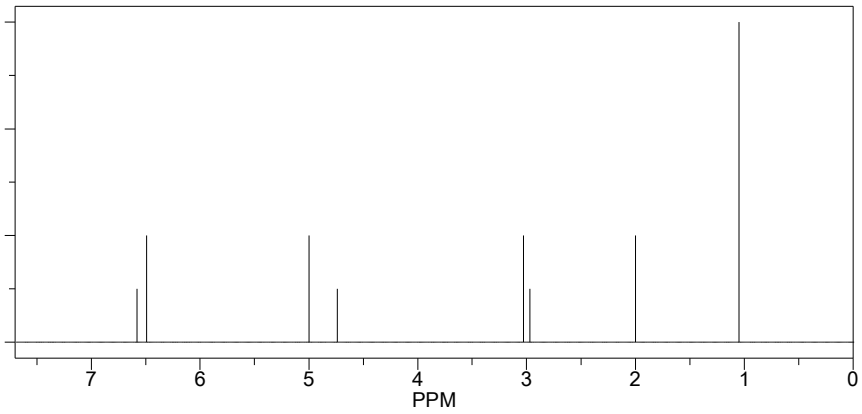
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	144.7	128.5	1-benzene
		28.8	1 -O
		0.2	1 -C-O
		-12.8	1 -O
CH	115.9	128.5	1-benzene
		-12.8	1 -O
		-1.2	1 -C-O
		1.4	1 -O
C	134.9	128.5	1-benzene
		1.4	1 -O
		12.4	1 -C-O
		-7.4	1 -O
CH	77.0	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		49.0	1 alpha -O
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.3	1 delta -O
		-12.2	steric corrections
CH2	61.4	-2.3	aliphatic
		9.1	1 alpha -C
		28.3	1 alpha -N
		9.3	1 beta -1:C*C*C*C*C*C*1
		9.4	1 beta -C
		10.1	1 beta -O
		-2.5	steric corrections
CH3	33.5	-2.3	aliphatic
		28.3	1 alpha -N
		9.4	1 beta -C
		-2.5	1 gamma -C
		0.3	1 delta -1:C*C*C*C*C*C*1
		0.3	1 delta -O
CH	121.3	128.5	1-benzene
		-7.4	1 -O
		-1.2	1 -C-O
		1.4	1 -O
CH	117.3	128.5	1-benzene
		1.4	1 -O
		0.2	1 -C-O
		-12.8	1 -O
C	143.4	128.5	1-benzene
		-12.8	1 -O
		-1.1	1 -C-O
		28.8	1 -O

ChemNMR H-1 Estimation



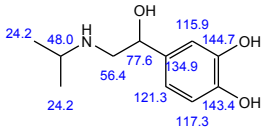
Estimation Quality: blue = good, magenta = medium, red = rough



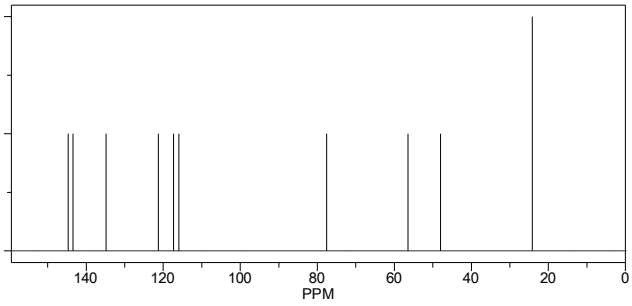
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH3	1.05	0.86	methyl
		0.14	1 beta -N
		0.05	1 beta -C
CH	2.97	1.50	methine
		0.34	2 alpha -C
		1.13	1 alpha -N
NH	2.0	2.00	amine
CH2	3.03	1.37	methylene
		1.22	1 alpha -N-C
		0.29	1 beta -1:C*C*C*C*C*C*1
		0.15	1 beta -O
CH	4.74	1.50	methine
		1.28	1 alpha -1:C*C*C*C*C*C*1
		1.73	1 alpha -O
		0.23	1 beta -N
CH	6.49	7.26	1-benzene
		-0.07	1 -C-O
		-0.53	1 -O
		-0.17	1 -O
OH	5.0	5.00	aromatic C-OH
OH	5.0	5.00	aromatic C-OH
CH	6.49	7.26	1-benzene
		-0.07	1 -C-O
		-0.17	1 -O
		-0.53	1 -O
CH	6.58	7.26	1-benzene
		-0.07	1 -C-O
		-0.44	1 -O
		-0.17	1 -O
OH	2.0	2.00	alcohol
CH3	1.05	0.86	methyl
		0.14	1 beta -N
		0.05	1 beta -C

ChemNMR C-13 Estimation



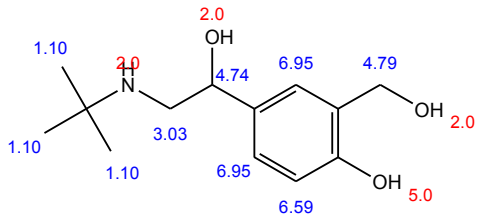
Estimation Quality: blue = good, magenta = medium, red = rough



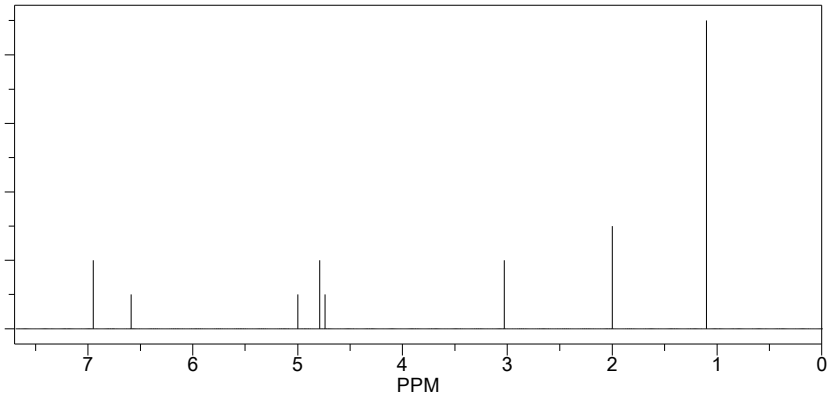
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH3	24.2	-2.3	aliphatic
		9.1	1 alpha -C
		9.4	1 beta -C
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.3	1 delta -C
		-1.1	steric corrections
CH	48.0	-2.3	aliphatic
		18.2	2 alpha -C
		28.3	1 alpha -N
		9.4	1 beta -C
		-2.5	1 gamma -C
		0.3	1 delta -1:C*C*C*C*C*C*1
		0.3	1 delta -O
		-3.7	steric corrections
CH2	56.4	-2.3	aliphatic
		9.1	1 alpha -C
		28.3	1 alpha -N
		9.3	1 beta -1:C*C*C*C*C*C*1
		9.4	1 beta -C
		10.1	1 beta -O
		-5.0	2 gamma -C
		-2.5	steric corrections
CH	77.6	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		49.0	1 alpha -O
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.6	2 delta -C
		0.3	1 delta -O
		-12.2	steric corrections
C	134.9	128.5	1-benzene
		12.4	1 -C-O
		1.4	1 -O
		-7.4	1 -O
CH	115.9	128.5	1-benzene
		-1.2	1 -C-O
		-12.8	1 -O
		1.4	1 -O
C	144.7	128.5	1-benzene
		0.2	1 -C-O
		28.8	1 -O
		-12.8	1 -O
C	143.4	128.5	1-benzene
		-1.1	1 -C-O
		-12.8	1 -O
		28.8	1 -O
CH	117.3	128.5	1-benzene
		0.2	1 -C-O
		1.4	1 -O
		-12.8	1 -O
CH	121.3	128.5	1-benzene
		-1.2	1 -C-O
		-7.4	1 -O
		1.4	1 -O
CH3	24.2	-2.3	aliphatic
		9.1	1 alpha -C
		9.4	1 beta -C
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.3	1 delta -C
		-1.1	steric corrections

ChemNMR H-1 Estimation



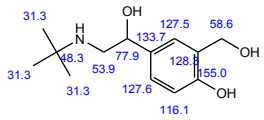
Estimation Quality: blue = good, magenta = medium, red = rough



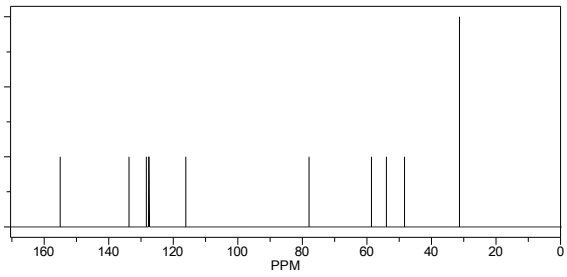
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH3	1.10	0.86	methyl
		0.14	1 beta -N
		0.10	2 beta -C
CH3	1.10	0.86	methyl
		0.14	1 beta -N
		0.10	2 beta -C
NH	2.0	2.00	amine
CH2	3.03	1.37	methylene
		1.22	1 alpha -N-C
		0.29	1 beta -1:C*C*C*C*C*C*1
		0.15	1 beta -O
CH	4.74	1.50	methine
		1.28	1 alpha -1:C*C*C*C*C*C*1
		1.73	1 alpha -O
		0.23	1 beta -N
CH	6.95	7.26	1-benzene
		-0.07	1 -C-O
		-0.07	1 -C-O
		-0.17	1 -O
CH2	4.79	1.37	methylene
		1.22	1 alpha -1:C*C*C*C*C*C*1
		2.20	1 alpha -O
OH	2.0	2.00	alcohol
OH	5.0	5.00	aromatic C-OH
CH	6.59	7.26	1-benzene
		-0.07	1 -C-O
		-0.07	1 -C-O
		-0.53	1 -O
CH	6.95	7.26	1-benzene
		-0.07	1 -C-O
		-0.07	1 -C-O
		-0.17	1 -O
OH	2.0	2.00	alcohol
CH3	1.10	0.86	methyl
		0.14	1 beta -N
		0.10	2 beta -C

ChemNMR C-13 Estimation



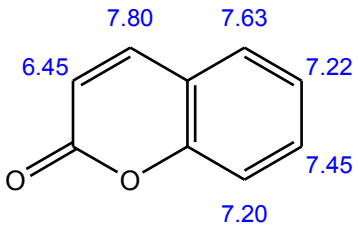
Estimation Quality: blue = good, magenta = medium, red = rough



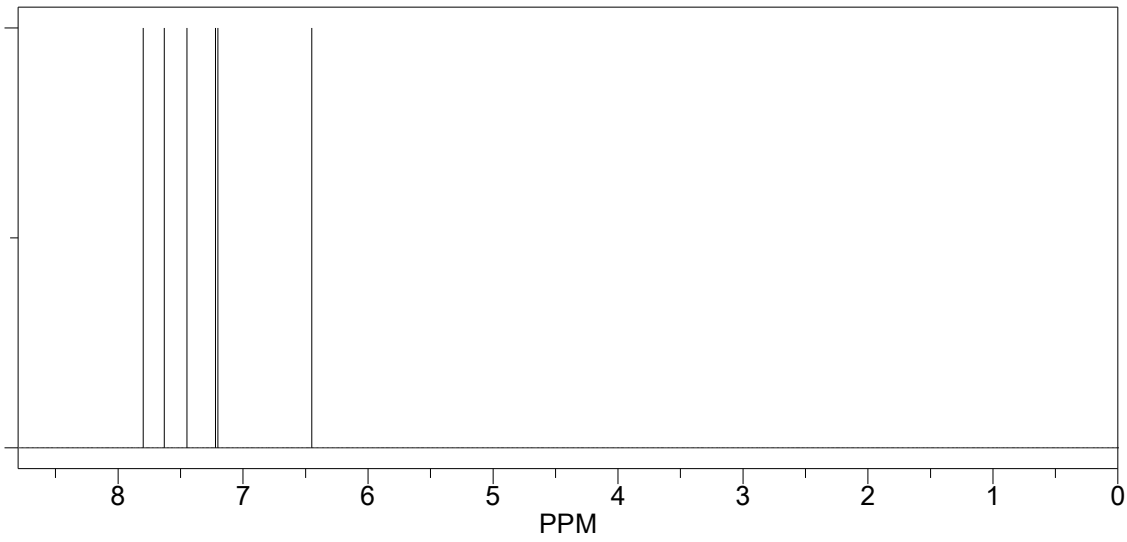
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH3	31.3	-2.3	aliphatic
		9.1	1 alpha -C
		18.8	2 beta -C
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.3	1 delta -C
		-3.4	steric corrections
C	48.3	-2.3	aliphatic
		27.3	3 alpha -C
		28.3	1 alpha -N
		9.4	1 beta -C
		-2.5	1 gamma -C
		0.3	1 delta -1:C*C*C*C*C*C*1
		0.3	1 delta -O
		-12.5	steric corrections
CH3	31.3	-2.3	aliphatic
		9.1	1 alpha -C
		18.8	2 beta -C
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.3	1 delta -C
		-3.4	steric corrections
CH2	53.9	-2.3	aliphatic
		9.1	1 alpha -C
		28.3	1 alpha -N
		9.3	1 beta -1:C*C*C*C*C*C*1
		9.4	1 beta -C
		10.1	1 beta -O
		-7.5	3 gamma -C
		-2.5	steric corrections
CH	77.9	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		9.1	1 alpha -C
		49.0	1 alpha -O
		11.3	1 beta -N
		-2.5	1 gamma -C
		1.2	4 delta -C
		-12.2	steric corrections
C	133.7	128.5	1-benzene
		12.4	1 -C-O
		0.2	1 -C-O
		-7.4	1 -O
CH	127.5	128.5	1-benzene
		-1.2	1 -C-O
		-1.2	1 -C-O
		1.4	1 -O
C	128.3	128.5	1-benzene
		0.2	1 -C-O
		12.4	1 -C-O
		-12.8	1 -O
CH2	58.6	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		49.0	1 alpha -O
		-6.2	1 gamma -O
		0.3	1 delta -C
		-2.5	steric corrections
		-4.0	gamma corrections
C	155.0	128.5	1-benzene
		-1.1	1 -C-O
		-1.2	1 -C-O
		28.8	1 -O
CH	116.1	128.5	1-benzene
		0.2	1 -C-O
		0.2	1 -C-O
		-12.8	1 -O
CH	127.6	128.5	1-benzene
		-1.2	1 -C-O
		-1.1	1 -C-O
		1.4	1 -O
CH3	31.3	-2.3	aliphatic
		9.1	1 alpha -C
		18.8	2 beta -C
		11.3	1 beta -N
		-2.5	1 gamma -C
		0.3	1 delta -C
		-3.4	steric corrections

ChemNMR H-1 Estimation



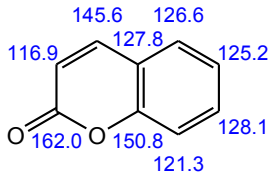
Estimation Quality: blue = good, magenta = medium, red = rough



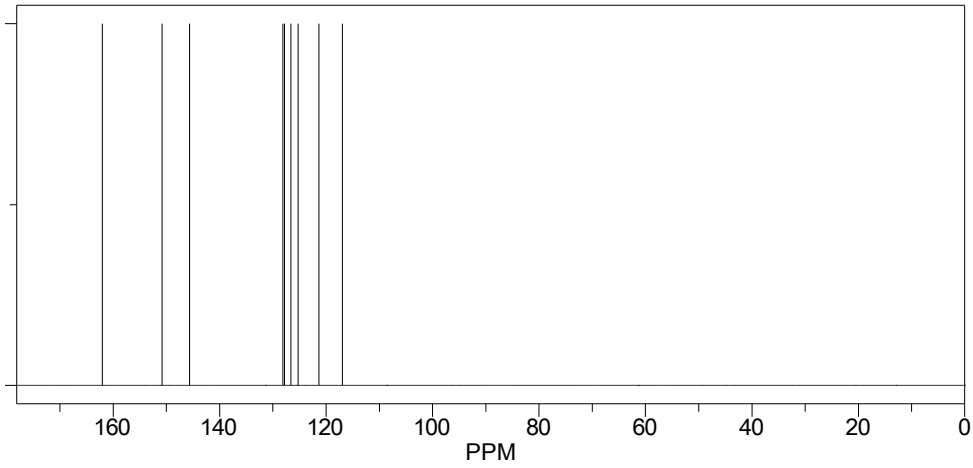
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH	6.45	6.45	coumarine
CH	7.80	7.80	coumarine
CH	7.63	7.63	coumarine
CH	7.22	7.22	coumarine
CH	7.45	7.45	coumarine
CH	7.20	7.20	coumarine

ChemNMR C-13 Estimation



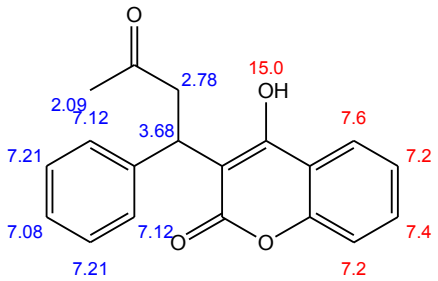
Estimation Quality: blue = good, magenta = medium, red = rough



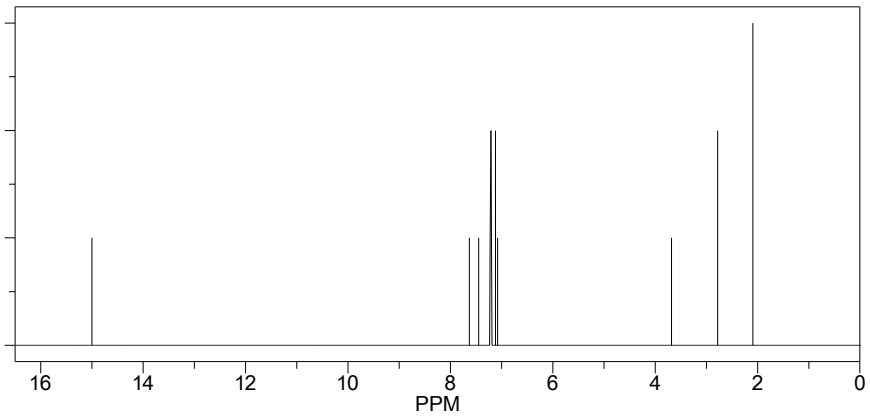
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	162.0	166.0	1-carboxyl
		4.0	1 -C=C
		-8.0	1 -1:C*C*C*C*C*C*1 from O-carboxyl
CH	116.9	123.3	1-ethylene
		4.6	1 -C(=O)-O
		-11.0	1 -1:C*C*C*C*C*C*1
CH	145.6	123.3	1-ethylene
		9.8	1 -C(=O)-O
		12.5	1 -1:C*C*C*C*C*C*1
C	127.8	128.5	1-benzene
		6.4	1 -C=C
		-7.1	1 -O-C(=O)
CH	126.6	128.5	1-benzene
		-2.3	1 -C=C
		0.4	1 -O-C(=O)
CH	125.2	128.5	1-benzene
		-0.1	1 -C=C
		-3.2	1 -O-C(=O)
CH	128.1	128.5	1-benzene
		-0.8	1 -C=C
		0.4	1 -O-C(=O)
CH	121.3	128.5	1-benzene
		-0.1	1 -C=C
		-7.1	1 -O-C(=O)
C	150.8	128.5	1-benzene
		-2.3	1 -C=C
		24.6	1 -O-C(=O)

ChemNMR H-1 Estimation



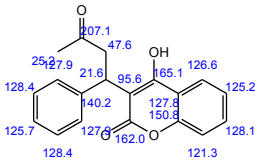
Estimation Quality: blue = good, magenta = medium, red = rough



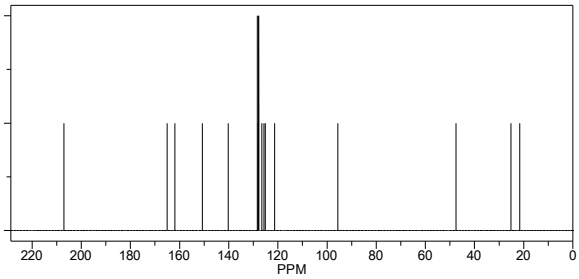
Protocol of the H-1 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH	3.68	1.50	methine
		1.28	1 alpha -1:C*C*C*C*C*C*1
		0.68	1 alpha -C=C
		0.22	1 beta -C=O
CH2	2.78	1.37	methylene
		1.12	1 alpha -C(=O)-C
		0.29	1 beta -1:C*C*C*C*C*C*1
		0.00	1 beta -C=C
CH3	2.09	0.86	methyl
		1.23	1 alpha -C(=O)C
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.08	7.26	1-benzene
		-0.18	1 -CC
CH	7.21	7.26	1-benzene
		-0.05	1 -CC
CH	7.12	7.26	1-benzene
		-0.14	1 -CC
OH	15.0	15.00	enol
CH	7.6	7.63	coumarine
			-> 1 increment(s) not found
CH	7.2	7.22	coumarine
			-> 1 increment(s) not found
CH	7.4	7.45	coumarine
			-> 1 increment(s) not found
CH	7.2	7.20	coumarine
			-> 1 increment(s) not found

ChemNMR C-13 Estimation



Estimation Quality: blue = good, magenta = medium, red = rough



Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	162.0	166.0	1-carboxyl
		4.0	1 -C=C
		-8.0	1 -1:C*C*C*C*C*C*1 from O-carboxyl
C	95.6	123.3	1-ethylene
		4.6	1 -C(=O)-O
		14.0	1 -C-C
		-11.0	1 -1:C*C*C*C*C*C*1
		-35.3	1 -O
CH	21.6	-2.3	aliphatic
		24.3	1 alpha -1:C*C*C*C*C*C*1
		19.5	1 alpha -C=C
		9.1	1 alpha -C
		2.0	1 beta -C(=O)-O
		0.5	1 beta -C(=O)-C
		-2.6	1 gamma -1:C*C*C*C*C*C*1
		-6.2	1 gamma -O
		-20.7	steric corrections
		-2.0	gamma corrections
CH2	47.6	-2.3	aliphatic
		29.3	1 alpha -C(=O)-C
		9.1	1 alpha -C
		9.3	1 beta -1:C*C*C*C*C*C*1
		6.9	1 beta -C=C
		-2.8	1 gamma -C(=O)-O
		0.3	1 delta -1:C*C*C*C*C*C*1
		0.3	1 delta -O
		-2.5	steric corrections
C	207.1	193.0	1-carbonyl
		7.6	1 -C-C
		6.5	1 -C
CH3	25.2	-2.3	aliphatic
		29.3	1 alpha -C(=O)-C
		-2.5	1 gamma -C
		0.3	1 delta -1:C*C*C*C*C*C*1
		0.4	1 delta -C=C
C	140.2	128.5	1-benzene
		11.7	1 -C-C
CH	127.9	128.5	1-benzene
		-0.6	1 -C-C
CH	128.4	128.5	1-benzene
		-0.1	1 -C-C
CH	125.7	128.5	1-benzene
		-2.8	1 -C-C
CH	128.4	128.5	1-benzene
		-0.1	1 -C-C
CH	127.9	128.5	1-benzene
		-0.6	1 -C-C
C	165.1	123.3	1-ethylene
		9.8	1 -C(=O)-O
		-8.2	1 -C-C
		12.5	1 -1:C*C*C*C*C*C*1
		27.7	1 -O
C	150.8	128.5	1-benzene
		24.6	1 -O-C(=O)
		-2.3	1 -C=C
C	127.8	128.5	1-benzene
		-7.1	1 -O-C(=O)
		6.4	1 -C=C
CH	126.6	128.5	1-benzene
		0.4	1 -O-C(=O)
		-2.3	1 -C=C
CH	125.2	128.5	1-benzene
		-3.2	1 -O-C(=O)
		-0.1	1 -C=C
CH	128.1	128.5	1-benzene
		0.4	1 -O-C(=O)
		-0.8	1 -C=C
CH	121.3	128.5	1-benzene
		-7.1	1 -O-C(=O)
		-0.1	1 -C=C

Mass spectroscopy :

Mass spectroscopy concept can be reduced to 3 words in my point of view ACCELERATION DETERMINATION RELATION

As we mainly accelerate the organic molecule and after that determination of its velocity and then relation between velocity and the molecular weight and determination of the molecular weight of the organic molecule.

One of the major problems during mass spectroscopy is FRAGMENTATION that when a molecule is accelerated to certain limit , after that it will be fragmented to small fragments .

But we can convert the disadvantage to advantage easily as we can predict the the structure of the organic molecule by identification of these fragments that is characteristic for each organic molecule.

: Chapter 4: Overall Outcomes

Relation between stereochemistry and medicinal chemistry :

Stereo of the drug is an impotant factor that affect its activity and side effects as all organic molecules with certain characters can affect light and rotate it towards right or towards left .

When the drug is a racemic that means that it has equal percent of the levo and dextro enantiomers and it is unfavorable condition as in most of cases only the levo enantiomer is active and induce response in human body so now you will acquire only half the activity and the total side effects .

If for certain reason there is racemization QUALITY CONTROL never give permission to the product to be released to the market unless it devoid of racemization so resolution mean that separation of the 2 enantiomers and so the levo enantiomer for example will be pure .

Special case that Quality assurance may accept to release the product although it is racemic that in which the dextro enantiomer will convert to the levo enantiomer and so we avoid in this case the useless resolution as it is expensive .

Organic reactions are mainly applications in synthesis and its reagents and precautions and the alternative reaction that is available and other complicated synthetic procedures .

As my field of interest is chemistry and specially medicinal chemistry and specifically stereo medicinal chemistry I will take in

consideration many types and methods of synthesis especially the reactions and synthesis that IS RELATED TO STEREO CHEMISTRY . and the following explanation ,,,,,,as Graham explained in Solomons Fryhle 2003 in page 216

- **Racemic synthesis**

(Graham, 2003) mentioned that Racemic synthesis is considered one of the most important synthesis as attack of the introducing group has 2 equal chances at the 2 homotopic faces so the result will be racemic which mean that there will be equal percent of the 2 products.

For*,(Wermuth2003)* mentioned in full details in his first chapter of his book *The practice of medicinal chemistry*,,, that the chemists always use all of their chemical information and expertise to perform the chemical synthesis efficiently as reactions and reagents and most of organic and medicinal chemistry studies aim finally to one target how to synthesize drugs.

: Chapter 5: Analysis

When we study the reaction in the theoretical point of view , it is highly different than performing of it in the laboratory so all the reactions and reagents are available in text books but the expertise of using those reactants and reagents differ from person to person according to his own work and qualification .

Also it is different to perform an industrial reaction And as*,(Wermuth2003) discussed* as to do laboratory one as there is great difference between the industrial method in synthesis and the laboratory synthesis . when we perform synthetic reaction on small scale we do not care for the cost of reagents as it is small scale and only small amount is needed to perform the reaction but if we intended to perform industrial procedure many precautions we should take in consideration like cost of reagents , availability of reagents .

Synthesis is complicated and tedious and time consuming especially if we treat with stereo selective reaction or stereo specific product as the most complicated application in synthesis is the synthesis that include stereo reactants and reagents .

Synthesis or pharmaceutical organic molecules is more than 1000 procedure and unlimited but I will choose one application in stereo synthesis and stereo reactions and stereo reagents to discuss in details and take in consideration all the precautions of these reactions .

- # Challenges in synthesis in medicinal chemistry :

According to different and most recently challenges as (*Dohersy 2003) mentioned :*

Protein crystallograghy and drug discovery
Classification as protein is one of challenging procedures as it is digested by human secretions so

need certain requirements and precautions to be discovered and isolated and synthesized.

- # Case study number 1 :
- ## Molecular modeling study and synthesis of novel β_1-antagonist of expected Antihypertensive and Cardiovascular blocking activity

Introduction about Hypertension and CVD, pharmacophoric features of β_1-antagonist, problems of adrenaline, lead compound (Atenolol) and its characteristics, the new hit compound, docking studies made for both the lead and the hit compounds to predict their binding mode, moreover the new hit compound exhibit a significant antihypertensive activity.

Cardiovascular disease :

Cardiovascular diseases that can affect the life style of the patient ,, include: coronary heart disease (heart attacks), cerebrovascular disease, hypertension, peripheral artery disease, rheumatic heart disease,. The major causes of cardiovascular disease are tobacco use, and many bad habits in the patient life style,, physical inactivity, and an unhealthy diet.

Hypertension *:*

Hypertension (HTN), or high blood pressure, occurs when the force of blood passing through blood vessels is above normal.

Atenolol

is a β_1 receptor selective antagonist, a drug belonging to the group of β-blockers, a class of drugs used primarily in cardiovascular diseases.
Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension it works by slowing down the heart and reducing its workload.

Indications

Atenolol (trade name Tenormin) can be used to treat cardiovascular diseases as hypertension, coronary heart disease, arrhythmias, angina, myocardial infarction. Atenolol is a so-called β_1-selective drug. That means that it exerts greater blocking activity on myocardial β_1-receptors than on β_2 ones in the lung.

Pharmacokinetic data

t_{cmax} = 2 to 4 hours after oral dosing. The mean elimination half-life is 6 hours.

Atenolol is a hydrophilic drug. The concentration found in brain tissue is approximately 15% of the plasma concentration only. The drug crosses the placenta barrier freely in the milk of breastfeeding mothers,

Contraindications

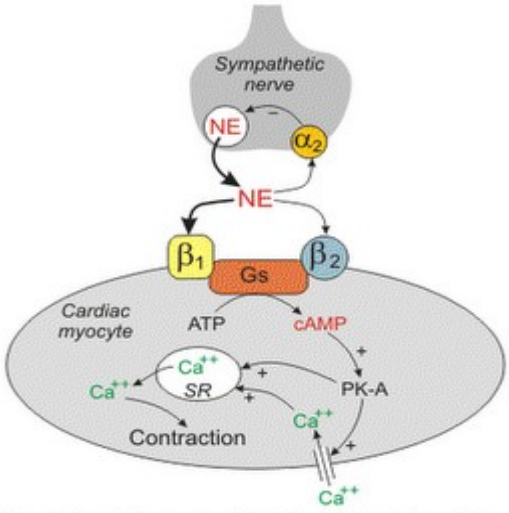
bradycardia (pulse less than 50 bpm), cardiogenic shock, asthma (may cause broncho-constriction), symptomatic hypotension (blood pressure of less than 100/60 mm Hg),

Side effect

indigestion, constipation, dry mouth, dizziness or faintness (especially cases of orthostatic hypotension), cold extremities, hair loss, problems with sexual function, runny/blocked nose, depression and confusion, difficulty sleeping,

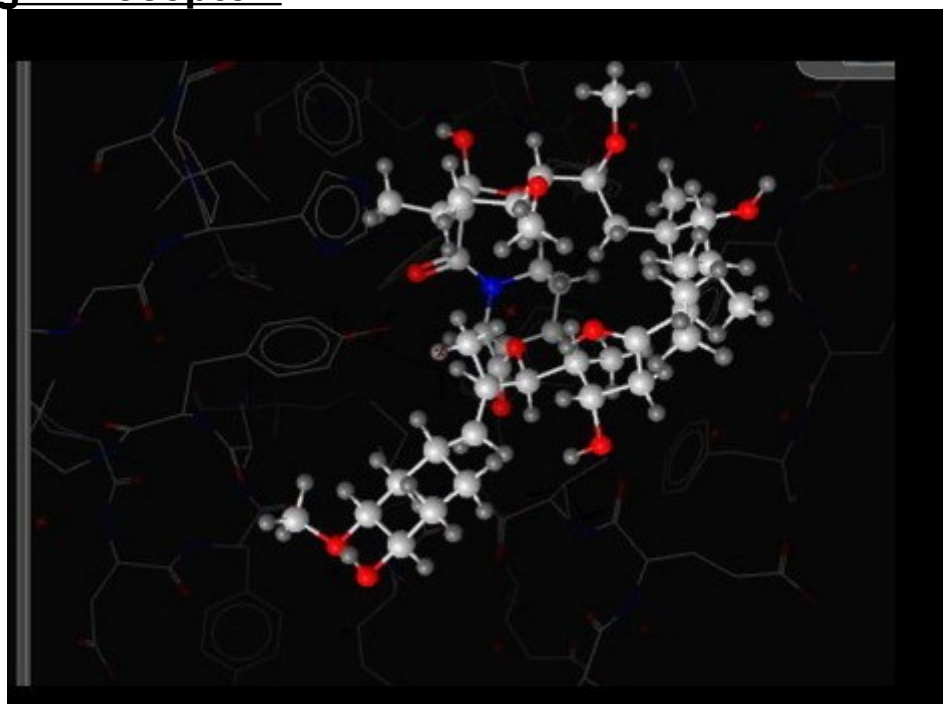
Mode Of Action (MOA):

Competitively blocks beta-adrenergic receptors in the heart and juxtoglomerular apparatus. They lead to decreased heart rate decreasing the work load by the heart. They do not produce coronary vasodilatation but lead to a shift and redistribution of coronary circulation to the ischemic areas. It decreases the release of renin from the kidney, thus lowering blood pressure.

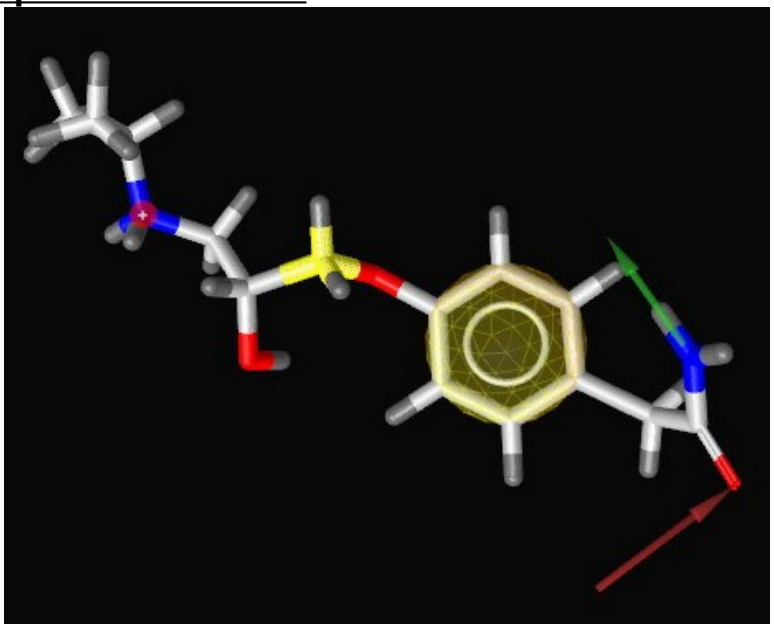


Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

Drug In Receptor:



Pharmacophoric Features:

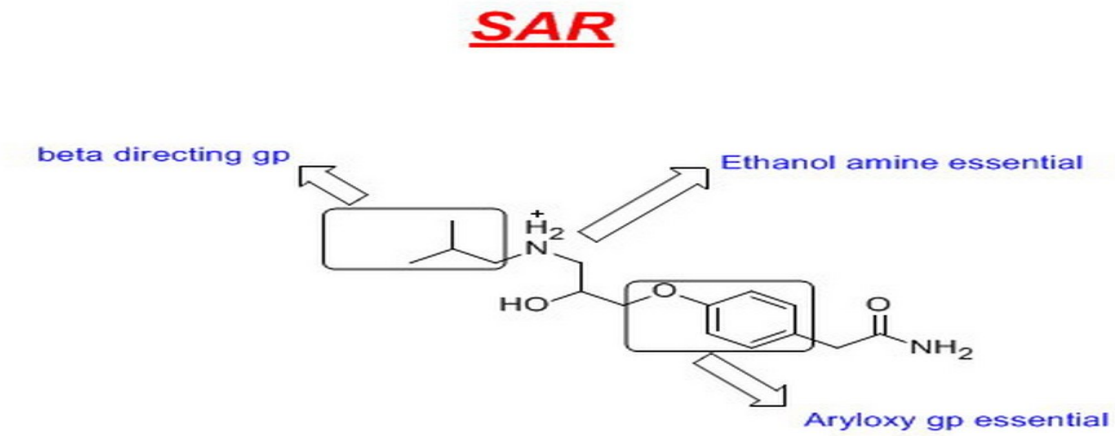


Hydrogen bond acceptor: 

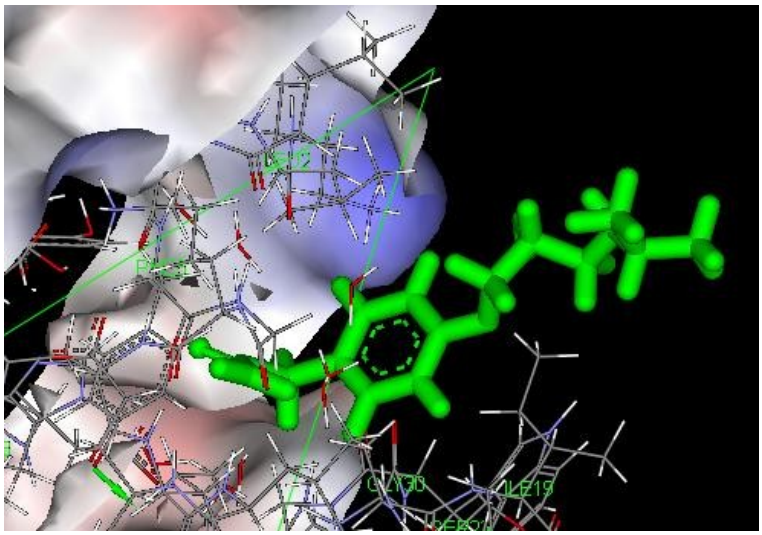
Hydrogen bond donar: 

Hydrophobic bond: 

Structure Activity Relationship (SAR):

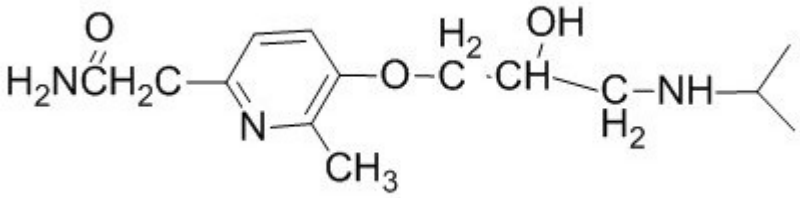


***receptor visualizer:**



So NOW after studying SAR and Pharmacophoric Characters of Atenolol and by Applying LEAD MODIFICATON STRATEGIES, The New β1 Antagonist

"Ceuticolol" was suggested



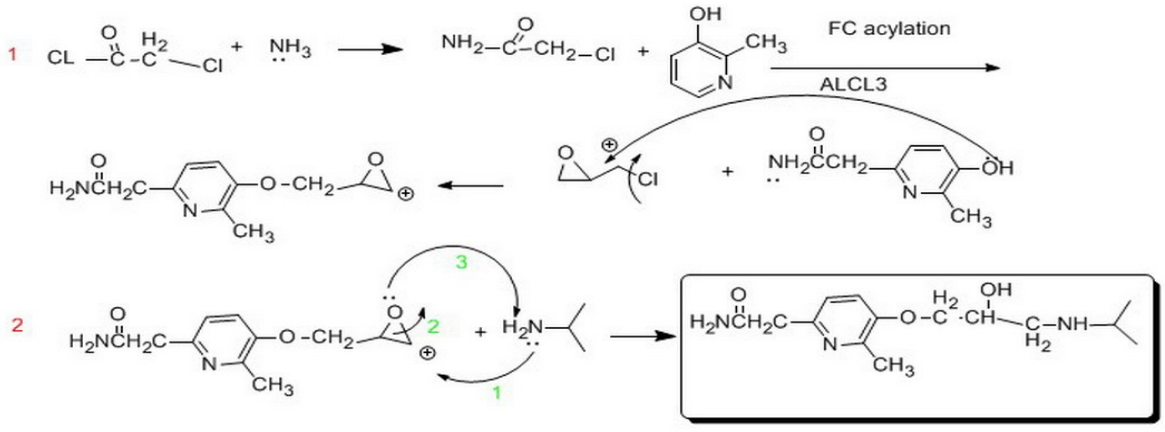
Suggested Synthesis for The New β1 Antagonist Ceuticolol:

Using the Lead modification strategies Studies and by applying:

1-classical bioisostere replacement of benzene ring so that we get EXTRA HYDROGEN BINDING

2-EXTENDING A CHAIN IN EXTRA HYDROPHOBIC POCKET

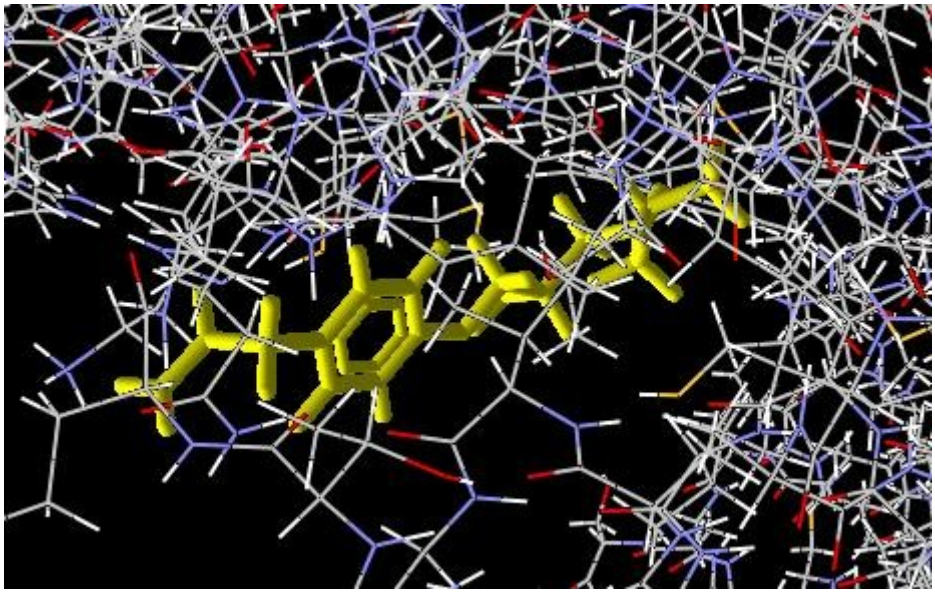
Synthesis of the betal antagonist "Ceuticolol"



Ceuticolol

Docking of Ceuticolol:

1)Atenolol docking:

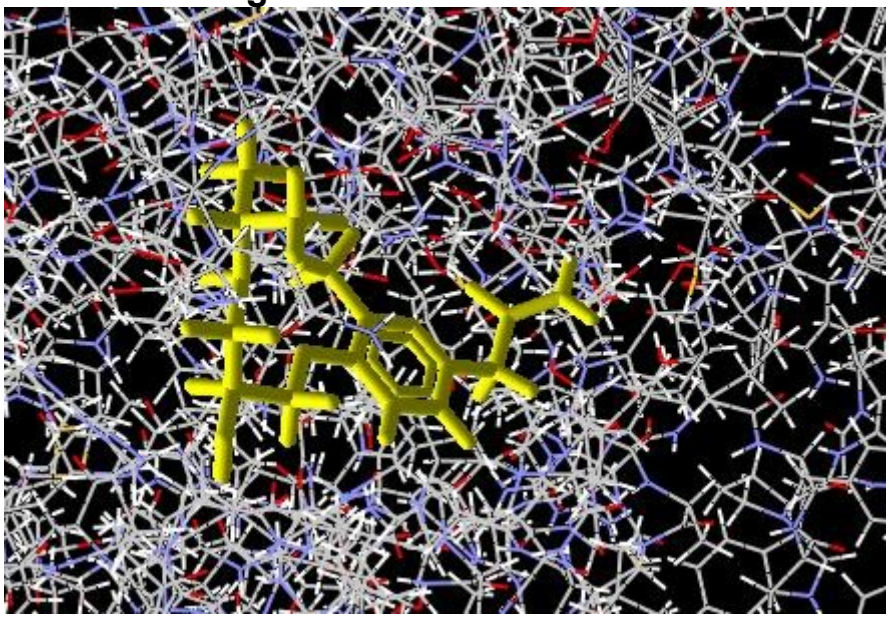


***atenolol docking score:**

Poses

Name	Ligand	MolDockScore	Rerank Score	HBond
[01] Mole...	Molecule-1	-107.361	-88.538	-11.335
[00] Mole...	Molecule-1	-105.095	-82.6761	-7.45163
[02] Mole...	Molecule-1	-95.538	-76.1055	-8.47128
[03] Mole...	Molecule-1	-95.8751	-74.4732	-6.3642
[04] Mole...	Molecule-1	-87.94	-71.8666	-3.60311

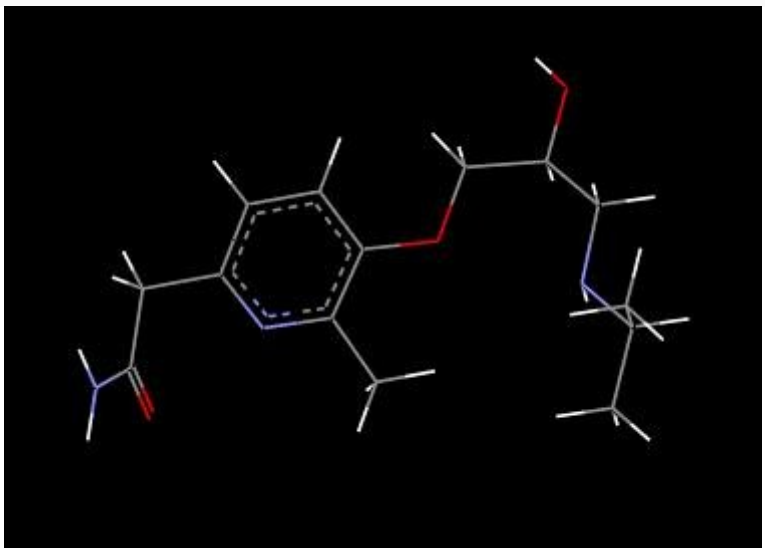
2) Ceuticolol docking:



***Ceuticolol docking score:**

Poses

Name	Ligand	MolDockScore	Rerank Score	RMSD	HBond
☐ [01] ceuti...	ceuticolol 2	-104.225	-75.8393	11.9859	-9.46079
☐ [00] ceuti...	ceuticolol 2	-103.311	-78.5035	11.3442	-9.57563
☐ [02] ceuti...	ceuticolol 2	-99.9431	-69.472	12.8622	-9.1171
☐ [03] ceuti...	ceuticolol 2	-92.5049	-68.4237	12.0727	0.733398
☐ [04] ceuti...	ceuticolol 2	-91.9655	-48.8849	12.8111	-8.79124

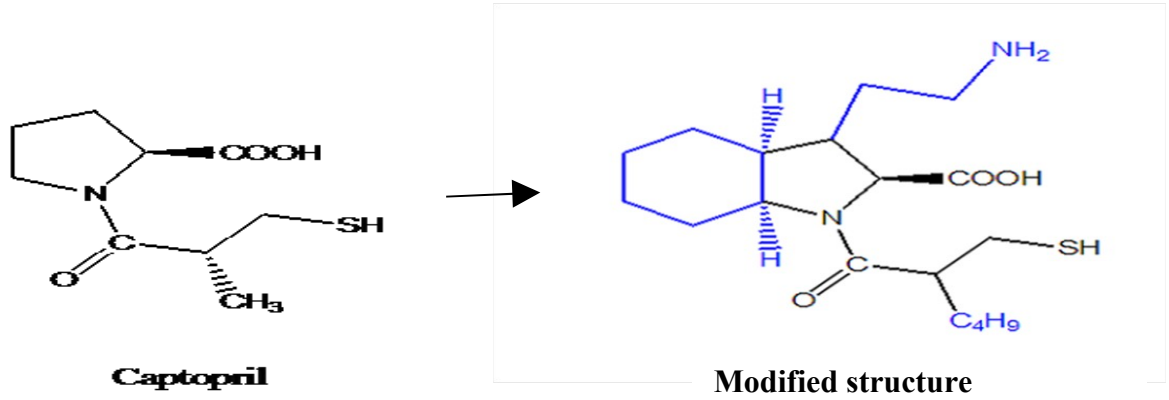


Case study number 2 :

We are trying to design new drug from the ACE inhibitor class.
The lead compound is captopril.
The strategy followed is extension of the structure, so that the interaction between the ligand and the receptor is increased, i.e. addition of extra binding groups:

- The addition of $-CH_2-CH_2-NH_2$ as a side chain on the pyrrolidine nucleus makes an extra H-bond.
- The ring extension by fusion of the pyrrolidine ring with cyclohexyl ring occupies a hydrophobic pocket.

- Also, substituting the methyl group with butyl make better hydrophobic interaction with the target.



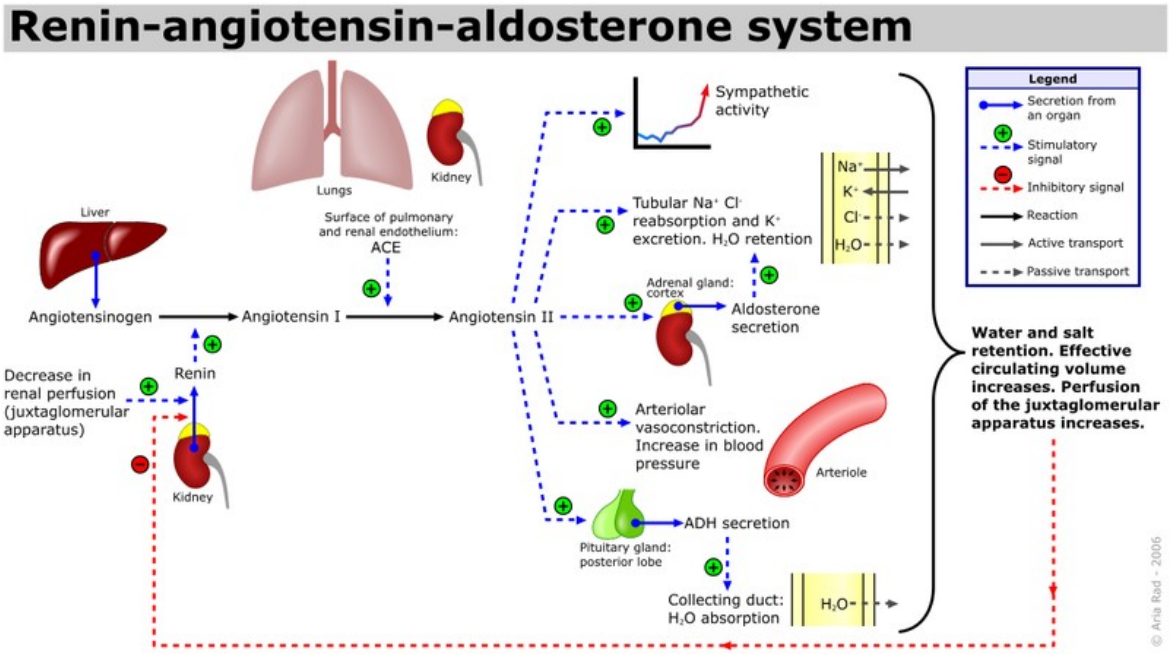
Captopril **Modified structure**

Introduction

ACE Inhibitors are competitive inhibitors of ACE, mimicking the structure of its substrate.

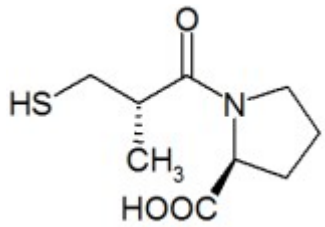
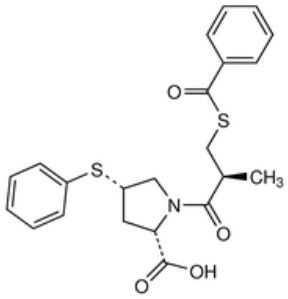
ACE inhibitors: (1) Directly block the formation of AT-II.
(2) Increase bradykinin level.

The net results are reduced vasoconstriction, reduced sodium and water retension, and increased vasodilation (through bradykinin).

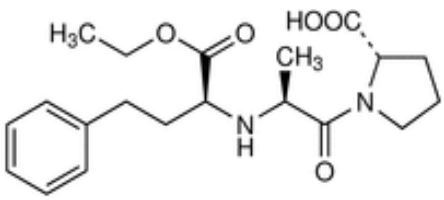
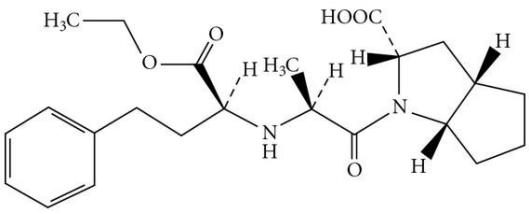


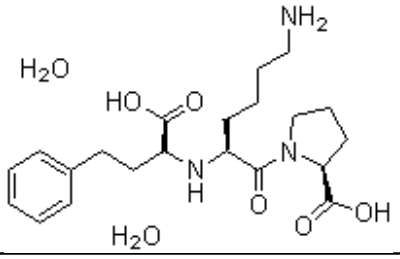
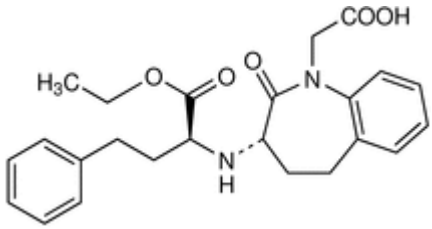
Examples of ACE inhibitors

A)Sulfhydryl-containing agents

Captopril (Capoten)	Zofenopril
	

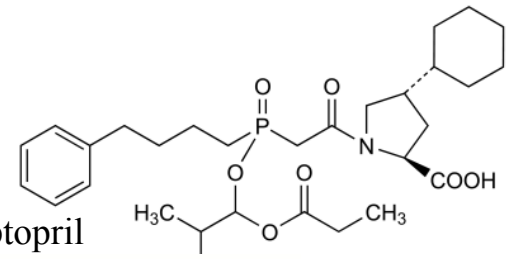
B)Dicarboxylate-containing agents

Enalapril (Vasotec, Renitec)	Ramipril (Altace, Tritace, Ramace)
	

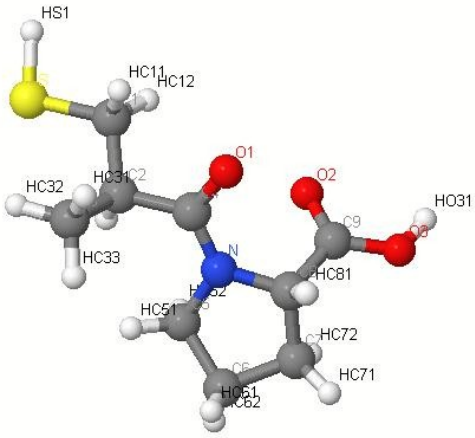
Lisinopril (Lisodur, Lopril, Novatec)	Benazepril (Lotensin)
	

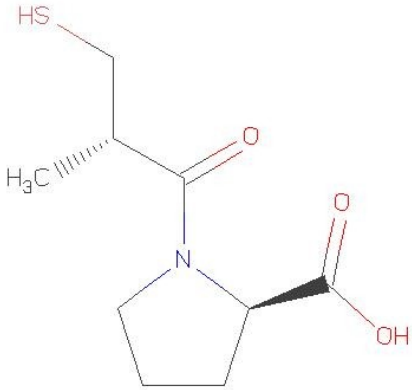
C)Phosphonate-containing agents

Fosinopril (Monopril)



lead Compound : Captopril





The development of captopril was amongst the earliest successes of the revolutionary concept of structure-based design.
The renin-angiotensin aldosterone system had been extensively studied in the mid-20th century and it had been decided that this system presented several opportune target in the development of the novel treatments for hypertension.
Captopril was the first angiotensin-converting enzyme (ACE) inhibitor developed for treatment of hypertension and some types of congestive heart failure.

It was considered a breakthrough both because of its novel mechanism of action and also because of the revolutionary development process.
Due to the increasing need for ACE inhibitors, modifications have been made in order to increase its activity. In this research, these modifications will be described and a synthetic pathway will be suggested.

Structure Activity Relationship (SAR)

The inhibitor should have a group that enables it to bind to the cationic binding site and another group that enables it to bind to the zinc binding site.

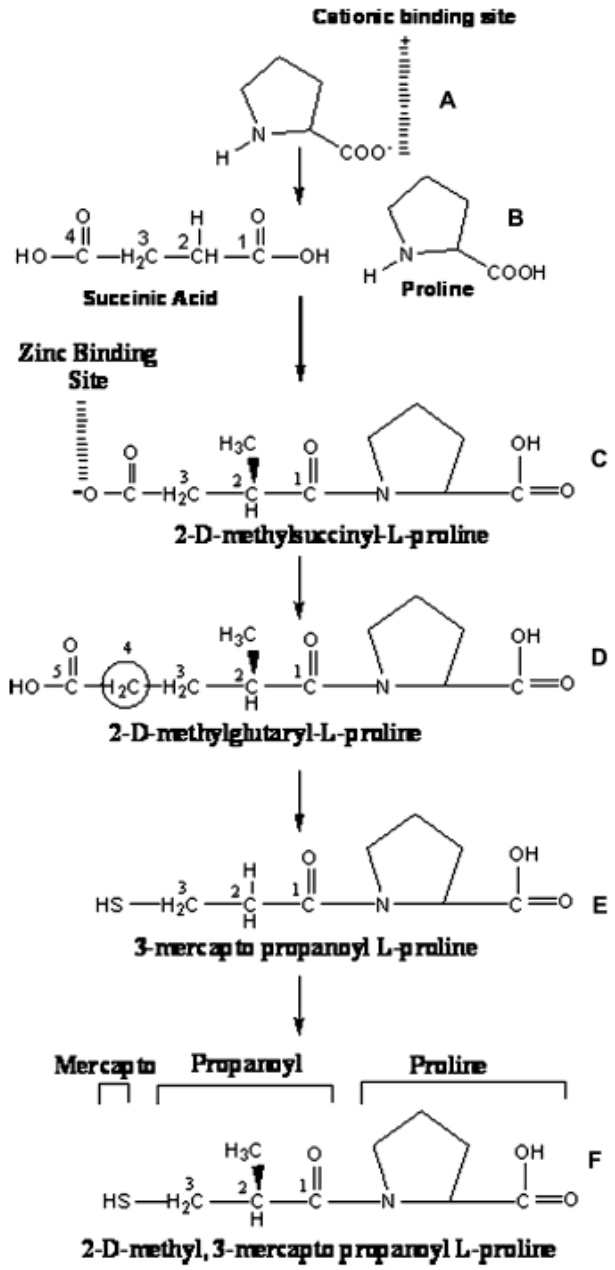


Figure 4. Illustration of the synthesis of captopril analogs.

Other auxiliary binding sites may also exist, and when accommodated will enhance the potency of ACEIs by increasing the binding affinity to ACE.
We also know that all naturally occurring peptidic inhibitors of ACE have proline as the carboxylic terminal residue.
The carboxyl group on proline is essential for ion-ion bonding to the cationic site on ACE

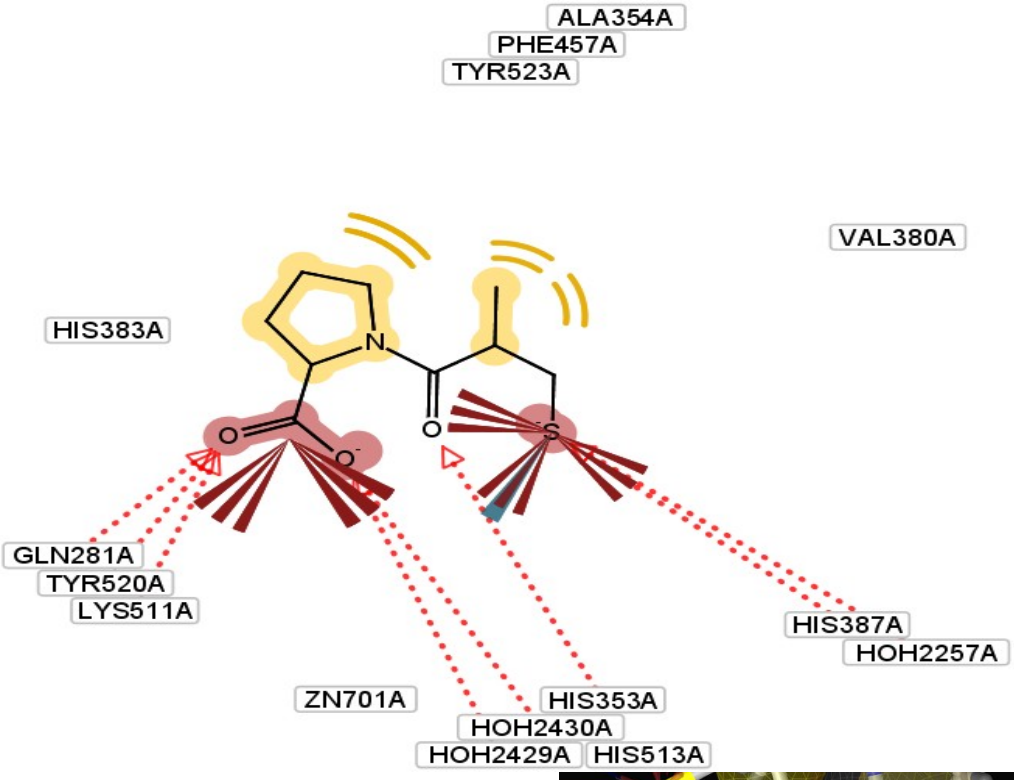
The addition of a methyl group at the $-C_2$ of succinic acid . resulted in considerable increase in inhibitory activity of the prototype compound.

Increasing the length of the side chain by adding another methyl to succinic acid (ie, glutamic acid) did not enhance the activity over the succinic acid derivative.

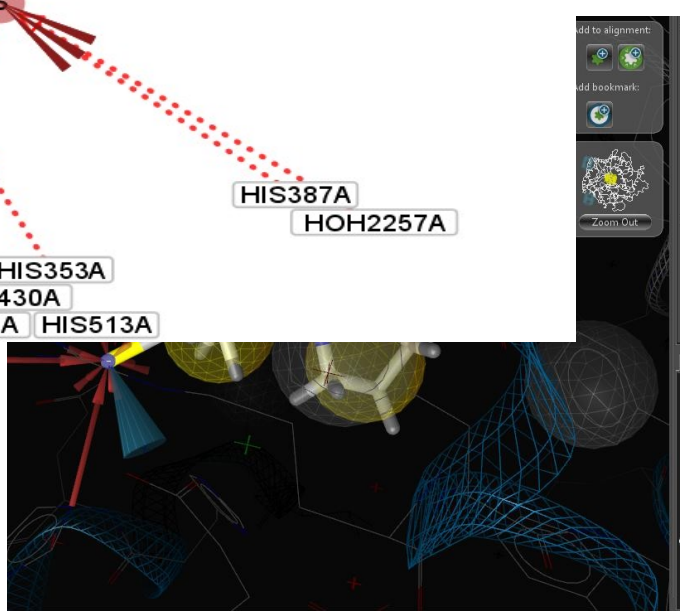
Replacement by a mercapto group (-SH) led to a dramatic improvement in inhibitory potency without any concomitant loss of specificity .

The 2-D-methyl of (MPP) improved activity and produced the first marketed ACEI, captopril

The Pharmacophoric Features



Hydrophobic Centres:



- The **methyl group** .
- The **pyrrolidine ring** .

H –Bond Acceptor:

- The **-SH** group from HIS 387A and

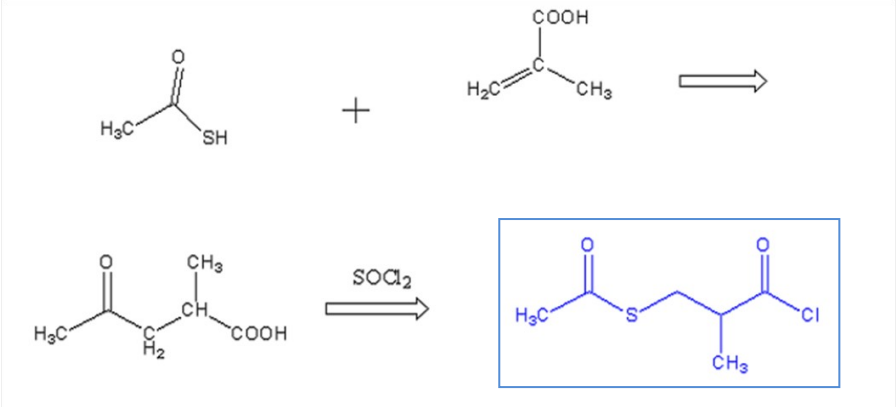
HOH 2257A.

- The **-C=O** group from HIS 353A.
- The **carboxylic group** from HOH 2430A ,

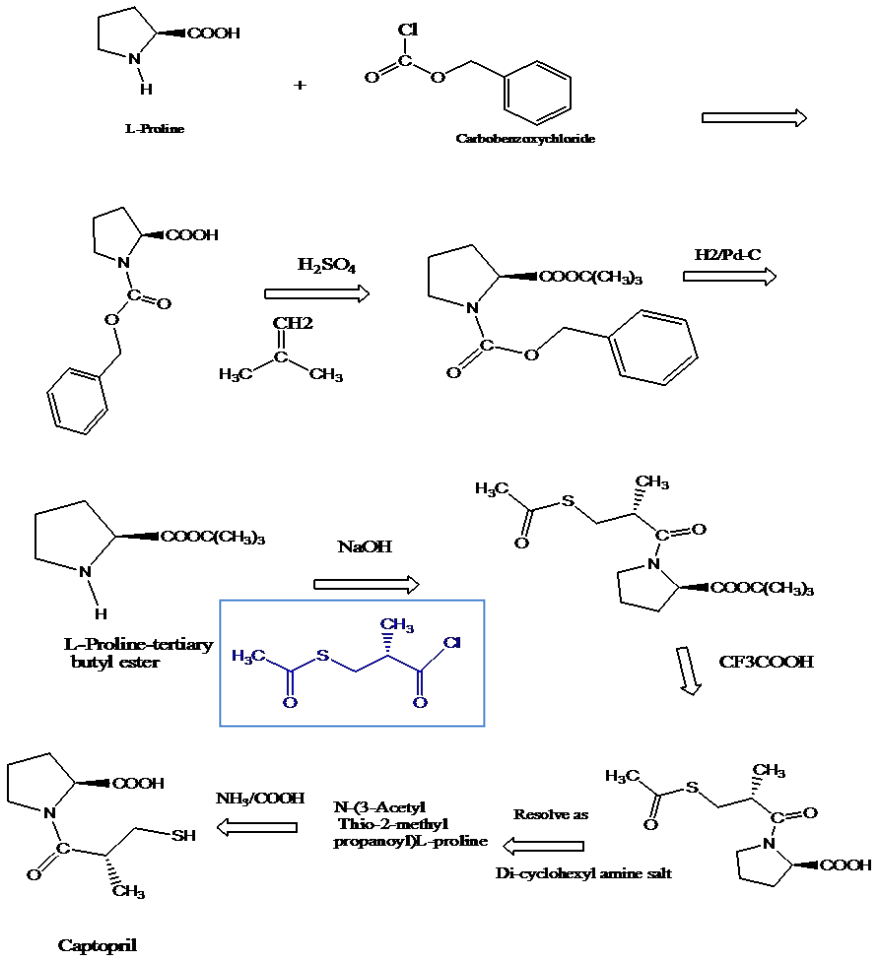
GLN 281A , TYR 520A and Lys 511A.

Synthesis of captopril

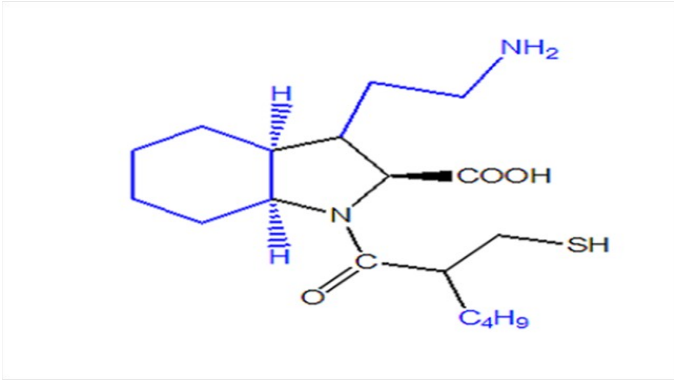
1st step



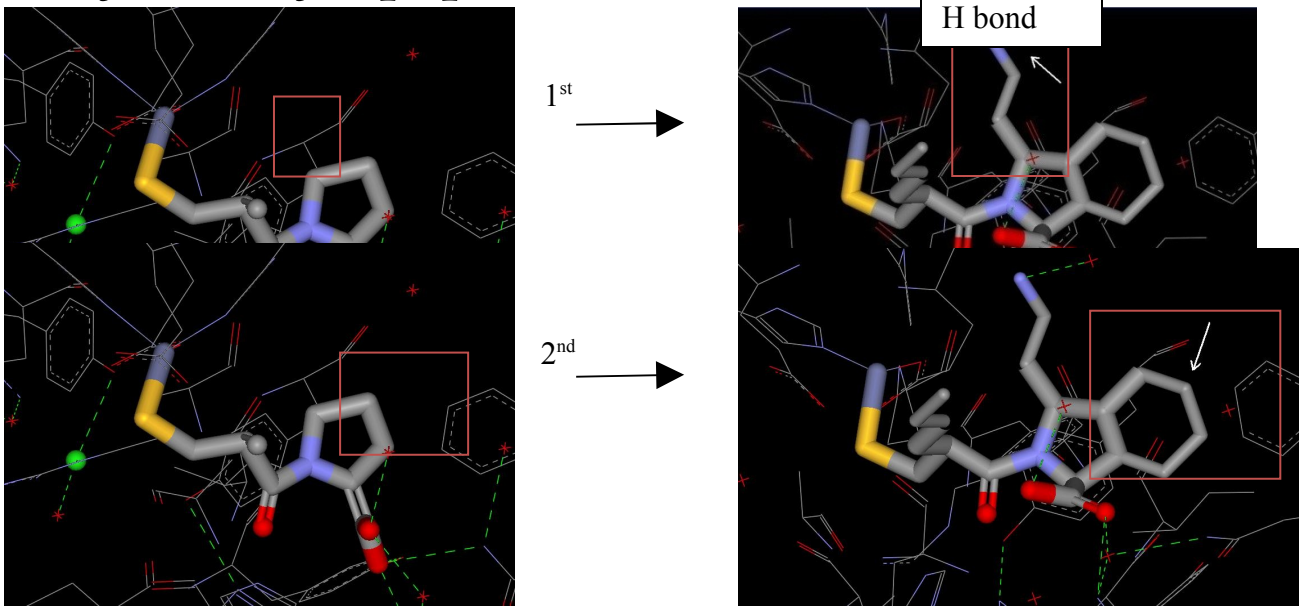
2nd step

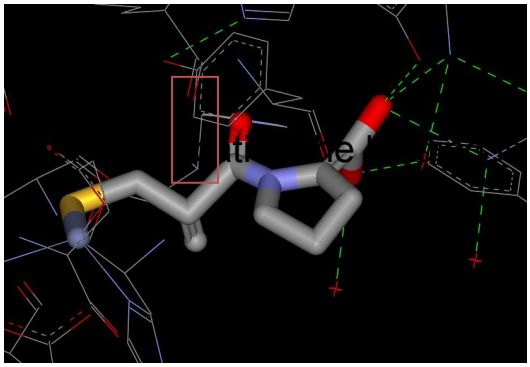


Modified Structure



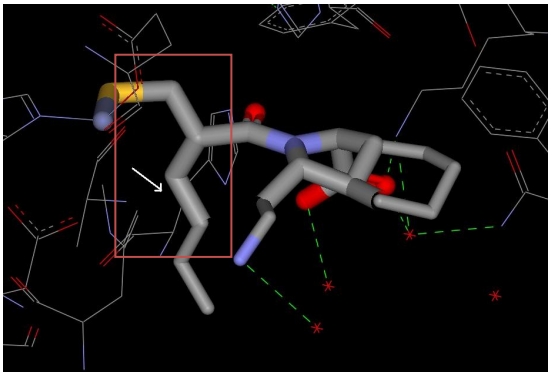
Modifications of Captopril

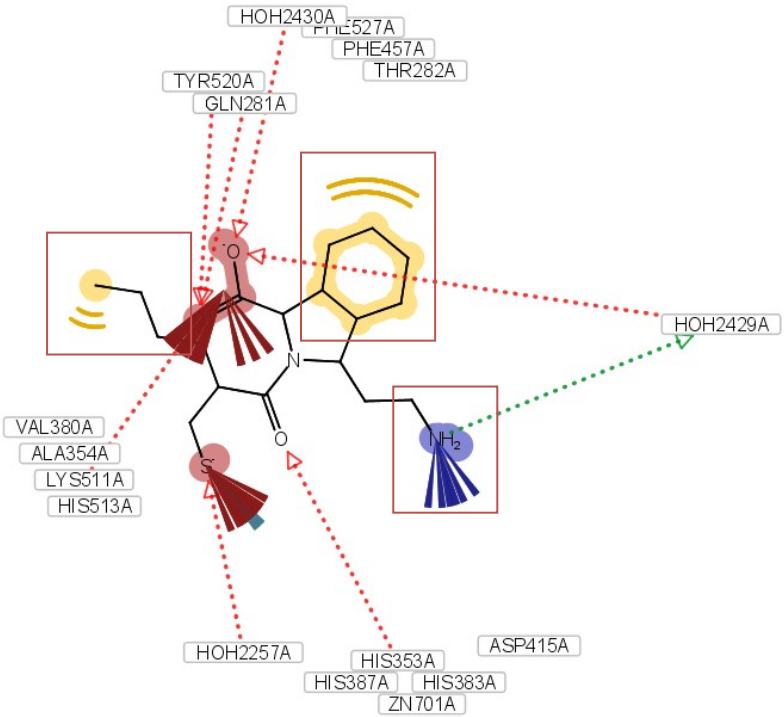




3rd

enhanced :



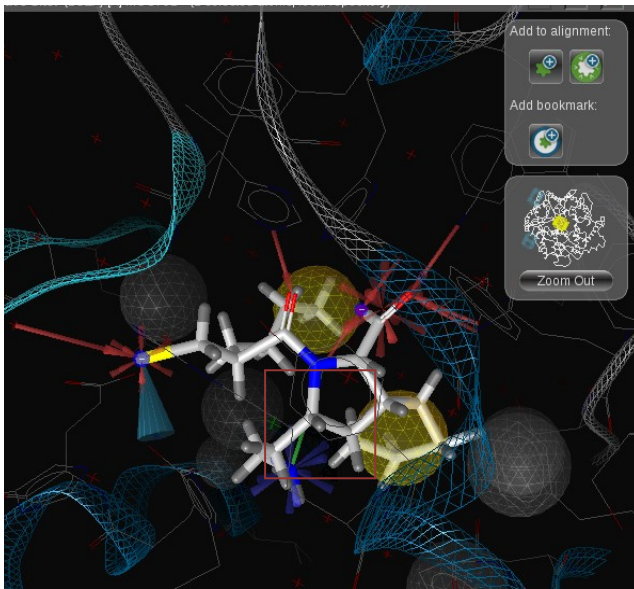


Hydrophobic Centres:

- The **butyl group** make better hydrophobic interaction with the target.
- The additional **cyclohexyl ring**.

H-Bond Acceptors:

- The **-SH** group from HOH 2257A .



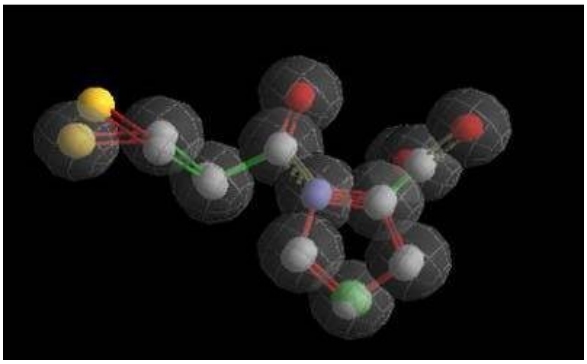
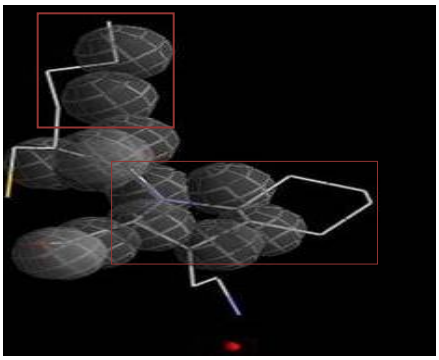
- The -**C=O** group from HIS 353A.
- The **carboxylic group** from HOH 2430A ,

GLN 281A , TYR 520A , Lys 511A
and HOH 2429A.

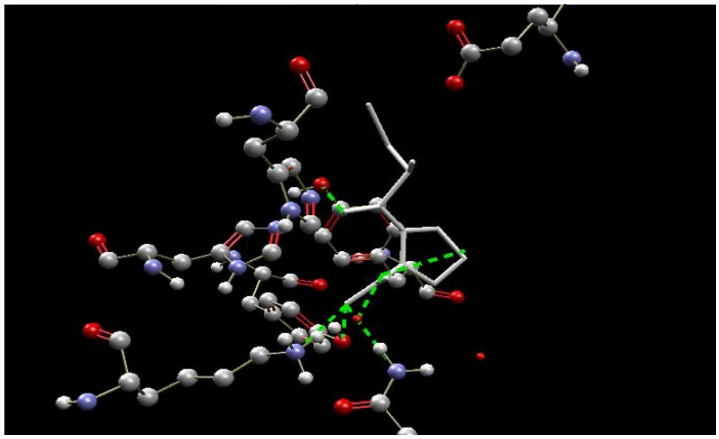
H-Bond Donor: (Additional H-Bond)

- The **amino** group to HOH2429A.

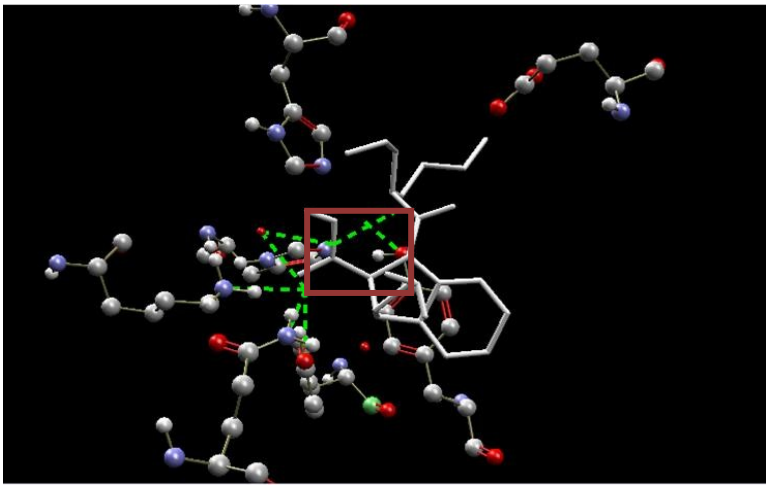
Docking Technique

Captopril	Modified structure
	

Captopril in its receptor



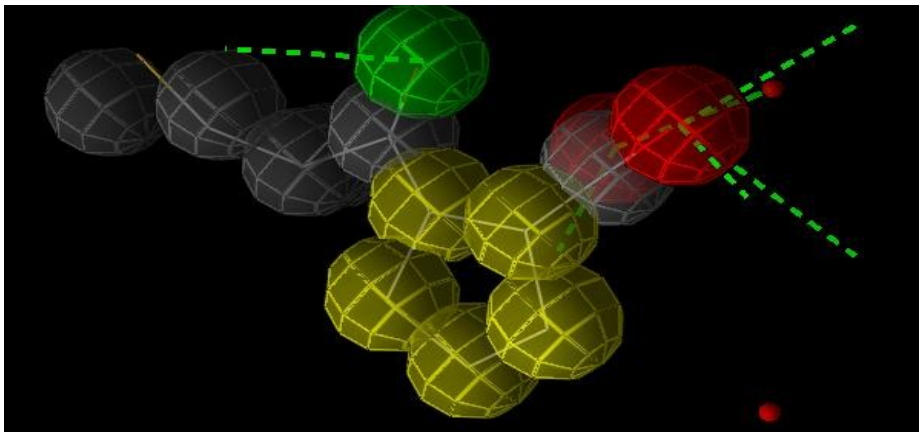
Modified structure in its receptor



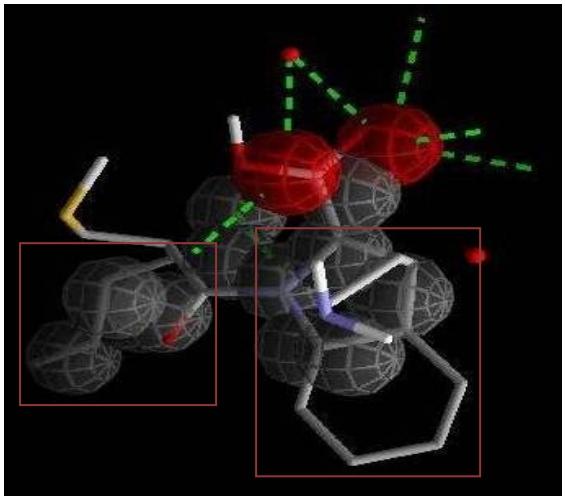
More H-Bond interactions due to the additional $–CH_2–CH_2–NH_2$ group.

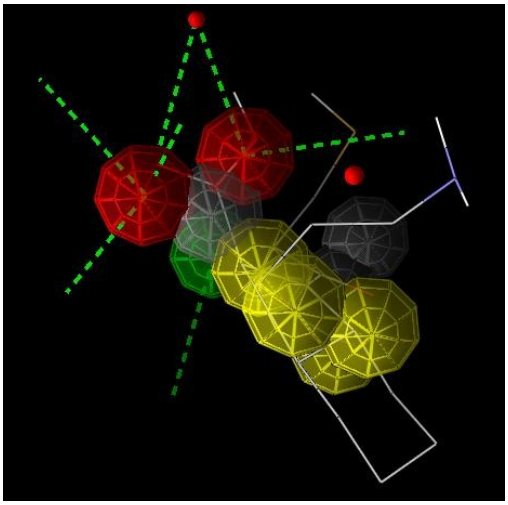
Hydrogen Bond interactions

Captopril



Modified structure





More hydrophobic interactions with the receptor due to the extra butyl group and the fusion with the cyclohexyl ring occupies a hydrophobic pocket.

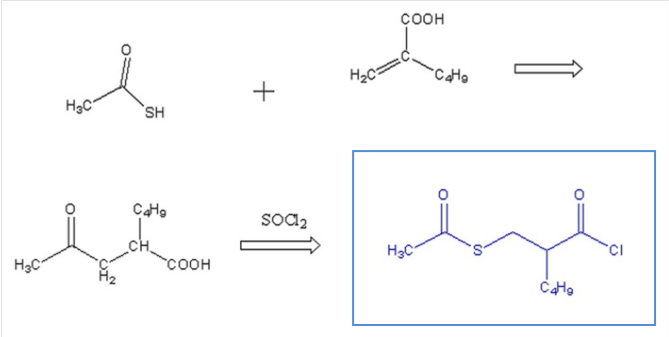
Docking Results:

Compound	Moldock score	Rerank score	H bond
Captopril	-99.2413	-92.7834	-6.32908
Modified molecule	-103.869	-61.5294	-10.7302

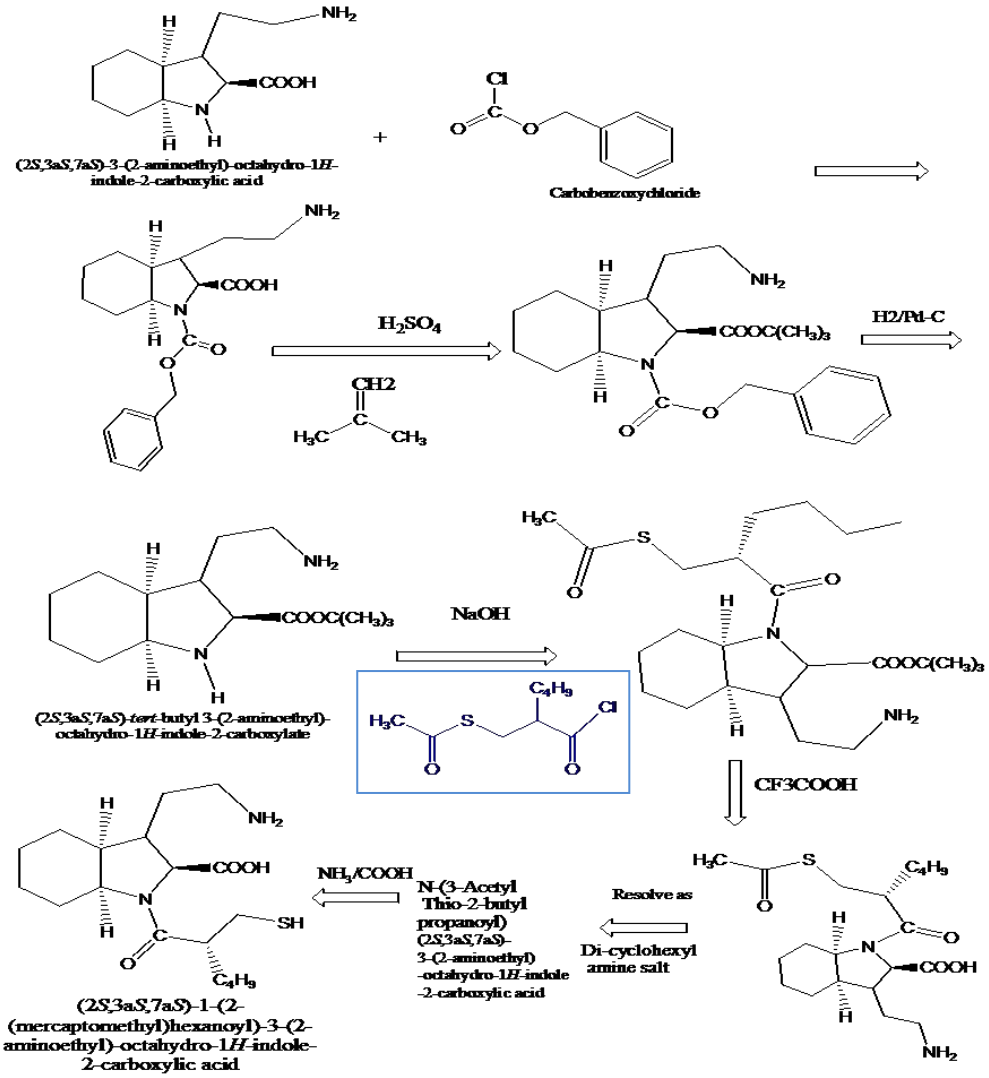
Since the energy of the modified structure is lower than the original structure of captopril , i.e. higher negative , therefore it is easier for the modified structure to bind to the receptor.

Synthesis of the modified drug

1st step



2nd step



Conclusion:

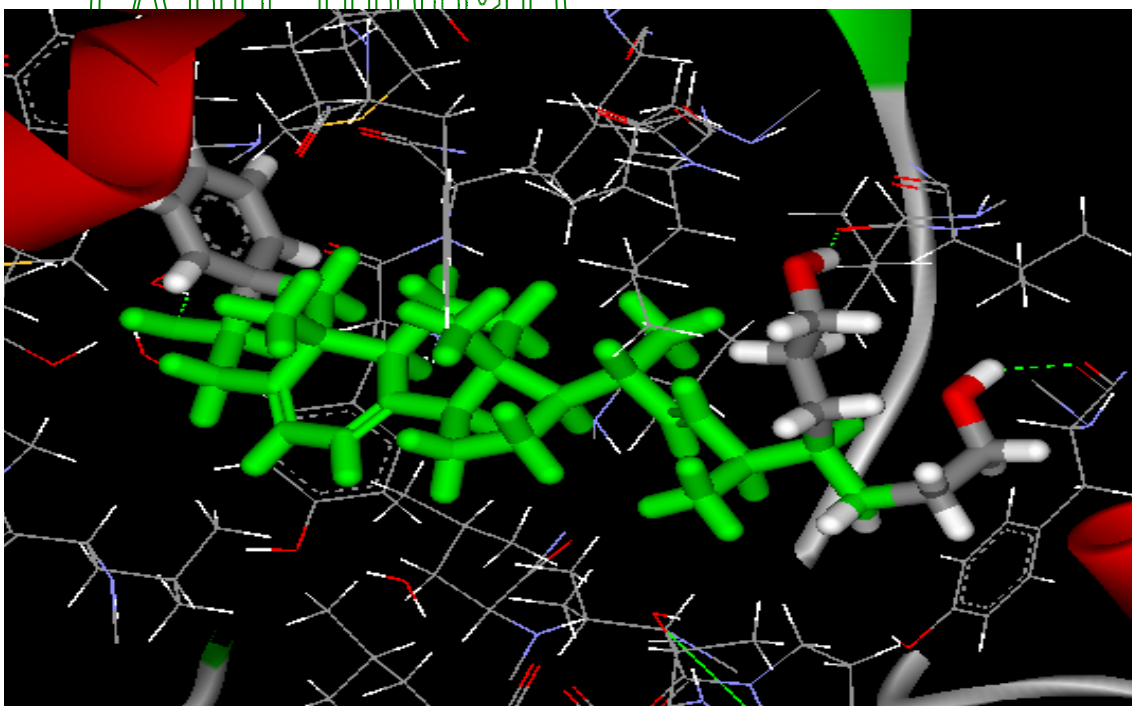
Our aim from all these modifications is to increase the binding of the ligand to the target and so increase the activity to some extent , where :

- The addition of -CH_2-CH_2-NH_2 as a side chain on the pyrrolidine nucleus makes an extra H-bond.
- The ring extension by fusion of the pyrrolidine ring with cyclohexyl ring occupies a hydrophobic pocket.
- Also, substituting the methyl group with butyl make better hydrophobic interaction with the target.

This is evidenced by the docking results where the modified structure has lower energy (higher negative) than the original structure of captopril , i.e. easier binding

Case study number 3:

Beta-Cryptogein inhibitor As (Anti-fungal)



(Protein) Beta-cryptogein

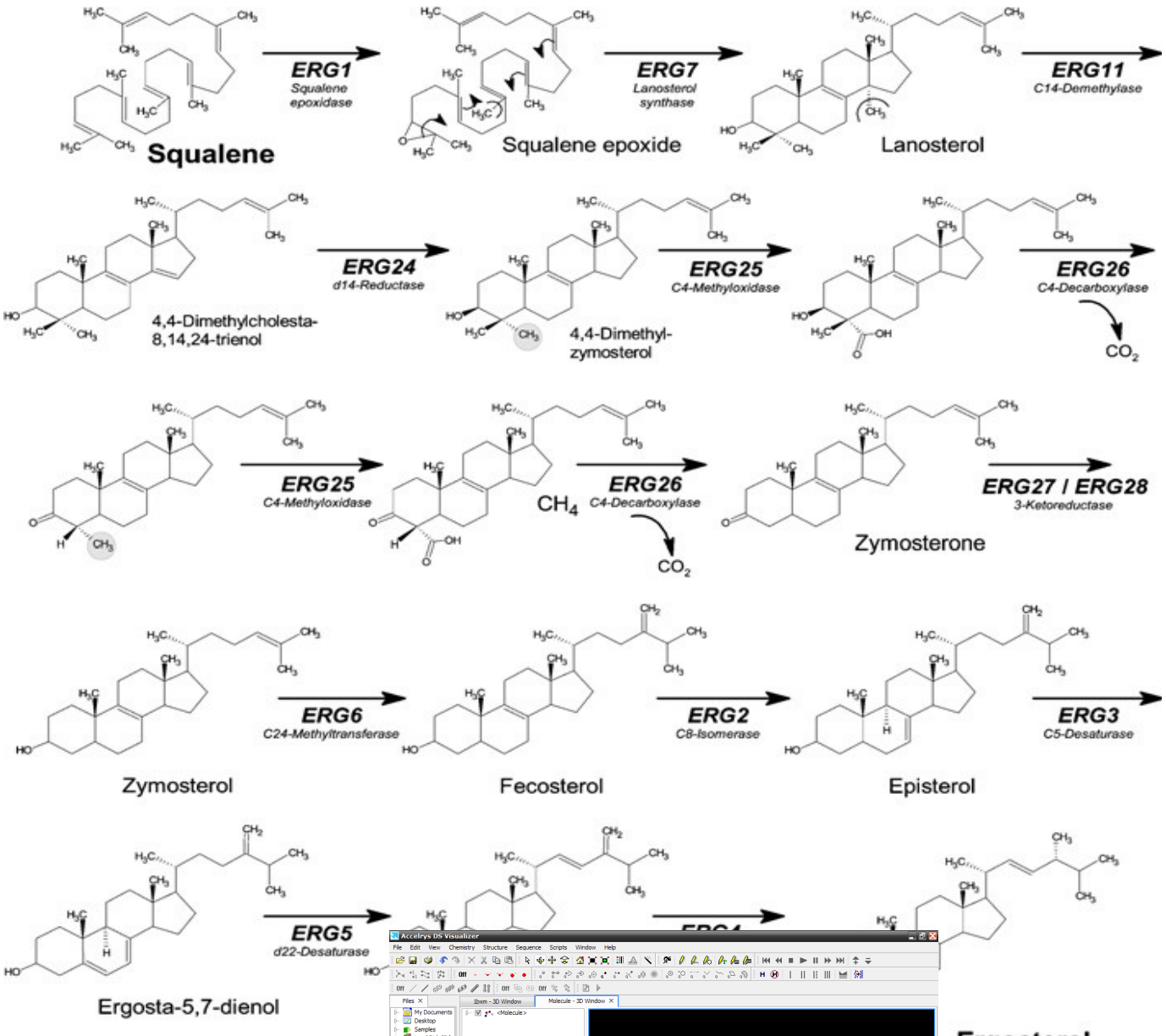
General characters:

-It is an ergosterol carrier protein found in fungi.

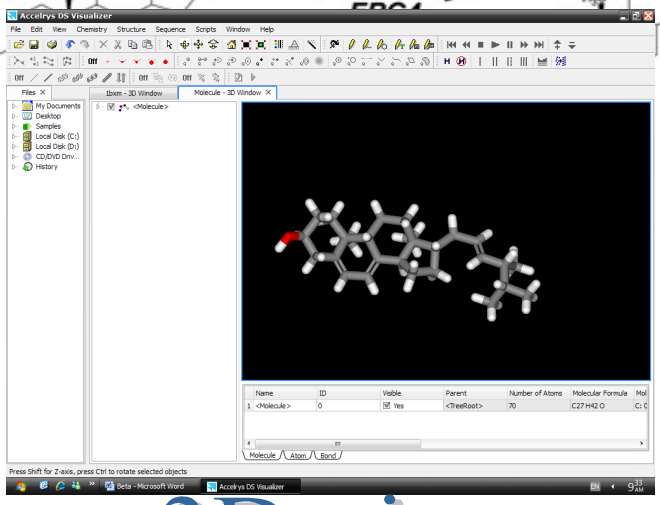
-Belongs to ELICTINS... (Group of necrotic proteins).
-Has a large hydrophobic pocket.
-This protein isolated first from plant fungi known as *phytophthora cryptogea*.

Function:

Sterol carrier protein in Cell wall biosynthesis.

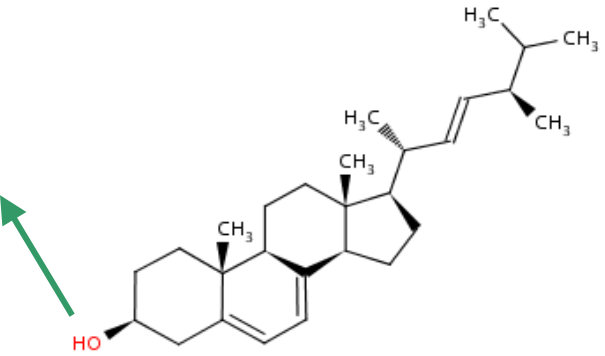


Ergosterol:

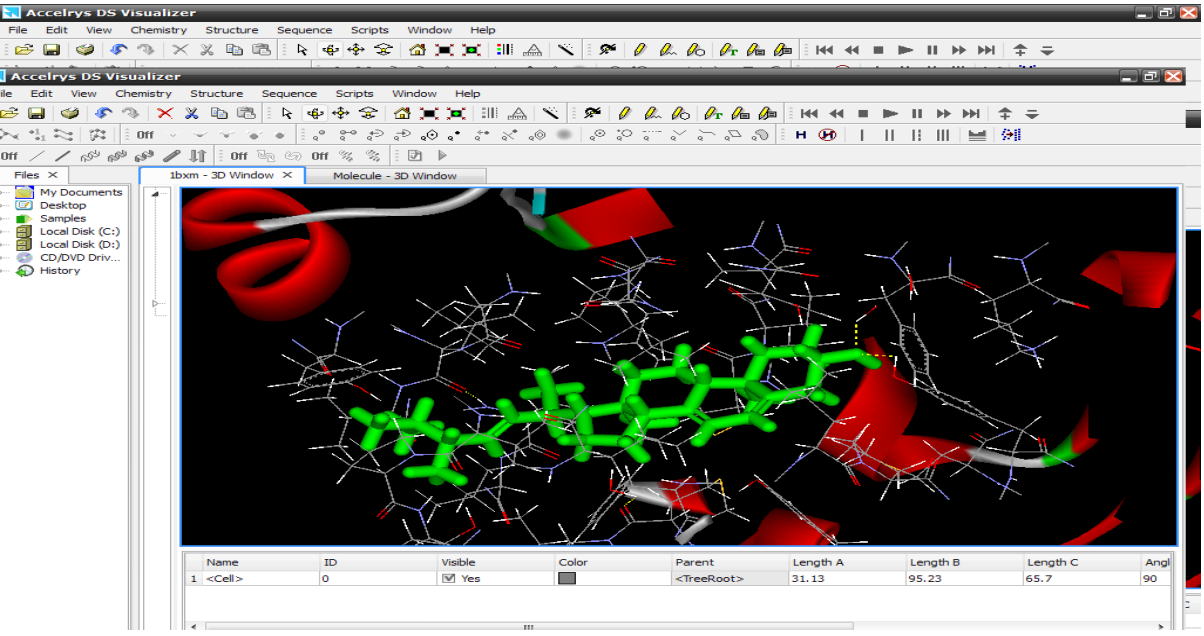


3D pic.

Ergosterol is the main substrate of Beta-cryptogein protein.
So Ergosterol will be the hit compound for our research



2D pic.



3D pic. of ergosterol fitting in the receptor

Beta-cryptogein inhibitor:

We have found that by modifying in ergosterol structure and obtain a structure that fit stronger to the receptor…it surly will compete with ergosterol on the active site & make inhibition of the receptor….

FUNCTION:

1-Inhibtion of ergosterol transport which is essential for fungus cell.

2-Inhibtion of the necrotic effect of beta-cryptogein.

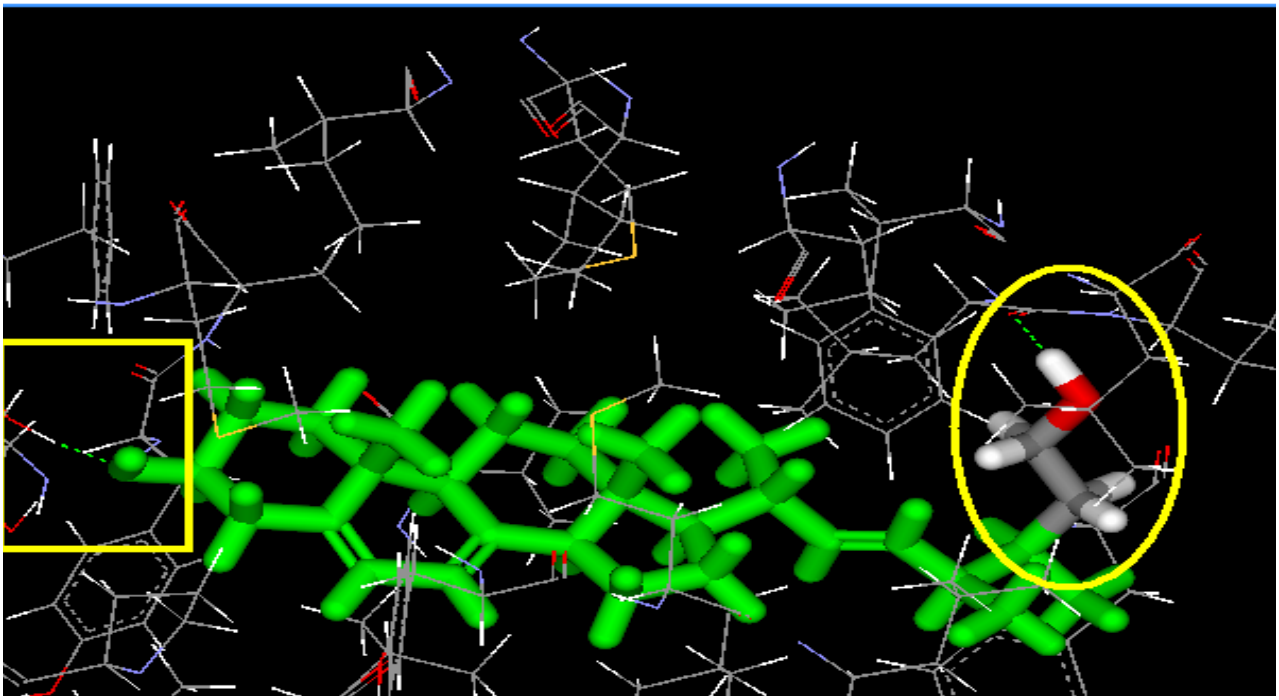
First modification:

We have found that: the active site contains (C=O) gp & by serial modifications….on c27

1-add OH…..

2-add CH2-OH….

3-add CH2-CH2-OH….EXTRA HYDROGEN BOND



Circled area: the modification (CH2-CH2-OH) with extra HB.
Squared area: HB already exists in Ergosterol-receptor interaction.

SAR:

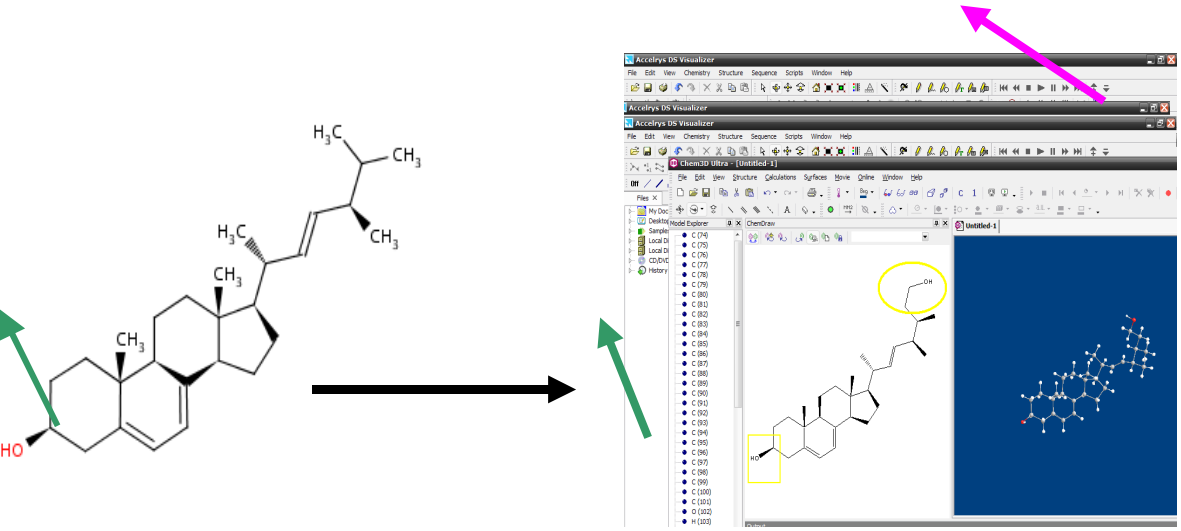
1-**OH** on C3 is essential for activity (resembling ergosterol)
As HB acceptor…make HB with the receptor.

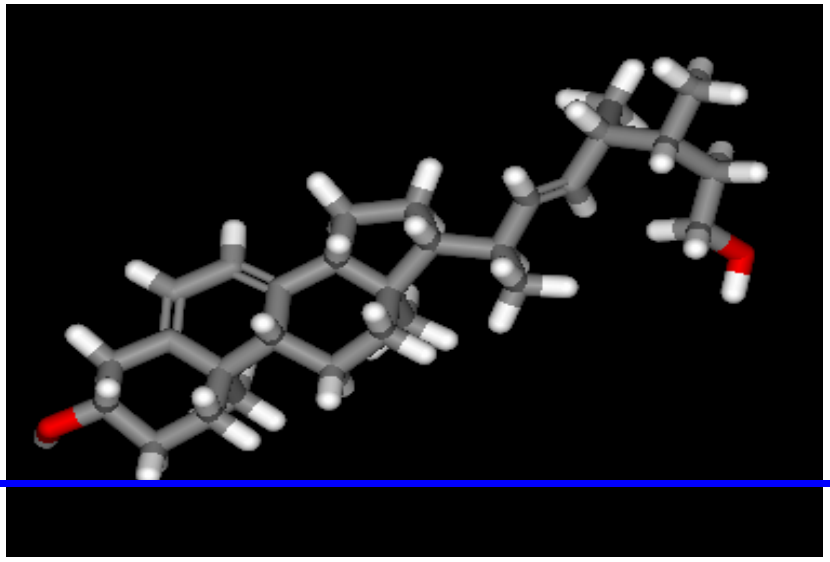
2-**Hydrophobic structure** essential for activity (resembling ergosterol)…fit in hydrophobic cavity of cryptogein.
3-**OH** on C29 (after elongation of aliphatic chain) increase activity, as it makes extra HB (HB donor).

Mechanism of modification:

1-Extension of the structure (by 2C).

2-Addition of substituent (OH).

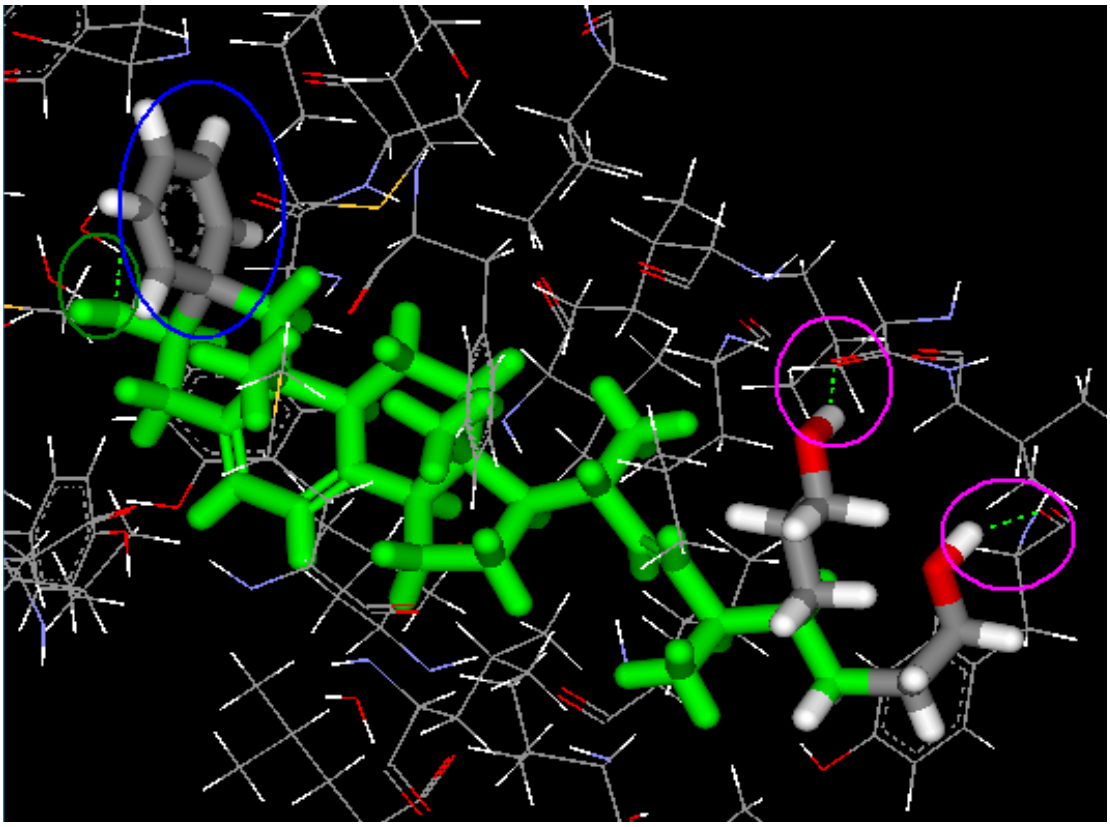




Second modification…

By modification of the drug resulted from the first modification…we made..

1-extra benzene ring at C2 (increase hydrophobicity).
2-addition of (CH2-CH2-OH) at C26 (extra HB).
3-extension of (CH2-CH2-OH) at C27 to (CH2-CH2-CH2-OH)... (Ensure presence of HB).



Blue: Benzene ring added (Extension modification).
Violet: (CH2-CH2-OH) added at C26 (extension modification)…. (CH2-CH2-OH) to (CH2-CH2-CH2-OH).
Green: HB already exists in Ergosterol-receptor interaction.

SAR:

1-OH gps added on the side chains at C26 & C27… *increase activity*...<u>forming two HB</u>…*extra fitting to the receptor*…as they are HB donor.

2- OH on C3 is *essential for activity* (resembling ergosterol)
As HB acceptor…<u>make HB with the receptor.</u>

3-Benzene ring added at C2 increase activity… increase hydrophobicity…*increase fitting* by VanDer Waal forces.

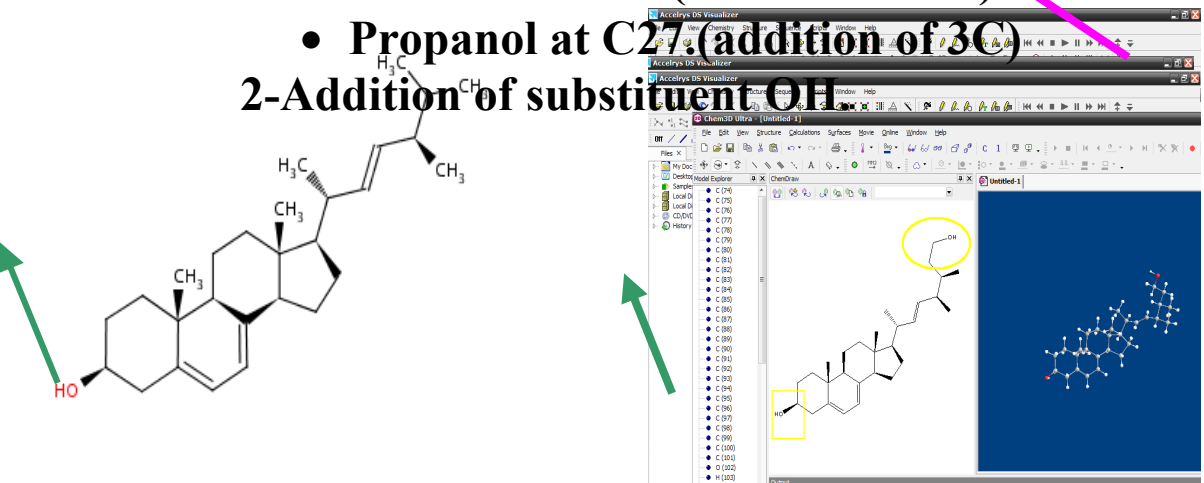
4-Addition of another OHs to make extra HB…will *decrease or abolish activity* (AS it decrease hydrophobicity).

5-Addition of another Alkyl (R) or Aryl (Ar) gps…*will decrease or abolish activity*…make it to bulky cannot enter the protein cavity.

<u>Mechanism of modification:</u>
1-Extension of the structure by

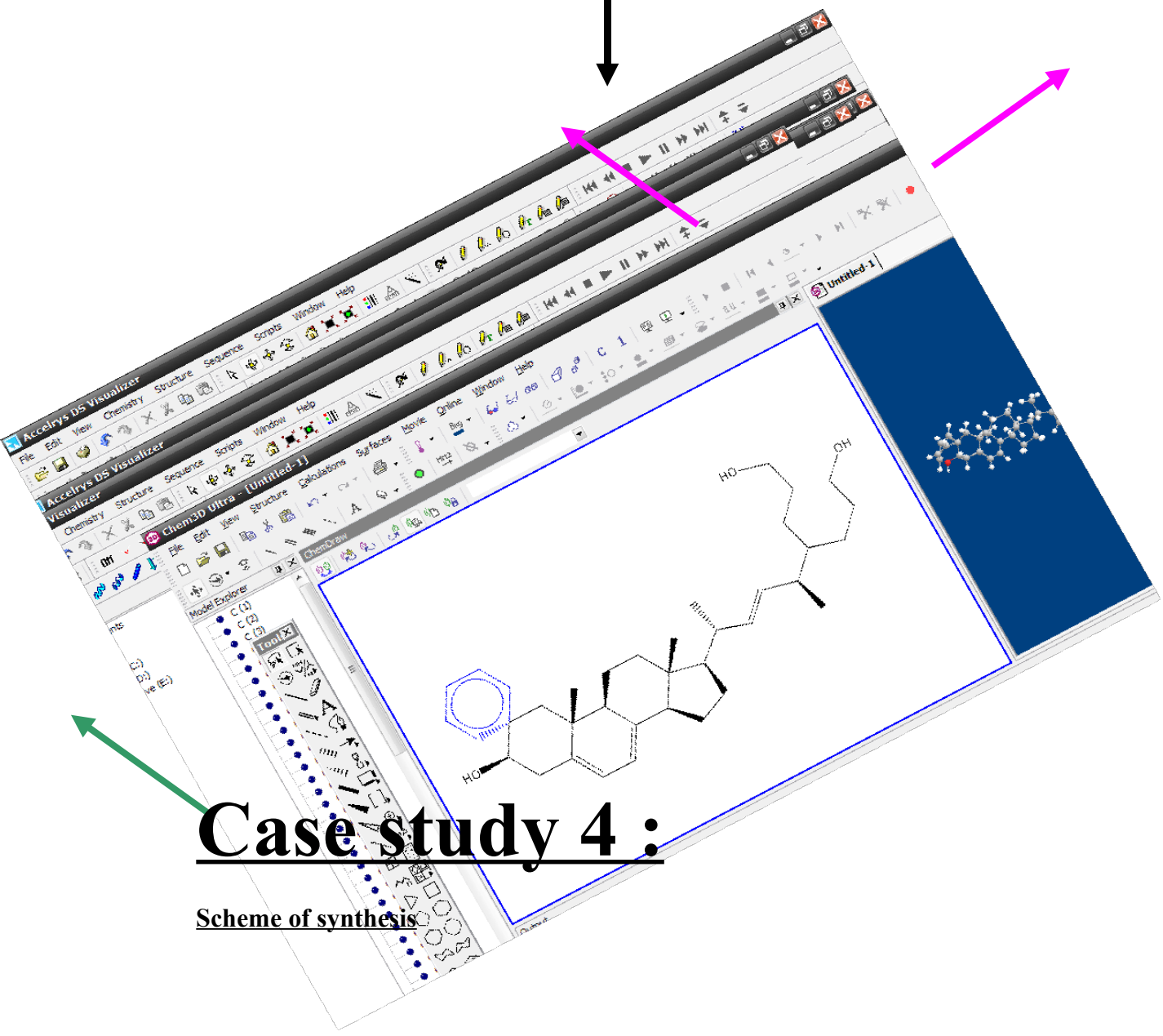
- **Benzene ring at C2.**
- **Ethanol at C26.(addition of 2C)**
- **Propanol at C27.(addition of 3C)**

2-Addition of substituent OH



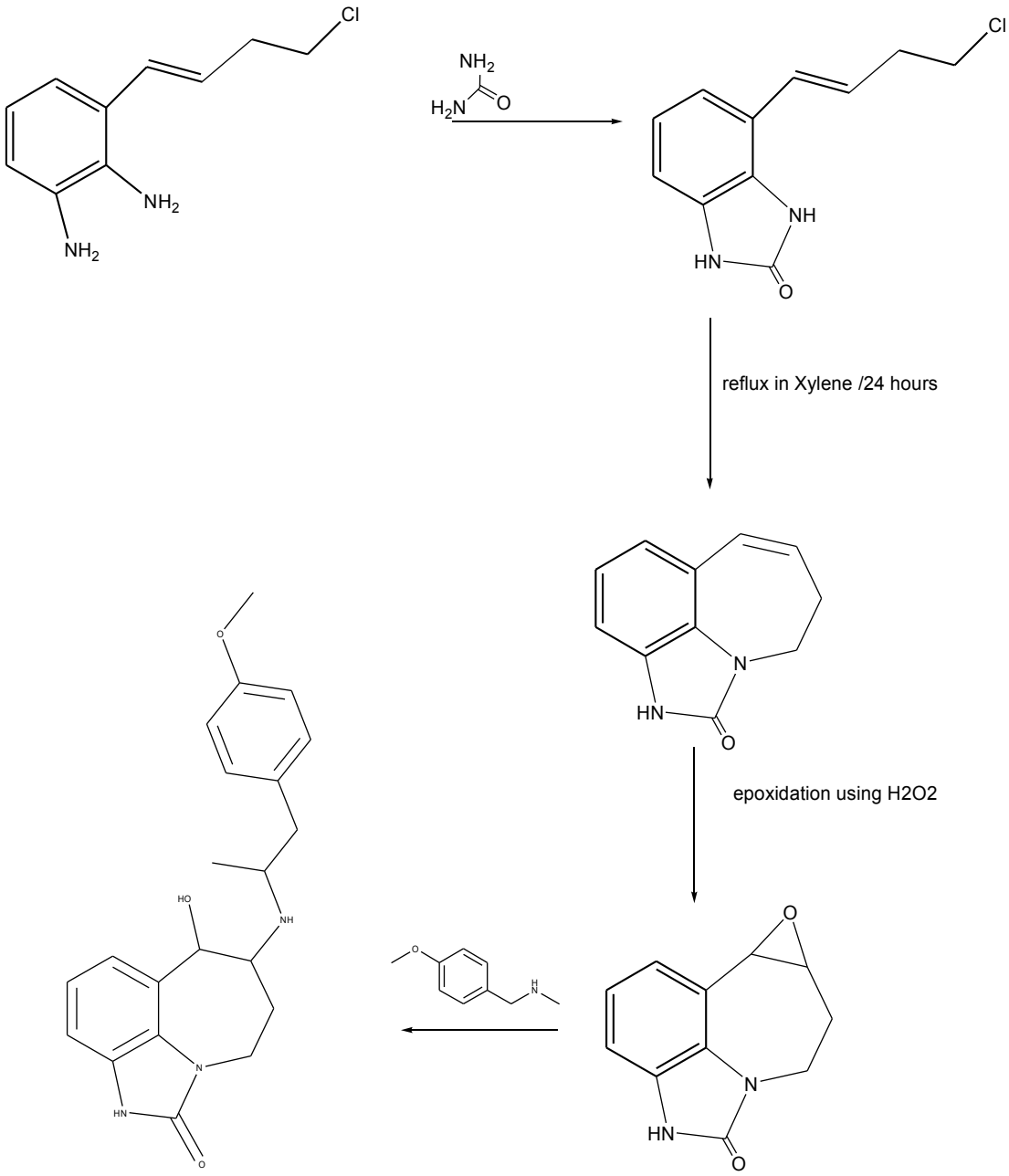
1st modification

2nd modification



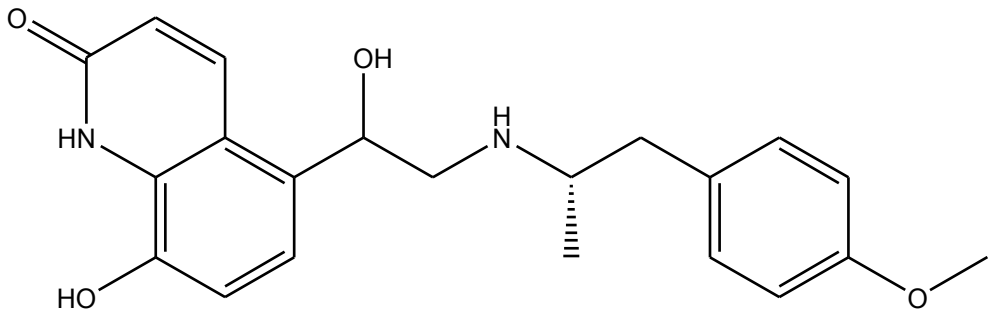
Case study 4 :

Scheme of synthesis

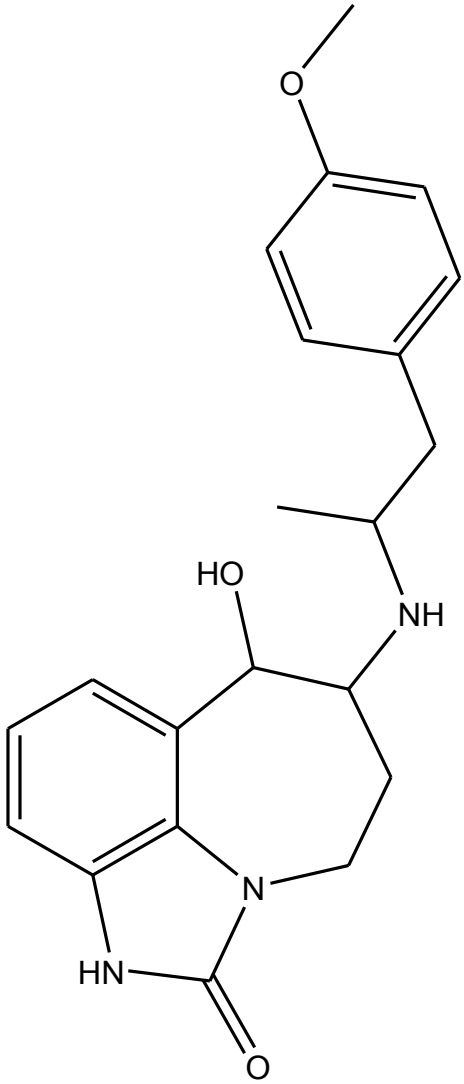


The concept of this idea is rigidification of the lead compound in the receptor pocket the proposed drug

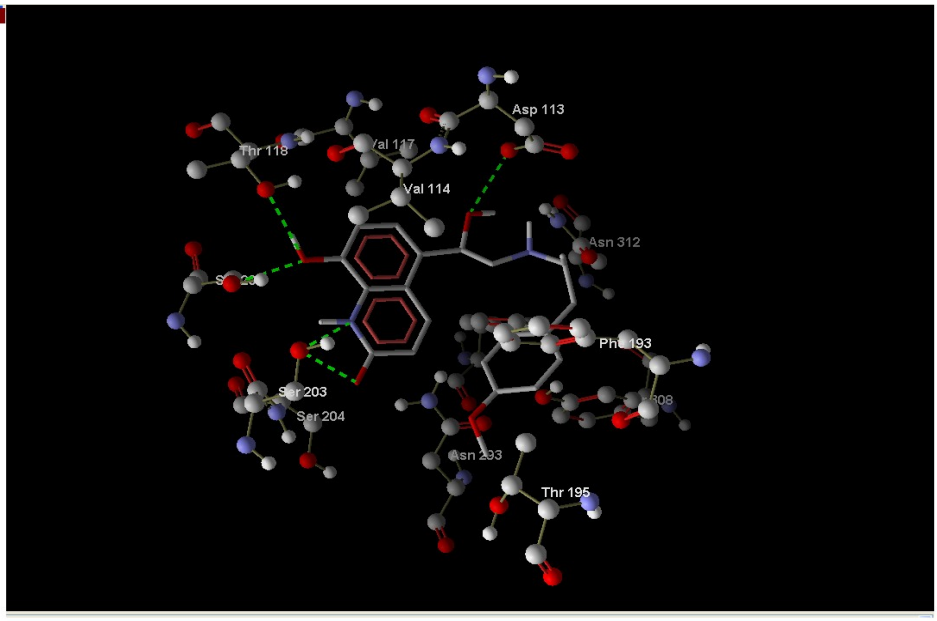
The lead compound structure



The proposed compound



Structure of lead co crystallised with beta-2 receptor



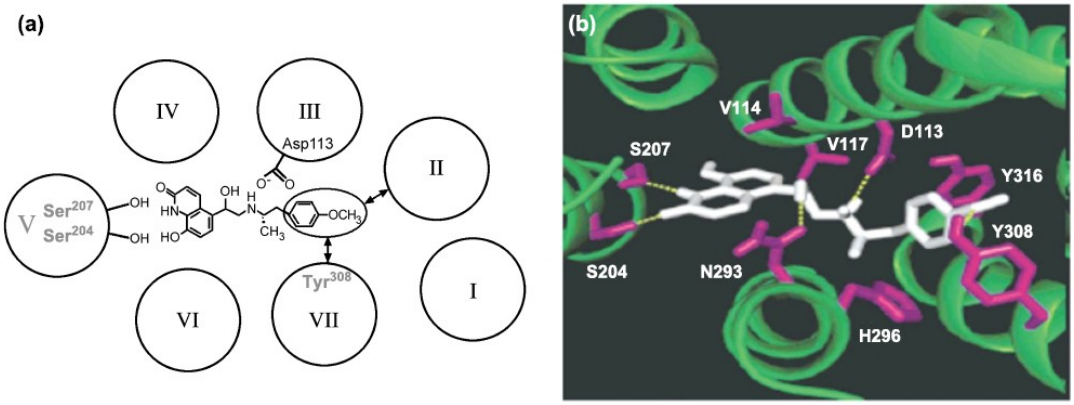
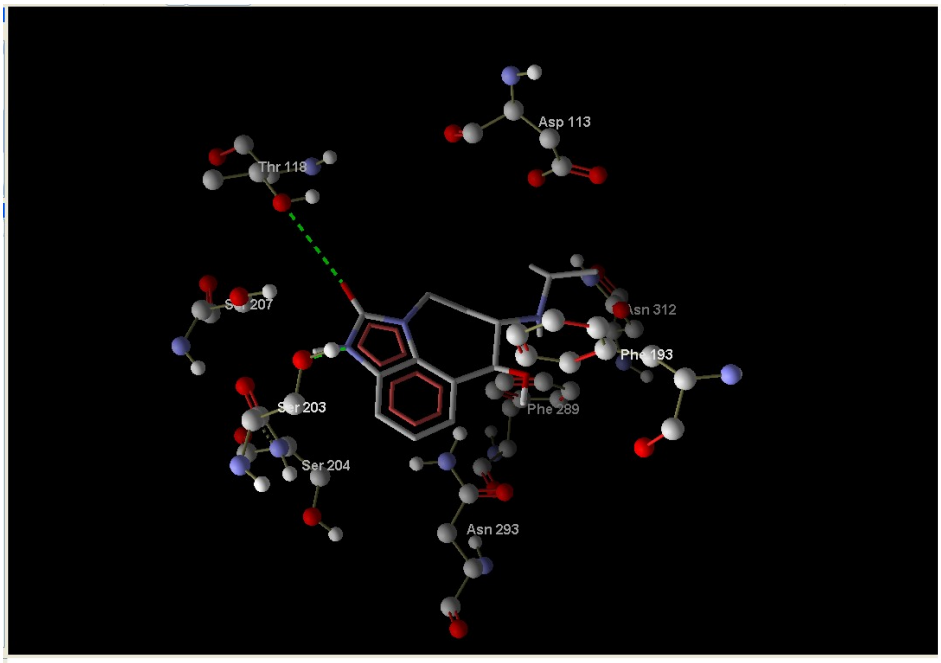


Fig. 3 A model of the β_2-adrenergic receptor–TA-2005 complex. TA-2005 is a β_2-adrenergic receptor-selective agonist that binds β_2-adrenergic receptors with high affinity. The methoxyphenyl group of TA-2005 interacts with Tyr^{308} in the seventh transmembrane domain (TM7), which plays a most important role in β_2-adrenergic receptor selectivity. (a) A schematic model of the β_2-adrenergic receptor–TA-2005 complex is shown to demonstrate the amino acids that interact with TA-2005. (b) Three-dimensional model of the TA-2005–β_2-adrenergic receptor complex complex (reproduced with permission from Furse and Lybrand[23]).

structure of the new compound co crystallised with the receptor



Case study number 5 :

Molecular Modeling Study and Synthesis of Novel β_2-agonist of expected Bronchodilator activity

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Abstract: - Introduction about asthma, pharmacophoric features of β_2-agonist for both the lead and the hit compounds to predict their binding :

Asthma is a chronic lung disease, a common chronic disorder of airways characterized by variable & recurring symptoms, airflow obstruction, bronchial hyperresponsiveness (bronchospasm),

Direct Acting Adrenomimetics on β_2-receptor present these features (pharmacophore):

1. A **six-membered aromatic ring** system make hydrophobic interaction through Wan der Waal forces.
2. An extended **ethylamine side chain** oriented almost perpendicularly to the aromatic ring system.
3. A **positively charged nitrogen atom** (at physiological pH) on ethylamine side chain make A hydrophilic & hydrophobic side of the molecule due to **β-hydroxyl group** being oriented on same side of the molecule (cis) as the **meta phenolic hydroxyl group** of the aromatic ring.
4. An **R** absolute configuration at the β-carbon atom

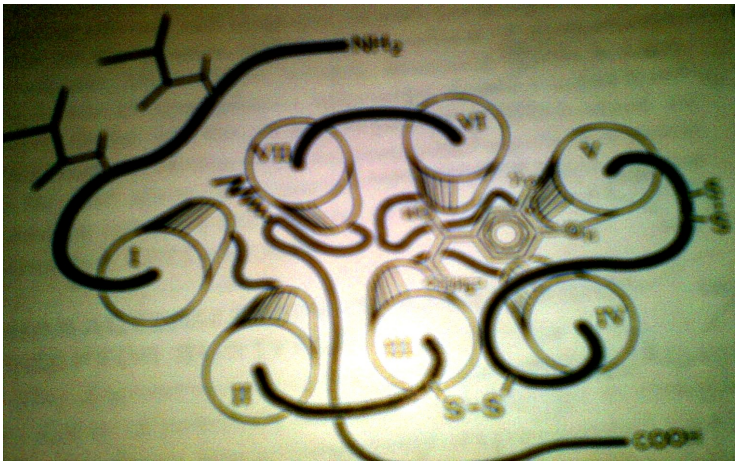
5. The **catechol OH at meta** position of the ligand make H.B interation with SER 204 and **OH at para** postion make H.B interaction with SER207.

For the activation of β-receptors:

- **Phenolic hydroxyl** function in **meta** at the catechol nucleus

- At the side chain: an **alcoholic hydroxyl in β** and **an amine with bulky group.**

- The activation of the receptors results from the disperse forces between the alkyl group and the receptor. This alkyl group appears to be more important than the nitrogen atom



This figure represents a proposed arrangement for the transmemberane helices of the β_2-adrenoreceptors depicting the binding site for adrenaline as viewed from the extracellular site.

Problems of adrenaline:

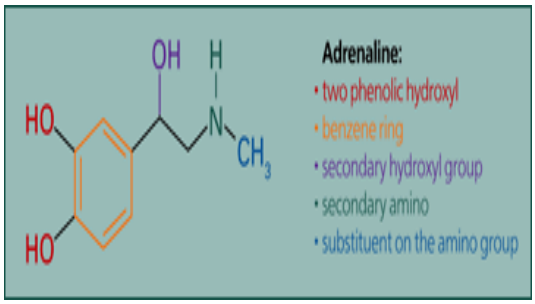
1- The **lack of selectivity** contributed to a significant rise in asthma mortality as causes anxiety, profound stimulation of the heart, increase of blood pressure and excessive stimulation of the brain.

2- It is a **short acting Catecholamine** taken up into tissue and inactivated by enzymes as Catechol-O-Methyl Transferase (COMT). The resulting methyl ethers are pharmacologically inert. So the drug is **inactive by mouth** unless given in doses large enough to overwhelm the capacity of the inactivating enzyme system.

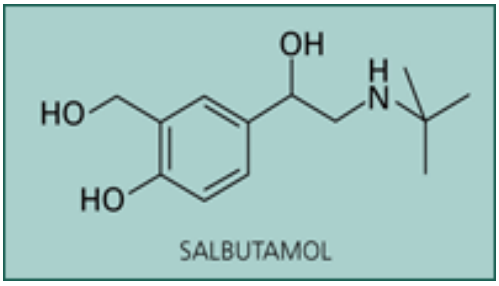
- Therefore, in addition to **improving the selectivity** of **Isoprenaline** (an adrenaline derivative) for the **β_2-receptor**, it was also necessary to improve the metabolic stability of the molecular template.

In particular, **hydrogen-bonding**, **chelation** powers & **acidity** are important properties, as the major binding features of the catecholamines at the receptor level.

- ***Adrenaline Structure*** reveals **5** structural fragments amenable to modification. It was found that variations on the **two phenolic hydroxyl** groups & on **secondary amino group** led to most pronounced changes in both the **metabolic and selectivity** profiles of the molecule.

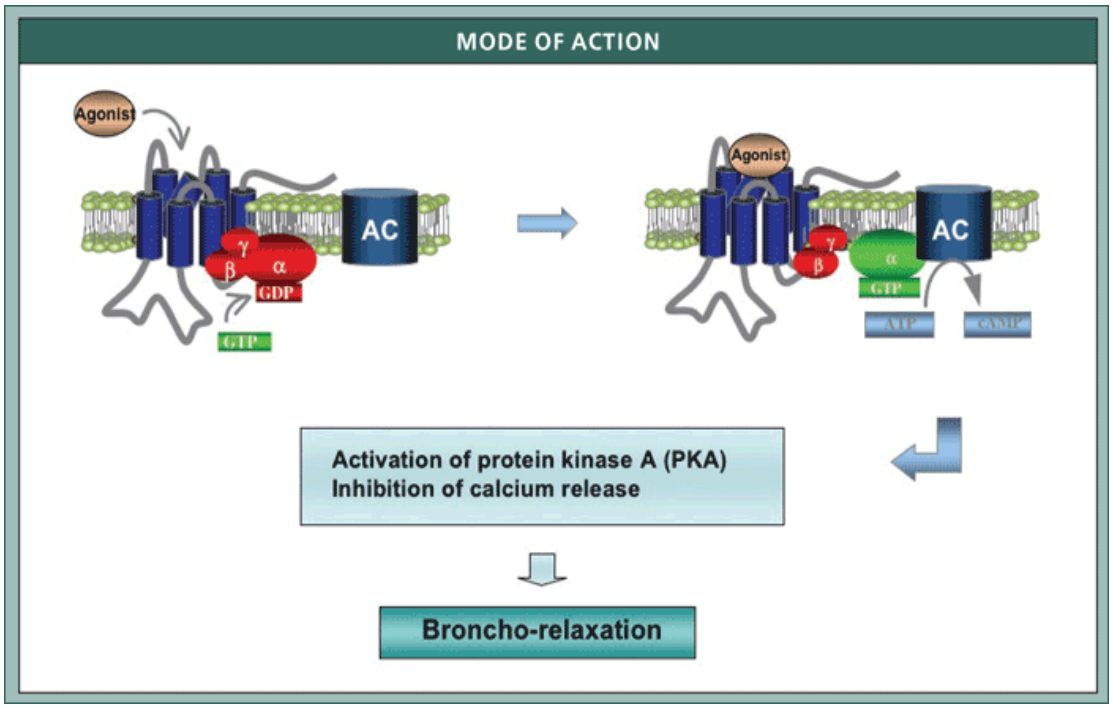


Developments continued till **"Salbutamol"** was found to be both a **highly selective** and **potent β_2-adrenoreceptors agonist** by replacement of the methyl group on the 2ry amine in adrenaline by a butyl group, with an adequate **metabolic stability** by the replacement of the phenolic OH by a methyl hydroxyl group so resistant to degradation by COMT which made it a highly effective bronchodilator in man. It is **orally active** with a duration of action of 4 hours. It was launched in 1969 as Ventolin™ and has become the world's most widely prescribed bronchodilator drug and considered as a **LEAD compound for the selective adrenergic agonists of β_2-adrenoreceptors whose source is Adrenaline.**



Mode of Action:

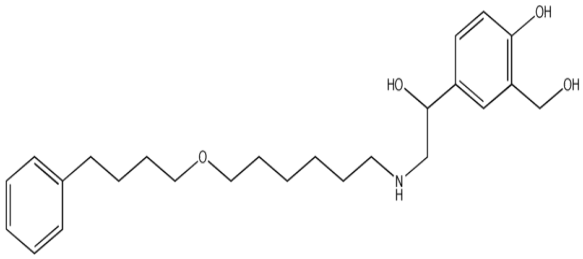
It increases the production of cyclic adenosine monophosphate (**cAMP**) at beta-adrenergic receptors, thus producing bronchodilation and inhibiting histamine release.



Salbutamol has contributed to improvement in life quality of many asthmatics, but its duration of action (**4hrs**) is considered a drawback in certain patients. Some asthmatics suffer from repeated episodes of nocturnal & early morning wakening due to breathlessness and wheeze. Clearly, **a similarly effective drug to salbutamol, but with a duration of action increased to 12 hours, would be more advantageous & useful for control of nocturnal asthma**.

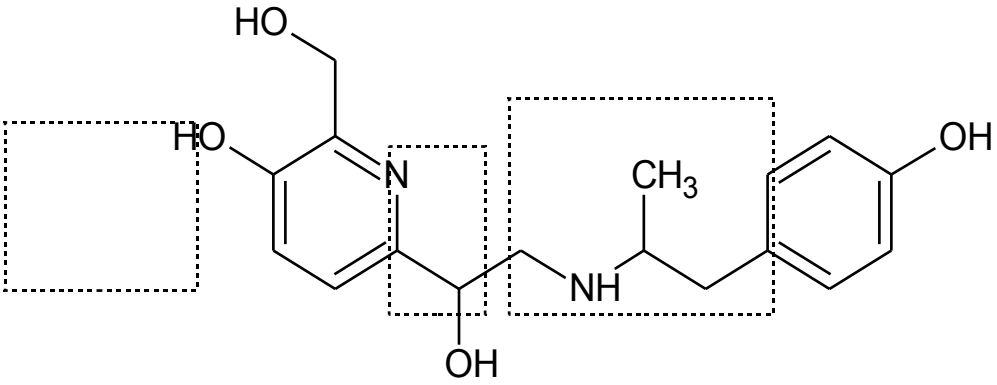
Salmeterol is a **long acting β_2 agonist** that solved problem of salbutamol but yet suffers a problem of the inherited **lack of exoreceptors**, the structural variations of receptor preventing

stable binding of salmeterol molecule, an inherited variation of β_2-receptor, or **partial receptor antagonism** of salmeterol, or may be genetically determined individual differences in the rapid development of tolerance to bronchoprotective effects & to bronchodilation (e.g., downregulation of β_2-adrenoreceptors) of salmeterol.



2. Results and discussion:

So the design of the new hit compound will help to eliminate this problem & yet maintain the beneficial long action of other long acting β_2 agonists.



Taking a look on the structure of Salbutamol and the structure of the new hit compound we find some DIFFERENCES:

1- The replacement of the aromatic ring with a **pyridine ring** (**ring equivalence**) provides **an extra H.B** binding with the receptor at TMD 4.

2- The replacement of the t-butyl group on the 2ry amine with a **para hydroxyl phenyl, 1 methyl ethylene** (**extension of the structure, structural variation**).

The phenyl ring provide **anchoring** of the compound in the receptor by an **extra hydrophobic interaction at TMD 4** of the receptor so the bulky side chain provide **lipophlicity** for the **slow release** of drug from cell membrane thus **longer duration** of action **also increase the selectivity on β2 receptor.**

The methyl group provides **resistance to MAO**; the OH added to the phenyl ring is to **improve the pharmacokinetics** of the drug.

3- The structure has **resistance to COMT** as it contain a **methyl hydroxyl group at 4** position attached to the pyridine ring.

Docking Study:

- The docking was performed using portable Molegro Virtual Docker on two compounds, salbutamol and the new hit compound
- The structures of the new hit compound & salbutamol were drawn using Visual Studio & were exported to portable Molegro Virtual Docker
- The receptor structure was downloaded from protein databank (pdb), pdb entry is 2R4R.
- The docking procedures took place using wizard docking default mechanism
- Ten runs were done for each compound
- We got 5 docked poses for each compound
- The poses were evaluated using the default empirical scoring function in portable molegro virtual docker
- The best member (in terms of docking score) was selected as the docking solution to be previewed in the **β2** receptor for both salbutamol and the new hit compound as in fig (1) & (3) respectively, also the docking scores for salbutamol and the new hit compound as in fig (2) & (4).
- The best pose of the new hit compound showed good mapping to the docked pose of salbutamol.

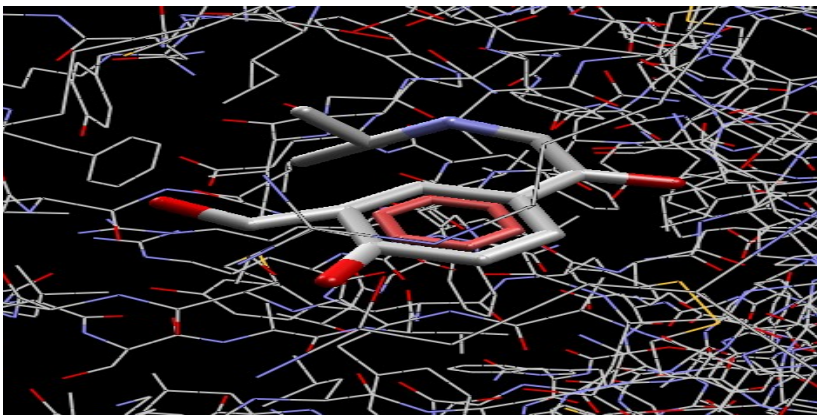


Fig (1) Salbutamol Docking

Filename	Name	Energy	RerankScore	Torsions
[00] Molecule-1.mol2	[00] Molecule-1	-61.4548	-28.1026	5
[01] Molecule-1.mol2	[01] Molecule-1	-55.9253	-39.3296	5
[02] Molecule-1.mol2	[02] Molecule-1	-46.7253	105.809	5
[03] Molecule-1.mol2	[03] Molecule-1	-36.8179	144.908	5
[04] Molecule-1.mol2	[04] Molecule-1	22.1589	452.68	5

Fig (2) Docking Score of Salbutamol

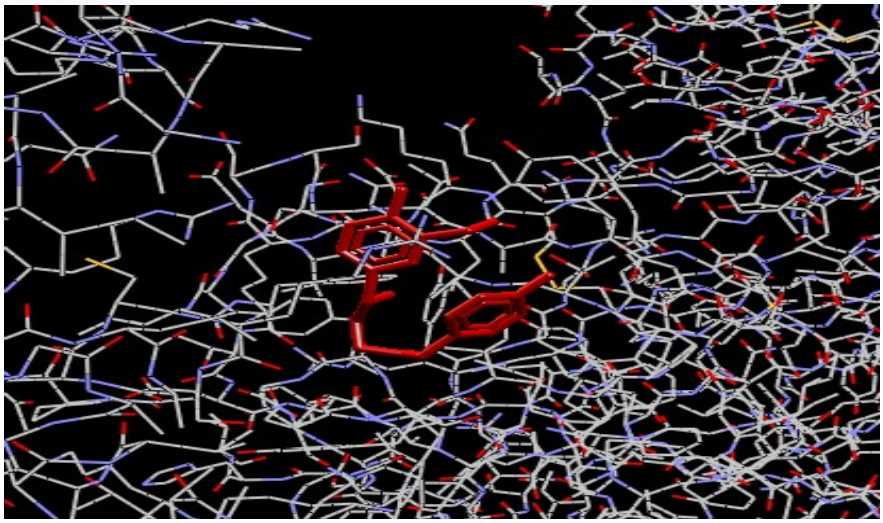


Fig (3) Hit Compound Docking

Filename	Name	Energy	RerankScore	Torsions
[00] Molecule-1.mol2	[00] Molecule-1	-69.0736	-39.1315	7
[01] Molecule-1.mol2	[01] Molecule-1	-54.2778	23.9707	7
[02] Molecule-1.mol2	[02] Molecule-1	-27.65	151.145	7
[03] Molecule-1.mol2	[03] Molecule-1	-11.9087	196.279	7
[04] Molecule-1.mol2	[04] Molecule-1	67.4213	880.863	7

Fig (4) Docking Score of Hit Compound

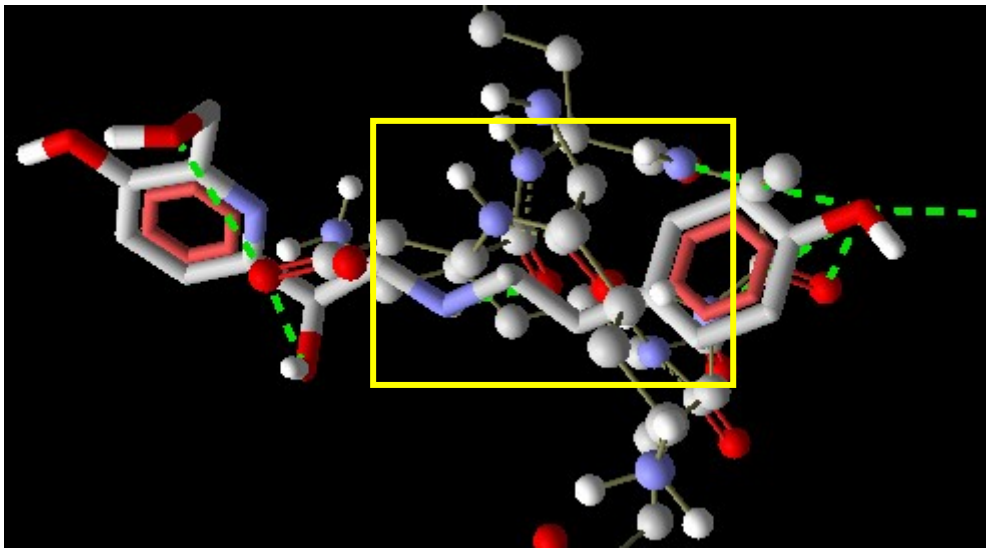
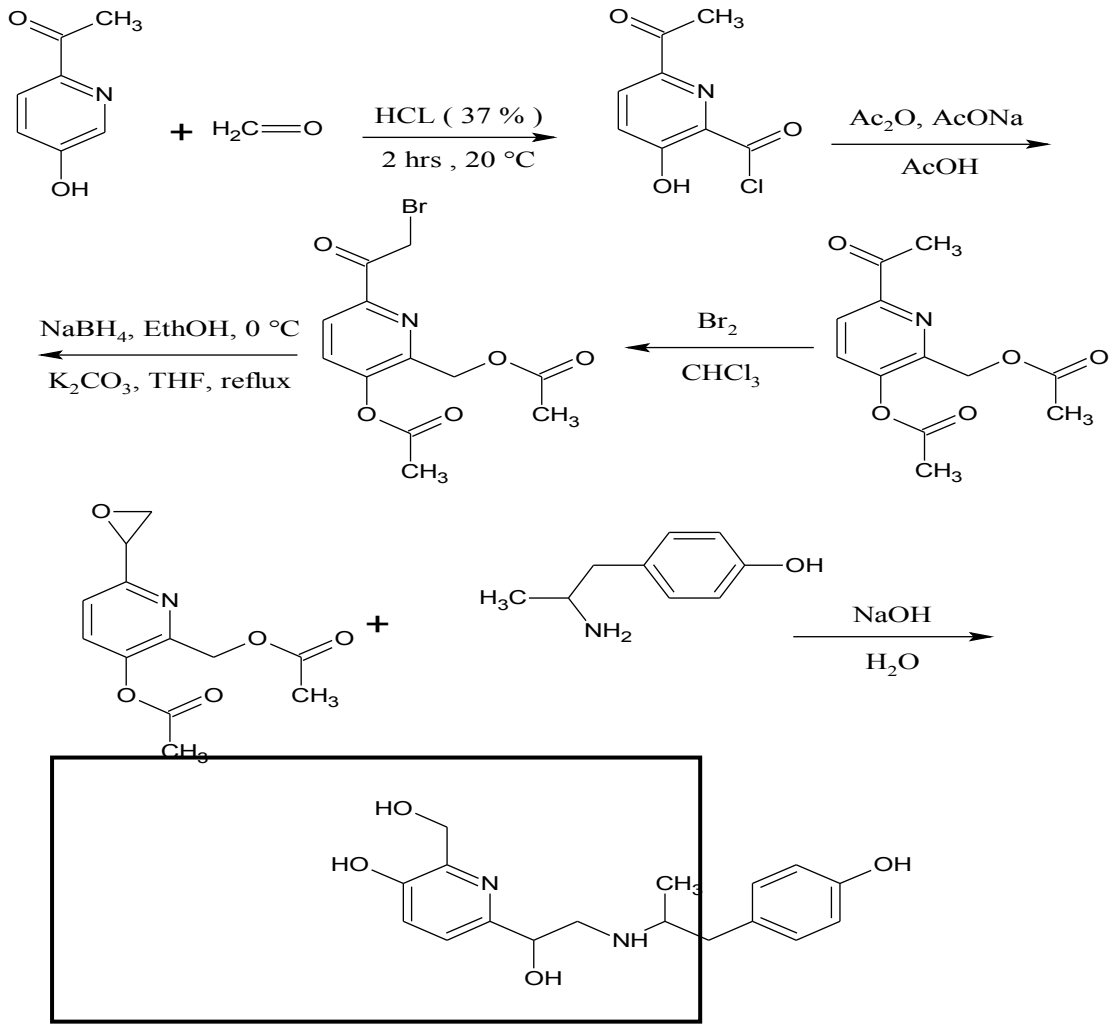


Fig (5) Hydrogen Bond Interactions of Hit Compound

Chemistry:

A suggested synthesis of the new hit compound is as follows:



3. Conclusion:

Therefore the new hit compound

- is considered **a long acting** and **selective β_2 adrenergic agonist**.

- has have a **faster onset** of action than Salmeterol as a result of **lower lipophilicity**, and is **more potent** so can be used with a **lower dose** decreasing side effects as it is taken over a long period of time.

- has **better docking energy score** than that of Salbutamol (lead compound) so has **better binding mode**.

4. References:

- http://asthmaguidebook.gsk.com/index.asp?fuseaction=asthma.proposed
- http://asthmaguidebook.gsk.com/index.asp?fuseaction=asthma.B-salbut
- http://en.wikipedia.org/wiki/Asthma
- http://en.wikipedia.org/wiki/Salmeterol
- http://ajrccm.atsjournals.org/cgi/content/full/160/1/244
- **Foye's principles of Medicinal Chemistry.**
- **Essentials of Medicinal Chemistry – 2nd edition.**

: Case study number 6

:Anticoagulant

An anticoagulant is a substance that prevents coagulation, i.e.: it stops blood from clotting. A group of pharmaceuticals called anticoagulants can .be used in vivo as a medication for thrombotic disorders

:An ideal anticoagulant should have

Reproducible pharmacodynamic and pharmacokinetic properties▪ such that no coagulation monitoring is necessary
A wide therapeutic window▪
A rapid onset and offset of action▪
Minimal adverse effects▪
Minimal interactions with food and other drugs▪

:Oral anticoagulants

There are two different chemical classes of orally active anticoagulant, namely coumarin derivatives and 1,3 phenindiones.

History

It has been known since 1921 that cattle eating spoiled sweet clover hay often would die from uncontrollable bleeding after suffering a minor .injury

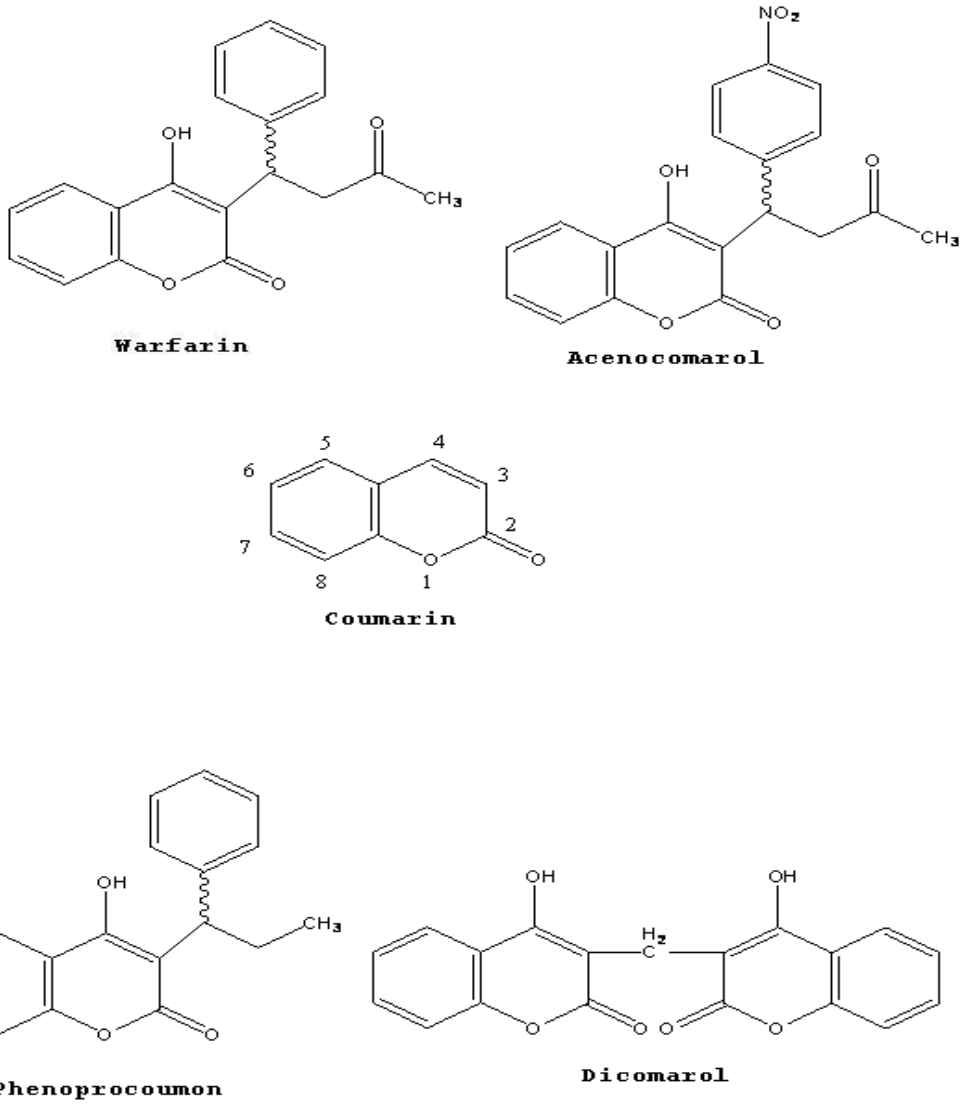
This discovery and other subsequent findings eventually led to the isolation of bishydroxycoumarin (i.e. dicoumarol) in 1934 by Link and Campbell. Its .use in humans was in 1954 as the first orally active anticoagulant drug

Coumarin Derivatives

Warfarin and other Vitamin K antagonists have been the main oral .anticoagulant therapy for more than 50 years

Although their effectiveness in the prophylaxis of thrombotic disorders has been established through many well-designed clinical trials, their usages in :clinical practice are challenging because of their

- Narrow therapeutic index
- Potential for drug-drug/food interactions
- Patient variability that requires close assessment and drug monitoring



Chemical structures of coumarin and coumarin derived drugs

Pharmacokinetics

The substituents at position 3 greatly affect the pharmacokinetic and .toxicological properties of warfarin and its derivatives

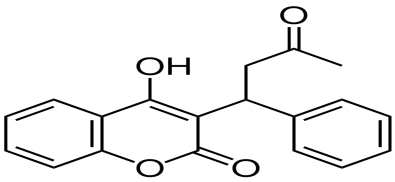
The kinetics of elimination and the biological effect of (S)-(-)-warfarin were determined in adult male rats before and after daily drug administration for 13 days. There was a small but statistically significant ($p < 0.05$) decrease in the body clearance of (S)-(-)-warfarin (from 4.84 to 4.37 ml/hr/kg), the concentration of (S)-(-)-warfarin in serum at which the synthesis rate of .prothrombin complex activity is one-half of the pre warfarin rate

The dose-response relationships for coumarin-induced toxicity and carcinogenicity are non-linear, with tumor formation only being observed at .high doses that are associated with hepatic and pulmonary toxicity

Dicoumarol is not completely absorbed in the gastrointestinal tract often is associated with gastrointestinal discomfort, so it is very rarely used .clinically

Today, the only coumarin used in the United States is warfarin, but .phenprocoumon and acenocomumarol are used in Europe

Warfarin



Warfarin sodium is rapidly and completely absorbed (~100% bioavailability) following oral, intramuscular, intravenous, or rectal administration. Peak plasma .concentration occurs approximately 3 hours

Warfarin

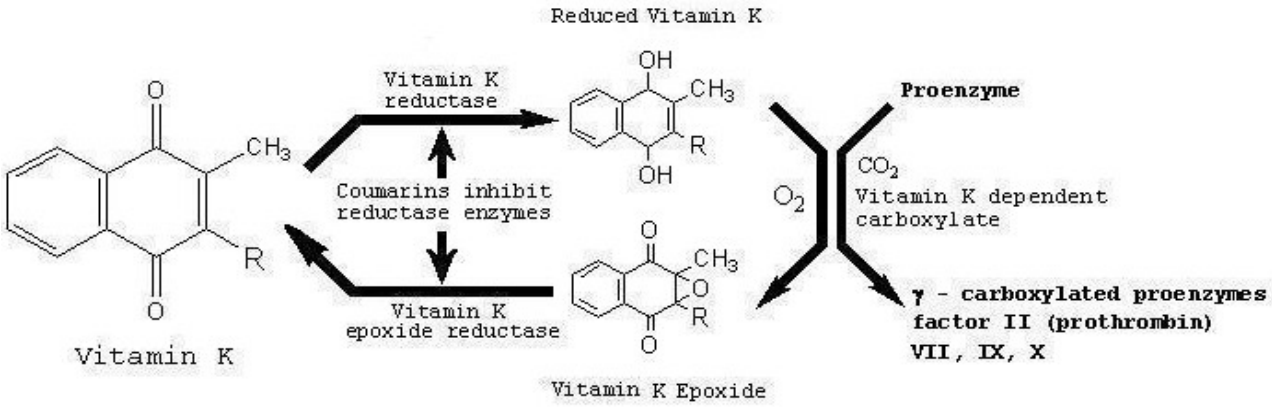
Warfarin also is highly protein bound (95-99%) and, as a result, has .numerous interations with other drugs

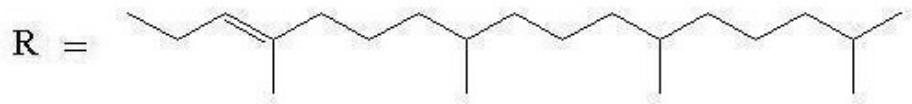
The volume of distribution is quite small (0.1 - 0.2 L/Kg), and the plasma .half life is quite long due to high degree of plasma protein binding

The clinically used preparation of warfarin is racemic, but the enantiomers are not equipotent. In fact (S)-warfarin is fourfold more potent then (R)-.warfarin

Warfarin undergoes extensive hepatic oxidative metabolism so those individuals with compromised hepatic function are at greater risk for .warfarin toxicity secondary to diminished clearance

Mechanism of action





Mechanism of vitamin K-dependent γ-carboxylation of proenzyme and inhibition by coumarin

Derivatives of coumarin produce their action by interfering with the .interconversion of Vitamin K and Vitamin K 2,3 - epoxide

Vitamin K is an essential cofactor for the carboxylation of glutamic acid residues on the N - terminal of the clotting factors (II, VII, IX and X) and .anticoagulant proteins such as protein

The carboxylated glutamic acid undergoes chelation with calcium ions causing the protein to undergo conformational changes, these changes make the clotting factors activated and bind to the **-** ve charged phospholipid .membrane during clotting cascade

The enzyme that carboxylates the clotting factors needs a reduced form of Vitamin K (Vitamin K hydroquinone). During carboxylation reaction .hydroquinone is oxidized to Vitamin K 2,3 - epoxide

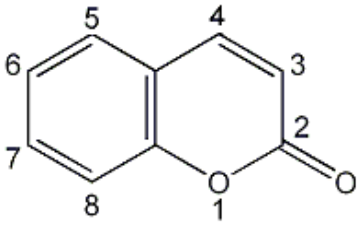
The return of Vitamin K epoxide to Vitamin K hydroquinone occurs by :two steps

- First step: Vitamin K epoxide is reduced to quinone by epoxide .reductase

- Second step: quinone is reduced to hydroquinone by quinone reductase.

Coumarin derivatives exert their action by inhibition of epoxide and quinone .reductases, which in turn inhibit the activation of the coagulation factors

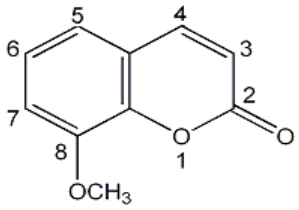
Structure Activity Relationship of Coumarin Derivatives



Coumarin

SAR requirements typically are based on substitution of the .lactone ring, specifically at the positions 3 and 4

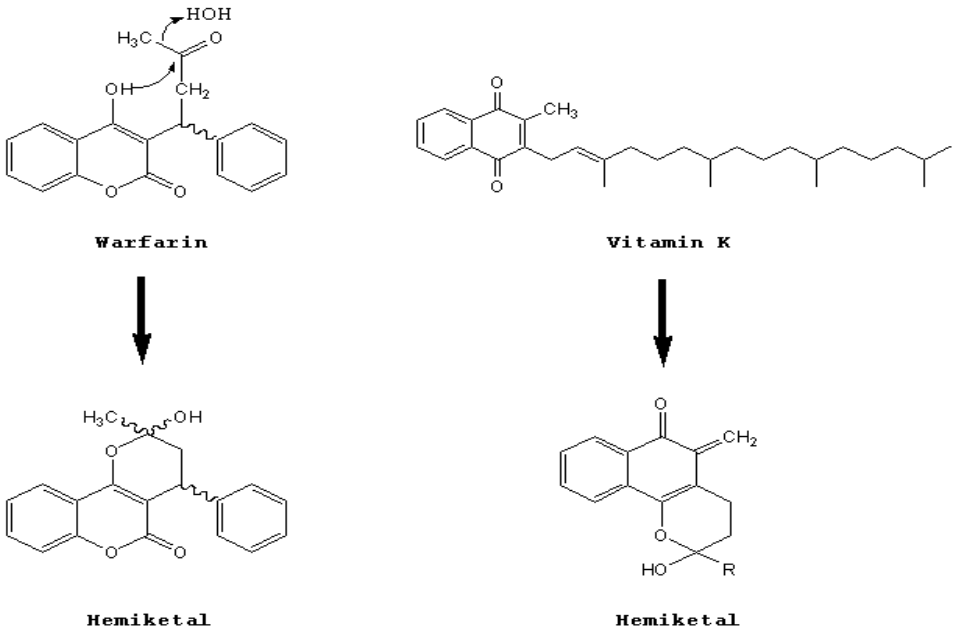
Coumarin is a neutral compound but by substitution of the 4 .position with hydroxyl group made it weakly acidic
The acidity of the proton on 4 - hydroxyl group allows the formation of water - soluble sodium salts for commercial .preparations



Recent studies have shown that substitution of methoxy .OCH3) at the 8 position shows more activity -)

It has been suggested that Vitamin K forms an active hemiketal in vivo, the cyclic hemiacetals of Vitamin K, such as warfarin, also may be the active conformer in vivo. Thus, the 4 - hydroxy is important, so that the warfarin can exist in solution as two diastereomic cyclic hemiketal .conformers in addition to its open chain conformer

Warfarin in vivo forms cyclic hemiketal in a ratio of 2:1 to the open chain conformer, and was concluded that the hemiketal conformer shows more .activity than the open chain conformer does

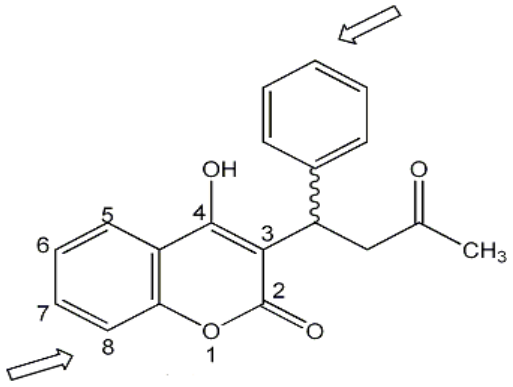


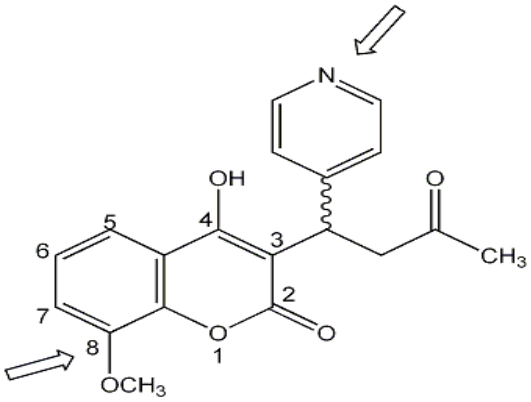
Structural similarity between Warfarin and Vitamin K

Proposing New Compound

After studying the structural relationship activity (SAR) of coumarin, we proposed a new coumarin derivative by using two modification strategies:

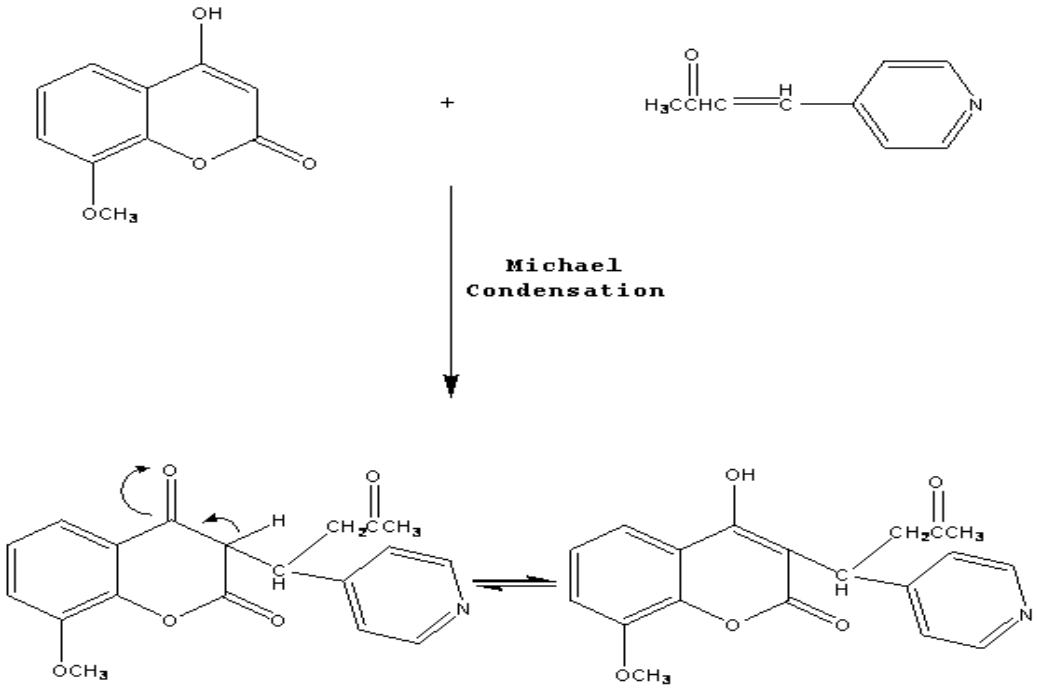
- **Variation of the substituents:** by adding a methoxy group in carbon number 4 of warfarin.
- **Ring variation:** by replacement of the benzene ring of warfarin by a pyridine ring and that to introduce extra hydrogen bonding interaction with the binding sites.





New Compound **Warfarin**

Proposed Synthesis of This New Compound



Abstract

In this research, we studied the oral anticoagulants that are a class▪ of pharmaceuticals, which act by antagonizing the effects of Vitamin K, and we specifically researched on the coumarin .derivatives & mainly the warfarin as the lead compound

- We studied its mechanism of action, structure activity relationship, other coumarin derivatives & its pharmacokinetics.

We proposed a new coumarin derivative structure, by using▪ different bioisosterism strategies, that may show a good score .activity. We also predicted its synthesis

Depending on different programs, we were able to identify the▪ pharmacophore of this drug, and thus it was able to propose a new chemical entity and here the programs that we used (Accelrys Discovery Studio, LigandScout, Molegro Virtual Docker and (ChemDraw

: References of the previous case study

Principles of Medicinal Chemistry (4th Edition) - William O. Foye•

Foye's Principles of Medicinal Chemistry (6th Edition) - William O. Foye•

Essentials of Medicinal Chemistry (2nd Edition) - Andrejus Korolkovas•

Pharmaceutical Substances (4th Edition) - A. Kleeman•

(Synthesis of Organic Medicinal Compounds (M.P.S•

Wikipedia free online encyclopedia: http://en.wikipedia.org/wiki/Anticoagulant•

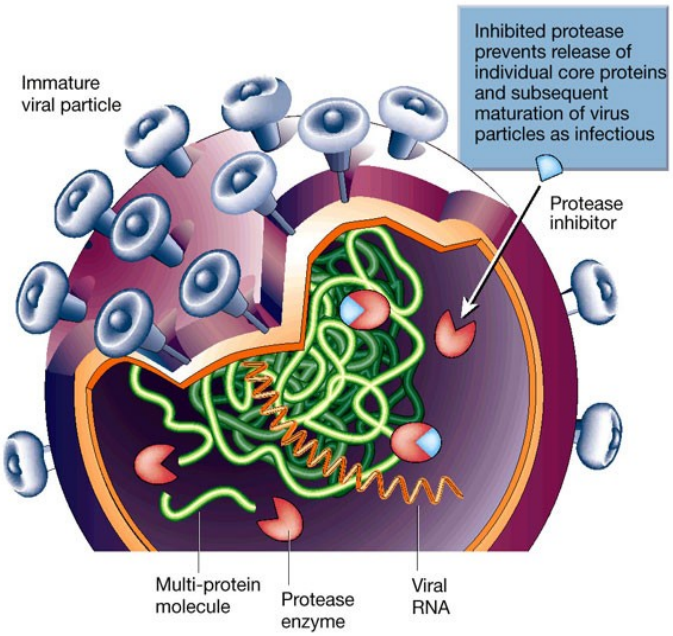
: Case study number 7

Synthesis of a New HIV Protease Inhibitor

Abstract

In this research, i studied the HIV protease inhibitors class that acts by inhibiting the protease enzymes of HIV viruses and we researched specifically on (Saquinavir) as our lead compound. We proposed a new HIV protease inhibitor structure, by using two strategies (bioisosterism and extension), that may show a good score activity.

Introduction



HIV protease inhibitors were first invented between 1989 and 1994. They are used in the treatment of patients with AIDS and were considered the first breakthrough in over a decade of AIDS .research

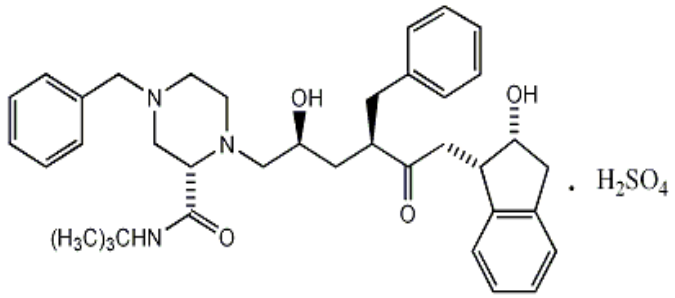
These medications work at the final stage of viral replication when core proteins are produced as part of long polypeptides, which must be cut into smaller fragments by the enzyme protease, our target, in order to form .mature and functional proteins

Therefore, HIV protease inhibitors bind to the site where protein cutting occurs, and so prevent the protease from releasing the individual core proteins. Thus, the new copies of HIV are unable to mature or become .infectious

Currently, there are five HIV protease inhibitors approved by the FDA (shown in the following figure)

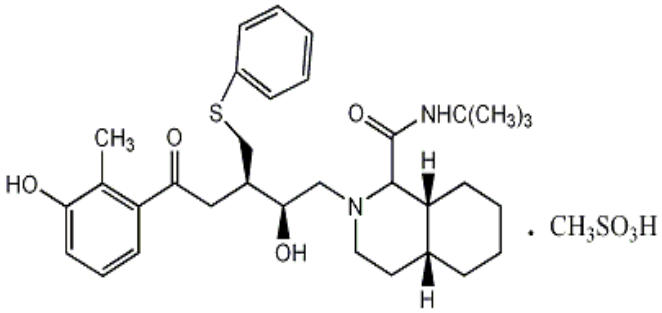
Indinavir Sulfate

$C_{36}H_{47}N_5O_4.H_2SO_4$



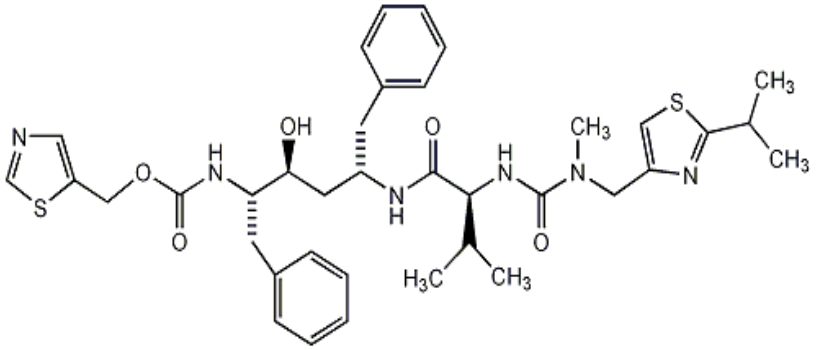
Nelfinavir Mesylate

$C_{32}H_{45}N_3O_4S.CH_4O_3S$



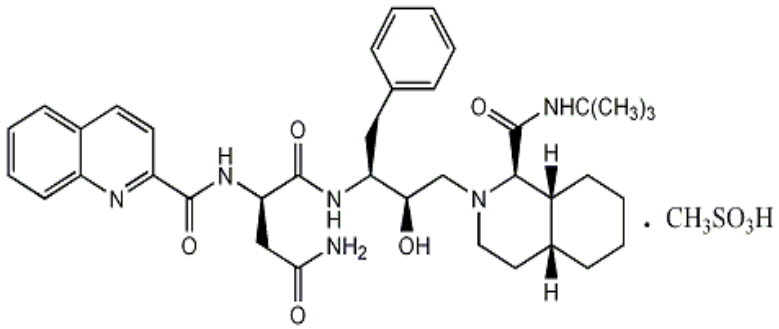
Ritonavir

$C_{37}H_{48}N_6O_5S_2$



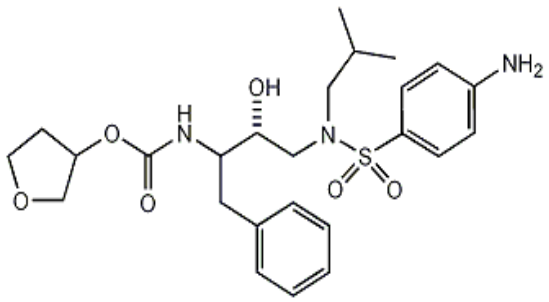
Saquinavir Mesylate

$C_{38}H_{50}N_6O_5.CH_4O_3S$

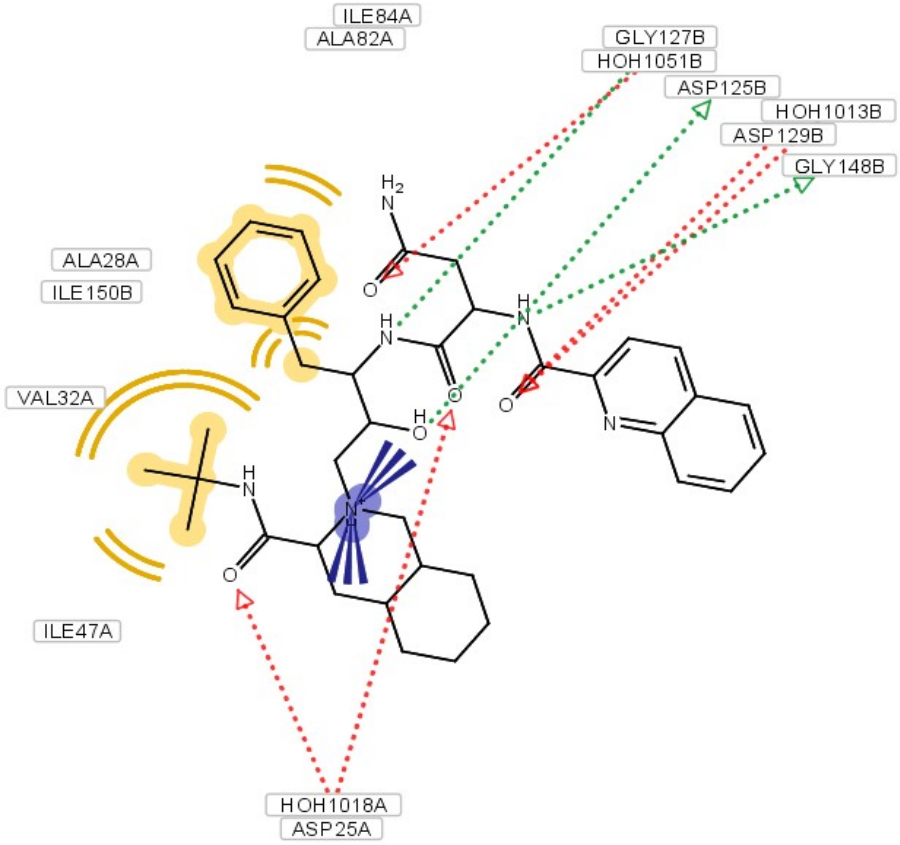


Amprenavir

$C_{25}H_{35}N_3O_6S$



Structure Activity Relationship and Pharmacophore



The above figure shows the pharmacophore model of our lead compound (Saquinavir) which was created by the (LigandScout) program.

We can conclude from it the following important points that are essential for the drug to bind with the receptor:

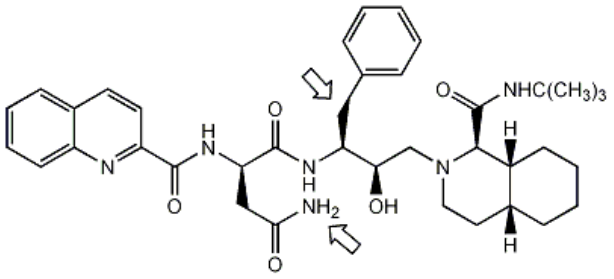
- Hydrophobic interactions that are seen at the tert-butyl group, the benzene ring and the methyl group
- The carbonyl groups represents the hydrogen bond acceptors
- Also this drug has hydrogen bond donors for example the NH & the OH groups

- There is also a positive ionizable area represented in the quaternary amine group
- The HIV protease inhibitor drugs should contain the hydroxyl ethyl amine group which is essential for activity
- If amide group is replaced by carboxylic group, activity will increase

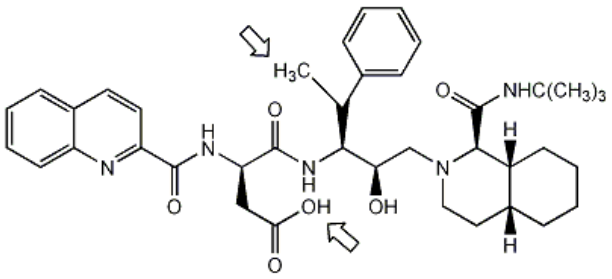
Molecular Modeling and Proposing A New Drug

After studying the structural relationship activity (SAR) of HIV protease inhibitors, we proposed a new inhibitor derivative by using two modification strategies:

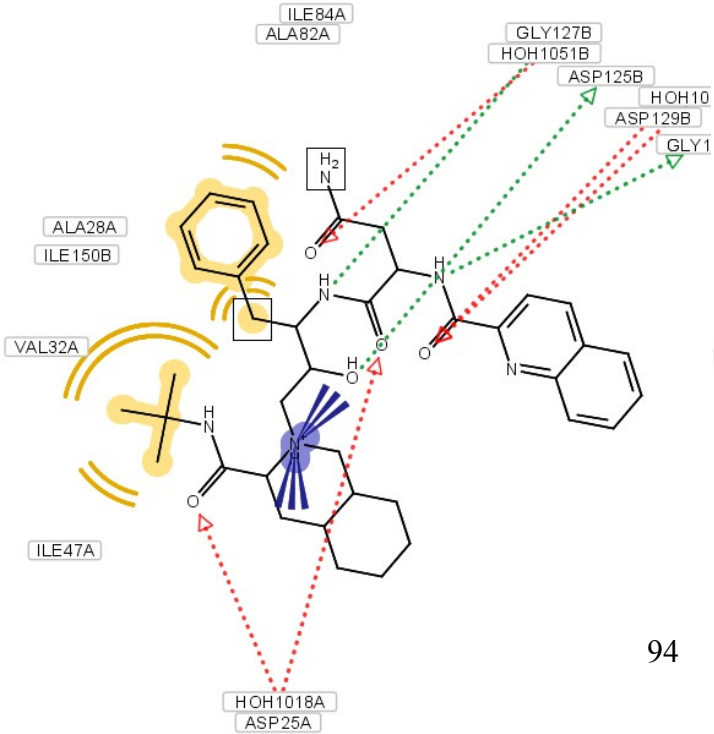
- **Extension of the structure:** by addition of a methyl group to the methyl attached to the benzene ring, this will increase the binding to the hydrophobic pocket
- **Monovalent classical bioisosterism:** by replacement of amino group by hydroxyl group, which will result in extra hydrogen bonding interaction, as the hydroxyl group will act as hydrogen bond acceptor

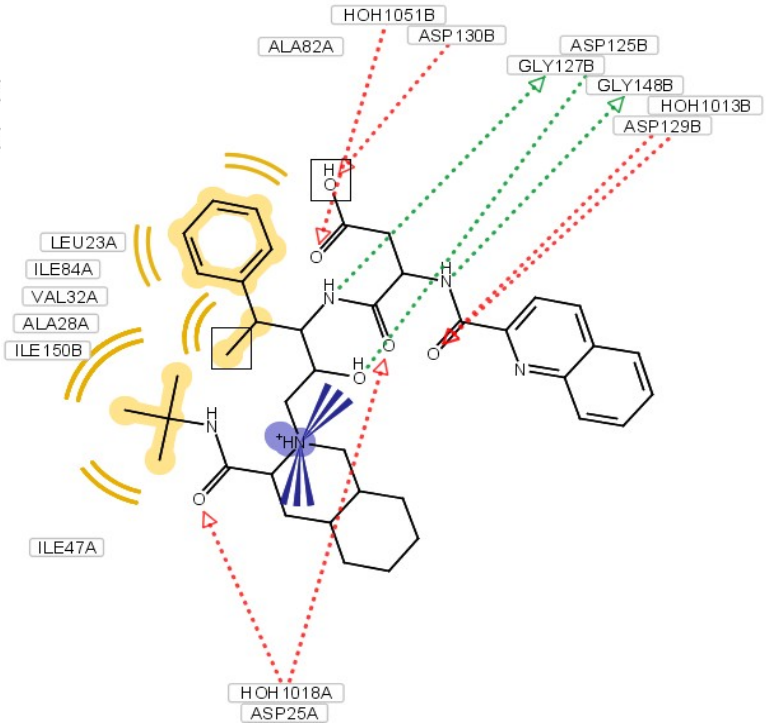


Drug (orginal)

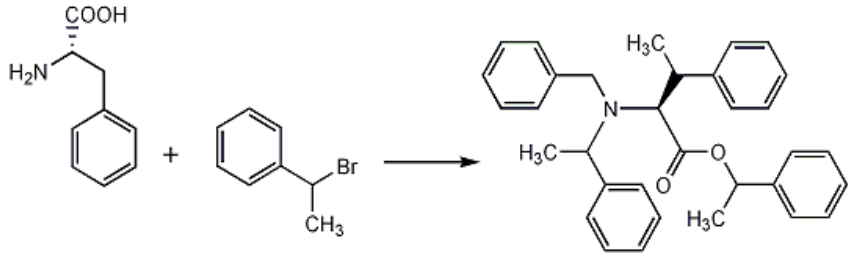


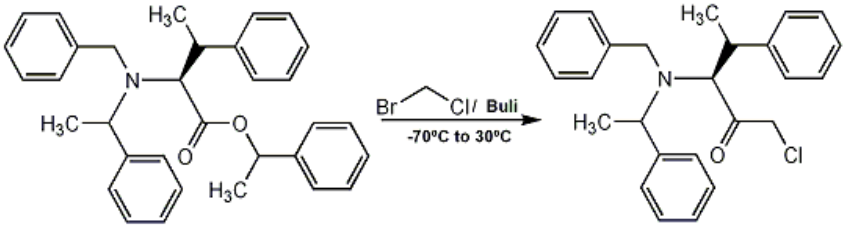
New Compund (modified)

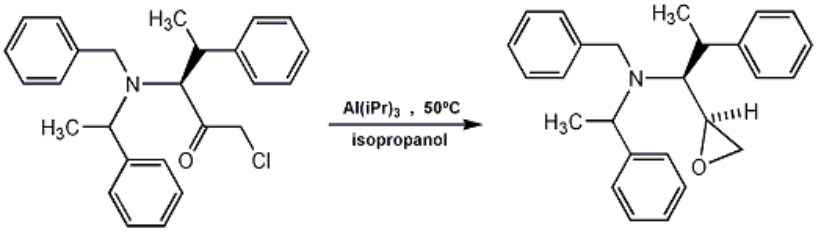


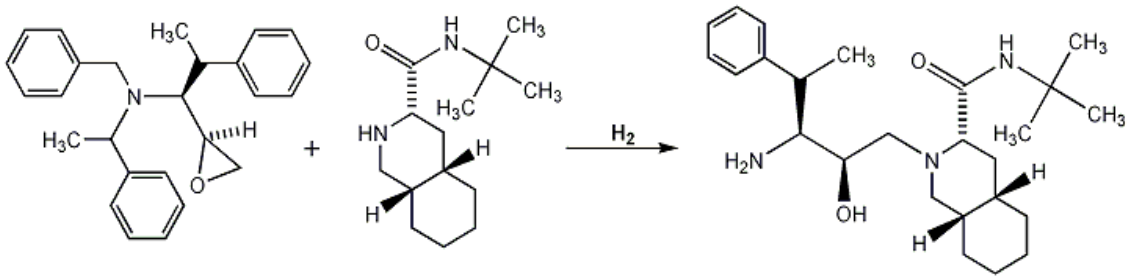


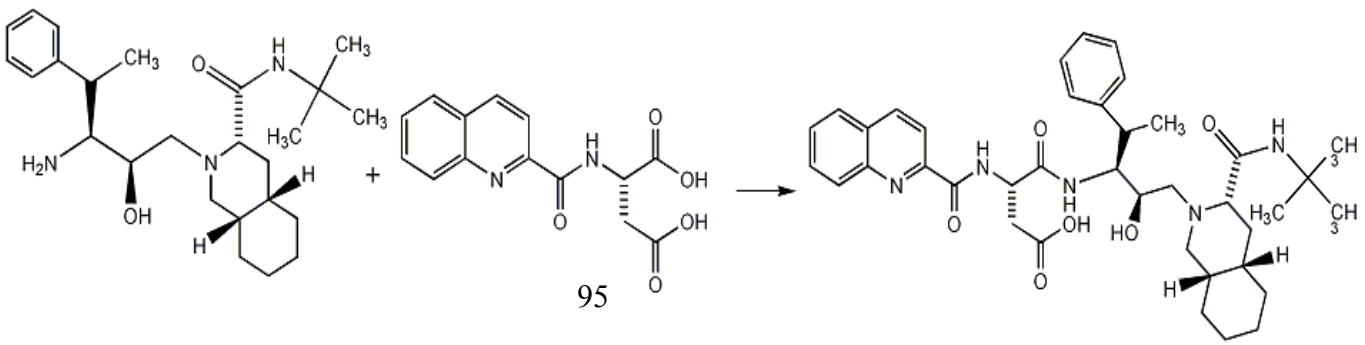
Suggested Synthesis For The New Compound











Conclusion

- In this research, we studied the HIV protease inhibitors, a class of pharmaceuticals, which act by inhibiting the protease enzymes of HIV viruses and we specifically researched on Saquinavir as our lead compound
- We studied its mechanism of action, structure activity relationship and its pharmacophore
- We proposed a new HIV protease inhibitor structure by using different bioisosterism strategies that may show a good score activity
- Depending on different programs we were able to identify the pharmacophore of this drug and thus it was able to propose a new chemical entity and predict its synthesis
- We also predicted its activity by the (Molegro Virtual Docker) program, which shows activity near to that of the reference ligand. In addition, here are some programs that we also used was (Accelrys Discovery Studio, LigandScout, Molegro Virtual Docker and ChemDraw)

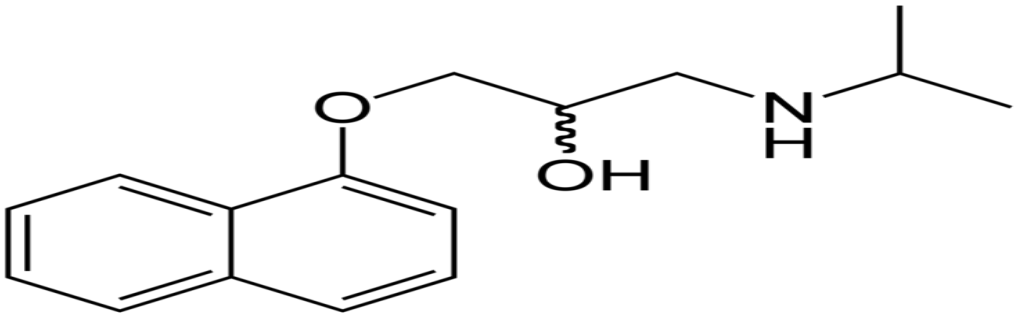
References of the previous case study :

- **Principles of Medicinal Chemistry (4th Edition) - William O.Foye'**
- **Foye's Principles of Medicinal Chemistry (6th Edition) - William O.Foye**
- **Essentials of Medicinal Chemistry (2nd Edition) - Andrejus Korolkovas**
- **Pharmaceutical Substances (4th Edition) - A. Kleeman**
- **Synthesis of Organic Medicinal Compounds (M.P.S)**
- **Wikipedia free online encyclopedia: http://en.wikipedia.org/wiki/HIV_protease_inhibitor**

case study number 8 :

First we will talk about our drug, the lead compound and its class.

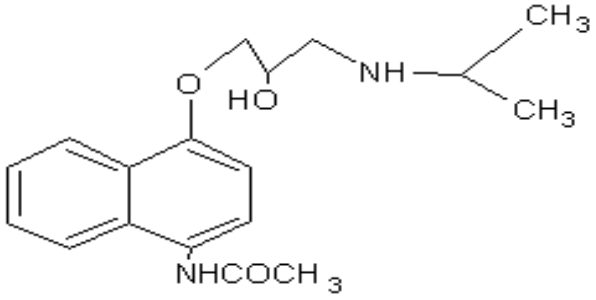
Our class: β blocker---non selective
Lead compound: propranolol



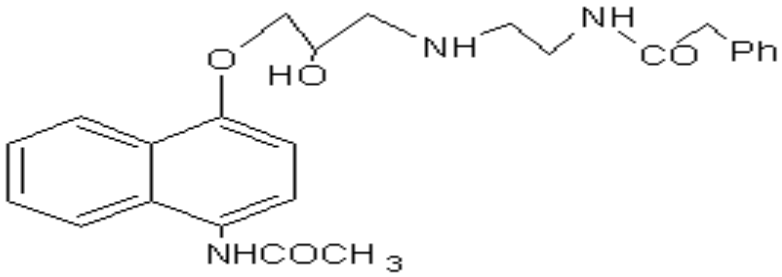
Propranolol is non selective β-blocker which acts as an antagonist at β_2-receptors as well as β_1-receptors. Normally this is not a problem. But it does pose serious problem is asthmatic since the use of propanolol could initiate an asthmatic attack by antagonizing the β_2 –receptors in bronchial smooth muscle. This would lead to contraction of bronchial smooth muscle and closure of the airways. So we think to make modification on it to make it selective cardiac β_1 antagonist which does not block vascular or bronchial β_2-raceptors. It was much safer for asthmatic patient and since it was more polar than propanolol it had fewer CNS effects.

After searching i found amido group had to be in para position of the aromatic ring rather than the ortho or meta positions if the structure was to retain selectivity for the

cardiac $\beta_1$reaceotors. This implied that there was an extra hydrogen bonding interaction in the β_1-receptors.

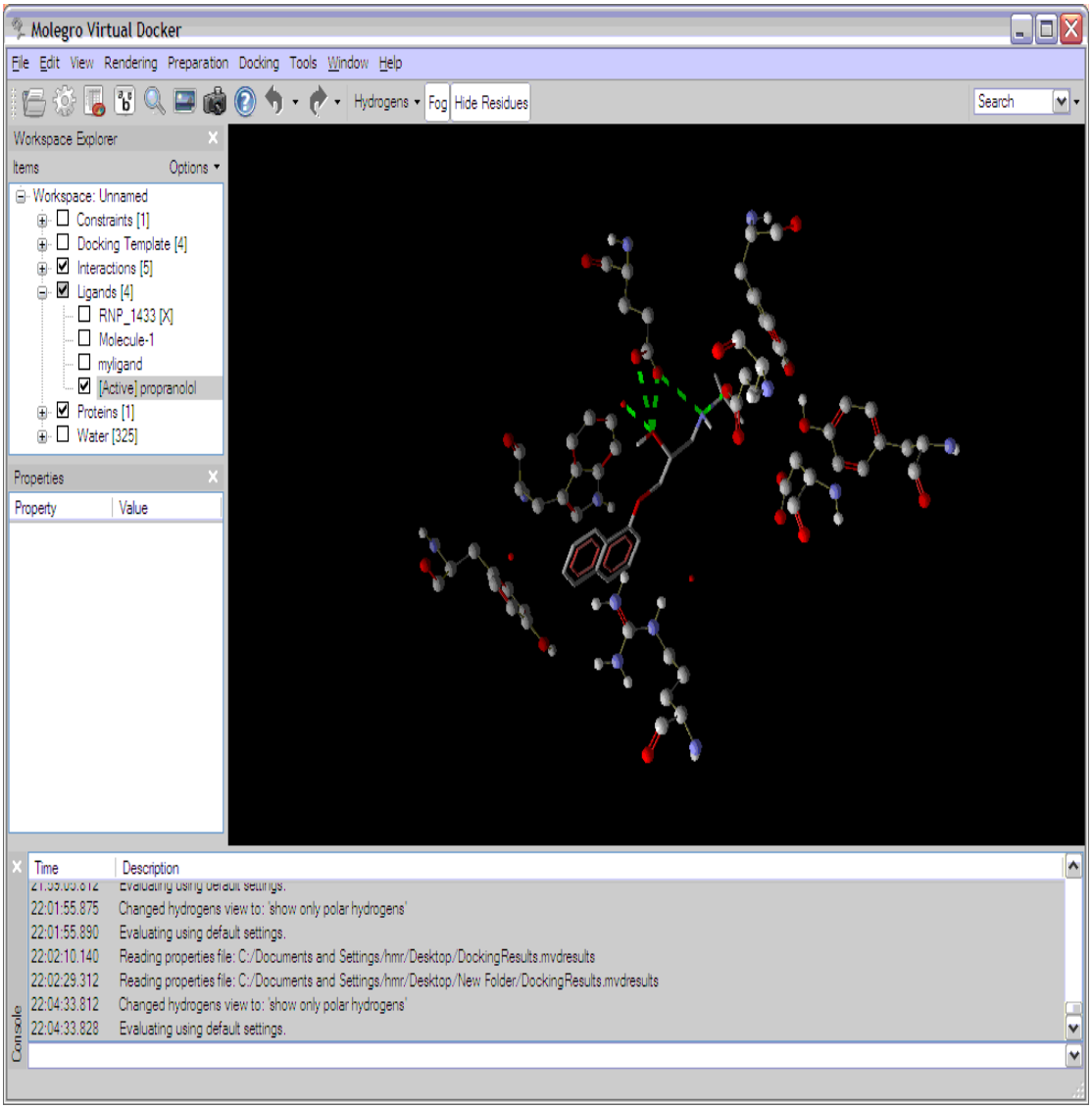


After more searching i can make third generation β-blockers by adding of arylalkyl groups to the nitrogen atom resulted in third generation which bind to the β_1-receptors using an additional hydrogen bonding interaction.

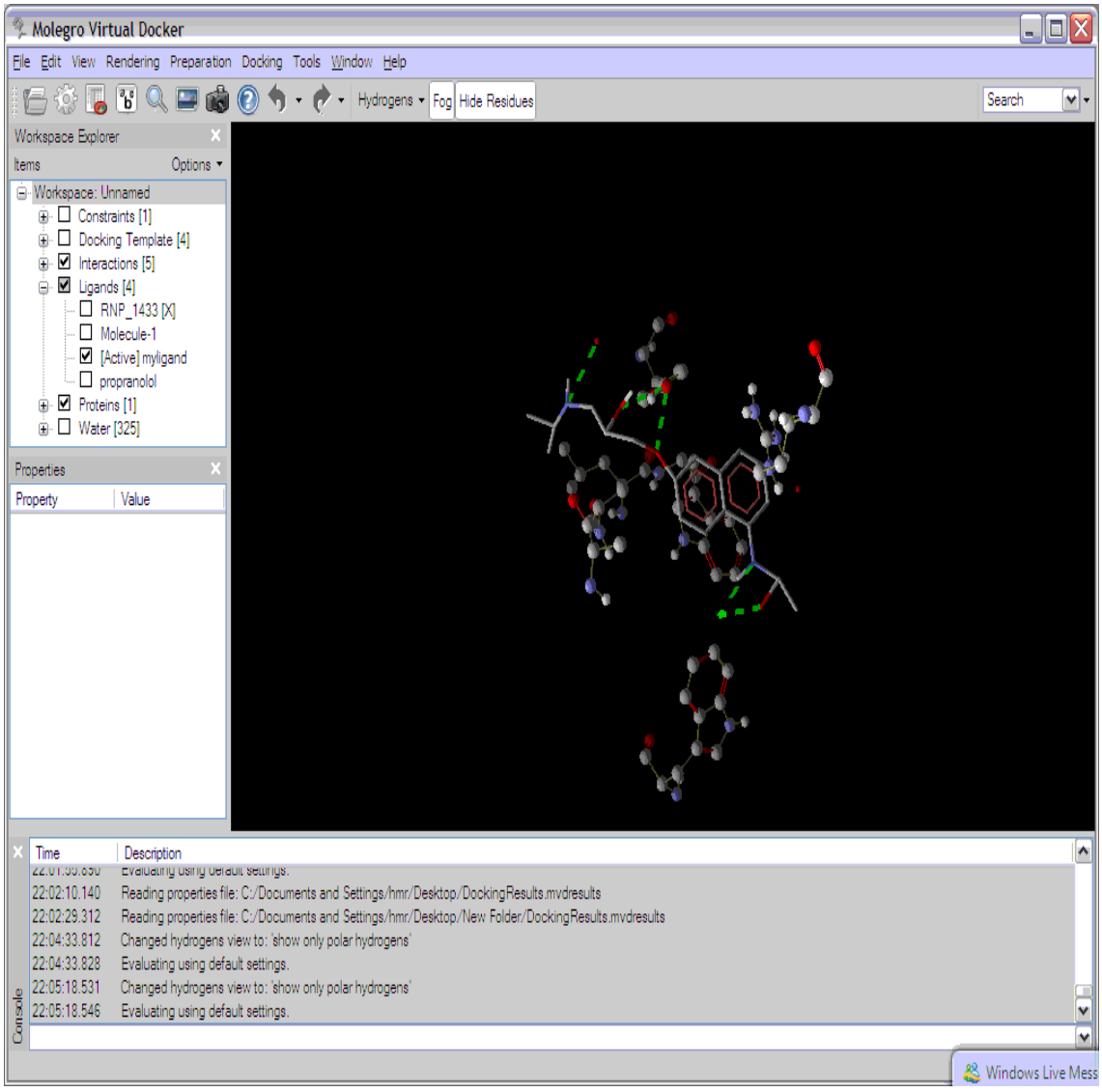


Our new drug is selective β_1 blocker for treatment of Hypertension and Angina without initiating an asthmatic attack.

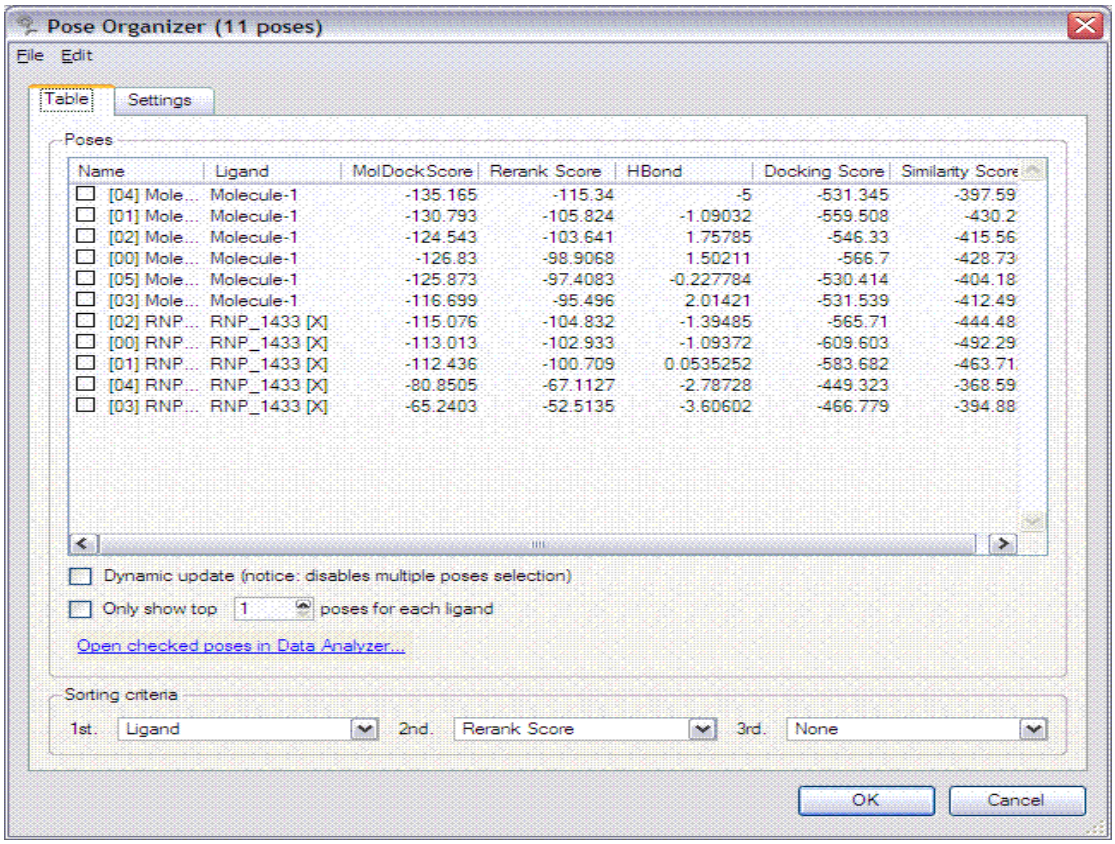
Docking (propranolol)



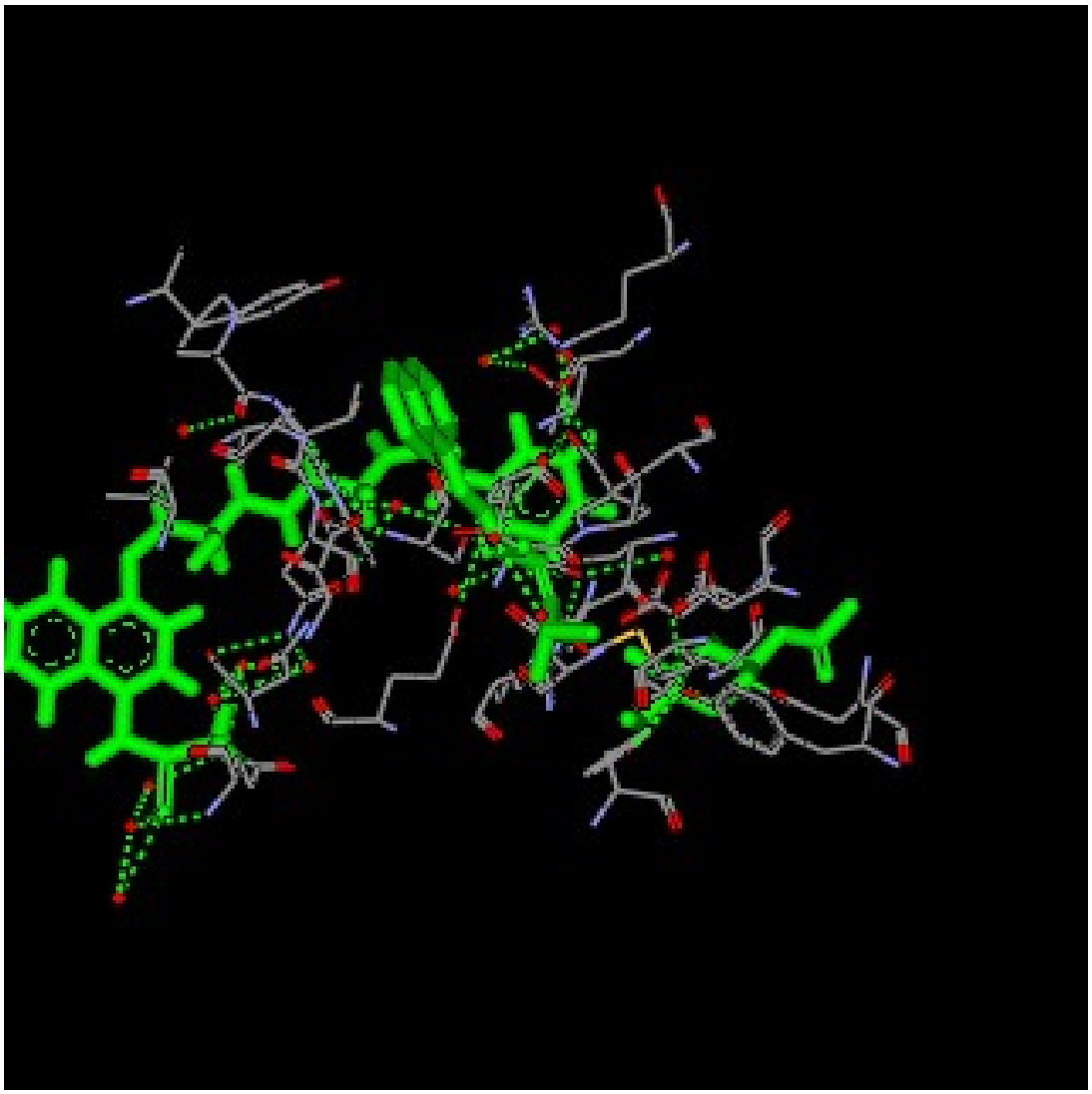
Docking of new drug



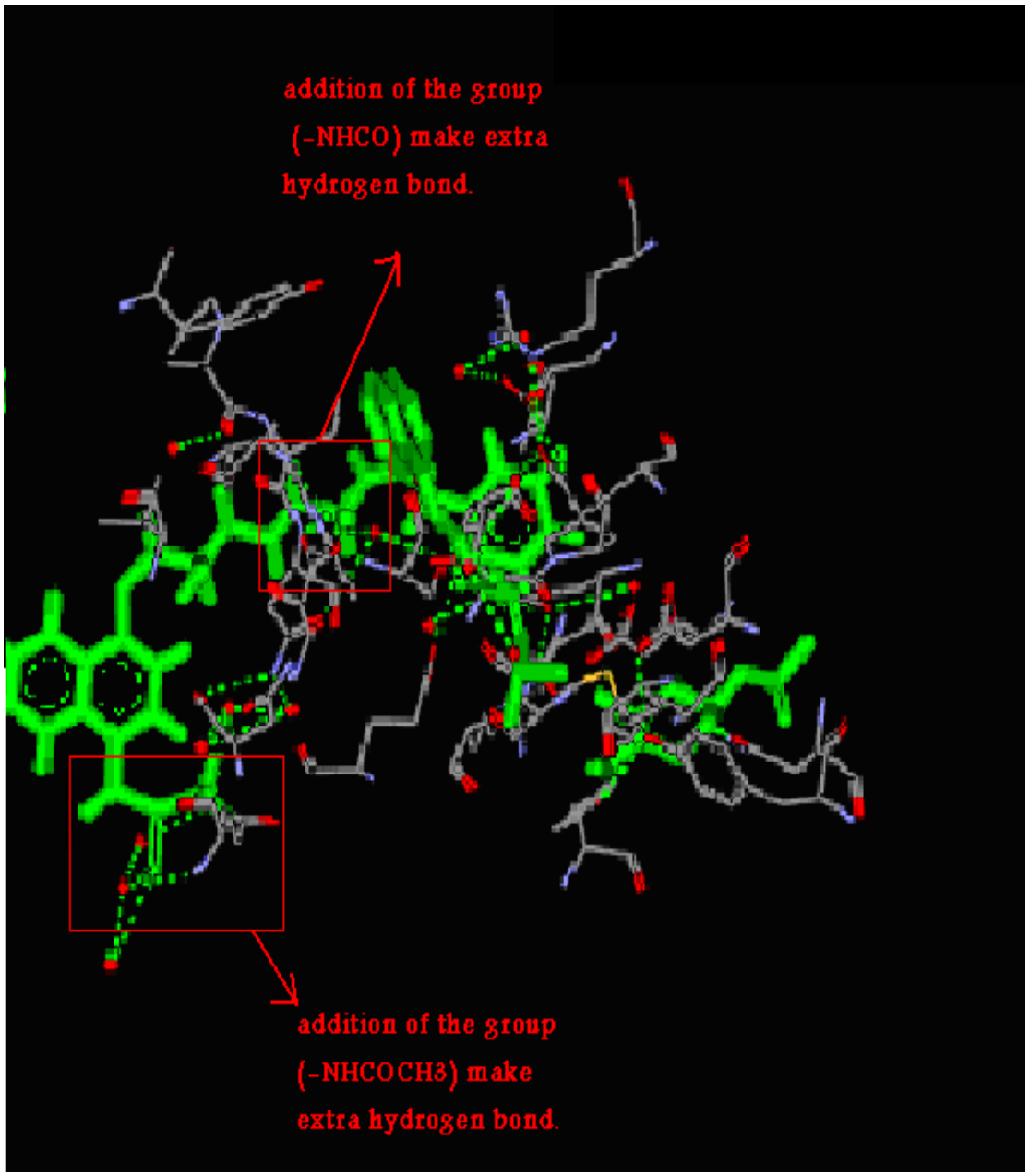
Results


Pose Organizer (11 poses)
File Edit
Table
Settings
Poses
Name | Ligand | MolDockScore | Rerank Score | HBond | Docking Score | Similarity Score
[04] Mole... | Molecule-1 | -135.165 | -115.34 | -5 | -531.345 | -397.59
[01] Mole... | Molecule-1 | -130.793 | -105.824 | -1.09032 | -559.508 | -430.2
[02] Mole... | Molecule-1 | -124.543 | -103.641 | 1.75785 | -546.33 | -415.56
[00] Mole... | Molecule-1 | -126.83 | -98.9068 | 1.50211 | -566.7 | -428.73
[05] Mole... | Molecule-1 | -125.873 | -97.4083 | -0.227784 | -530.414 | -404.18
[03] Mole... | Molecule-1 | -116.699 | -95.496 | 2.01421 | -531.539 | -412.49
[02] RNP... | RNP_1433 [X] | -115.076 | -104.832 | -1.39485 | -565.71 | -444.48
[00] RNP... | RNP_1433 [X] | -113.013 | -102.933 | -1.09372 | -609.603 | -492.29
[01] RNP... | RNP_1433 [X] | -112.436 | -100.709 | 0.0535252 | -583.682 | -463.71
[04] RNP... | RNP_1433 [X] | -80.8505 | -67.1127 | -2.78728 | -449.323 | -368.59
[03] RNP... | RNP_1433 [X] | -65.2403 | -52.5135 | -3.60602 | -466.779 | -394.88
Dynamic update (notice: disables multiple poses selection)
Only show top 1 poses for each ligand
Open checked poses in Data Analyzer...
Sorting criteria
1st. Ligand
2nd. Rerank Score
3rd. None
OK
Cancel

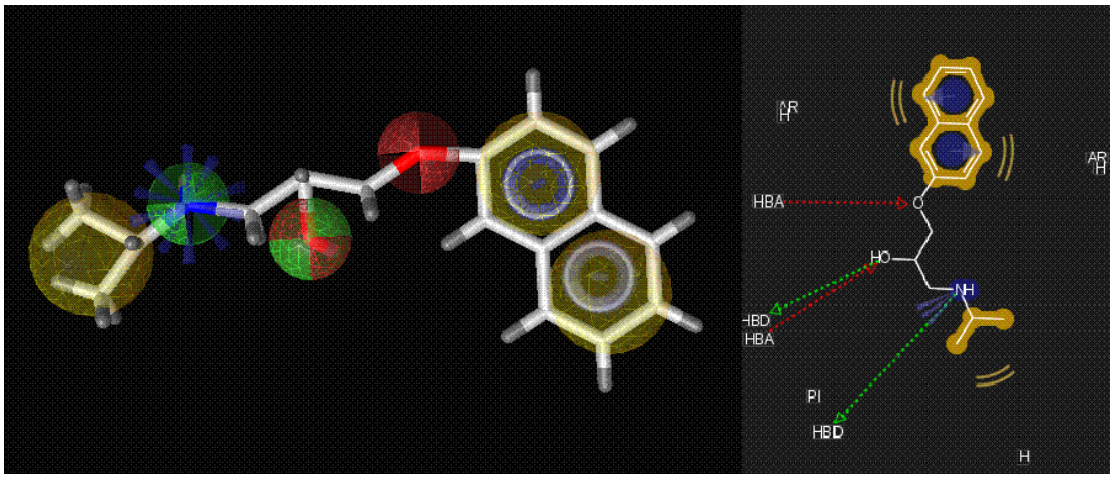
Name	Ligand	MolDockScore	Rerank Score	HBond	Docking Score	Similarity Score
[02] Mole...	Molecule-1	-180.33	-153.475	-3.47643	-630.588	-450.47
[01] RNP...	RNP_1433 [X]	-116.516	-105.275	-3.86375	-585.003	-469.47



New drug with β Receptor



Structure-activity relationship of propranolol



- **Branched bulky N-alkyl groups are good for β-antagonist activity.**

- **Variation of the aromatic ring system is possible and heteroaromatic rings can be introduced.**

- **The alcohol group on the side chain is essential for activity.**

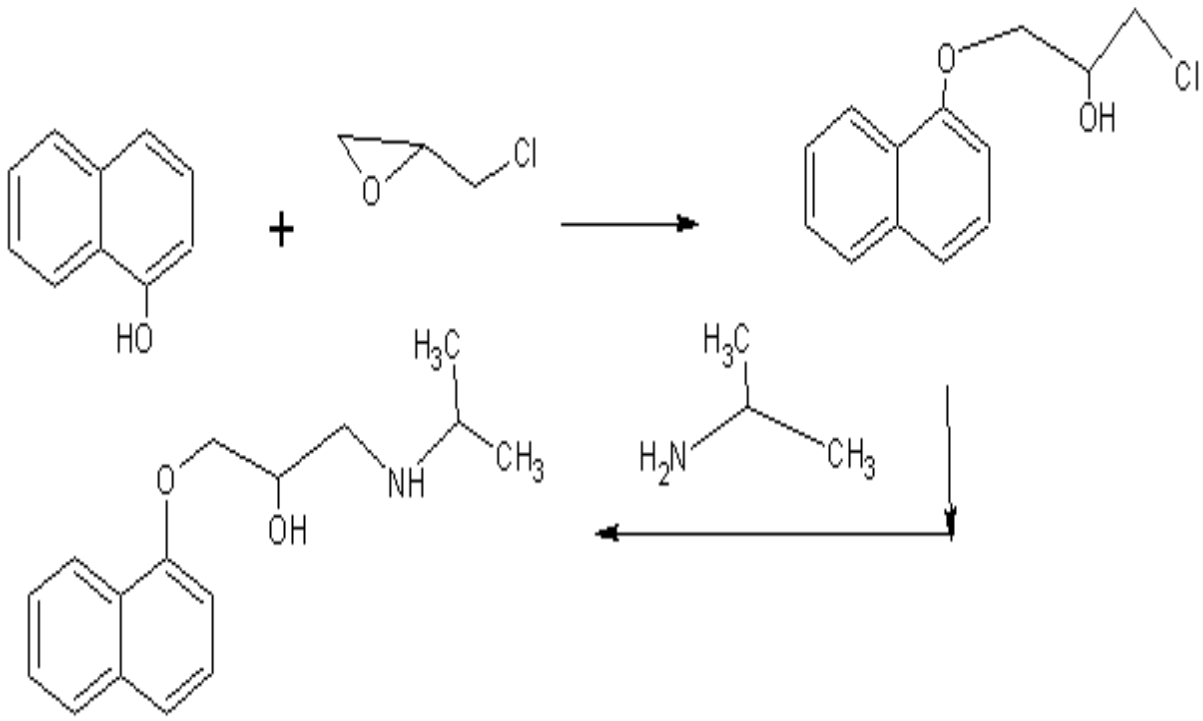
- **Substitution on the side chain methylene group increases metabolic stability but lowers activity.**

- **Replacing the ether O on the side chain with S,CH_2 is detrimental although a tissue selective β-Blocker has been obtained using NH for O.**

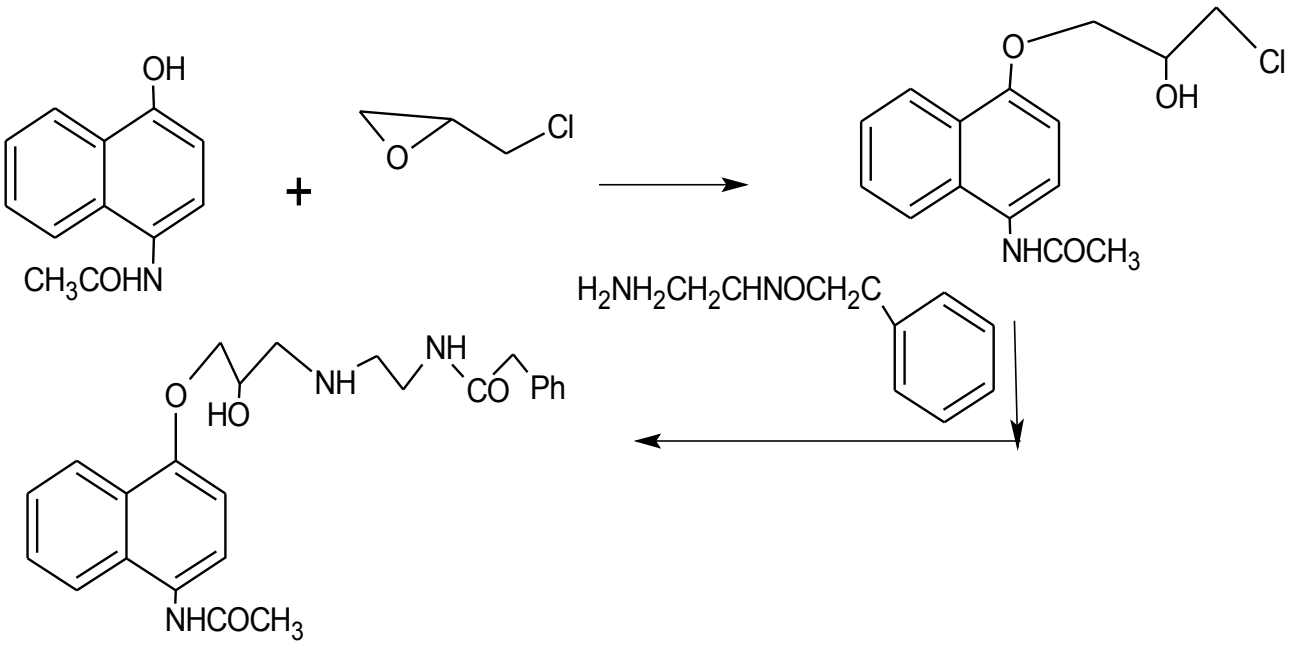
- **Longer alkyl substations than isopropyl or tert-butyl are less effective <u>BUT</u> adding an arylethyl group such as $CHMe_2$-CH_2Ph or CHMe-CH_2Ph is beneficial.**

- **The amine nitrogen must be secondary.**

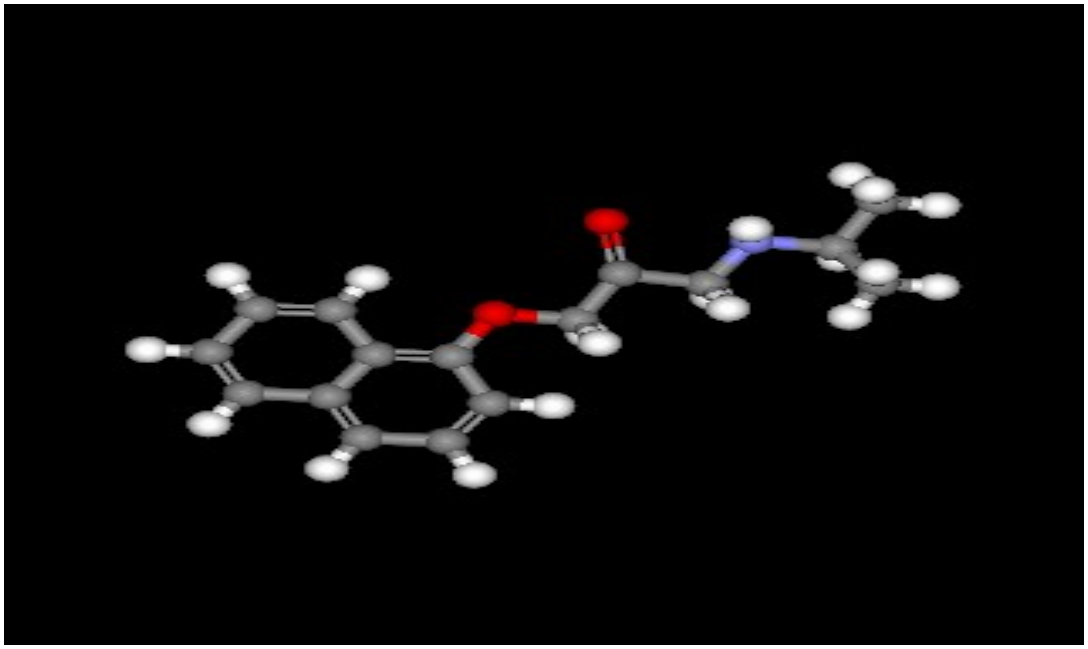
<u>Synthesis of propanolol</u>



<u>Synthesis of new Drug</u>



The lead compound "Propranolol"



Metabolism

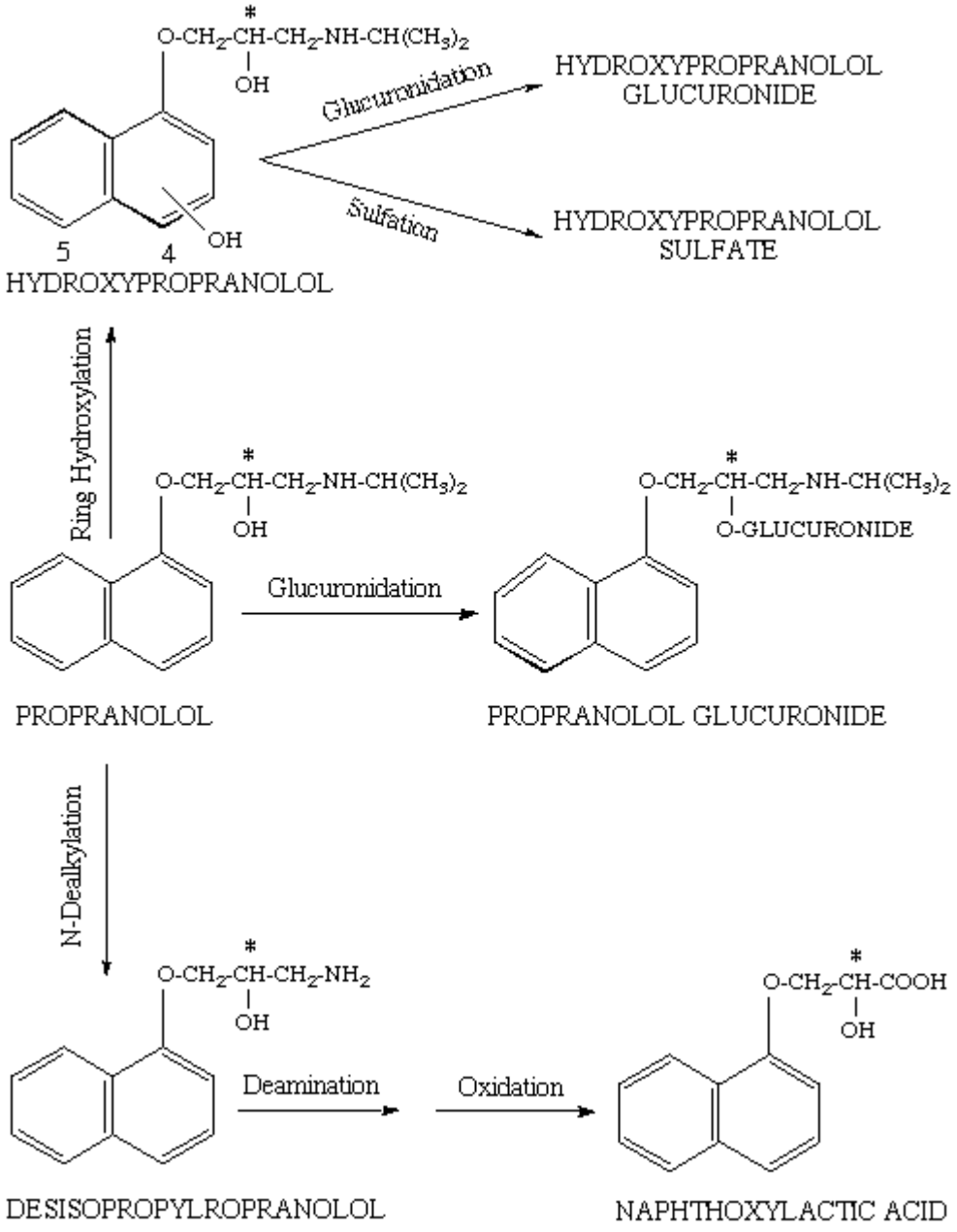
Propranolol is extensively metabolized with most metabolites appearing in the urine. Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct glucuronidation. It has been estimated that the percentage contributions of these routes to total metabolism are 42%, 41% and 17%, respective

Mode of action

In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6. Propranolol is also a substrate of CYP2C19 and a substrate for the intestinal efflux transporter, p-glycoprotein (p-gp).

The mechanism of action:

The mechanism of the antihypertensive effects of propranolol has not been established. Among the factors that may be involved are decreased cardiac output, inhibition of renin release by the kidneys, and diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. It has been suggested, but not established, that propranolol may achieve a better antihypertensive effect in patients with normal or elevated plasma renin activity (PRA) than those with low PRA.


O-CH2-CH-CH2-NH-CH(CH3)2
OH
Glucuronidation
HYDROXYPROPRANOLOL GLUCURONIDE
Sulfation
HYDROXYPROPRANOLOL SULFATE
5
4
OH
HYDROXYPROPRANOLOL
Ring Hydroxylation
Glucuronidation
O-GLUCURONIDE
PROPRANOLOL
PROPRANOLOL GLUCURONIDE
N-Dealkylation
O-CH2-CH-CH2-NH2
Deamination
Oxidation
O-CH2-CH-COOH
DESISOPROPYLROPRANOLOL
NAPHTHOXYLACTIC ACID

Case study number nine :

Cox-1 inhibitor

Pdb code: 1eqh

FLURBIPROFEN (flp 701 [A])

Ligandscout pharmacophore of FLURBIPROFEN

Modification of FLURBIPROFEN by visualizer

Strategy of modification: Trivalent Classical Bioisosterism

(replacement of phenyl ring by pyridine)

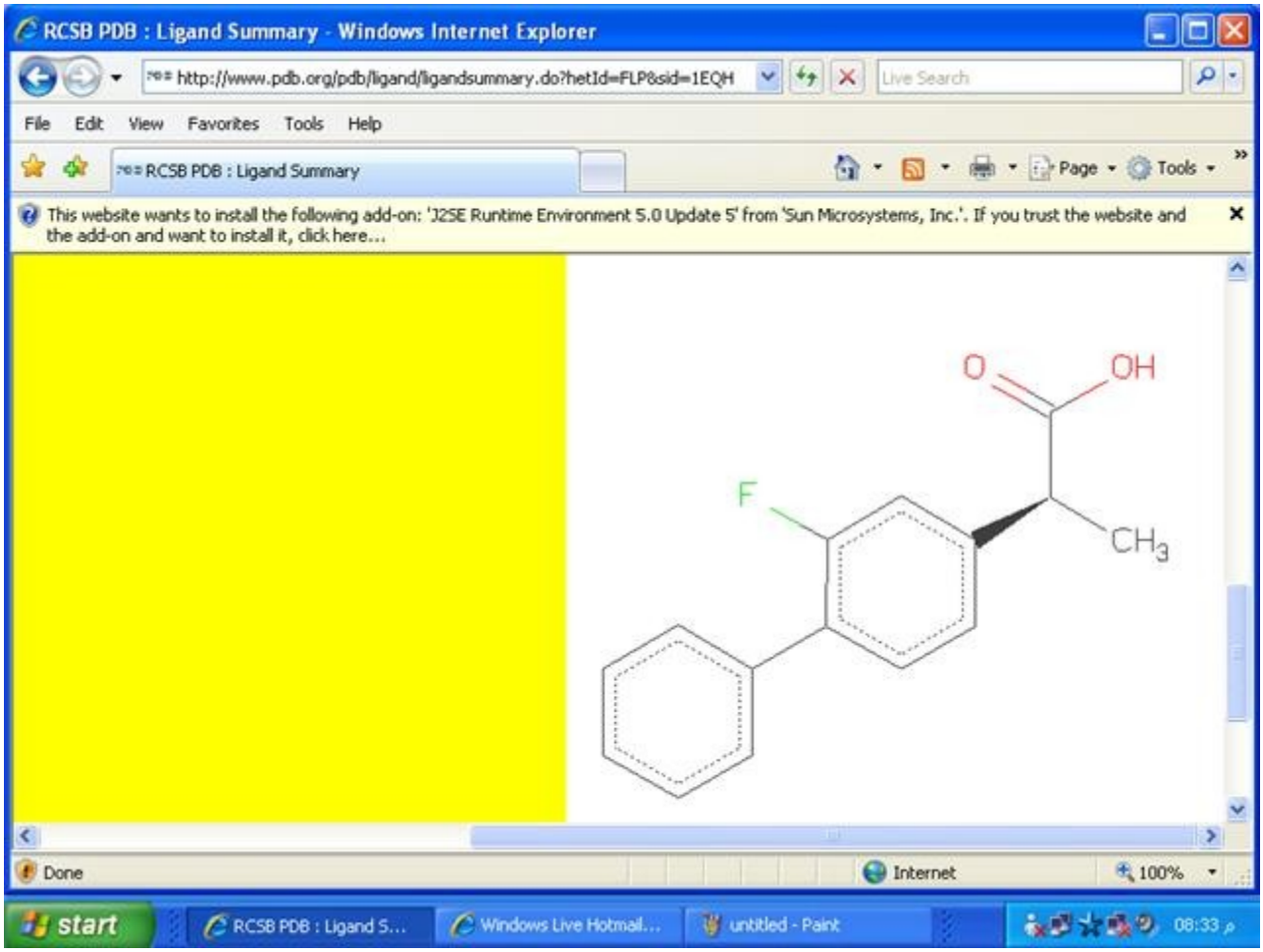
Docking results

programs:

Accelrys DS Visualizer 2.0

Ligandscout 2.0

Molegro Virtual Docker


RCSB PDB : Ligand Summary - Windows Internet Explorer
http://www.pdb.org/pdb/ligand/ligandsummary.do?hetId=FLP&sid=1EQH
File Edit View Favorites Tools Help
RCSB PDB : Ligand Summary
This website wants to install the following add-on: 'J2SE Runtime Environment 5.0 Update 5' from 'Sun Microsystems, Inc.'. If you trust the website and the add-on and want to install it, click here...
O
OH
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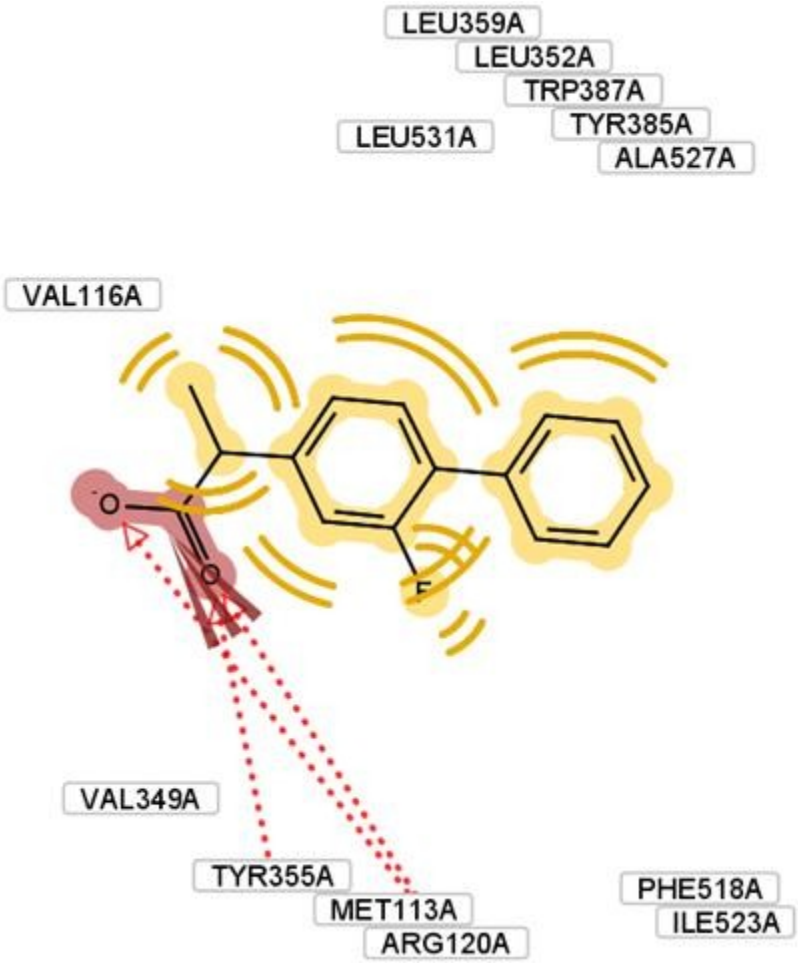
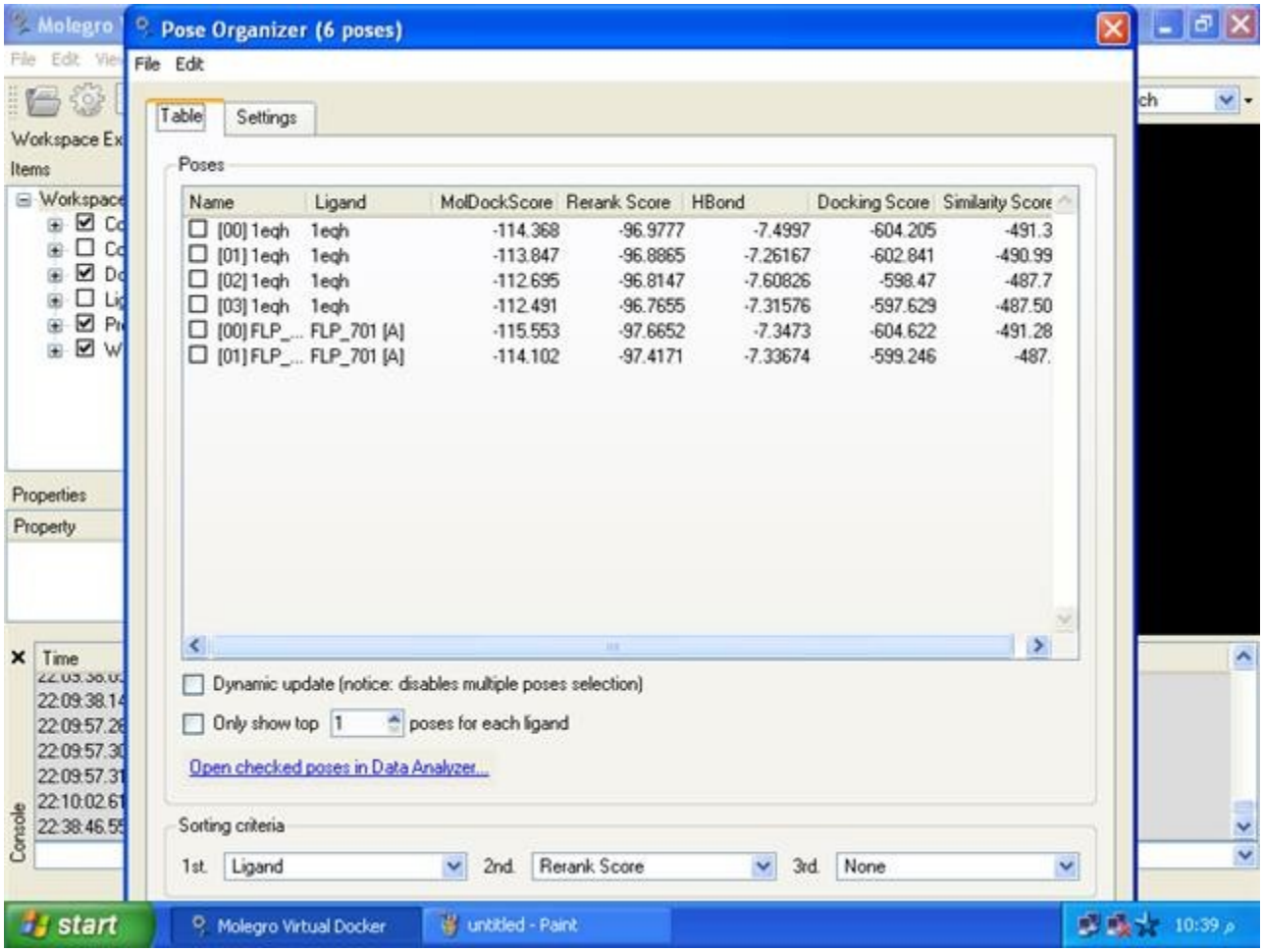
CH3
Done
Internet
100%
start
RCSB PDB : Ligand S...
Windows Live Hotmail...
untitled - Paint
08:33

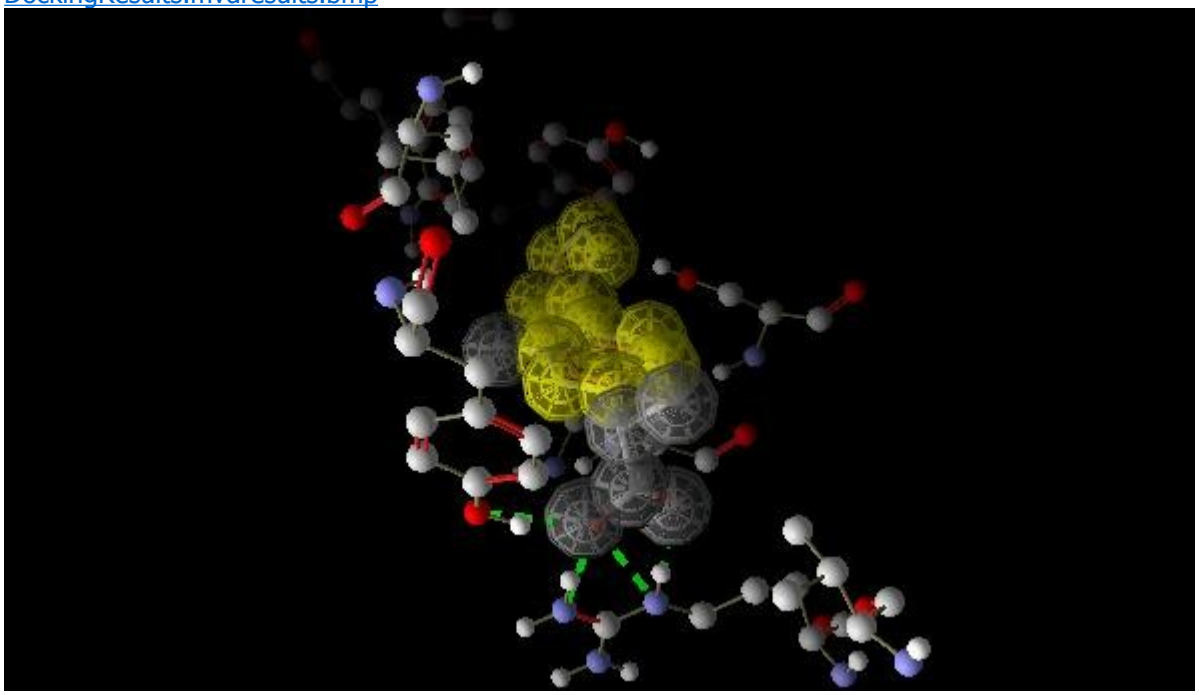
1eqh.bmp



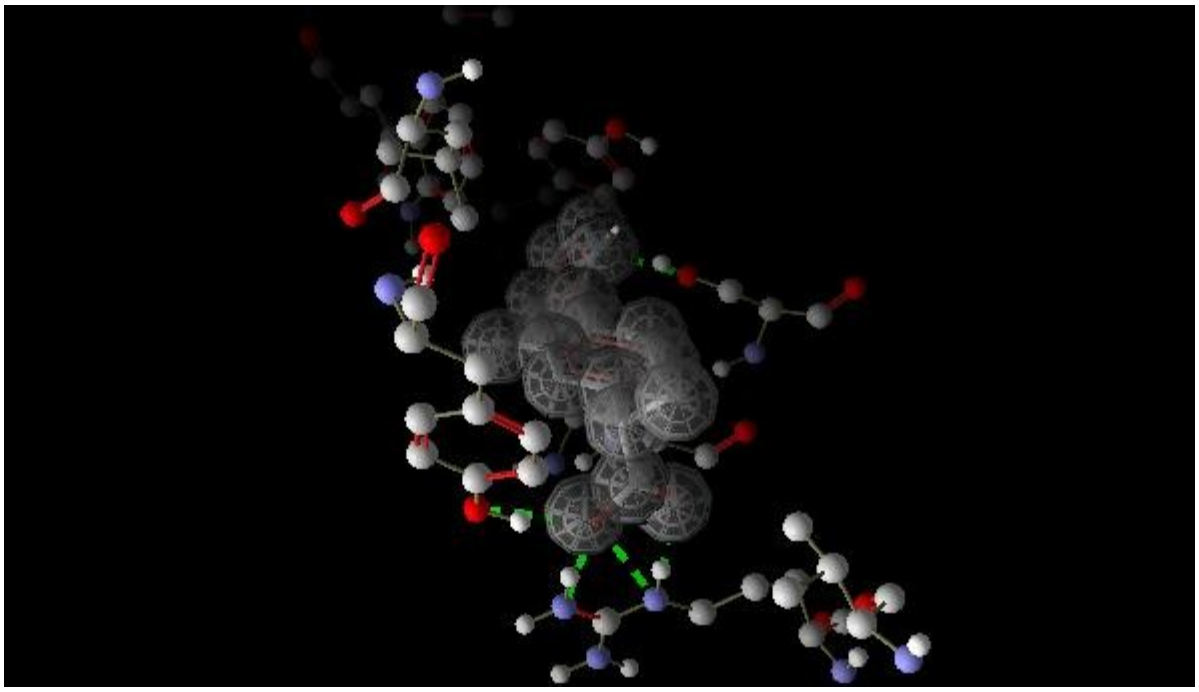
pharmacophore.png



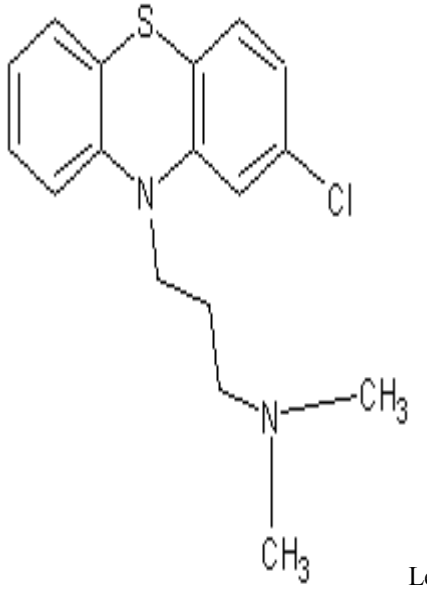
DockingResults.mvdresults.bmp



screenshot of Flp.png

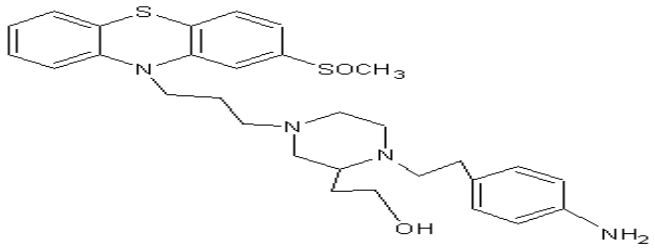


Case number ten :



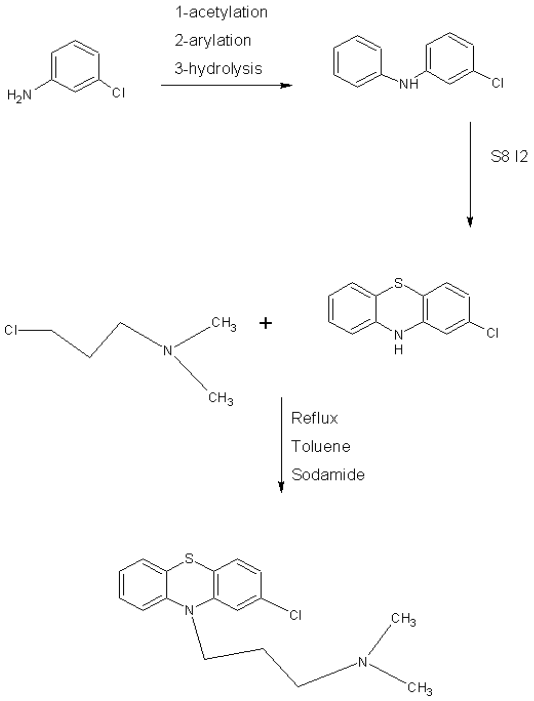
Lead compound (chloropromazine)

Modifications of the lead to obtain new drug

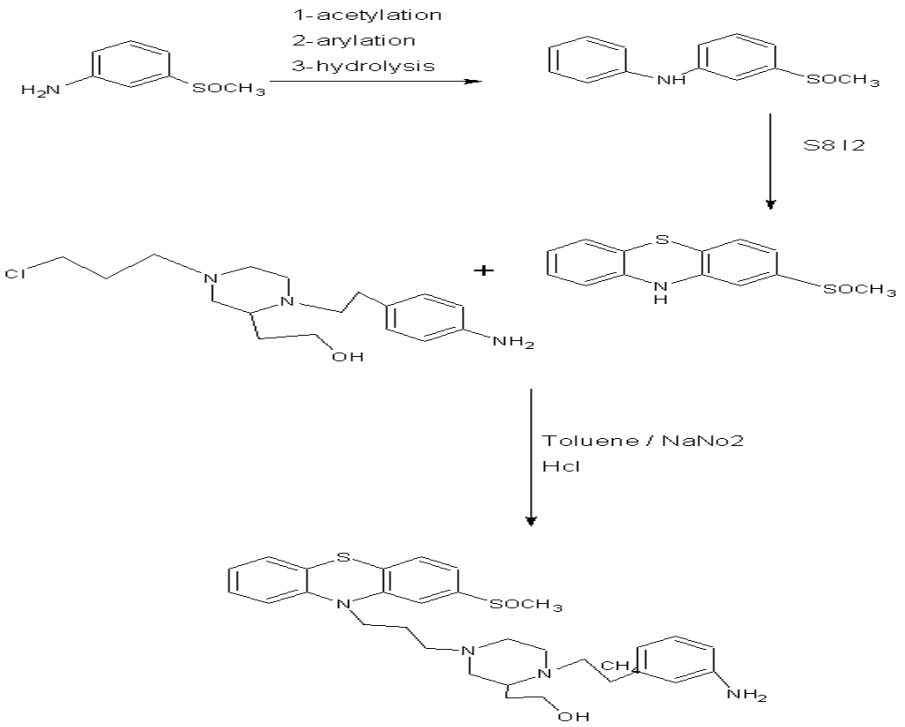


reasons for these modifications

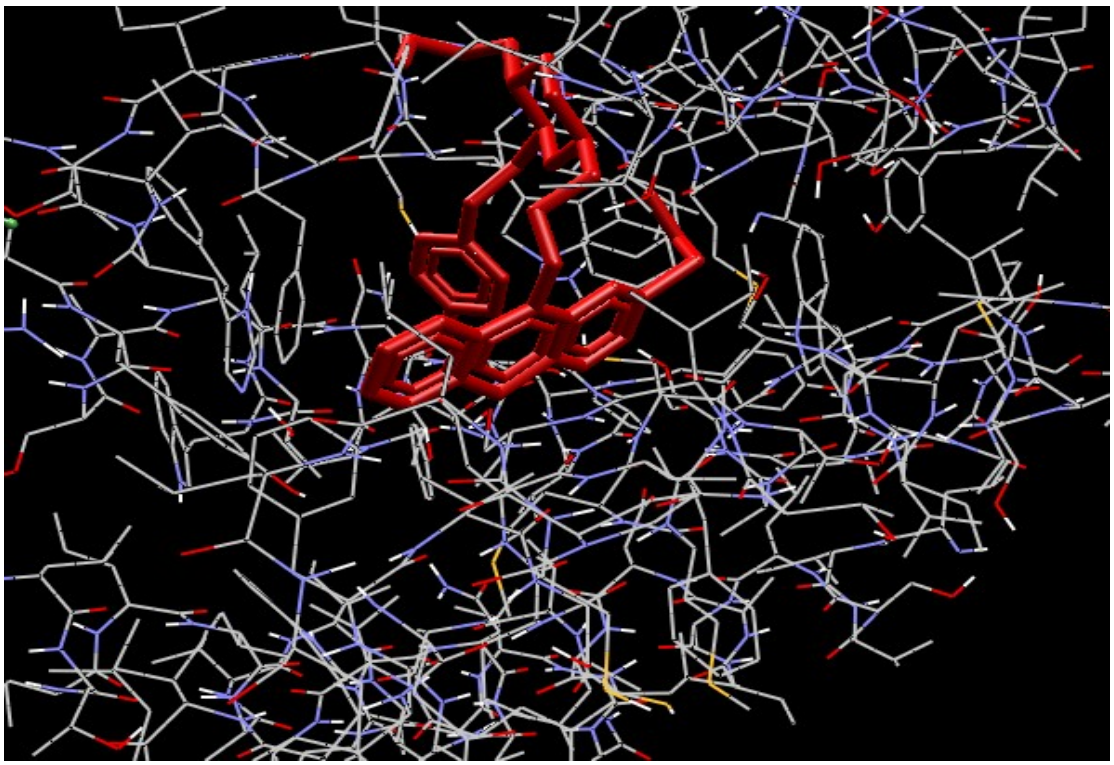
- Distance beween N of pheno thaizine ring and basic n of piperazine is 3 c to maintain greatest potency (this resemble dopamine)
- piprazine ring which is responsible for increasing activity - in which its N4 is attached to p amine phenyl ethyl ,this increases the activity
- addition of hydroxy ethy to piperazine ring is responsible for increasing activity

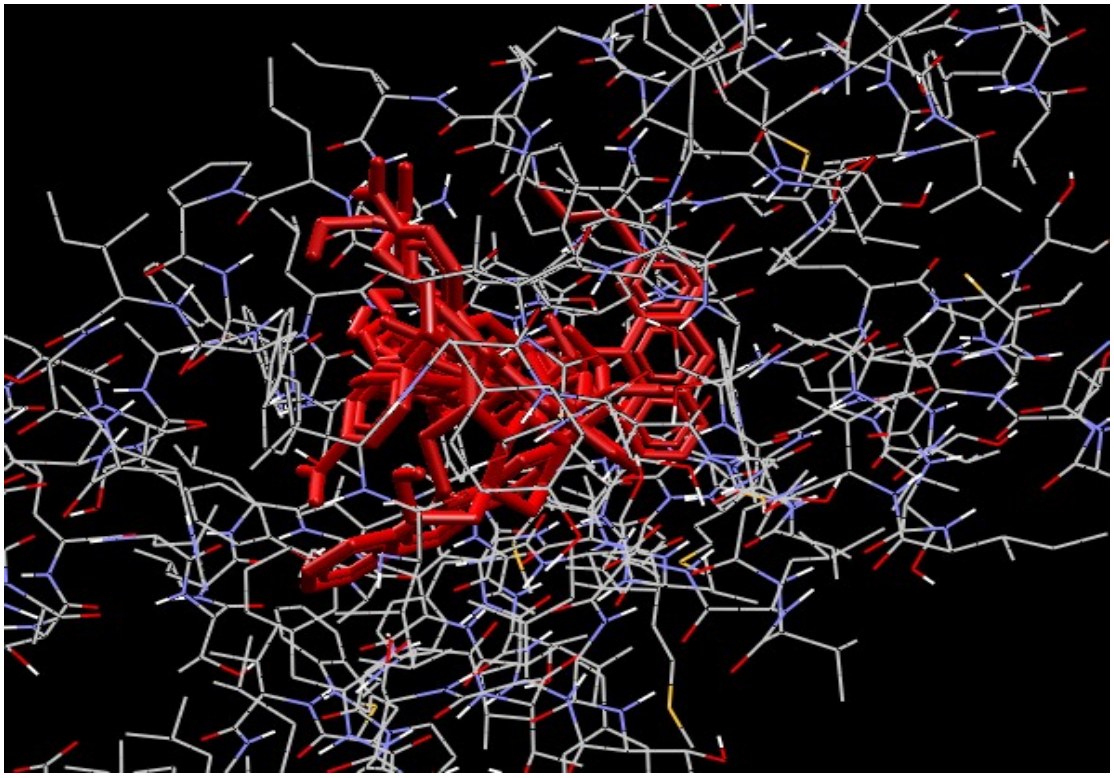


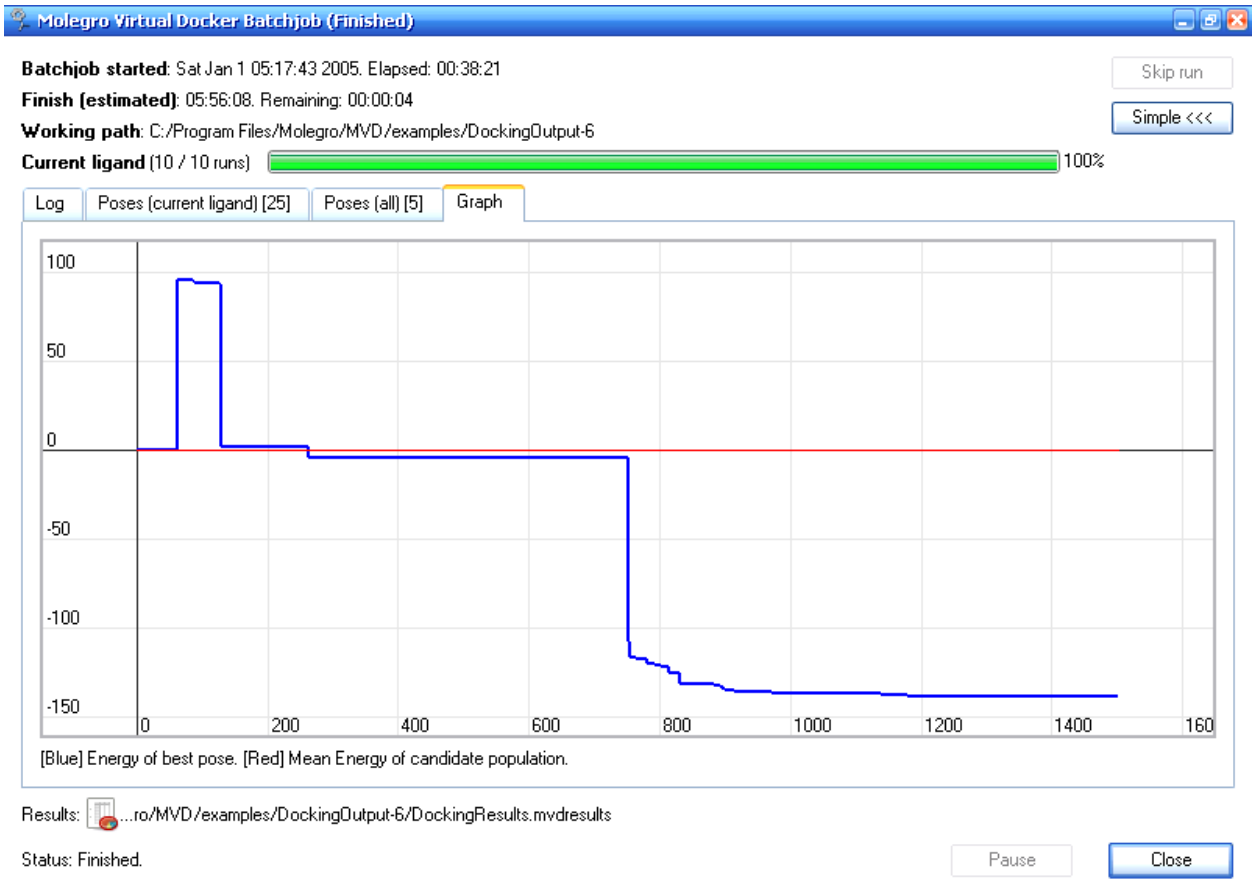
Synthesis of new drug

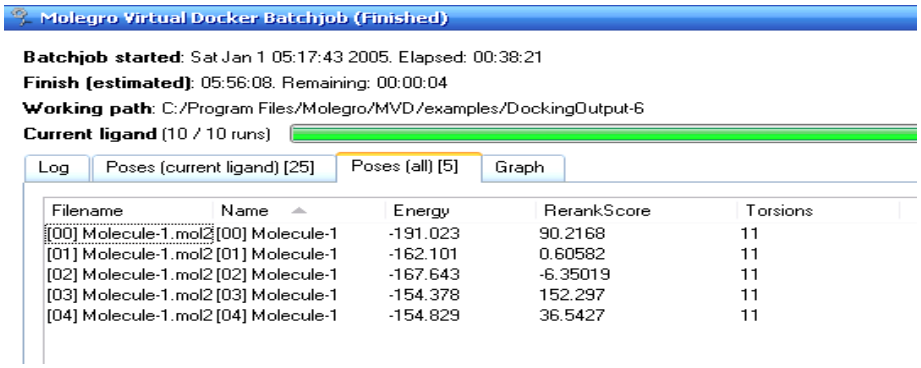


Docking and other calculations :









Chapter 6 : Conclusion :

Medicinal chemistry as a one of the most important fields of drug discovery and drug synthesis is considered the leader of pharmacy in its development as medicinal chemistry is the study of all or most of the previous strategies in synthesis and discovery of the drugs and so we can suggest novel methods to synthesize drugs or new drugs to avoid disease or to treat the disease and so improve the health state of our society.

Medicinal chemistry is complicated and not simple issue to talk about as drug synthesis and drug analysis in medicinal chemistry is limited Because there is limitation in the raw materials and also in the availability of these raw materials and there is a problem in the availability of modern instruments especially in developed country .

• References : (bibliograghy) :

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Allergology International(2004)53: 321–330Review Article
-Adrenergic receptors: Structure, regulation and signaling by partial and full agonists Hitoshi Kurose,Department of Pharmacology and Toxicology, Graduate School of Pharmaceutical Sciences,,Kyushu University, Fukuoka, Japan

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Katrin Kneipp 2007 ,new Approaches in biomedical spectroscopy , Oxford Univ Pr

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2. http://www.faqs.org/nutrition/Ca-De/Cardiovascular-Disease.html
3. http://www.doctorslounge.com/cardiology/drugs/beta_blocker/propranolol.htm
4. http://rmtcardiology.blogspot.com
5. Carlberg B, Samuelsson O, Lindholm LH (2004). "Atenolol in hypertension: is it a wise choice?". *Lancet* **364** (9446)

6. Sheetal Ladva (2006-06-30). "Updated NICE guideline on the management of hypertension in adults in primary care". National Institute for Health and Clinical Excellence.
7. Agon P, Goethals P, Van Haver D, Kaufman JM (August 1991). "Permeability of the blood-brain barrier for atenolol studied by positron emission tomography". *J. Pharm. Pharmacol.*
8. Wu A (November 2007). "Should beta-blockers still be used as initial antihypertensive agents in uncomplicated hypertension?". *Ann. Acad. Med. Singap.* **36** (11): 962–4.
9. *Patient Information Leaflet — Atenolol tablets BP*. CP Pharmaceuticals Limited. 2003.
10. http://asthmaguidebook.gsk.com/index.asp?fuseaction=asthma.proposed
11. http://asthmaguidebook.gsk.com/index.asp?fuseaction=asthma.B-salbut
12. http://en.wikipedia.org/wiki/Asthma
13. http://en.wikipedia.org/wiki/Salmeterol
14. http://ajrccm.atsjournals.org/cgi/content/full/160/1/244
15. **Foye's principles of Medicinal Chemistry.**
16. **Essentials of Medicinal Chemistry – 2nd edition.**
17.

Programs assist me in my research:

- **Accelrys DS visualiser.**
- **Chem3D Ultra.**
- **Chemdraw Ultra.**
- **LigandScout for pharmacophore .**
- **Molebro docker,pdb:1uzf,synthesis is from grahampatric,modified interaction on DS**