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Computational Chemistry, Drug Design, and Drug Re-Discovery Aimed at Theory-Directed Synthesis of Cannabinoids and Computational Methods to Predict Bioactivity from Ligand Structure

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Chemistry

by

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Dedicated to my mom for her unconditional love and support,

and my dad, the greatest man I've ever known.

ABSTRACT OF THE DISSERTATION

Computational Chemistry, Drug Design, and Drug Re-Discovery Aimed at Theory-Directed Synthesis of Cannabinoids and Computational Methods to Predict Bioactivity from Ligand Structure

by

Angie Garcia

Doctor of Philosophy, Graduate Program in Chemistry
University of California, Riverside, June 2012
Prof. Michael J. Marsella, Chairperson

The aim of this thesis is the discovery or re-discovery of drug-like compounds having therapeutic value; although two distinct strategies are reported, both share a strong dependence on computational chemistry.

The first project to be reported describes synthetic strategies applied to the synthesis of cannabinoids; successful strategies evolved from computational analysis of cannabinoid isomerization via pericyclic reactions. This project exemplifies a strategy designed to predict the best ligand for a specific receptor protein.

The second project reports our strategy to classify drugs according to their predicted indication. Here, structure of a drug-like compound is the only required input. The output will then report the indication class that is predicted to best describe the compound's drug-activity.

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Chapter 1

The Synthesis and Therapeutic Effects of Cannabinoids and their Analogues

1.1 Introduction

The discovery of cannabinoid receptors in the 1980's caused an increasing interest in cannabinoid synthesis.[1] This is largely due to the cannabinoids great therapeutic potential in areas like anxiety disorders, Parkinson's and Huntington's disease, multiple sclerosis, cancer, stroke, myocardial infarction, hypertension, and glaucoma.[2] Therapy for these diseases or conditions is achieved by developing a type of agonist or antagonist that targets one or both of the two main cannabinoid receptors. The following sections will focus on cannabinoid ligands, their therapeutic activity, and biosynthetic pathways. An emphasis will also be placed on Δ^1-THC and previous synthetic methods to this cannabinoid. The impact of side-chain modifications on biological activity will also be discussed.

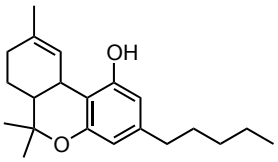
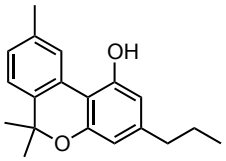
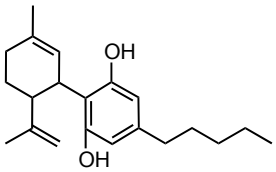
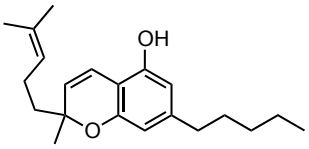
1.2 Cannabinoid Receptors

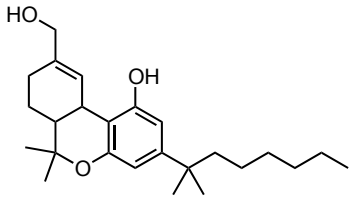
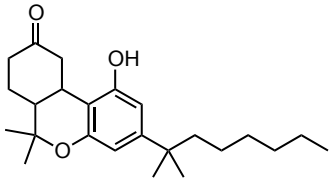
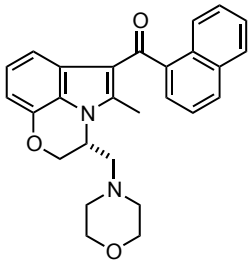
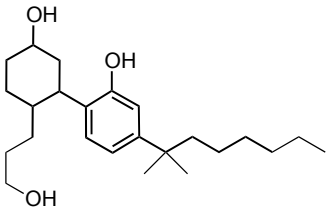
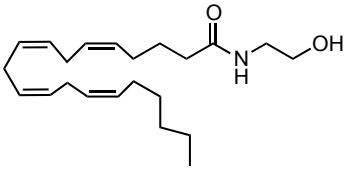
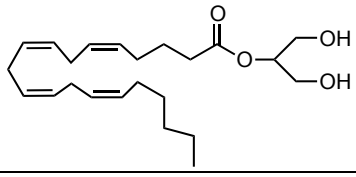
There are two main types of cannabinoid receptors. Cannabinoid receptor 1 (CB_1) is found predominantly in the central nervous system and cannabinoid receptor 2 (CB_2) is found more peripherally and seems to play a role in the immune system. They are G protein-coupled receptors and it has been predicted that both receptors have 44% similarity in amino acid sequence.[3,4] Evidence has shown that when activated, CB_1 receptors can mobilize arachidonic acid and close 5-HT_3 receptor ion channels.

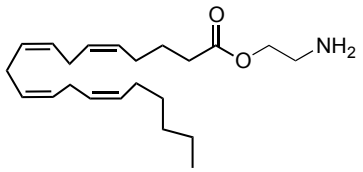
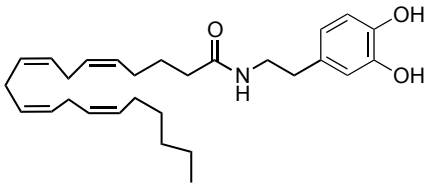
1.3 Cannabinoids and their Biological Activity

There are over 60 different types of cannabinoids that can be derived from the plant *Cannabis sativa*. These types of cannabinoids are considered the phytocannabinoids. Some examples can be found in Table **1.1**[2] along with any activity towards a cannabinoid receptor. There are also the synthetic cannabinoids, some of which are modeled after the phytocannabinoids, and the endogenous cannabinoids, which are produced within the body.

Table 1.1 Cannabinoids and their known receptor activity.[2]

Phytocannabinoids			
Entry	**Structure**	**Name**	**Activity**
1		Δ^1-tetrahydrocannabinol	CB_1 and CB_2 agonist
2		cannabivarin	CB_1 and CB_2 antagonist
3		cannabidiol	no activity
4		cannabichromene	no activity

Synthetic Cannabinoids			
5		(-) HU-210	activity at both CB_1 and CB_2
6		nabilone	activity at both CB_1 and CB_2
7		WIN 55,212-2	CB_1 and CB_2 agonist
8		(-) CP55940	CB_1 and CB_2 agonist
Endogenous Cannabinoids			
9		anandamide	CB_1 and CB_2 agonist
10		2-arachidonoyl	CB_1 and CB_2 agonist

11		*O*-arachidonoyl ethanolamine	CB_1 and CB_2 agonist
12		*N*-arachidonoyl dopamine	CB_1 and CB_2 agonist

Δ^1-Tetrahydrocannabinol (Δ^1-THC) is the most highly recognized cannabinoid. It is also known as Δ^9-THC, depending on the numbering scheme that is used (Fig. **1.1a**). This review will use the numbering of the structure found on the left side of Fig. **1.1a**. It is the cannabinoid found most abundantly in the cannabis plant. Its bioactivity is found in the (*R*,*R*)-*trans*-isomer of THC and is psychoactive (Fig. **1.1b**). It behaves as both a CB_1 and CB_2 agonist.[2]

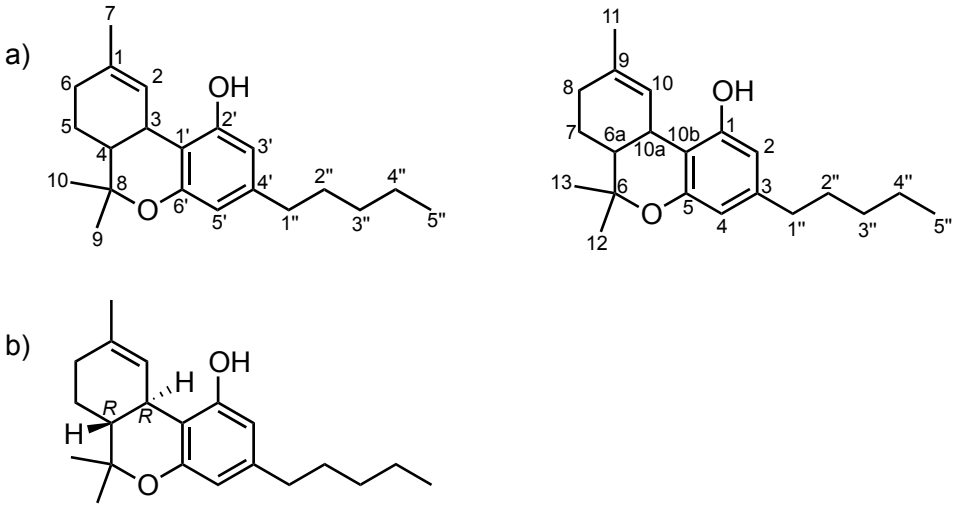


Figure 1.1 Δ^1-THC: a) different numbering schemes b) biologically active isomer.

Cannabivarin is found to be a cannabinoid receptor antagonist. (-)-Cannabidiol (CBD) is also a major component of the cannabis plant. While it does not show any cannabinoid receptor activity, analogues of this cannabinoid possess therapeutic effects as seen in some animal and human studies.[5] It is being investigated for its potential biological activity towards epilepsy and for its anti-inflammatory properties. In a mouse study, CBD was actually shown to antagonize two other cannabinoid agonists (WIN 55,212, CP 55,940) and one antagonist (SR 141716A).[5] Cannabichromene also lacks cannabinoid receptor activity, but appears to have antimicrobial effects. [6]

Cannabinoids have been shown to have an effect on disorders of the central nervous system (CNS). The high abundance of CB_1 receptors in the brain, in particular, its location in the cortex, cerebellum, hippocampus, and basal ganglia, have targeted conditions that affect movement as well as mood and anxiety disorders.[2] For example, cannabinoid HU-211, which is similar to HU-210 (Table **1.1**, entry 5), but has the double bond at position 6 instead of 1 (Fig. **1.1a**), has been shown to posses a protective effect in traumatic brain injury. In a rat model study, the cannabinoid was able to reduce brain damage as well as improve motor and cognitive function.[7,8] In another example, the brain levels of mice with closed head injury showed an increase in the endogenous cannabinoid, 2-arachidonoyl or 2-AG, (Table **1.1**, entry 10). An hour after the injury, administration of exogenous 2-AG, showed an infarct size reduction and ameliorated the neurological outcome. [9]

Anandamide (Table **1.1**, entry 9), 2-AG, and WIN 55,212-2 (Table **1.1**, entry 7) showed signs of protecting against ischemic strokes. Its major cause is the disruption of blood that is allocated to the brain due to the thrombotic occlusion of blood vessels. It can cause death and permanent disability to its victims. These cannabinoids guard against hypoxia and glucose deprivation which helps protect against the effects of the stroke.[10,11,12]

There has also been some therapeutic effects in multiple sclerosis (MS). MS is an inflammatory disease that affects the brain and spinal cord by slowing down or stopping nerve signals.[13] It affects about 2 to 5 million people worldwide[14] and symptoms often include tremor, cognitive and visual impairment, paralysis, difficulties in speech, loss of bladder control, and painful muscle spasms.[15] Based on an MS laboratory model in rats, THC was shown to lower CNS inflammation and improve survival rates against those that were administered the placebo.[16] HU-211 was also shown to stop inflammation in the brain and spinal cord of rats, leading to less objectionable symptoms.[17] In a separate mouse model, THC, WIN 55,212-2, and another cannabinoid (JWH-133) were found to diminish tremor and spasticity.[18]

Human studies for treating MS have also yielded promising results. There is a report that marijuana smoking can alleviate some of the symptoms of MS.[19,20] And when nabilone (Table **1.1**, entry 6) was administered to a single MS patient, there was an improvement in muscle spasms.[21] Furthermore, in a study containing almost 20 MS patients, subjects

reported a decline in spasticity and better bladder control when administered THC and CBD (Table **1.1**, entry 3).[22]

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a neurodegenerative disease that targets the brain and spinal cord. It eventually results in escalating weakness, paralysis, and early death.[23] However, based on a mouse model, THC appears to delay the progression of ALS if administered before or after visible signs of the disease. Mice that were treated with THC showed slowed motor impairment and an increase in their survival rate.[24]

Clinical studies on cannabinoid targets are ongoing as there is great therapeutic potential in a wide pool of compounds.

1.4 Cannabinoid-Based Drugs

There are currently several cannabinoid-based drugs on the market. As previously mentioned, the combination of THC and CBD showed therapeutic effects towards MS. This combination is actually marketed as Sativex® and is composed of marijuana extracts of THC and CBD in a 1:1 ratio. It is designed as a mouth spray for MS to deal with neuropathic pain and spasticity.

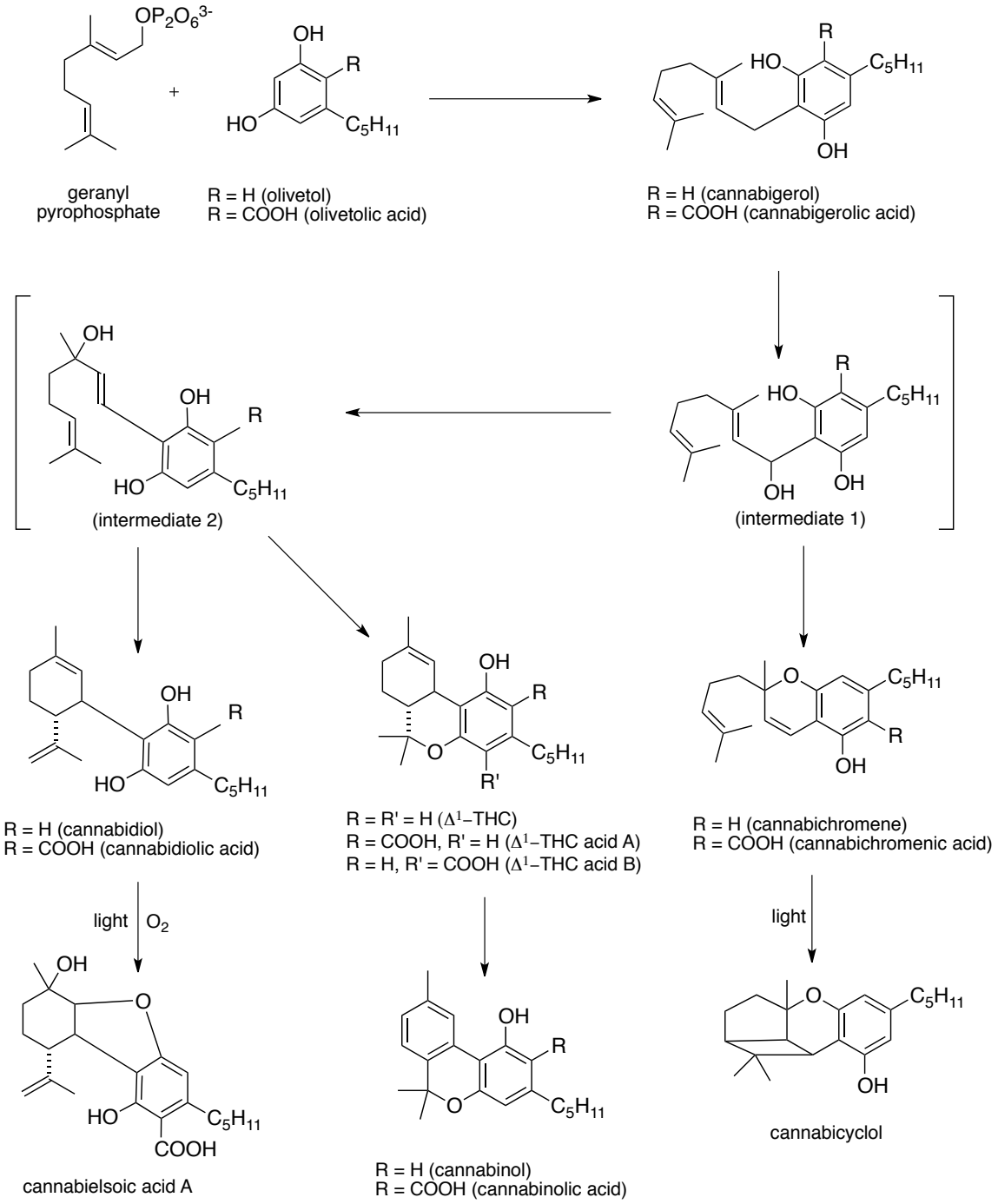
Marinol,® also known as dronabinol, is probably the most well known cannabinoid-based drug. It is made up of a synthetic version of the active isomer of THC and is found

in capsule form. Its main purpose is to relieve nausea and vomiting due to chemotherapy. It also helps to deal with the loss of weight and appetite in AIDS patients.

Another cannabinoid-based drug that also works as an antiemetic is Cesamet.® It is also found in capsule form and is composed of racemic nabilone, which is a synthetic cannabinoid that is structurally similar to THC.

1.5 The Biosynthetic Pathway of Cannabinoids

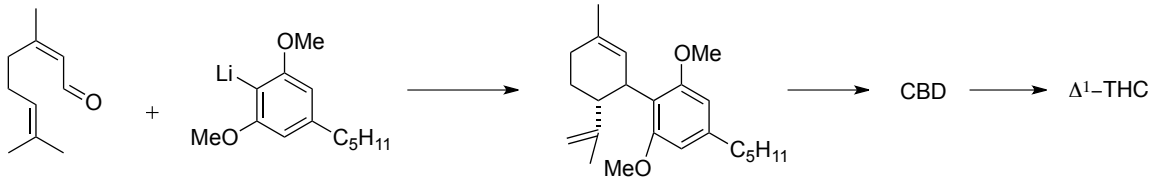
The actual biosynthetic pathway for the formation of cannabinoids in the cannabis plant is still under study. However, Scheme **1.1** gives a good idea of this process.[25] It is suggested that geranyl pyrophosphate and olivetolic acid form cannabigerolic acid. It then goes through the proposed intermediate 1, undergoes an allylic rearrangement to the proposed intermediate 2 to yield cannabidiolic acid, and can then form cannabielsoic acid A. Δ^1-THC acid A can then be directly obtained from cannabigerolic acid (through the same proposed intermediates), bypassing the formation of cannabidiolic acid, via an enzymatic oxidation-cyclization process.[26] It can then produce cannabinolic acid. Lastly, cannabichromenic acid can be obtained from the proposed intermediate 1, which can then produce cannabicyclol.[25]



Scheme 1.1 Cannabinoids and their biosynthetic pathway.

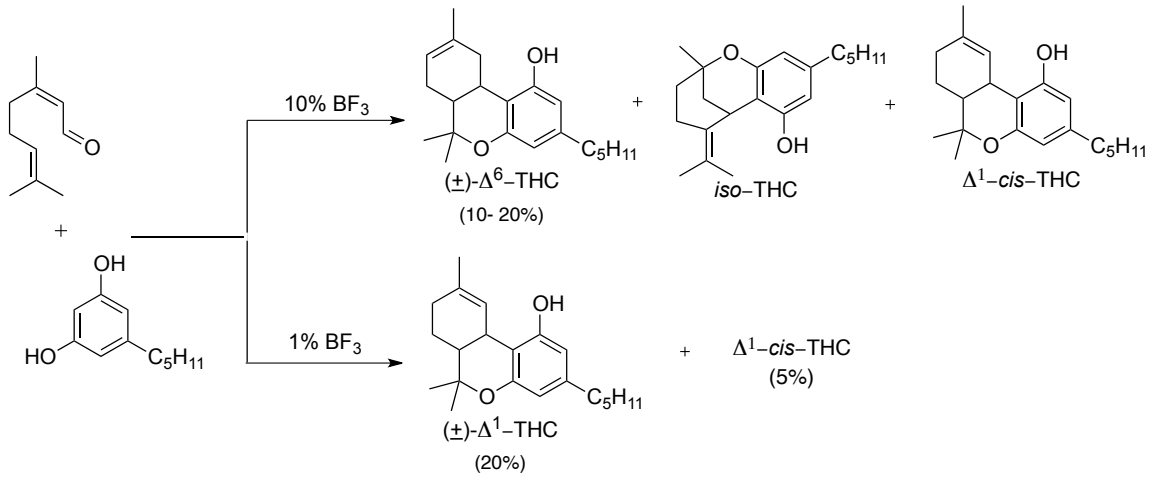
1.6 Previous Olivetol-Based Syntheses to Δ^1-Tetrahydrocannabinol (Δ^1-THC)

Previous syntheses to Δ^1-THC involve the use of olivetol at some point during the synthesis. The first synthesis was developed in 1965 (Scheme **1.2**). Reaction of citral with the lithium olivetol derivative produced the methoxy-protected cannabidiol compound. Then heating with methylmagnesium iodide gave racemic cannabidiol. Then continued heating with hydrochloric acid produced a mixture of starting material and racemic Δ^1-THC in a 2% overall yield.[27]



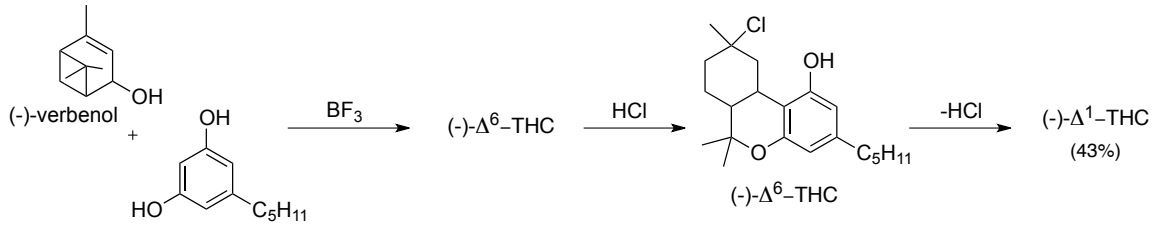
Scheme 1.2 The first synthesis to *rac*-Δ^1-THC.

Another synthesis by Mechoulam and co-workers leading to *dl*-Δ^1-THC used olivetol and a catalytic amount of boron trifluoride (BF_3). The amount of BF_3 that was used had an affect on the number and types of products (Scheme **1.3**). Using 10% BF_3 produced a racemic mixture of Δ^6-THC with trace amounts of Δ^1-THC that was not easy to isolate, as well as *iso*-THC and the *cis*-isomer of Δ^1-THC. However, decreasing the amount of BF_3 to just 1%, produced Δ^1-THC as a racemic mixture in 20% yield, along with some of the *cis*-isomer.[28]



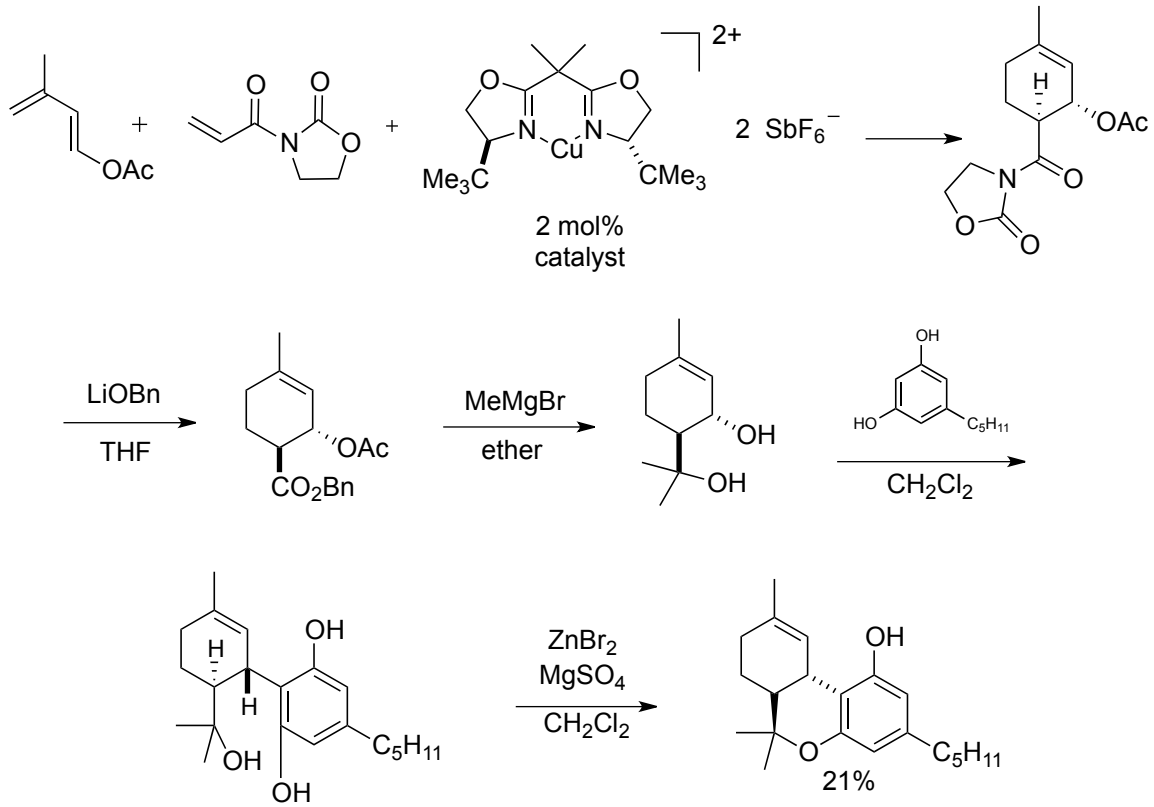
Scheme 1.3 BF_3 route to (±) Δ^1-THC and isomers.

Eventually, an attempt was made to synthesize only the naturally occurring isomer of Δ^1-THC (Scheme **1.4**). Using (-)-verbenol , instead of citral, produces (-)-Δ^6-THC, which is then treated with acid to produce the chloro-hexahydrocannabinol. Dehydrochlorination will then produce (-)-Δ^1-THC in a 43% overall yield. In a similar fashion, use of (+)-verbenol will result in (+)-Δ^1-THC.[28]



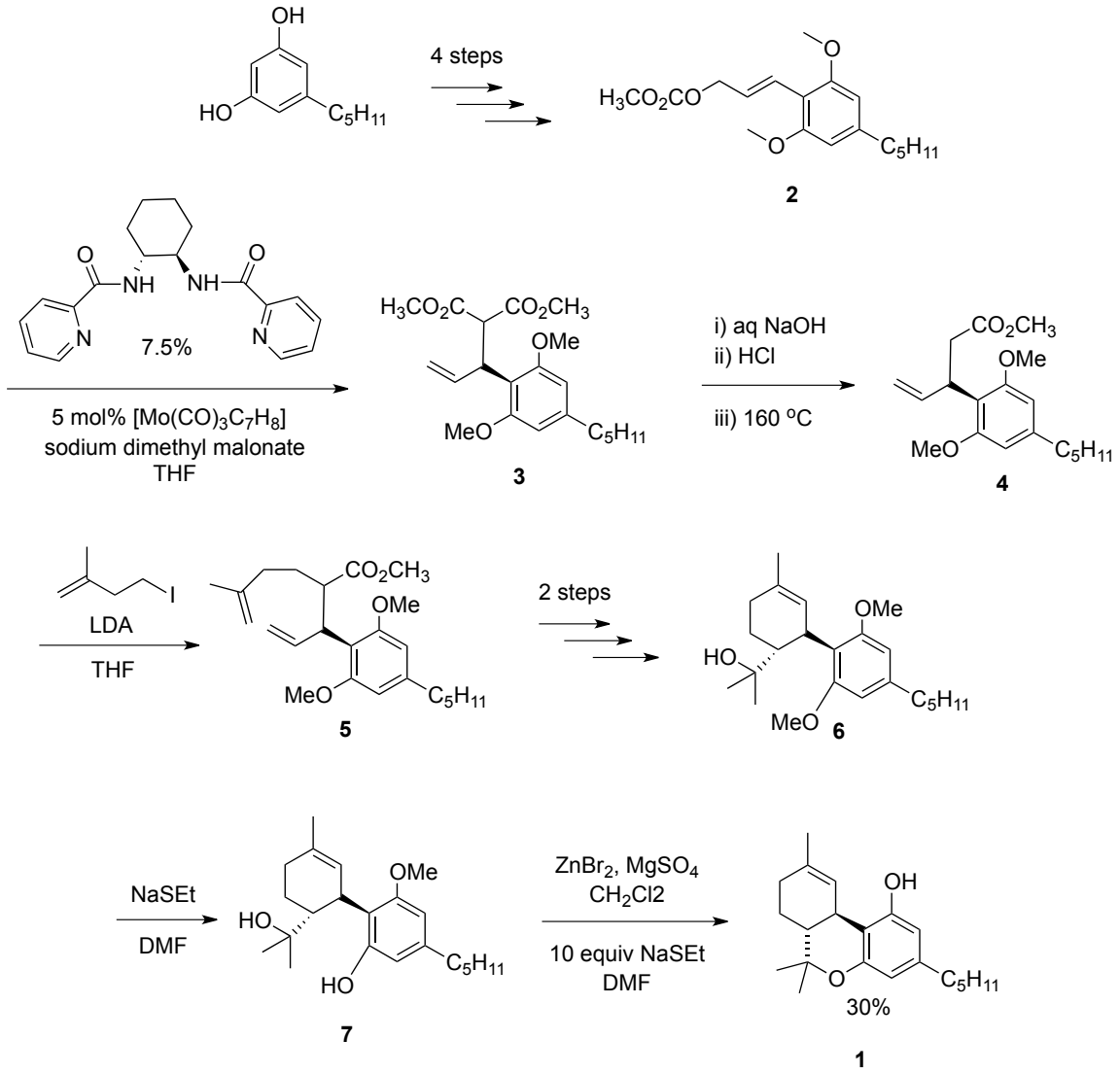
Scheme 1.4 Synthesis of (-) Δ^1-THC.

Evans and Trost have also designed olivetol-based syntheses. In 1997, Evans and co-workers used a cationic bis(oxazoline)copper (II) catalyst, to synthesize the non-active (*S*,*S*)-isomer of Δ^1-THC (Scheme **1.5**).[29] This was the first asymmetric synthesis that utilized an enantioselective Diels-Alder reaction. This was achieved by reacting the diene and acrylamide, along with the selected Cu(II) catalyst, resulting in the shown cycloadduct. LiOBn was then used to cleave the imide, which was then treated with methylmagnesium bromide to give the diol. At that point, reaction with olivetol and *p*-TSA produces the triol, which is then cyclized to give (*S*,*S*)- Δ^1-THC in an overall yield of 21%.[29]



Scheme 1.5 Evans synthesis to (*S*,*S*)- Δ^1-THC.

Then in 2007, Trost introduced his synthesis of enantioselective Δ^1-THC with an overall yield of 30% via a molybdenum-catalyzed asymmetric allylic alkylation reaction (Scheme **1.6**).[30] This synthesis also allows for creation of THC analogues by substituting compound **2** for other aromatic derivatives as well as the alkylating reagent that results in compound **5**. The synthesis starts with olivetol to make the desired aromatic compound in four steps. Then, along with the chiral ligand, the molybdenum catalyst is added to afford compound **3**. Treatment with aqueous sodium hydroxide and hydrochloric acid then yields compound **4**. Alkylation then proceeds using the selected iodide and lithium diisopropylamide to yield compound **5**, which is eventually converted to the alcohol over two steps. Next, NaSEt is used to selectively deprotect one of the hydroxyl groups. The reaction then proceeds to yield (*R*,*R*)- Δ^1-THC synthesis when treated with zinc bromide, magnesium sulfate, and NaSEt one last time.[30]

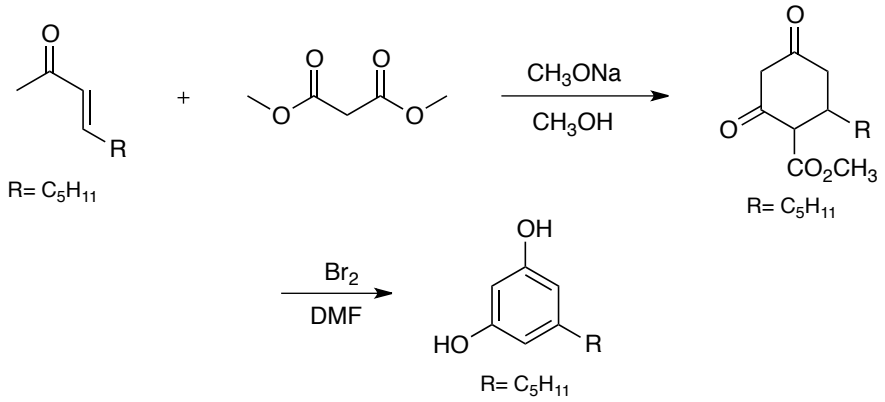


Scheme 1.6 Trost's (*R*,*R*)- Δ^1-THC synthesis.

These syntheses make it difficult to design analogues of Δ^1-THC that include facile substitution of the bioactive R-group, a pentyl sidechain attached to the aromatic ring. This is mainly due to the fact that analogues are usually made via resorcinol derivatives.

1.7 Synthesis of Olivetol and Potential Derivatives

Focella and co-workers synthesize olivetol by taking 3-nonen-2-one and reacting it with dimethyl malonate using sodium methoxide in methanol (Scheme **1.7**).[31] The synthesis allows for the development of analogues through substitution of the α**,** β-unsaturated ketone. However, one of the major drawbacks of this synthesis involves aromatization of the 1,3-cyclohexanedione. The purification process can take days and small amounts of impurities often remain. Also, most of the desired α**,** β-unsaturated ketone are not commercially available; therefore the synthesis may need to proceed with additional steps.



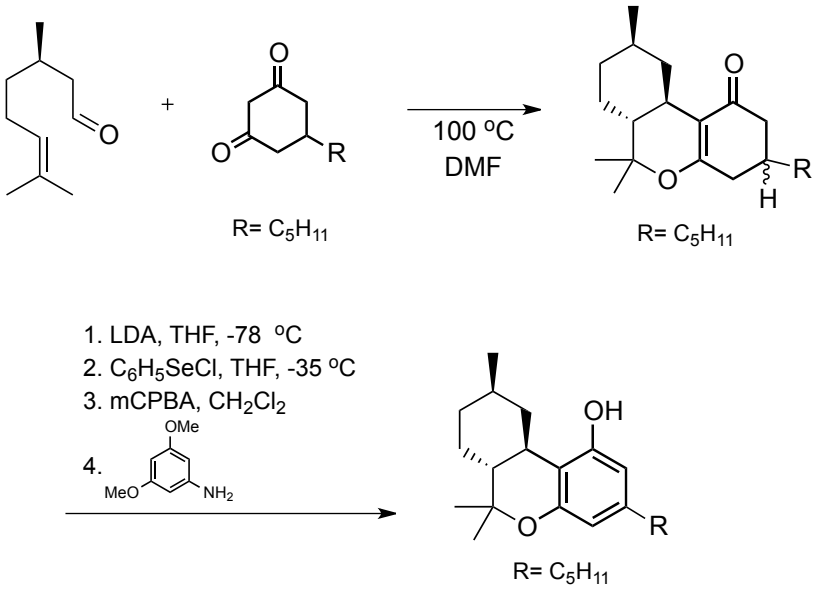
Scheme 1.7 Focella's synthesis to olivetol.

1.8 Alternatives to Olivetol

Alternatives to olivetol are highly desired, not only because of the difficulty with purification after aromatization, but because the scope of potential analogues is

dependent on the commercial availability of the desired α, β-unsaturated ketone or the degree of difficulty in synthesizing the starting material. It would also be difficult to start off with 1,3-dihydroxybenzene. Since the starting material would be ortho/para directing, it would be difficult to target the meta position with a different R group.

Tietze has shown that you can use analogues of the 1,3-cyclohexanedione to synthesize analogues of THC and then aromatize as a last step (Scheme **1.8**).[32] (*R*)-citronellal and 5-*n*-pentyl-1,3-cyclohexanedione are heated in DMF at 100 °C to yield the non-aromatic THC analogue. Then deprotonation with LDA and reaction with phenylselenium chloride provides a selenide intermediate (not shown). Upon oxidation with *m*-chloroperbenzoic acid the selenium oxide is obtained (not shown) and lastly, a *syn*-elimination yields the aromatic THC analogue.



Scheme 1.8 Tietze's synthesis to aromatic THC analogues.

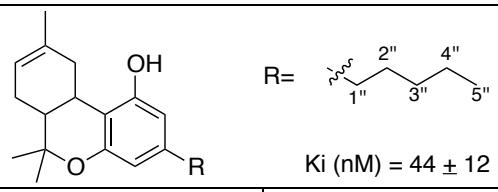
1.9 Modifications to the Side Chain

The most desired analogues model after Δ^1-THC and simply differ at the alkyl side-chain. Looking at Table **1.1**, it is evident that the cannabinoids have different types of side-chains at position 4', whether it be length of the chain or any substituent branching off of it (Fig. **1.1a**). It is known that the type of side-chain can have a definite impact on a cannabinoid compound's biological activity and a better representation of the types of modifications can be found in Table **1.2**.

It has been found that in order to produce any type of activity the chain must be at least three carbon atoms long, with the optimal length being between five to seven carbon atoms long.[5] Branching of the side chain at the 1" position (Fig. **1.1a**) with two methyl groups has been shown to increase activity. A 1",2"- dimethylheptyl side chain has also shown high affinity for the receptor. Most of these SAR studies have been performed using Δ^6-THC since it has been found easier to synthesize and its potency and activity is still similar to Δ^1-THC.[5]

Table **1.2** compared binding affinity data for some Δ^6-THC analogues, modified at the R group side-chain. The analogues were bound to the CB_1 receptor preparation of a rat cortex. The binding affinity for Δ^6-THC (K_i) was found to be 44 + 12 nM.[33] By looking at Table **1.2**, the ones with a lower K_i value than Δ^6-THC posses better binding affinity.

Table 1.2 Δ^6-THC side chain modification K_i values. Shown in parenthesis in nM.[33-43]



Ki (nM) = 44 ± 12

	A	B	C	D
1	(7.6 ± 0.6)	(20 ± 4)	(19 ± 5)	(11 ± 1)
2	(38 ± 3)	(53 ± 1)	(141 ± 52)	(0.46 ± 0.04)
3	(0.60 ± 0.15)	(0.84 ± 0.21)	(0.81 ± 0.08)	(0.77 ± 0.11)
4	(2.17 ± 0.46)	S S (0.32 ± 0.08)	O (21.7 ± 7.1)	OH (86.4 ± 17.9)
5	Br (10.8 ± 1.8)	I (11.0 ± 3.4)	CF_3 (34.9 ± 8.1)	F (81.0 ± 3.5)
6	Br (0.43 ± 0.09)	CN (0.36 ± 0.14)	CN (0.6 ± 0.05)	O N (0.86 ± 0.06)
7	O N–N H (1.2 ± 0.2)	(4 ± 1)	(11 ± 1)	N_3 (2.85)

As previously mentioned, branching the alkyl chain was shown to improve affinity, as represented by the lower K_i values (Table **1.2**, examples **1A**- **1D**). However, once the branching starts at the 3" of the side chain, affinity starts to decrease (higher K_i). Although analogue **2A** is still somewhat more active than Δ^6-THC, its isomer, analogue

2B, is actually worse than Δ^6-THC. Further extending into the 4" position (example **2C**) makes the analogue's affinity three times as bad as that of Δ^6-THC. The addition of an extra methyl group (examples **3A**-**4A**) greatly improves affinity and seems to produce the optimal analogue. With the exception of fluorine (**5D**), halogens (**5A** and **5B**) seem to improve affinity and when combined with a gem dimethyl (**6A**), the analogues further increase in affinity. Amides (**6D** and **7A**) and some acetylenes (**7B** and **7D**) show good affinity, while ketones (**4C**), and hydroxyl groups (**4D**) do not. However, the best affinities were seen with the addition of a dithiolane (**4B**) and the cyano- *gem*-dimethyl (**6B**) and are found to be potent CB_1 agonists.[41] Therefore, optimal affinity is reached with a seven-carbon atom chain and a bulky group at the 1" position.[33]

Based on these SAR studies, the ideal analogue contains a side-chain that allows itself to loop back towards the phenolic ring it is attached to. This will allow for optimal receptor affinity and potency.[5]

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Chapter 2

The Design, Synthesis, Computational Analysis, and *in silico* and Biological Screening of Cannabinoids and their Analogues

2.1 Introduction

The great therapeutic potential of cannabinoids and their analogues has caused much interest in finding more efficient methods that allow facile development of these analogues. Focusing on the thermal isomerization of cannabinoid analogues and using the most well known cannabinoid, Δ^1-THC, as a starting point, we built off of the seminal work of Tietze. Then, based on computational docking studies, we later discovered that aromaticity was not essential for CB_1 receptor affinity and that all isomers of Δ^1-THC showed a similar affinity for the receptor. Besides *in silico* screening, our cannabinoid analogues were also biologically screened and preliminary studies showed they possessed therapeutic potential towards ALS.

2.2 Isomerization of Cannabinoids and its Effects

Our interest in thermal isomerization of cannabinoid analogues stems from a N.Y. State Psychiatric Institute report that compared behavioral effects between cannabis smokers and those who were orally administered equivalent dosages of Δ^1-THC after they abruptly quit. It was found that there was a significantly higher observation of withdrawal symptoms in the cannabis smokers versus those of oral intake.[1]

As mentioned in the previous chapter, marijuana is composed of a mixture of several cannabinoids including Δ^1-THC, CBD, and CBC. Currently, there are few studies on the thermolysis product resulting from smoking marijuana. If marijuana were heated along with tobacco, we would see an increase in THC at the expense of CBD, as CBD is known

to convert to THC. A representation of this can be found in Figure **2.1**. Based on results to be discussed, it is also proposed that if Δ^1-THC were heated by itself, as in the process of smoking marijuana, there will be an increase in the amount of Δ^1-THC at the expense of CBC in the form of all stereoisomers (Fig. **2.1**). However, if Δ^1-THC is taken orally, for example as in the form of Marinol®, only the *trans*-(*R,R*) isomer of Δ^1-THC is consumed since this form of intake does not require heating.

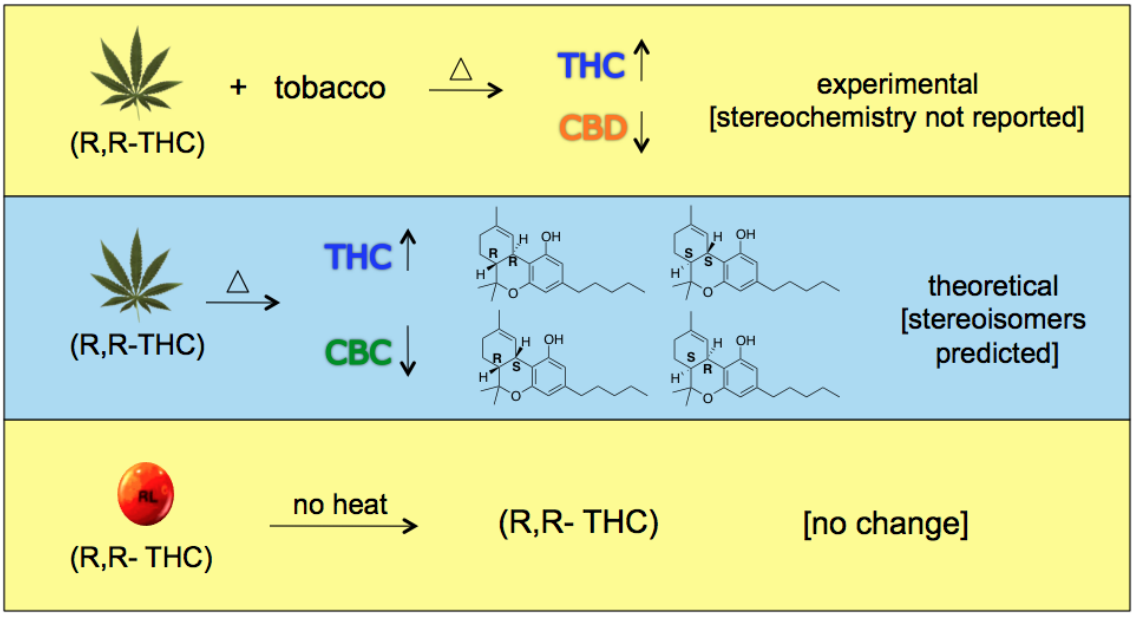


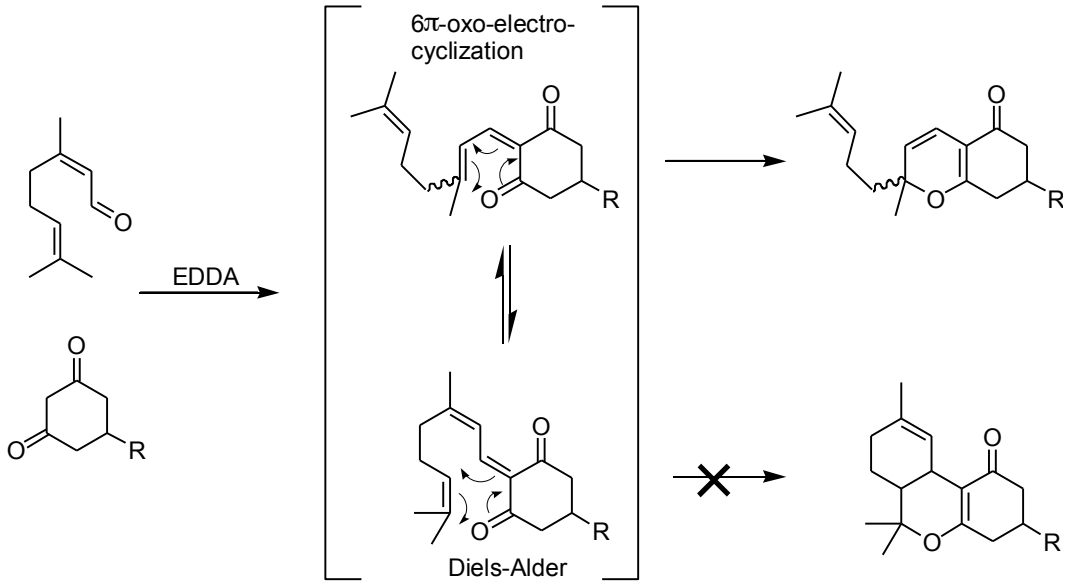
Figure 2.1 Isomerization Effects.

Therefore, we are predicting that the formation of the unnatural isomers of Δ^1-THC during the process of smoking marijuana could be the cause of the withdrawal symptoms. While no human studies reported on the effects of these unnatural isomers of Δ^1-THC

currently exist, there is evidence for the isolation of the unnatural, *cis*- isomer of Δ^1-THC from confiscated marijuana, based on routine analysis.[2]

2.3 Thermal Isomerization of Cannabinoid Analogues.

In synthesizing these cannabinoid analogues, we have built off of Tietze's work and adopted the concept of a tandem Knoevenagel – Diels-Alder cascade reaction.[3] In our synthetic plan, non-aromatic analogues of CBC and THC (CBC_{an} and THC_{an}) share the same intermediate Knoevenagel product. The product depends on the competition between a Diels-Alder reaction and an oxo-6π electrocyclization (Scheme **2.1**).



Scheme 2.1 The oxo-6π electrocyclization reaction versus the Diels-Alder.

Trauner provides evidence that EDDA catalyzes both the Knoevenagel reaction and the oxo-6π-cyclization.[5] To investigate this further, we performed a computational analysis using Spartan, a molecular modeling and computational program, at B3LYP/6-31G* level of theory.[6] Starting materials, products, and transition states associated with Scheme **2.1** were studied and predict the transition state for the oxo-6π-electrocyclization (no EDDA) to be lower in energy than both the *cis*- and *trans*- Diels-Alder transition states. However, THC_{an} product is thermodynamically favored over CBC_{an} by ca. 13 kcal/mol (Fig. **2.2**). Given this prediction, we targeted thermodynamic control of this reaction.

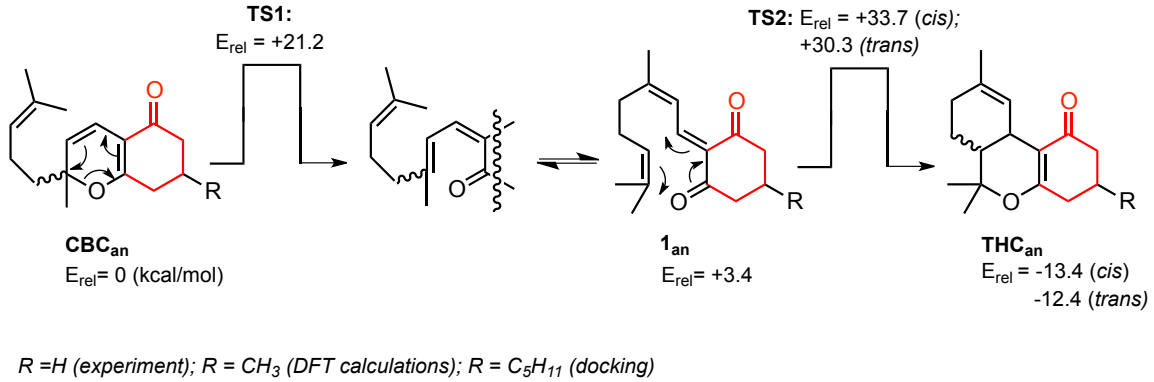
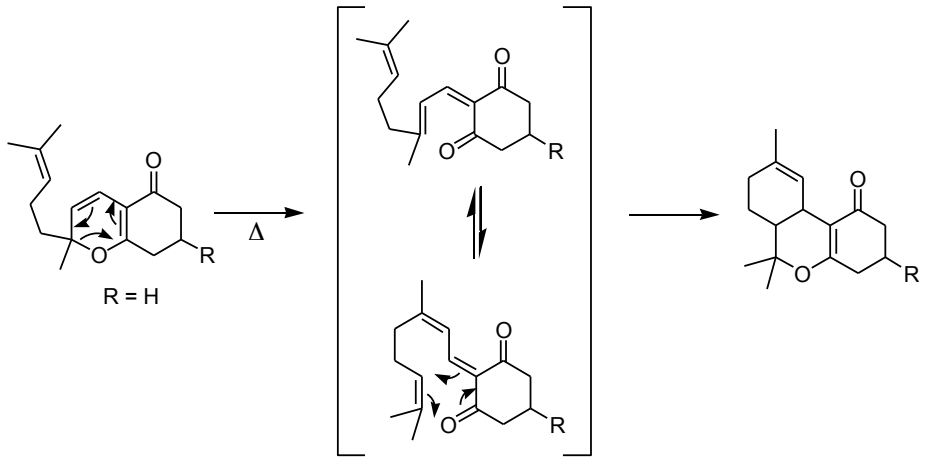


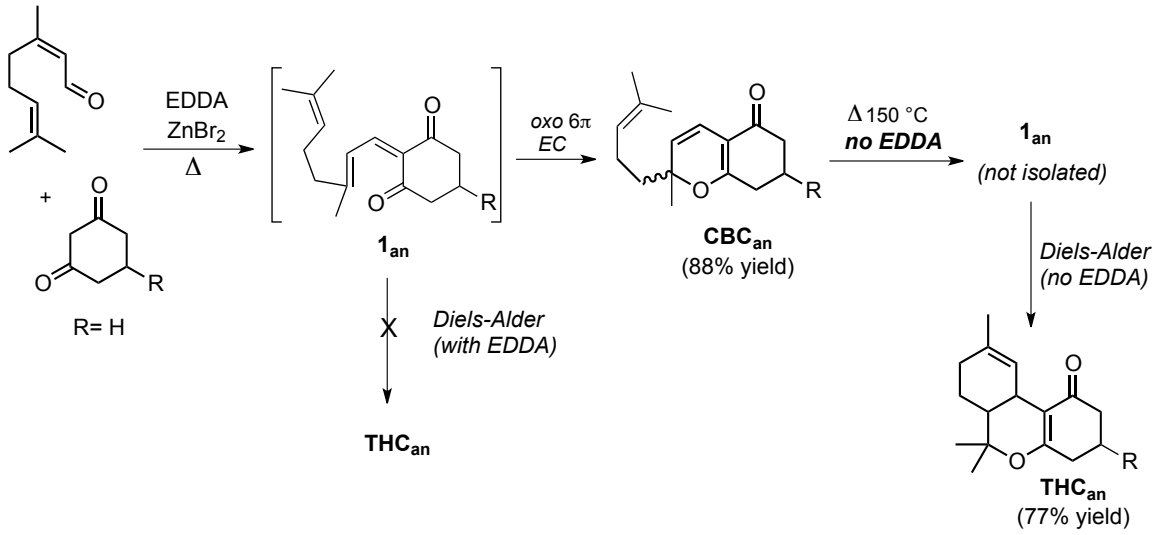
Figure 2.2 Spartan calculations (B3LYP/6-31G*) for starting material, products, and transition states of compounds found in Scheme 2.1.

By adsorbing CBC_{an} onto silica and heating to 150 °C, CBC_{an} was cleanly converted to a mixture of *cis*- and *trans*- Δ^1-THC_{an} (Scheme **2.2**). This result established a previously unknown thermal conversion between two phytocannabinoid analogues, CBC_{an} to THC_{an}.



Scheme 2.2 Thermal isomerization.

Scheme **2.3** then shows the complete THC_{an} synthesis. Reaction of citral and a 1,3-cyclohexanedione, catalyzed by $ZnBr_2$ and ethylenediamine diacetate (EDDA) results exclusively in a tandem Knoevenagel – oxo-6π-electrocyclization to afford CBC_{an} in excellent yield. CBC_{an} is then isomerized to Δ^1-THC_{an} at 150 °C.[4]



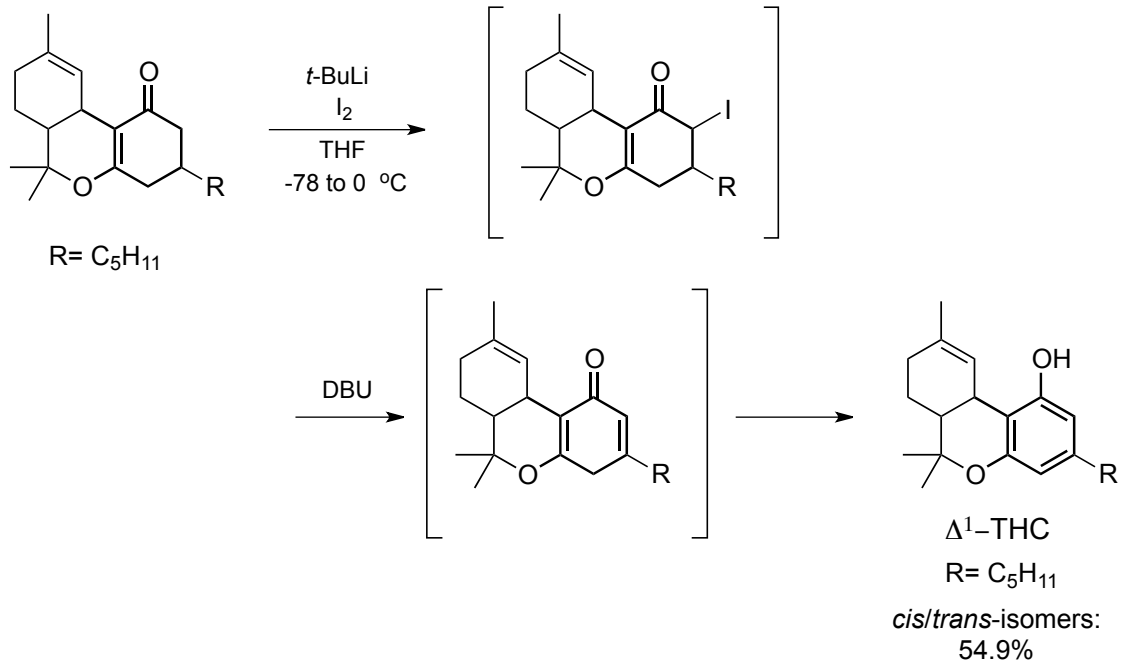
Scheme 2.3 Synthesis of Δ^1-THC analogue.

When looking at the synthesis, it is important to note that we cannot directly heat the reaction to 150 °C and obtain THC_{an} without first isolating CBC_{an} and to prove that, we ran two thermal isomerization reactions (Table **2.1**). The first followed the standard procedure of adsorbing CBC onto silica and the second was adsorbed onto an admixture of silica and EDDA. Both reactions were heated side-by-side at 150 °C for 40 minutes. Reaction one showed full conversion of CBC_{an} to THC_{an}. In reaction 2, when you adsorb CBC_{an} onto an admixture of silica and EDDA, you get a mixture of CBC_{an} and THC_{an} in a 1:2 ratio. Even continued heating of reaction 2 for another 40 minutes, will not result in full conversion to THC_{an}. Therefore, EDDA lowers the reaction rate. We also cannot completely eliminate EDDA from the reaction. Repeating the reaction in the absence of EDDA does not produce CBC_{an} in any amount; only starting materials are obtained.

Table 2.1. Thermal isomerization comparison reactions: the affects of EDDA.

Reaction	**Adsorbent**	**Time** (minutes)	**Temperature** (°C)	**CBC_{an}: THC_{an} ratio**
1	silica	40	150	0:1
2	admix mass ratio: silica (98): EDDA (2)	40	150	1:2

Aromatization of THC_{an} was then achieved by using *t*-BuLi and iodine to iodinate alpha to the carbonyl. Elimination with 1,8-Diazabicycloundec-7-ene (DBU) then allows the compound to tautomerize to Δ^1-THC in a mixture of *cis* and *trans*- isomers (Scheme **2.4**).



Scheme 2.4 Aromatization of Δ^1-THC_{an} to Δ^1-THC.

Similar energy calculations were also performed for CBC and Δ^1-THC (Fig. **2.3**). The results followed a similar trend, favoring Δ^1-THC as the thermodynamic product and leading to our proposition that CBC can thermally isomerize to Δ^1-THC during the process of marijuana smoking.

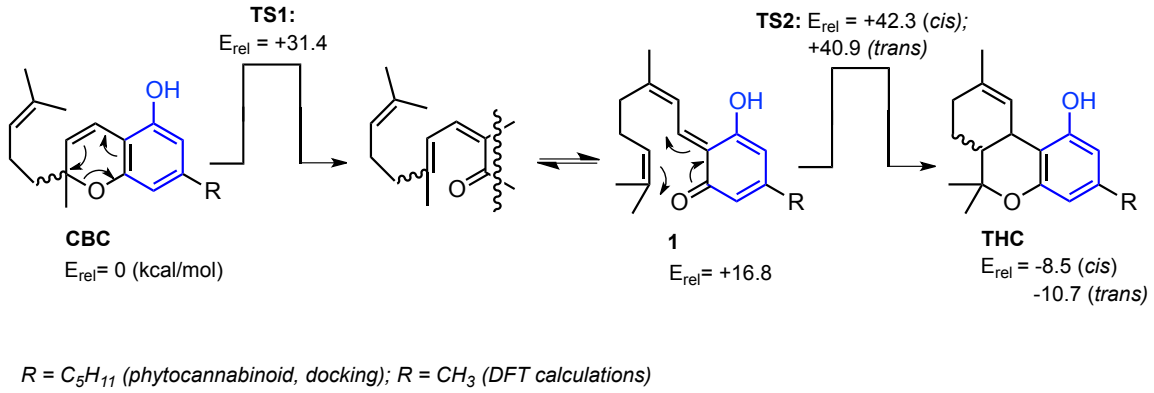
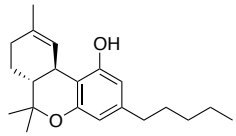
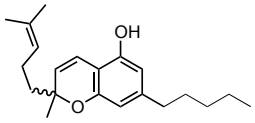
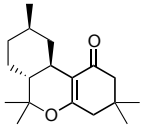
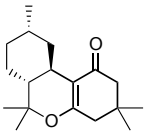
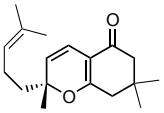
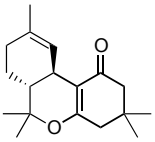
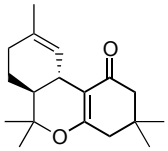
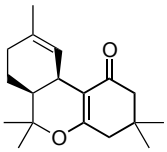
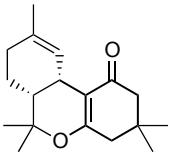


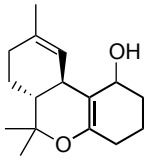
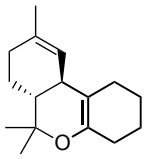
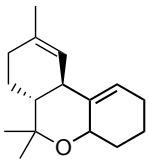
Figure 2.3 Spartan calculations (B3LYP/6-31G*) for starting material, products, and transition states for the aromatic version of compounds found in Scheme 2.1.

2.4 Cannabinoid Analogues

Computational docking using the molecular modeling program PyRx,[7] was used to established different cannabinoid analogues. Using an X-ray crystal structure or homology model of a protein, in this case CB_1, we can test the potential of the ligand to bind to the protein.[8] Table **2.2** shows the CB_1 receptor affinity of these analogues and compares them to that of Δ^1-THC (entry 1), which has known therapeutic activity for the CB_1 receptor. Any score that is equal or lower (higher negative number) in value to that of Δ^1-THC is considered to have good affinity for the CB_1 receptor.

Table 2.2 CB_1 receptor binding affinity for Δ^1-THC and other cannabinoid analogues.

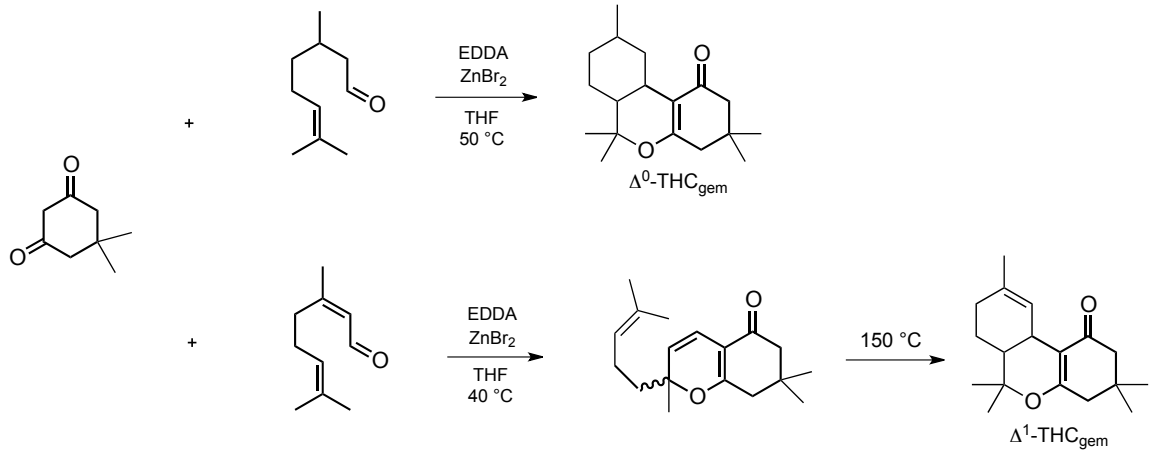
Entry	**Compound**	**Binding Affinity (kcal/mol)**
1		-7.0
2		-6.0
3		-7.4
4		-7.3
5		-6.2
6		-7.6
7		-7.3
8		-7.8
9		-7.6

10		-6.9
11		-7.3
12		-6.6

Entries **3** and **4** (Table **1**) show the binding affinity for isomers of the same compound to be -7.4 and -7.3 kcal/mol, respectively, and higher than that of Δ^1-THC (-7.0 kcal/mol). Entries **6-9** show the binding affinities for the Δ^1-version of this analogue and most show a significantly higher affinity for the CB_1 receptor, with entry **8** showing the greatest affinity (-7.8 kcal/mol).

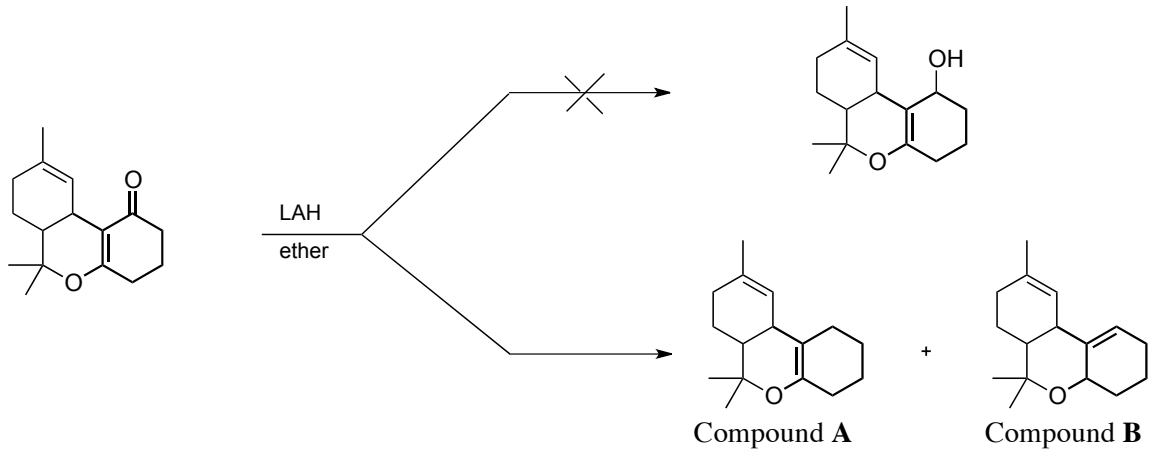
The syntheses of these analogues follow similar synthetic methods. Substitution of 1,3-cyclohexanedione with 5,5- dimethyl-1,3- cyclohexandione, and reaction with citronellal produces the THC- *gem*-dimethyl analogue (Δ^0-THC_{gem}), shown in Scheme **2.5**. Synthesis of Δ^1-THC_{gem} follows a similar pathway as THC_{an}, which also proceeds via a CBC analogue (Scheme **2.5**). A previous synthesis to this CBC intermediate analogue (CBC_{gem}) currently exists, however it involves the use of a synthetically prepared phosphoric acid and reaction in methylene chloride to yield the chromene in 95% yield.[9]

The previously known chromene was then adsorbed onto silica, following our established procedure, and isomerized to the Δ^1-THC analogue in quantitative yield as a mixture of *cis* and *trans*- isomers.



Scheme 2.5 Synthesis of THC-*gem*-dimethyl analogues.

Another interesting reaction involves reducing Δ^1-THC$_{an}$ with an excess amount of lithium aluminum hydride (LAH) to produce a mixture of the tricyclic compounds (Scheme **2.6**). The initial target was the alcohol shown as entry **10** (table **1**) with an estimated binding affinity of -6.9 kcal/mol, still relatively close to that of Δ^1-THC.



Scheme 2.6 LAH reduction.

However, this did not undergo the expected reduction. The excess LAH causes complete removal of the oxygen atom to produce compounds **A** and **B** in a ratio of 4:1, with the major of these two products showing higher CB_1 affinity than the initial alcohol target and Δ^1-THC.

2.5 Computational Docking Studies

Our previously mentioned hypothesis targeting unnatural cannabinoid isomers as the origin of withdrawal symptoms contributed to our collaboration with Dr. Chia-En Chang at UCR. Computational docking analysis found little difference in CB_1 receptor affinity among natural and unnatural THC isomers.[4] By looking at Fig. **2.4** we can see that, when aligning the global minimum-energy conformers of all isomers of Δ^1-THC_{an} (where R= C_5H_{11}), the pentyl side-chain in extended outward for all isomers.

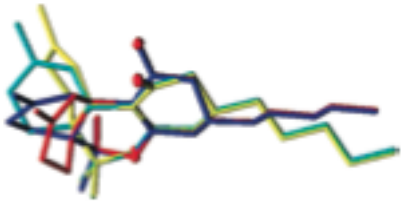


Figure 2.4 Alignment of Δ^1-THC$_{an}$ stereoisomers, showing pentyl side-chain in extended conformation for all isomers. Blue, *trans*-(*R*,*R*); cyan, *trans*-(*S*,*S*); yellow, *cis*-(*R*,*S*); red, *cis*-(*S*,*R*).

Using a modeled CB_1 receptor, the minimum-energy conformers for all stereoisomers of Δ^1-THC and Δ^1-THCan were docked to compare their interaction energies. The best ranked conformer of the naturally occurring (*R*,*R*)- Δ^1-THC stereoisomer is shown docked to the CB_1 receptor in Fig. **2.5**. The ligand interacts with both aromatic and hydrophobic residues and the binding is predominantly motivated by attractive van der Waals interactions. The interaction energies of (*R*,*R*)- Δ^1-THC and (*R*,*R*)- Δ^1-THC$_{an}$ were then compared and found to be similar with a ΔE of approximately -34 kcal/mol.[4]

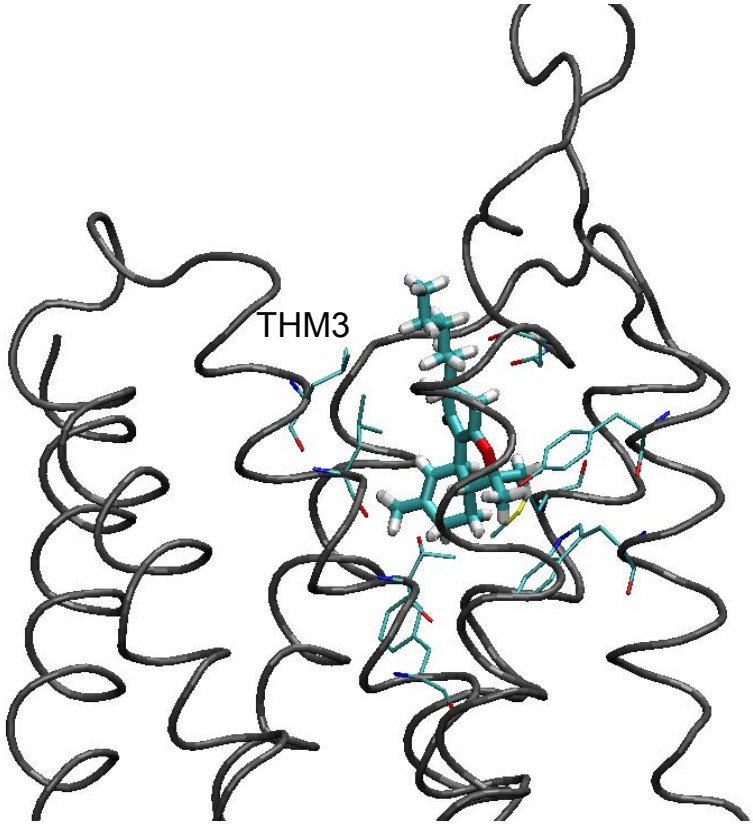


Figure 2.5 (*R*,*R*)-Δ^1-THC_{an} docked into a modeled CB_1 receptor. The receptor is represented by the gray tube while residues interacting with the ligand (cyan) are represented by thin line.

The high negative value is due to the fact that our calculations did not include entropy losses and the electrostatic desolvation penalty. However, since the structures of both Δ^1-THC and Δ^1-THC_{an} are similar it suggests that the entropy and desolvation are alike.[4]

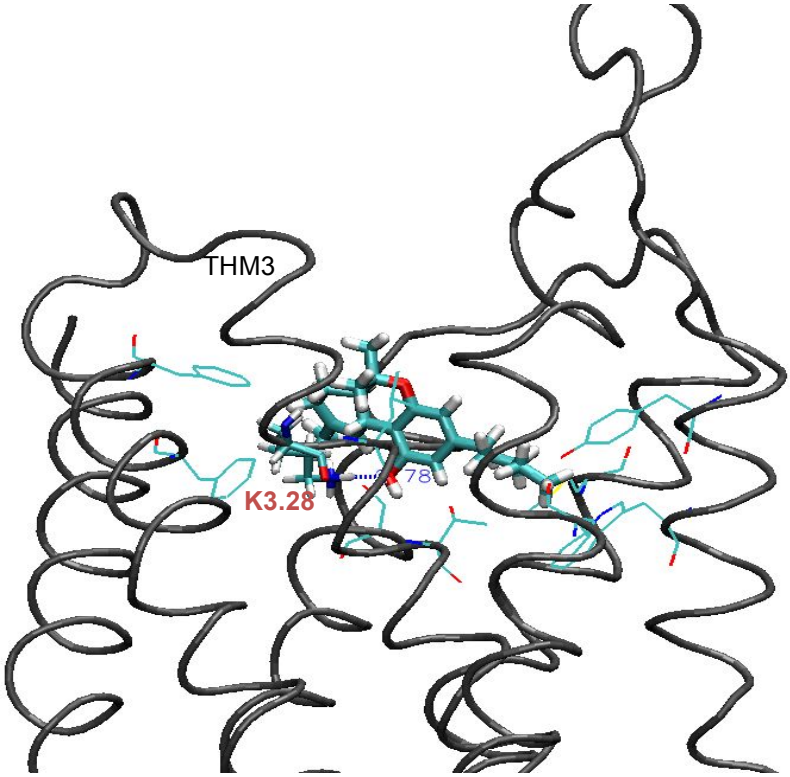


Figure 2.6 (*R*,*R*)-Δ^1-THC docked into a modeled CB_1 receptor. The receptor is represented by gray tube while interacting residues are represented by thin line. Ligand shown in cyan.

Figure **2.6** shows the phytocannabinoid, (*R*,*R*)-Δ^1-THC docked to the same modeled CB_1 receptor. The docking results were found to be similar to earlier findings.[8] There is a predicted hydrogen bond between the phenolic hydrogen of (*R*,*R*)-Δ^1-THC and residue K3.28 (192), containing an N-O distance of approximately 2.78 Å. Figure **2.7** then shows how the pentyl side-chains of the most stable conformers face opposing directions when docked to the receptor, while the ring part of the compounds interact with the residues, T3.33 (197), Y5.39 (275), W5.43 (279), and M6.55 (363).[4]

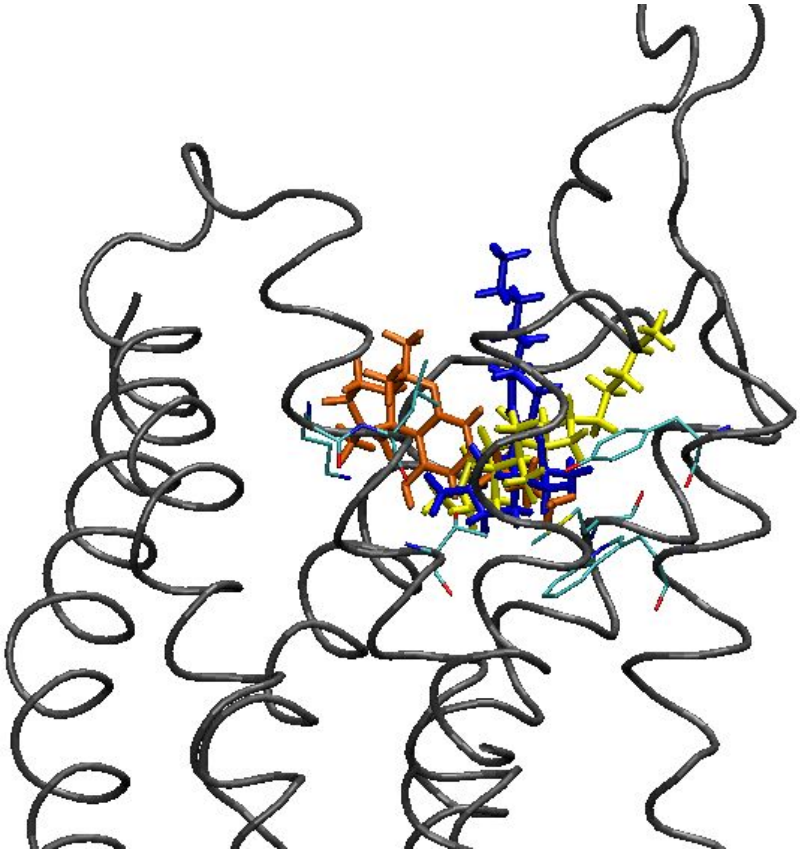


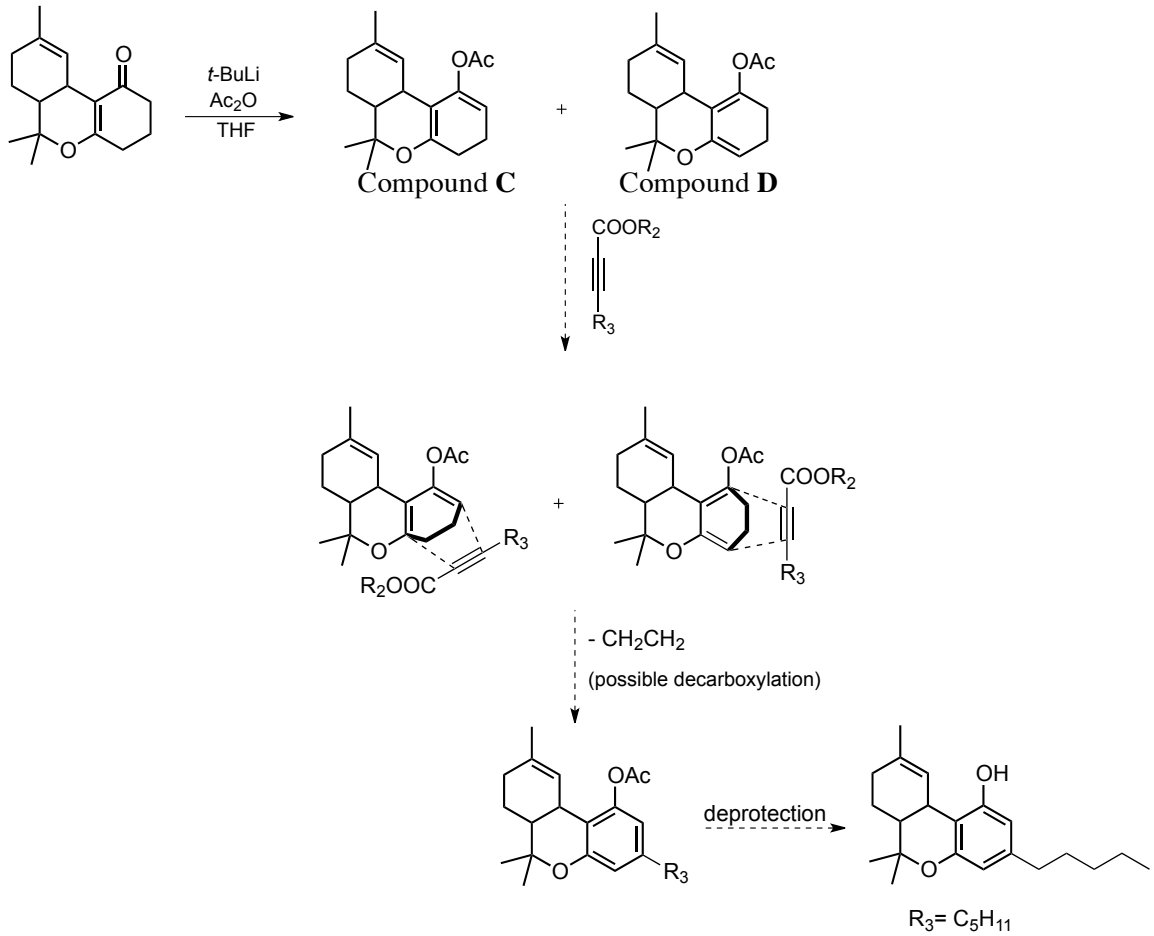
Figure 2.7 *Trans*-(R,R)-THC_{an} (blue), *cis*-(R,S)-THC_{an} (yellow), and *trans*-(R,R)-THC (orange) docked to the modeled CB1 receptor.

The *cis*-(R,S)- Δ^1THC_{an} and *cis*-(S,R)- Δ^1-THC_{an} isomers also showed strong interactions to the modeled CB_1 receptor with a ΔE of approximately -33 kcal/mol.[4]

2.6 Aromatic Cannabinoid Analogues

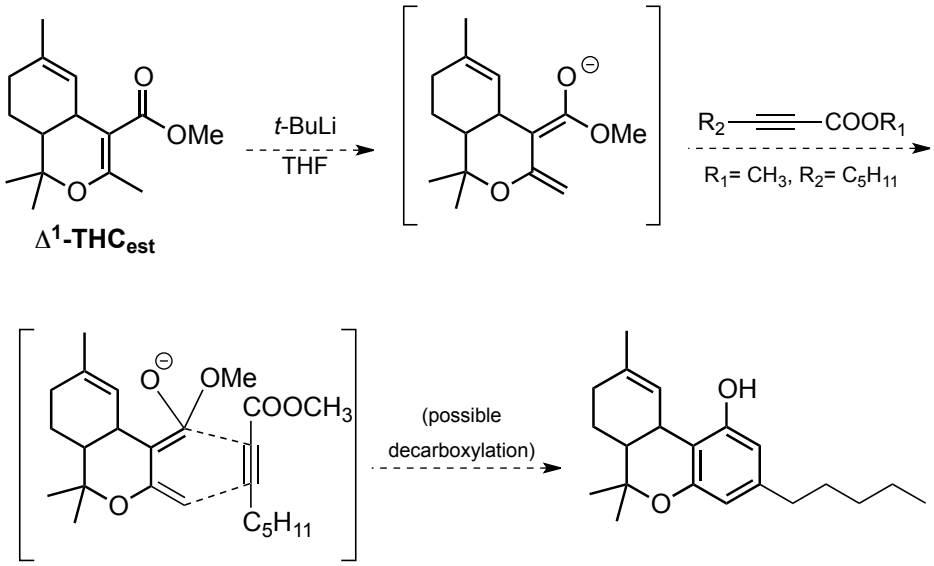
Despite the evidence showing that aromaticity was not essential for CB_1 receptor affinity, efforts were put into developing a facile synthesis toward aromatic cannabinoid analogues in order to expand the pool of available drug candidates. Initial studies focused on using THC_{an} (R=H) as starting material and creating a diene that can undergo a Diels-

Alder reaction with various different acetylenes (varying at R_3). A retro-Diels-Alder reaction would then cause elimination of ethylene. A possible decarboxylation, followed by deprotection of the hydroxyl group would yield an aromatic ring. Assuming commercially available methyl 2-octynoate (R_2= CH_3, R_3= C_5H_{11}) was used as the acetylene, the resulting product would be *rac*- Δ^1-THC. (Scheme **2.7**).



Scheme 2.7 Proposed synthetic route towards Δ^1-THC.

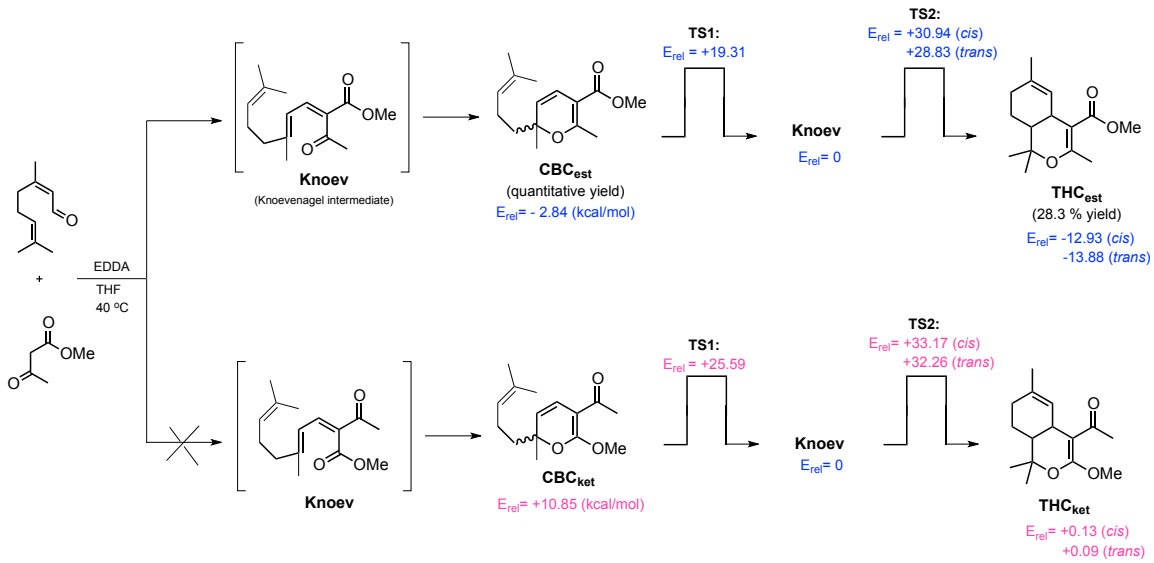
Formation of the acetate-diene, compounds **C** and **D** (Scheme **2.7**), with LDA or *t*-BuLi predominantly results in recovered starting material (THC_{an}). Therefore the approach shown in Scheme **2.8** was taken to ensure the formation of one diene product (*cis*/*trans* isomers) and the opening of the ring would allow for quicker formation of the Diels-Alder adduct, not requiring the elimination of ethylene.



Scheme 2.8 New synthetic plan towards Δ^1-THC.

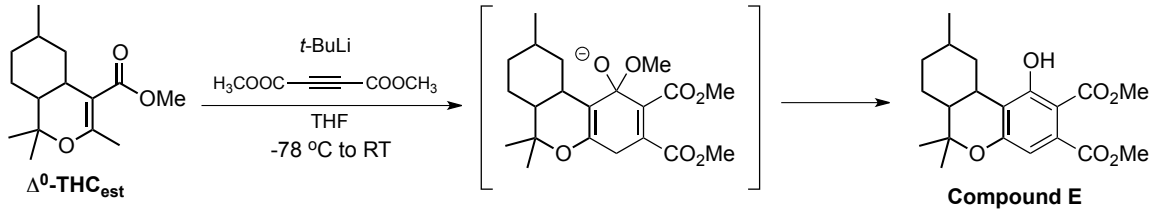
The THC_{ester} was prepared in a somewhat similar fashion as THC_{an} (Scheme **2.9**), excluding the use of zinc bromide, which was found to inhibit the reaction. Even with the use of an asymmetric 1,3-dione, the product results exclusively in the desired CBC-ester analogue (CBC_{est}). Spartan[6] calculations at the B3LYP 6-31G* level of theory were performed on the products and transition states for both the ester and ketone products of CBC and THC (CBC_{est}, CBC_{ket}, THC_{est}, and THC_{ket}) and it was found that the reaction

favors the formation of the ester products (CBC_{est} and THC_{est}), which is consistent with experimental results (Scheme **2.9**).



Scheme 2.9 Synthesis of THC_{est} and Spartan calculation results.

Initial work on the synthesis involved the use of dimethyl acetylenedicarboxylate as the acetylene and the Δ^0-THC_{est} to test out the Diels-Alder chemistry (Scheme **2.10**). Previous synthetic methods to Δ^0-THC_{est} have reported the THC-ester analogue (versus the ketone) as the major product, with only trace amounts of the ketone present.[10] Reaction with *t*-BuLi then resulted in the aromatic compound **E**. Recovered Δ^0-THC_{est} is the major result of the reaction with only trace amounts of the target aromatic species obtained. While optimization is still required, the reaction showed the potential of this route to aromatic THC analogues and the delta-one version of THC_{est} can easily be obtained and used (Scheme **2.9**) to yield Δ^1-THC analogues as well.



Scheme 2.10 Synthesis of aromatic analogue.

2.7 ALS Studies

In collaboration with Dr. Milan Fiala at UCLA's department of Medicine, some of the cannabinoid analogues were tested as pharmaceutical targets for amyotrophic lateral sclerosis (ALS). ALS is a neurodegenerative disease that affects the brain and spinal cord, having poor effective treatment.[11,12] And, as mentioned in the previous chapter, a link has already been found between ALS and cannabinoids, with THC showing some biological activity towards it.[13]

The tests were based on the compounds' inhibition of Interleukin-17, IL-17, (a cytokine) in macrophages of ALS patients.[14] IL-17 is known to have a role in inflammatory processes and a hypothesized role in ALS so inhibition or regulation of these proteins might be therapeutically beneficial. Therefore, targeting inhibition of IL-17 in ALS patients could lead to potential ALS therapy.

Figure **2.8** shows some of the results of this collaboration. One of our compounds, CBC_{an} (Scheme **2.3**), where R= C_5H_{11}, was tested for its potential inhibition of IL-17. This process entails using macrophages of ALS patients that are treated with stimulated superoxide dismutase 1 (SOD-1). Fig. **2.8a** is the negative control; therefore it is not treated with stimulated SOD-1. It is considered healthy as represented by the green coloring. The predominantly red coloring shown in Fig. **2.8b** is representative of a macrophage that is treated with stimulated SOD-1 and therefore the positive control. Fig **2.8c** then shows the results of the test compound. The macrophage was treated with SOD-1, followed by CBC_{an} (R=C_5H_{11}). While there is some red coloring, the macrophage shows that it is primarily green. This would imply that the cannabinoid analogue was in fact found to partially inhibited IL-17.

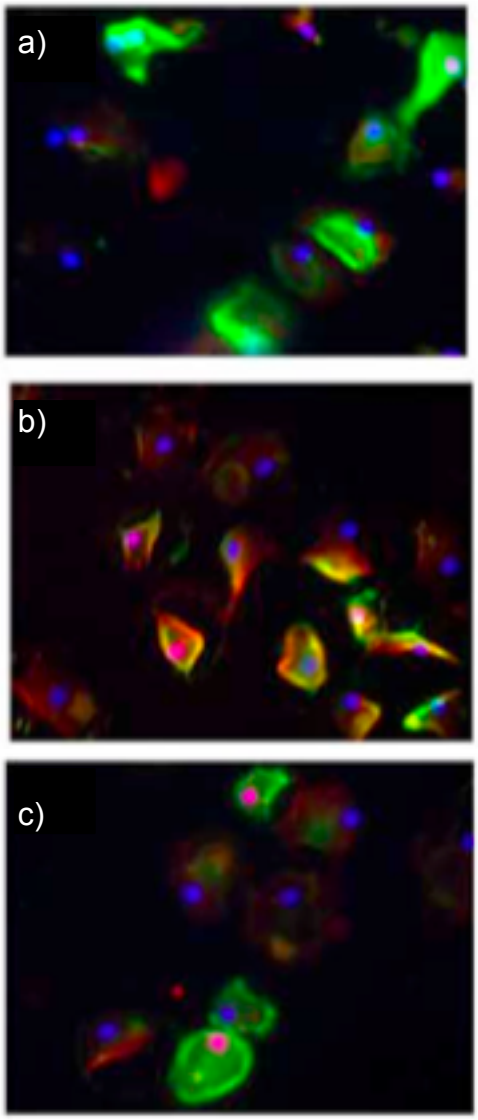


Figure 2.8 ALS macrophages treated with stimulated superoxide dismutase 1 (SOD-1). **a)** negative control (not treated with stimulated SOD-1); **b)** positive control (treated with stimulated SOD-1); **c)** treated with SOD-1 then CBC_{an} ($R=C_5H_{11}$).

2.8 Conclusion

The great therapeutic potential of cannabinoids and their analogues has increased the need to find more efficient methods towards these compounds. In an effort to design a

facile synthesis, we investigated the thermal isomerization of cannabinoid analogues, involving a tandem Knoevenagel-Diels-Alder cascade reaction. This allowed us to produce several cannabinoid analogues and by looking at *in silico* screening results, some have the potential to possess some therapeutic benefit. Biological screening showed that CBC_{an} served as a partial inhibitor of IL-17 and therefore could be useful as ALS therapy. Our collaborative docking studies then led us to hypothesize that unnatural THC isomers might be the cause of marijuana withdrawal symptoms and showed us that these unnatural isomers have a similar CB_1 receptor affinity to the natural THC isomer.

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Chapter 3

Molecular Docking: A CADD Approach for Known Targets

3.1 Introduction

Computer-aided drug design (CADD) covers a range of different techniques that predominantly incorporates use of known data as a means of establishing new leads or hits for the development of new drugs. It typically involves the use of some type of software that can allow the screening of multiple structures. The selected approach to drug design will typically depend on whether the target is known or not. This chapter will focus on the method most commonly used when the target protein is known.

3.2 Molecular Docking Overview

The overall best approach to CADD involves molecular docking. It is a process that can save time and efforts by giving some insight into the potential biological activity of compounds without the necessity of their synthesis. It is computationally based and involves the binding of drug candidates to the actual protein that is known to trigger the therapeutic effects via that binding interaction. Figure **3.1** gives an idea of what would typically be displayed on a computer screen if working with a docking program. The first image is the ball and stick representation of the residues that make up the protein (Fig **3.1a**). This example uses 17-beta-hydroxysteroid-dehydrogenase as the protein and estradiol as the bound ligand (shown in cyan). The red dots around the protein illustrate water (Fig **3.1a**). Figure **3.1b** is then the ribbon representation of the same protein and makes the estradiol ligand easier to see (mint green).[1] The potential biological activity is determined by comparing its binding affinity to the targeted protein with that of a reference drug (a compound that is already known to be active towards that protein). Any

candidates that score well (by displaying the lowest energy binding affinity) pass on to the next phase of drug design, which includes their synthesis to allow for biological screening.

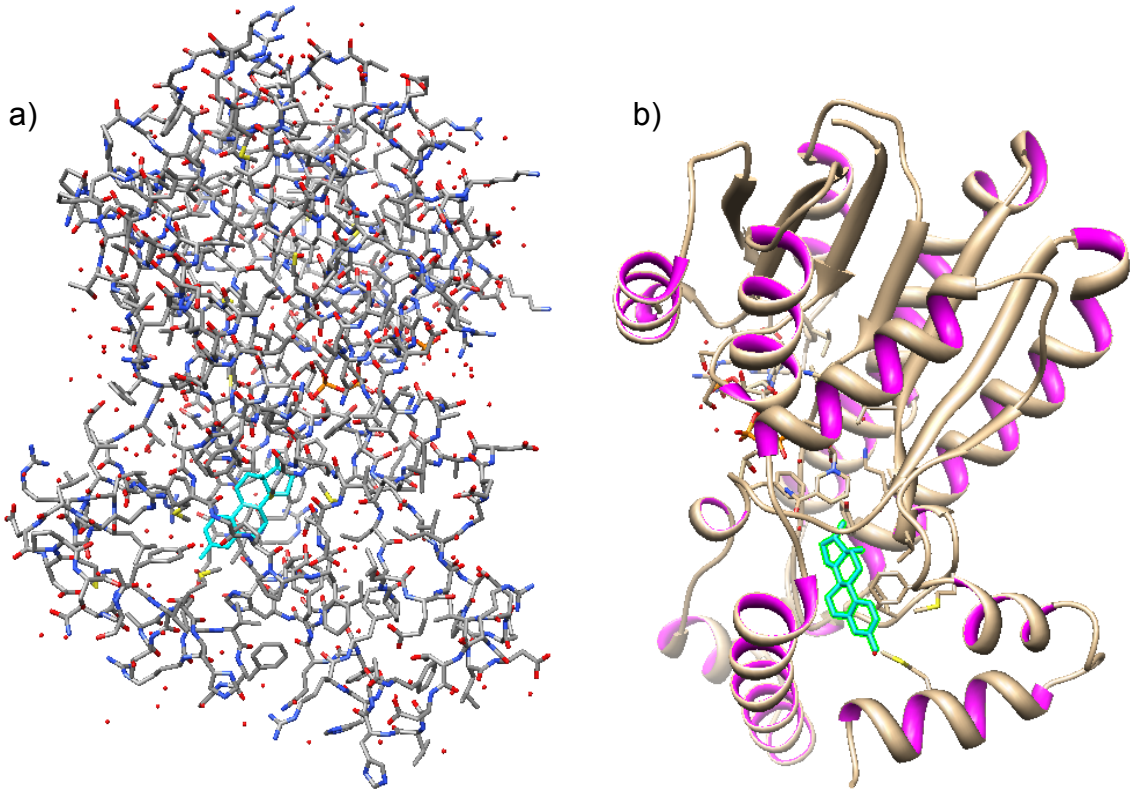

Figure 3.1 a) Ball and stick representation of 17-beta-hydroxysteroid-dehydrogenase (PDB 1A27)[1] complexed with estradiol (cyan) **b)** ribbon representation of the same protein with estradiol (mint green).

The major advantage of molecular docking is the ability to screen a large library of compounds without physically obtaining the molecules required for biological assaying. Docking also gives structural insight into how the ligand binds to the protein with regards to its conformation and the residues it interacts with.[2]

One of the major restrictions to molecular docking however is that the protein target must be known and there must be an available X-ray crystal structure of the protein. Some of the other drawbacks are that docking studies do not give insight into the compounds toxicity, bioavailability, or other factors essential to its conversion into a drug; docking only gives information on how well the compound will bind to the protein.[2] Also, depending on the size of the compound library, the computational cost can be very high, so there might be a limit to how many compounds can actually be docked at a given time.[2]

3.3 The Search Algorithms

Docking includes the generation of a series of different conformations or poses for each screened compound to aid in the search for the lowest binding energy conformer. A searching algorithm helps determine how a docking program will look for different ligand conformations within the binding site of a protein.[2] Some of the available algorithms are Monte Carlo, simulated annealing, tabu, and genetic algorithm.

Monte Carlo is based on randomly selecting a molecule's position in the binding site, which in this case refers to its conformation and orientation (fixed center of mass with rotations around the Cartesian axes) and it tests a large set of different ones.[2] Simulated annealing and tabu algorithms follow this similar process, however, they do not require as much time. This is due to the fact that Monte Carlo tends to repeat some of the positions it has already tested where as simulated annealing and the tabu algorithms keep

a record of which ones have already been tested and therefore avoid repetition. Simulated annealing then goes a step further and will spend more time testing positions that are close to positions that have already been shown to be low in energy.[2]

A genetic algorithm on the other hand is quite different and follows a "survival of the fittest" approach. It starts off by creating a large set of different positions at random. Then it will select the best positions (lowest energy) and generate more positions.[2] As it keeps generating newer positions, it will keep the best positions from each set every time.[2]

3.4 Scoring

Every conformation that was generated for binding to the protein is assigned a score typically in the form of an energy value, which is a measure of binding affinity. That binding affinity or score decides which conformation is necessary for biological activity.

The different types of scoring functions are attempting to roughly calculate the binding free energy for the binding of the ligand to the receptor. An ideal scoring function would take into account all of the components in the following equation:[3]

$$\Delta G_{binding} = \Delta G_{solvent} + \Delta G_{conf} + \Delta G_{interaction} + \Delta G_{rotation} + \Delta G_{t/r} + \Delta G_{vib}$$

$\Delta G_{solvent}$ deals with the solvent effects, ΔG_{conf} stands for any conformational changes, ΔG_{int} accounts for any interactions between the protein and the ligand, $\Delta G_{rotation}$ deals with the protein and ligand freezing internal rotations, $\Delta G_{t/r}$ takes into account the translational and rotational energy loss, and ΔG_{vib} includes changes from vibrational modes.[3] Not all of these components are usually included in docking calculations, nor are they easy to figure out. They use simpler versions of these calculations. Despite the function that is used, it has been found that the combination of different scoring functions has delivered more favorable results than the application of just one type of function (consensus scoring).[3]

3.5 Docking Procedure

3.5.1 Preparing the Protein

All docking procedures begin with an X-ray crystal structure of the protein. The most widely used source of proteins is the Protein Data Bank website.[4] Usually proteins that have a bound ligand in the active site are used. The ligand is eventually removed before docking, along with any water molecules. Hydrogen atoms are also added to the protein since they are usually not found on the protein. Then based on the selected force field, the protein is minimized.[2]

3.5.2 The Ligand Set

The ligands can be set up to dock automatically one after another or ligands from a particular database can be used. The automated process will usually involve the

generation of the different ligand conformations and poses. However, this can also be done separately before docking. [2]

3.5.3 The Binding Box

Since protein structures are generally made up of multiple residues their large size can tend to increase computational time. One way around this is to set up a type of box around the binding site to focus computational efforts in that area, since residues faraway from the ligand do not seem to have an affect on the output score.[2] The box is usually set around the area of the bound ligand (if present).

3.5.4 The Results

After the docking has been performed, more can be obtained from the output than just a binding score. The key benefit of using molecular docking is that one can observe the interactions between the ligand and the protein. Based on what residues are interacting with a specific part of the ligand, the important features of the ligand can be determined. The trivial parts of the structure can also be determined and the ligand can continue to be modified in this manner. [2] There are several available docking programs, some of which can be downloaded for free from the internet. DOCK was one of the first established docking programs, created by UCSF and incorporates a force field based scoring method. Developed by the Scripps Research Institute, AutoDock is another docking program that is available free of charge. It uses a linear regression analysis to establish its scoring

method. Some other programs include FlexX, FRED, Glide, GOLD, and Slide, but these are just a few examples from dozens of available docking programs.[2]

3.6 Error in CADD

There is some error associated with CADD and the software devoted to it. Error in CADD can be found through the types of docking programs that are used and whether or not their accuracy is good enough to use the results.[5] Error can also result from the person running the program and their interpretation of the results. For example, when the QSAR (to be explained more thoroughly in the next chapter) technique was just developed, a lot of the computational methods were created out of pure curiosity, to test to see if something was possible and not so much because it was essential to CADD in terms of accuracy or efficiency.[5] The inability to comprehend basic principles in designing programs led to inaccurate interpretations of the results. If a better understanding of the methods that can be applied as well as the possible errors resulting from the calculations is obtained it will allow the opportunity for improvement and the realization of what is possible.[5]

Other errors can lie with the applied force fields. The force fields are considered approximations and these approximations affect the way torsion, dihedral, van der Waals, and electrostatic interactions are calculated.[5] Any changes made to the force field parameters can have an effect on the software and the time needed to run any calculations.[5]

However, the field of computational drug design is growing and there is great potential for its growth and improvement. Only through continued use of computational programs can specific weaknesses be identified and resolved. And if they cannot be resolved, how it can be avoided in order to reach the overall objective.[5] Error must be taken into account in order to establish CADD reliability to allow computational screening to continue in the drug discovery process.[5]

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Chapter 4

CADD Approaches for Unknown Targets

4.1 Introduction

The previous section focused on molecular docking. As previously mentioned, an X-ray crystal structure of the target protein must have been deciphered in order to incorporate molecular docking in the drug design process. There are about 500,000 proteins in the human proteome and only 10,000 of these proteins possess an identified X-ray crystal structure.[1] Also, not only is there often not an available crystal structure, but usually the target protein(s) is not even known. The following sections will give a brief overview of current CADD programs and techniques that are used when the protein target is not available or known.

4.2 Predicting Intestinal Absorption: Lipinski's 'Rule of Five'

One of the most widely used methods for filtering through a list of New Chemical Entities (NCEs) involves the application of Lipinki's 'Rule of Five'.[2] In fact, some of the methods to be discussed incorporate aspects of this method. By simply looking at the structure of a NCE, it can be determined whether it fits the likely criteria of a drug. In 1997, Lipinski and co-workers established a set of rules based on an analysis of 2245 drugs. If more than two of the following rules were violated, the NCE was likely going to have poor absorption. The necessary criteria for good absorption were i) a molecular weight less than 500 ii) less than 10 hydrogen bond acceptors (HBA) iii) less than five hydrogen bond donors (HBD) and iv) a calculated logP value less than five (for ClogP) or less than 4.15 (for MlogP).[2,3] Any oxygen and nitrogen atoms are considered HBAs. Any NH or OH groups are HBDs. The logP is the octanol/water partition coefficient and

assesses the lipophilicity of a compound. The ClogP is used synonymously with logP and is just one method of calculating the coefficient. The MlogP is a different way of calculating it that was established by Moriguchi and co-workers in 1992.[3,4]

4.3 Similarity and Substructure Searching

Sometimes simple structural searches are performed on biologically active compounds. Substructure searches look for compounds that contain the same atoms and bonds that make up part of the active molecule.[1] For example, a search can be performed on molecules that integrate an indole within their structure. Similarity searching, on the other hand, helps find analogues of a particular compound. So instead of just searching for indoles, the search is expanded to quinolines (a bigger size ring system). These types of searches are rather easy to carry out and often just require drawing the part of the structure that is desired. For similarity searches, it can be decided how close or how far away from the structure the results should be.[1]

4.4 Pharmacophore models

Molecules can also be searched based on pharmacophore. A pharmacophore includes the key parts of a drug and their placement that have been found necessary for protein binding or activity.[5] These type of searches allow for more chemical variability and can lead to what is called scaffold hopping; this involves altering lead structures to come up with an entirely new class of compounds that might turn out to be structurally different, but have similar affinity for the same receptor.[1,6] Not all molecules that were found to

have the same pharmacophore are necessarily that close in structure. Paclitaxel and Epothilone A (Fig. **4.1a**) are a great example of this. They do not look structurally similar, but their lowest energy conformers (as bound to the tubulin receptor) show similar pharmacophores when aligned against one another[1,7,8,9] (similarities are circled in yellow in Fig. **4.1b**[10,11]).

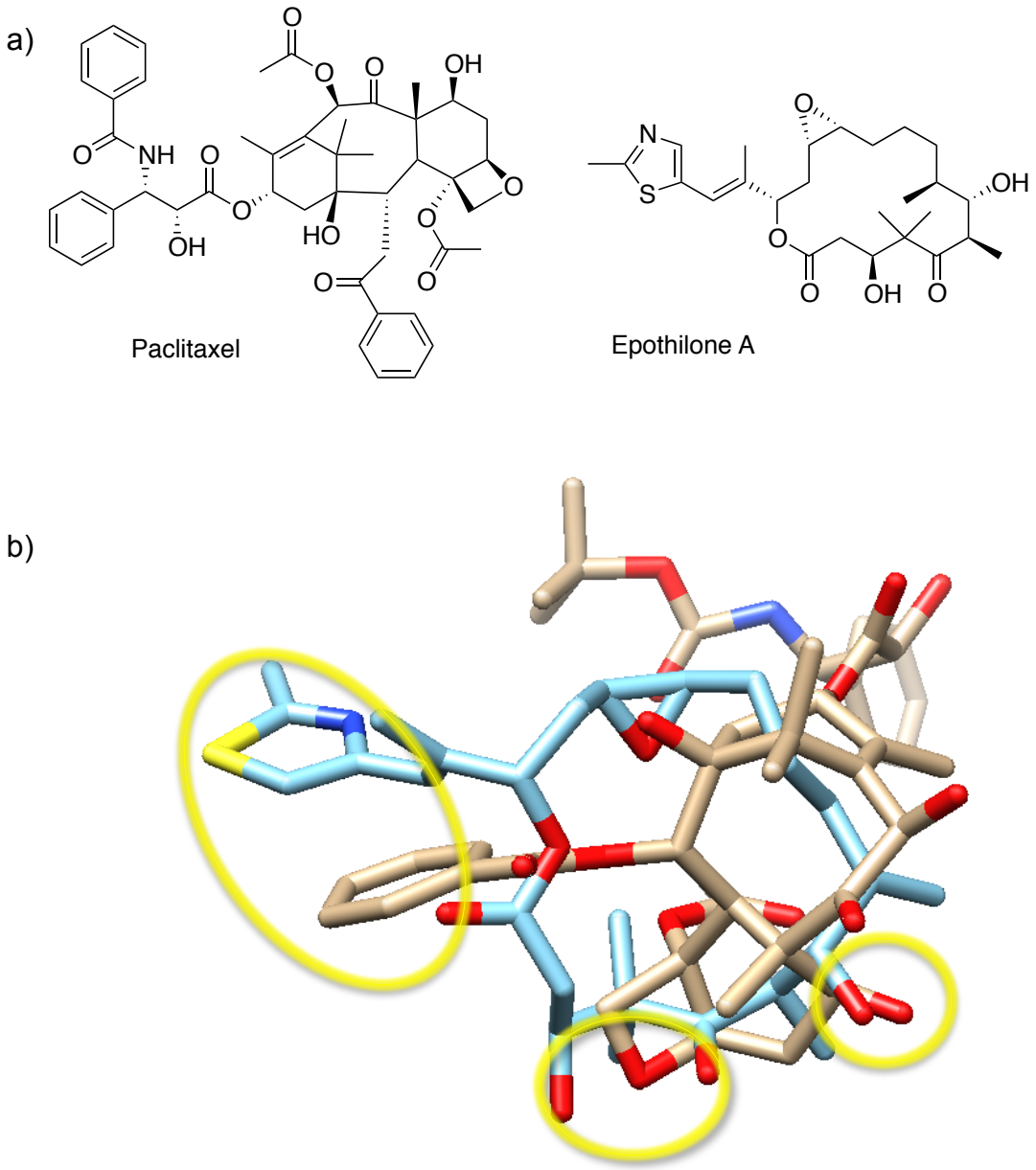

Figure 4.1 a) Chemical structures of Paclitaxel and Epothilone A **b)** alignment of the lowest energy conformers of Paclitaxel (tan) and Epothilone A (cyan), as bound to tubulin receptors 1TUB[8] and 1TVK,[9] respectively (receptor omitted for clarity). The yellow circles show the similarities in pharmacophore (i.e., overlapping of aromatic or hydrophobic regions and hydrogen bond donors and acceptors).

Some of the key characteristics that can be included in a pharmacophore search are hydrogen bond donors and acceptors, aromaticity, hydrophobic regions, acidic or basic groups, and bulky groups that are involved in steric interactions.

Although this method is based on biologically active molecules, one of the disadvantages is that the lowest energy conformer for these molecules has to be known. Therefore, if the target protein is not known, this can be very difficult to determine.[1] It is also possible that there could be a key functional group present in all active compounds that might not be essential for binding. However, one-way around this is to use compounds that are not analogues of each other and do not have the same core structure.[1]

The first actual step to this process is to align the biologically active compounds, starting with the ones that are the most rigid in order to establish the pharmacophore model. Subsequent structures are then rotated and appropriately positioned to those structures to give the best alignment.[1] This can either be done manually or automatically through some software program, which overall can work rather well. MOE from the Chemical Computing Group, is one program that will allow manual manipulation.[1] Next, based on the established model, the compound searching can begin. The output is a ranking of the compounds that were found to best fit the model and is usually produced reasonably quickly.[1]

The pharmacophore model can also be established by using the active binding site of the protein and often works best this way since the actual interactions between the residues and molecule can be observed.[1]

4.5 QSAR

A common approach to computational drug design is the use of quantitative structure-activity relationships (QSAR). This method involves incorporating a mathematical formula to establish a relationship between a compounds biological activity and its physicochemical properties.[5] The molecular properties used in the equation are referred to as descriptors. A descriptor is a numerical value that details a specific part of a compound (e.g. molecular weight, log P value) and is not limited to the same set of descriptors every time this method is used. [1,5]

QSAR models generally work by establishing a training set of compounds with known biological activity. This "activity" is then going to be the desired value to predict for NCEs. The activity in the training set should cover a wide range of possible values. Every chosen parameter would then have at least 10 compounds in the set as part of the QSAR equation to avoid biasing the data. [1,5]

The compound descriptors for the test set are then calculated. This process should be relatively quick since computationally time-consuming descriptors are not usually chosen. Then the descriptors selection process begins. This includes choosing the one

with the highest correlation coefficient; Since QSAR models use equations that are mostly linear, taking into account the correlation coefficient tells how accurately the activity is being measured by the descriptors. In order to avoid descriptors that are too similar, the second descriptor that is chosen should not correlate too closely to the first selected descriptor, but should still have a high correlation with the activity. Figuring out the best fit from this data can then lead to the activity prediction of the test compounds.[1,5] QSAR models can also use nonlinear equations. However, some of these methods are considered to be trial-and-error since correlation coefficients cannot be used, and therefore descriptor selection becomes somewhat trickier.[1]

As previously mentioned, the types of descriptors that are chosen are usually computationally inexpensive, since computations of very large data sets can lead to an even bigger increase in computational cost. Among some of the different types of descriptors are constitutional, topological, electrostatic, geometrical, and quantum chemical.[1]

Constitutional descriptors can include properties like the molecular weight of a compound, the number of heteroatoms within a given structure, and the amount of rings encompassing it. These types of descriptors are usually used when molecule size changes with the resulting predicted activity value.[1] Topological descriptors are typically not directly related to the structure of the compound, but have been found to usually give the best predictions. These types of descriptors give details about the bonding arrangements

and can shed some light on a molecule's rigidity.[1] Electrostatic descriptors can give facts about the molecular charge distribution and includes properties like polarizability and topological polar surface area (TPSA). The TPSA is often used and gives information on the amount of polar groups compared to non-polar ones. The octanol-water partition coefficient (LogP) also falls into this category.[1] The geometrical descriptors can then give information about a compounds shape and size. A list of these types of descriptors can include molecule volume, moments of inertia, the molecular surface area, and other factors that can give information on a compounds height, length, and width.[1] Lastly, the quantum chemical descriptors give details about a compound's electronic structure. Some of these factors can include HOMO and LUMO energies, electron affinity, energy of protonation, and refractivity.[1]

The selected descriptors can manually be selected, but there are available software programs that can make the appropriate selections, which can often lead to more accurate predictions in a less amount of time. However, one of the disadvantages of using the available software is that the selected descriptors are chosen based solely on the inputted algorithms, with no scientific reasoning behind it. This leads to equations that are considered over-fitted, which work well for the training set, but give bad results for predicting test compounds.[1] Codessa by Semichem is one of the most widely used QSAR programs that allows for both manual and automatic descriptor selection. However, programs can also be obtained from Accelrys, the Chemical Computing Group, Schrödinger, and Tripos.[1]

The major disadvantage to using 2D-QSAR methods is that it does not take into account the 3D structure of the test drug or NCE. This makes it harder to see its potential interaction with the target receptor. One approach to dealing with this is to use 3D-QSAR methods.[12]

4.6 Group Additivity

Group additivity is also designed to run fast calculations of molecular properties for a set of compounds. This approach separates a molecule's parts into different groups, based on its backbone, its rings, and attached functional groups and each of these groups then contributes to a total added score. These methods have shown to be very good at anticipating toxicity.[1]

4.7 Neural networks

Neural networks use a training set of compounds to train a network that later goes on to predict the properties of a new molecule.[1] Neural networks are good for interpolation, which is making good predictions when the properties of the NCE lie within the range of the network or training set. However, accuracy decreases when it falls outside that specific area (extrapolation).[1]

4.8 Hologram QSAR

Hologram QSAR (HQSAR) deals with breaking down a molecule into its different fragments and arranging them into an array that is sort of like a fingerprint. The

fingerprint, represented in numerical values, is referred to as a hologram and is used to make the predictions.[1]

QSAR methods are usually utilized for predicting pharmacokinetic properties (e.g., permeability of the blood-brain barrier and passive intestinal absorption). Since more accurate methods exist, it is not really used for predicting whether or not a molecule will have biological activity.[1]

4.9 3D-QSAR

Three-dimensional QSAR is somewhat similar to 2D-QSAR, but incorporates properties in a grid type form around the molecule.[1] 3D-QSAR's main purpose is to try to figure out the properties of a target protein's binding site, without actually using or knowing the structure of the binding site, by incorporating the electrostatic and steric interactions around a biologically active molecule. This information is gathered for a training set of biologically active compounds and then a partial least squares (PLS) algorithm helps figure out what spatial arrangement of features might be present in the active site of the target protein that could interact with the training set.[1]

Much like the QSAR method, the 3D-QSAR process requires a training set (composed of at least 20 compounds) ranging in biological activity. Predictions tend to be more accurate when test compounds are somewhat structurally similar to those in the training

set. However, the training set should not be based on compounds that have the same framework.[1]

The next step is to establish a shape that is based on the biologically active conformer. However, since this information is not known at this stage of the process, the following three conditions help determine the likely conformer, a) every conformation that is used should have an energy close to that of the lowest energy conformer (within 10 kcal/mol) b) all conformations should have a similar shape and c) conformations should allow for easy alignment of pharmacophoric features. This can either be done automatically with a specific program or manually.[1]

Manual selection commences will all molecules in their ground state conformation. From this batch, the most rigid molecules are overlaid to establish a template based on shape and pharmacophore. The lowest energy conformers for similar molecules can then be aligned to this template, with non-similar compound conformations being modified to best fit the template. Then, based on the key features of the template, the best field parameters must be chosen. While the steric and electrostatic fields are normally included, other options can be based on hydrogen bonding, molecular lipophilic potential, and desolvation.[1,5]

The lowest energy conformer of each compound is then fit into a lattice, positioned to allow alignment of all compounds based on the pharmacophore. The steric and

electrostatic fields around the molecule are then measured by using a probe atom, located at each grid point. The probe atom can be a proton or sp^3 hybridized carbocation. It then calculates the interactions amidst itself and the compound. The energy derived at each grid point can then be coupled using contour lines to figure out the shape (sterics) and positive and negative regions (electrostatics) of the compound.[1,5] Then, as briefly mentioned above, a PLS algorithm is used to help establish the best fit and select the most integral components. Then a simple equation based on the resulting data allows for predictions of biological activity by showing whether or not there is a relation between steric or electronic effects of the molecules and biological activity.[1,5] Figure **4.2** shows a brief schematic summarizing this entire process.

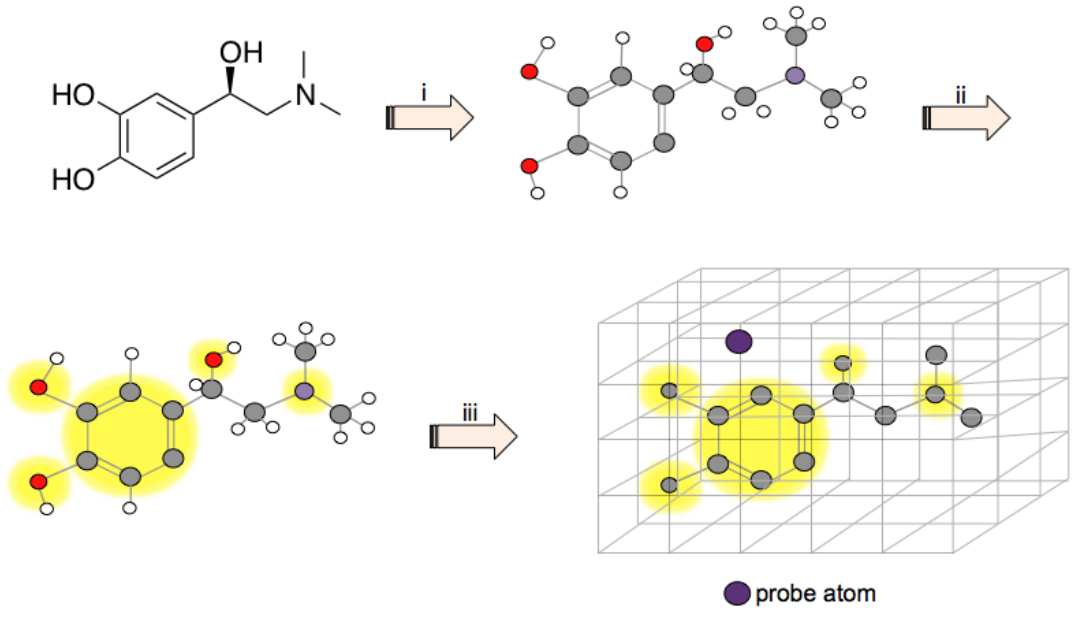

Figure 4.2 3D-QSAR process: i) starting with a training set ii) the lowest energy conformer is determined iii) which then establishes the pharmacophore iv) that is placed in a lattice to determine the interactions via a probe atom.

The most widely known software for performing 3D-QSAR methods is CoMFA (Comparative Molecular Field Analysis) from Tripos. Also from Tripos is Comparative Molecular Shape Indices Analysis (CoMSIA). It differs from CoMFA in that it is more selective in its activity predictions. Therefore the list of drugs predicted to be biologically active might be shorter, but its drawback is that it might not catch all biologically active compounds.[1]

3D-QSAR techniques have been found to be the most accurate of all ligand-based approaches.[1]

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Chapter 5

A New Approach to Computational Drug Design and Drug Rediscovery

5.1 Introduction

It takes approximtely $800 million over about 15 years to introduce just one drug into market, with only 20-30 drugs receiving FDA approval each year.[1] Based on these results, it seems logical to look into existing drugs, where time and efforts have already been devoted as well as some biological testing performed. This alone can reduce cost by 40% since some of the biological assessments can be excluded as pharmacokinetic and toxicological profiles have already been established.[1] Drug rediscovery also decreases the amount of time necessary to attain next-generation lead compounds by eliminating the synthesis part of conventional drug discovery. Also, the rediscovery process has already been found to be effective as there are several drugs currently undergoing clinical and animal testing for an alternate use. Table **5.1** lists some of these drugs.[1-11] Therefore, it is worth designing a technique devoted to drug rediscovery. We have proposed an *in silico* approach to drug rediscovery that makes use of the binding affinity of non-target receptors (UBANTR) as a way of establishing new purposes for existing drugs. This approach can also be used to determine the potential indication of new chemical entities (NCEs). Discussion will focus on repurposing efforts, but hopefully it will be evident how this approach can be used in a similar fashion for NCEs.

Table 5.1 Drugs Undergoing Testing for New Uses.[1-11]

Drug	Current Use	New Use
Amphotericin	Antifungal	Leishmaniasis
Ceftriaxone	Antibiotic	Amyotrophic Lateral Sclerosis
Dapsone	Leprosy	Malaria
Eflornithine	Cancer	African trypanosomes
Fosmidomycin	Urinary tract infections	Antimalarial
Miltefosine	Cancer	Visceral leishmania
Thalidomide	Sedative	Cancer

5.2 The UBANTR Approach

The UBANTR approach's only requirement is the structures for a library of drug-like compounds to predict the indication class. The major advantage of this technique is that an X-ray crystal structure of the target protein is not required nor is prior knowledge of the protein(s). This is extremely valuable as one of the major disadvantages to the molecular docking approach to CADD is this requirement. And, as stated in the previous chapter, molecular docking is the preferred method to CADD.

This new approach only requires a three-dimensional coordinate file for each drug in the library. The actual docking to different receptors gives insight into a compound's actual behavior. Therefore, if the ligands are bound to other proteins, we should be able to derive certain information that allows us to see how the ligands interact, regardless of the fact that the target protein is not used. The gathering of this information should produce

enough data to analyze the potential biological activity of the screened compounds. By obtaining the binding affinity to a random set of proteins, specific “bits” of information can be derived and used to classify drugs by their major indication and give insights into potential new uses when they are groups with drugs of a different indication. Figure **5.1** explains how this process works. When a drug is docked to each receptor it produces a piece of a bar code or fingerprint. Once it has been docked to all 15 receptors, each drug is labeled with a very unique fingerprint. Each drug in the library is then grouped to other drugs that are found to have a similar fingerprint.

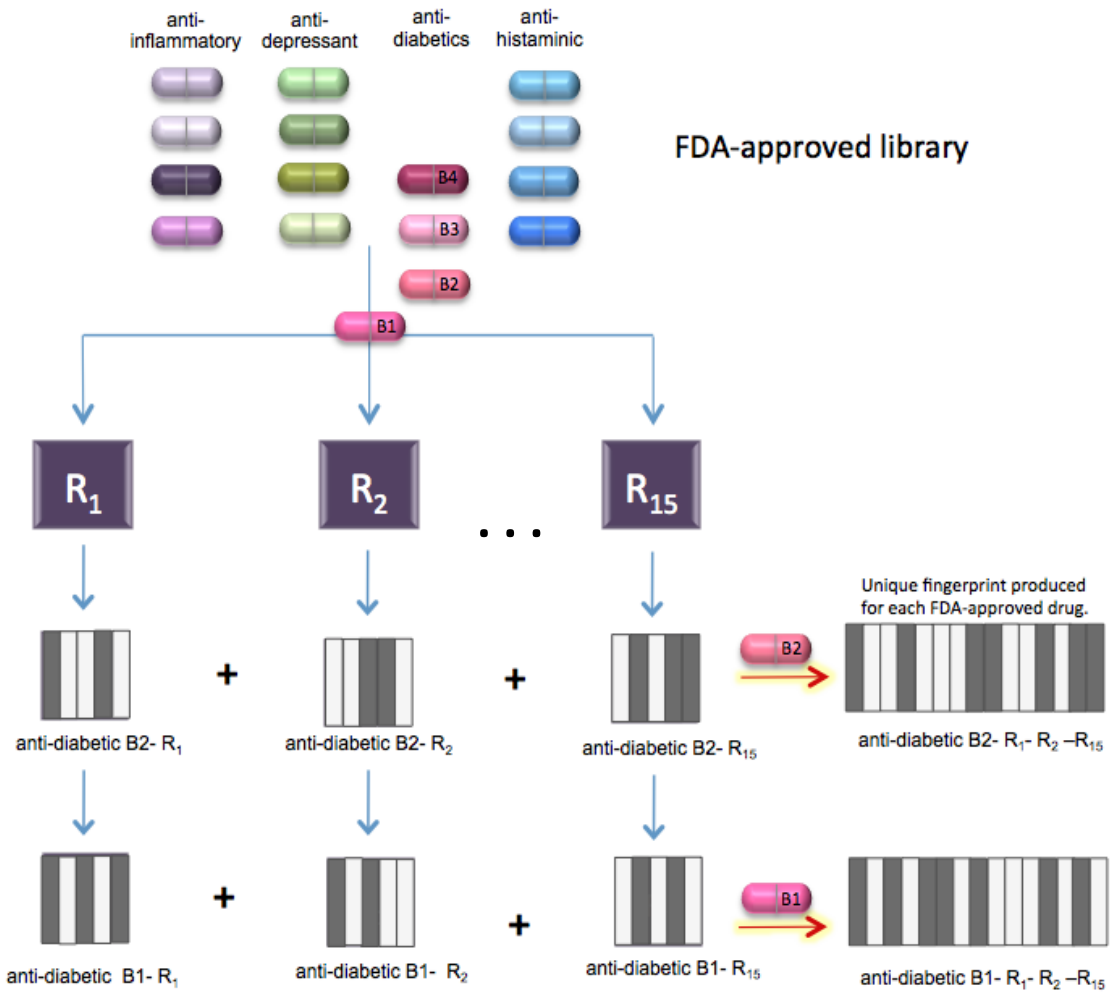

Figure 5.1 Docking FDA-approved library to receptors produces unique fingerprint.

The concept of this approach is somewhat similar to the game "20 questions," which is based on Shannon's Theory.[12] Entropy is measured to be the amount of uncertainty about an object or event and information is then determined to be the degree of association between two systems, for example, between a ligand and receptor. Each of these interactions is a piece or "bit" of information that gives us insight into the properties of

the ligand.[12] Every question (or in this case, receptor) can help determine a bit of information, with most objects (drug activity) being identified (by indication) with a maximum of 20 questions. In our case, since we have 15 receptors, it would be 15 questions.

5.3 The Process

A SMILES file containing information for each 487 FDA-approved drugs in the library was prepared. The stereochemistry for all compounds was specified and if a drug is found in its racemic form, both isomers were included. The SMILES file was then run through Omega (Open Eye Software)[13] to establish conformers of each drug, with the maximum amount of conformers generated set to 100. Then the file was run through Spartan '08 to add partial charges to the structures.[14]

X-ray crystal structures were obtained from the Protein Data Bank. The only requirement for the receptors was that the X-ray crystal structures must contain bound ligands ranging in volume similar to that of the drug library. The PDB files of 15 receptors were then run through FRED Receptor (Open Eye Software)[15] for optimization. The binding site was automatically selected based on the bound ligand.

All ligands were then docked to all 15 receptors by a batch process using FRED (Open Eye Software).[16] Every single conformer that was generated for each drug was docked. Then approximately 700,000 structures were examined to determine the lowest binding

energy conformer for the 487 drugs, which were then carried over to the data processing stage. Besides this, all default parameters were used, including the chemgauss3 scoring method, for all docking calculations. This produced 15 attributes for every FDA-approved drug. The volume of each 487 drugs was also included as a 16th attribute.

Once the binding affinities of the lowest energy conformers for each drug were selected, the data was normalized using values from 1 to 100. This data was then inputted into Orange[17], a data mining and machine learning software, discretized, and applied a hierarchical clustering algorithm to group all FDA-approved drugs based on the binding affinity. Figure **5.2** shows a typical output from Orange.

From the 487 drugs, 80 were considered to be outliers based on a Euclidean distance metrics, resulting in only 407 drugs included in the hierarchical cluster.

5.4 Results and Discussion

In an effort to stress the effectiveness of this method, focus is placed on certain sections of the data, instead of an analysis of all 407 drugs. Although it should be noted that the size and drug content of the library is significant and has an effect on the overall hierarchical clustering.

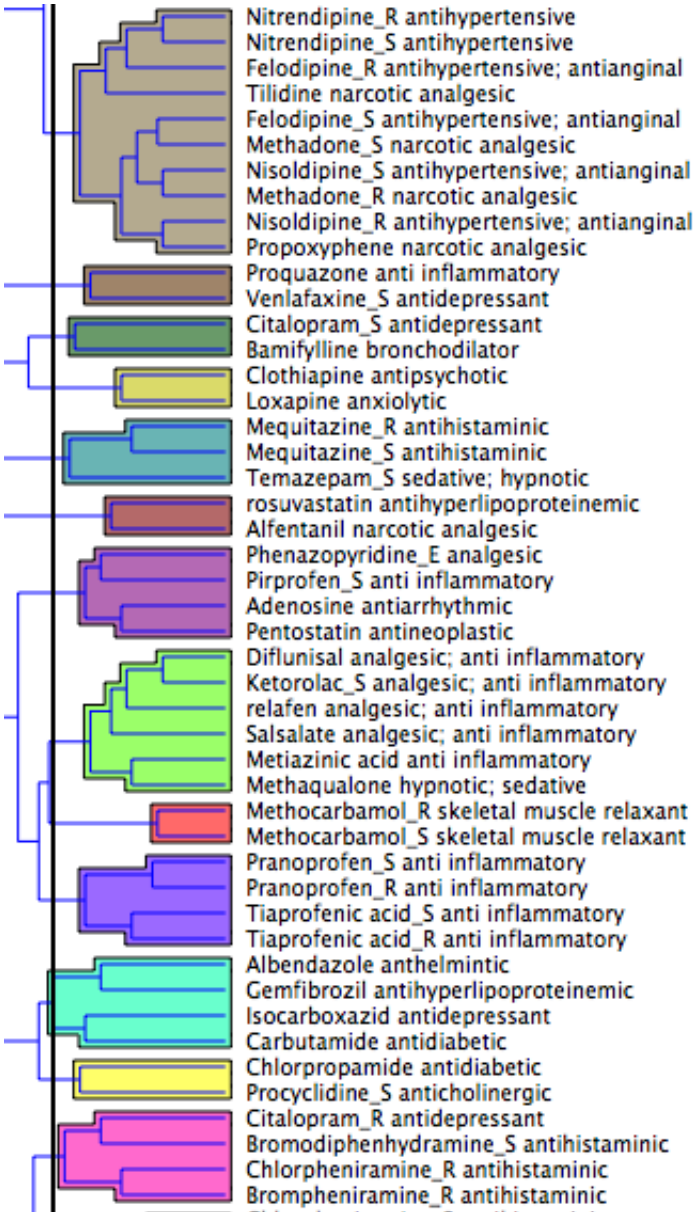

Figure 5.2 Hierarchical clustering produced from Orange.[17]

Figure **5.2** is just a small representation of the 407 drugs. The drugs cluster into groups based on their binding similarity across all 15 non-target receptors. One of these clusters

or groupings is found in Figure **5.3**, which shows a clustered group of anti-histaminic drugs. Ideally what we are looking for are drugs to group or cluster together based on their indication class. Figure **5.3** is showing an example of this grouping.

S-Chlorpheniramine (antihistaminic)
S-Brompheniramine (antihistaminic)
S-Carbinoxamine (antihistaminic)
R-Bromodiphenhydramine (antihistaminic)

Figure 5.3 Clustered group of anti-histaminic drugs.

Figure **5.4** shows a drug cluster where not every drug that was shown to group together possesses the same indication. There are three anti-histaminic drugs and one anti-depressant. Based on the UBANTR approach, the first level of analysis includes looking for direct indication matches. The second level of analysis involves a deeper look into the connection between matching drugs.

R-Citalopram (antidepressant)
S-Bromodiphenhydramine (antihistaminic)
R-Chlorpheniramine (antihistaminic)
R-Brompheniramine (antihistaminic)

Figure 5.4 Clustered group of anti-histaminic drugs with one antidepressant.

This deeper connection can include secondary indications or alternate drug purposes, as well as any possible side effects. One method of investigating this deeper connection involves using STITCH.[18] STITCH will show a given interaction between chemicals and proteins by searching experiments, databases, and the literature.[18] It is important to note

that in our case, STITCH is used as a complimentary analysis, it is not complete, and it is not predictive. Inputting the drugs found in Figure **5.4** into the STITCH program will produce the diagram shown in Figure **5.5**.[18]

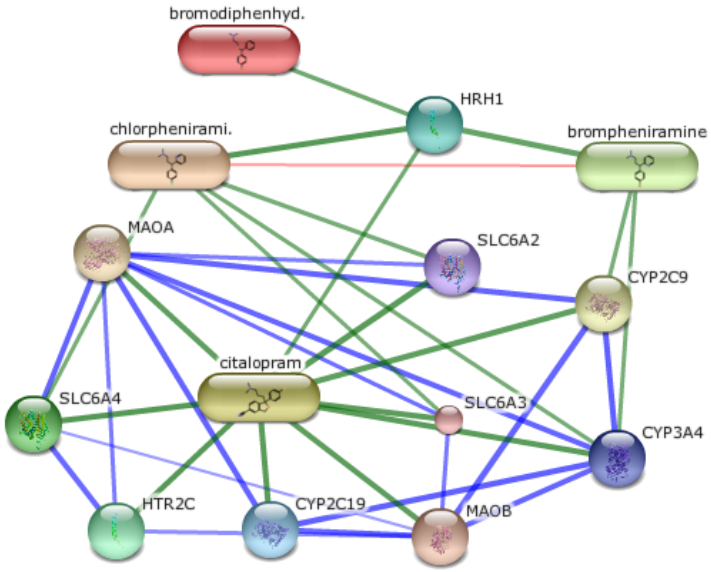

Figure 5.5 STITCH output for clustered drugs from Figure 5.4[18]

Looking at the STITCH output, bromodiphenhydramine, brompheniramine and chlorpheniramine (all antihistamines) are linked to the HRH1 receptor, which is the histamine receptor. However, citalopram, the antidepressant, also shows a connection to the same histamine receptor. Therefore, the UBANTR approach is implying that there is a similarity between these four drugs and STITCH showed that the connection between all four of these drugs does exist.

Figure **5.6** lists another drug cluster example. The drugs are divided into two major indications, antihypertensive drugs and narcotic analgesics. A connection between both of these indications was not discovered through STITCH. However, this should not imply that a connection does not exist. In fact, this is one of the major objectives to the UBANTR approach. It is stating that there is a similarity amongst these drugs, which could lead to repurposing.

R-Nitrendipine (antihypertensive)
S-Nitrendipine (antihypertensive)
R-Felodipine (antihypertensive; antianginal)
S-Felodipine (antihypertensive; antianginal)
S-Nisoldipine (antihypertensive; antianginal)
R-Nisoldipine (antihypertensive; antianginal)
Tilidine (narcotic analgesic)
S-Methadone (narcotic analgesic)
R-Methadone (narcotic analgesic)
Propoxyphene (narcotic analgesic)

Figure 5.6 Drug cluster dividing into two major indications.

Drug repurposing involves taking existing drugs and discovering new uses for them (drug re-discovery). In this instance, we are implying that any of the antihypertensive drugs listed in Figure 5.6 should be screened as potential analgesics and/or the narcotic analgesics should be tested as antihypertensive drugs. The UBANTR approach is showing a similarity between all of these drugs, this is implying that they might have similar indications or some other potential connection, for example in the form of side-effects. This approach should be used as a starting point of where we can begin testing

particular drugs for other indications instead of randomly testing them for any available indication.

Two more clustered examples are shown in (Figure **5.7**). The orange cluster is showing a group of diuretic; antihypertensive drugs clustered with one anticonvulsant drug. Again, the UBANTR approach is implying that Sulthiame, the anticonvulsant, might have biological properties as a diuretic; antihypertensive and/or any of the diuretic; antihypertensive drugs might also serve as an anticonvulsant drug. We are implying that testing for repurposing of these drugs should begin with the other matching indication. The UBANTR approach is showing a similarity, which should justify this screening. Despite the fact that a connection is not found through STITCH, does not imply that it does not exist; it just might not be known.

S-Trichlormethiazide (diuretic; antihypertensive)
R-Trichlormethiazide (diuretic; antihypertensive)
Sulthiame (anticonvulsant)
S-Methyclothiazide (diuretic; antihypertensive)
R-Methyclothiazide (diuretic; antihypertensive)

Diflunisal (analgesic; anti inflammatory)
S-Ketorolac_S (analgesic; anti inflammatory)
relafen (analgesic; anti inflammatory)
Salsalate (analgesic; anti inflammatory)
Metiazinic acid (anti inflammatory)
Methaqualone (sedative; hypnotic)

Figure 5.7 Two different drug clusters.

The same reasoning can be applied to the second grouping in Figure **5.7.** It shows predominantly analgesic; anti-inflammatory drugs with one sedative; hypnotic. There is an implied similarity base on the UBANTR approach and any repurposing efforts should begin with these matching indications.

In one more example (Figure **5.8**), we see an anti-histaminic drug, triprolidine, amid anti-depressant drugs. In this example, a connection between amitriptyline, nortriptyline, doxepin, and triprolidine is known and can be seen in the STITCH output (Figure **5.8**).

Protriptyline (anti-depressant)
Nortriptyline (anti-depressant)
Z- Dothiepin (anti-depressant)
E- Dothiepin (anti-depressant)
E- Doxepin (anti-depressant)
Z- Doxepin (anti-depressant)
Amitriptyline (anti-depressant)
E-Triprolidine (antihistaminic)
Dibenzepin (anti-depressant)

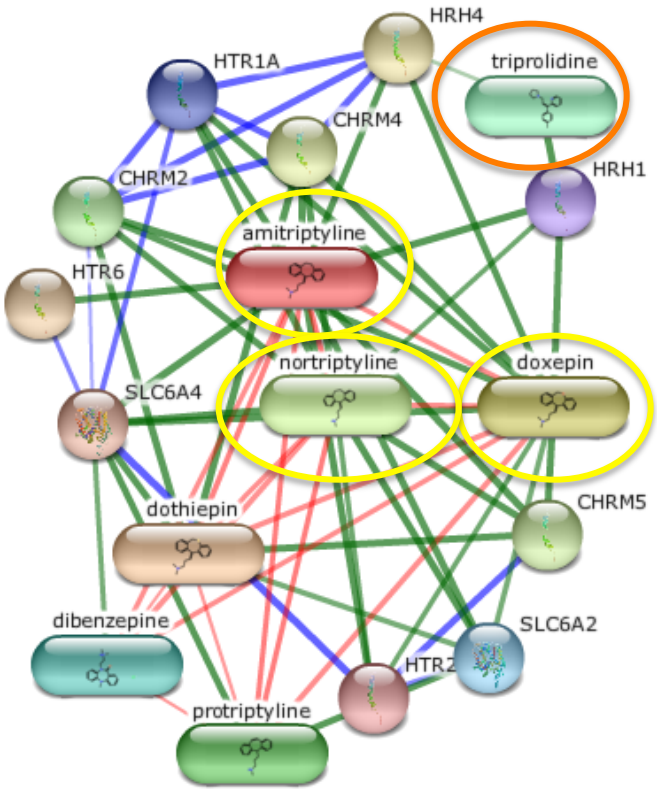

Figure 5.8 Drug cluster with its STITCH output.[18]

All four drugs are linked by the HRH1 (histamine) receptor and the three anti-depressant drugs are actually known to possess anti-histaminic effects.[18] This last cluster example is showing that a correlation does in fact exist for drugs that were determined to have similar properties by the UBANTR approach.

By looking at the previous clusters (Figures **5.3** to **5.7**), it can be noticed that not all drugs of the same indication will always group together. For example, not all anti-histaminic drugs will appear within the same cluster or not all anti-hypertensive drugs will be grouped together. This has to do with the fact that not all drugs of the same indication will operate by the same biological pathway.

To analyze this further, focus was placed on antidepressants. The UBANTR drug library contains 25 anti-depressant drugs (not including isomers) that can be separated into 7 different types. For two of those types, only one drug is included in the library that follows that particular mechanism. Three other types each contain two drugs that follow that particular mechanism. The two major types of anti-depressants, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), each consist of four and 13 drugs, respectively. Out of the four SSRIs, two of them were found to group together, fluoxetine and luvox (Fig. **5.9**) and out of the 13 TCAs, 9 were found to group together in two different clusters. Six of them group together in the first cluster and three in the second (Fig. **5.9**), which could imply that even among the TCAs, the drugs operate through two different methods.

No two antidepressants from different classes or types were found to group together; Groupings were only observed between their own types. Meaning, there were no SSRIs and TCAs (or any other types) found within the same cluster.

SSRIs

R- fluoxetine
S- fluoxetine
luvox

TCAs

Protriptyline
Nortriptyline
Z- Dothiepin
E- Dothiepin
E- Doxepin
Z- Doxepin
Amitriptyline
E-Triprolidine (antihistaminic)
Dibenzepin

Clomipramine
Imipramine
Azatadine (antihistaminic)
S-Trimipramine
R-Trimipramine

Figure 5.9 Orange outputs for clustered SSRIs and TCA. Unless otherwise specified, all drugs are anti-depressants.

Taking a closer look at the ligand-protein interactions, focus will be place on the SSRI cluster, consisting of both isomers of fluoxetine (Fig. **5.10a**) and luvox (Fig. **5.10b**). Figure **5.11a** shows *R*-fluoxetine bound into one of the 15 random receptors. Through this depiction, the interaction between the ligand and neighboring residues can be determined. Figure **5.11b** then shows all clustered SSRIs aligned within the same random

protein. From this alignment it can be seen that the aromatic-CF_3 part of the molecule for each drug in this cluster have the same interactions with the same residues. Their similarity is apparent and helps explain why the three compounds were clustered together.

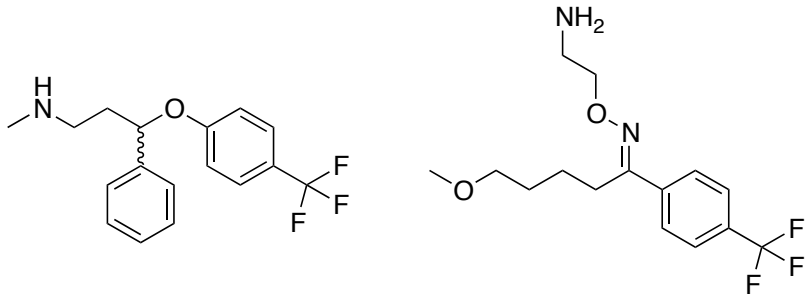

Figure 5.10 a) fluoxetine **b)** luvox.

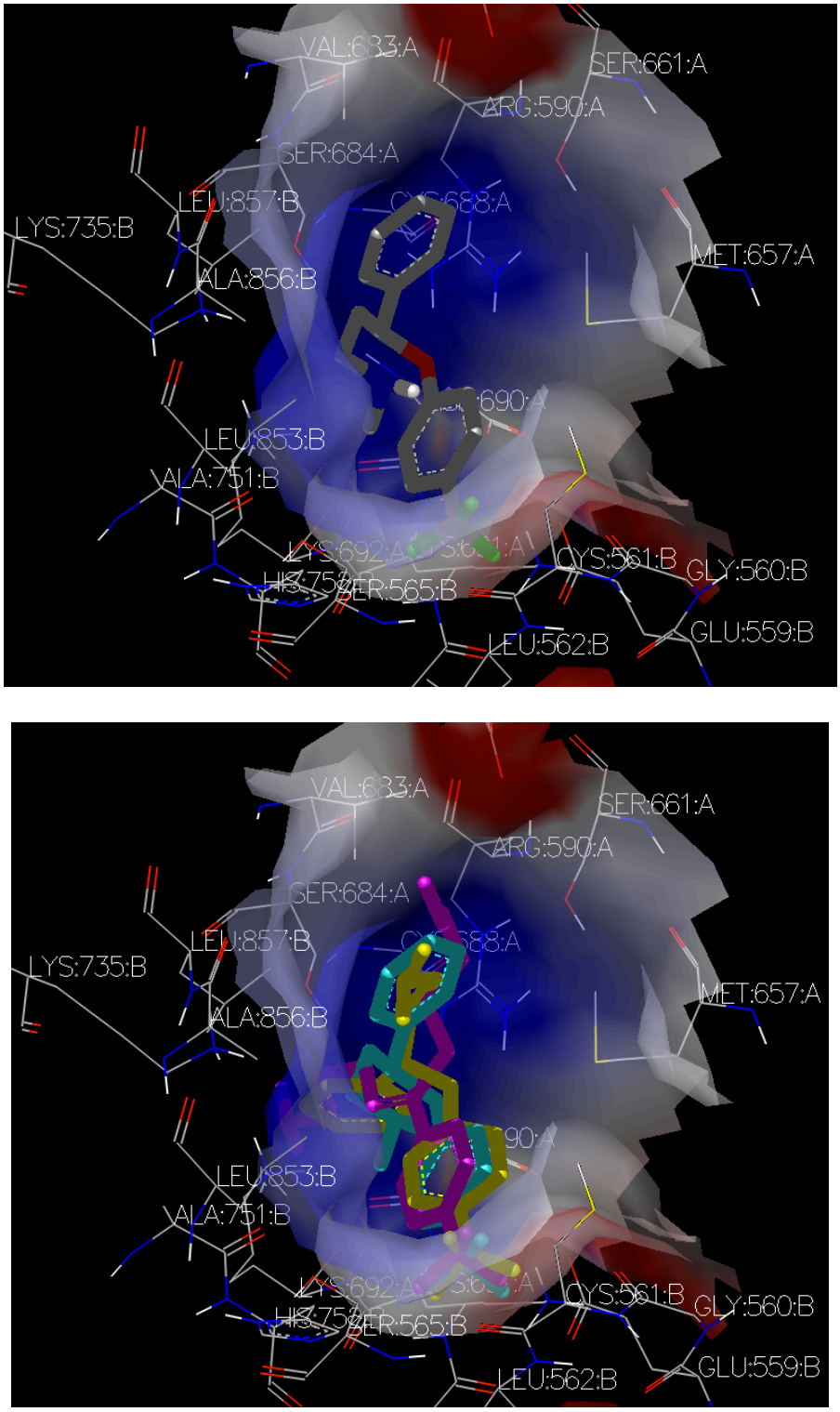

Figure 5.11 a) *R*-fluoxetine bound into one of the 15 receptors. **b)** all SSRIs: cyan: (*R*)-fluoxetine (cyan), yellow: (*S*)- fluoxetine magenta (yellow), and luvox (magenta) bound into the same random receptor.[19]

This similarity is emphasized further through the depiction in Figure **5.12**. This figure shows the alignment for the binding conformers of the same three compounds, for most of the 15 receptors. Looking through the sets of different overlaid structures, we can see how the structures align better for some of the proteins than for others. Therefore the UBANTR approach is helping to find drugs with a similar footprint across all 15 non-specific receptors.

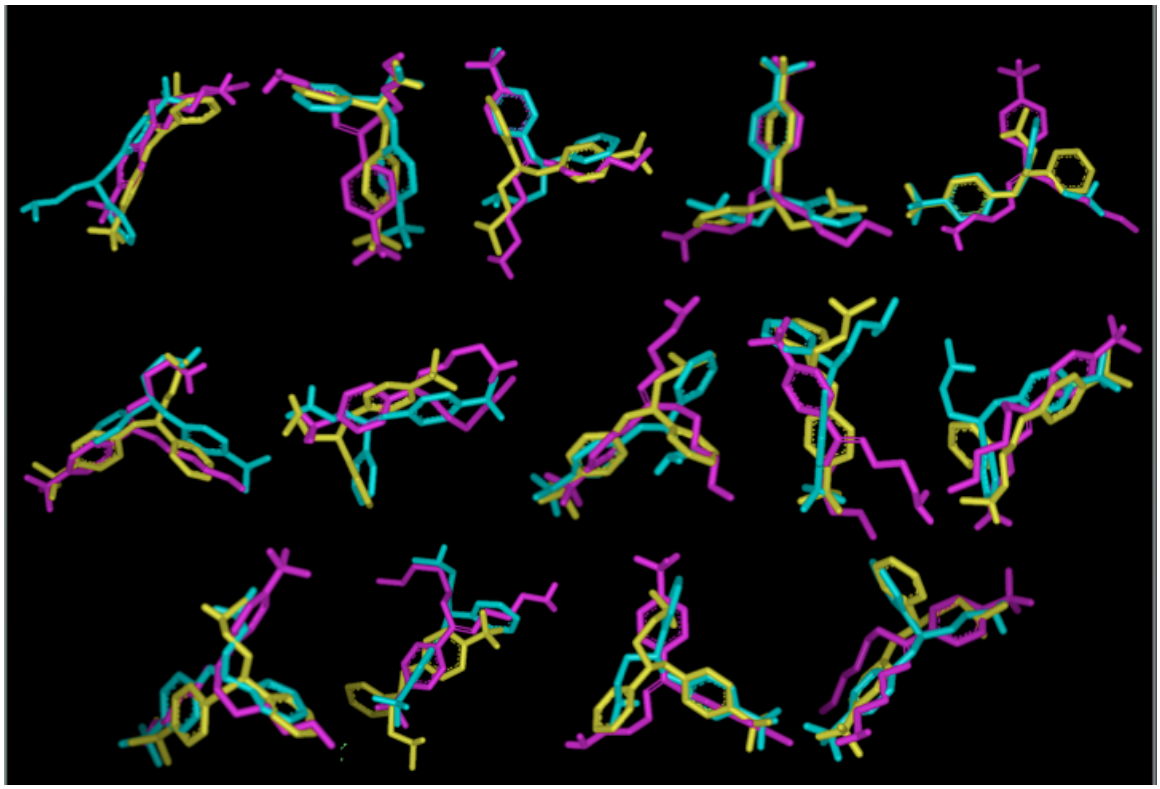

Figure 5.12 Representation of lowest binding conformers for all clustered SSRIs to most of the 15 random receptors.[19]

A control was performed to help prove that there was no statistical bias with the UBANTR approach. Since the original data used for the UBANTR approach was normalized between values of one and 100, the control consisted of randomly generating numbers also between one and 100. Table **5.2** compares the data that was inputted into Orange for *S*-trimipramine in the UBANTR approach versus the control and shows the great difference in both data sets. Figure **5.13** then shows the results of this control test. The different clusters are represented by the alternating colors and as expected, it is evident that the outputted groupings are more random than the results produced through the UBANTR approach. The first four clusters of the control do not produce any drugs with the same indication. In the last cluster, there does appear to be three anti-depressant drugs that have been grouped together. However, paroxetine is an SSRI, trimipramine is a TCA, and nomifensine functions through a third differing pathway. Therefore, despite the fact that it does group drugs of the same indication, it does not distinguish between their biological pathways; a fact that differs greatly from the UBANTR approach.

Table 5.2 Inputted data for trimipramine using the UBANTR (U) approach versus the control (C).

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}	R_{13}	R_{14}	R_{15}
U	46	17	93	54	72	94	68	97	64	21	98	77	48	49	62
C	18	72	86	66	54	45	4	24	2	93	38	1	47	50	44

S-Mazindol (anorexic)
E-Vinbarbital (sedative; hypnotic)
S-Cifenline (antiarrhythmic)
R-Carbinoxamine (antihistaminic)

S-Oxybutynin (anticholinergic)
S,R-Mesoridazine (antipsychotic)
R-Lorazepam (anxiolytic)
Methylprednisolone (glucocorticoid)
R-Thalidomide (sedative; hypnotic)

Ethenzamide (analgesic)
Phenacemide (anticonvulsant)
Levamisole (anthelmintic)

R-Butriptyline (antidepressant)
R,S-Secobarbital (sedative; hypnotic)
Promazine (antipsychotic)
Chlorambucil (antineoplastic)

bextra (analgesic; anti inflammatory)
Paroxetine (antidepressant)
S-Trimipramine (antidepressant)
R-Nomifensine (antidepressant)
S-Cetirizine (antihistaminic)
Z-Triprolidine (antihistaminic)
R,R-Secobarbital (sedative; hypnotic)

Figure 5.13 Control results showing random groupings of drugs.

The UBANTR approach can be used for NCEs as well. Any NCEs are docked to the same 15 random receptors and the data is normalized along with the entire FDA-approved drug library. The entire set is then inputted into Orange and depending on what the NCEs cluster with, it will predict its potential indication. For example, if we looked at Figure **5.3** and assumed we did not know the indication of *S*-Carbinoxamide, (so it is playing the role of a NCE for the purposes of this example) and it turned out to group

with three anti-histaminic drugs, we would imply that this NCE (*S*-Carbinoxamide) would be an anti-histamine or possess some anti-histaminic properties. Therefore NCEs would be treated in a similar fashion to the rest of the FDA-approved library and depending on which indications it grouped with, it is predicted to possess those similar properties, an approach that still only requires the structure of a biologically active compound.

5.5 Conclusion

The UBANTR approach uses the data of a library of FDA-approved drugs docked to 15 non-specific receptors. This data allows insight into the properties of drugs included in the library without knowledge or availability of target receptors. There are two main objectives to the UBANTR approach; i) to repurpose drugs and ii) to predict the indication for New Chemical Entities (NCEs).

The first objective relates to any mismatches in indication from known drugs. These mismatches are revealing indications for potential repurposing, giving insight into a drug's alternate uses. For our purposes, STITCH was used to help find any known connections between drug matches and not as a method of validating the UBANTR approach. Therefore, a search resulting in no connection should not imply a link does not exist; it is possible this connection has simply not been established. The UBANTR approach can be a great starting point for testing existing drugs for alternate purposes.

The second objective is to predict the indication for NCEs. Although this was briefly discussed, this objective can be achieved through a similar process. Any known drug matching with unknown drugs (NCEs) is revealing their potential indication.

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Appendix A:

Experimental Procedures and Spectroscopic Data

CBC_{an}

To a flask containing 1,3- Cyclohexanedione (2.50g, 22.3 mmol) dissolved in THF (19 mL), was added citral (3.09g, 20.3 mmol), freshly prepared $ZnBr_2$ (20.3 mmol) in THF (20mL), and EDDA (0.63g, 3.50 mmol). Mixture was then heated using either oil bath or microwave (100 Watts) at 40 ˚C for 10 minutes. Mixture was then extracted 3x with diethyl ether and water. CBC_{an} was then purified by column chromatography using a 1:4 Ethyl Acetate: Hexane solution. (4.41g, 88%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.475-6.441 p.p.m. (d, *J* = 10.1 Hz, 1H), 5.201- 5.167 (d, *J* = 10.08 Hz, 1H), 5.086 (m, 1H), 2.425- 2.165 (m, 6H), 2.079- 1.949 (m, 4H), 1.676 (bs, 3H), 1.589 (bs, 3H), 1.365 (s, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 194.76, 172.09, 132.15, 123.87, 121.85, 116.67, 110.52, 82.53, 41.91, 36.65, 28.80, 27.62, 25.86, 22.74, 20.87, 17.82. HRMS (*m/z*): $[M]^+$ calcd for $C_{16}H_{22}O_2$, 246.1620; found, 246.1701.

THC_{an}

CBC_{an} (1.51g) was adsorbed onto silica (3.02g) and heated to 150 ˚C by microwave, under vacuum (300 Watts), for about 60 minutes. Compound was then filtered, concentrated, and columned with 1:4 Ethyl Acetate: Hexane solution, giving 1.16g (77%) of the product. Heating CBC_{an} in the presence of EDDA decreases the rate of THC_{an} formation (Table S1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.09 p.p.m. (m, 1H), 6.02 (m, 1H), 3.18 (bs, 1H), 2.86-2.83 (br, 1H), 2.47- 2.20 (cm, 17H), 2.13-2.10 (m, 4H), 1.94- 1.78

(cm, 15H), 1.71 (s, 1H), 1.65 (s, 11H), 1.60 (m, 2H), 1.39-1.37 (d, *J*=5.00 Hz, 12H), 1.28-1.26 (m, 4H), 1.22 (s, 6H), 1.07 (s, 6H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 198.04, 197.57, 170.94, 168.91, 133.67, 133.52, 123.84, 122.40, 114.18, 113.59, 80.84, 79.13, 45.59, 40.22, 37.65, 37.43, 32.22, 31.46, 30.17, 30.05, 29.60, 29.46, 27.21, 25.89, 25.24, 24.71, 23.68, 23.37, 20.41, 20.33, 20.00 (Ratio= 1.2:1 *trans*:*cis*). *Data is for a mixture of isomers. Isolation of isomers proved to be difficult. Due to the peak overlap, multiplicity cannot be accurately determined for individual isomers. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{22}O_2$, 246.1620; found, 246.1693.

Δ^1-THC

THC_{an} (with C_5H_{11} alkyl side chain) (0.1777g, 0.5615 mmol) was dissolved in anhydrous THF (3.43 mL) and placed in a acetone/ dry ice bath (-78 °C). *t*-BuLi in pentanes (1.202M, 0.4671 mL) was then added to the mixture. After 15 minutes, I_2 was added and bath was replaced with a regular ice bath (0 °C). Fifteen minutes after I_2 was dissolved, 1,8-Diazabicycloundec-7-ene was added and mixture was allowed to stir at room temperature over night. Mixture was then extracted with 10% HCl and ether, dried over magnesium sulfate, and concentrated in vacuo. 0.0970g, 54.9% as a mixture of *cis*/*trans*-isomers. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.39- 6.23 ppm (cm, 5H), 6.16- 6.13 (cm, 2H), 5.68 (d, *J*= 3.8, 1H), 5.21 (bs, 1H), 3.58* (bs, 1H), 3.21 (d, *J*= 10.6, 2H), 2.62- 2.55* (dd, *J*= 4.3, 9.3, 2H), 2.45- 2.38 (dd, *J*= 6.8, 13.3, 5H), 2.18- 2.11 (cm, 4H), 1.98- 1.89 (cm, 6H), 1.69 (d, *J*= 3.8, 9H), 1.64- 1.50 (cm, 12H), 1.42- 1.26 (cm, 33H), 1.11- 1.06 (m, 6H), 0.93- 0.85 (q, *J*= 6.9, 11H). Data is for a mixture of *cis*- [(*S*,*R*) and (*R*,*S*)] and *trans*-

[(*R*,*R*) and (*S*,*S*)] isomers in a 1:2 ratio. *denotes peaks known to belong to *cis*- isomers. Underlined peaks denote those known to belong to the *trans*- isomers. Remaining peaks are for overlapping *cis*/*trans*- isomer peaks. Experimental integration is slightly higher for some peaks due to impurities. ^{13}C-NMR (300 MHz, $CDCl_3$): δ 155.14, 154.93, 154.55, 154.01, 153.38, 153.01, 152.86, 144.01, 143.76, 142.95, 142.57, 134.99, 134.40, 124.06, 123.98, 122.31, 122.14, 111.21, 111.04, 110.12, 110.05, 108.21, 107.79, 77.84, 77.38, 76.36, 46.01, 45.10, 41.11, 40.28, 35.98, 35.63, 34.66, 33.81, 31.95, 31.73, 31.39, 30.79, 29.97, 29.77, 28.10, 27.78, 27.28, 26.08, 25.23, 24.74, 23.57, 22.75, 20.90, 19.47, 14.23. Data is for a mixture of *cis*- [(*S*,*R*) and (*R*,*S*)] and *trans*- [(*R*,*R*) and (*S*,*S*)] isomers in a 1:2 ratio. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{30}O_2$, 314.2246; found, 314.2318.

Compound A

THC_{an} (1.37g, 5.58 mmol) was dissolved in anhydrous ether (24.3 mL) and added to a suspension of lithium aluminum hydride (1.22g, 32.03 mmol) in ether (97.1 mL). Mixture was stirred for half an hour at room temperature and then refluxed for an hour and a half. Then ammonium chloride (8.48g, 158.5mmol) was added to the mixture, followed by water (68.7 mL). It was then extracted with ether and dried with magnesium sulfate. Product was purified by column chromatography using 1:9 Ethyl Acetate: Hexane solution to yield separation of two major compounds (A and B) in a 1:4 ratio as *cis*/*trans* isomers (3:1 for compound A). Crude= 0.88g, 68.2%, Compound X= ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.62 p.p.m. (bs, 1H), 5.53 (d, J = 5.1, 3H), 2.69 (bs, 3H), 2.47 (bs, 1H), 2.24- 2.16 (cm, 2H), 2.12- 2.03 (cm, 6H), 1.98- 1.86 (cm, 21H), 1.79- 1.69 (cm,

15H), 1.68 (bs, 9H), 1.67 (bs, 5H), 1.60 (s, 1H), 1.55- 1.31 (cm, 18H), 1.29 (s, 5H), 1.28 (s, 9H), 1.27- 1.22 (cm, 2H), 1.20 (s, 9H), 1.05 (s, 3H). Isolated fraction used for NMR experiments of this compound contained a *cis*:*trans* ratio of 3:1. Experimental integration is slightly higher for some cm due to impurities. ^{13}C-NMR (500 MHz, $CDCl_3$): δ 144.64, 142.27, 134.54, 134.00, 122.10, 121.89, 105.24, 104.53, 76.16, 74.67, 45.84, 40.53, 36.47, 34.83, 31.68, 30.70, 28.33, 28.09, 27.83, 26.20, 25.06, 24.79, 23.79, 23.44, 23.23, 20.35, 19.92. *Data is for a mixture of isomers. Isolation of isomers proved to be difficult. Due to the peak overlap, multiplicity cannot be accurately determined for individual isomers. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{24}O$, 232.1827; found, 232.1902.

Compound B

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.54 p.p.m. (bs, 1H), 5.51 (bs, 1H), 5.47 (d, J = 4.1, 1H), 5.39 (bs, 1H), 4.14 (bs, 1H), 4.08 (t, J = 6.5, 1H), 3.08 (bs,1H), 2.70 (d, J = 9.0, 1H), 2.09- 1.90 (cm, 12H)[a], 1.71 (bs, 3H), 1.69 (bs, 3H), 1.71- 1.64 (cm, 5H)[b], 1.57- 1.43 (cm, 6H), 1.41-1.40 (cm, 1H), 1.39 (s, 3H), 1.36- 1.24 (cm, 3H)[c], 1.23 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H). Experimental integration is slightly higher for some cm due to impurities: a) 12H should integrate to 10H b) 5H should integrate to 4H and c) 3H should integrate to 1H. Isolated fraction used for NMR experiments of this compound contained a *cis*:*trans* ratio of 1:1. ^{13}C-NMR (500 MHz, $CDCl_3$): δ 139.79, 138.37, 135.23, 135.02, 124.33, 122.10, 120.53, 117.81, 74.66, 72.91, 67.83, 67.70, 49.81, 43.30, 38.60, 36.77, 31.39, 30.91, 30.60, 30.53, 28.88, 28.04, 25.83, 25.42, 25.17, 24.43, 23.72, 23.24, 20.68, 20.30,

19.00, 18.16. (Ratio= 1:1 *trans*:*cis*). *Data is for a mixture of isomers. Isolation of isomers proved to be difficult. Due to the peak overlap, multiplicity cannot be accurately determined for individual isomers. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{24}O$, 232.18; found, 232.19.

Δ^0-THC $_{gem}$

5,5-dimethyl -1,3-cyclohexanedione (1.49, 10.62 mmol) was dissolved in THF (18.6 mL), then (±) citronellal (1.74 mL, 9.65 mmol) was added, followed by zinc bromide (2.17g, 9.65 mmol), and EDDA (0.30g, 1.66 mmol). The mixture was then heated to 40 °C, for 30 minutes. It was then cooled, extracted with water and ether, dried over magnesium sulfate, and concentrated. Compound was recrystallized from hexane to afford white crystals. (0.337g, 12.7%) ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.84 ppm (m, 1H), 2.23- 2.03 (cm, 5H), 1.81-1.20 (cm, 4H), 1.31 (s, 3H), 1.09- 0.96 (cm, 2H), 1.04 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.88 (d *J* = 6.6, 3H), 0.46 (dd, *J*= 11.5, 24.0, 1H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 197.78, 168.55, 113.32, 80.42, 51.69, 48.91, 43.33, 38.73, 35.69, 33.66, 32.47, 31.67, 29.42, 27.66, 27.36, 22.56, 19.62. Data is for a mixture of isomers. Isolation of isomers proved to be difficult. Due to the peak overlap, multiplicity cannot be accurately determined for individual isomers. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{28}O_2$, 276.2089; found, 276.2174.

CBC_{gem}

5,5-dimethyl -1,3-cyclohexanedione (1.84, 13.12 mmol) was dissolved in THF (21.0 mL), then (±) citral (1.87 mL, 10.93 mmol) was added, followed by zinc bromide (2.46g, 10.93 mmol), and EDDA (0.339g, 1.880 mmol). The mixture was then heated to 40 °C, for 40 minutes. It was then cooled, extracted with water and ether, dried over magnesium sulfate, and concentrated. Compound was purified by column chromatography with 1:3 Ethyl Acetate: Hexanes (2.28g, 75.9%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.45 ppm (d, *J*= 10.1, 1H, 5.17 (d, *J*= 10.0, 1H), 5.13-5.04 (m, 1H), 2.27 (d, *J*=2.2, 2H), 2.25 (s, 2H), 2.10- 1.99 (cm, 2H), 1.77-1.52 (cm, 2H), 1.68 (d, *J*= 1.0, 3H), 1.59 (s, 3H), 1.37 (s, 3H), 1.07 (d, *J*= 3.2, 6H).

Δ^1-THC $_{gem}$

CBCgem (0.506g) was adsorbed onto silica (1.00g) and heated to 150 °C for 50 minutes, then mixture was filtered through sand. No purification needed (0.641g, quantitative yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.09 ppm (bs, 1H), 6.06 (s, 1H), 3.17 (bs, 1H), 2.81 (bs, 1H), 2.35- 2.10 (cm, 15H), 1.98- 1.76 (cm, 7H), 1.64 (bs, 6H), 1.62- 1.43 (cm, 5H), 1.38 (s, 3H), 1.36 (s, 4H), 1.30 (d, *J* = 2.2, 1H), 1.22 (s, 3H), 1.06 (s, 6H), 1.02 (d, *J* = 2.2, 9H). Experimental integration is slightly higher for some cm due to impurities. ^{13}C-NMR (400 MHz, $CDCl_3$): δ 198.26, 197.74, 169.13, 167.25, 133.62, 133.42, 122.15, 112.12, 80.89, 79.30, 51.66, 51.59, 45.67, 43.35, 43.22, 40.15, 32.17, 32.04, 31.47, 30.04, 28.97, 27.21, 25.45, 24.76, 23.44, 20.60, 20.11. Isolated fraction used for NMR experiments of this compound contained a *cis*:*trans* ratio of 1:1. Isolation of isomers

proved to be difficult. Due to the peak overlap, multiplicity cannot be accurately determined for individual isomers. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{26}O_2$, 274.1933; found, 274.2241.

Δ^0-THC $_{est}$

Methyl acetoacetate (3.30 mL, 30.56 mmol) and (±)citronellal (4.99 mL, 27.78 mmol) were mixed with THF (53.42 mL). Then zinc bromide (6.25g, 27.78 mmol) and EDDA (1.00g, 5.55 mmol) were added, respectively. The mixture was then heated to 40 °C for 2.5 hours. It was then extracted with water and ether, dried with magnesium sulfate, and concentrated. Crude = 6.50g, 92.7%. Crude compound (6.2g, 24.57 mmol) was dissolved in methylene chloride (61.4 mL). Then acetic acid (6.4 mL, 112.04 mmol) and HCl (2.0 mL, 24.57 mmol, 12.1 N) were added. Mixture was allowed to stir at room temperature for 2 hours. Methylene chloride was evaporated and residue was dissolved in ether and extracted with water. Organic phase was washed with saturated sodium bicarbonate solution, water, then brine. Then it was dried over magnesium sulfate and concentrated (5.91g, 90.9% crude). Compound was then run through a silica plug and eluted with 5:95 Ethyl acetate: Hexanes (1.6g, 47.1%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.69 ppm (s, 3H), 2.13- 2.07 (cm, 2H), 2.07 (d, *J*= 1.3, 3H), 1.79- 1.46 (cm, 5H), 1.29 (s, 3H), 1.26- 0.91 (cm, 4H), 1.07 (s, 3H), 0.90 (d, *J*= 6.5, 3H), 0.61 (dd, *J*= 11.7, 24.3, 1H). Integration slightly higher due to some impurity, but seems consistent with the literature.

CBC_{est}

(±)Citral (19.4 mL, 0.1132 mol) is mixed with THF (218 mL), then methyl acetoacetate (13.44 mL, 0.1245 mol) is added, followed by EDDA (2.04g, 11.3 mmol). Mixture is stirred for 2 hours and 35 minutes at 40 °C. It is then extracted with ether and water, dried with sodium sulfate, and concentrated. Product was next purified for next reaction (quantitative yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.32 ppm (d, *J* = 10.0, 1H), 5.11-5.06 (cm, 2H), 3.72 (s, 3H), 2.39- 2.34 (cm, 2H), 2.27 (s, 3H), 2.23- 2.11 (cm, 3H), 2.06-1.92 (cm, 4H), 1.67 (bs, 6H), 1.59 (bs, 6H), 1.32 (s, 3H). Experimental integration is higher for some peaks due to the presence of some uncyclized product (the result of the Knoevenagel reaction, prior to the 6π-oxo-electrocyclization.^{13}C-NMR (400 MHz, $CDCl_3$): δ 167.15, 166.51, 156.67, 156.51, 140.45, 140.32, 131.98, 124.09, 124.01, 123.22, 120.40, 119.99, 119.91, 102.53, 80.86, 52.25, 51.22, 41.20, 41.06, 33.30, 33.11, 31.49, 27.18, 26.65, 26.46, 25.88, 25.80, 22.74, 20.36, 17.81, 17.74. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{22}O_3$, 250.1569; found, 250.1683.

Δ^1-THC_{est}

CBC_{est} (5.26g) was adsorbed onto silica (10.5g) and heated at 150 °C for 4.5 hours. Compound was purified by column chromatography using 1:4 Ethyl acetate: Hexanes (1.43g, 28.3%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.59 ppm (bs, 1H) 5.49 (s, 2H), 3.75 (d, *J*= 1.0, 4H), 3.74 (d, *J*= 0.9, 3H), 3.21 (bs, 1H), 2.84 (bs, 2H), 2.12 (dd, 6H), 2.08 (s, 4H), 1.94 (d, *J*= 7.7, 2H), 1.82- 1.79 (cm, 3H), 1.64 (bs, 8H), 1.33 (d, *J* = 5.0, 9H), 1.25 (s, 3H), 1.09 (s, 5H). Experimental integration is higher than expected due to a mixture of

cis:*trans* isomers (1:2) and slight impurities. ^{13}C-NMR (400 MHz, $CDCl_3$): δ 168.99, 160.96, 158.73, 135.22, 134.13, 124.35, 121.94, 120.40, 119.38, 104.22, 78.91, 77.48, 50.90, 45.29, 39.89, 34.03, 31.37, 30.11, 29.87, 27.32, 25.32, 23.74, 23.47, 23.39, 20.17, 20.04, 18.74. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{22}O_3$, 250.1569; found, 250.1729.

Compound E

per-THC $_{est}$ (0.4845g, 1.920 mmol) and tetramethylethylenediamine (TMEDA) (0.288 mL, 1.920 mmol) were diluted in anhydrous diethyl ether (11.9 mL) and the temperature was lowered to -20 °C. Then *t*-BuLi in pentanes (2.3 mL, 2.304 mmol) was added dropwise. After 45 minutes, the dimethyl acetylenedicarboxylate (0.235 mL, 1.920 mmol) was added. It was left to stir at -20 °C for 2 hours and then left to stir at room temperature over night. Mixture was then extracted with 10% HCl, dried over sodium sulfate, and concentrated. (< 1% yield recovered). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.62 p.p.m. (s, 1H), 6.39 (s, 1H), 3.85 (d, *J*= 2.7, 6H), 3.16 (d, *J*= 12.8, 1H), 2.48 (td, J= 2.7, 11.0, 1H), 1.88-1.83 (m, 3H), 1.71- 1.57 (cm, 2H), 1.38 (s, 4H), 1.35- 1.29 (cm, 1H), 1.16- 1.08 (cm, 4H), 1.05 (s, 4H), 0.95 (d, J= 6.5, 4H), 0.93-0.84 (cm, 2H), 0.66 (dd, J= 11.5, 24.0, 1H) Data is for a mixture of *cis* and *trans*- isomers. ^{13}C-NMR (400 MHz, $CDCl_3$): δ 170.27, 169.80, 162.77, 159.48, 134.65, 131.19, 129.07, 129.00, 115.03, 110.05, 101.44, 79.14, 68.36, 66.04, 52.67, 48.90, 38.94, 38.31, 35.61, 35.53, 32.96, 29.90, 29.11, 28.11, 27.61, 23.91, 23.16, 22.69, 19.33, 15.46, 14.30, 14.24, 11.15. *Data is for a mixture of isomers. Isolation of isomers proved to be difficult. Due to the peak

overlap, multiplicity cannot be accurately determined for individual isomers. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{26}O_6$, 362.1729; found, 362.1808.

Appendix B:

NMR spectra for THC_{an} with C_5 alkyl chain and NMR Analysis

THC_{an} with the C_5 alkyl chain was obtained as a mixture of all stereoisomers by the same pathway as CBC_{an} to THC_{an} (with no alkyl chain). The following table gives the carbon and proton assignments for the 4 isomers produced from the reaction. The NMR spectra show groupings of four for all atoms in the structure, representing four stereoisomers. One of the key factors used in the identification of all four isomers involves the *gem*-dimethyl groups (labeled 8 and 9) and the NOESY spectrum. For the *cis* isomers, it was found that one of the methyl groups correlated to both protons 1 and 6, while the methyl group from the *trans* isomers showed correlation to only one proton, either 1 or 6. Formal stereochemical designation of *cis* and *trans* isomers could not be determined.

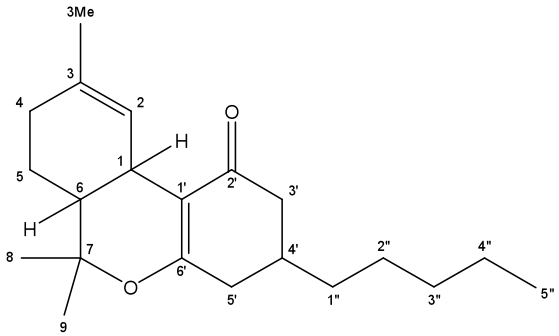
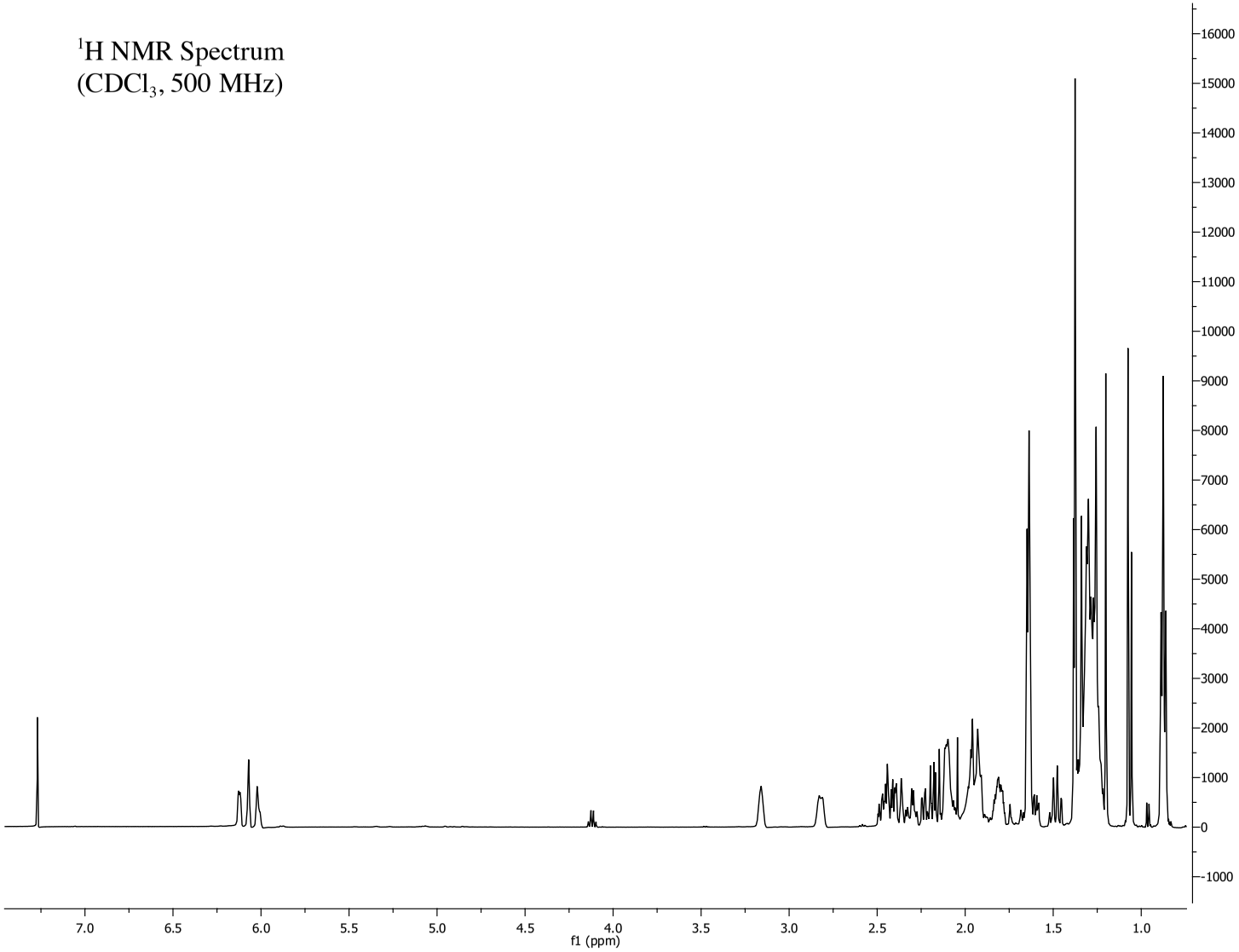


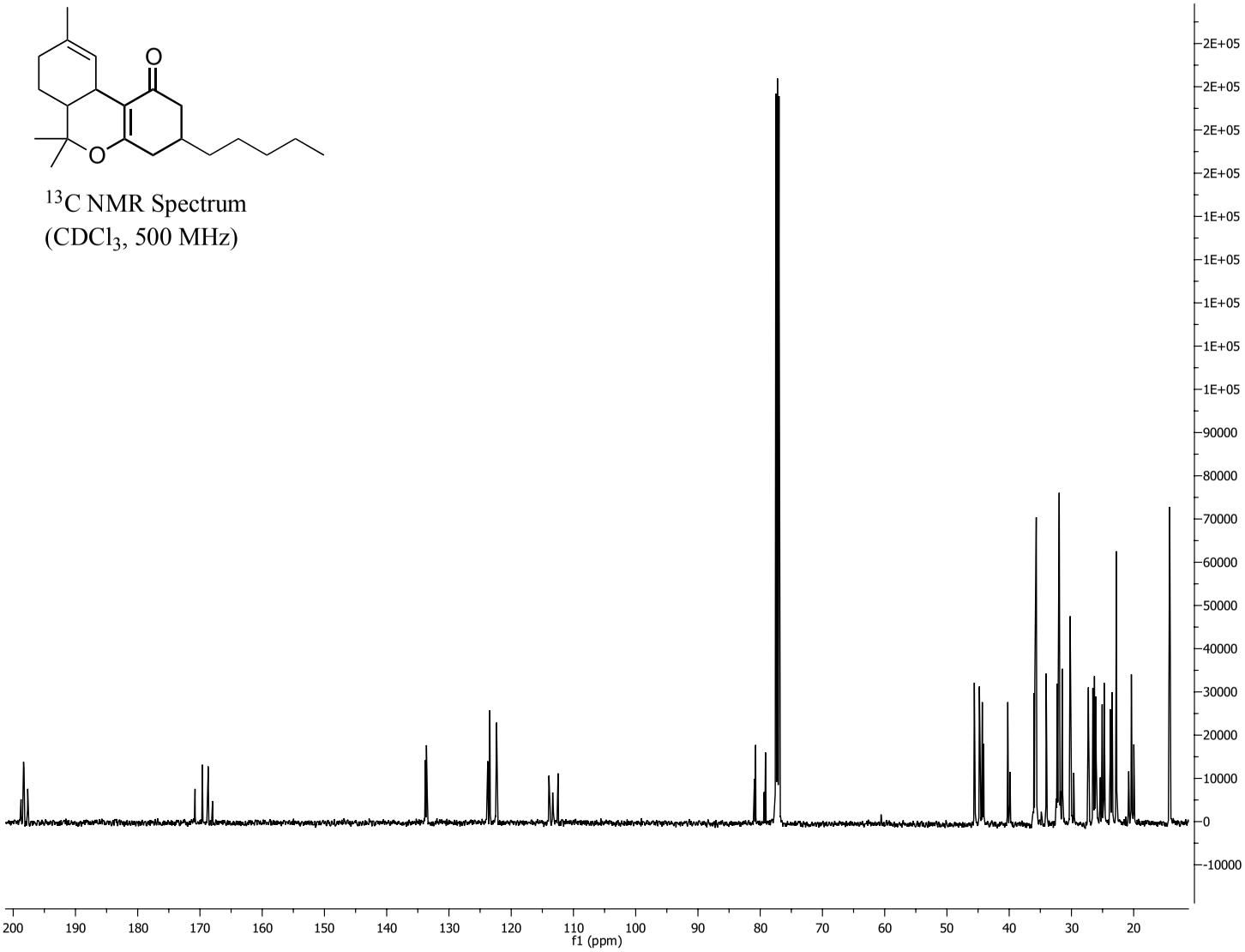
Table analysis on next page.

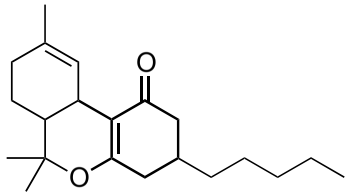
	cis I				*cis* II				*trans* I				*trans* II			
Position	^{1}H	^{13}C	NOESY	HMBC	^{1}H	^{13}C	NOESY	HMBC	^{1}H	^{13}C	NOESY	HMBC	^{1}H	^{13}C	NOESY	HMBC
1	3.14	29.97	4,5,6,9,5"	2,3,5,6,1',6'	3.15	29.79	4,5,6,8		2.81	31.90	4,5,9,5"		2.81	32.05	4,5,8	
2	6.11	122.12	1,4,3_{Me}	4,3_{Me},6,1'	5.99	122.03	1,4,3_{Me}	4,3_{Me},6	6.06	123.20	1,4,3_{Me}, 6	1,3_{Me},4,6,1'	6.01	123.55	1,4,3_{Me}, 6	1,3_{Me},4,6,1'
3		133.55				133.25				133.39				133.34		
3_{Me}	1.64	23.52	2,4	2,3,4	1.61	23.45	2,4	2,3,4	1.62	23.23	2,4	2,3,4	1.62	23.18	2,4	2,3,4
4	1.92	29.97	3_{Me},5,6	2,3,3_{Me},5,6,1'	1.91	29.39	3_{Me},5,6	2,3,3_{Me},5,6	2.09	31.22	3_{Me},5,6	2,3,3_{Me},5,6	2.10	31.24	3_{Me},5,6	2,3,3_{Me},5,6
5	1.23,1.80	20.08	4,6	1,3,4,6	1.31,1.84	20.57	4,6	1,4,6,7	1.33,1.79	24.53	4,6	1,3,6,7,1'	1.33,1.80	24.49	4,6	1,3,6,1'
6	1.59	39.99	1,5,8,9	1,2,5,1'	1.64	39.65	1,5,8,9	1,2,7,5,1'	1.48	45.37	5,8,9	1,2,5,7,9	1.48	45.37	5,8,9	1,2,5,7,9
7		78.92				79.13				80.50				80.70		
8	1.37	25.88	6,9	1,7,6,9	1.25	25.81	1,6,9	6,7,9	1.37	27.05	6,9	1,7,6,9	1.05	19.75	1,9	6,7,9
9	1.19	24.83	1,6,8	6,7,8	1.33	25.13	6,8	6,7,8	1.07	20.14	1,8	6,7,8	1.37	27.03	6,8	6,7,8
1'		113.71				112.99				112.25				113.10		
2'		198.03				197.44				198.11				198.51		
3'	1.92,2.44	44.09	4'	1',2',4',5'	1.92,2.44	43.87	4'	2',4',5'	2.17,2.42	44.56	4'	1',2',4',5'	2.11,2.40	44.51	4'	1',2',4',5'
4'	1.95	32.06	3',5'	2',5',1"	1.98	32.20	3',5'	5',1"	2.05	33.84	3',5'	2',3',5',6',1"	2.05	33.73	3',5'	3',5',6',1"
5'	1.90,2.36	35.79	4'	1',3',4',6'	1.92,2.36	35.90	4'	3',4',6'	2.20,2.31	35.65	4'	1',3',4',6'	2.16,2.29	35.65	4'	3',4',6'
6'		168.47				170.57				169.39				167.75		
1"	1.31	31.73	2"	3',4',5',2", 3"	1.31	31.73	2"	3',4',5',2", 3"	1.31	31.73	4'	3',4',5',2", 3"	1.31	31.73	4'	3',4',5',2", 3"
2"	1.27	26.33		1",3"	1.27	26.25		1",3"	1.27	26.08		1",3"	1.27	26.06		1",3"
3"	1.23	31.73		2",4"	1.23	31.73		2",4"	1.23	31.73		2",4"	1.23	31.73		2",4"
4"	1.27	22.53		3",5"	1.27	22.53		3",5"	1.27	22.53		3",5"	1.27	22.53		3",5"
5"	0.86	13.99	1,4"	3",4"	0.86	13.99	4"	3",4"	0.86	13.99	1,4"	3",4"	0.86	13.99	4"	3",4"

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)

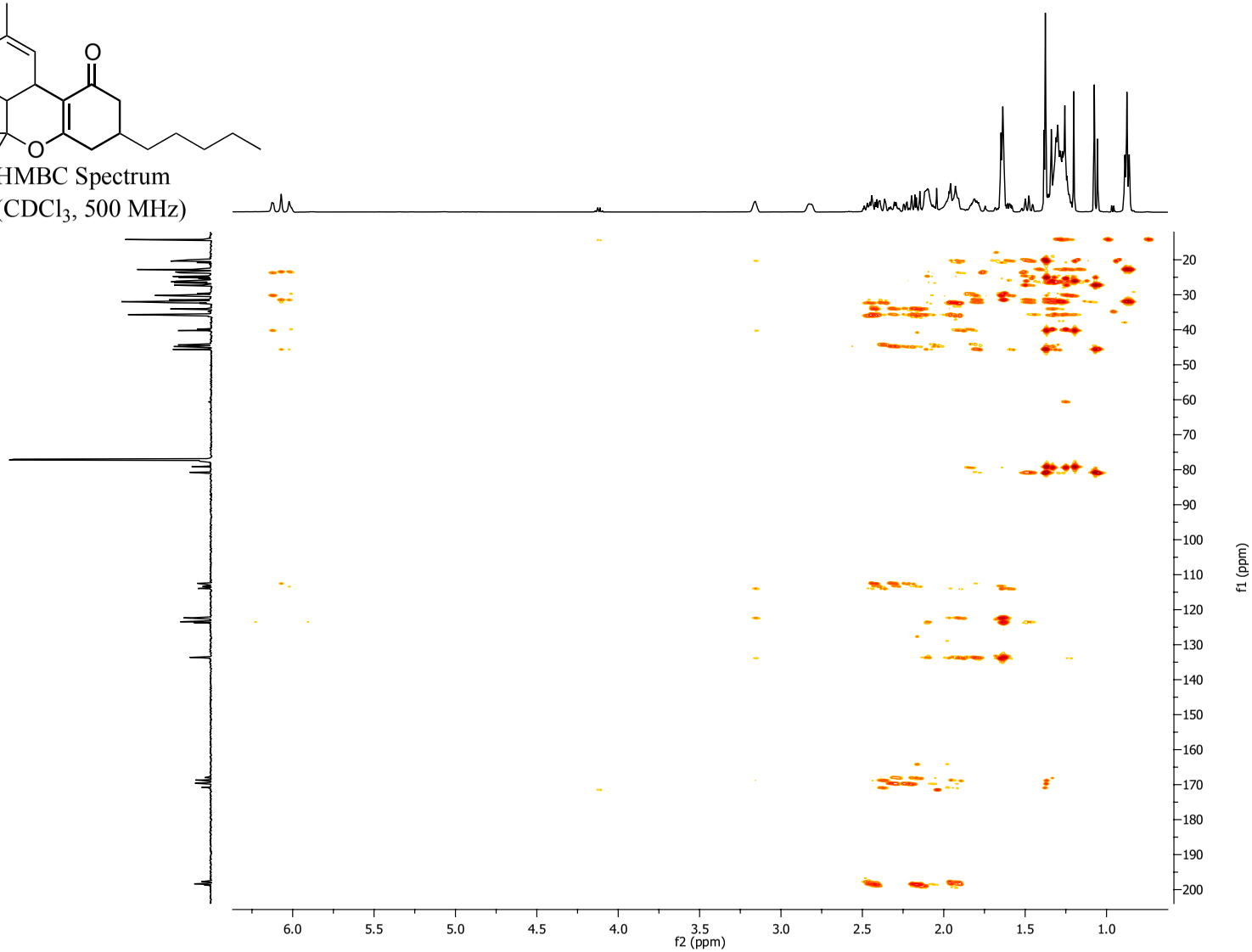


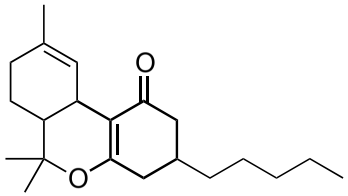
^{13}C NMR Spectrum
($CDCl_3$, 500 MHz)



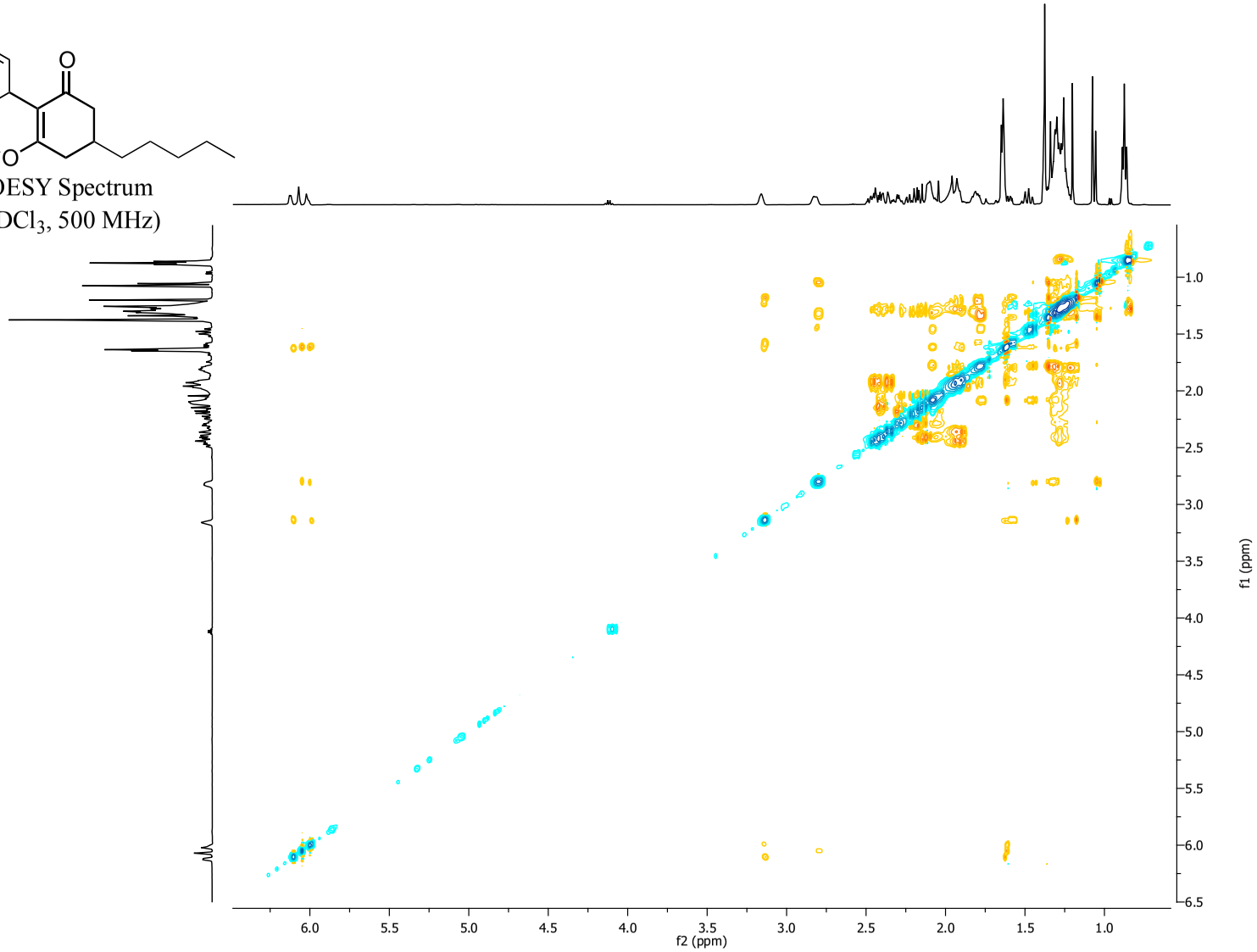


HMBC Spectrum
($CDCl_3$, 500 MHz)





NOESY Spectrum
($CDCl_3$, 500 MHz)



Appendix C:

Ground State and TS Coordinates (DFT B3LYP/6-31G*)

Figure 2.3 (p.32)
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HETATM	15	C	UNK	0001	-1.941	-0.015	0.729
HETATM	16	H	UNK	0001	-1.673	1.005	1.027
HETATM	17	H	UNK	0001	-2.533	-0.445	1.549
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CONECT    3   2
CONECT    4   1   5   10
CONECT    5   4   7    9
CONECT    6   2   7   36
CONECT    7   8   5    6
CONECT    8   7
CONECT    9   5
CONECT   10  11   4   12
CONECT   11  10
CONECT   12  13  10   14
CONECT   13  12
CONECT   14  12  15   32
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CONECT   18  19  20   15   21
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CONECT   41  40
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TS CBC (14.6 kcal/mol)
Energy= -509185.065 kcal/mol

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HETATM  13  C   UNK  0001      2.029  -2.666   0.571
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HETATM  15  C   UNK  0001     -1.351  -0.289   2.476
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HETATM  17  H   UNK  0001     -0.534  -0.506   3.165
HETATM  18  H   UNK  0001     -1.820  -1.225   2.164
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HETATM  27  C   UNK  0001     -2.821   2.018  -3.019
HETATM  28  C   UNK  0001     -4.033   2.074  -3.918
HETATM  29  H   UNK  0001     -3.739   2.071  -4.978
HETATM  30  H   UNK  0001     -4.606   2.999  -3.759
HETATM  31  H   UNK  0001     -4.705   1.226  -3.752
HETATM  32  C   UNK  0001     -1.856   3.164  -3.201
HETATM  33  H   UNK  0001     -1.487   3.202  -4.236
HETATM  34  H   UNK  0001     -0.988   3.110  -2.540
HETATM  35  H   UNK  0001     -2.358   4.125  -3.017
HETATM  36  C   UNK  0001      4.021  -4.183   0.737
HETATM  37  H   UNK  0001      3.535  -4.717  -0.085
HETATM  38  H   UNK  0001      4.085  -4.866   1.594
HETATM  39  H   UNK  0001      5.051  -3.951   0.437
HETATM  40  O   UNK  0001      3.821  -0.009   3.244
HETATM  41  H   UNK  0001      3.158   0.598   3.607
CONECT   1   2   3
CONECT   2   1   8  13
CONECT   3   1   4  15  19
CONECT   4   5   3   6
CONECT   5   4
CONECT   6   7   4   8
CONECT   7   6
CONECT   8   6   2   9
CONECT   9   8  10  40
CONECT  10  11   9  12
CONECT  11  10
CONECT  12  10  13  36
```

```
CONECT   13   14    2   12
CONECT   14   13
CONECT   15   16   17   18    3
CONECT   16   15
CONECT   17   15
CONECT   18   15
CONECT   19   20   21    3   22
CONECT   20   19
CONECT   21   19
CONECT   22   23   24   19   25
CONECT   23   22
CONECT   24   22
CONECT   25   26   22   27
CONECT   26   25
CONECT   27   25   28   32
CONECT   28   29   30   31   27
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35   27
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   12
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41    9
CONECT   41   40
END
```

TS *cis*-THC (25.5 kcal/mol)
Energy= -509174.181 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      0.172  -1.858   2.407
HETATM    2  C   UNK  0001      1.039  -1.670   1.405
HETATM    3  H   UNK  0001      2.064  -2.025   1.539
HETATM    4  C   UNK  0001     -1.282  -1.443   2.363
HETATM    5  H   UNK  0001     -1.500  -0.821   3.243
HETATM    6  H   UNK  0001     -1.897  -2.349   2.495
HETATM    7  C   UNK  0001     -1.733  -0.707   1.094
HETATM    8  H   UNK  0001     -2.830  -0.628   1.108
HETATM    9  H   UNK  0001     -1.352   0.321   1.103
HETATM   10  C   UNK  0001     -1.271  -1.430  -0.159
HETATM   11  H   UNK  0001     -1.125  -2.503  -0.033
HETATM   12  C   UNK  0001      0.803  -1.062   0.071
HETATM   13  H   UNK  0001      0.986  -1.725  -0.772
HETATM   14  C   UNK  0001      1.076   0.284  -0.265
HETATM   15  C   UNK  0001     -1.619  -1.035  -1.449
```

```
HETATM  16  O   UNK  0001      0.462  -0.290  -2.463
HETATM  17  C   UNK  0001      0.902   0.604  -1.686
HETATM  18  C   UNK  0001      1.446   1.344   0.624
HETATM  19  C   UNK  0001      1.729   2.604   0.141
HETATM  20  H   UNK  0001      2.064   3.379   0.830
HETATM  21  C   UNK  0001      1.601   2.912  -1.246
HETATM  22  C   UNK  0001      1.170   1.948  -2.124
HETATM  23  H   UNK  0001      1.041   2.160  -3.182
HETATM  24  C   UNK  0001      0.604  -2.526   3.689
HETATM  25  H   UNK  0001     -0.007  -3.414   3.904
HETATM  26  H   UNK  0001      0.479  -1.848   4.546
HETATM  27  H   UNK  0001      1.653  -2.835   3.654
HETATM  28  C   UNK  0001     -1.678  -2.044  -2.560
HETATM  29  H   UNK  0001     -2.711  -2.408  -2.675
HETATM  30  H   UNK  0001     -1.044  -2.912  -2.350
HETATM  31  H   UNK  0001     -1.365  -1.606  -3.510
HETATM  32  C   UNK  0001     -2.219   0.318  -1.691
HETATM  33  H   UNK  0001     -3.233   0.371  -1.264
HETATM  34  H   UNK  0001     -2.280   0.549  -2.757
HETATM  35  H   UNK  0001     -1.633   1.106  -1.202
HETATM  36  C   UNK  0001      1.945   4.306  -1.712
HETATM  37  H   UNK  0001      3.016   4.512  -1.580
HETATM  38  H   UNK  0001      1.401   5.066  -1.137
HETATM  39  H   UNK  0001      1.706   4.443  -2.771
HETATM  40  O   UNK  0001      1.557   1.055   1.958
HETATM  41  H   UNK  0001      1.861   1.857   2.412
CONECT   1   2   4  24
CONECT   2   3   1  12
CONECT   3   2
CONECT   4   5   6   1   7
CONECT   5   4
CONECT   6   4
CONECT   7   8   9   4  10
CONECT   8   7
CONECT   9   7
CONECT  10  11   7  12  15
CONECT  11  10
CONECT  12  13  10   2  14
CONECT  13  12
CONECT  14  12  17  18
CONECT  15  10  16  28  32
CONECT  16  15  17
CONECT  17  14  16  22
CONECT  18  14  19  40
CONECT  19  20  18  21
CONECT  20  19
CONECT  21  19  22  36
CONECT  22  23  17  21
CONECT  23  22
CONECT  24  25  26  27   1
CONECT  25  24
```

```
CONECT   26   24
CONECT   27   24
CONECT   28   29   30   31   15
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35   15
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   21
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41   18
CONECT   41   40
END
```

TS *trans*-THC (24.1 kcal/mol)
Energy= -509175.659 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      0.874   0.658  -0.458
HETATM    2  C   UNK  0001      1.558   1.701   0.241
HETATM    3  C   UNK  0001      1.653  -0.501  -0.885
HETATM    4  C   UNK  0001      3.073  -0.500  -0.665
HETATM    5  H   UNK  0001      3.630  -1.367  -1.006
HETATM    6  C   UNK  0001      3.699   0.562  -0.057
HETATM    7  C   UNK  0001      2.926   1.665   0.407
HETATM    8  H   UNK  0001      3.427   2.496   0.904
HETATM    9  C   UNK  0001     -0.518   0.553  -0.722
HETATM   10  C   UNK  0001     -1.347  -1.026   0.412
HETATM   11  H   UNK  0001     -1.225  -0.482   1.348
HETATM   12  C   UNK  0001     -0.517  -2.139   0.245
HETATM   13  O   UNK  0001      1.041  -1.500  -1.375
HETATM   14  C   UNK  0001     -2.746  -0.994  -0.182
HETATM   15  H   UNK  0001     -3.338  -1.834   0.210
HETATM   16  H   UNK  0001     -2.695  -1.152  -1.268
HETATM   17  C   UNK  0001     -3.506   0.305   0.105
HETATM   18  H   UNK  0001     -4.458   0.289  -0.445
HETATM   19  H   UNK  0001     -3.797   0.336   1.168
HETATM   20  C   UNK  0001     -2.777   1.589  -0.211
HETATM   21  C   UNK  0001     -1.473   1.667  -0.526
HETATM   22  H   UNK  0001     -1.042   2.658  -0.637
HETATM   23  H   UNK  0001     -0.699  -0.105  -1.569
HETATM   24  C   UNK  0001      0.568  -2.385   1.254
HETATM   25  H   UNK  0001      1.361  -3.018   0.849
HETATM   26  H   UNK  0001      0.151  -2.886   2.142
HETATM   27  C   UNK  0001     -0.896  -3.269  -0.670
HETATM   28  H   UNK  0001     -1.687  -3.880  -0.207
```

```
HETATM   29  H   UNK  0001      -0.039  -3.914  -0.876
HETATM   30  H   UNK  0001      -1.280  -2.902  -1.625
HETATM   31  C   UNK  0001      -3.609   2.840  -0.072
HETATM   32  H   UNK  0001      -4.034   2.924   0.938
HETATM   33  H   UNK  0001      -4.460   2.826  -0.767
HETATM   34  H   UNK  0001      -3.022   3.742  -0.270
HETATM   35  C   UNK  0001       5.193   0.578   0.159
HETATM   36  H   UNK  0001       5.672  -0.296  -0.293
HETATM   37  H   UNK  0001       5.440   0.583   1.230
HETATM   38  H   UNK  0001       5.648   1.478  -0.276
HETATM   39  H   UNK  0001       1.013  -1.443   1.595
HETATM   40  O   UNK  0001       0.816   2.753   0.717
HETATM   41  H   UNK  0001       1.423   3.385   1.132
CONECT    1    2    3    9
CONECT    2    1    7   40
CONECT    3    1    4   13
CONECT    4    5    3    6
CONECT    5    4
CONECT    6    4    7   35
CONECT    7    8    6    2
CONECT    8    7
CONECT    9    1   10   23   21
CONECT   10   11    9   12   14
CONECT   11   10
CONECT   12   10   13   24   27
CONECT   13   12    3
CONECT   14   15   16   10   17
CONECT   15   14
CONECT   16   14
CONECT   17   18   19   14   20
CONECT   18   17
CONECT   19   17
CONECT   20   17   21   31
CONECT   21   22   20    9
CONECT   22   21
CONECT   23    9
CONECT   24   25   26   12   39
CONECT   25   24
CONECT   26   24
CONECT   27   28   29   30   12
CONECT   28   27
CONECT   29   27
CONECT   30   27
CONECT   31   32   33   34   20
CONECT   32   31
CONECT   33   31
CONECT   34   31
CONECT   35   36   37   38    6
CONECT   36   35
CONECT   37   35
CONECT   38   35
```

```
CONECT   39   24
CONECT   40   41    2
CONECT   41   40
END
```

CBC (-16.8 kcal/mol)
Energy= -509216.547 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  O   UNK  0001       0.844  -0.324   0.872
HETATM    2  C   UNK  0001       2.062  -0.170   0.281
HETATM    3  C   UNK  0001       0.004   0.845   1.115
HETATM    4  C   UNK  0001       0.163   1.867   0.011
HETATM    5  H   UNK  0001      -0.642   2.585  -0.119
HETATM    6  C   UNK  0001       1.278   1.926  -0.731
HETATM    7  H   UNK  0001       1.414   2.686  -1.493
HETATM    8  C   UNK  0001       2.333   0.942  -0.535
HETATM    9  C   UNK  0001       3.594   1.004  -1.154
HETATM   10  C   UNK  0001       4.539  -0.004  -0.967
HETATM   11  H   UNK  0001       5.512   0.073  -1.452
HETATM   12  C   UNK  0001       4.246  -1.112  -0.159
HETATM   13  C   UNK  0001       2.999  -1.190   0.464
HETATM   14  H   UNK  0001       2.738  -2.032   1.097
HETATM   15  C   UNK  0001       0.421   1.449   2.468
HETATM   16  H   UNK  0001      -0.202   2.317   2.711
HETATM   17  H   UNK  0001       1.464   1.779   2.430
HETATM   18  H   UNK  0001       0.315   0.706   3.267
HETATM   19  C   UNK  0001      -1.430   0.291   1.190
HETATM   20  H   UNK  0001      -2.101   1.115   1.468
HETATM   21  H   UNK  0001      -1.468  -0.435   2.012
HETATM   22  C   UNK  0001      -1.929  -0.372  -0.108
HETATM   23  H   UNK  0001      -1.931   0.365  -0.918
HETATM   24  H   UNK  0001      -1.200  -1.141  -0.394
HETATM   25  C   UNK  0001      -3.281  -1.008   0.069
HETATM   26  H   UNK  0001      -3.301  -1.818   0.802
HETATM   27  C   UNK  0001      -4.441  -0.705  -0.535
HETATM   28  C   UNK  0001      -5.702  -1.471  -0.212
HETATM   29  H   UNK  0001      -6.116  -1.950  -1.111
HETATM   30  H   UNK  0001      -6.487  -0.803   0.172
HETATM   31  H   UNK  0001      -5.526  -2.249   0.537
HETATM   32  C   UNK  0001      -4.616   0.381  -1.569
HETATM   33  H   UNK  0001      -4.977  -0.040  -2.518
HETATM   34  H   UNK  0001      -3.696   0.931  -1.778
HETATM   35  H   UNK  0001      -5.376   1.106  -1.245
HETATM   36  C   UNK  0001       5.278  -2.197   0.041
HETATM   37  H   UNK  0001       4.901  -2.991   0.694
HETATM   38  H   UNK  0001       6.195  -1.799   0.494
HETATM   39  H   UNK  0001       5.565  -2.657  -0.913
HETATM   40  O   UNK  0001       3.839   2.097  -1.943
HETATM   41  H   UNK  0001       4.717   1.999  -2.342
```

```
CONECT    1    2    3
CONECT    2    1    8   13
CONECT    3    1    4   15   19
CONECT    4    5    3    6
CONECT    5    4
CONECT    6    7    4    8
CONECT    7    6
CONECT    8    6    2    9
CONECT    9    8   10   40
CONECT   10   11    9   12
CONECT   11   10
CONECT   12   10   13   36
CONECT   13   14    2   12
CONECT   14   13
CONECT   15   16   17   18    3
CONECT   16   15
CONECT   17   15
CONECT   18   15
CONECT   19   20   21    3   22
CONECT   20   19
CONECT   21   19
CONECT   22   23   24   19   25
CONECT   23   22
CONECT   24   22
CONECT   25   26   22   27
CONECT   26   25
CONECT   27   25   28   32
CONECT   28   29   30   31   27
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35   27
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   12
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41    9
CONECT   41   40
END
```

***cis*-THC** (-25.4 kcal/mol)
Energy= -509225.085 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       2.571   1.482   0.147
HETATM    2  C   UNK  0001       1.238   1.432   0.281
HETATM    3  H   UNK  0001       0.728   1.974   1.077
```

```
HETATM    4  C   UNK  0001      3.174   0.602  -0.926
HETATM    5  H   UNK  0001      4.265   0.561  -0.838
HETATM    6  H   UNK  0001      2.958   1.014  -1.924
HETATM    7  C   UNK  0001      2.581  -0.823  -0.821
HETATM    8  H   UNK  0001      2.983  -1.450  -1.626
HETATM    9  H   UNK  0001      2.944  -1.259   0.116
HETATM   10  C   UNK  0001      1.030  -0.844  -0.858
HETATM   11  H   UNK  0001      0.713  -1.190  -1.851
HETATM   12  C   UNK  0001      0.426   0.584  -0.686
HETATM   13  C   UNK  0001     -1.058   0.528  -0.390
HETATM   14  C   UNK  0001      0.392  -1.850   0.133
HETATM   15  O   UNK  0001     -1.040  -1.879  -0.101
HETATM   16  C   UNK  0001     -1.709  -0.686  -0.144
HETATM   17  C   UNK  0001     -1.852   1.690  -0.442
HETATM   18  C   UNK  0001     -3.232   1.640  -0.260
HETATM   19  H   UNK  0001     -3.798   2.566  -0.310
HETATM   20  C   UNK  0001     -3.866   0.413  -0.026
HETATM   21  C   UNK  0001     -3.096  -0.748   0.037
HETATM   22  H   UNK  0001     -3.550  -1.716   0.224
HETATM   23  C   UNK  0001      3.479   2.297   1.025
HETATM   24  H   UNK  0001      4.192   1.654   1.560
HETATM   25  H   UNK  0001      2.918   2.874   1.767
HETATM   26  H   UNK  0001      4.080   2.999   0.431
HETATM   27  C   UNK  0001      0.838  -3.282  -0.176
HETATM   28  H   UNK  0001      1.904  -3.415   0.029
HETATM   29  H   UNK  0001      0.649  -3.529  -1.226
HETATM   30  H   UNK  0001      0.276  -3.987   0.446
HETATM   31  C   UNK  0001      0.618  -1.524   1.617
HETATM   32  H   UNK  0001      1.680  -1.523   1.879
HETATM   33  H   UNK  0001      0.118  -2.283   2.228
HETATM   34  H   UNK  0001      0.201  -0.549   1.880
HETATM   35  C   UNK  0001     -5.364   0.358   0.165
HETATM   36  H   UNK  0001     -5.891   0.755  -0.712
HETATM   37  H   UNK  0001     -5.680   0.958   1.028
HETATM   38  H   UNK  0001     -5.709  -0.668   0.326
HETATM   39  O   UNK  0001     -1.305   2.921  -0.698
HETATM   40  H   UNK  0001     -0.337   2.852  -0.702
HETATM   41  H   UNK  0001      0.534   1.051  -1.682
CONECT    1    2    4   23
CONECT    2    3    1   12
CONECT    3    2
CONECT    4    5    6    1    7
CONECT    5    4
CONECT    6    4
CONECT    7    8    9    4   10
CONECT    8    7
CONECT    9    7
CONECT   10   11    7   12   14
CONECT   11   10
CONECT   12   10   13   41    2
CONECT   13   12   16   17
```

```
CONECT   14   10   15   27   31
CONECT   15   14   16
CONECT   16   13   15   21
CONECT   17   13   18   39
CONECT   18   19   17   20
CONECT   19   18
CONECT   20   18   21   35
CONECT   21   22   16   20
CONECT   22   21
CONECT   23   24   25   26    1
CONECT   24   23
CONECT   25   23
CONECT   26   23
CONECT   27   28   29   30   14
CONECT   28   27
CONECT   29   27
CONECT   30   27
CONECT   31   32   33   34   14
CONECT   32   31
CONECT   33   31
CONECT   34   31
CONECT   35   36   37   38   20
CONECT   36   35
CONECT   37   35
CONECT   38   35
CONECT   39   40   17
CONECT   40   39
CONECT   41   12
END
```

***trans*-THC** (-27.5 kcal/mol)
Energy= -509227.168 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       2.611   1.679  -0.241
HETATM    2  C   UNK  0001       1.326   1.695   0.140
HETATM    3  H   UNK  0001       0.800   2.642   0.195
HETATM    4  C   UNK  0001       3.417   0.400  -0.321
HETATM    5  H   UNK  0001       4.373   0.532   0.209
HETATM    6  H   UNK  0001       3.695   0.224  -1.374
HETATM    7  C   UNK  0001       2.676  -0.830   0.232
HETATM    8  H   UNK  0001       3.155  -1.742  -0.141
HETATM    9  H   UNK  0001       2.759  -0.851   1.327
HETATM   10  C   UNK  0001       1.194  -0.766  -0.165
HETATM   11  H   UNK  0001       1.150  -0.565  -1.246
HETATM   12  C   UNK  0001       0.553   0.447   0.542
HETATM   13  H   UNK  0001       0.686   0.318   1.630
HETATM   14  C   UNK  0001      -0.945   0.485   0.269
HETATM   15  C   UNK  0001       0.364  -2.048   0.030
HETATM   16  O   UNK  0001      -0.942  -1.805  -0.564
```

```
HETATM  17  C   UNK  0001     -1.590  -0.634  -0.283
HETATM  18  C   UNK  0001     -1.772   1.574   0.606
HETATM  19  C   UNK  0001     -3.134   1.590   0.309
HETATM  20  H   UNK  0001     -3.729   2.462   0.575
HETATM  21  C   UNK  0001     -3.739   0.490  -0.312
HETATM  22  C   UNK  0001     -2.959  -0.627  -0.589
HETATM  23  H   UNK  0001     -3.389  -1.520  -1.031
HETATM  24  C   UNK  0001      3.338   2.940  -0.634
HETATM  25  H   UNK  0001      3.732   2.868  -1.658
HETATM  26  H   UNK  0001      4.204   3.124   0.019
HETATM  27  H   UNK  0001      2.684   3.816  -0.584
HETATM  28  C   UNK  0001      0.908  -3.220  -0.789
HETATM  29  H   UNK  0001      1.842  -3.604  -0.368
HETATM  30  H   UNK  0001      1.087  -2.919  -1.827
HETATM  31  H   UNK  0001      0.175  -4.033  -0.792
HETATM  32  C   UNK  0001      0.169  -2.460   1.496
HETATM  33  H   UNK  0001      1.133  -2.675   1.971
HETATM  34  H   UNK  0001     -0.447  -3.364   1.546
HETATM  35  H   UNK  0001     -0.331  -1.679   2.075
HETATM  36  C   UNK  0001     -5.208   0.523  -0.665
HETATM  37  H   UNK  0001     -5.390   1.147  -1.550
HETATM  38  H   UNK  0001     -5.808   0.940   0.152
HETATM  39  H   UNK  0001     -5.587  -0.480  -0.886
HETATM  40  O   UNK  0001     -1.189   2.630   1.266
HETATM  41  H   UNK  0001     -1.872   3.296   1.436
CONECT   1   2   4  24
CONECT   2   3   1  12
CONECT   3   2
CONECT   4   5   6   1   7
CONECT   5   4
CONECT   6   4
CONECT   7   8   9   4  10
CONECT   8   7
CONECT   9   7
CONECT  10  11   7  12  15
CONECT  11  10
CONECT  12  13  10   2  14
CONECT  13  12
CONECT  14  12  17  18
CONECT  15  10  16  28  32
CONECT  16  15  17
CONECT  17  14  16  22
CONECT  18  14  19  40
CONECT  19  20  18  21
CONECT  20  19
CONECT  21  19  22  36
CONECT  22  23  17  21
CONECT  23  22
CONECT  24  25  26  27   1
CONECT  25  24
CONECT  26  24
```

```
CONECT   27   24
CONECT   28   29   30   31   15
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35   15
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   21
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41   18
CONECT   41   40
END
```

Figure 2.2 (p.28)

1$_{an}$ (set to 0 kcal/mol)
Energy= -509971.466 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      3.006  -0.005   1.455
HETATM    2  C   UNK  0001      4.272  -0.846   1.349
HETATM    3  H   UNK  0001      4.492  -1.233   2.358
HETATM    4  H   UNK  0001      5.093  -0.169   1.091
HETATM    5  C   UNK  0001      1.687  -0.667   1.195
HETATM    6  C   UNK  0001      1.631  -2.105   0.821
HETATM    7  C   UNK  0001      4.155  -2.026   0.377
HETATM    8  H   UNK  0001      3.969  -1.624  -0.631
HETATM    9  C   UNK  0001      2.946  -2.877   0.783
HETATM   10  H   UNK  0001      3.119  -3.286   1.793
HETATM   11  H   UNK  0001      2.799  -3.735   0.119
HETATM   12  O   UNK  0001      3.085   1.181   1.755
HETATM   13  O   UNK  0001      0.584  -2.690   0.559
HETATM   14  C   UNK  0001      0.581   0.137   1.325
HETATM   15  H   UNK  0001      0.825   1.159   1.607
HETATM   16  C   UNK  0001     -0.799  -0.201   1.138
HETATM   17  H   UNK  0001     -1.014  -1.227   0.867
HETATM   18  C   UNK  0001     -1.834   0.676   1.264
HETATM   19  C   UNK  0001     -3.245   0.190   1.032
HETATM   20  H   UNK  0001     -3.836   0.368   1.944
HETATM   21  H   UNK  0001     -3.235  -0.893   0.867
HETATM   22  C   UNK  0001     -3.982   0.876  -0.151
HETATM   23  H   UNK  0001     -4.099   1.945   0.053
HETATM   24  H   UNK  0001     -5.001   0.460  -0.173
```

```
HETATM  25  C   UNK  0001     -3.312   0.634  -1.478
HETATM  26  H   UNK  0001     -3.076  -0.413  -1.674
HETATM  27  C   UNK  0001     -2.984   1.524  -2.427
HETATM  28  C   UNK  0001     -2.316   1.074  -3.705
HETATM  29  H   UNK  0001     -1.344   1.569  -3.839
HETATM  30  H   UNK  0001     -2.922   1.338  -4.584
HETATM  31  H   UNK  0001     -2.149  -0.008  -3.720
HETATM  32  C   UNK  0001     -3.236   3.010  -2.348
HETATM  33  H   UNK  0001     -2.297   3.571  -2.454
HETATM  34  H   UNK  0001     -3.711   3.322  -1.414
HETATM  35  H   UNK  0001     -3.884   3.336  -3.174
HETATM  36  C   UNK  0001     -1.695   2.132   1.618
HETATM  37  H   UNK  0001     -0.703   2.400   1.984
HETATM  38  H   UNK  0001     -2.428   2.410   2.386
HETATM  39  H   UNK  0001     -1.906   2.760   0.742
HETATM  40  C   UNK  0001      5.442  -2.856   0.329
HETATM  41  H   UNK  0001      5.675  -3.276   1.316
HETATM  42  H   UNK  0001      6.297  -2.245   0.017
HETATM  43  H   UNK  0001      5.349  -3.690  -0.375
CONECT   1   2   5  12
CONECT   2   3   4   1   7
CONECT   3   2
CONECT   4   2
CONECT   5   1   6  14
CONECT   6   5   9  13
CONECT   7   8   2   9  40
CONECT   8   7
CONECT   9  10  11   6   7
CONECT  10   9
CONECT  11   9
CONECT  12   1
CONECT  13   6
CONECT  14  15   5  16
CONECT  15  14
CONECT  16  17  14  18
CONECT  17  16
CONECT  18  16  19  36
CONECT  19  20  21  18  22
CONECT  20  19
CONECT  21  19
CONECT  22  23  24  19  25
CONECT  23  22
CONECT  24  22
CONECT  25  26  22  27
CONECT  26  25
CONECT  27  25  28  32
CONECT  28  29  30  31  27
CONECT  29  28
CONECT  30  28
CONECT  31  28
CONECT  32  33  34  35  27
```

```
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   18
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41   42   43    7
CONECT   41   40
CONECT   42   40
CONECT   43   40
END
```

TS CBC$_{an}$ (17.8 kcal/mol)
Energy= -509953.660 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  O   UNK  0001      -0.145  -1.172   0.724
HETATM    2  C   UNK  0001       1.043  -1.297   1.120
HETATM    3  C   UNK  0001      -0.984   0.722   1.286
HETATM    4  C   UNK  0001       0.183   1.508   1.253
HETATM    5  H   UNK  0001       0.154   2.449   0.704
HETATM    6  C   UNK  0001       1.408   1.064   1.730
HETATM    7  H   UNK  0001       2.218   1.779   1.865
HETATM    8  C   UNK  0001       1.780  -0.294   1.845
HETATM    9  C   UNK  0001       3.131  -0.578   2.368
HETATM   10  C   UNK  0001       3.684  -1.985   2.169
HETATM   11  H   UNK  0001       3.306  -2.627   2.982
HETATM   12  H   UNK  0001       4.771  -1.932   2.282
HETATM   13  C   UNK  0001       3.265  -2.580   0.817
HETATM   14  H   UNK  0001       3.635  -1.910   0.026
HETATM   15  C   UNK  0001       1.735  -2.603   0.741
HETATM   16  H   UNK  0001       1.375  -2.881  -0.256
HETATM   17  H   UNK  0001       1.349  -3.374   1.428
HETATM   18  O   UNK  0001       3.790   0.277   2.955
HETATM   19  C   UNK  0001      -1.435   0.072   2.566
HETATM   20  H   UNK  0001      -2.144   0.758   3.055
HETATM   21  H   UNK  0001      -0.606  -0.100   3.255
HETATM   22  H   UNK  0001      -1.959  -0.869   2.374
HETATM   23  C   UNK  0001      -2.075   0.975   0.271
HETATM   24  H   UNK  0001      -2.519   1.957   0.499
HETATM   25  H   UNK  0001      -2.877   0.241   0.413
HETATM   26  C   UNK  0001      -1.609   0.956  -1.201
HETATM   27  H   UNK  0001      -0.829   1.709  -1.350
HETATM   28  H   UNK  0001      -1.135  -0.018  -1.381
HETATM   29  C   UNK  0001      -2.755   1.151  -2.157
HETATM   30  H   UNK  0001      -3.506   0.359  -2.123
HETATM   31  C   UNK  0001      -2.964   2.156  -3.021
HETATM   32  C   UNK  0001      -4.186   2.169  -3.910
HETATM   33  H   UNK  0001      -3.901   2.180  -4.972
```

```
HETATM   34  H   UNK  0001      -4.789   3.073  -3.743
HETATM   35  H   UNK  0001      -4.827   1.298  -3.741
HETATM   36  C   UNK  0001      -2.046   3.340  -3.209
HETATM   37  H   UNK  0001      -1.688   3.391  -4.247
HETATM   38  H   UNK  0001      -1.171   3.319  -2.555
HETATM   39  H   UNK  0001      -2.584   4.279  -3.021
HETATM   40  C   UNK  0001       3.861  -3.972   0.584
HETATM   41  H   UNK  0001       3.560  -4.374  -0.391
HETATM   42  H   UNK  0001       3.528  -4.678   1.356
HETATM   43  H   UNK  0001       4.957  -3.941   0.611
CONECT    1    2    3
CONECT    2    1    8   15
CONECT    3    1    4   19   23
CONECT    4    5    3    6
CONECT    5    4
CONECT    6    7    4    8
CONECT    7    6
CONECT    8    6    2    9
CONECT    9    8   10   18
CONECT   10   11   12    9   13
CONECT   11   10
CONECT   12   10
CONECT   13   14   10   15   40
CONECT   14   13
CONECT   15   16   17    2   13
CONECT   16   15
CONECT   17   15
CONECT   18    9
CONECT   19   20   21   22    3
CONECT   20   19
CONECT   21   19
CONECT   22   19
CONECT   23   24   25    3   26
CONECT   24   23
CONECT   25   23
CONECT   26   27   28   23   29
CONECT   27   26
CONECT   28   26
CONECT   29   30   26   31
CONECT   30   29
CONECT   31   29   32   36
CONECT   32   33   34   35   31
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   31
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41   42   43   13
CONECT   41   40
```

```
CONECT   42   40
CONECT   43   40
END
```

TS *cis*-THC$_{an}$ (29.3 kcal/mol)
Energy= -509942.187 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM   1  C   UNK  0001     -1.290  -2.123   0.129
HETATM   2  C   UNK  0001     -0.622  -3.476   0.383
HETATM   3  H   UNK  0001     -1.399  -4.172   0.718
HETATM   4  H   UNK  0001     -0.262  -3.860  -0.586
HETATM   5  C   UNK  0001     -0.488  -0.931   0.380
HETATM   6  C   UNK  0001      0.925  -0.999   0.605
HETATM   7  C   UNK  0001      1.562  -2.355   0.895
HETATM   8  H   UNK  0001      2.364  -2.201   1.627
HETATM   9  H   UNK  0001      2.053  -2.706  -0.026
HETATM  10  C   UNK  0001      0.550  -3.405   1.374
HETATM  11  H   UNK  0001      0.149  -3.067   2.341
HETATM  12  O   UNK  0001     -2.453  -2.071  -0.284
HETATM  13  C   UNK  0001     -1.095   0.357   0.194
HETATM  14  H   UNK  0001     -2.168   0.240   0.028
HETATM  15  C   UNK  0001     -0.818   1.073  -1.536
HETATM  16  H   UNK  0001     -1.317   0.263  -2.070
HETATM  17  C   UNK  0001      0.574   1.092  -1.766
HETATM  18  O   UNK  0001      1.640   0.019   0.484
HETATM  19  C   UNK  0001      1.432   2.279  -1.478
HETATM  20  H   UNK  0001      1.076   3.166  -2.021
HETATM  21  H   UNK  0001      2.475   2.097  -1.747
HETATM  22  H   UNK  0001      1.389   2.509  -0.406
HETATM  23  C   UNK  0001      1.168  -0.118  -2.409
HETATM  24  H   UNK  0001      0.716  -1.025  -1.981
HETATM  25  H   UNK  0001      2.253  -0.165  -2.297
HETATM  26  H   UNK  0001      0.922  -0.133  -3.482
HETATM  27  C   UNK  0001      1.206  -4.774   1.584
HETATM  28  H   UNK  0001      1.618  -5.162   0.643
HETATM  29  H   UNK  0001      0.481  -5.508   1.957
HETATM  30  H   UNK  0001      2.028  -4.713   2.307
HETATM  31  C   UNK  0001     -0.742   1.460   1.133
HETATM  32  H   UNK  0001     -0.310   1.135   2.076
HETATM  33  C   UNK  0001     -0.933   2.775   0.939
HETATM  34  C   UNK  0001     -1.395   3.353  -0.375
HETATM  35  H   UNK  0001     -2.298   3.960  -0.212
HETATM  36  H   UNK  0001     -0.634   4.075  -0.707
HETATM  37  C   UNK  0001     -1.692   2.333  -1.489
HETATM  38  H   UNK  0001     -1.642   2.839  -2.462
HETATM  39  H   UNK  0001     -2.727   1.986  -1.385
HETATM  40  C   UNK  0001     -0.630   3.782   2.020
HETATM  41  H   UNK  0001     -0.252   3.300   2.927
HETATM  42  H   UNK  0001     -1.530   4.353   2.288
```

```
HETATM   43  H   UNK  0001      0.117   4.517   1.688
CONECT    1    2    5   12
CONECT    2    3    4    1   10
CONECT    3    2
CONECT    4    2
CONECT    5    1    6   13
CONECT    6    5    7   18
CONECT    7    8    9    6   10
CONECT    8    7
CONECT    9    7
CONECT   10   11    7    2   27
CONECT   11   10
CONECT   12    1
CONECT   13   14    5   15   31
CONECT   14   13
CONECT   15   16   13   17   37
CONECT   16   15
CONECT   17   15   18   19   23
CONECT   18   17    6
CONECT   19   20   21   22   17
CONECT   20   19
CONECT   21   19
CONECT   22   19
CONECT   23   24   25   26   17
CONECT   24   23
CONECT   25   23
CONECT   26   23
CONECT   27   28   29   30   10
CONECT   28   27
CONECT   29   27
CONECT   30   27
CONECT   31   32   13   33
CONECT   32   31
CONECT   33   31   34   40
CONECT   34   35   36   33   37
CONECT   35   34
CONECT   36   34
CONECT   37   38   39   34   15
CONECT   38   37
CONECT   39   37
CONECT   40   41   42   43   33
CONECT   41   40
CONECT   42   40
CONECT   43   40
END
```

TS *trans*-THC$_{an}$ (26.9 kcal/mol)
Energy= -509944.552 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
```

```
HETATM   1  C   UNK  0001      0.683   0.542  -0.321
HETATM   2  C   UNK  0001      1.262   1.661   0.425
HETATM   3  C   UNK  0001      1.489  -0.582  -0.694
HETATM   4  C   UNK  0001      3.002  -0.532  -0.542
HETATM   5  H   UNK  0001      3.278  -1.064   0.382
HETATM   6  H   UNK  0001      3.439  -1.109  -1.366
HETATM   7  C   UNK  0001      3.546   0.901  -0.495
HETATM   8  C   UNK  0001      2.786   1.681   0.585
HETATM   9  H   UNK  0001      3.091   2.732   0.626
HETATM  10  H   UNK  0001      3.018   1.254   1.574
HETATM  11  C   UNK  0001     -0.715   0.406  -0.616
HETATM  12  C   UNK  0001     -1.597  -0.968   0.494
HETATM  13  H   UNK  0001     -1.543  -0.389   1.417
HETATM  14  C   UNK  0001     -0.798  -2.124   0.486
HETATM  15  O   UNK  0001      0.945  -1.642  -1.091
HETATM  16  O   UNK  0001      0.596   2.567   0.930
HETATM  17  C   UNK  0001     -2.975  -0.993  -0.162
HETATM  18  H   UNK  0001     -3.576  -1.812   0.258
HETATM  19  H   UNK  0001     -2.869  -1.215  -1.231
HETATM  20  C   UNK  0001     -3.741   0.322   0.013
HETATM  21  H   UNK  0001     -4.639   0.301  -0.621
HETATM  22  H   UNK  0001     -4.123   0.395   1.045
HETATM  23  C   UNK  0001     -2.948   1.571  -0.283
HETATM  24  C   UNK  0001     -1.624   1.578  -0.509
HETATM  25  H   UNK  0001     -1.127   2.540  -0.600
HETATM  26  H   UNK  0001     -0.862  -0.218  -1.498
HETATM  27  C   UNK  0001      0.223  -2.284   1.571
HETATM  28  H   UNK  0001      0.970  -3.044   1.330
HETATM  29  H   UNK  0001     -0.269  -2.567   2.513
HETATM  30  C   UNK  0001     -1.129  -3.304  -0.376
HETATM  31  H   UNK  0001     -1.972  -3.859   0.066
HETATM  32  H   UNK  0001     -0.280  -3.983  -0.467
HETATM  33  H   UNK  0001     -1.432  -2.997  -1.380
HETATM  34  C   UNK  0001     -3.733   2.857  -0.230
HETATM  35  H   UNK  0001     -4.214   2.987   0.750
HETATM  36  H   UNK  0001     -4.540   2.858  -0.976
HETATM  37  H   UNK  0001     -3.097   3.728  -0.413
HETATM  38  H   UNK  0001      3.332   1.374  -1.465
HETATM  39  C   UNK  0001      5.061   0.934  -0.269
HETATM  40  H   UNK  0001      5.593   0.393  -1.060
HETATM  41  H   UNK  0001      5.323   0.468   0.690
HETATM  42  H   UNK  0001      5.437   1.964  -0.253
HETATM  43  H   UNK  0001      0.728  -1.327   1.761
CONECT   1   2   3  11
CONECT   2   1   8  16
CONECT   3   1   4  15
CONECT   4   5   6   3   7
CONECT   5   4
CONECT   6   4
CONECT   7   4   8  38  39
CONECT   8   9  10   7   2
```

```
CONECT    9    8
CONECT   10    8
CONECT   11    1   12   26   24
CONECT   12   13   11   14   17
CONECT   13   12
CONECT   14   12   15   27   30
CONECT   15   14    3
CONECT   16    2
CONECT   17   18   19   12   20
CONECT   18   17
CONECT   19   17
CONECT   20   21   22   17   23
CONECT   21   20
CONECT   22   20
CONECT   23   20   24   34
CONECT   24   25   23   11
CONECT   25   24
CONECT   26   11
CONECT   27   28   29   14   43
CONECT   28   27
CONECT   29   27
CONECT   30   31   32   33   14
CONECT   31   30
CONECT   32   30
CONECT   33   30
CONECT   34   35   36   37   23
CONECT   35   34
CONECT   36   34
CONECT   37   34
CONECT   38    7
CONECT   39   40   41   42    7
CONECT   40   39
CONECT   41   39
CONECT   42   39
CONECT   43   27
END
```

CBC_{an} (-3.4 kcal/mol)
Energy= -509974.861 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  O   UNK  0001      -0.690  -1.054  -0.508
HETATM    2  C   UNK  0001      -1.734  -0.258  -0.791
HETATM    3  C   UNK  0001       0.578  -0.970  -1.266
HETATM    4  C   UNK  0001       0.720   0.370  -1.953
HETATM    5  H   UNK  0001       1.711   0.618  -2.324
HETATM    6  C   UNK  0001      -0.326   1.184  -2.138
HETATM    7  H   UNK  0001      -0.241   2.129  -2.666
HETATM    8  C   UNK  0001      -1.637   0.834  -1.603
HETATM    9  C   UNK  0001      -2.810   1.672  -1.878
```

```
HETATM  10  C   UNK  0001     -4.141   1.213  -1.284
HETATM  11  H   UNK  0001     -4.619   0.536  -2.010
HETATM  12  H   UNK  0001     -4.788   2.092  -1.200
HETATM  13  C   UNK  0001     -3.983   0.488   0.061
HETATM  14  H   UNK  0001     -3.540   1.199   0.773
HETATM  15  C   UNK  0001     -2.995  -0.679  -0.093
HETATM  16  H   UNK  0001     -2.728  -1.111   0.879
HETATM  17  H   UNK  0001     -3.462  -1.494  -0.671
HETATM  18  O   UNK  0001     -2.738   2.683  -2.570
HETATM  19  C   UNK  0001      0.539  -2.110  -2.294
HETATM  20  H   UNK  0001      1.470  -2.131  -2.871
HETATM  21  H   UNK  0001     -0.291  -1.960  -2.992
HETATM  22  H   UNK  0001      0.414  -3.077  -1.795
HETATM  23  C   UNK  0001      1.684  -1.209  -0.221
HETATM  24  H   UNK  0001      2.644  -1.250  -0.752
HETATM  25  H   UNK  0001      1.529  -2.200   0.224
HETATM  26  C   UNK  0001      1.754  -0.144   0.889
HETATM  27  H   UNK  0001      1.910   0.841   0.438
HETATM  28  H   UNK  0001      0.773  -0.103   1.382
HETATM  29  C   UNK  0001      2.811  -0.460   1.914
HETATM  30  H   UNK  0001      2.636  -1.383   2.471
HETATM  31  C   UNK  0001      3.921   0.234   2.212
HETATM  32  C   UNK  0001      4.868  -0.249   3.286
HETATM  33  H   UNK  0001      4.973   0.498   4.085
HETATM  34  H   UNK  0001      5.877  -0.413   2.881
HETATM  35  H   UNK  0001      4.529  -1.185   3.741
HETATM  36  C   UNK  0001      4.337   1.525   1.551
HETATM  37  H   UNK  0001      4.393   2.339   2.288
HETATM  38  H   UNK  0001      3.660   1.843   0.755
HETATM  39  H   UNK  0001      5.343   1.432   1.118
HETATM  40  C   UNK  0001     -5.327   0.017   0.625
HETATM  41  H   UNK  0001     -5.200  -0.488   1.590
HETATM  42  H   UNK  0001     -5.818  -0.686  -0.060
HETATM  43  H   UNK  0001     -6.007   0.863   0.778
CONECT   1   2   3
CONECT   2   1   8  15
CONECT   3   1   4  19  23
CONECT   4   5   3   6
CONECT   5   4
CONECT   6   7   4   8
CONECT   7   6
CONECT   8   6   2   9
CONECT   9   8  10  18
CONECT  10  11  12   9  13
CONECT  11  10
CONECT  12  10
CONECT  13  14  10  15  40
CONECT  14  13
CONECT  15  16  17   2  13
CONECT  16  15
CONECT  17  15
```

```
CONECT   18    9
CONECT   19   20   21   22    3
CONECT   20   19
CONECT   21   19
CONECT   22   19
CONECT   23   24   25    3   26
CONECT   24   23
CONECT   25   23
CONECT   26   27   28   23   29
CONECT   27   26
CONECT   28   26
CONECT   29   30   26   31
CONECT   30   29
CONECT   31   29   32   36
CONECT   32   33   34   35   31
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36   37   38   39   31
CONECT   37   36
CONECT   38   36
CONECT   39   36
CONECT   40   41   42   43   13
CONECT   41   40
CONECT   42   40
CONECT   43   40
END
```

***cis*-THC$_{an}$** (-16.8 kcal/mol)
Energy= -509988.300 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      -2.537  -1.884   0.033
HETATM    2  C   UNK  0001      -1.559  -1.615  -0.840
HETATM    3  H   UNK  0001      -1.209  -2.389  -1.516
HETATM    4  C   UNK  0001      -3.031  -0.846   1.011
HETATM    5  H   UNK  0001      -3.193  -1.309   1.995
HETATM    6  H   UNK  0001      -4.024  -0.483   0.695
HETATM    7  C   UNK  0001      -2.063   0.334   1.151
HETATM    8  H   UNK  0001      -2.546   1.132   1.723
HETATM    9  H   UNK  0001      -1.184   0.017   1.726
HETATM   10  C   UNK  0001      -1.616   0.851  -0.230
HETATM   11  H   UNK  0001      -2.521   1.117  -0.794
HETATM   12  C   UNK  0001      -0.879  -0.267  -1.014
HETATM   13  C   UNK  0001       0.602  -0.301  -0.643
HETATM   14  C   UNK  0001      -0.743   2.125  -0.159
HETATM   15  O   UNK  0001       0.521   1.800   0.507
HETATM   16  C   UNK  0001       1.166   0.681   0.113
HETATM   17  C   UNK  0001       1.472  -1.338  -1.215
HETATM   18  C   UNK  0001       3.194  -0.738   0.584
```

```
HETATM  19  C   UNK  0001     -3.209  -3.233   0.086
HETATM  20  H   UNK  0001     -3.076  -3.706   1.070
HETATM  21  H   UNK  0001     -2.812  -3.913  -0.674
HETATM  22  H   UNK  0001     -4.294  -3.144  -0.070
HETATM  23  C   UNK  0001     -0.415   2.676  -1.555
HETATM  24  H   UNK  0001     -1.335   2.981  -2.066
HETATM  25  H   UNK  0001      0.092   1.936  -2.179
HETATM  26  H   UNK  0001      0.235   3.553  -1.469
HETATM  27  C   UNK  0001     -1.342   3.239   0.702
HETATM  28  H   UNK  0001     -2.344   3.501   0.344
HETATM  29  H   UNK  0001     -0.713   4.133   0.648
HETATM  30  H   UNK  0001     -1.412   2.943   1.751
HETATM  31  O   UNK  0001      1.070  -2.139  -2.056
HETATM  32  H   UNK  0001     -0.942  -0.042  -2.090
HETATM  33  C   UNK  0001      2.943  -1.356  -0.795
HETATM  34  H   UNK  0001      3.287  -2.394  -0.853
HETATM  35  H   UNK  0001      3.511  -0.797  -1.557
HETATM  36  C   UNK  0001      2.587   0.668   0.606
HETATM  37  H   UNK  0001      2.600   1.098   1.616
HETATM  38  H   UNK  0001      3.187   1.348  -0.020
HETATM  39  H   UNK  0001      2.657  -1.344   1.329
HETATM  40  C   UNK  0001      4.680  -0.726   0.956
HETATM  41  H   UNK  0001      5.091  -1.742   0.968
HETATM  42  H   UNK  0001      4.838  -0.289   1.949
HETATM  43  H   UNK  0001      5.263  -0.138   0.235
CONECT   1   2   4  19
CONECT   2   3   1  12
CONECT   3   2
CONECT   4   5   6   1   7
CONECT   5   4
CONECT   6   4
CONECT   7   8   9   4  10
CONECT   8   7
CONECT   9   7
CONECT  10  11   7  12  14
CONECT  11  10
CONECT  12  10  13  32   2
CONECT  13  12  16  17
CONECT  14  10  15  23  27
CONECT  15  14  16
CONECT  16  13  15  36
CONECT  17  13  31  33
CONECT  18  33  39  36  40
CONECT  19  20  21  22   1
CONECT  20  19
CONECT  21  19
CONECT  22  19
CONECT  23  24  25  26  14
CONECT  24  23
CONECT  25  23
CONECT  26  23
```

```
CONECT   27   28   29   30   14
CONECT   28   27
CONECT   29   27
CONECT   30   27
CONECT   31   17
CONECT   32   12
CONECT   33   34   35   18   17
CONECT   34   33
CONECT   35   33
CONECT   36   37   38   16   18
CONECT   37   36
CONECT   38   36
CONECT   39   18
CONECT   40   41   42   43   18
CONECT   41   40
CONECT   42   40
CONECT   43   40
END
```

***trans*-THC$_{an}$** (-15.8 kcal/mol)
Energy= -509987.258 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       2.824   1.728  -0.108
HETATM    2  C   UNK  0001       1.542   1.730   0.282
HETATM    3  H   UNK  0001       1.024   2.670   0.433
HETATM    4  C   UNK  0001       3.616   0.451  -0.294
HETATM    5  H   UNK  0001       4.585   0.540   0.219
HETATM    6  H   UNK  0001       3.865   0.337  -1.362
HETATM    7  C   UNK  0001       2.877  -0.803   0.204
HETATM    8  H   UNK  0001       3.348  -1.698  -0.218
HETATM    9  H   UNK  0001       2.972  -0.877   1.295
HETATM   10  C   UNK  0001       1.390  -0.714  -0.171
HETATM   11  H   UNK  0001       1.334  -0.465  -1.241
HETATM   12  C   UNK  0001       0.755   0.466   0.594
HETATM   13  H   UNK  0001       0.860   0.283   1.677
HETATM   14  C   UNK  0001      -0.733   0.538   0.277
HETATM   15  C   UNK  0001       0.572  -2.007  -0.012
HETATM   16  O   UNK  0001      -0.788  -1.738  -0.500
HETATM   17  C   UNK  0001      -1.369  -0.545  -0.254
HETATM   18  C   UNK  0001      -1.529   1.720   0.642
HETATM   19  C   UNK  0001      -3.669   0.418   0.156
HETATM   20  C   UNK  0001       3.569   3.008  -0.393
HETATM   21  H   UNK  0001       3.974   3.013  -1.416
HETATM   22  H   UNK  0001       4.429   3.128   0.282
HETATM   23  H   UNK  0001       2.924   3.885  -0.279
HETATM   24  C   UNK  0001       1.061  -3.125  -0.934
HETATM   25  H   UNK  0001       2.021  -3.524  -0.592
HETATM   26  H   UNK  0001       1.178  -2.761  -1.960
HETATM   27  H   UNK  0001       0.334  -3.943  -0.941
```

```
HETATM   28  C   UNK  0001      0.448  -2.508   1.432
HETATM   29  H   UNK  0001      1.434  -2.765   1.836
HETATM   30  H   UNK  0001     -0.177  -3.406   1.461
HETATM   31  H   UNK  0001     -0.004  -1.756   2.085
HETATM   32  C   UNK  0001     -5.110   0.492  -0.358
HETATM   33  H   UNK  0001     -5.143   0.849  -1.396
HETATM   34  H   UNK  0001     -5.708   1.179   0.251
HETATM   35  H   UNK  0001     -5.594  -0.492  -0.328
HETATM   36  O   UNK  0001     -1.068   2.641   1.313
HETATM   37  C   UNK  0001     -2.975   1.784   0.154
HETATM   38  H   UNK  0001     -3.501   2.512   0.779
HETATM   39  H   UNK  0001     -2.966   2.186  -0.872
HETATM   40  H   UNK  0001     -3.694   0.056   1.195
HETATM   41  C   UNK  0001     -2.822  -0.569  -0.657
HETATM   42  H   UNK  0001     -2.895  -0.324  -1.729
HETATM   43  H   UNK  0001     -3.193  -1.594  -0.549
CONECT    1    2    4   20
CONECT    2    3    1   12
CONECT    3    2
CONECT    4    5    6    1    7
CONECT    5    4
CONECT    6    4
CONECT    7    8    9    4   10
CONECT    8    7
CONECT    9    7
CONECT   10   11    7   12   15
CONECT   11   10
CONECT   12   13   10    2   14
CONECT   13   12
CONECT   14   12   17   18
CONECT   15   10   16   24   28
CONECT   16   15   17
CONECT   17   14   16   41
CONECT   18   14   36   37
CONECT   19   32   37   40   41
CONECT   20   21   22   23    1
CONECT   21   20
CONECT   22   20
CONECT   23   20
CONECT   24   25   26   27   15
CONECT   25   24
CONECT   26   24
CONECT   27   24
CONECT   28   29   30   31   15
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35   19
CONECT   33   32
CONECT   34   32
CONECT   35   32
```

```
CONECT   36   18
CONECT   37   38   39   19   18
CONECT   38   37
CONECT   39   37
CONECT   40   19
CONECT   41   42   43   17   19
CONECT   42   41
CONECT   43   41
END
```

Scheme 2.9 (p.43)

trans-Δ^1-THC$_{est}$ (-13.88 kcal/mol)
Energy= -508606.086 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      2.034  -0.765  -1.594
HETATM    2  C   UNK  0001      1.325   1.660  -1.222
HETATM    3  C   UNK  0001     -0.108  -0.208  -0.381
HETATM    4  C   UNK  0001      0.637   1.080   0.021
HETATM    5  C   UNK  0001      0.902  -1.164  -0.999
HETATM    6  C   UNK  0001      2.426   0.695  -1.697
HETATM    7  H   UNK  0001      1.762   2.644  -1.019
HETATM    8  H   UNK  0001      0.666  -2.223  -0.971
HETATM    9  H   UNK  0001      2.709   0.929  -2.734
HETATM   10  H   UNK  0001      0.585   1.798  -2.021
HETATM   11  H   UNK  0001     -0.841   0.042  -1.166
HETATM   12  H   UNK  0001      1.429   0.784   0.725
HETATM   13  H   UNK  0001      3.342   0.856  -1.106
HETATM   14  C   UNK  0001     -0.869  -0.773   0.817
HETATM   15  C   UNK  0001     -0.273   2.024   0.819
HETATM   16  O   UNK  0001     -0.700   1.296   2.014
HETATM   17  C   UNK  0001     -1.071  -0.006   1.927
HETATM   18  C   UNK  0001      3.009  -1.748  -2.192
HETATM   19  H   UNK  0001      4.000  -1.659  -1.722
HETATM   20  H   UNK  0001      3.156  -1.562  -3.265
HETATM   21  H   UNK  0001      2.669  -2.781  -2.070
HETATM   22  C   UNK  0001      0.485   3.226   1.385
HETATM   23  H   UNK  0001      1.400   2.905   1.895
HETATM   24  H   UNK  0001     -0.144   3.753   2.109
HETATM   25  H   UNK  0001      0.754   3.929   0.591
HETATM   26  C   UNK  0001     -1.531   2.481   0.069
HETATM   27  H   UNK  0001     -1.259   3.032  -0.837
HETATM   28  H   UNK  0001     -2.127   3.142   0.707
HETATM   29  H   UNK  0001     -2.157   1.632  -0.219
HETATM   30  C   UNK  0001     -1.503  -2.104   0.713
HETATM   31  O   UNK  0001     -1.861  -2.849   1.610
HETATM   32  O   UNK  0001     -1.698  -2.440  -0.597
HETATM   33  C   UNK  0001     -2.331  -3.706  -0.816
HETATM   34  H   UNK  0001     -3.332  -3.720  -0.376
HETATM   35  H   UNK  0001     -1.744  -4.517  -0.375
```

```
HETATM   36  H   UNK  0001      -2.388  -3.821  -1.899
HETATM   37  C   UNK  0001      -1.725  -0.408   3.218
HETATM   38  H   UNK  0001      -2.052  -1.444   3.201
HETATM   39  H   UNK  0001      -2.571   0.260   3.423
HETATM   40  H   UNK  0001      -1.005  -0.268   4.034
CONECT    1    5    6   18
CONECT    2    7   10    4    6
CONECT    3   11    5    4   14
CONECT    4    2    3   12   15
CONECT    5    1    3    8
CONECT    6    1    2    9   13
CONECT    7    2
CONECT    8    5
CONECT    9    6
CONECT   10    2
CONECT   11    3
CONECT   12    4
CONECT   13    6
CONECT   14    3   17   30
CONECT   15    4   16   22   26
CONECT   16   15   17
CONECT   17   16   14   37
CONECT   18   19   20   21    1
CONECT   19   18
CONECT   20   18
CONECT   21   18
CONECT   22   23   24   25   15
CONECT   23   22
CONECT   24   22
CONECT   25   22
CONECT   26   27   28   29   15
CONECT   27   26
CONECT   28   26
CONECT   29   26
CONECT   30   14   31   32
CONECT   31   30
CONECT   32   30   33
CONECT   33   34   35   36   32
CONECT   34   33
CONECT   35   33
CONECT   36   33
CONECT   37   38   39   40   17
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

cis-Δ^1-THC_{est} (-12.93 kcal/mol)
Energy= -508605.137 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       2.330  -0.677  -0.956
HETATM    2  C   UNK  0001       2.346   1.020   0.947
HETATM    3  C   UNK  0001       0.412  -0.584   0.704
HETATM    4  C   UNK  0001       0.813   0.869   1.028
HETATM    5  C   UNK  0001       1.181  -1.163  -0.471
HETATM    6  C   UNK  0001       2.982   0.557  -0.375
HETATM    7  H   UNK  0001       2.758   0.401   1.755
HETATM    8  H   UNK  0001       0.681  -1.198   1.578
HETATM    9  H   UNK  0001       0.765  -2.071  -0.901
HETATM   10  H   UNK  0001       2.970   1.362  -1.126
HETATM   11  H   UNK  0001       2.649   2.049   1.173
HETATM   12  H   UNK  0001       0.535   1.050   2.076
HETATM   13  H   UNK  0001       4.050   0.356  -0.203
HETATM   14  C   UNK  0001      -1.101  -0.723   0.566
HETATM   15  C   UNK  0001      -0.035   1.899   0.241
HETATM   16  O   UNK  0001      -1.440   1.639   0.560
HETATM   17  C   UNK  0001      -1.914   0.370   0.568
HETATM   18  C   UNK  0001      -1.581  -2.113   0.575
HETATM   19  O   UNK  0001      -0.866  -3.072   0.821
HETATM   20  O   UNK  0001      -2.896  -2.272   0.252
HETATM   21  C   UNK  0001      -3.360  -3.628   0.258
HETATM   22  H   UNK  0001      -2.815  -4.226  -0.478
HETATM   23  H   UNK  0001      -4.419  -3.575  -0.001
HETATM   24  H   UNK  0001      -3.228  -4.082   1.244
HETATM   25  C   UNK  0001      -3.420   0.414   0.610
HETATM   26  H   UNK  0001      -3.840   0.233  -0.386
HETATM   27  H   UNK  0001      -3.726   1.411   0.938
HETATM   28  H   UNK  0001      -3.834  -0.342   1.277
HETATM   29  C   UNK  0001       0.189   3.320   0.763
HETATM   30  H   UNK  0001       1.180   3.687   0.480
HETATM   31  H   UNK  0001       0.100   3.356   1.854
HETATM   32  H   UNK  0001      -0.559   3.996   0.336
HETATM   33  C   UNK  0001       0.069   1.875  -1.290
HETATM   34  H   UNK  0001       1.070   2.159  -1.623
HETATM   35  H   UNK  0001      -0.643   2.597  -1.703
HETATM   36  H   UNK  0001      -0.159   0.889  -1.698
HETATM   37  C   UNK  0001       3.042  -1.322  -2.117
HETATM   38  H   UNK  0001       4.060  -1.631  -1.839
HETATM   39  H   UNK  0001       3.148  -0.623  -2.959
HETATM   40  H   UNK  0001       2.506  -2.206  -2.477
CONECT    1    5    6   37
CONECT    2    7   11    4    6
CONECT    3    8    5    4   14
CONECT    4    2    3   12   15
CONECT    5    1    3    9
CONECT    6    1    2   10   13
CONECT    7    2
CONECT    8    3
CONECT    9    5
CONECT   10    6
```

```
CONECT   11    2
CONECT   12    4
CONECT   13    6
CONECT   14    3   17   18
CONECT   15    4   16   29   33
CONECT   16   15   17
CONECT   17   16   14   25
CONECT   18   14   19   20
CONECT   19   18
CONECT   20   18   21
CONECT   21   22   23   24   20
CONECT   22   21
CONECT   23   21
CONECT   24   21
CONECT   25   26   27   28   17
CONECT   26   25
CONECT   27   25
CONECT   28   25
CONECT   29   30   31   32   15
CONECT   30   29
CONECT   31   29
CONECT   32   29
CONECT   33   34   35   36   15
CONECT   34   33
CONECT   35   33
CONECT   36   33
CONECT   37   38   39   40    1
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

CBC_{est} (-2.84 kcal/mol)
Energy= -508595.047 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       0.542  -1.775  -1.179
HETATM    2  C   UNK  0001       1.252  -0.215   0.605
HETATM    3  C   UNK  0001      -0.226  -2.126   1.093
HETATM    4  O   UNK  0001       0.225  -0.897   1.412
HETATM    5  C   UNK  0001      -0.052  -2.648  -0.163
HETATM    6  C   UNK  0001       1.113  -0.612  -0.843
HETATM    7  H   UNK  0001       1.524   0.061  -1.591
HETATM    8  H   UNK  0001       0.475  -2.087  -2.215
HETATM    9  C   UNK  0001      -0.524  -3.998  -0.517
HETATM   10  O   UNK  0001      -0.998  -4.839   0.230
HETATM   11  O   UNK  0001      -0.358  -4.244  -1.848
HETATM   12  C   UNK  0001       2.616  -0.640   1.169
HETATM   13  H   UNK  0001       3.423  -0.137   0.624
HETATM   14  H   UNK  0001       2.754  -1.720   1.057
```

```
HETATM  15  H   UNK  0001      2.694  -0.380   2.231
HETATM  16  C   UNK  0001      1.007   1.285   0.837
HETATM  17  H   UNK  0001      1.805   1.838   0.325
HETATM  18  H   UNK  0001      1.122   1.489   1.909
HETATM  19  C   UNK  0001     -0.366   1.792   0.357
HETATM  20  H   UNK  0001     -1.142   1.202   0.863
HETATM  21  H   UNK  0001     -0.477   1.587  -0.713
HETATM  22  C   UNK  0001     -0.567   3.252   0.666
HETATM  23  H   UNK  0001     -0.569   3.488   1.732
HETATM  24  C   UNK  0001     -0.725   4.277  -0.186
HETATM  25  C   UNK  0001     -0.745   4.156  -1.691
HETATM  26  H   UNK  0001     -1.697   4.521  -2.098
HETATM  27  H   UNK  0001     -0.604   3.132  -2.045
HETATM  28  H   UNK  0001      0.042   4.779  -2.139
HETATM  29  C   UNK  0001     -0.906   5.686   0.327
HETATM  30  H   UNK  0001     -0.120   6.352  -0.057
HETATM  31  H   UNK  0001     -0.882   5.730   1.421
HETATM  32  H   UNK  0001     -1.863   6.111  -0.008
HETATM  33  C   UNK  0001     -0.956  -2.726   2.254
HETATM  34  H   UNK  0001     -0.238  -3.022   3.030
HETATM  35  H   UNK  0001     -1.529  -3.601   1.959
HETATM  36  H   UNK  0001     -1.605  -1.960   2.695
HETATM  37  C   UNK  0001     -0.785  -5.539  -2.285
HETATM  38  H   UNK  0001     -0.245  -6.326  -1.751
HETATM  39  H   UNK  0001     -0.560  -5.576  -3.352
HETATM  40  H   UNK  0001     -1.857  -5.673  -2.114
CONECT   1   8   5   6
CONECT   2   4   6  12  16
CONECT   3   5   4  33
CONECT   4   2   3
CONECT   5   1   3   9
CONECT   6   1   2   7
CONECT   7   6
CONECT   8   1
CONECT   9   5  10  11
CONECT  10   9
CONECT  11   9  37
CONECT  12  13  14  15   2
CONECT  13  12
CONECT  14  12
CONECT  15  12
CONECT  16  17  18   2  19
CONECT  17  16
CONECT  18  16
CONECT  19  20  21  16  22
CONECT  20  19
CONECT  21  19
CONECT  22  23  19  24
CONECT  23  22
CONECT  24  22  25  29
CONECT  25  26  27  28  24
CONECT  26  25
```

```
CONECT   27   25
CONECT   28   25
CONECT   29   30   31   32   24
CONECT   30   29
CONECT   31   29
CONECT   32   29
CONECT   33   34   35   36    3
CONECT   34   33
CONECT   35   33
CONECT   36   33
CONECT   37   38   39   40   11
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

Knoev$_{est}$ (0 kcal/mol)
Energy= -508592.209 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      0.306  -2.064   0.932
HETATM    2  C   UNK  0001      1.780  -2.145   0.634
HETATM    3  C   UNK  0001      2.599  -3.343   1.084
HETATM    4  H   UNK  0001      3.512  -3.369   0.485
HETATM    5  H   UNK  0001      2.050  -4.284   0.980
HETATM    6  H   UNK  0001      2.866  -3.242   2.141
HETATM    7  O   UNK  0001      2.322  -1.265  -0.024
HETATM    8  C   UNK  0001     -0.360  -2.862   1.992
HETATM    9  O   UNK  0001     -1.547  -3.130   2.047
HETATM   10  O   UNK  0001      0.506  -3.249   2.965
HETATM   11  C   UNK  0001     -0.075  -4.003   4.039
HETATM   12  H   UNK  0001     -0.539  -4.919   3.663
HETATM   13  H   UNK  0001     -0.834  -3.411   4.557
HETATM   14  H   UNK  0001      0.752  -4.238   4.710
HETATM   15  C   UNK  0001     -0.402  -1.175   0.170
HETATM   16  H   UNK  0001      0.216  -0.631  -0.539
HETATM   17  C   UNK  0001     -1.801  -0.849   0.202
HETATM   18  H   UNK  0001     -2.438  -1.427   0.862
HETATM   19  C   UNK  0001     -2.348   0.157  -0.533
HETATM   20  C   UNK  0001     -3.813   0.471  -0.407
HETATM   21  H   UNK  0001     -4.322   0.334  -1.372
HETATM   22  H   UNK  0001     -3.964   1.524  -0.128
HETATM   23  H   UNK  0001     -4.309  -0.158   0.337
HETATM   24  C   UNK  0001     -1.560   1.060  -1.457
HETATM   25  H   UNK  0001     -2.234   1.485  -2.211
HETATM   26  H   UNK  0001     -0.795   0.502  -2.007
HETATM   27  C   UNK  0001     -0.860   2.225  -0.697
HETATM   28  H   UNK  0001     -1.617   2.769  -0.115
HETATM   29  H   UNK  0001     -0.164   1.797   0.030
```

```
HETATM  30  C   UNK  0001     -0.167   3.181  -1.631
HETATM  31  H   UNK  0001     -0.835   3.849  -2.179
HETATM  32  C   UNK  0001      1.149   3.283  -1.876
HETATM  33  C   UNK  0001      2.219   2.434  -1.234
HETATM  34  H   UNK  0001      2.908   3.059  -0.648
HETATM  35  H   UNK  0001      2.830   1.944  -2.004
HETATM  36  H   UNK  0001      1.836   1.648  -0.580
HETATM  37  C   UNK  0001      1.670   4.309  -2.855
HETATM  38  H   UNK  0001      2.373   4.998  -2.365
HETATM  39  H   UNK  0001      0.864   4.904  -3.296
HETATM  40  H   UNK  0001      2.227   3.830  -3.673
CONECT   1   2   8  15
CONECT   2   1   3   7
CONECT   3   4   5   6   2
CONECT   4   3
CONECT   5   3
CONECT   6   3
CONECT   7   2
CONECT   8   1   9  10
CONECT   9   8
CONECT  10   8  11
CONECT  11  12  13  14  10
CONECT  12  11
CONECT  13  11
CONECT  14  11
CONECT  15  16   1  17
CONECT  16  15
CONECT  17  18  15  19
CONECT  18  17
CONECT  19  17  20  24
CONECT  20  21  22  23  19
CONECT  21  20
CONECT  22  20
CONECT  23  20
CONECT  24  25  26  19  27
CONECT  25  24
CONECT  26  24
CONECT  27  28  29  24  30
CONECT  28  27
CONECT  29  27
CONECT  30  31  27  32
CONECT  31  30
CONECT  32  30  33  37
CONECT  33  34  35  36  32
CONECT  34  33
CONECT  35  33
CONECT  36  33
CONECT  37  38  39  40  32
CONECT  38  37
CONECT  39  37
CONECT  40  37
END
```

TS *trans*-Δ^1-THC_{est} (+28.83 kcal/mol)
Energy= -508563.376 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM   1  C   UNK  0001      1.179   0.463  -0.424
HETATM   2  C   UNK  0001      1.634   1.560   0.437
HETATM   3  C   UNK  0001      1.979  -0.658  -0.843
HETATM   4  C   UNK  0001      3.491  -0.732  -0.722
HETATM   5  H   UNK  0001      3.816  -0.698   0.323
HETATM   6  H   UNK  0001      3.817  -1.673  -1.174
HETATM   7  C   UNK  0001     -0.214   0.341  -0.745
HETATM   8  C   UNK  0001     -1.126  -1.024   0.323
HETATM   9  H   UNK  0001     -1.060  -0.470   1.260
HETATM  10  C   UNK  0001     -0.346  -2.194   0.283
HETATM  11  O   UNK  0001      1.378  -1.668  -1.292
HETATM  12  O   UNK  0001      0.905   2.286   1.099
HETATM  13  C   UNK  0001     -2.508  -1.014  -0.324
HETATM  14  H   UNK  0001     -3.119  -1.831   0.084
HETATM  15  H   UNK  0001     -2.414  -1.216  -1.399
HETATM  16  C   UNK  0001     -3.247   0.310  -0.118
HETATM  17  H   UNK  0001     -4.163   0.310  -0.727
HETATM  18  H   UNK  0001     -3.597   0.383   0.925
HETATM  19  C   UNK  0001     -2.437   1.544  -0.432
HETATM  20  C   UNK  0001     -1.115   1.526  -0.656
HETATM  21  H   UNK  0001     -0.613   2.482  -0.783
HETATM  22  H   UNK  0001     -0.340  -0.261  -1.645
HETATM  23  C   UNK  0001      0.679  -2.394   1.356
HETATM  24  H   UNK  0001      1.399  -3.177   1.106
HETATM  25  H   UNK  0001      0.188  -2.661   2.303
HETATM  26  C   UNK  0001     -0.700  -3.344  -0.609
HETATM  27  H   UNK  0001     -1.552  -3.898  -0.182
HETATM  28  H   UNK  0001      0.137  -4.036  -0.723
HETATM  29  H   UNK  0001     -1.000  -3.003  -1.604
HETATM  30  C   UNK  0001     -3.203   2.841  -0.401
HETATM  31  H   UNK  0001     -3.680   2.995   0.577
HETATM  32  H   UNK  0001     -4.012   2.842  -1.145
HETATM  33  H   UNK  0001     -2.556   3.701  -0.599
HETATM  34  H   UNK  0001      1.219  -1.455   1.543
HETATM  35  H   UNK  0001      3.973   0.111  -1.226
HETATM  36  O   UNK  0001      2.989   1.733   0.440
HETATM  37  C   UNK  0001      3.458   2.798   1.276
HETATM  38  H   UNK  0001      4.545   2.792   1.173
HETATM  39  H   UNK  0001      3.170   2.633   2.318
HETATM  40  H   UNK  0001      3.048   3.757   0.949
CONECT   1   2   3   7
CONECT   2   1  12  36
CONECT   3   1   4  11
CONECT   4   5   6   3  35
```

```
CONECT    5    4
CONECT    6    4
CONECT    7    1    8   22   20
CONECT    8    9    7   10   13
CONECT    9    8
CONECT   10    8   11   23   26
CONECT   11   10    3
CONECT   12    2
CONECT   13   14   15    8   16
CONECT   14   13
CONECT   15   13
CONECT   16   17   18   13   19
CONECT   17   16
CONECT   18   16
CONECT   19   16   20   30
CONECT   20   21   19    7
CONECT   21   20
CONECT   22    7
CONECT   23   24   25   10   34
CONECT   24   23
CONECT   25   23
CONECT   26   27   28   29   10
CONECT   27   26
CONECT   28   26
CONECT   29   26
CONECT   30   31   32   33   19
CONECT   31   30
CONECT   32   30
CONECT   33   30
CONECT   34   23
CONECT   35    4
CONECT   36    2   37
CONECT   37   38   39   40   36
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

TS CBC_{est} (+19.31 kcal/mol)
Energy= -508572.900 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  O   UNK  0001       0.068  -1.548   0.586
HETATM    2  C   UNK  0001       1.262  -1.708   0.956
HETATM    3  C   UNK  0001      -0.743   0.333   1.115
HETATM    4  C   UNK  0001       0.435   1.099   1.058
HETATM    5  H   UNK  0001       0.424   2.026   0.487
HETATM    6  C   UNK  0001       1.650   0.645   1.551
HETATM    7  H   UNK  0001       2.466   1.352   1.688
HETATM    8  C   UNK  0001       1.999  -0.714   1.706
```

```
HETATM   9  C   UNK  0001      3.316  -0.946   2.335
HETATM  10  C   UNK  0001      1.921  -2.981   0.444
HETATM  11  H   UNK  0001      1.332  -3.341  -0.403
HETATM  12  H   UNK  0001      1.905  -3.743   1.232
HETATM  13  O   UNK  0001      4.056  -0.062   2.735
HETATM  14  C   UNK  0001     -1.203  -0.276   2.414
HETATM  15  H   UNK  0001     -1.898   0.435   2.888
HETATM  16  H   UNK  0001     -0.375  -0.447   3.104
HETATM  17  H   UNK  0001     -1.742  -1.212   2.248
HETATM  18  C   UNK  0001     -1.841   0.584   0.105
HETATM  19  H   UNK  0001     -2.299   1.556   0.348
HETATM  20  H   UNK  0001     -2.631  -0.163   0.243
HETATM  21  C   UNK  0001     -1.384   0.589  -1.370
HETATM  22  H   UNK  0001     -0.610   1.347  -1.515
HETATM  23  H   UNK  0001     -0.905  -0.380  -1.566
HETATM  24  C   UNK  0001     -2.537   0.791  -2.315
HETATM  25  H   UNK  0001     -3.284  -0.006  -2.288
HETATM  26  C   UNK  0001     -2.758   1.809  -3.162
HETATM  27  C   UNK  0001     -3.986   1.830  -4.042
HETATM  28  H   UNK  0001     -3.709   1.859  -5.106
HETATM  29  H   UNK  0001     -4.592   2.727  -3.856
HETATM  30  H   UNK  0001     -4.621   0.953  -3.882
HETATM  31  C   UNK  0001     -1.848   3.000  -3.338
HETATM  32  H   UNK  0001     -1.495   3.069  -4.376
HETATM  33  H   UNK  0001     -0.969   2.975  -2.689
HETATM  34  H   UNK  0001     -2.389   3.934  -3.132
HETATM  35  H   UNK  0001      2.963  -2.840   0.153
HETATM  36  O   UNK  0001      3.621  -2.262   2.504
HETATM  37  C   UNK  0001      4.870  -2.514   3.162
HETATM  38  H   UNK  0001      5.703  -2.089   2.595
HETATM  39  H   UNK  0001      4.957  -3.601   3.216
HETATM  40  H   UNK  0001      4.871  -2.080   4.166
CONECT   1   2   3
CONECT   2   1   8  10
CONECT   3   1   4  14  18
CONECT   4   5   3   6
CONECT   5   4
CONECT   6   7   4   8
CONECT   7   6
CONECT   8   6   2   9
CONECT   9   8  13  36
CONECT  10  11  12   2  35
CONECT  11  10
CONECT  12  10
CONECT  13   9
CONECT  14  15  16  17   3
CONECT  15  14
CONECT  16  14
CONECT  17  14
CONECT  18  19  20   3  21
CONECT  19  18
CONECT  20  18
```

```
CONECT   21   22   23   18   24
CONECT   22   21
CONECT   23   21
CONECT   24   25   21   26
CONECT   25   24
CONECT   26   24   27   31
CONECT   27   28   29   30   26
CONECT   28   27
CONECT   29   27
CONECT   30   27
CONECT   31   32   33   34   26
CONECT   32   31
CONECT   33   31
CONECT   34   31
CONECT   35   10
CONECT   36    9   37
CONECT   37   38   39   40   36
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

TS *cis*-Δ^1-THC_{est} (+30.94 kcal/mol)
Energy= -508561.268 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      -1.091  -2.443   0.254
HETATM    2  C   UNK  0001      -0.233  -1.303   0.574
HETATM    3  C   UNK  0001       1.187  -1.323   0.817
HETATM    4  C   UNK  0001       1.969  -2.574   1.184
HETATM    5  H   UNK  0001       2.978  -2.268   1.469
HETATM    6  H   UNK  0001       2.028  -3.267   0.337
HETATM    7  O   UNK  0001      -2.231  -2.354  -0.191
HETATM    8  C   UNK  0001      -0.840  -0.011   0.405
HETATM    9  H   UNK  0001      -1.912  -0.116   0.231
HETATM   10  C   UNK  0001      -0.543   0.742  -1.309
HETATM   11  H   UNK  0001      -1.032  -0.059  -1.866
HETATM   12  C   UNK  0001       0.851   0.773  -1.518
HETATM   13  O   UNK  0001       1.818  -0.249   0.678
HETATM   14  C   UNK  0001       1.694   1.970  -1.222
HETATM   15  H   UNK  0001       1.351   2.845  -1.793
HETATM   16  H   UNK  0001       2.745   1.790  -1.458
HETATM   17  H   UNK  0001       1.621   2.221  -0.157
HETATM   18  C   UNK  0001       1.461  -0.414  -2.192
HETATM   19  H   UNK  0001       1.014  -1.338  -1.796
HETATM   20  H   UNK  0001       2.545  -0.456  -2.071
HETATM   21  H   UNK  0001       1.226  -0.398  -3.267
HETATM   22  C   UNK  0001      -0.499   1.079   1.366
HETATM   23  H   UNK  0001      -0.080   0.740   2.310
HETATM   24  C   UNK  0001      -0.698   2.395   1.195
```

```
HETATM  25  C   UNK  0001     -1.147   2.996  -0.113
HETATM  26  H   UNK  0001     -2.054   3.598   0.050
HETATM  27  H   UNK  0001     -0.385   3.726  -0.425
HETATM  28  C   UNK  0001     -1.426   1.995  -1.249
HETATM  29  H   UNK  0001     -1.369   2.521  -2.212
HETATM  30  H   UNK  0001     -2.460   1.641  -1.163
HETATM  31  C   UNK  0001     -0.415   3.383   2.299
HETATM  32  H   UNK  0001     -0.050   2.884   3.203
HETATM  33  H   UNK  0001     -1.320   3.947   2.565
HETATM  34  H   UNK  0001      0.336   4.125   1.993
HETATM  35  H   UNK  0001      1.492  -3.121   2.002
HETATM  36  O   UNK  0001     -0.519  -3.661   0.488
HETATM  37  C   UNK  0001     -1.354  -4.787   0.196
HETATM  38  H   UNK  0001     -0.769  -5.665   0.477
HETATM  39  H   UNK  0001     -1.607  -4.821  -0.867
HETATM  40  H   UNK  0001     -2.282  -4.744   0.774
CONECT   1   2   7  36
CONECT   2   1   3   8
CONECT   3   2   4  13
CONECT   4   5   6   3  35
CONECT   5   4
CONECT   6   4
CONECT   7   1
CONECT   8   9   2  10  22
CONECT   9   8
CONECT  10  11   8  12  28
CONECT  11  10
CONECT  12  10  13  14  18
CONECT  13  12   3
CONECT  14  15  16  17  12
CONECT  15  14
CONECT  16  14
CONECT  17  14
CONECT  18  19  20  21  12
CONECT  19  18
CONECT  20  18
CONECT  21  18
CONECT  22  23   8  24
CONECT  23  22
CONECT  24  22  25  31
CONECT  25  26  27  24  28
CONECT  26  25
CONECT  27  25
CONECT  28  29  30  25  10
CONECT  29  28
CONECT  30  28
CONECT  31  32  33  34  24
CONECT  32  31
CONECT  33  31
CONECT  34  31
CONECT  35   4
CONECT  36   1  37
```

```
CONECT   37   38   39   40   36
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

CBC_{ketv} (+10.85 kcal/mol)
Energy= -508581.358 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      1.587  -1.304  -2.103
HETATM    2  C   UNK  0001      1.591   0.088  -0.055
HETATM    3  C   UNK  0001      0.533  -2.129  -0.115
HETATM    4  O   UNK  0001      0.618  -0.918   0.444
HETATM    5  C   UNK  0001      1.026  -2.430  -1.361
HETATM    6  C   UNK  0001      1.811  -0.113  -1.533
HETATM    7  H   UNK  0001      2.210   0.728  -2.093
HETATM    8  H   UNK  0001      1.797  -1.488  -3.151
HETATM    9  C   UNK  0001      0.961  -3.738  -2.040
HETATM   10  O   UNK  0001      1.372  -3.842  -3.195
HETATM   11  C   UNK  0001      2.887  -0.132   0.738
HETATM   12  H   UNK  0001      3.643   0.597   0.425
HETATM   13  H   UNK  0001      3.281  -1.134   0.543
HETATM   14  H   UNK  0001      2.714  -0.015   1.814
HETATM   15  C   UNK  0001      0.956   1.446   0.285
HETATM   16  H   UNK  0001      1.691   2.220   0.025
HETATM   17  H   UNK  0001      0.813   1.507   1.372
HETATM   18  C   UNK  0001     -0.378   1.733  -0.429
HETATM   19  H   UNK  0001     -1.099   0.956  -0.160
HETATM   20  H   UNK  0001     -0.221   1.641  -1.513
HETATM   21  C   UNK  0001     -0.901   3.109  -0.114
HETATM   22  H   UNK  0001     -0.242   3.923  -0.426
HETATM   23  C   UNK  0001     -2.047   3.451   0.495
HETATM   24  C   UNK  0001     -3.083   2.477   1.003
HETATM   25  H   UNK  0001     -3.271   2.638   2.074
HETATM   26  H   UNK  0001     -2.799   1.431   0.866
HETATM   27  H   UNK  0001     -4.044   2.632   0.494
HETATM   28  C   UNK  0001     -2.399   4.903   0.719
HETATM   29  H   UNK  0001     -3.347   5.161   0.226
HETATM   30  H   UNK  0001     -1.625   5.576   0.336
HETATM   31  H   UNK  0001     -2.538   5.117   1.788
HETATM   32  C   UNK  0001      0.402  -4.964  -1.334
HETATM   33  H   UNK  0001     -0.658  -4.832  -1.092
HETATM   34  H   UNK  0001      0.919  -5.156  -0.387
HETATM   35  H   UNK  0001      0.522  -5.819  -2.002
HETATM   36  O   UNK  0001     -0.150  -3.007   0.631
HETATM   37  C   UNK  0001     -0.551  -2.633   1.958
HETATM   38  H   UNK  0001      0.310  -2.331   2.560
HETATM   39  H   UNK  0001     -1.006  -3.532   2.374
HETATM   40  H   UNK  0001     -1.280  -1.819   1.933
```

```
CONECT    1    8    5    6
CONECT    2    4    6   11   15
CONECT    3    5    4   36
CONECT    4    2    3
CONECT    5    1    3    9
CONECT    6    1    2    7
CONECT    7    6
CONECT    8    1
CONECT    9    5   10   32
CONECT   10    9
CONECT   11   12   13   14    2
CONECT   12   11
CONECT   13   11
CONECT   14   11
CONECT   15   16   17    2   18
CONECT   16   15
CONECT   17   15
CONECT   18   19   20   15   21
CONECT   19   18
CONECT   20   18
CONECT   21   22   18   23
CONECT   22   21
CONECT   23   21   24   28
CONECT   24   25   26   27   23
CONECT   25   24
CONECT   26   24
CONECT   27   24
CONECT   28   29   30   31   23
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35    9
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36    3   37
CONECT   37   38   39   40   36
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

trans-Δ^1-THC$_{ket}$ (+0.09 kcal/mol)
Energy= -508592.119 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       2.447  -0.654  -1.670
HETATM    2  C   UNK  0001       1.338   1.630  -1.376
HETATM    3  C   UNK  0001       0.095  -0.459  -0.782
HETATM    4  C   UNK  0001       0.570   0.909  -0.260
```

```
HETATM    5  C   UNK  0001       1.316  -1.236  -1.251
HETATM    6  C   UNK  0001       2.626   0.851  -1.702
HETATM    7  H   UNK  0001       1.595   2.658  -1.093
HETATM    8  H   UNK  0001       1.225  -2.316  -1.276
HETATM    9  H   UNK  0001       3.008   1.158  -2.686
HETATM   10  H   UNK  0001       0.708   1.694  -2.273
HETATM   11  H   UNK  0001      -0.540  -0.296  -1.668
HETATM   12  H   UNK  0001       1.284   0.714   0.554
HETATM   13  H   UNK  0001       3.418   1.129  -0.987
HETATM   14  C   UNK  0001      -0.751  -1.181   0.266
HETATM   15  C   UNK  0001      -0.581   1.688   0.395
HETATM   16  O   UNK  0001      -1.045   0.860   1.523
HETATM   17  C   UNK  0001      -1.195  -0.464   1.342
HETATM   18  C   UNK  0001       3.634  -1.461  -2.134
HETATM   19  H   UNK  0001       4.528  -1.235  -1.535
HETATM   20  H   UNK  0001       3.892  -1.229  -3.177
HETATM   21  H   UNK  0001       3.441  -2.536  -2.064
HETATM   22  C   UNK  0001      -0.118   2.977   1.074
HETATM   23  H   UNK  0001       0.759   2.794   1.703
HETATM   24  H   UNK  0001      -0.919   3.376   1.705
HETATM   25  H   UNK  0001       0.136   3.736   0.329
HETATM   26  C   UNK  0001      -1.779   1.955  -0.523
HETATM   27  H   UNK  0001      -1.470   2.563  -1.380
HETATM   28  H   UNK  0001      -2.556   2.502   0.021
HETATM   29  H   UNK  0001      -2.213   1.025  -0.902
HETATM   30  C   UNK  0001      -1.197  -2.550  -0.048
HETATM   31  O   UNK  0001      -0.986  -3.010  -1.172
HETATM   32  O   UNK  0001      -1.848  -1.037   2.371
HETATM   33  C   UNK  0001      -2.512  -0.200   3.327
HETATM   34  H   UNK  0001      -3.234   0.463   2.841
HETATM   35  H   UNK  0001      -1.796   0.400   3.894
HETATM   36  H   UNK  0001      -3.029  -0.893   3.993
HETATM   37  C   UNK  0001      -1.925  -3.419   0.969
HETATM   38  H   UNK  0001      -2.902  -2.996   1.229
HETATM   39  H   UNK  0001      -1.363  -3.506   1.904
HETATM   40  H   UNK  0001      -2.064  -4.404   0.519
CONECT    1    5    6   18
CONECT    2    7   10    4    6
CONECT    3   11    5    4   14
CONECT    4    2    3   12   15
CONECT    5    1    3    8
CONECT    6    1    2    9   13
CONECT    7    2
CONECT    8    5
CONECT    9    6
CONECT   10    2
CONECT   11    3
CONECT   12    4
CONECT   13    6
CONECT   14    3   17   30
CONECT   15    4   16   22   26
CONECT   16   15   17
```

```
CONECT   17   16   14   32
CONECT   18   19   20   21    1
CONECT   19   18
CONECT   20   18
CONECT   21   18
CONECT   22   23   24   25   15
CONECT   23   22
CONECT   24   22
CONECT   25   22
CONECT   26   27   28   29   15
CONECT   27   26
CONECT   28   26
CONECT   29   26
CONECT   30   14   31   37
CONECT   31   30
CONECT   32   17   33
CONECT   33   34   35   36   32
CONECT   34   33
CONECT   35   33
CONECT   36   33
CONECT   37   38   39   40   30
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

cis-Δ^1-THC_{ket} (+0.13 kcal/mol)
Energy= -508592.074 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      2.499  -0.790  -0.801
HETATM    2  C   UNK  0001      2.245   1.201   0.768
HETATM    3  C   UNK  0001      0.579  -0.692   0.859
HETATM    4  C   UNK  0001      0.751   0.841   0.894
HETATM    5  C   UNK  0001      1.434  -1.349  -0.212
HETATM    6  C   UNK  0001      2.958   0.609  -0.458
HETATM    7  H   UNK  0001      2.729   0.801   1.668
HETATM    8  H   UNK  0001      0.943  -1.081   1.823
HETATM    9  H   UNK  0001      1.162  -2.371  -0.463
HETATM   10  H   UNK  0001      2.839   1.259  -1.340
HETATM   11  H   UNK  0001      2.391   2.287   0.805
HETATM   12  H   UNK  0001      0.431   1.178   1.890
HETATM   13  H   UNK  0001      4.042   0.600  -0.268
HETATM   14  C   UNK  0001     -0.889  -1.098   0.789
HETATM   15  C   UNK  0001     -0.224   1.566  -0.069
HETATM   16  O   UNK  0001     -1.585   1.159   0.324
HETATM   17  C   UNK  0001     -1.833  -0.134   0.582
HETATM   18  C   UNK  0001     -1.180  -2.508   1.096
HETATM   19  O   UNK  0001     -0.255  -3.254   1.426
HETATM   20  C   UNK  0001     -0.232   3.077   0.167
```

```
HETATM  21  H   UNK  0001      0.706   3.525  -0.174
HETATM  22  H   UNK  0001     -0.363   3.309   1.229
HETATM  23  H   UNK  0001     -1.053   3.542  -0.390
HETATM  24  C   UNK  0001     -0.105   1.263  -1.567
HETATM  25  H   UNK  0001      0.840   1.634  -1.970
HETATM  26  H   UNK  0001     -0.918   1.772  -2.096
HETATM  27  H   UNK  0001     -0.165   0.193  -1.777
HETATM  28  C   UNK  0001      3.309  -1.514  -1.846
HETATM  29  H   UNK  0001      4.355  -1.634  -1.530
HETATM  30  H   UNK  0001      3.333  -0.952  -2.792
HETATM  31  H   UNK  0001      2.902  -2.509  -2.054
HETATM  32  O   UNK  0001     -3.153  -0.388   0.670
HETATM  33  C   UNK  0001     -4.087   0.627   0.283
HETATM  34  H   UNK  0001     -4.001   1.511   0.919
HETATM  35  H   UNK  0001     -5.067   0.166   0.412
HETATM  36  H   UNK  0001     -3.946   0.918  -0.763
HETATM  37  C   UNK  0001     -2.587  -3.083   1.005
HETATM  38  H   UNK  0001     -3.237  -2.661   1.779
HETATM  39  H   UNK  0001     -2.512  -4.164   1.142
HETATM  40  H   UNK  0001     -3.057  -2.858   0.042
CONECT   1   5   6  28
CONECT   2   7  11   4   6
CONECT   3   8   5   4  14
CONECT   4   2   3  12  15
CONECT   5   1   3   9
CONECT   6   1   2  10  13
CONECT   7   2
CONECT   8   3
CONECT   9   5
CONECT  10   6
CONECT  11   2
CONECT  12   4
CONECT  13   6
CONECT  14   3  17  18
CONECT  15   4  16  20  24
CONECT  16  15  17
CONECT  17  16  14  32
CONECT  18  14  19  37
CONECT  19  18
CONECT  20  21  22  23  15
CONECT  21  20
CONECT  22  20
CONECT  23  20
CONECT  24  25  26  27  15
CONECT  25  24
CONECT  26  24
CONECT  27  24
CONECT  28  29  30  31   1
CONECT  29  28
CONECT  30  28
CONECT  31  28
CONECT  32  17  33
```

```
CONECT   33   34   35   36   32
CONECT   34   33
CONECT   35   33
CONECT   36   33
CONECT   37   38   39   40   18
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

TS CBC_{ket} (+25.59 kcal/mol)
Energy= -508566.621 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  O   UNK  0001      0.261  -1.397   0.791
HETATM    2  C   UNK  0001      1.447  -1.569   1.195
HETATM    3  C   UNK  0001     -0.486   0.389   1.300
HETATM    4  C   UNK  0001      0.677   1.206   1.275
HETATM    5  H   UNK  0001      0.631   2.155   0.745
HETATM    6  C   UNK  0001      1.893   0.756   1.742
HETATM    7  H   UNK  0001      2.713   1.457   1.881
HETATM    8  C   UNK  0001      2.251  -0.609   1.896
HETATM    9  C   UNK  0001      3.589  -0.866   2.484
HETATM   10  O   UNK  0001      4.255   0.075   2.912
HETATM   11  C   UNK  0001     -0.981  -0.151   2.620
HETATM   12  H   UNK  0001     -1.645   0.607   3.060
HETATM   13  H   UNK  0001     -0.162  -0.325   3.320
HETATM   14  H   UNK  0001     -1.559  -1.070   2.488
HETATM   15  C   UNK  0001     -1.566   0.616   0.265
HETATM   16  H   UNK  0001     -2.066   1.562   0.526
HETATM   17  H   UNK  0001     -2.328  -0.165   0.367
HETATM   18  C   UNK  0001     -1.077   0.680  -1.196
HETATM   19  H   UNK  0001     -0.322   1.465  -1.299
HETATM   20  H   UNK  0001     -0.564  -0.267  -1.412
HETATM   21  C   UNK  0001     -2.215   0.877  -2.161
HETATM   22  H   UNK  0001     -2.957   0.076  -2.149
HETATM   23  C   UNK  0001     -2.427   1.895  -3.010
HETATM   24  C   UNK  0001     -3.640   1.909  -3.910
HETATM   25  H   UNK  0001     -3.347   1.940  -4.969
HETATM   26  H   UNK  0001     -4.254   2.805  -3.734
HETATM   27  H   UNK  0001     -4.274   1.030  -3.760
HETATM   28  C   UNK  0001     -1.520   3.091  -3.170
HETATM   29  H   UNK  0001     -1.153   3.163  -4.203
HETATM   30  H   UNK  0001     -0.651   3.070  -2.509
HETATM   31  H   UNK  0001     -2.070   4.022  -2.972
HETATM   32  O   UNK  0001      2.051  -2.731   0.864
HETATM   33  C   UNK  0001      1.257  -3.699   0.166
HETATM   34  H   UNK  0001      0.339  -3.922   0.716
HETATM   35  H   UNK  0001      1.887  -4.588   0.095
HETATM   36  H   UNK  0001      0.997  -3.340  -0.834
```

```
HETATM  37  C   UNK  0001      4.145  -2.276   2.622
HETATM  38  H   UNK  0001      5.026  -2.224   3.266
HETATM  39  H   UNK  0001      4.433  -2.678   1.645
HETATM  40  H   UNK  0001      3.410  -2.968   3.046
CONECT   1   2   3
CONECT   2   1   8  32
CONECT   3   1   4  11  15
CONECT   4   5   3   6
CONECT   5   4
CONECT   6   7   4   8
CONECT   7   6
CONECT   8   6   2   9
CONECT   9   8  10  37
CONECT  10   9
CONECT  11  12  13  14   3
CONECT  12  11
CONECT  13  11
CONECT  14  11
CONECT  15  16  17   3  18
CONECT  16  15
CONECT  17  15
CONECT  18  19  20  15  21
CONECT  19  18
CONECT  20  18
CONECT  21  22  18  23
CONECT  22  21
CONECT  23  21  24  28
CONECT  24  25  26  27  23
CONECT  25  24
CONECT  26  24
CONECT  27  24
CONECT  28  29  30  31  23
CONECT  29  28
CONECT  30  28
CONECT  31  28
CONECT  32   2  33
CONECT  33  34  35  36  32
CONECT  34  33
CONECT  35  33
CONECT  36  33
CONECT  37  38  39  40   9
CONECT  38  37
CONECT  39  37
CONECT  40  37
END
```

TS *trans*-Δ^1-THC_{ket} (+32.26 kcal/mol)
Energy= -508559.948 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001       1.145   0.700  -0.250
HETATM    2  C   UNK  0001       1.593   1.767   0.650
HETATM    3  C   UNK  0001       1.934  -0.403  -0.714
HETATM    4  C   UNK  0001      -0.263   0.547  -0.574
HETATM    5  C   UNK  0001      -1.135  -0.675   0.473
HETATM    6  H   UNK  0001      -1.059  -0.128   1.416
HETATM    7  C   UNK  0001      -0.406  -1.894   0.481
HETATM    8  O   UNK  0001       1.405  -1.447  -1.146
HETATM    9  O   UNK  0001       0.769   2.432   1.288
HETATM   10  C   UNK  0001      -2.554  -0.688  -0.107
HETATM   11  H   UNK  0001      -3.143  -1.490   0.358
HETATM   12  H   UNK  0001      -2.511  -0.922  -1.179
HETATM   13  C   UNK  0001      -3.269   0.648   0.093
HETATM   14  H   UNK  0001      -4.214   0.640  -0.470
HETATM   15  H   UNK  0001      -3.565   0.761   1.149
HETATM   16  C   UNK  0001      -2.445   1.846  -0.310
HETATM   17  C   UNK  0001      -1.130   1.773  -0.551
HETATM   18  H   UNK  0001      -0.598   2.697  -0.764
HETATM   19  H   UNK  0001      -0.365  -0.016  -1.505
HETATM   20  C   UNK  0001       0.625  -2.079   1.540
HETATM   21  H   UNK  0001       1.280  -2.934   1.352
HETATM   22  H   UNK  0001       0.143  -2.212   2.520
HETATM   23  C   UNK  0001      -0.788  -3.041  -0.396
HETATM   24  H   UNK  0001      -1.672  -3.550   0.022
HETATM   25  H   UNK  0001       0.020  -3.771  -0.479
HETATM   26  H   UNK  0001      -1.057  -2.704  -1.401
HETATM   27  C   UNK  0001      -3.181   3.160  -0.349
HETATM   28  H   UNK  0001      -3.632   3.389   0.627
HETATM   29  H   UNK  0001      -4.006   3.135  -1.076
HETATM   30  H   UNK  0001      -2.518   3.989  -0.613
HETATM   31  H   UNK  0001       1.232  -1.164   1.629
HETATM   32  C   UNK  0001       3.073   2.096   0.810
HETATM   33  H   UNK  0001       3.606   1.288   1.324
HETATM   34  H   UNK  0001       3.147   3.012   1.400
HETATM   35  H   UNK  0001       3.567   2.228  -0.158
HETATM   36  O   UNK  0001       3.289  -0.308  -0.610
HETATM   37  C   UNK  0001       4.022  -1.459  -1.041
HETATM   38  H   UNK  0001       5.075  -1.184  -0.950
HETATM   39  H   UNK  0001       3.782  -1.712  -2.077
HETATM   40  H   UNK  0001       3.803  -2.326  -0.409
CONECT    1    2    3    4
CONECT    2    1    9   32
CONECT    3    1    8   36
CONECT    4    1    5   19   17
CONECT    5    6    4    7   10
CONECT    6    5
CONECT    7    5    8   20   23
CONECT    8    7    3
CONECT    9    2
CONECT   10   11   12    5   13
```

```
CONECT   11   10
CONECT   12   10
CONECT   13   14   15   10   16
CONECT   14   13
CONECT   15   13
CONECT   16   13   17   27
CONECT   17   18   16    4
CONECT   18   17
CONECT   19    4
CONECT   20   21   22    7   31
CONECT   21   20
CONECT   22   20
CONECT   23   24   25   26    7
CONECT   24   23
CONECT   25   23
CONECT   26   23
CONECT   27   28   29   30   16
CONECT   28   27
CONECT   29   27
CONECT   30   27
CONECT   31   20
CONECT   32   33   34   35    2
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36    3   37
CONECT   37   38   39   40   36
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

TS *cis*-Δ^1-THC_{ket} (+33.17 kcal/mol)
Energy= -508559.040 kcal/mol

```
HEADER
REMARK Spartan `06 exported M001
HETATM    1  C   UNK  0001      -1.330  -2.621   0.178
HETATM    2  C   UNK  0001      -0.497  -1.455   0.478
HETATM    3  C   UNK  0001       0.913  -1.427   0.720
HETATM    4  O   UNK  0001      -2.480  -2.469  -0.259
HETATM    5  C   UNK  0001      -1.117  -0.149   0.301
HETATM    6  H   UNK  0001      -2.194  -0.310   0.193
HETATM    7  C   UNK  0001      -0.872   0.562  -1.293
HETATM    8  H   UNK  0001      -1.370  -0.207  -1.889
HETATM    9  C   UNK  0001       0.528   0.605  -1.591
HETATM   10  O   UNK  0001       1.582  -0.389   0.558
HETATM   11  C   UNK  0001       1.378   1.799  -1.333
HETATM   12  H   UNK  0001       1.016   2.666  -1.906
```

```
HETATM  13  H   UNK  0001      2.423   1.617  -1.596
HETATM  14  H   UNK  0001      1.327   2.065  -0.271
HETATM  15  C   UNK  0001      1.084  -0.586  -2.285
HETATM  16  H   UNK  0001      0.711  -1.496  -1.783
HETATM  17  H   UNK  0001      2.175  -0.599  -2.313
HETATM  18  H   UNK  0001      0.697  -0.642  -3.314
HETATM  19  C   UNK  0001     -0.806   0.916   1.313
HETATM  20  H   UNK  0001     -0.431   0.549   2.266
HETATM  21  C   UNK  0001     -0.987   2.236   1.162
HETATM  22  C   UNK  0001     -1.421   2.851  -0.145
HETATM  23  H   UNK  0001     -2.317   3.469   0.020
HETATM  24  H   UNK  0001     -0.648   3.567  -0.462
HETATM  25  C   UNK  0001     -1.725   1.844  -1.268
HETATM  26  H   UNK  0001     -1.656   2.348  -2.241
HETATM  27  H   UNK  0001     -2.765   1.513  -1.174
HETATM  28  C   UNK  0001     -0.726   3.206   2.286
HETATM  29  H   UNK  0001     -0.376   2.694   3.188
HETATM  30  H   UNK  0001     -1.636   3.766   2.545
HETATM  31  H   UNK  0001      0.030   3.954   2.006
HETATM  32  C   UNK  0001     -0.812  -4.037   0.389
HETATM  33  H   UNK  0001      0.067  -4.240  -0.233
HETATM  34  H   UNK  0001     -1.614  -4.731   0.130
HETATM  35  H   UNK  0001     -0.500  -4.195   1.426
HETATM  36  O   UNK  0001      1.520  -2.595   1.082
HETATM  37  C   UNK  0001      2.939  -2.522   1.245
HETATM  38  H   UNK  0001      3.249  -3.522   1.556
HETATM  39  H   UNK  0001      3.209  -1.786   2.008
HETATM  40  H   UNK  0001      3.432  -2.248   0.306
CONECT   1   2   4  32
CONECT   2   1   3   5
CONECT   3   2  10  36
CONECT   4   1
CONECT   5   6   2   7  19
CONECT   6   5
CONECT   7   8   5   9  25
CONECT   8   7
CONECT   9   7  10  11  15
CONECT  10   9   3
CONECT  11  12  13  14   9
CONECT  12  11
CONECT  13  11
CONECT  14  11
CONECT  15  16  17  18   9
CONECT  16  15
CONECT  17  15
CONECT  18  15
CONECT  19  20   5  21
CONECT  20  19
CONECT  21  19  22  28
CONECT  22  23  24  21  25
CONECT  23  22
CONECT  24  22
```

```
CONECT   25   26   27   22    7
CONECT   26   25
CONECT   27   25
CONECT   28   29   30   31   21
CONECT   29   28
CONECT   30   28
CONECT   31   28
CONECT   32   33   34   35    1
CONECT   33   32
CONECT   34   32
CONECT   35   32
CONECT   36    3   37
CONECT   37   38   39   40   36
CONECT   38   37
CONECT   39   37
CONECT   40   37
END
```

Appendix D:

Proteins and Ligands used in UBANTR approach

DOCKING: Open Eye Software used for conformer generation (Omega) and for docking (FRED) all conformers using default parameters, including a Chemgauss3 scoring method. Electrostatic charges were applied to all FDA-approved drug conformers before docking using Spartan '08.

PROTEINS:

PDB: 1A27 (17-beta-Hydroxysteroid-Dehydrogenase)

Mazza, C., Human Type I 17Beta-Hydroxysteroid Dehydrogenase: Site Directed Mutagenesis and X-Ray Crystallography Structure-Function Analysis, Thesis, Universite Joseph Fourier, 1997.

PDB: 1B59 (Methionine Aminopeptidase)

Liu, S.; Widom, J.; Kemp, C.W.; Crews, C.M.; Clardy, J., *Science*, **1998**, 282, 1324-1327.

PDB: 1CX2 (Cyclooxygenase-2)

Kurumbail, R.G.; Stevens, A.M.; Gierse, J.K.; McDonald, J.J.; Stegeman, R.A.; Pak, J.Y.; Gildehaus, D.; Miyashiro, J.M.; Penning, T.D.; Seibert, K.; Isakson, P.C.; Stallings, W.C., *Nature*, **1996**, 384, 644-648.

PDB: 1HWK (HMG-CoA Reductase)

Istvan, E.S.; Deisenhofer, J.; *Science*, **2001**, 292, 1160-1164.

PDB: 1R9O (Cytochrome P450 2C9)

Wester, M.R.; Yano, J.K.; Schoch, G.A.; Yang, C.; Griffin, K.J.; Stout, C.D.; Johnson, E.F.; *J.Biol.Chem.,* **2004**, 279, 35630-35637.

PDB: 1TGM (Phospholipase A2)

Singh, N.; Jabeen, T.; Sharma, S.; Bhushan, A.; Singh, T.P., Crystal structure of a complex formed between group II phospholipase A2 and aspirin at 1.86 A resolution.

PDB: 1UZE (Angiotensin Converting Enzyme)

Natesh, R.; Schwager, S.L.U.; Evans, H.R.; Sturrock, E.D.; Acharya, K.R., *Biochemistry*, **2004**, 43, 8718.

PDB: 1VRT (HIV-1 Reverse Transcriptase)

Ren, J.; Esnouf, R.; Garman, E.; Somers, D.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Jones, Y.; Stuart, D., *Nat.Struct.Biol.,* **1995**, 2, 293-302.

PDB: 1X70 (Dipeptidyl peptidase IV)

Kim, D.; Wang, L.; Beconi, M.; Eiermann, G.J.; Fisher, M.H.; He, H.; Hickey, G.J.; Kowalchick, J.E.; Leiting, B.; Lyons, K.; Marsilio, F.; McCann, M.E.; Patel, R.A.; Petrov, A.; Scapin, G.; Patel, S.B.; Roy, R.S.; Wu, J.K.; Wyvratt, M.J.; Zhang, B.B.; Zhu, L.; Thornberry, N.A.; Weber, A.E.; *J.Med.Chem.*, **2005**, 48, 141-151.

PDB: 2F16 (Yeast 20S proteasome)

Groll, M.; Berkers, C.R.; Ploegh, H.L.; Ovaa, H., *Structure*, **2006**, 14, 451-456.

PDB: 2HT8 (Neuraminidase)

Russell, R.J.; Haire, L.F.; Stevens, D.J.; Collins, P.J.; Lin, Y.P.; Blackburn, G.M.; Hay, A.J.; Gamblin, S.J.; Skehel, J.J.; *Nature*, **2006**, 443, 45-49.

PDB: 2JEY (Acetylcholinesterase)

Ekstrom, F.J.; Astot, C.; Pang, Y., *Clin.Pharmacol.Ther.*, **2007**, 82, 282.

PDB: 2VT4 (Beta-1 Adrenergic receptor)

Warne, A.; Serrano-Vega, M.J.; Baker, J.G.; Moukhametzianov, R.; Edwards, P.C.; Henderson, R.; Leslie, A.G.W.; Tate, C.G.; Schertler, G.F.X., *Nature*, **2008**, 454, 486.

PDB: 3G45 (cAMP-specific 3',5'-cyclic phosphodiesterase 4B)

Burgin, A.B.; Magnusson, O.T.; Singh, J.; Witte, P.; Staker, B.L.; Bjornsson, J.M.; Thorsteinsdottir, M.; Hrafnsdottir, S.; Hagen, T.; Kiselyov, A.S.; Stewart, L.J.; Gurney, M.E., *Nat.Biotechnol.*, **2010**, 28, 63-70.

PDB: 3MHJ (Tankyrase-2 (catalytic PARP domain))

Wahlberg, E.; Karlberg, T.; Kouznetsova, E.; Markova, N.; Macchiarulo, A.; Thorsell, A.G.; Pol, E.; Frostell, A.; Ekblad, T.; Oncu, D.; Kull, B.; Robertson, G.M.; Pellicciari, R.; Schuler, H.; Weigelt, J., *Nat.Biotechnol.*, **2012**, 30, 283-8.

DRUGS:

analgesic: Salicylamide, Trolamine, Ethenzamide, Phenazopyridine_Z, Phenazopyridine_E, Hydromorphone, Ethoheptazine_R, Ethoheptazine_S, Tramadol, Hydrocodone, Methotrimeprazine

analgesic; anti inflammatory: Diflunisal, Emorfazone, Relafen, Flufenamic acid, Fenoprofen_R, Fenoprofen_S, Ketorolac_R, Ketorolac_S, Benoxaprofen_R, Benoxaprofen_S, Bextra, Rofecoxib, Vioxx, Azapropazone dihydrate_R, Azapropazone dihydrate_S

anti inflammatory: Mofebutazone_R, Mofebutazone_S, Pirprofen_S, Pirprofen_R, Niflumic acid, Pranoprofen_S, Pranoprofen_R, Tiaprofenic acid_S, Tiaprofenic acid_R, Mefenamic acid, Metiazinic acid, Fenbufen, Diclofenac, Bucloxic acid, Proquazone, Fentiazac, Phenylbutazone, Ibuprofen piconol_S, Ibuprofen piconol_R, Budesonide, Feprazone, Sulindac_E_R, Sulindac_Z_R, Sulindac_E_S, Sulindac_Z_S

anorexic: Clortermine, Chlorphentermine, Phendimetrazine_RR, Phendimetrazine_SR, Phendimetrazine_RS, Phendimetrazine_SS, Fenfluramine_R, Fenfluramine_S, Mazindol_R, Mazindol_S, Benzphetamine, Sibutramine_S, Sibutramine_R

anthelmintic: Arecoline, Levamisole, Pyrantel_Z, Pyrantel_E, Diethylcarbamazine, Dichlorophen, Albendazole, Oxamniquine_R, Oxamniquine_S, Flubendazole, Bephenium, Bephenium hydroxynaphthoate

antiarrhythmic: Adenosine, Alinidine, Procainamide, Adenosine-5-phosphate, Cifenline_S
Cifenline_R, Esmolol_R, Esmolol_S, Flecainide_R, Flecainide_S, Aprindine, Encainide_R, Encainide_S

anticholinergic: Etomidate_R, Etomidate_S, Homatropine_R, dl methylbromide, Homatropine_S, dl methylbromide, Atropine N-oxide_R, Atropine N-oxide_S, Diphemanil, Anisotropine methylbromide, Pentapiperide_SS, Pentapiperide_RS, Pentapiperide_SR, Pentapiperide_RR, Timepidium_R bromide, Timepidium_S bromide, Adiphenine, Proglumide_S, Proglumide_R, Dicyclomine, Glycopyrrolate_SS, Glycopyrrolate_SR, Glycopyrrolate_RS, Glycopyrrolate_RR, Hexocyclium_R, Hexocyclium_S, Oxyphencyclimine_R, Oxyphencyclimine_S, Mepenzolate_S, Mepenzolate_R, Clidinium bromide_S, Clidinium bromide_R, Tridihexethyl_S, Tridihexethyl_R, Pipenzolate bromide_RR, Pipenzolate bromide_SR, Pipenzolate

bromide_RS, Pipenzolate bromide_SS, Oxybutynin_S, Oxybutynin_R, Propantheline bromide,

anticonvulsant: Trimethadione, Ethosuximide_R, Ethosuximide_S, Paramethadione_R Paramethadione_S, Levetiracetam, Phenacemide, Gabapentin, Phensuximide_S, Phensuximide_R, Metharbital, Ethotoin_R, Ethotoin_S, Lamotrigine, Methsuximide_S, Methsuximide_R, Albutoin_R, Albutoin_S, Primidone, Mephenytoin_R, Mephenytoin_S Aminoglutethimide_R, Aminoglutethimide_S, Clonazepam

antidepressant: Fenpentadiol_S, Fenpentadiol_R, Isocarboxazid, Bupropion_R, Bupropion_S, Nomifensine_R, Nomifensine_S, Amoxapine, Desipramine, Protriptyline, Fluoxetine_R, Fluoxetine_S, Nialamide, Doxepin_E, Doxepin_Z, Venlafaxine_R, Venlafaxine_S Cymbalta, Dibenzepin, Amitriptyline, Dothiepin_Z, Dothiepin_E, Clomipramine, Trimipramine_S, Trimipramine_R, Dimetacrine, Citalopram_R, Citalopram_S, Butriptyline_R Butriptyline_S, Sultopride_S, Sultopride_R

antidiabetic: Chlorpropamide, Glybuzole, Glycodiazine, Tolazamide, Acetohexamide Gliclazide_RR, Gliclazide_RS, Gliclazide_SR, Gliclazide_SS, Rosiglitazone maleate_R, Rosiglitazone maleate_S

antihistaminic: Tripelennamine, Chlorpheniramine_R, Phenindamine_R, Phenindamine_S Chlorpheniramine_S, Antazoline, Phenyltoloxamine, Dexbrompheniramine, Brompheniramine_R, Brompheniramine_S, Carbinoxamine_R, Carbinoxamine_S Bromodiphenhydramine_S, Bromodiphenhydramine_R, Triprolidine_E, Triprolidine_Z, Diphenylpyraline, Pyrilamine, Mequitazine_R, Mequitazine_S, Dimethindene_S Dimethindene_R, Oxomemazine_R, Oxomemazine_S, Pyrrobutamine_E, Pyrrobutamine_Z Clemastine, Acrivastine_ZZ, Acrivastine_ZE, Acrivastine_EE, Acrivastine_EZ, Cetirizine_S Cetirizine_R

antihyperlipoproteinemic: Clofibrate, Ciprofibrate_R, Ciprofibrate_S, Gemfibrozil Clofibride, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin

antihypertensive: Hydralazine, Guancydine_S, Guancydine_R, Diazoxide, Pargyline, Clonidine, Bethanidine_Z, Bethanidine_E, Methyldopa, Lofexidine_R, Lofexidine_S, Mebutamate_S, Mebutamate_R, Cyclopenthiazide_R, Cyclopenthiazide_S, Phenoxybenzamine_R, Phenoxybenzamine_S, LabetaloL_RR, LabetaloL_SR, LabetaloL_RS LabetaloL_SS, Nitrendipine_R, Nitrendipine_S, Terazosin_R, Terazosin_S, Bunazosin, Enalapril, Moveltipril, Bopindolol_S, Bopindolol_R, Losartan, Eprosartan_Z, Eprosartan_E Candesartan, Ramipril, Irbesartan, Trandolapril, Valsartan

antihypertensive; antianginal: Nadolol_S, Nadolol_R, Felodipine_R, Felodipine_S, Isradipine_R, Isradipine_S, Nisoldipine_R, Nisoldipine_S, Celiprolol_R, Celiprolol_S, Carvedilol_S, Carvedilol_R

antineoplastic: Thioguanine, Mechlorethamine, Nitrogen mustard oxide, Dacarbazine, Tegafur-Uracil_R, Tegafur-Uracil_S, Thio-TEPA, Dibromodulcitol, Dibromomannitol, Azacytidine, 5- Busulfan, Lomustine, Altretamine, Streptozocin, Cladribine, Procarbazine, ICRF-159_S, ICRF-159_R, Pipobroman, Chlorozotocin, Mannomustine, Fludarabine phosphate, Melphalan, Letrozole, Testolactone, Exemestane, Dromostanolone, Calusterone, Trimetrexate, AMSA, M-, Dromostanolone proprionate, Mycophenolate mofetil_Z, Mycophenolate, mofetil_E, Proreside, Carminomycin

antipsychotic: Molindone_S, Molindone_R, Promazine, Chlorprothixene_Z Chlorprothixene_E, Clozapine, Clothiapine, Triflupromazine, Bromperidol, Thioridazine_R Thioridazine_S, Quetiapine, Mesoridazine_SS, Mesoridazine_RS, Mesoridazine_RR, Mesoridazine_SR, Spiclomazine, Acetophenazine, Piperacetazine, Butaperazine, Carphenazine

anxiolytic: Oxazepam_R, Oxazepam_S, Lorazepam_R, Lorazepam_S, Chlordiazepoxide Alprazolam, Tybamate_R, Tybamate_S, Clotiazepam, Pinazepam, Halazepam, Loxapine, Prazepam

bronchodilator: Theophylline, Ephedrine, Methoxyphenamine_S, Methoxyphenamine_R, Isoproterenol_R, Isoproterenol_S, Dyphylline_S, Dyphylline_R, Doxofylline, Oxitropium bromide, Tretoquinol, Reproterol_S, Reproterol_R, Etofylline clofibrate, Bamifylline

diuretic; antihypertensive: Trichlormethiazide_S, Trichlormethiazide_R, Furosemide, Chlorthalidone_R, Chlorthalidone_S, Buthiazide_R, Buthiazide_S, Xipamide, Bendroflumethiazide_R, Bendroflumethiazide_S, Benzthiazide

glucocorticoid: Prednisolone acetate, Cortisone, Prednisolone, Meprednisone, Methylprednisolone, Paramethasone, Prednisolone sodium succinate, Cortisone acetate, Methylprednisolone acetate, Paramethasone acetate

narcotic analgesic: Dezocine, Meperidine, Levorphanol, Alphaprodine, Tilidine, Oxycodone, Propiram_R, Propiram_S, Pentazocine, Butorphanol, Methadone_S, Methadone_R, Fentanyl, Anileridine Propoxyphene, Sufentanil, Dextromoramide, Alfentanil

sedative; hypnotic: Paraldehyde, Triclofos, Barbital, Ethinamate, Carbromal Methyprylon_R, Methyprylon_S, Dichloralphenazone, Aprobarbital, Butabarbital_S, Butabarbital_R, Butalbital, Vinbarbital_Z, Vinbarbital_E, Glutethimide_R, Glutethimide_S, Chloralose-alpha, Cyclobarbital, Thalidomide_R, Thalidomide_S,

Secobarbital_RS, Secobarbital_SS, Secobarbital_RR, Secobarbital_SR, Methaqualone, Estazolam, Temazepam_R, Temazepam_S, Brotizolam, Zaleplon, Doxefazepam_R, Doxefazepam_S, Propiomazine_S, Propiomazine_R

skeletal muscle relaxant: Mephenesin_R, Mephenesin_S, Tizanidine, Metaxalone_R, Metaxalone_S, Methocarbamol_R, Methocarbamol_S, Afloqualone, Dantrolene_Z, Dantrolene_E, Tolperisone_R, Tolperisone_S, Succinylcholine, Decamethonium bromide