ENANTIOSELECTIVE FORMAL SYNTHESIS OF
PREGABALIN
WITH
BIFUNCTIONAL ACID/BASE ORGANOCATALYSTS

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**ENANTIOSELECTIVE FORMAL SYNTHESIS OF
PREGABALIN
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ABSTRACT

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Pregabalin, which is marketed under the brand name of *Lyrica* by Pfizer, is an important chiral drug in the treatment of epilepsy and neuropathic pain. Since only *S*-Pregabalin is active for the treatment, asymmetric synthesis was accomplished in 6 steps and the chiral induction was done by transition metal catalysis in industrial production. In this thesis, we applied an alternative synthetic route taken place in 3 steps. The key step comprised the chiral induction done by organocatalysis and the formal asymmetric synthesis of Pregabalin has been performed by Michael type addition of diethyl malonate to *(E)*-4-Methyl-1-nitro-1-pentene in 81% ee. Parallel to this work, different Michael acceptors and donors were used to test our catalyts' activities.

Keywords: Pregabalin, formal asymmetric synthesis, organocatalysis, Michael addition, enantioselectivity

ÖZ

BİFONKSİYONEL ASIT/BAZ ORGANOKATALİZÖRLER
İLE
ENANTİYOSEÇİCİ
PREGABALİN SENTEZİ

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Aralık 2013, 78 sayfa

Pregabalin epilepsi ve nöropatik ağrı tedavisinde kullanılan önemli kiral bir ilaçtır ve Pfizer tarafından *Lyrica* adı altında satılmaktadır. Tedavi için, Pregabalin'in sadece *S*-enantiyomeri aktif olduğundan, asimetrik sentez hedeflenmiş ve endüstride geçiş metalleri kullanılarak 6 basamakta gerçekleştirilmiştir. Bu çalışmada ise, 3 basamakta tamamlanabilen alternatif bir sentez yolu uygulanmıştır. Pregabalin'in asimetrik formal sentezinde, organokatalizörlerin kullanıldığı, dietilmalonat'ın *(E)*-4-metil-1-nitro-penten'e Michael türü katılma reaksiyonu en önemli basamağı oluşturmaktadır ve bu katılma reaksiyonu %81 seçicilik ile gerçekleştirilmiştir. Bu çalışmaya ek olarak, farklı Michael alıcıları ve donörleri kullanılarak, organokatalizörlerimizin aktiviteleri test edilmiştir.

Anahtar kelimeler: Pregabalin, formal asimetrik sentez, organokatalizör, Michael katılma reaksiyonu, enantiyoseçicilik

To my dear family…

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

DMAP: 4-Dimethylaminopyridine

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

DMSO: Dimethyl sulfoxide

DABCO: 1,4-diazabicyclo[2.2.2]octane

THF: Tetrahydrofuran

DCM: Dichloromethane

GABA: Ɣ-Aminobutyric acid

ent: Enantiomerically enriched compound

CHAPTER 1

INTRODUCTION

1.1 Importance of Asymmetric Synthesis

Enantiomers have same physical properties except for their ability to rotate plane polarized light. However, their interactions within the living organisms show diastereomeric character which means that during the interaction with a human body, different effects of enantiomers such as different pharmacological properties or different smells, tastes have been examined. Because most biomolecules such as DNA, RNA, all the enzymes and receptors are chiral.[1] That is why; asymmetric synthesis plays an important role for scientists.

If we look at from pharmaceutical aspect, obtaining only one enantiomer is much more vital because, generally one enantiomer is more effective than the other one. In today's world, it is known that more than half of the drugs are chiral and their effectiveness in the living organisms is different.[2] For example, penicillamine is a chiral drug which is used to treat cystinuria and rheumatoid arthritis. But only *S* enantiomer shows desired pharmacological effect and the *R* one can cause optic atrophy.[3] Many of other examples can be given for chiral drugs such as Thalidomide, Timolol, and Carvedilol and their enantiomers also show different pharmacological effects (Figure 1).[4]
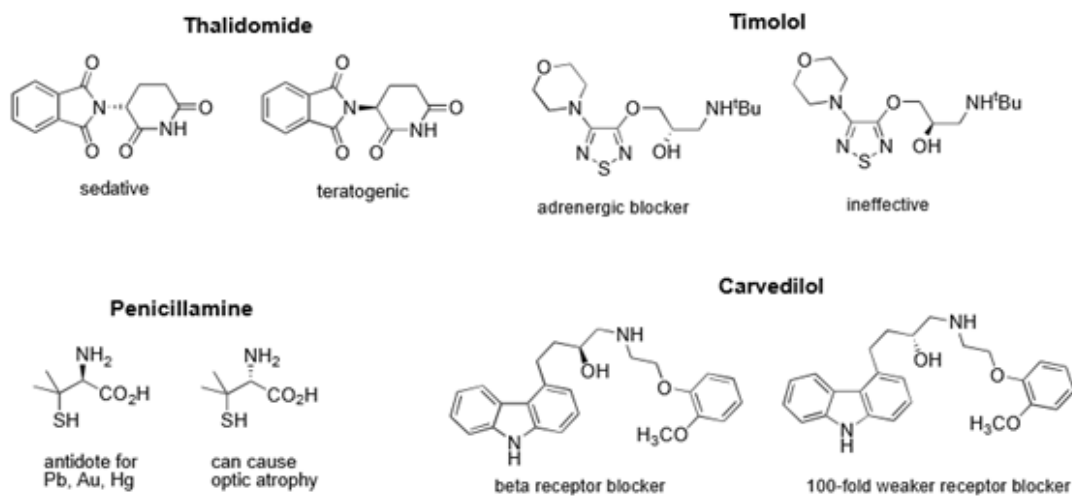
Figure 1. Examples for chiral drugs

1.2 Asymmetric Catalysis

Asymmetric catalysis can be defined as an integral part of asymmetric synthesis. The purpose in asymmetric catalysis is to convert racemic or prochiral substances into valuable enantioenriched compounds by using enantioenriched catalysts.[5]

The first asymmetric catalytic reaction was conducted in 1858 by Louis Pasteur. He utilized a microorganism which was named as *Penicilium Glauca* for the kinetic resolution reaction of racemic ammonium tartarate solution. At the end of the reaction, it was observed that this organism destroys the *d* enantiomer of the solution and only *l* enantiomer exists.[6] Therefore, it was determined that the first catalyst for the acceleration of chemical reactions is enzymes.[7]

In addition to enzymes, transition metal based complexes have been widely used for the synthesis of enantioselective compounds. Moreover, in recent years, small organic molecules named as organocatalysts that do not contain any transition metal have been used for the asymmetric catalysis reactions.

1.3 Organocatalysis

In 2000, MacMillan defined *"organocatalysis"* as the acceleration of chemical reactions with the usage of substoichiometric amount of an organic compound. The important property of organocatalysts is that they do not contain any transition metal and basically they are composed of carbon, hydrogen, nitrogen, oxygen and phosphorous atoms.[8] Some examples for common organocatalysts are shown in Figure 2.
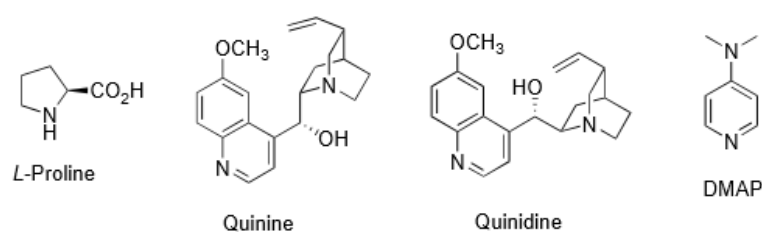
Figure 2. Examples for organocatalysts

Organocatalysts offer a number of advantages. They have the properties of non-toxicity, and wide range of applications. They have also easy purification techniques. Moreover, organocatalysts are inert toward moisture and oxygen; therefore, demanding reaction conditions are not necessary. Absence of transition metal is an attractive property to avoid metal contamination especially for the pharmaceutical industry.[8] All of these advantages are taken into consideration, after the organocatalysis field had been discovered, the interest has increased rapidly. It can be seen from the number of publications of organocatalysis per year in Figure 3.[9]
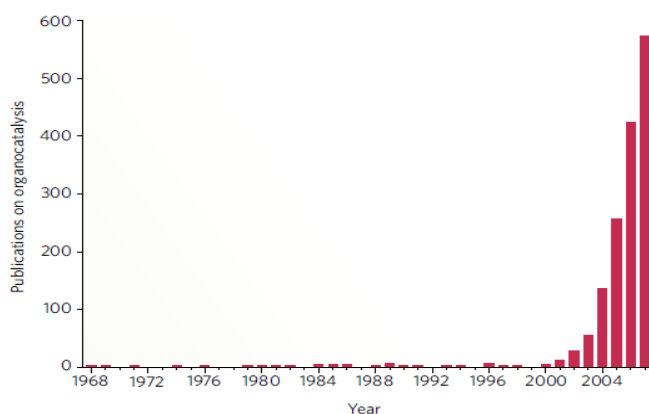
Figure 3. An increase of interest in organocatalysis field

1.3.1 Asymmetric Organocatalysis

Since 2000, a new area which is named as organocatalysis has begun to evolve for the asymmetric catalysis reactions. The usage of these pure small organic molecules in the field of asymmetric synthesis overlaps with the "Green Chemistry" approach that targets environmentally friendly chemical applications both in industry and academic world. Because this type of catalysis is performed under metal-free conditions, especially in pharmaceutical field, the usage of organocatalysis is in demand to prevent metal contamination and possible toxicity.

1.3.2 Historical Background

The first organocatalytic asymmetric reaction was performed by Bredig and Fiske in 1912. They carried out a C-C bond forming reaction and by the addition of HCN to benzaldehyde (**1**), they synthesized mandelonitrile (**2**) enantioselectively in the presence of quinine and quinidine alkoloids. However, at the end of the reaction, less than 10 percent selectivity was obtained (Scheme 1).[10]

4
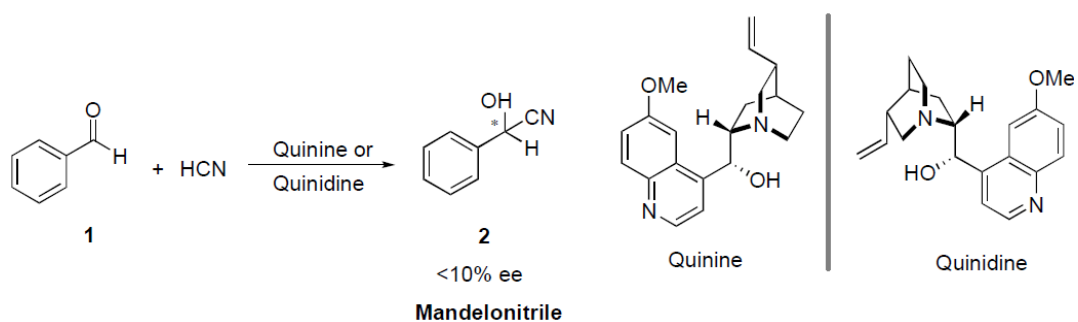
Scheme 1. The first organocatalytic asymmetric reaction

Then in 1960, Pracejus and his co-workers performed a methanolysis reaction of pheny(methyl)ketene (**3**) in the presence of *O*-acetyl-quinine as organocatalyst. Only with 1 mol% catalyst loading, quite good ee value which is 74% was obtained at -111°C (Scheme 2).[11]
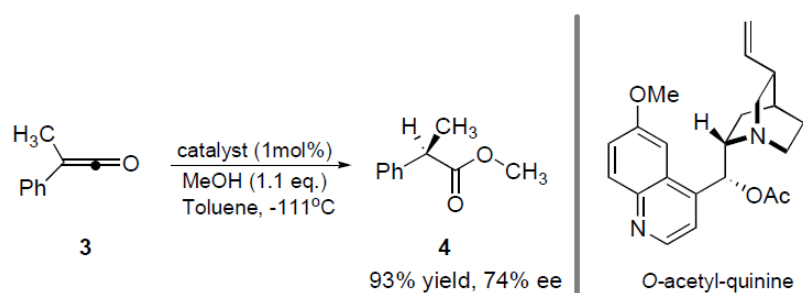
Scheme 2. Pracejus' work

A breakthrough came in 1971 with an asymmetric organocatalytic intramolecular aldol reaction. Hajos, Parrish, Eder, Sauer and Wiechert worked together and by using proline as a catalyst, starting from achiral trione **5**, they obtained Wieland-Miescher enone **6** enantioselectively. This ketone is an important compound because it can be used as a precursor in the synthesis of steroids. Then this intramolecular aldol reaction is named as Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 3).[12]
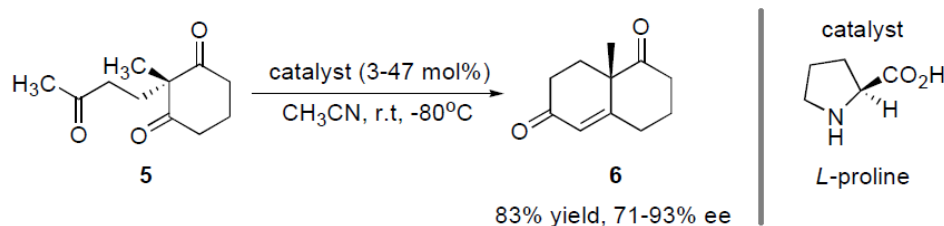
Scheme 3. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

In the early 1980s, an important discovery was made by Juliá and Colonna *et al.* in the field of epoxidation of chalcones. Alanine derived poly-amino acid was used as an organocatalyst and epoxidation of given chalcone **(7)** was accomplished with high enantioselectivities of the product **8** up to 93% (Scheme 4).[13]
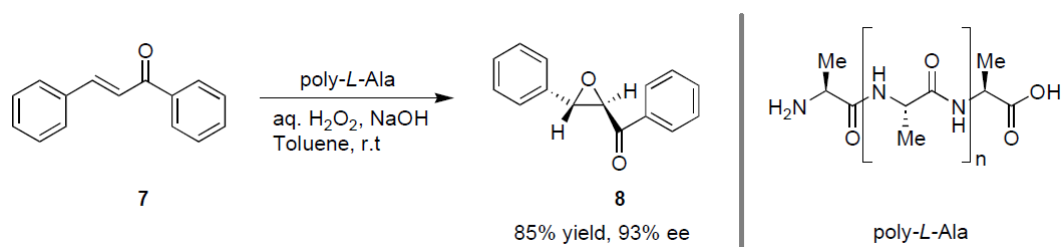
Scheme 4. Juliá-Colonna epoxidation

Again in 1980, for the investigation of the mechanism of asymmetric Michael addition reaction, Wynberg and his co-workers tried conjugate addition of thiophenol **9** to cyclohexenone **10** in the presence of cinchona alkaloids. The best enantioselectivity (75% ee) for the Michael addition product **11** was obtained with quinine organocatalyst. This reaction is important because Wynberg proposed that quinine shows bifunctional activation with both nucleophile and electrophile during the reaction (Scheme 5).[14]
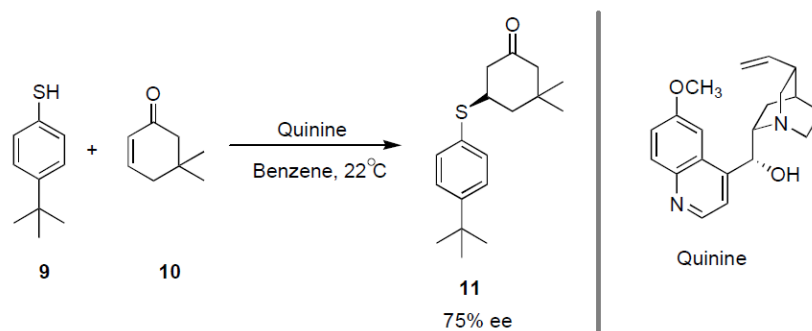
Scheme 5. Enantioselective Michael addition reaction

In 1981, parallel to Bredig's work, Inoue and his co-workers used cyclic dipeptide **12** to catalyze the cyanohydrine formation reaction. This cyclic peptide could be obtained directly from *L*-histidine and *L*-phenylalanine. When it is compared with Bredig's work, it showed quite high enantioselectivity (97%) for the synthesis of mandelonitrile **(2)** (Scheme 6).[15]
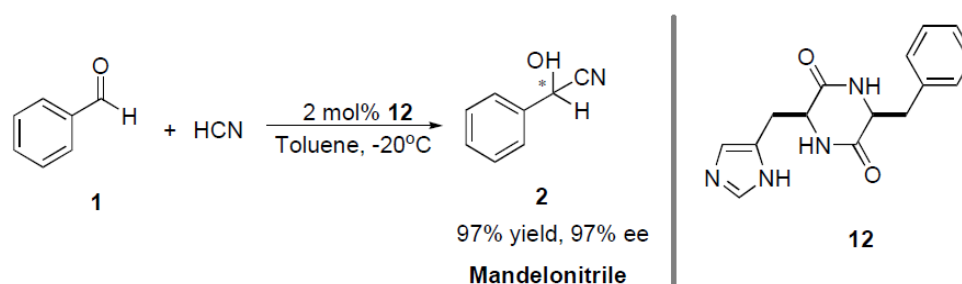
Scheme 6. Synthesis of Mandelonitrile with cyclic peptide

In 1984, researchers at Merck brought out phase transfer catalysis term in the literature. Using a quaternary ammonium salt of cinchonidine **15**, they succeed α-alkylation of an achiral ketone **13** with quite good enantioselectivity of the product **14** (Scheme 7).[16]
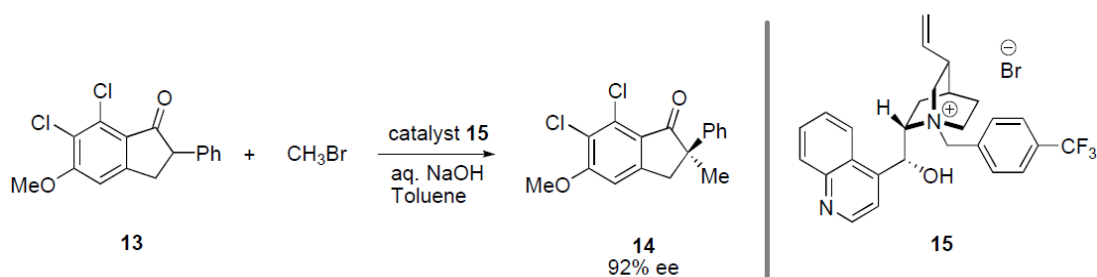
Scheme 7. Phase transfer catalysis reaction by Merck researchers

In 1996, Yang and Shi achieved catalytic epoxidation reaction by using chiral ketones **16** and **17** respectively. Moreover after one year same asymmetric epoxidation reaction was done by Denmark with another chiral ketone **18** (Scheme 8).[17]
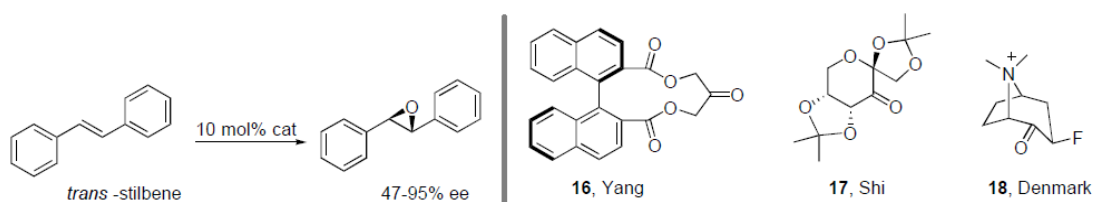
Scheme 8. Chiral ketones as organocatalysts in epoxidation reaction

In 1997, Jacobsen used thiourea based chiral Schiff base as organocatalyst **21** and in the following year, Corey presented bicyclic quanidine **22** in the asymmetric Strecker reaction (Scheme 9).[18] Starting from corresponding imine **19**, the cyanation product **20** was obtained selectively.
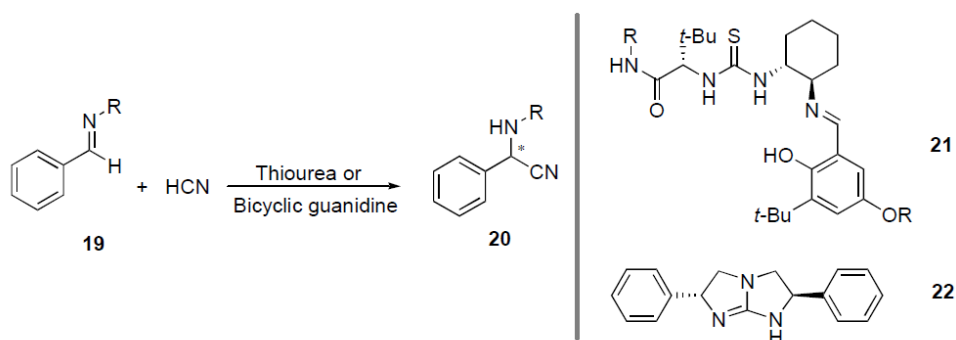
Scheme 9. Jacobsen's and Corey's organocatalysts

After 2000, organocatalysis field has drawn much more attention because for the first time MacMillan defined 'organocatalyst' and 'organocatalysis' terms together with his work in 2000. MacMillan succeed asymmetric Diels-Alder reaction starting from cyclohexa-1,3-diene **(23)** and acrolein **(24)**. At the end of the reaction, bicyclic adduct **25** was obtained with quite 94% *ee* and also 14 to 1 endo/exo isomeric ratio by using imidazolidone **26** as organocatalyst (Scheme 10).[19]
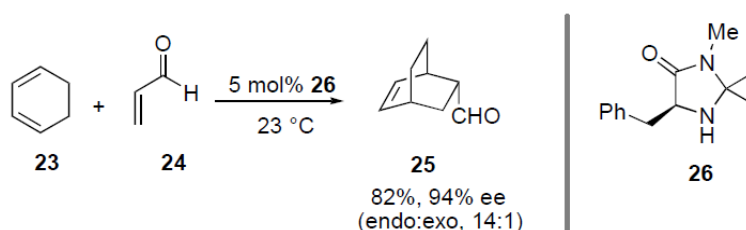
Scheme 10. Organocatalyzed Diels-Alder reaction by MacMillan

Another striking work in the literature for the asymmetric organocatalysis area was presented by List and Barbas. They succeed asymmetric intermolecular aldol reaction of acetone **(27)** with *iso*-butyraldehyde **(28)** which was catalyzed by *L*-proline with quite good yield and enantioselectivity shown in Scheme 11.[20]

9
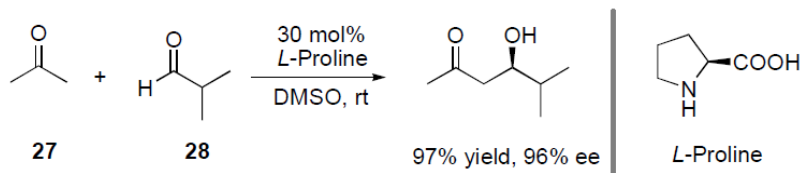
Scheme 11. L-proline catalyzed intermolecular aldol reaction

1.3.3 Classification of Asymmetric Organocatalysis

After the emergence of organocatalysis term in the asymmetric catalysis area, some classifications have been made to get better understanding about how they work. The most common classification has been presented by Berkessel and Gröger according to their interaction with the substrate. They can be divided into two groups which are covalent and non-covalent catalysis.[8]

In covalent catalysis, covalent bond formation occurs between catalyst and substrate. In that type, generally high catalyst loading is performed and amine based reactions can be given as major examples. Therefore, enamine and iminium ion intermediates are formed during the reaction. In non-covalent type, generally, low catalyst loading is performed and non-covalent interactions are formed such as hydrogen bonding or ion pairs between catalyst and substrate. Phase transfer catalysts and hydrogen bonded adducts involves in the non-covalent catalysis mechanism.[8]

Another classification has been made by List with respect to acidic or basic type of the catalytic cycle. According to this type of classification, organocatalysis fall into four major classes which are Lewis acid, Lewis base, Brønsted acid and Brønsted base (Figure 4).[21]
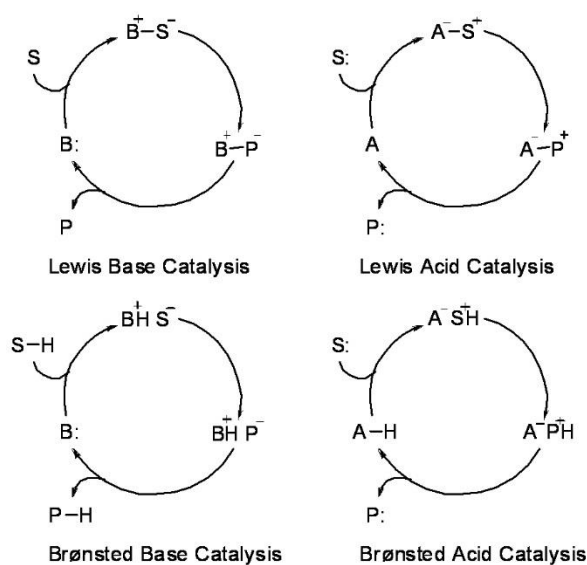
Figure 4. Classification of organocatalysis with respect to List

Another classification which is based on the generic activation mode of organocatalysts has been reported by MacMillan in 2008. According to him, organocatalysis can be divided into five groups which are enamine catalysis, iminum catalysis, SOMO catalysis, counterion catalysis and hydrogen-bonding catalysis.[9]

1.3.4 Bifunctional Organocatalysis

Hydrogen bonding catalysis has an increasing importance day by day because it can be considered as a powerful strategy for the enantioselective synthesis.[22] With the growing importance, it brought out a new name which is called as "bifunctional organocatalysis" or "multifunctional organocatalysis".[9, 23]

Bifuntional organocatalysts involves a basic unit for the highest-occupied molecular orbital (HOMO) increase of nucleophiles and an acidic moiety for the lowest-unoccupied molecular orbital (LUMO) decrease of electrophiles. Therefore, a decrease in activation energy together with HOMO and LUMO activation renders

reactions possible. In other words, bifunctionality can be described as the dual activation of both electrophile and nucleophile with the combination of an acid/base catalyst in enantioselective reactions (Figure 5).[24]
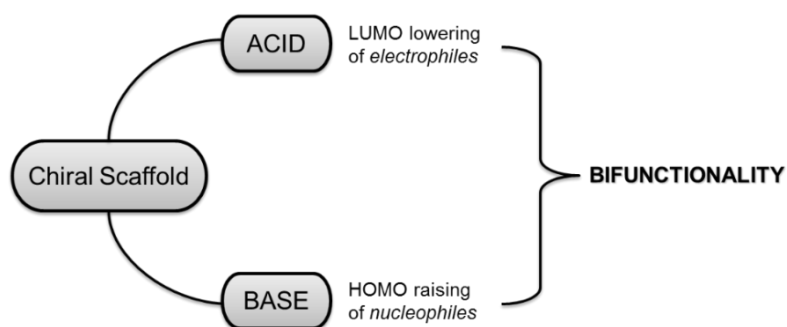
Figure 5. Bifunctionality of an organocatalyst

In this field, a breakthrough came in 2003 by Takemoto and co-workers. They performed conjugate addition reaction of malonates to nitroolefins in the presence of tertiary amine/thiourea catalyst **29**. With this designed organocatalyst, this work has been accepted as the first truly stereoselective acid/base bifunctional organocatalysis reaction (Scheme 12).[23]
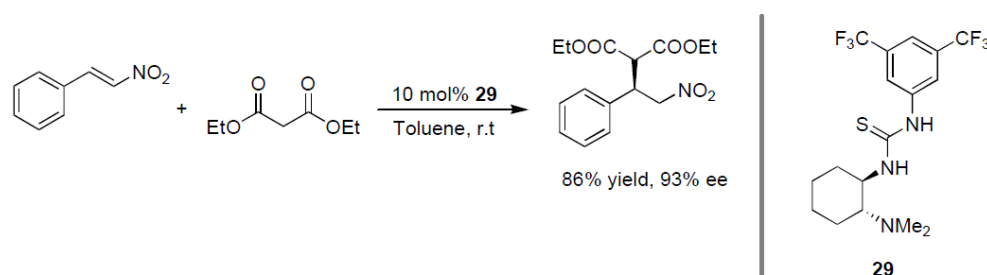
Scheme 12. Takemoto, 2003

In 2005, to extend this work, Takemoto and co-workers published another paper and in this work they have tested different Michael acceptors and donors in the presence

of different thiourea based organocatalysts. They proposed a transition state which shows the bifunctionality of the thiourea based organocatalyst (Figure 6).[25] According to proposed transition state, thiourea moiety makes double hydrogen bonding with the electrophile which decreases LUMO level; on the other hand, deprotonation of nucleophile with the basic dimethyl amino group of the catalyst results in the increasing HOMO level. As a result of this activation, the reaction rate and the enantioselectivity enhanced in the presence of bifunctional thiourea based organocatalyst.
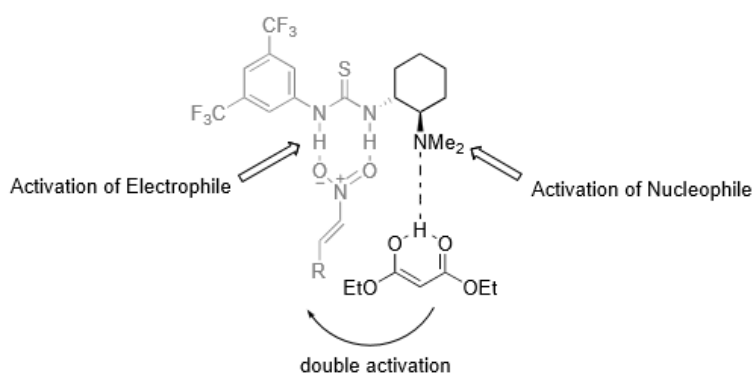
Figure 6. Possible transition state for Takemoto's thiourea based organocatalyst

There are many other bifunctional organocatalysts which are used in the important chemical reactions such as Morita-Baylis Hillman, Michael addition and Strecker reactions. Some known examples for bifunctional organocatalysts are shown in Figure 7.[26,27,28,29,30]
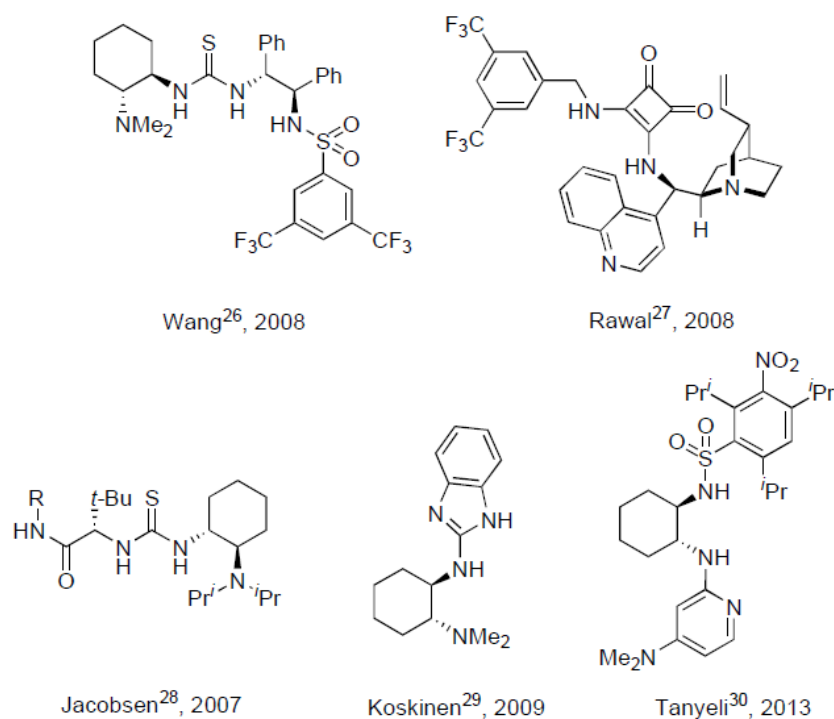
Figure 7. Some examples to bifunctional organocatalysts

1.3.4.1 Conjugate Addition of 1,3-Dicarbonyls to *trans-(β)*-nitroolefins

After Takemoto's work with bifunctional organocatalysts, the demand and application of them has increased significantly. Many of new bifunctional organocatalysts has been designed and also most of the known ones have been tested in different reaction types.

In 2005, by using Takemoto's catalyst **29**, Chen and co-workers tested conjugate addition reactions of aryl thiols **31** to cyclic enones **30** to get high enantioselectivity and yield of the product (Scheme 13).[31]
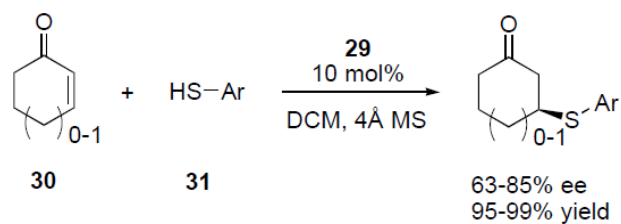
Scheme 13. Michael addition reaction of thiols by Chen

In the same year, again with the use of Takemoto's catalyst **29**, Berkessel and his co-workers performed a dynamic kinetic resolution reaction to synthesize α-aminoacid derivatives **33** starting from azalactone **32** (Scheme 14).[32]
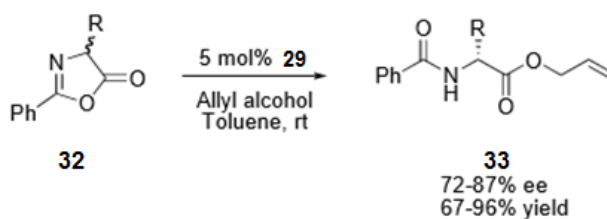
Scheme 14. Berkessel's work with the Takemoto's catalyst **29**

After one year, Deng and his co-workers designed a bifunctional organocatalyst **37** which was derived from chincona alkaloids family to test the Michael addition reactions of dimethyl malonate (**35**) and ethyl acetoacetate (**36**) to different nitroolefins **34**. At the end of the reaction they obtained quite good yields and enantioselectivities (Scheme 15).[33]
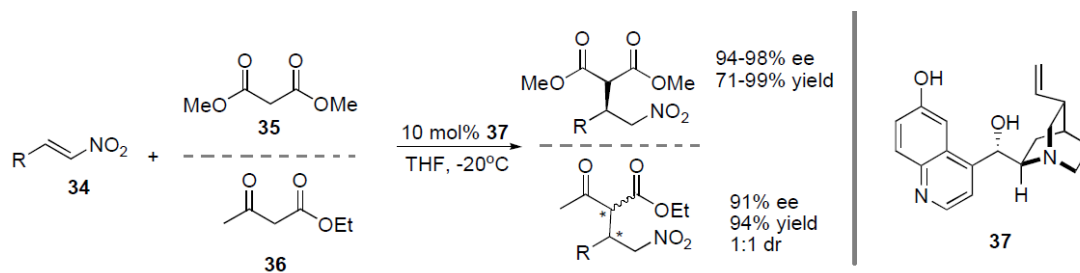
Scheme 15. Michael addition reaction by Deng and his co-workers

Soós and his co-workers performed conjugate addition of nitromethane to chalcones **38** to produce γ-nitro ketones **39** with good enantioselectivity in the presence of bifunctional thiourea based organocatalyst **40** which was derived from chincona alkaloids (Scheme 16).[34]
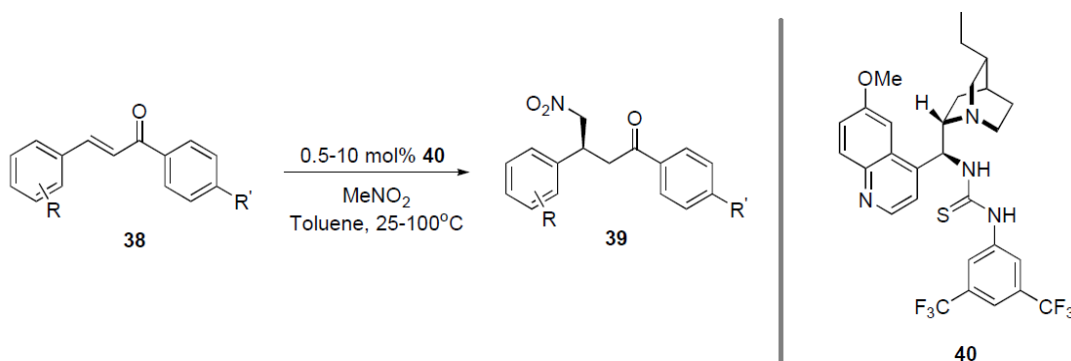
Scheme 16. Conjugate addition of nitromethane to chalcones

In the same year, Connon and his co-workers tested same catalyst in the conjugate addition reaction of dimethylmalonate (**35**) to various nitroolefins **34**.[35] Moreover, same reaction was performed by Dixon and co-workers with another thiourea based organocatalyst **41** (Scheme 17).[36]
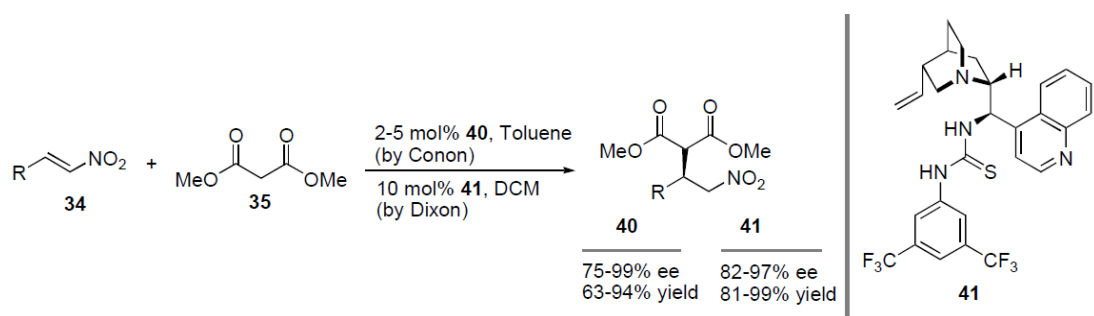
Scheme 17. Michael addition reaction with Connon's and Dixon's catalysts

1.3.4.2 Chiral 2-AminoDMAP Analogues as Bifunctional Organocatalysts

4-(*N,N*-dimethylamino)pyridine (DMAP) analogues can be given as known examples for Lewis base catalysts with good reactivity and also high versatility. However, multistep procedures for introducing chirality to DMAP unit could be compulsive most of the time.[30] Therefore, more practical procedures are required. Chiral 2-aminoDMAP **44** which is derived from halo-DMAP **42** and (*1R,2R*)-1,2-diaminocyclohexane (**43**) could be given as a good example for Lewis basic catalaphore and it plays an important role for the synthesis of different bifunctional acid/base organocatalysts.[19]

In the last three years, Tanyeli and his co-workers have designed various bifunctional organocatalysts which are derived from chiral 2-aminoDMAP **44** and only by changing acidic moiety, nearly twenty different organocatalysts have been obtained.[19,30] They belongs to the mainly three separate groups which are sulfonamides, squaramides and urea/thiourea as depicted in Scheme 18. The first one **45** is an example for 2-aminoDMAP/Sulfonamide group[30], the second one **46** is for the 2-aminoDMAP/squaramide group and the last one **47** is 2-aminoDMAP/urea.[19]
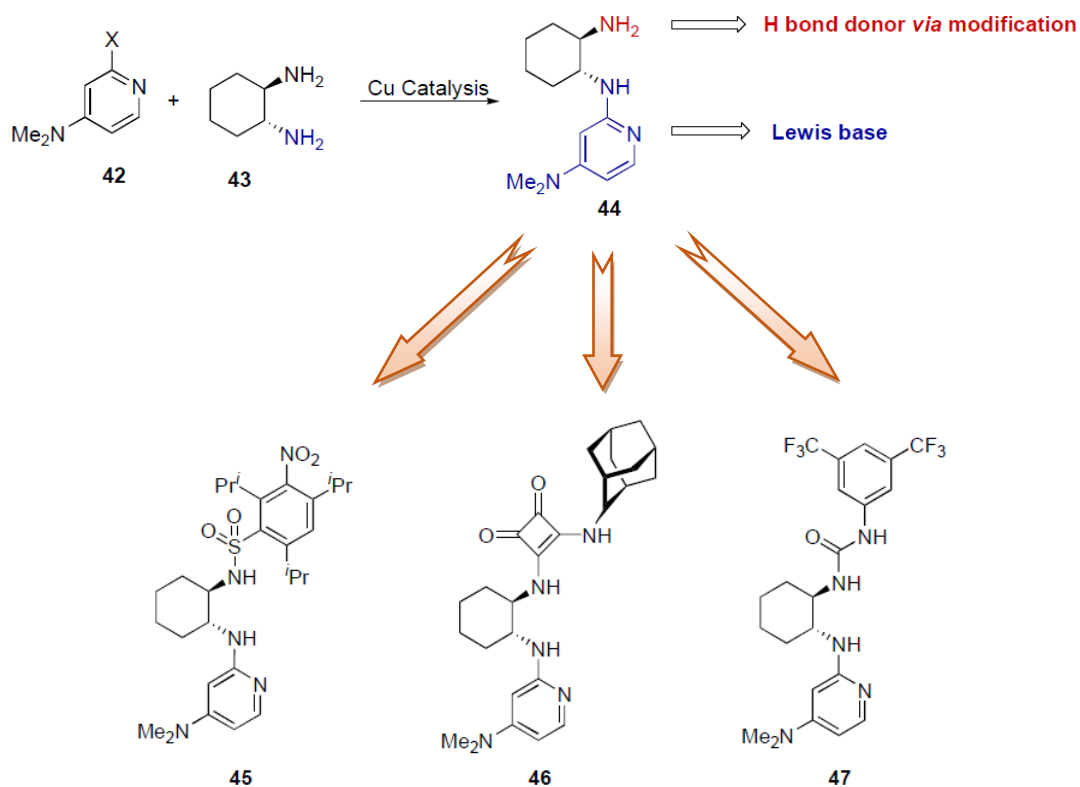
Scheme 18. Organocatalyst design strategy

Developed bifunctional organocatalsyts have been tested for a lot of different type of reactions and most of the time, high enantioselectivities and also good yields have been obtained. For example, in 2003, in the Michael addition reaction of acetylacetone (**49**) (Michael donor) to various nitrostyrenes **48a-h** (Michael acceptors)**,** Tanyeli and Işık obtained high yields (87−93%) and excellent selectivities (up to 99%) by using 2-aminoDMAP/sulfonamide catalyst **45** (Scheme 19).[30]
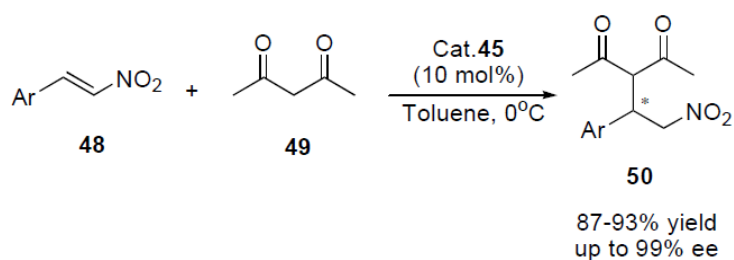
Scheme 19. Michael addition reaction with 2-aminoDMAP organocatalyst **45**

1.4 Pregabalin

Pregabalin is one of the most important chiral drugs because of its high therapeutic activity and blockbuster status. Pfizer markets Pregabalin with the brand name of Lyrica®. It belongs to the group of 3-substituted analogues of ɣ-aminobutyric acid (GABA) and also Baclofen, Gabapentin can be given as other known examples for this group (Figure 8).[37]
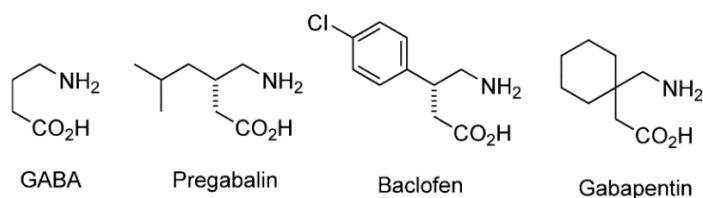
Figure 8. GABA Analogues

Pregabalin which is also known as (3*S*)-3-(aminomethyl)-5-methylhexanoic acid is an anticonvulsant drug and it is used for the treatment of epilepsy and also neuropathic pain. However for the treatment, only *S* enantiomer shows desired effect so asymmetric synthesis is important.

First of all, racemic synthesis was performed and then with kinetic resolution reaction, enantioselectivity was obtained. However, because of low yields and poor

selectivities, much more practical and simple procedures for the construction of chiral center of Pregabalin have been researched. Then, in most cases transition metal based catalysts were used and excellent enantioselectivities and yield were obtained.[29]

If we examine *Pfizer*'s manufacturing process for the enantioselective synthesis of Pregabalin (Scheme 20), the key step is the asymmetric hydrogenation of tert-butylammonium salt with rhodium based transition metal catalyst *(R,R)*-(Me DuPHOS)Rh(COD)]-BF$_4$. After the reduction of the nitrile group, the desired product is obtained with excellent enantioselectivitiy.[37]
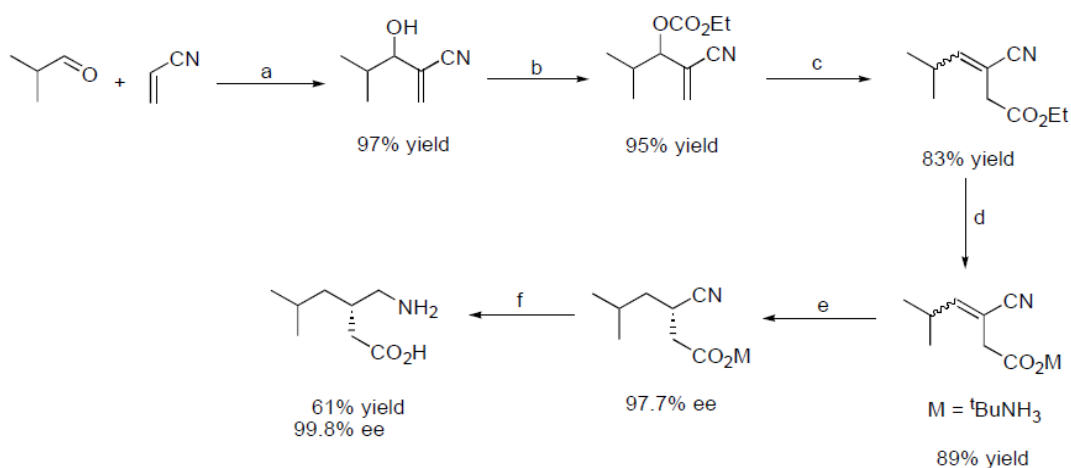
*Reagents and conditions: (a) DABCO, H$_2$O, 2,6-di-tert-butyl-4-methylphenol, 50 °C, 97%; (b) ClCO$_2$Et, pyridine, CH$_2$Cl$_2$,rt, 95%; (c) Pd(OAc)$_2$, PPh$_3$, EtOH, CO (300 psi), 50 °C, 83%; (d) (i) LiOH, H$_2$O, THF, rt; (ii) HCl; (iii) tert-BuNH$_2$, EtOAc, 89% (e) [(R,R)-(Me DuPHOS)Rh(COD)]-BF$_4$, H$_2$ (45 psi), MeOH, 55 °C, 100% conversion (f) (i) Sponge Ni, KOH, H$_2$ (50 psi), H$_2$, EtOH; (ii) AcOH, 61%.

Scheme 20. Synthetic pathway of *Pfizer*

After the creation of organocatalysis term, organocatalysts have been actively used for the construction of chiral center of Pregabalin. In the literature, there are many examples for the enantioselective synthesis of Pregabalin.

20

The first attractive example was conducted by Bassas and his co-workers in 2009.[29] In that work, a synthetic procedure which was based on a Michael addition reaction of Meldrum's acid **52** to nitroalkene **51** was performed in the presence of a variety of novel catalysts bearing different groups at the thiourea moiety. The best result is taken with a quinidine derived thiourea organocatalyst **54** for the synthesis of the key intermediate **53** (Scheme 21).[37]
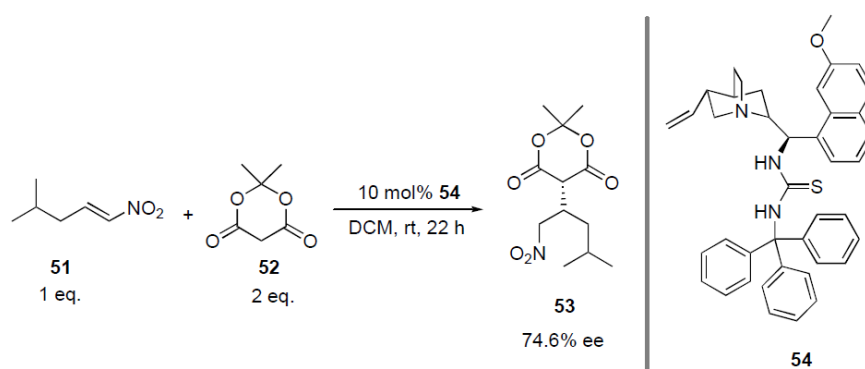
Scheme 21. Michael addition reaction by Bassas *et al.*

In 2011, asymmetric Michael addition reaction of diethyl malonate **(55)** to nitroalkene **51** was performed by using thiourea derived organocatalyst **57** as a second important example in the literature.[38] With 20 moles percent catalyst loading, the precursor **56** for the construction of chiral center of Pregabalin was obtained with 89% ee (Scheme 22).[39]
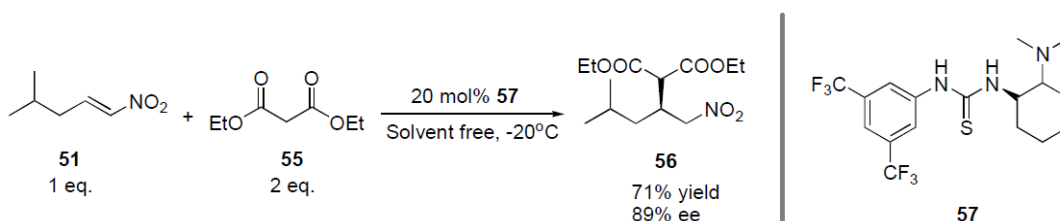
Scheme 22. Michael addition reaction of diethyl malonate by Liu et al.

For these reactions, the most important step is to obtain the key intermediates which are Michael addition products. Because they are important precursors for the enantioselective synthesis of Pregabalin and after some additional steps such as hydrogenation and decarboxylation, it is performed with good selectivities.

1.5 Aim of Work

Bifunctional organocatalysis has an increasing demand for asymmetric synthesis reactions. A lot of different types of chemical reactions have been performed in the presence of bifunctional acid/base organocatalysts. Because high yields and excellent enantioselectivities have been obtained in most cases, various organocatalysts have been designed and tested up to date.

In our group, nearly twenty different bifunctional organocatalysts have been designed and tested in various experiments and based on the experimental results, it is expected that high enantioselectivities could have been obtained to construct the chiral precursor of Pregabalin.

In this context, by performing Michael addition reaction in the presence of developed bifunctional organocatalysts, high enantioselectivities and yields were aimed for the formal synthesis of Pregabalin. For this purpose, firstly, we aimed to find best functioning catalyst and to screen reaction conditions i.e catalyst loading, temperature, concentration and then, solvent.

Our synthetic strategy for the construction of chiral Pregabalin precursor is being shown in Scheme 23. Starting from isovaleraldehyde **(58)** and nitromethane, nitroolefin **51** as Michael acceptor is going to be synthesized. Subsequently, the key Michael adduct **56** will be synthesized with various organocatalysts developed in our research group.
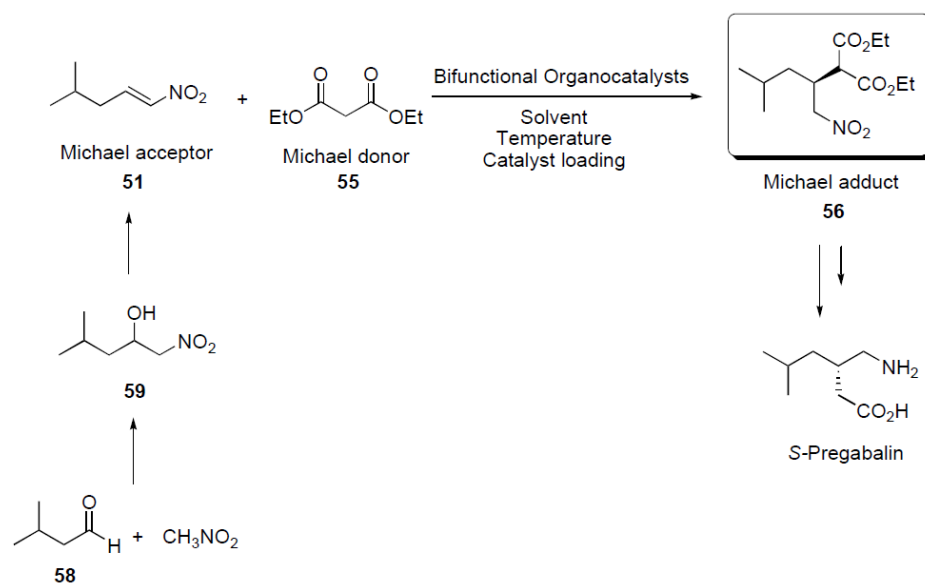
Scheme 23. Synthetic pathway for the formal synthesis of Pregabalin

Parallel to this work, formal synthesis of another GABA analogue known as Baclofen is going to be performed by using the proper β-nitroalkene (*trans*-4-chloro-β-nitrostyrene) in the presence of our organocatalyst.
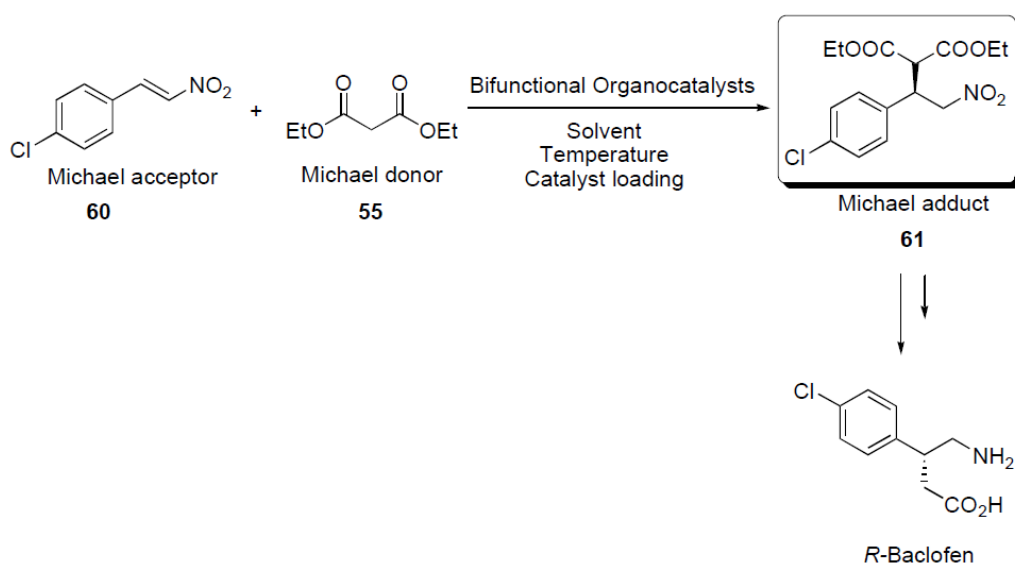
Scheme 24. Synthetic pathway for the formal synthesis of Baclofen

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 2-aminoDMAP as Basic Counterpart for Bifunctional Organocatalysts

In this work, 3 different bifunctional organocatalysts were chosen from Tanyeli's research group catalyst library. Synthesis of these organocatalysts is mainly accomplished by 2 steps. Firstly, 2-aminoDMAP **44** was synthesized according to literature procedure.[30] Starting from (*1R,2R*)-1,2-diaminocyclohexane (**43**) and 2-bromoDMAP (**62**), C-N coupling reaction was performed in the presence of potassium phosphate as a base and copper (I) bromide as a catalyst (Scheme 25).
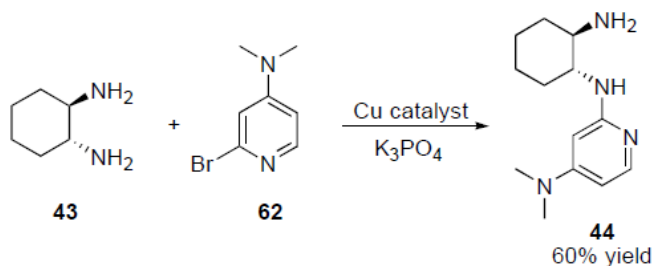
Scheme 25. General pathway for the synthesis of 2-aminoDMAP

2.2 Synthesis of Bifunctional Acid/Base Organocatalysts

After the successful synthesis of 2-aminoDMAP unit, the second stage is to anchore the acidic catalaphores to the skeletons of bifunctional organocatalysts.

2-AminoDMAP/sulfonamide organocatalyst **45** was chosen firstly because sulfonamides offers some advantages such as ready availability and giving good results when we compared with thioureas. Organocatalyst **45** was chosen as the most effective among 10 different sulfonamide organocatalysts depending upon the results done already in our group.[30] The synthesis of organocatalyst was started with nitration of commercially available 2,4,6-triisopropylbenzene sulfonylchloride **(63)**. After stirring for 5 h in a water bath at 40 °C, 2,4,6-triisopropyl-3-nitrobenzene-1-sulfonyl chloride **(64)** was easily obtained. The second step was to mixing basic catalophore **44** and sulfonylchloride group **64** in dichloromethane only in 1 hour, with quite good yield which is 95% (Scheme 26).[30]

Scheme 26. Synthetic pathway of organocatalyst **45**

In terms of squaramide type acidic catalophoric unit, almost 10 different bifunctional organocatalysts have been synthesized in Tanyeli's research group. According to experimental results which have been taken by our group members, catalyst **46** was chosen and since it has bulky adamantly group, it could be helpful for increasing enantioselectivity of Michael addition reactions. Moreover, it has two acidic hydrogens on squaramide moiety as an acidic counterpart for the bifunctional organocatalyst.

For the synthesis of target organocatalyst **46**, the route is shown in Scheme 27. After reflux for 3 hours, diethylsquarate **(66)** was easily synthesized from squaric acid **(65)**. The next step was the reaction of 2-adamantyl amine with diethylsquarate **(66)**

to obtain monosquaramide **67**. Finally, at the end of the reaction of 2-aminoDMAP with monosquaramide, organocatalyst **46** was synthesized with good yield (68%) despite multistep reactions.
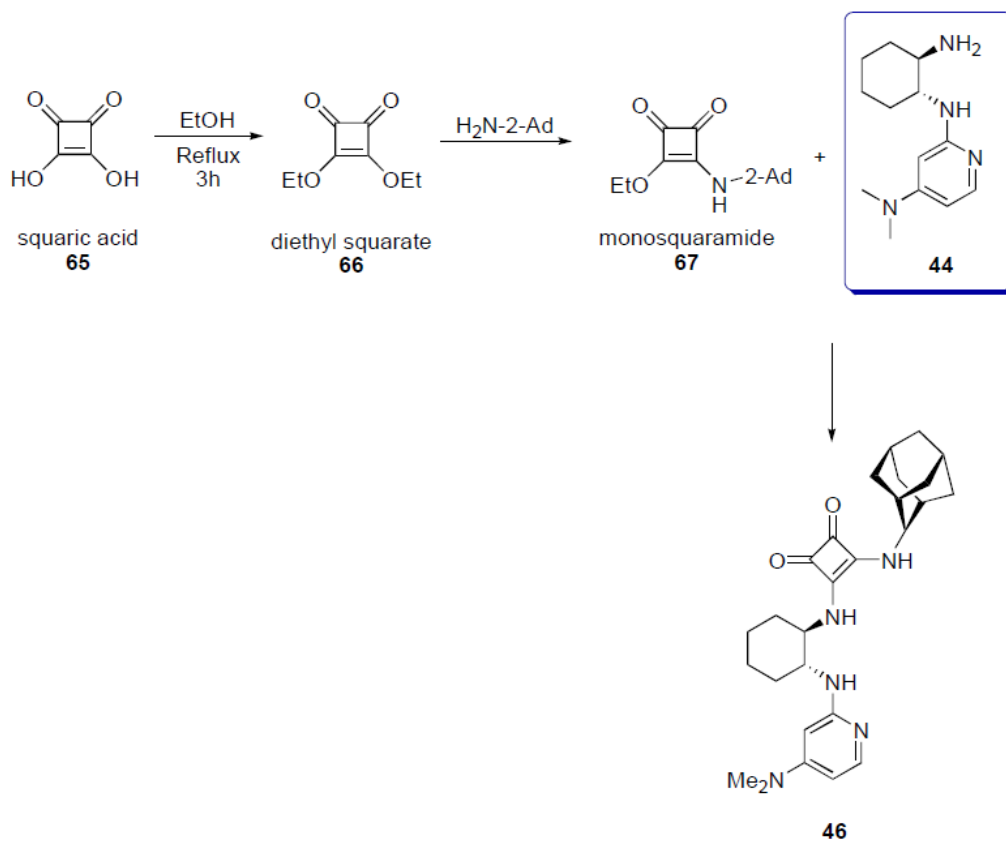
Scheme 27. Synthetic pathway for the synthesis of catalyst **46**

For the third group, 2-aminoDMAP/urea was chosen. As a result of mixing of commercially available 3,5-bis(trifluoromethyl)phenyl isocyanate **(68)** with our basic catalophore **44** in one to one ratio, target bifunctional organocatalyst **47** was synthesized with quite good yield (Scheme 28).

Scheme 28. Synthetic pathway for the synthesis of catalyst **47**

2.3 Synthesis of the 4-Methyl-1-nitro-1-pentene (51) as a Starting Material

In this work, parallel to formal synthesis of Pregabalin, we used different Michael acceptors and donors to test our organocatalyst systems. Most of them were supplied commercially; however, nitroolefin **51** was synthesized according to literature procedure.[38]

In the first part, by using Henry reaction, isovaleraldehyde (**58**) and nitromethane were mixed in ethanol overnight. As a result of C-C bond formation, the product **59** was formed in 85% yield (Scheme 29). Subsequent elimination reaction was performed with methanesulfonyl chloride in THF in 1 h resulted in Michael acceptor **51** in 82% yield. Characterizations of both nitroalcohol and nitroolefin were done with ^{1}H NMR and ^{13}C NMR spectroscopy.

Scheme 29. Synthesis of desired nitroolefin **51**

2.4 Evaluation of Bifunctional Organocatalysts in Asymmetric Michael Additions

2.4.1 Optimization Studies for the Formal Synthesis of Pregabalin

In the formal synthesis of Pregabalin, 4-methyl-1-nitro-1-pentene (**51**) and diethyl malonate (**55**) were chosen as Michael acceptor and Michael donor, respectively. Generally malonates have lower reactivity and higher pKa value by comparing with much more used Michael donors such as acetylacetone and meldrum's acid. With such informations in mind, three different bifunctional organocatalysts were screened in Michael addition reaction (Scheme 30).
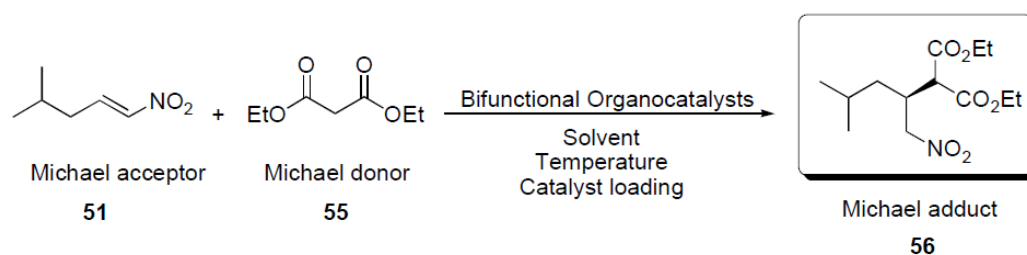
Scheme 30. Control reaction for the formal synthesis of Pregabalin

To begin with, we chose toluene as solvent and all experiments to determine the most effective organocatalyst were conducted at room temperature with 10 mol% catalyst loading. Preliminary results indicated that organocatalysts **45** and **46** have very long duration, seven and six days, respectively (Table 1). Since none of the stains which was used to monitor the reaction on TLC did not work due to saturated and non-conjugated structure, conversions were determined according to the consumption of nitroolefin and in some situations, it was needed to wait for a long time during the reaction. However, in the presence 2-aminoDMAP/sulfonamide organocatalyst **45**, no conversion was observed at the end of the seven days. Because, normally it would give better results where isopropyl unit is replaced with the aromatic system and the some π-π stacking effect may occur between the substrate and the organocatalyst
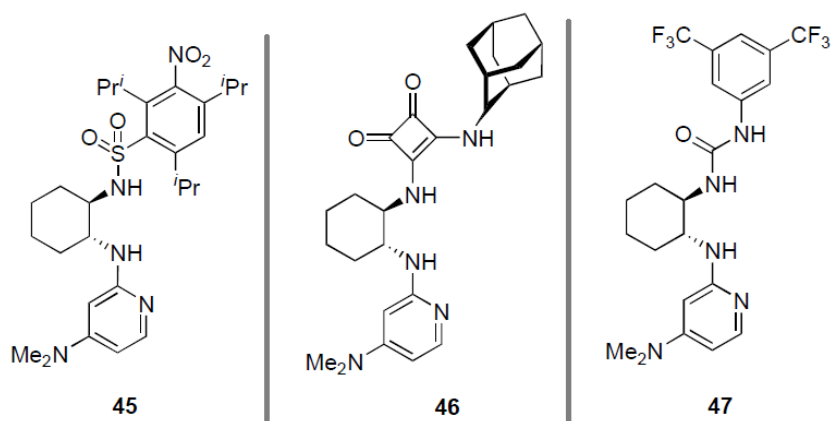
system for phase selectivity. However, in our structure, fully saturated isopropyl moiety cannot give that kind of interaction.

**Table 1.** Catalyst screening results for the synthesis of **56**
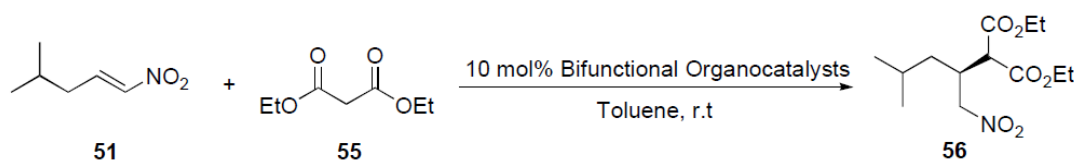
entry	cat.	cat. loading (mol %)	solvent	temp.	time	yield %^{a}	ee %
1	45	10	toluene	rt	7 days	-	-
2	46	10	toluene	rt	6 days	75	50
3	**47**	**10**	**toluene**	**rt**	**3 days**	**90**	**73**

^{a} Isolated yields

2-AminoDMAP/squaramide organocatalyst **46** afforded Michael adduct in 75% yield and 50% ee at the end of the 6 days with 10% mol catalyst loading. Considering the fact that catalyst aggregation, we tried to decrease the catalyst amount and also neat conditions were examined (Table 2). With decreasing catalyst loading, selectivity increased as expected, but also reaction time extended. In solvent free media, reaction time shortened; however, a decrease in selectivities was observed.

30

Table 2. Catalyst loading results for 2-aminoDMAP/squaramide **46**

46
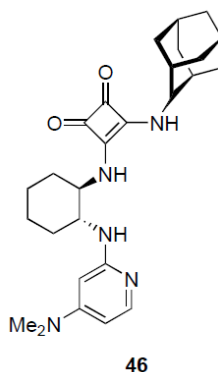
entry	cat. loading (mol %)	solvent	temp.	time	yield (%)^a	ee (%)
1	**5**	**toluene**	**rt**	**8 days**	**70**	**60**
2	10	toluene	rt	6 days	75	50
3	5	neat	rt	2 days	76	43
4	10	neat	rt	1 day	75	44

^{a} Isolated yields

Since we could not obtain acceptable good results for the first two organocatalysts, we changed our organocatalyst system to 2-aminoDMAP/urea **47**. As the first parameter, the effect of catalyst loading was checked in toluene. Concentrations were fixed at 0.4 M and the reactions were conducted at room temperature (Table 3). The best catalyst loading for the reaction was found as 5 mol%.

Table 3. Catalyst loading results for 2-aminoDMAP/urea **47**

47
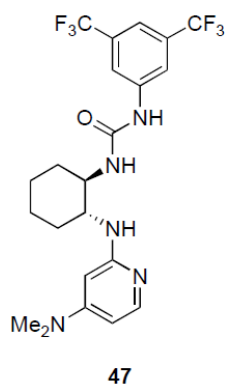
entry	cat. loading (mol %)	solvent	temp.	time (h)	yield (%)^a	ee (%)
1	10	toluene	rt	72	90	73
2	**5**	**toluene**	**rt**	**72**	**86**	**81**
3	2	toluene	rt	72	50	53
4	1	toluene	rt	72	35	54

^{a} Isolated yields

The next optimization parameters were the temperature and molarity. It could be concluded that when the temperature decreases, slight decrease was observed in terms of selectivity and chemical yield (Table 4, entries 1, 2 and 3). Therefore, the best reaction temperature was chosen as room temperature. Subsequently, three different molarities were screened and with increasing molarity, parallel increase in selectivity was observed (Table 4, entries 3, 4 and 5).

Table 4. Temperature and concentration screening results for the synthesis of **56**

| entry	molarity (M)	solvent	temp.	time (h)	yield (%)^a	ee (%)
1	0.4	toluene	10 ˚C	72	78	77
2	0.4	toluene	5 ˚C	72	71	74
3	**0.4**	**toluene**	**rt**	**72**	**86**	**81**
4	0.2	toluene	rt	72	74	80
5	0.1	toluene	rt	72	66	76

^{a} Isolated yields

Lastly, to determine the best solvent in terms of selectivity and yield, 10 different solvents and neat condition were examined (Table 5). Generally, all selectivity results were close to each other. However, in the case of ethanol, a drastic decrease in selectivity and yield (15% ee, 27% yield) was observed as expected (Table 5, entry 11). Since ethanol is polar protic solvent, it could make hydrogen bonding with organocatalyst so activation of nitroolefin and diethyl malonate could be blocked by ethanol. As a result of solvent screening, toluene gave the best enantioselectivity and yield (81% ee, 86% yield) than the other ones (Table 5, entry 1). Moreover, xylene which has similar polarity with toluene also gave good results (78% ee, 80% yield) and if the reaction durations are compared, it could be seen that in xylene case, reaction time shortened (Table 5, entry 9).

Table 5. Solvent screening results for the synthesis of **56**

| entry	cat. loading (mol%)	solvent	temp.	time (h)	yield (%)^a	ee (%)
1	**5**	**toluene**	**rt**	**72**	**86**	**81**
2	5	neat	rt	22	52	64
3	5	DCM	rt	72	51	68
4	5	hexane	rt	24	56	70
5	5	THF	rt	72	70	67
6	5	chloroform	rt	72	71	73
7	5	cyclohexane	rt	20	76	75
8	5	*n*-heptane	rt	20	72	70
9	5	xylene	rt	21	80	78
10	5	diethylether	rt	48	66	71
11	5	ethanol	rt	72	27	15

^{a} Isolated yields

As a result of screening studies, 2-aminoDMAP/urea **47** was found as the best organocatalyst with 5 mol% catalyst loading. Room temperature, 0.4 M concentration and toluene as solvent were assigned as the optimized reaction condition for the Michael addition reaction (Scheme 31).
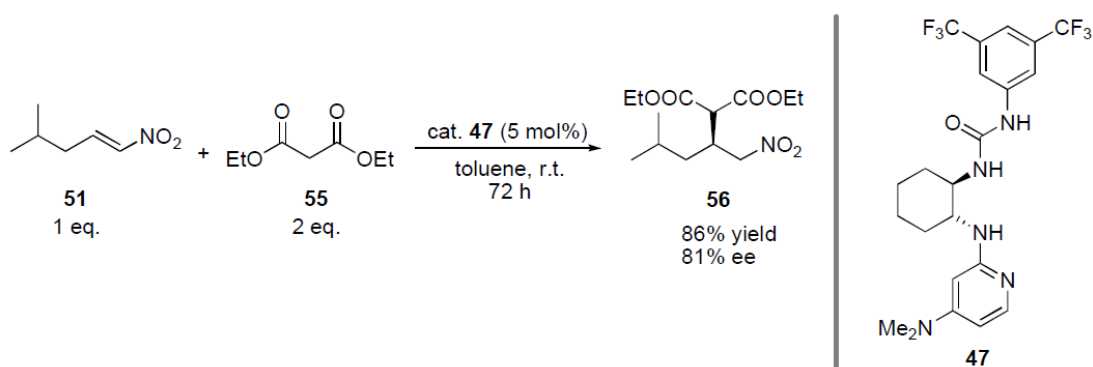
Scheme 31. Optimized condition for Michael addition reaction of diethyl malonate to nitroolefin

2.4.2 Optimization Studies for the Formal Synthesis of Baclofen

Parallel to this work, Michael acceptor was changed to *trans*-4-chloro-β-nitrostyrene (**60**), since the Michael adduct **61** could be used as a precursor for the synthesis of an important chiral drug Baclofen. Therefore, by using 2-aminoDMAP/urea **47** bifunctional organocatalyst, Michael addition reaction was performed (Scheme 32).
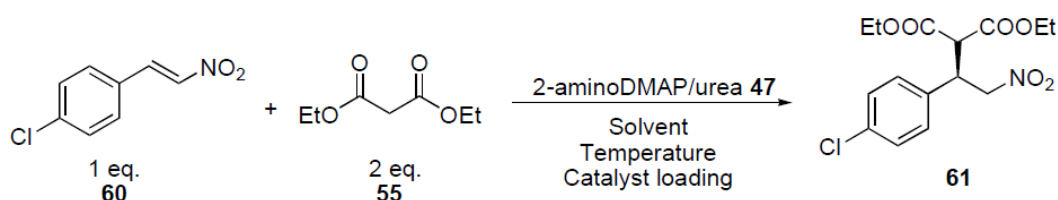
Scheme 32. Control reaction for the formal synthesis of Baclofen

First of all, to determine the amount of catalyst, reaction was performed in toluene with 0.2 M concentration. According to screening results, the best enantioselectivity (90% ee) was obtained with 1 mol% organocatalyst **47** (Table 6, entry 4).

Table 6. Catalyst loading results for the synthesis of **61**

entry	cat. loading (mol %)	solvent	temp.	time (h)	yield (%)^a	ee (%)
1	10	toluene	rt	3.5	91	79
2	5	toluene	rt	5	84	88
3	2	toluene	rt	24	88	88
4	1	toluene	rt	24	72	90

^{a} Isolated yields

Secondly, the reaction duration was fixed to 24 h and with 1 mol% catalyst loading, different temperatures were screened. It is seen that as temperature decreases, selectivity increases. However, the yield also decreased, hence the optimized temperature was chosen as room temperature. The results are summarized in Table 7.

Table 7. Temperature screening results for the synthesis of **61**

entry	solvent	temp. (˚C)	time (h)	yield (%)^a	ee (%)
1	toluene	10 ˚C	24	68	92
2	toluene	5 ˚C	24	66	92
3	toluene	0	24	62	92
4	toluene	-5	24	57	92
5	toluene	-15	24	52	93

^{a} Isolated yields

Lastly, 9 different solvents were tested at room temperature with 0.2 M concentration. We kept the temperature and the reaction duration as room temperature and 24 h, respectively. However in some solvents such as chloroform, tetrahydrofuran and ethanol, we had to wait longer time since no conversion has been observed at the end of 24 h (Table 8). Xylene gave an excellent enantioselectivity which was 93%, and the other results were in acceptable range except ethanol. Since ethanol is polar protic solvent, the quite low result is presumably, due to the existence of hydrogen bonding between ethanol and the organocatalyst.

Table 8. Solvent screening results for the synthesis of **61**

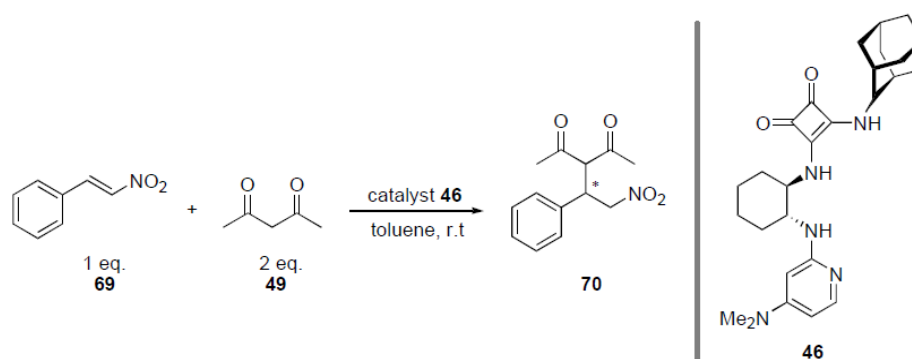| entry	cat. loading (mol%)	solvent	temp.	time (h)	yield (%)^a	ee (%)
1	1	toluene	rt	24	72	90
2	1	DCM	rt	24	80	81
3	**1**	**xylene**	**rt**	**24**	**71**	**93**
4	1	chloroform	rt	48	82	83
5	1	cyclohexnae	rt	24	75	88
6	1	hexane	rt	24	82	82
7	1	*n*-heptane	rt	24	81	83
8	1	THF	rt	48	81	68
9	1	ethanol	rt	72	15	5

^{a} Isolated yields

As a result of optimization studies, for the Michael adduct **61**, the best reaction condition was determined as 1 mol% catalyst loading, 0.2 M concentration and at room temperature. At the end of the 24 h, 93% enantioselectivity was obtained with quite good yield in the presence of 2-aminoDMAP/urea organocatalyst **47.**

Absolute configurations of Michael adducts **56** and **61** were found to be *S* and *R* respectively, according to the specific rotations which were reported in the literature.[25,39]

2.4.3 Optimization Studies for the Michael Addition Reaction of Acetylacetone to Nitrostyrene Derivatives

To extend the work and also to test the activity of 2-aminoDMAP/squaramide organocatalyst's **46**, acetylacetone (**49**) was chosen. First of all, catalyst loading parameter was tested for the addition of acetylacetone (**49**) to nitrostyrene (**69**). It was assigned that 2 mol% catalyst loading is suitable although the result of 1% organocatalyst loading gave higher selectivity. Because with 2 mol%, within only 4 h, full conversion of nitrostyrene was observed (Table 9, entry 2).

Table 9. Catalyst loading results for the addition of acetylacetone to nitrostyrene

entry	cat. loading (mol %)	solvent	temp.	time (h)	yield (%)^a	ee (%)
1	5	toluene	rt	3	74	52
2	**2**	**toluene**	**rt**	**4**	**78**	**68**
3	1	toluene	rt	48	82	71

^{a} Isolated yields

As a final step, the scope of the reaction with various nitrostyrene derivatives was tested in the presence of catalyst **46** (Table 10). Enantioselectivities were obtained as in the range of 37-65% ee except for nitro substituted nitrostyrene derivative **71a** in *ortho* position. The reason could be that the competitive hydrogen-bonding interaction of the nitro group with the hydrogens of squaramide unit of the catalyst. This might be prevent the activation of the Michael acceptor. In halogen substituted series, *o-* and *m*-Cl substituted derivatives **72b-c** gave moderate enantioselectivities and quite good yields; however, for *para* position, a drastic decrease in selectivities was observed (Table 10, entries 4 and 5). As a result of derivatization, addition products **72a-g** were obtained in moderate yields (Table 10). It could be concluded that this organocatalyst system is not suitable for acetylacetone (**49**) addition.

Table 10. Derivatization of asymmetric Michael addition reaction
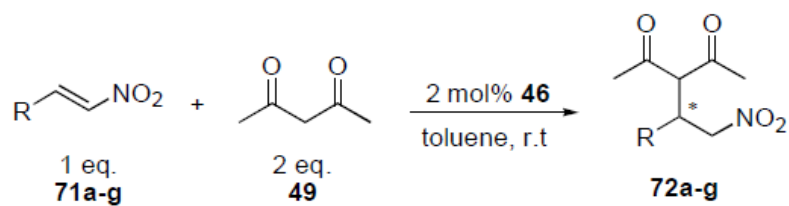
entry	Ar	product	time (h)	% yield^a	% ee
1	2-NO$_2$-C$_6$H$_4$	**72a**	72	82	racemic
2	2-Cl-C$_6$H$_4$	**72b**	2	72	64
3	3-Cl-C$_6$H$_4$	**72c**	24	80	65
4	4-Cl-C$_6$H$_4$	**72d**	23	78	39
5	4-F-C$_6$H$_4$	**72e**	48	71	37
6	2-furyl	**72f**	48	67	39
7	4-BnO-C$_6$H$_4$	**72g**	48	68	60

^{a} Isolated yields

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

Pırification and characterization studies of were done with the instruments as written below.

^{1}H-NMR and ^{13}C-NMR spectra were recorded in CDCl$_3$ or d$_6$-DMSO as solvents on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in parts per million (ppm) with TMS as internal reference. Spin multiplicities were specified as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dq (doublet of quartet), t (triplet), q (quartet), m (multiplet), and coupling constants (J) were reported in Hertz (Hz). ^{1}H and ^{13}C NMR spectra of products are given in appendix A.

Polarimetric measurements were made by Rudolph Scientific Autopol III polarimeter and reported as follows $[\alpha]_D^T$ (c in g/ml). HPLC chromatograms were recorded Thermo-Finnigan HPLC system. Chiral columns OD-H, IA and AD-H were used with different solvent systems. HPLC chromatograms of chiral products and racemic forms of them were given in Appendix B.

All reactions were monitored by TLC using precoated silica gel plates (Merck Silica Gel 60 F254), visualized by UV-light. Column chromatography was performed on silica gel 60 with a particle size of 0.063–0.200 mm.

Compounds were named by using ChemDraw Ultra 12.0

3.2 Synthesis of *R,R* configured 2-AminoDMAP (44)

CuBr (200.83 mg, 0.2 mmol) and K_3PO_4 (2.971 g, 2.0 mmol) was added to an oven-dried Schlenk tube which was evacuated, and backfilled with argon twice. After the addition of (*R,R*)-cyclohexane-1,2-diamine (**43**) (960 mg, 1.20 mmol), and 2-bromoDMAP (**62**) (1.407 g, 1.0 mmol), dioxane (1.0 mL) that was distilled over Na-benzophenone added as solvent under Ar atmosphere to the Schlenk tube. The reaction mixture was stirred at 110 °C for 24 h. The resulting green-blue suspension was allowed to reach room temperature. Then, extraction was done with dichloromethane thrice (3 × 25 mL) and the combined dichloromethane phase was extracted with brine and dried with MgSO4. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel using dichloromethane that was saturated with concentrated aqueous ammonia to afford the product **44** as brown solid (141 mg, 60% yield).
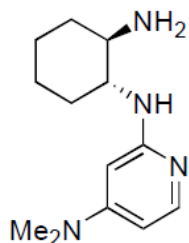

44

^{1}**H NMR (400 MHz, CDCl₃)** δ 7.67 (d, *J* = 6.1 Hz, 1H), 5.98 – 5.83 (m, 1H), 5.52 (d, *J* = 2.2 Hz, 1H), 4.13 (d, *J* = 9.3 Hz, 1H), 3.24 (*J* = 4.0, 9.6 Hz, 1H), 2.89 (s, 6H), 2.42 (td, *J* = 10.5, 4.1 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.91 (dt, *J* = 9.3, 3.3 Hz, 1H), 1.78 (s, 2H), 1.72 – 1.60 (m, 2H), 1.36 – 1.12 (m, 3H), 1.04 (m, 1H).

^{13}**C NMR (100 MHz, CDCl₃)** δ 159.9, 156.1, 147.8, 99.3, 96.1, 58.4, 56.4, 39.3, 34.9, 32.9, 25.4, 25.1.

3.3 Synthesis of 2-AminoDMAP/Sulfonamide Bifunctional Organocatalyst (45)

Sulfonyl chloride **64** (53 mg, 0.2 mmol) was added to the solution of (*R,R*) 2-aminoDMAP **44** (47 mg, 0.2 mmol) and TEA (22.2 mg, 30 μL, 0.22 mmol) in DCM (1 mL) at 0 °C. Then the mixture was brought to room temperature and stirred for

1 hour. After column chromatography with EtOAc:TEA (98:2), the product was obtained as pale yellow fluffy solid (88 mg, 96% yield). Spectroscopic data have been reported previously.[19]



45
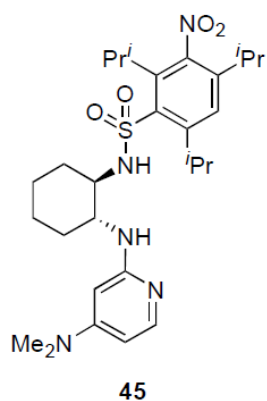
$[\alpha]_D^{27}$ +43.2 ° (c= 0.25, CH_2Cl_2)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, J = 6.2 Hz, 1H), 7.26 (s, 1H), 5.95 (dd, J = 2.3, 6.3 Hz, 1H), 5.48 (d, J = 2.1 Hz, 1H),4.21 − 4.41 (m, 1H), 3.92 − 4.18 (m, 2H), 3.48 − 3.66 (m, 1H), 3.14 (dt, J = 3.9, 10.7 Hz, 1H),2.85 (s, 6H),2.01 − 1.89 (m, 2H), 2.62 (sept, J = 6.8 Hz, 1H), 1.66 (d, J = 10.0 Hz, 1H), 1.56 (d, J = 11.2 Hz, 1H), 1.34 − 1.06 (m, 24H)

1 exchangeable sulfonamide H not located.

^{13}C NMR (100 MHz, CDCl$_3$) δ 156.0, 152.4, 150.0, 143.2, 139.0, 138.5, 124.4, 100.5, 89.6, 55.1, 39.2, 33.6, 33.4, 30.5, 29.1, 28.9, 25.1, 24.8, 24.6, 24.1, 23.7, 21.7, 21.6

3.4 Synthesis of 2-AminoDMAP/Squaramide Bifunctional Organocatalyst (46)

Solid mono-squaramide (55 mg, 0.2 mmol) was added to the solution of (*R,R*) 2-aminoDMAP **44** (47 mg, 0.2 mmol) in one to one volume DCM:MeOH mixture (1 mL). The solution was stirred for 48 hour at room temperature and the resulting mixture was directly purified with column chromatography using DCM:MeOH (90 : 10) to obtain the organocatayst with 66% yield. Spectroscopic data have been reported previously.[19]

41
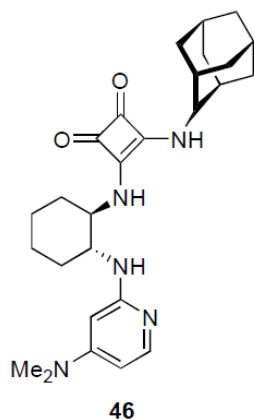
$[\alpha]_D^{31}$ -50.9 ° (c=0.25, DMSO)

¹H NMR (400 MHz, DMSO) δ 7.69 (d, *J* = 2.4 Hz, 1H), 7.42 – 7.64 (m, 2H), 6.01 (bs, 1H), 5.74 (bs, 1H), 5.57 (bs, 1H), 4.12 (bs, 1H), 3.93 (bs, 1H), 3.78 (s, 1H), 2.02 –2.23 (m, 2H), 2.91 (s, 6H), 1.69 – 2.02 (m, 14H), 1.09 – 1.69 (m, 8H). Two protons extra located.

¹³C NMR (100 MHz, DMSO) δ 181.2, 180.2, 166.3, 165.5, 157.9, 153.8, 145.6, 97.4, 87.3, 60.6, 56.3, 55.6, 52.4, 37.2, 35.4, 34.9, 34.9, 32.3, 31.4, 31.3, 30.9, 28.9, 28.8, 25.2, 24.9, 24.0, 23.1, 23.0.

3.5 Synthesis of 2-AminoDMAP/Urea Bifunctional Organocatalyst (47)

To the solution of *R,R* configured 2-AminoDMAP **44** (47 mg, 0.2 mmol) in THF (1 mL, dried on Na wire), 3,5-bis(trifluoromethyl)phenyl isocyanate (**68**) (54 mg, 35 μL, 0.2 mmol) was added dropwise at room temperature. The reaction mixture was stirred overnight and then directly loaded to column which was eluted with 90:10 MeOH:sat'd DCM. After purification, 2-aminoDMAP/urea organocatalyst was obtained with 85% yield as a light brown amorphous solid.
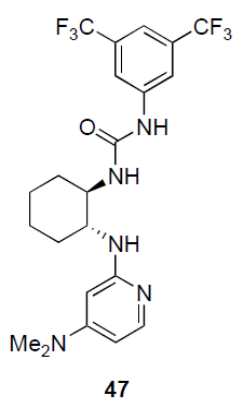
¹H NMR (400 MHz, CDCl₃) δ 7.69 (s, 2H), 7.52 (d, *J* = 13.8 Hz, 1H), 7.27 (s, 1H), 6.52 (s, 1H), 5.88 (d, *J* = 6.1 Hz, 1H), 5.45 (s, 1H), 5.23 (s, 1H), 4.55 (s, 1H), 3.59 (bs,1H), 3.53 – 3.35 (bs, 1H), 2.81 (s, 6H), 1.99 (m, 2H), 1.60 (m, 2H), 1.15 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ 157.9, 155.1, 154.9, 144.5, 140.5, 131.2, 130.9, 130.6, 130.2, 123.7, 120.9, 118.3, 117.0, 113.7, 98.9, 88.0, 54.5, 38.0, 31.5, 29.9, 28.7, 23.5.

IR (neat) 2921, 2852, 1609, 1526, 1473, 1387, 1275, 1169, 1125, 877, 702, 681.

3.6 Synthesis of 4-methyl-1-nitropentan-2-ol (59)

To the solution of isovaleraldehyde (**58)** (7.75 g, 9.88 mL, 0.09 mol) and nitromethane (5.62 g, 5 mL, 0.092 mol) in cold EtOH (40 mL), aqueous 10 M NaOH solution (30 mL, 0.09 mol) was added at 0°C. During the addition of NaOH, a yellow foam was observed and after stirring for 10 min, the reaction mixture was brought to room temperature and stirred overnight. Then acetic acid (5.14 mL, 0.09 mol) was added and the aquesous layer was extracted with diethyl ether twice (30 mLx2). Until the pH of washings was 6, extracts were washed with distilled water. After drying with $MgSO_4$, filtration and concentration in vacuum, the residues was loaded on column which was eluted with 1:5 EtOAc:Hexane to afford the desired nitoalcohol as light yellow oil (8.44 g, 65%).
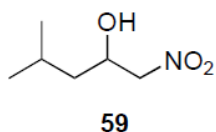
1H NMR (400 MHz, CDCl3) δ 4.42 − 4.06 (m, 3H), 3.52 − 2.70 (bs, 1H), 1.62 − 1.88 (m, 1H), 1.49 − 1.29 (m, 1H), 1.25 − 1.06 (m, 1H), 0.88 (m, 6H).

13C NMR (100 MHz, CDCl3) δ 81.1, 67.2, 42.7, 24.3, 23.1, 21.7.

3.7 Synthesis of (*E*)-4-methyl-1-nitropent-1-ene (51)

To the solution of obtained nitroalcohol **58** (4 g, 3.78 mL, 0.027 mol) and MsCl (2.53 mL, 0.033 mol) in THF (27.1 mL), TEA (8.13 mL, 0.057 mol) was added at 0°C. The reaction mixture was stirred for 1 hour at the same temperature, and saturated ammonium chloride (20 mL) was added. The aqueous layer was extracted with diethyl ether twice (100 mLx2) and then the extract was washed with 1N HCl twice. After the addition of saturated $NaHCO_3$ and brine, the residue was dried over $MgSO_4$, filtrated and concentrated in vacuum. After purification step by column

chromatography with 1:10 EtOAc:hexane, the afforded product was obtained with 72% yield.
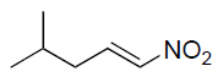
51

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.16 (dt, J = 13.4, 8.0, 1.2 Hz, 1H), 6.90 (d, J = 13.4, 0.9 Hz, 1H), 2.13 – 2.06 (m, 2H), 1.83 – 1.66 (m, 1H), 0.89 (dd, J = 9.9, 5.0 Hz, 6H).

**^{13}C NMR (100 MHz, CDCl$_3$)** δ 141.2, 140.1, 96.1, 37.1, 27.7, 22.2.

3.8 General Procedure for Asymmetric Michael Additions of Diethyl malonate

To a solution of nitoalkene derivative (0.2 mmol) in solvent (0.5 to 1.0 mL) was added 2-aminoDMAP/urea **47** (0.002 to 0.01 mmol) and diethyl malonate **55** (64 mg, 61 µL, 0.4 mmol). Upon consumption of the limiting agent (nitroalkene) which was monitored by TLC, the reaction mixture was directly loaded to column chromagraphyusing 1:10 EtOAc:Hexane as eluent to afford the conjugate addition products.

3.8.1 Synthesis of (*S*)-Diethyl-2-(4-methyl-1-nitropentan-2-yl)malonate (56)

General procedure starting from (*E*)-4-methyl-1-nitropent-1-ene (**51**) (25.83 mg, 27 µL, 0.2 mmol) afforded to desired chiral product **56** as yellow oil with 86% yield and 81% ee in 72 hours.
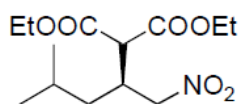
56

HPLC (OD-H, 98:2 n-Hexane:Isopropanol, 0.5 mL/min, 210 nm): t_{major}= 24.1 min, t_{minor}= 15.3 min, $[\alpha]_D^{24}$ = +4.4 (c=0.25, CHCl$_3$)

^{1}H NMR (400 MHz, CDCl$_3$) δ 4.64 (dd, J = 13.3, 5.1 Hz,

1H), 4.46 (dd, J = 13.3, 6.6 Hz, 1H), 4.16 (dq, J = 7.1, 1.4 Hz, 4H), 3.55 (d, J = 5.5 Hz, 1H), 2.96 – 2.83 (m, 1H), 1.59 (dt, J = 13.4, 6.7 Hz, 1H), 1.26 (t, J = 5.7 Hz, 2H), 1.22 (t, J = 7.1 Hz, 6H), 0.85 (dd, J = 6.5, 3.8 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 166.9, 166.8, 75.9, 60.9, 60.7, 51.7, 37.9, 33.9, 24.1, 21.3, 21.2, 13.0, 12.9.

3.8.2 Synthesis of Diethyl 2-((*R*)-1-(4-chlorophenyl)-2-nitroethyl)malonate (61)

General procedure starting from *(E)*-1-chloro-4-(2-nitrovinyl)benzene (**60**) (36.72 mg, 0.2 mmol) afforded to desired chiral product **61** with 71% yield and 93% ee in 24 hours.
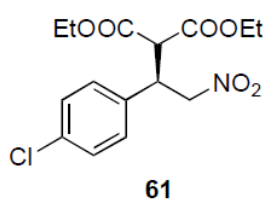
HPLC (IA, 90:10 n-Hexane:Isopropanol, 1.0 mL/min, 254 nm): t_{major}= 9.9 min, t_{minor}= 26.7 min, $[\alpha]_D^{24}$= -5.4 (c=0.25, CHCl$_3$)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 – 7.19 (m, 2H), 7.15 – 7.10 (m, 2H), 4.84 (dd, J = 13.2, 4.8 Hz, 1H), 4.76 (dd, J = 13.2, 9.4 Hz, 1H), 4.23 – 4.08 (m, 3H), 3.96 (q, J = 7.1 Hz, 2H), 3.71 (d, J = 9.3 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 166.2, 165.6, 133.8, 133.3, 128.5, 128.1, 76.4, 61.3, 61.0, 53.8, 41.3, 12.9, 12.8.

3.9 General Procedure for Asymmetric Michael Additions of Acetylacetone

To a solution of nitostyrene derivative (0.2 mmol) in toluene (1.0 mL) was added 2-aminoDMAP/squaramide **46** (1.85 mg, 0.004 mmol) and acetylacetone (**49**) (40 mg, 41 μL, 0.4 mmol). Upon consumption of the limiting agent by monitoring with TLC,

the reaction mixture was directly loaded to column chromagraphy using 1:5 EtOAc:Hexane as eluent to afford the conjugate addition products.

3.9.1 Synthesis of (*R*)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione (70)

General procedure starting from *trans*-(*β*)-nitrostyre (**69**) (29.8 mg, 0.2 mmol) afforded to desired chiral product **70** with 78% yield and 68% ee in 4 h.
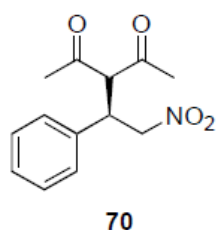
HPLC (AD-H, 90:10 n-Hexane:Isopropanol, 1.0 mL/min, 220 nm): t_{major}= 17.5 min, t_{minor}= 13.1 min, $[\alpha]_D^{24}$= -38.5 (c=0.25, CHCl$_3$)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 − 7.17 (m, 3H), 7.14 − 7.09 (m, 2H), 4.64 − 4.49 (m, 2H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.17 (ddd, *J* = 10.8, 7.7, 4.9 Hz, 1H), 2.22 (s, 3H), 1.87 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 200.7, 199.9, 135.0, 128.3, 127.5, 126.9, 77.2, 69.7, 41.8, 29.4, 28.5.

3.9.2 Synthesis of 3-(2-nitro-1-(2-nitrophenyl)ethyl)pentane-2,4-dione (72a)

General procedure starting from *(E)*-1-nitro-2-(2-nitrovinyl)benzene (38.82 mg, 0.2 mmol) afforded to desired product **72a** with 82% yield, no ee in 72 hours at room temperature.
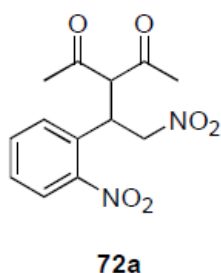
HPLC (IA, 90:10 n-Hexane:Isopropanol, 1.0 mL/min, 210 nm): retention times: 31.6, 34.9 min.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 − 7.82 (dd, J = 8.0, 1.4 Hz, 1H), 7.49 − 7.38 (m, 2H), 7.42 − 7. (m, 1H), 4.97 (dd, J = 13.3, 7.1 Hz, 1H), 4.84 (dd, J = 13.3, 3.7 Hz, 1H), 4.61 (d, J = 8.7 Hz,

1H), 4.52 (m, 1H)2.23 (s, 3H), 1.93 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 200.3, 199.5, 137.2, 134.2, 129.6, 127.8, 127.2, 125.1, 76.7, 69.3, 41.3, 29.5, 28.7.

3.9.3 Synthesis of (*R*)-3-(1-(2-chlorophenyl)-2-nitroethyl)pentane-2,4-dione (72b)

General procedure starting from 1-chloro-2-(*(E)*-2-nitrovinyl)benzene(36.72 mg, 0.2 mmol) afforded to desired product **72b** with 72% yield, 64% ee in 2 hours at room temperature.
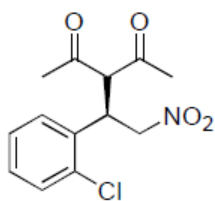

72b
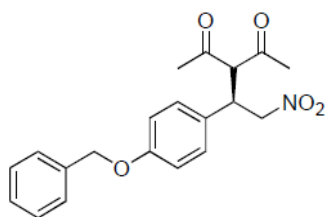
HPLC (IA, 90:10 n-Hexane:Isopropanol, 1.0 mL/min, 210 nm): t_{major}= 23.2 min, t_{minor}= 19.9 min, $[\alpha]_D^{24}$= -38.5 (c=0.25, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.16 (m, 2H), 7.16 (d, *J* = 19.1 Hz, 1H), 7.06 – 6.97 (m, 1H), 4.66 – 4.48 (m, 2H), 4.28 (d, *J* = 10.6 Hz, 1H), 4.16 (dd, *J* = 7.6, 5.0 Hz, 1H), 2.23 (s, 3H), 1.93 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 200.3, 199.4, 137.2, 134.2, 129.6, 127.9, 127.2, 125.1, 76.7, 69.4, 41.4, 29.5, 28.7.

3.9.4 Synthesis of (*R*)-3-(1-(3-chlorophenyl)-2-nitroethyl)pentane-2,4-dione (72c)

General procedure starting from 1-chloro-3-(*(E)*-2-nitrovinyl)benzene (36.72 mg, 0.2 mmol) afforded to desired product **72c** with 80% yield, 65% ee in 24 hours at room temperature.
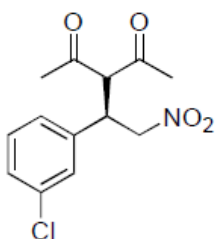
72c

HPLC (IA, 90:10 n-Hexane:Isopropanol, 0.6 mL/min, 210 nm): t_{major}= 13.5 min, t_{minor} = 12.3 min, $[\alpha]_D^{24}$= -38.5 (c=0.25, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.17 (m, 2H), 7.14 (d, *J* = 0.6 Hz, 1H), 7.04 – 6.98 (m, 1H), 4.56 (dd, *J* = 13.3, 7.1 Hz,

1H), 4.45 (dd, J = 13.0, 7.1 Hz, 1H), 4.28 (d, J = 10.6 Hz, 1H), 4.16 (ddd, J = 10.6, 7.5, 5.2 Hz, 1H), 2.23 (s, 3H), 1.95 (s, 3H).

13C NMR (100 MHz, CDCl3) δ 200.3, 199.4, 137.2, 134.2, 129.6, 127.9, 127.2, 125.1, 76.7, 69.4, 41.4, 29.5, 28.7.

3.9.5 Synthesis of (*R*)-3-(1-(4-chlorophenyl)-2-nitroethyl)pentane-2,4-dione (72d)

General procedure starting from 1-chloro-4-*((E)*-2-nitrovinyl)benzene (36.72 mg, 0.2 mmol) afforded to desired product **72d** with 79% yield, 38% ee in 23 hours at room temperature.
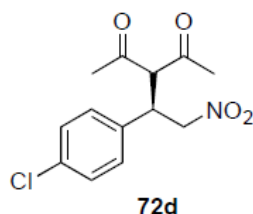
HPLC (AD-H, 80:20 n-Hexane:Isopropanol, 0.8 mL/min, 210 nm): t_{major}= 11.6 min, t_{minor}= 10.2 min, , $[\alpha]_D^{24}$ = -22.5 (c=0.25, CHCl₃)

1H NMR (400 MHz, CDCl₃) δ 7.26 − 7.19 (m, 2H), 7.09 − 7.05 (m, 2H), 4.57 − 4.50 (m, 2H), 4.26 (d, J = 10.7 Hz, 1H), 4.16 (ddd, J = 10.7, 7.1, 5.5 Hz, 1H), 2.22 (s, 3H), 1.91 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 199.2, 198.4, 132.4, 132.4, 127.4, 127.2, 75.8, 68.4, 39.9, 28.3, 27.5.

3.9.6 Synthesis of (*R*)-3-(1-(4-fluorophenyl)-2-nitroethyl)pentane-2,4-dione (72e)

General procedure starting from 1-fluoro-4-*((E)*-2-nitrovinyl)benzene (33.42 mg, 0.2 mmol) afforded to desired product **72e** with 71% yield, 37% ee in 48 hours at room temperature.
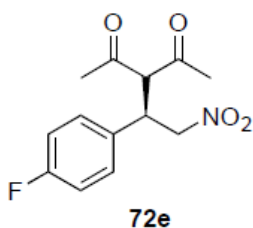
HPLC (AD-H, 90:10 n-Hexane:Isopropanol, 0.8 mL/min, 210 nm): t_{major}= 23.1 min, t_{minor}= 20.4 min, $[\alpha]_D^{24}$ = -6.4 (c=0.25, CHCl₃).

1H NMR (400 MHz, CDCl₃) δ 7.20 − 7.07 (m, 2H), 7.00 − 6.92

(m, 2H), 4.56 – 4.52 (m, 2H), 4.26 (d, J = 10.8 Hz, 1H), 4.17 (ddd, J = 10.8, 7.0, 5.5 Hz, 1H), 2.23 (s, 3H), 1.90 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 199.8, 198.9, 130.1, 128.0, 127.9, 114.8, 114.6, 76.4, 69.0, 40.4, 28.7, 27.9.

3.9.7 Synthesis of *(R)*-3-(1-(furan-2-yl)-2-nitroethyl)pentane-2,4-dione (72f)

General procedure starting from 2-(*(E)*-2-nitrovinyl)furan (27.82 mg, 0.2 mmol) afforded to desired product **72f** with 67% yield, 39% ee in 48 hours at room temperature.
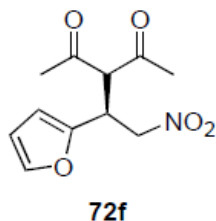
HPLC (AD-H, 90:10 n-Hexane:Isopropanol, 1.0 mL/min, 210 nm): t_{major}= 16.1 min, t_{minor}= 13.6 min, $[\alpha]_D^{24}$= -4.2 (*c*=0.25, CHCl$_3$).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, J = 1.4 Hz, 1H), 6.23 (dd, J = 3.2, 1.9 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 4.60 (d, J = 5.6 Hz, 2H), 4.33 (d, J = 9.8 Hz, 1H), 4.31 – 4.24 (m, 1H), 2.21 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 200.5, 199.8, 148.5, 141.9, 109.8, 107.8, 74.8, 66.9, 35.6, 29.6, 28.3.

3.9.8 Synthesis of *(R)*-2-(1-(4-(benzyloxy)phenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (72g)

General procedure starting from *(E)*-1-(benzyloxy)-4-(2-nitrovinyl)benzene (51.06 mg, 0.2 mmol) afforded to desired product **72g** with 68% yield, 60% ee in 48 hours at room temperature.

72g

HPLC (AD-H, 70:30 n-Hexane:Isopropanol, 1.0 mL/min, 210 nm): t_{major}= 14.2 min, t_{minor}= 10.9 min, $[\alpha]_D^{24}$= −14.5 (c=0.25, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.36 − 7.25 (m, 5H), 7.06 − 7.02 (m, 2H), 6.86 − 6.83 (m, 2H), 4.95 (s, 2H), 4.52 (dd, *J* = 7.1, 5.2 Hz, 2H), 4.26 (d, *J* = 10.9 Hz, 1H), 4.17 − 4.07 (m, 1H), 2.22 (s, 3H), 1.87 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 200.9, 200.8, 157.8, 135.6, 128.1, 127.6, 127.1, 126.5, 114.6, 113.9, 77.4, 69.9, 69.1, 41.1, 29.4, 28.4.

CHAPTER 4

CONCLUSION

For the formal synthesis of Pregabalin, Michael addition reaction of diethyl malonate **(55)** to *(E)*-4-methyl-1-nitro-1-pentene **(51)** was performed in the presence of 2-aminoDMAP/urea **47**. As a result of optimization studies, 81% ee was obtained in the synthesis of Michael adduct **56** which could be used as important chiral precursor. It can be concluded that synthesis of Pregabalin could be totally accomplished in 3 steps by using organocatalysts.

Another study which includes the formal synthesis of Baclofen was completed in 93% ee by using bifunctional organocatalyst. *Trans*-4-chloro-β-nitrostyrene **(60)** as a Michael acceptor was reacted with diethyl malonate **(55)** as a Michael donor in the presence of only 1 mol% 2-aminoDMAP/urea **47**.

To extend the work and to test the activity of squaramide type organocatalyst, Michael addition reactions of acetylacetone to various nitrostyrene derivatives were performed and enantioselectivities are varied between 37 - 69% with 2 mol% catalyst loading.

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A. NMR DATA
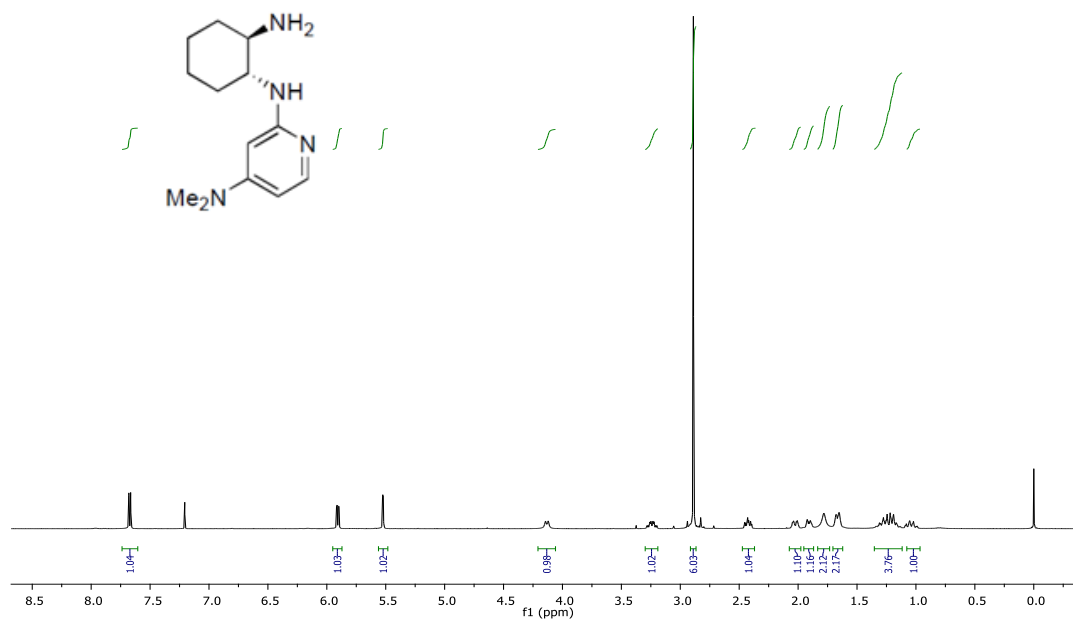
Figure A 1. ^{1}H NMR spectrum of compound **44**
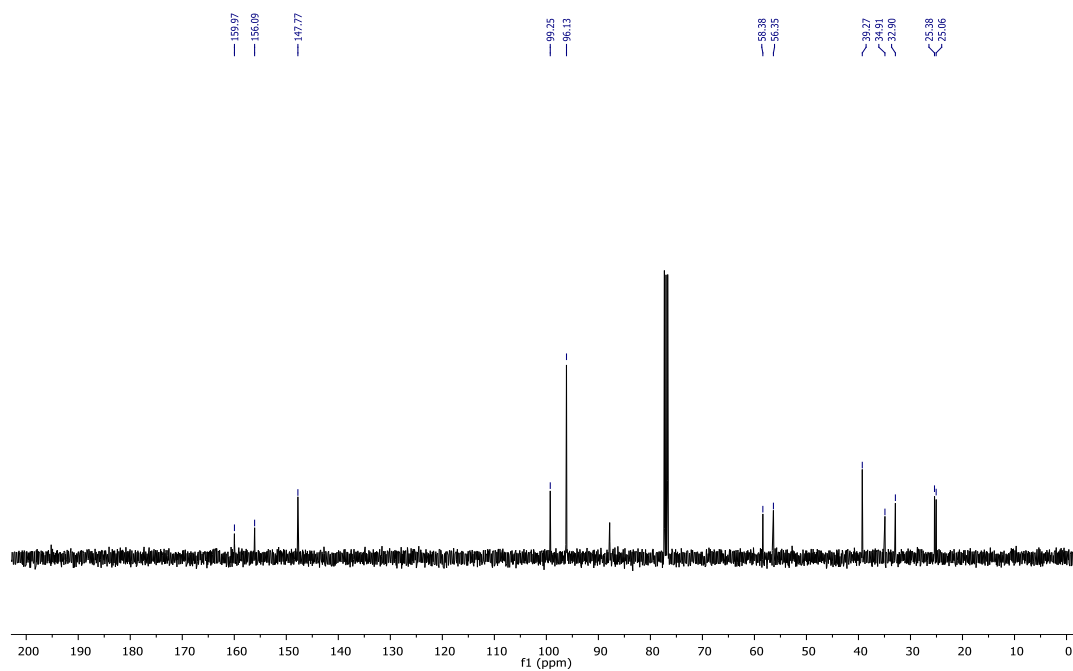
Figure A 2. ^{13}C NMR spectrum of compound **44**
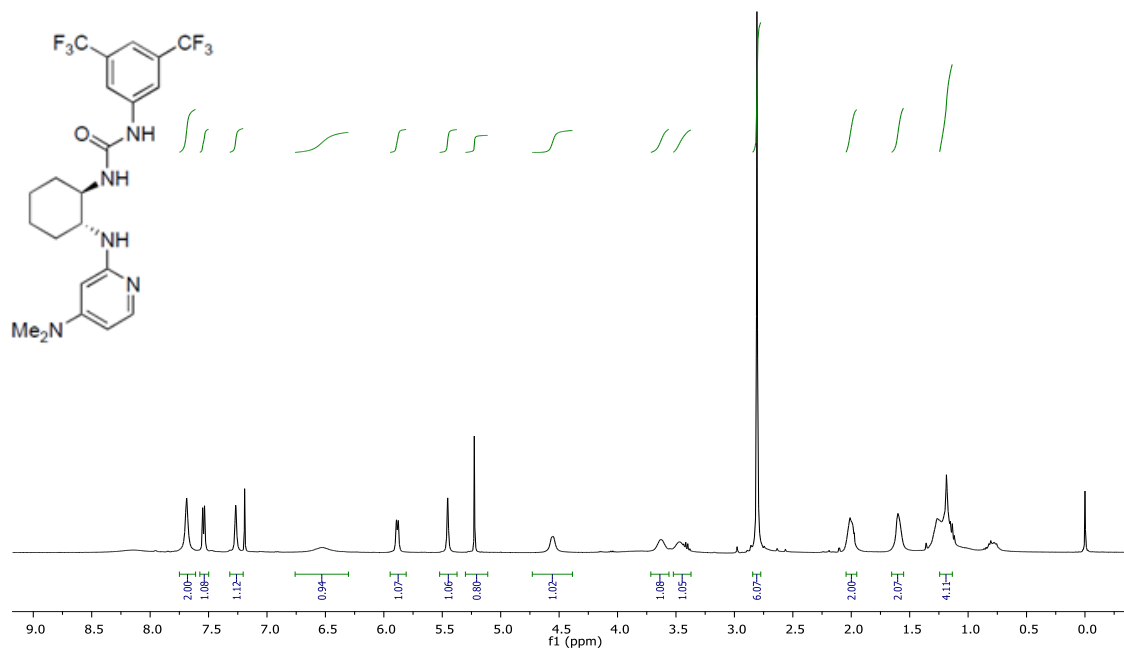
Figure A 3. ^{1}H NMR spectrum of compound **47**
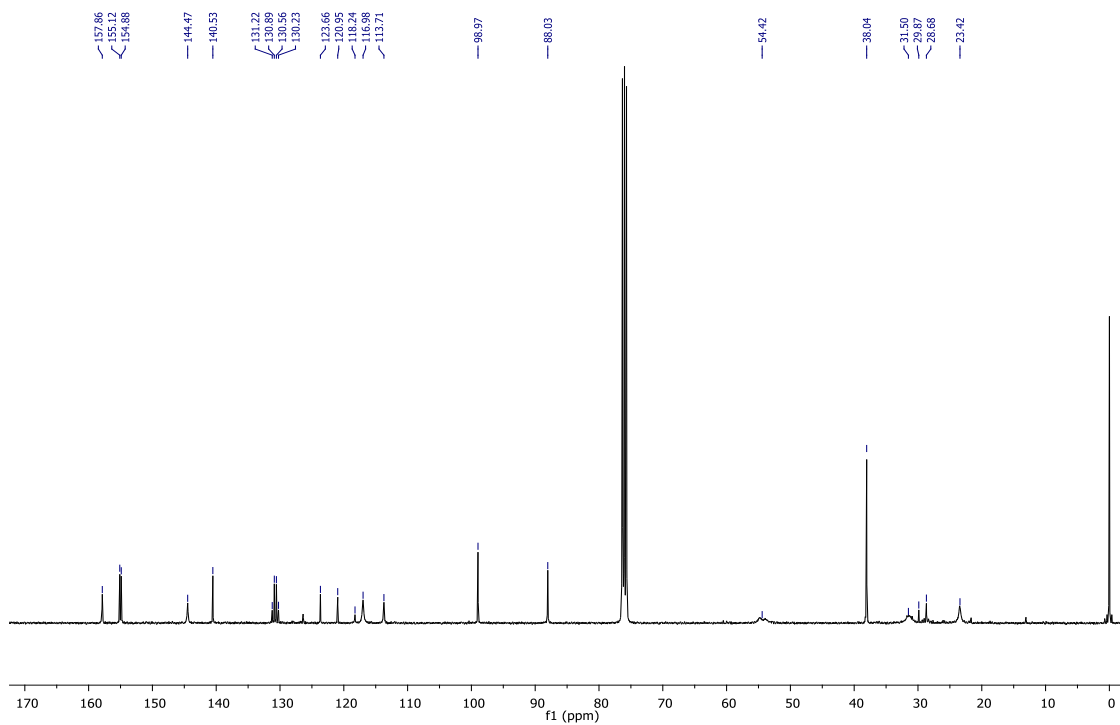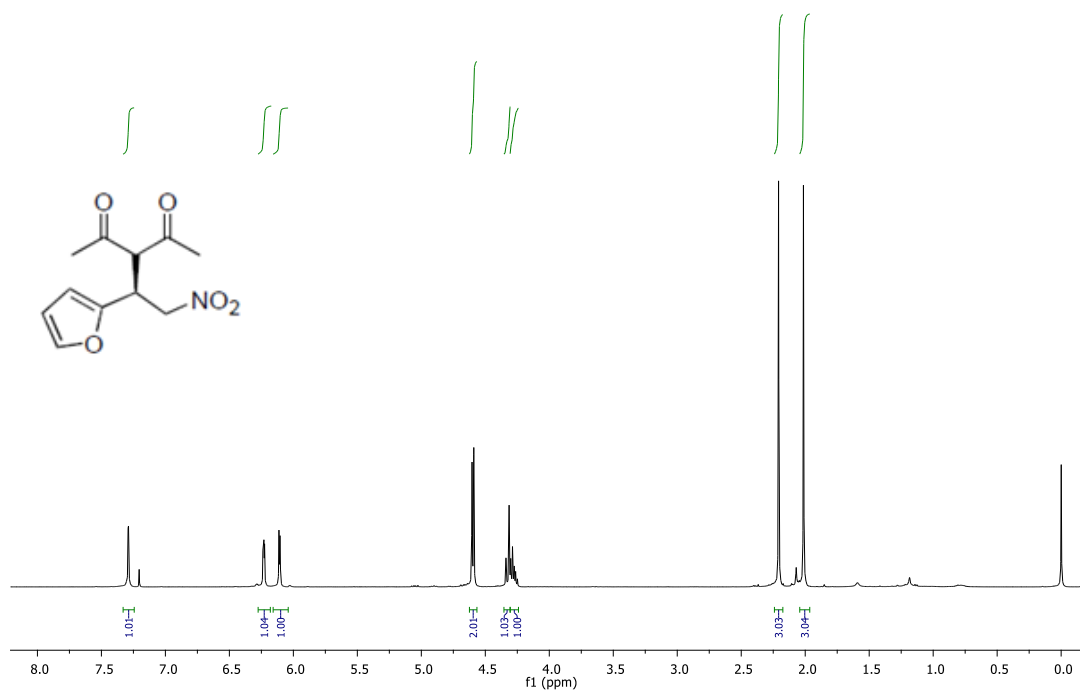

Figure A 4. ^{13}C NMR spectrum of compound **47**
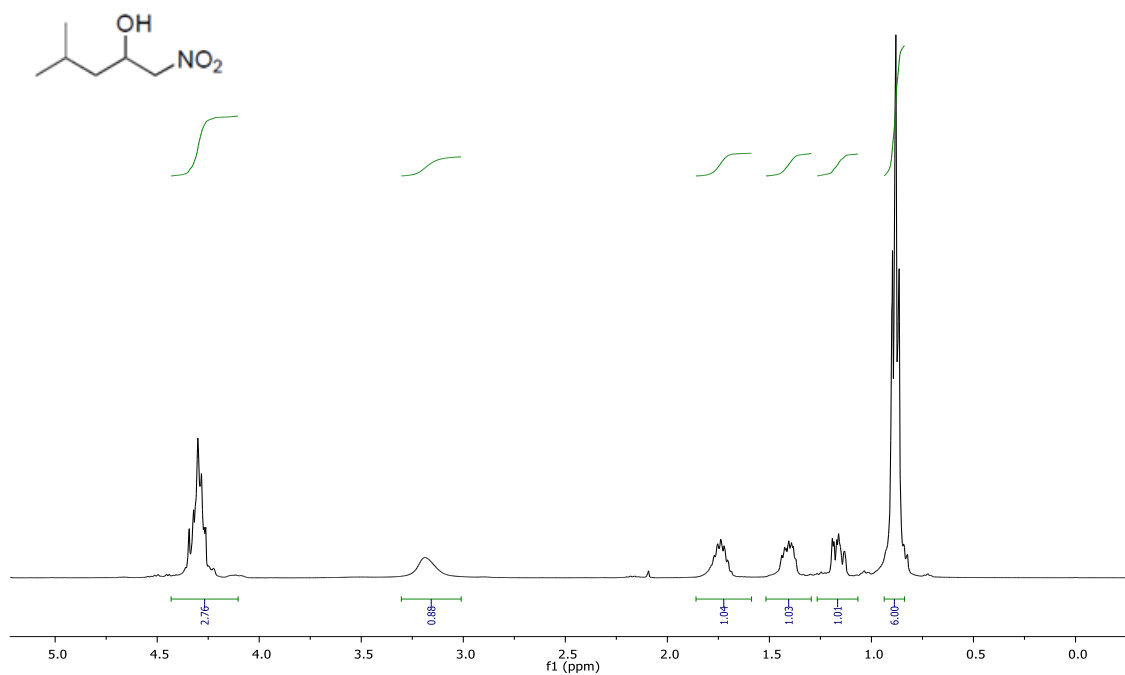
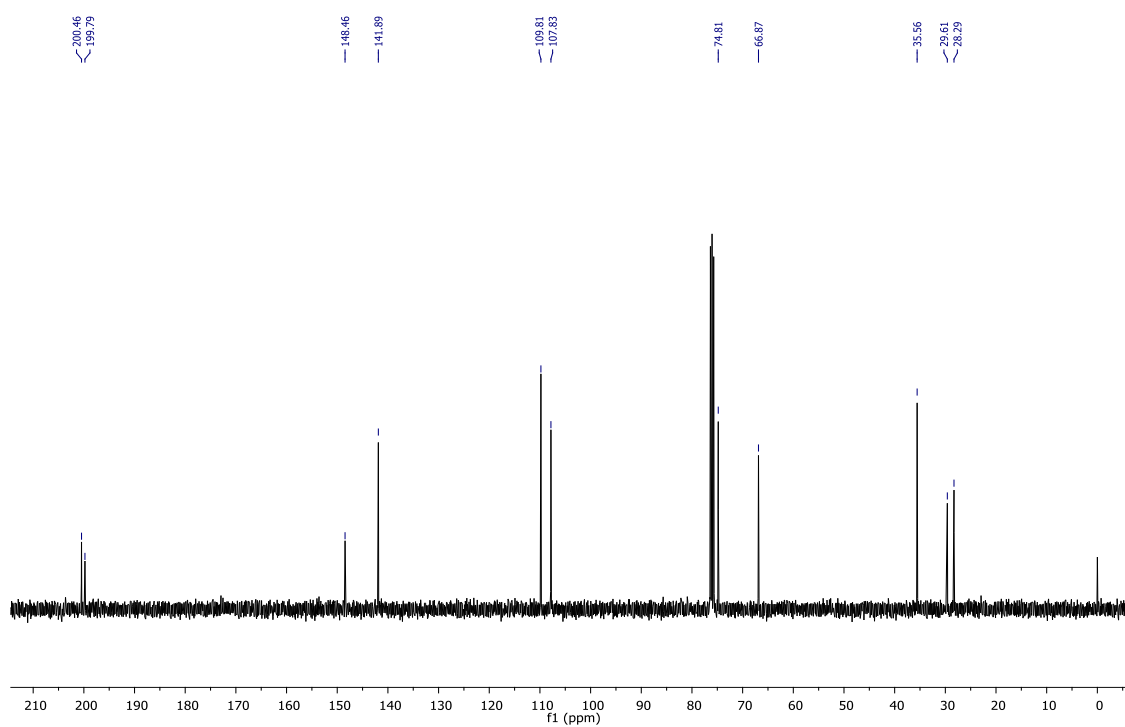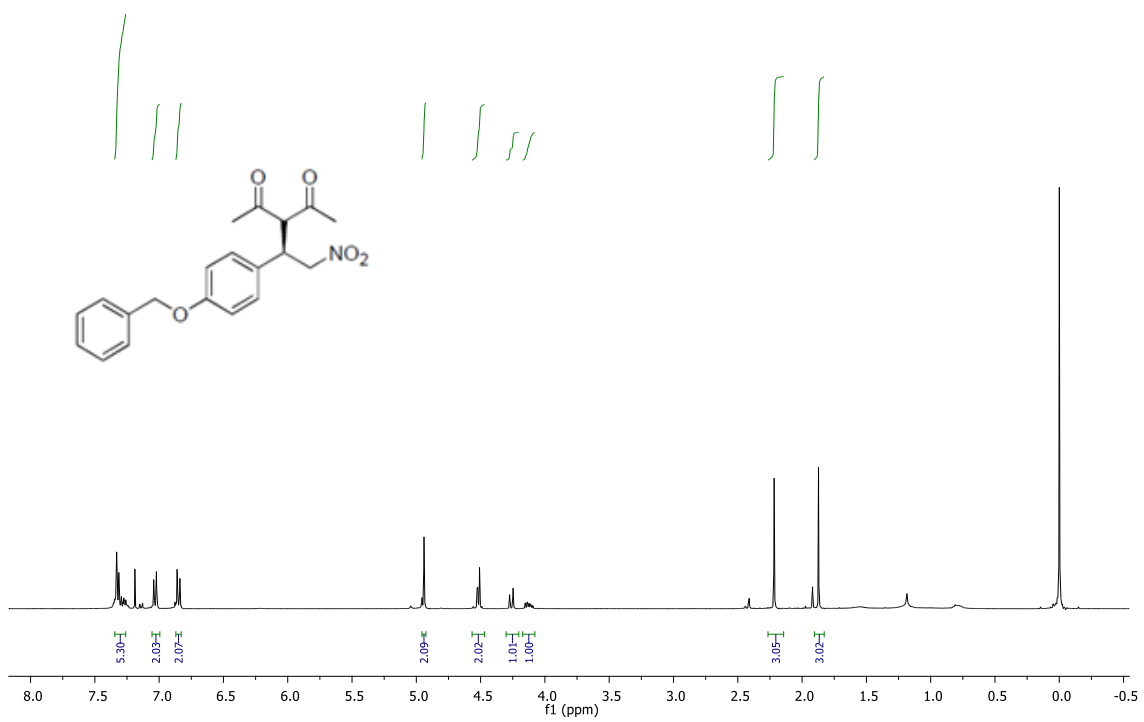**Figure A 5.** ^{1}H NMR spectrum of compound **59**
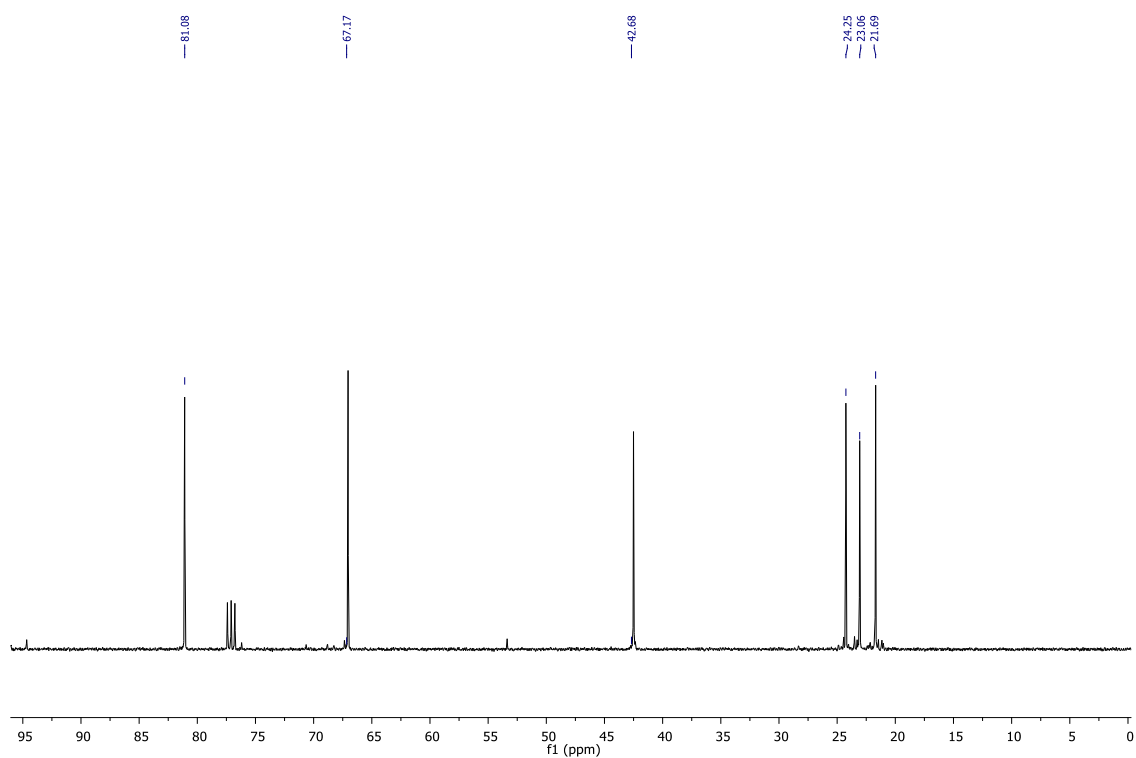
Figure A 6. ^{13}C NMR spectrum of compound **59**
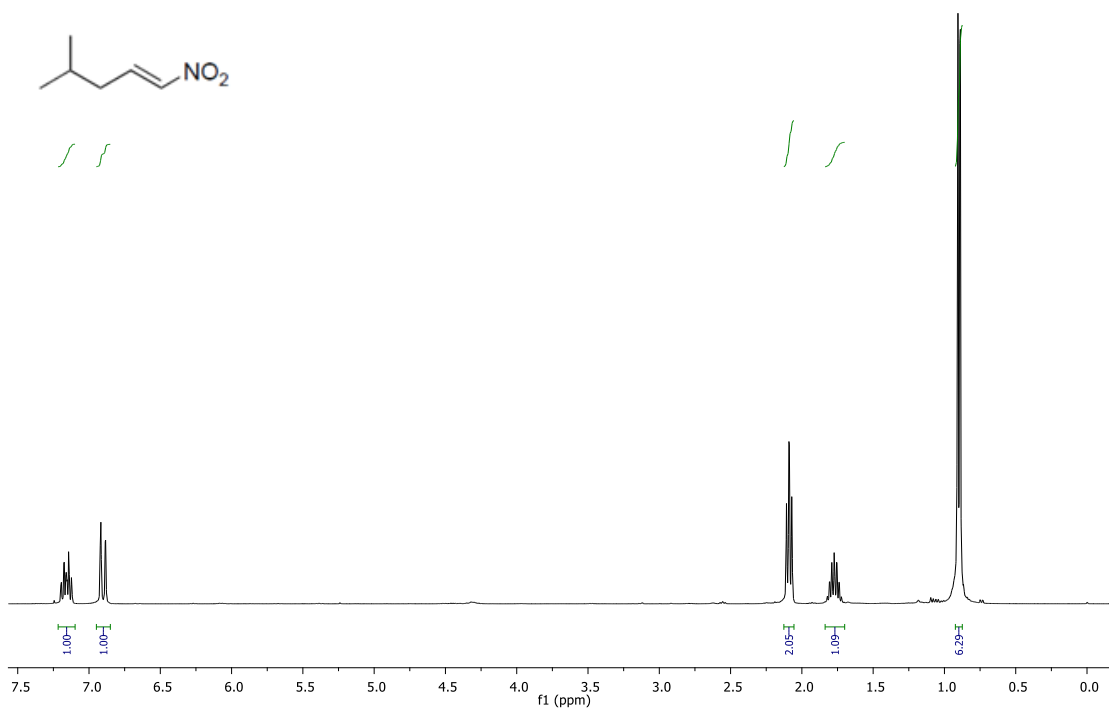
Figure A 7. ^{1}H NMR spectrum of compound **51**
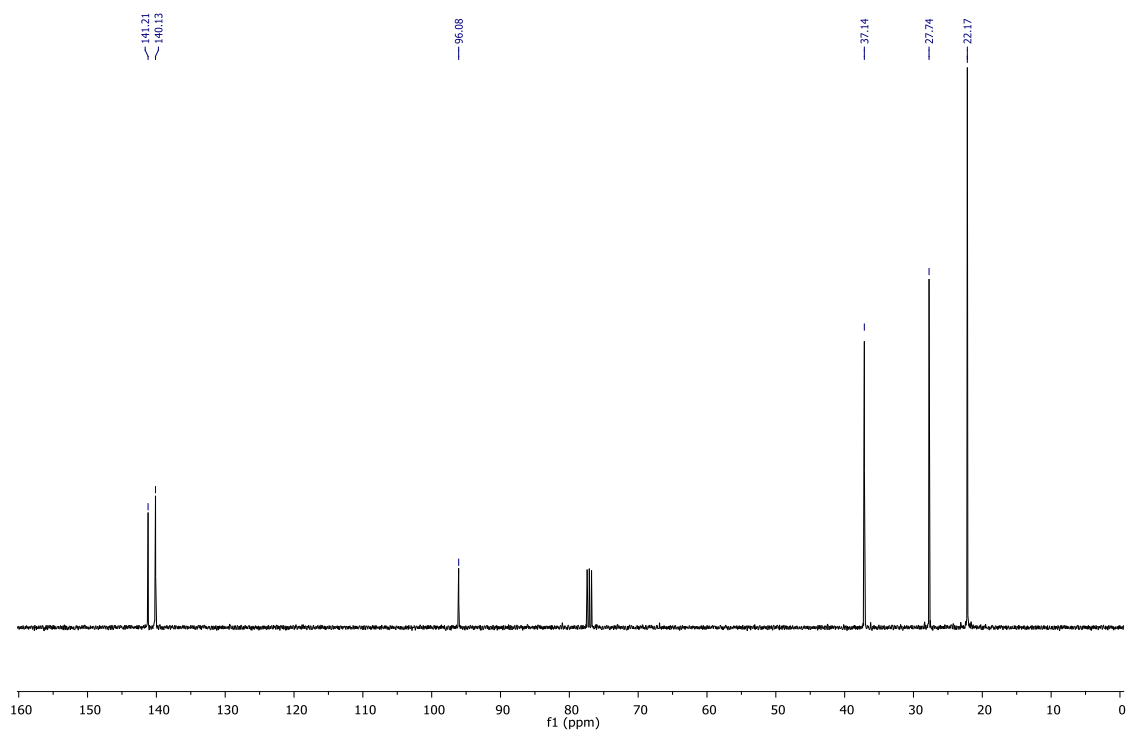
Figure A 8. ^{13}C NMR spectrum of compound **51**
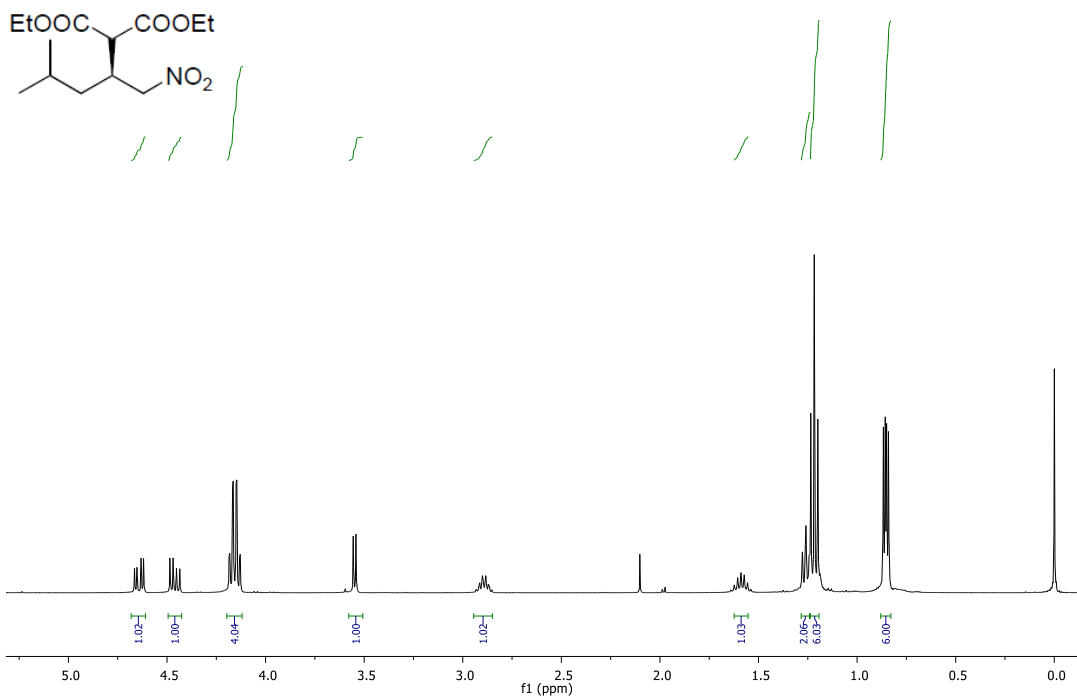
Figure A 9. ^{1}H NMR spectrum of compound **56**
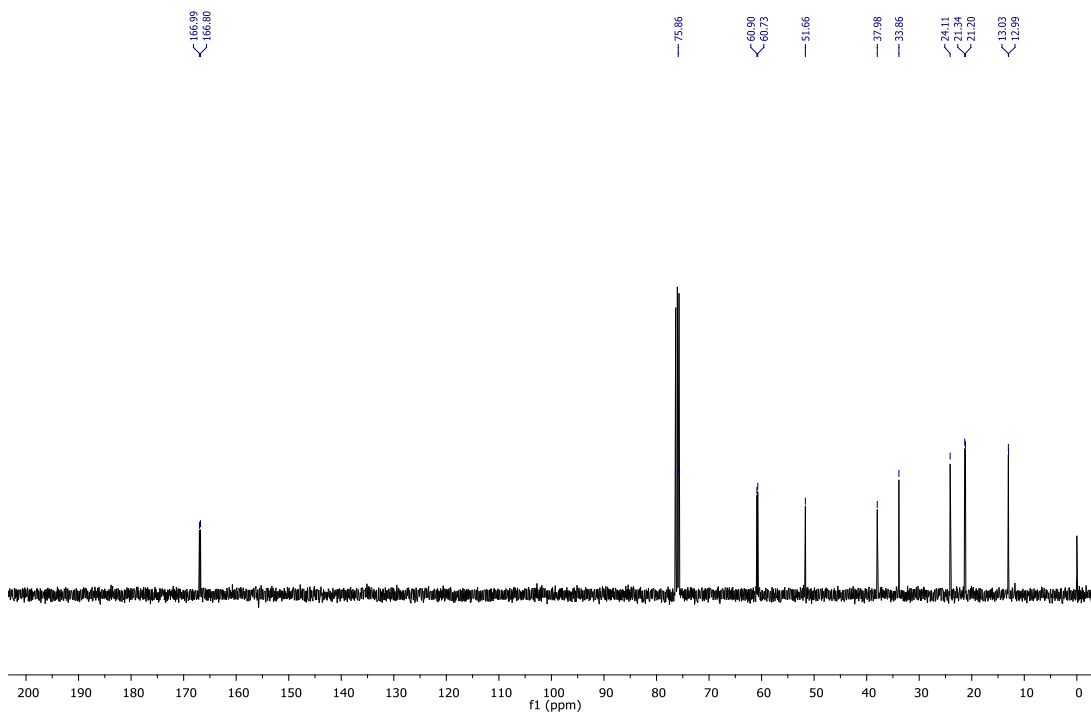
Figure A 10. ^{13}C NMR spectrum of compound **56**
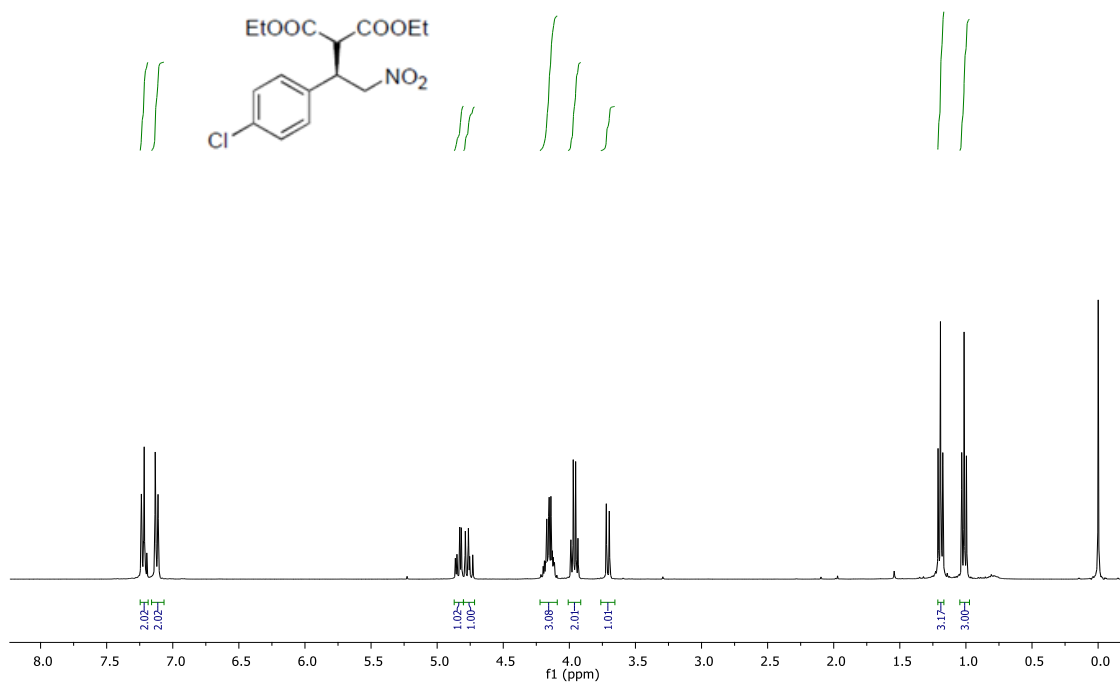
Figure A 11. ¹H NMR spectrum of compound **61**
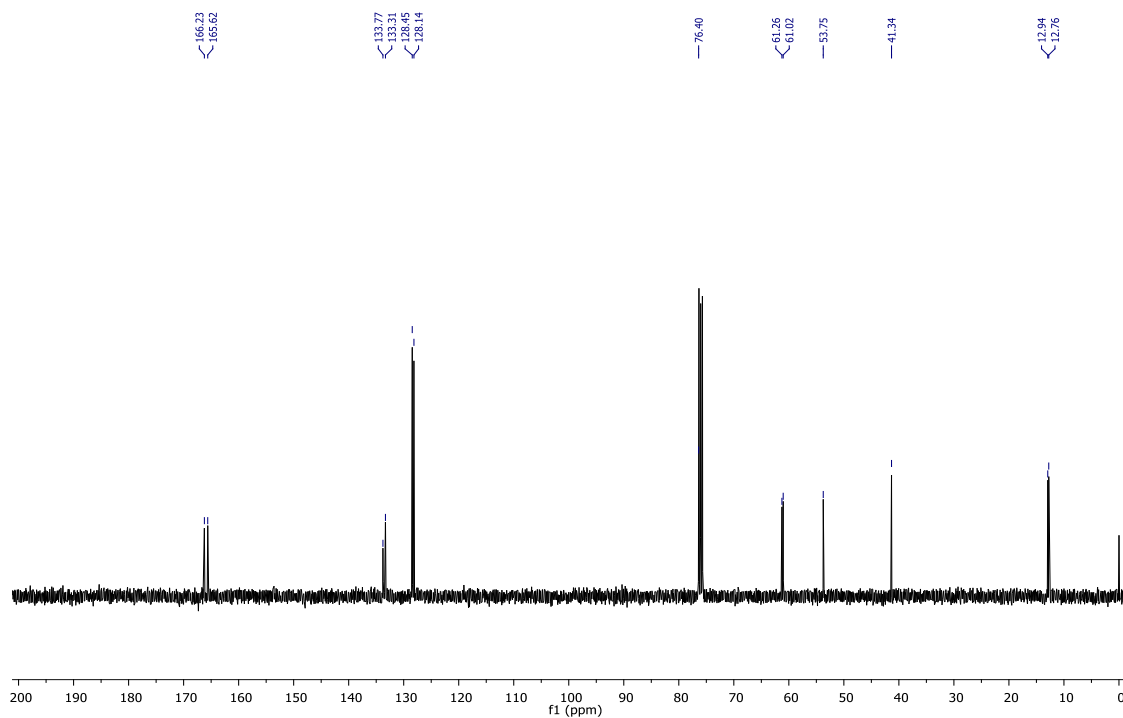
Figure A 12. ¹³C NMR spectrum of compound **61**
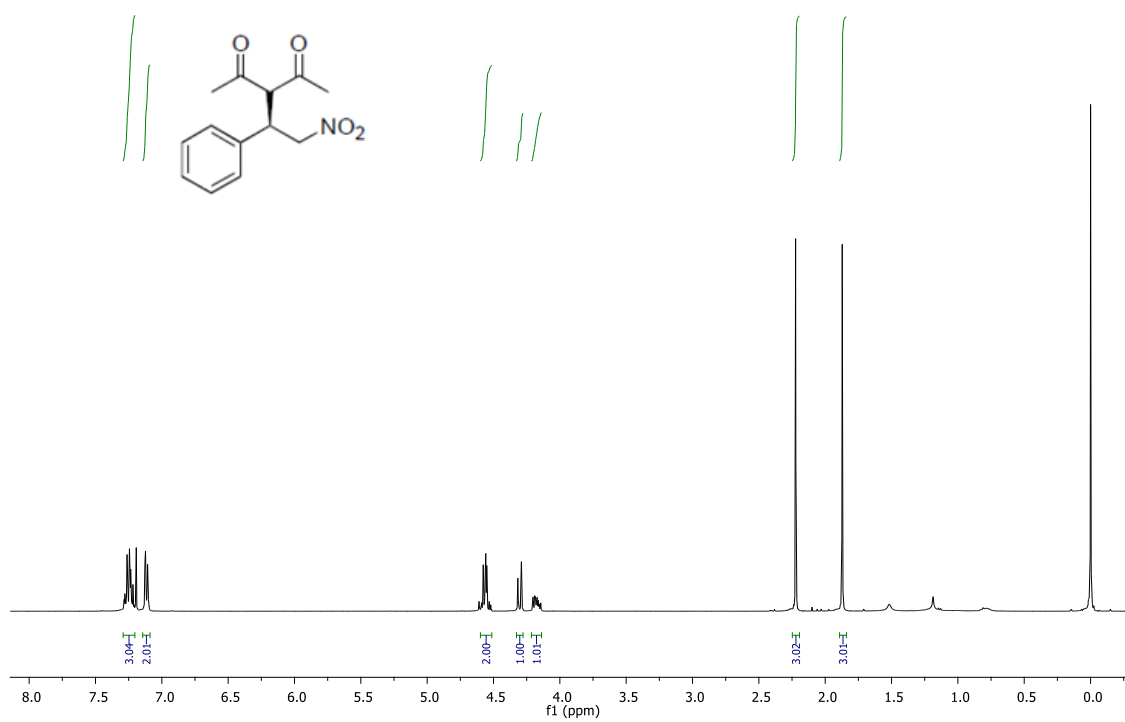
Figure A 13. ^{1}H NMR spectrum of compound **70**
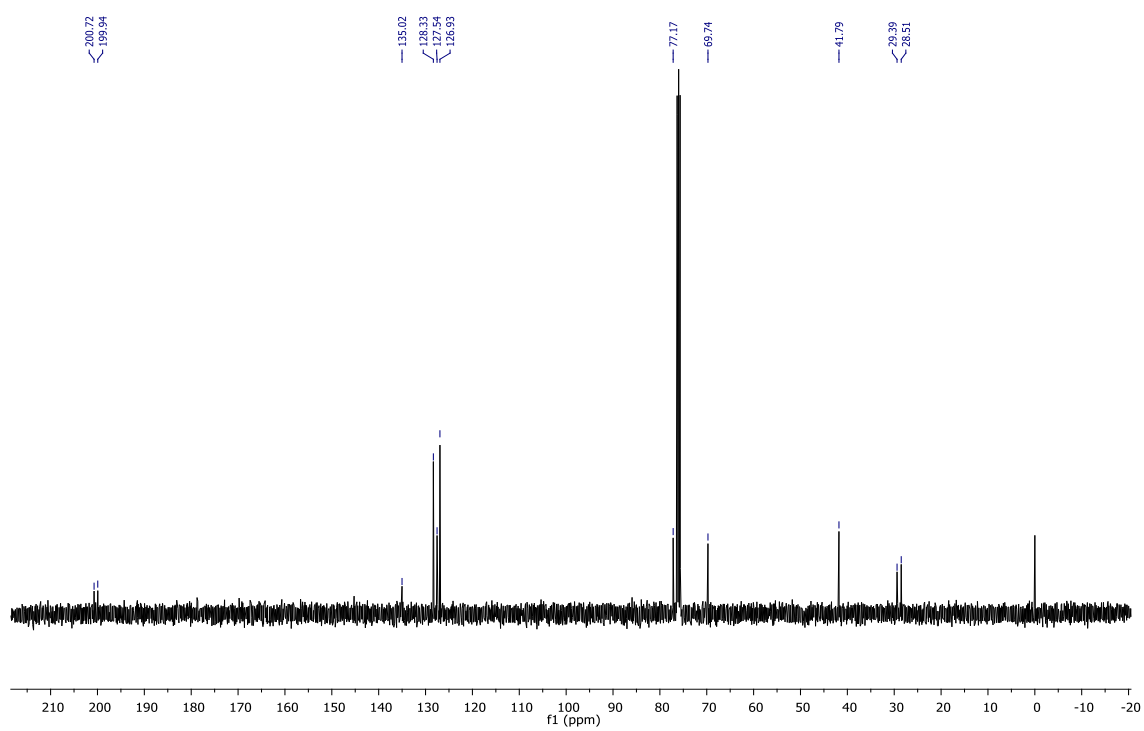
Figure A 14. ^{13}C NMR spectrum of compound **70**
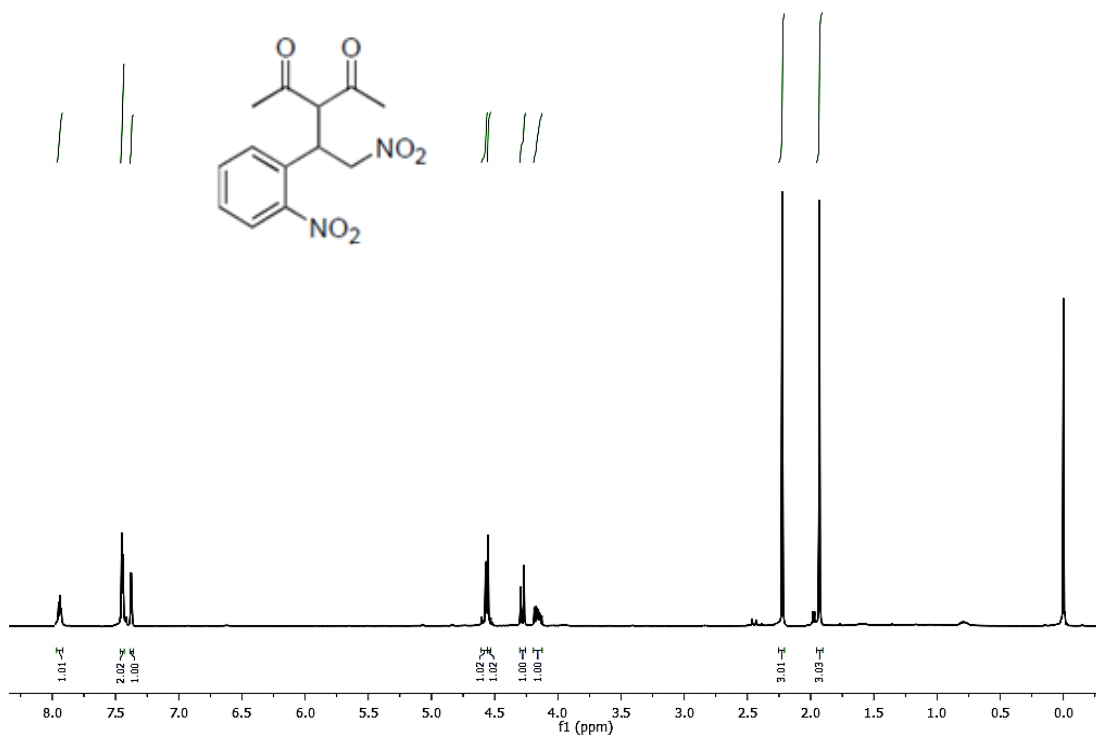
Figure A 15. ^{1}H NMR spectrum of compound **72a**
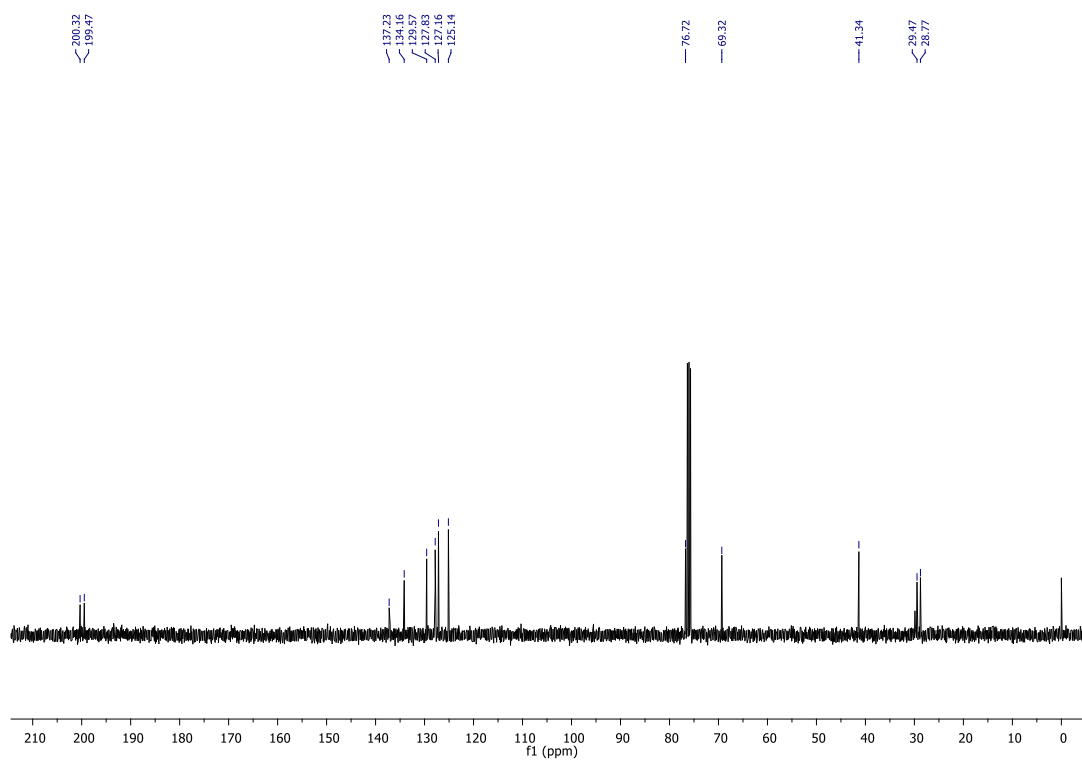
Figure A 16. ^{13}C NMR spectrum of compound **72a**

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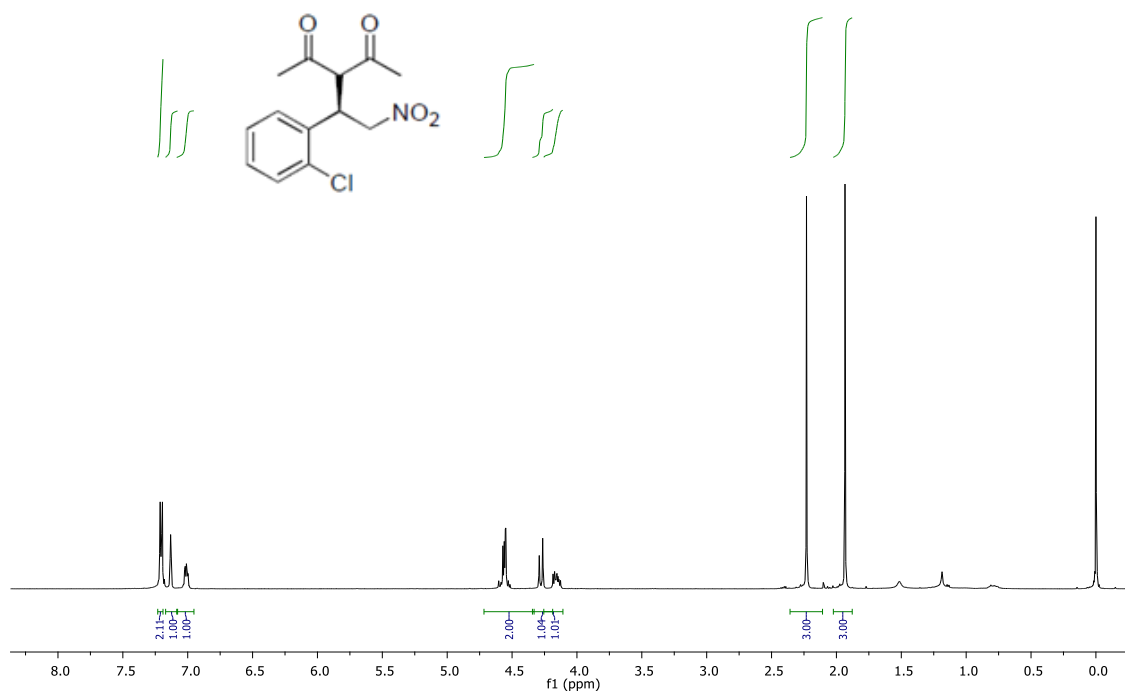
Figure A 17. ^{1}H NMR spectrum of compound **72b**
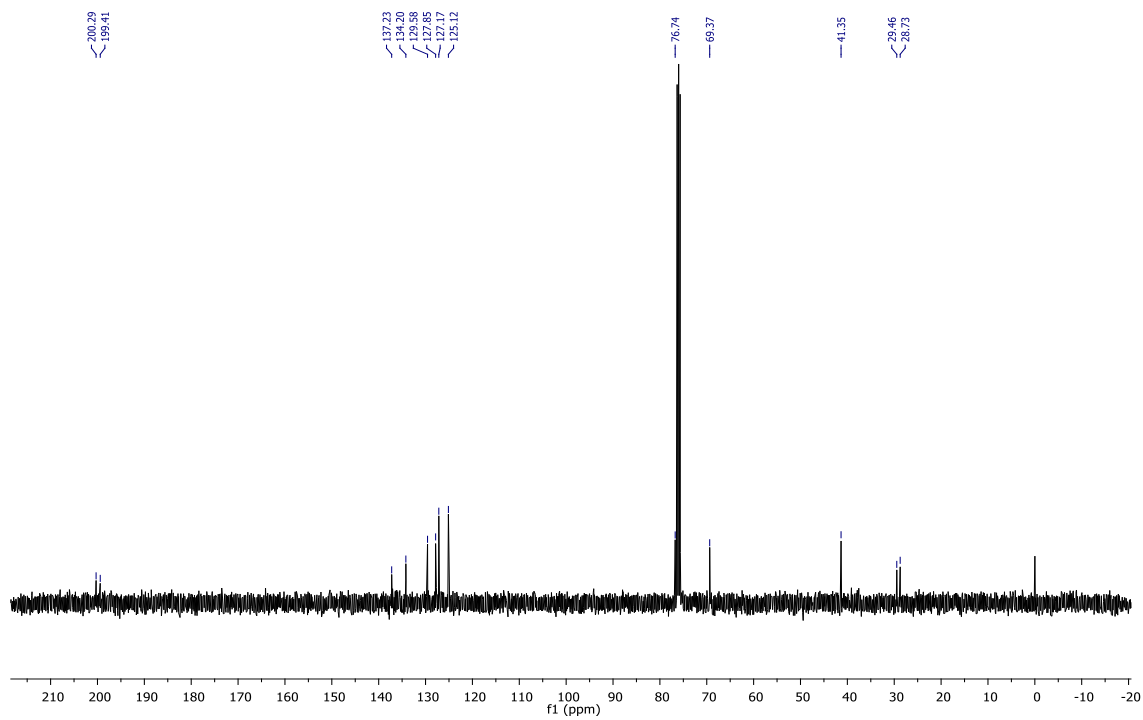
Figure A 18. ^{13}C NMR spectrum of compound **72b**
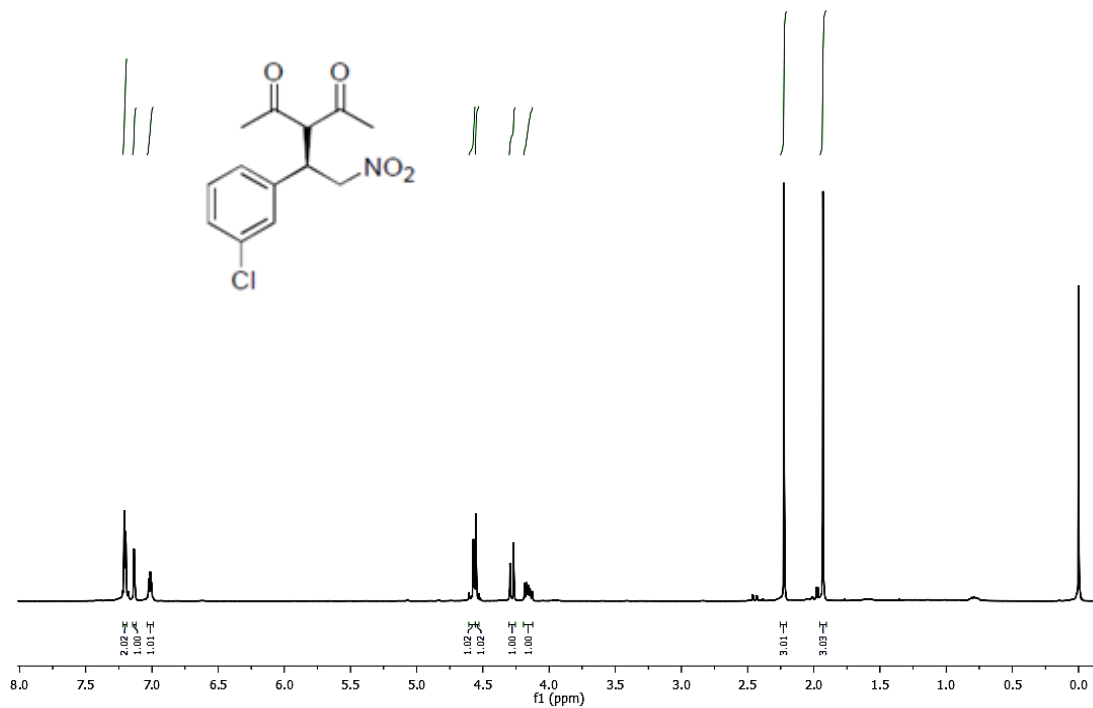
Figure A 19. ^{1}H NMR spectrum of compound **72c**
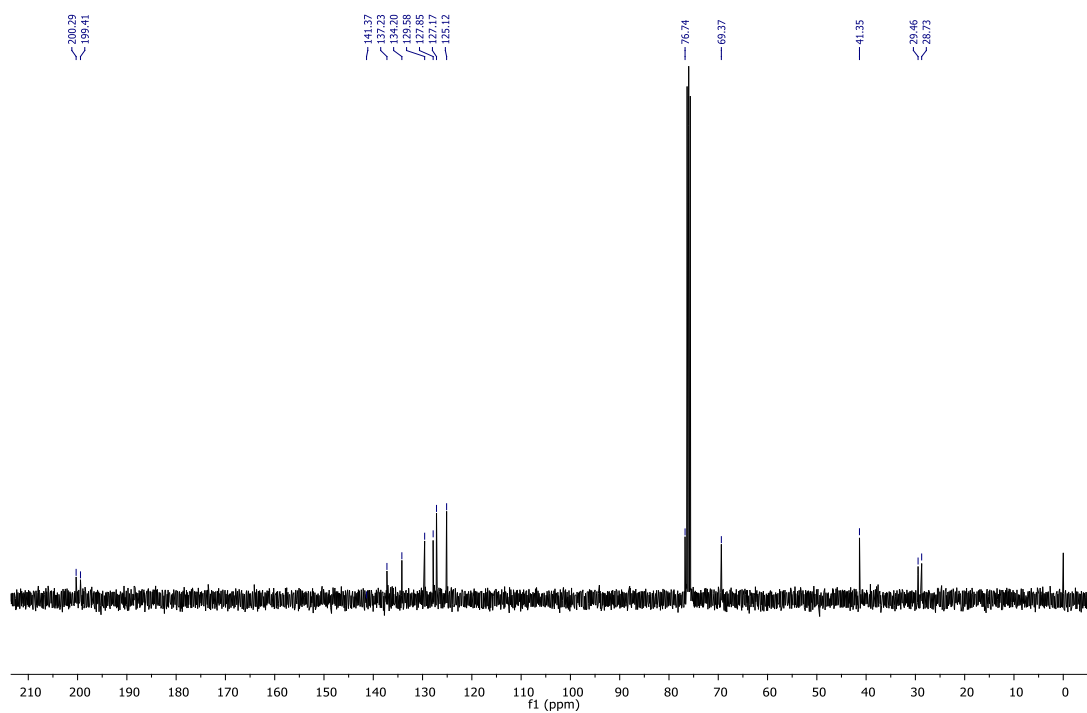
Figure A 20. ^{13}C NMR spectrum of compound **72c**
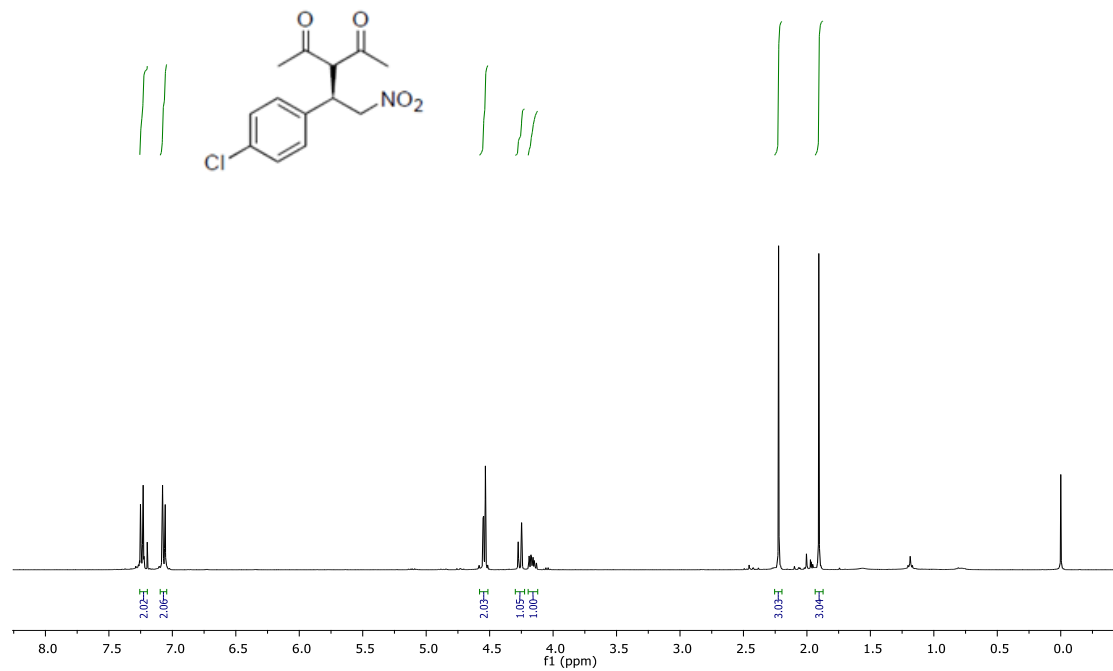
Figure A 21. ^{1}H NMR spectrum of compound **72d**
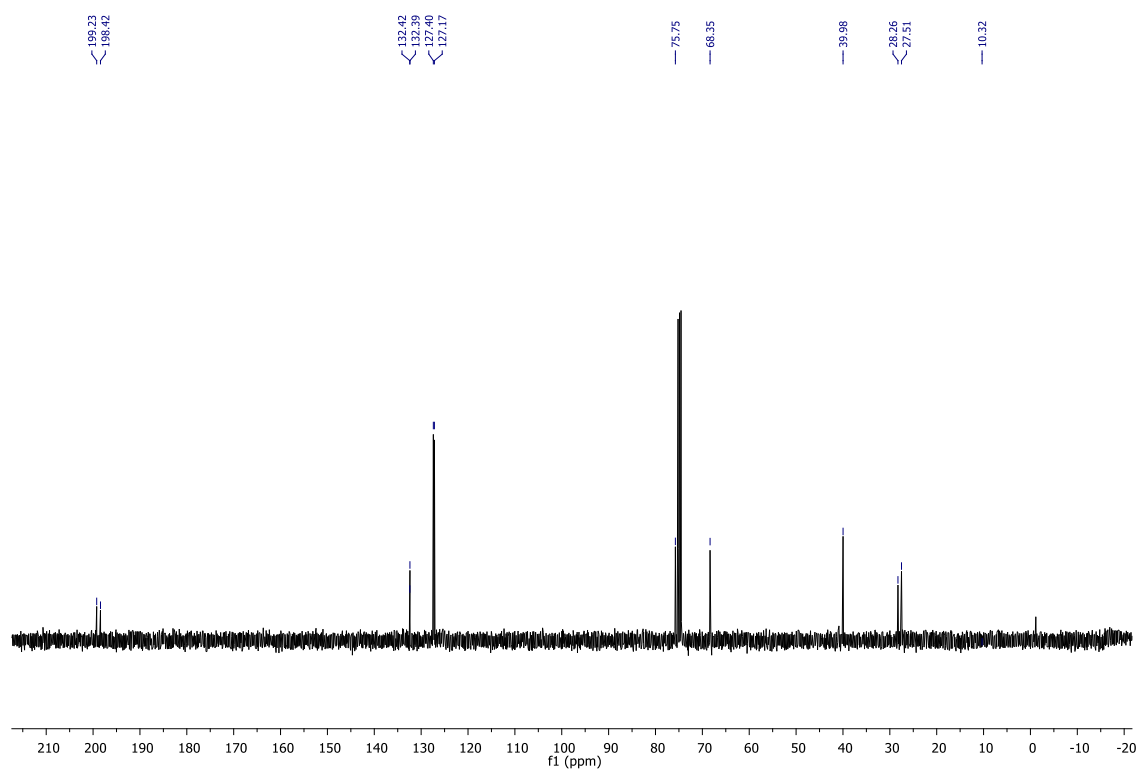
Figure A 22. ^{13}C NMR spectrum of compound **72d**

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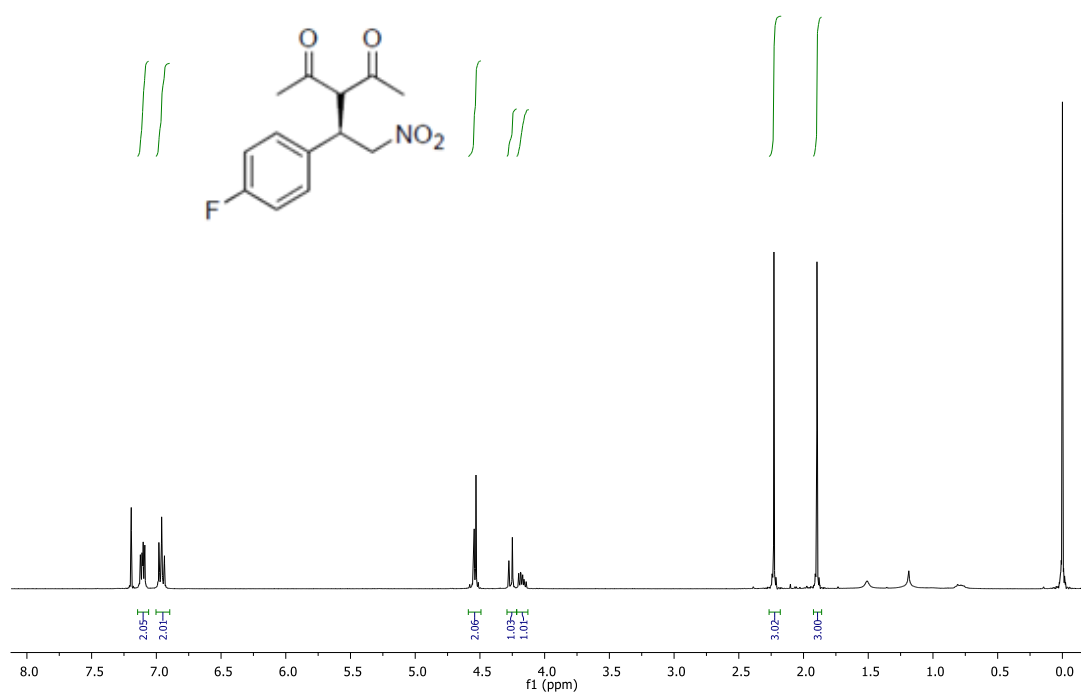
Figure A 23. ^{1}H NMR spectrum of compound **72e**
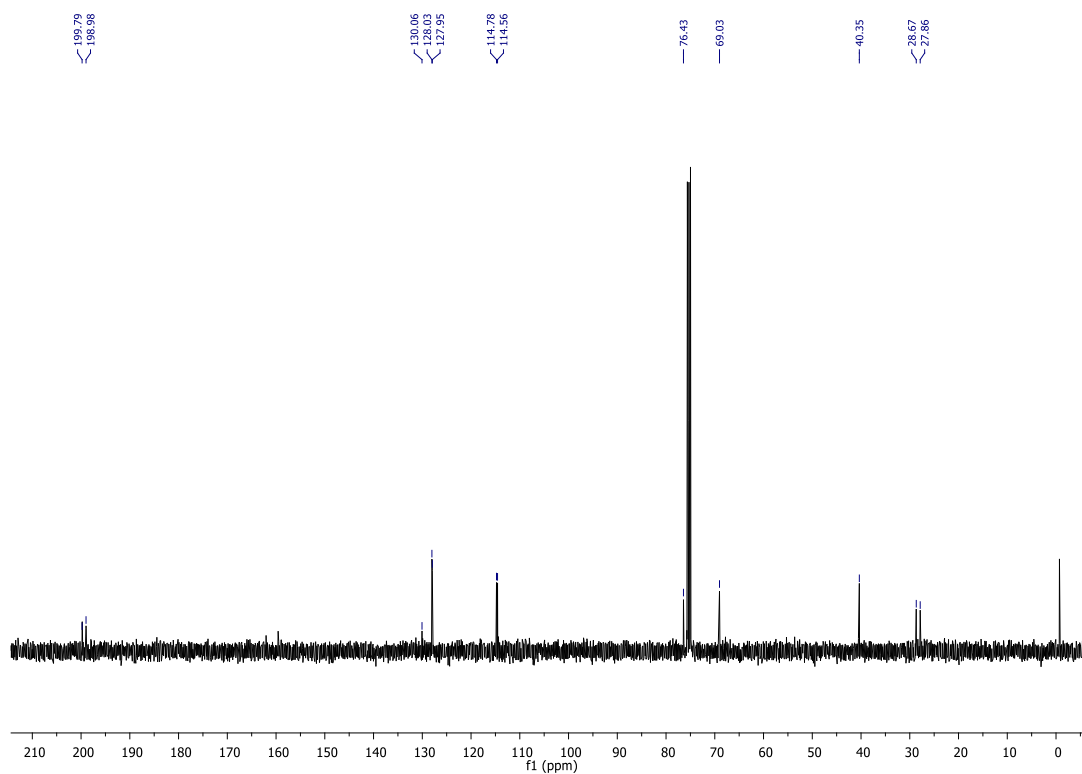
Figure A 24. ^{13}C NMR spectrum of compound **72e**

Figure A 25. ^{1}H NMR spectrum of compound **72f**

Figure A 26. ^{13}C NMR spectrum of compound **72f**

Figure A 27. ^{1}H NMR spectrum of compound **72g**

Figure A 28. ^{1}H NMR spectrum of compound **72g**

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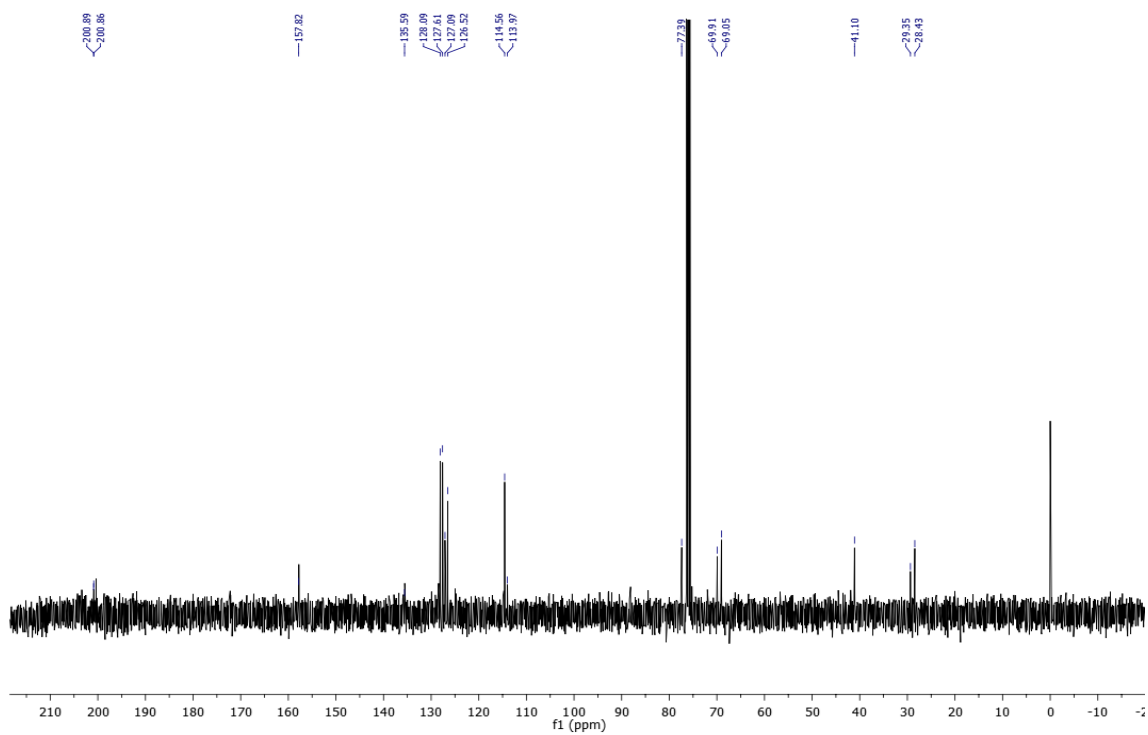
B. HPLC DATA
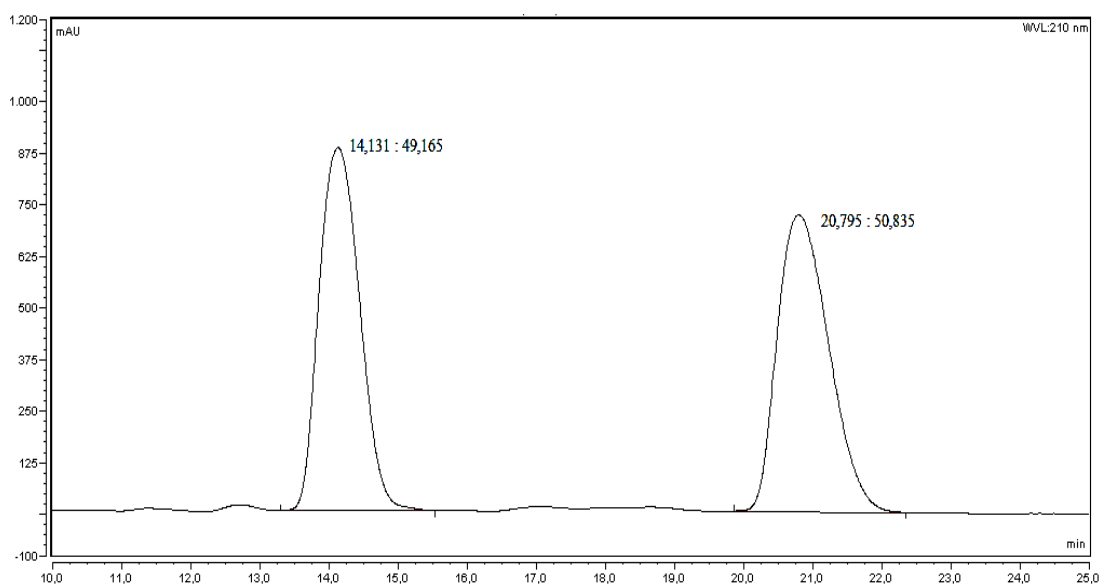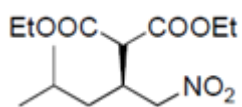
Figure B 1. HPLC chromatogram of *rac-56*
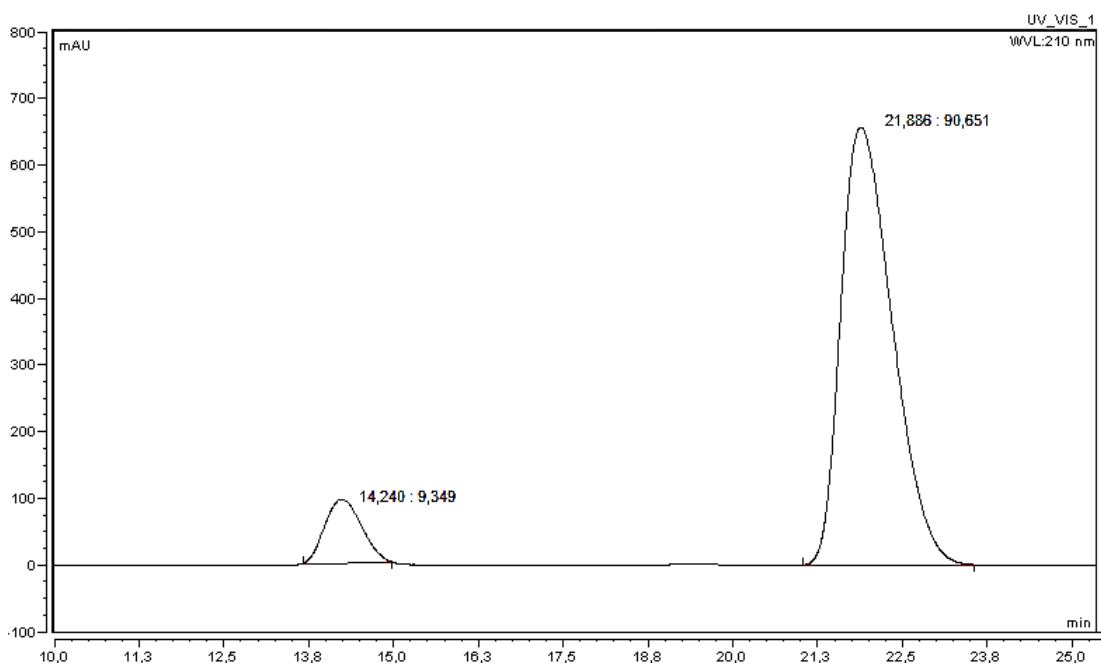
Figure B 2. HPLC chromatogram of **ent-56**

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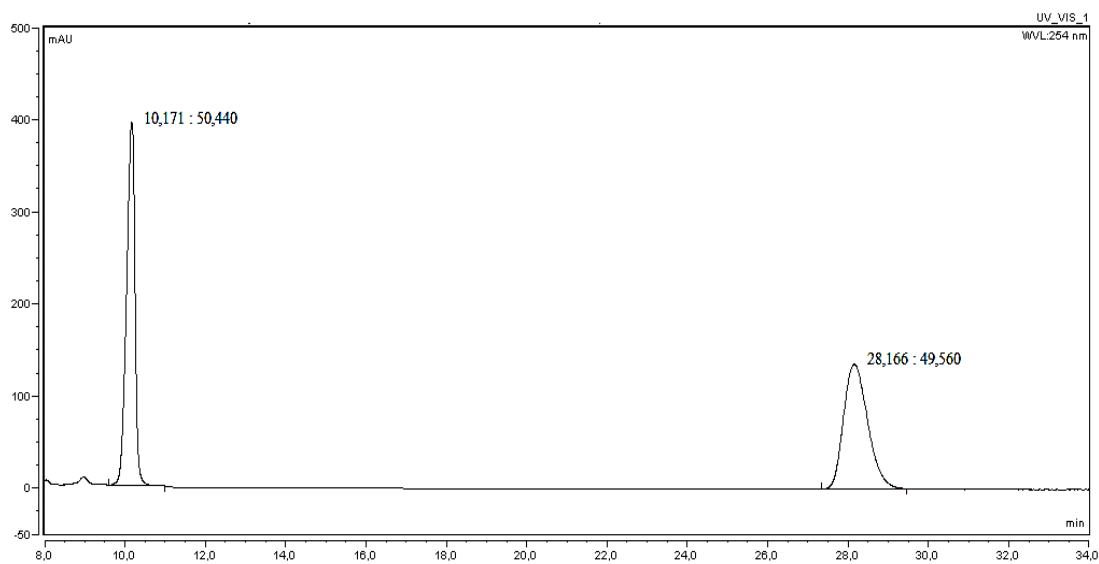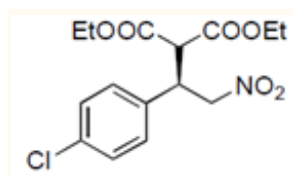
Figure B 3. HPLC chromatogram of *rac*-**61**
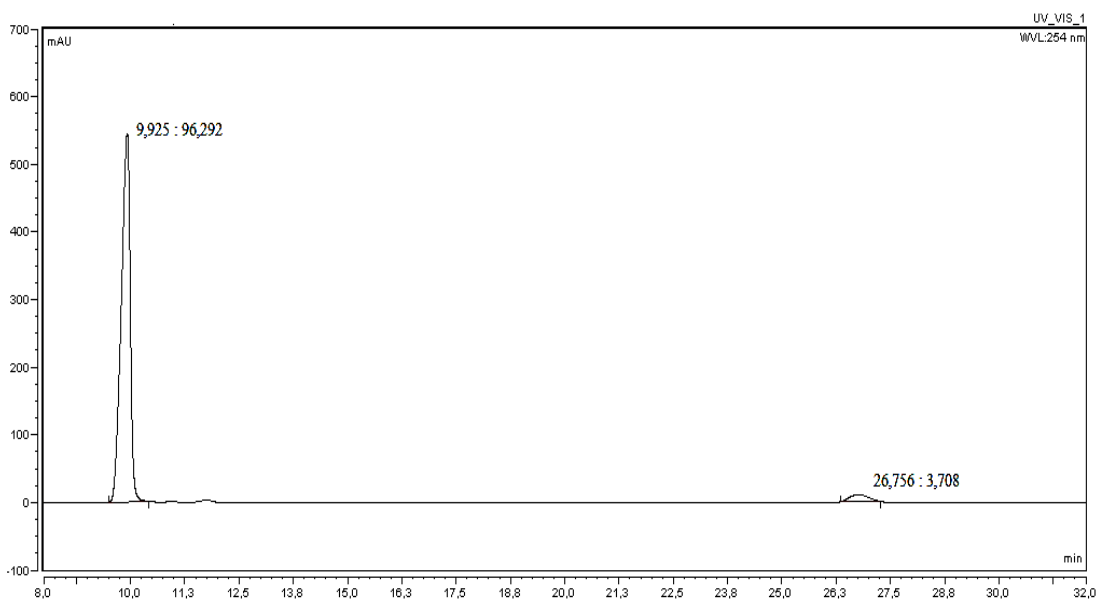
Figure B 4. HPLC chromatogram of *ent*-**61**
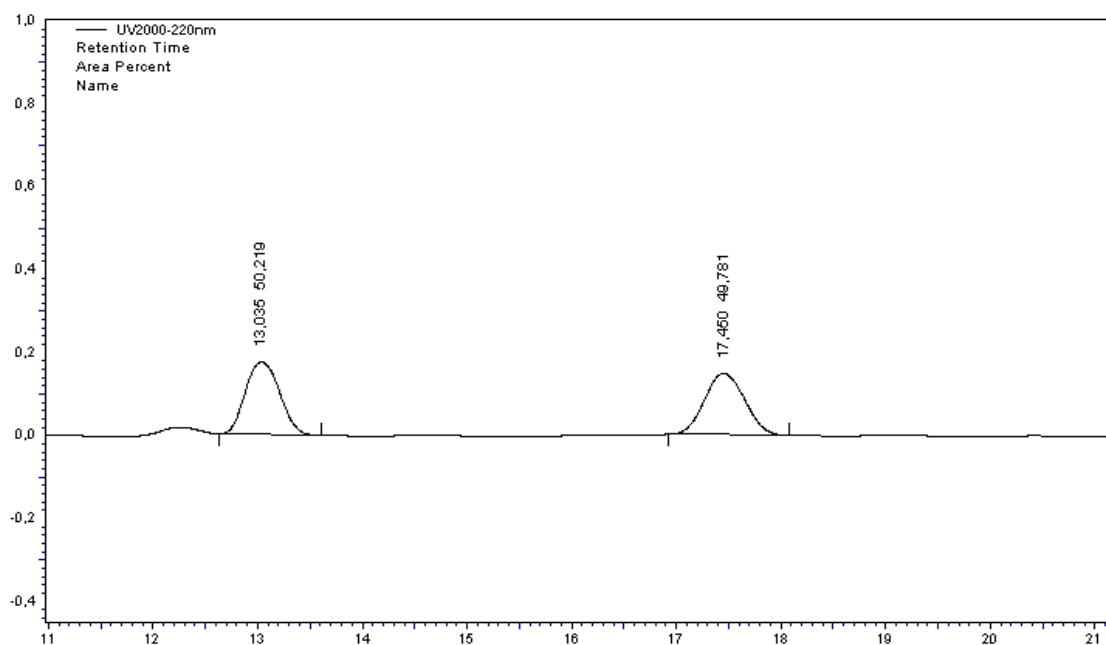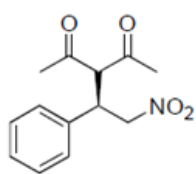
Figure B 5. HPLC chromatogram of *rac*-**70**
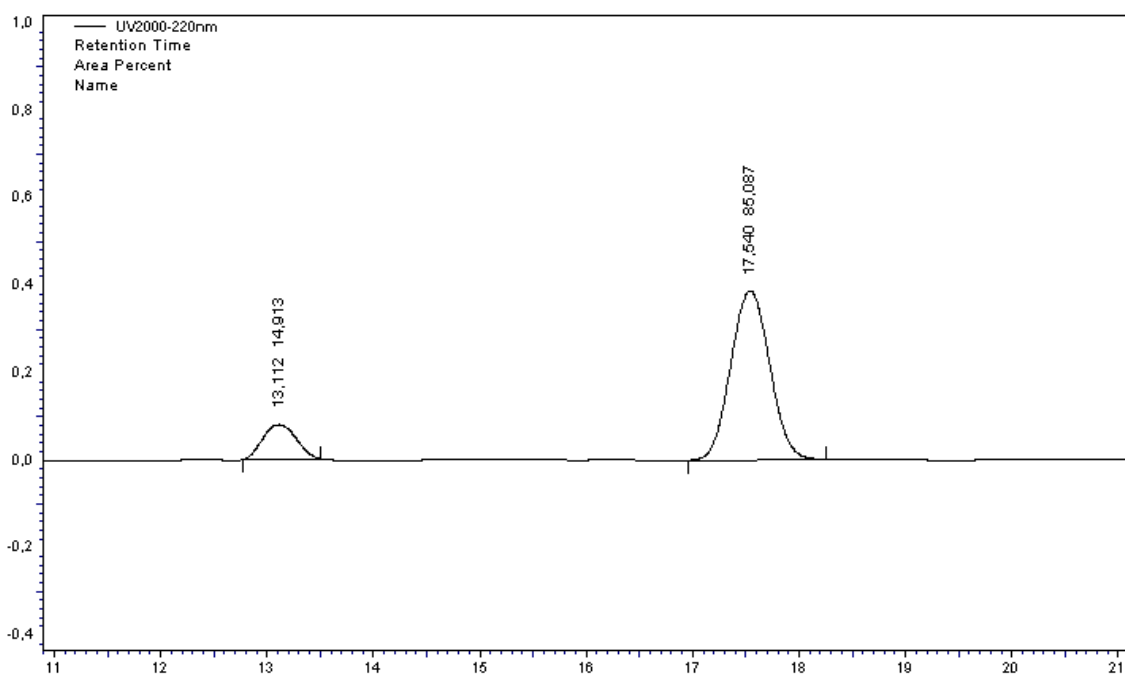
Figure B 6. HPLC chromatogram of *ent*-**70**
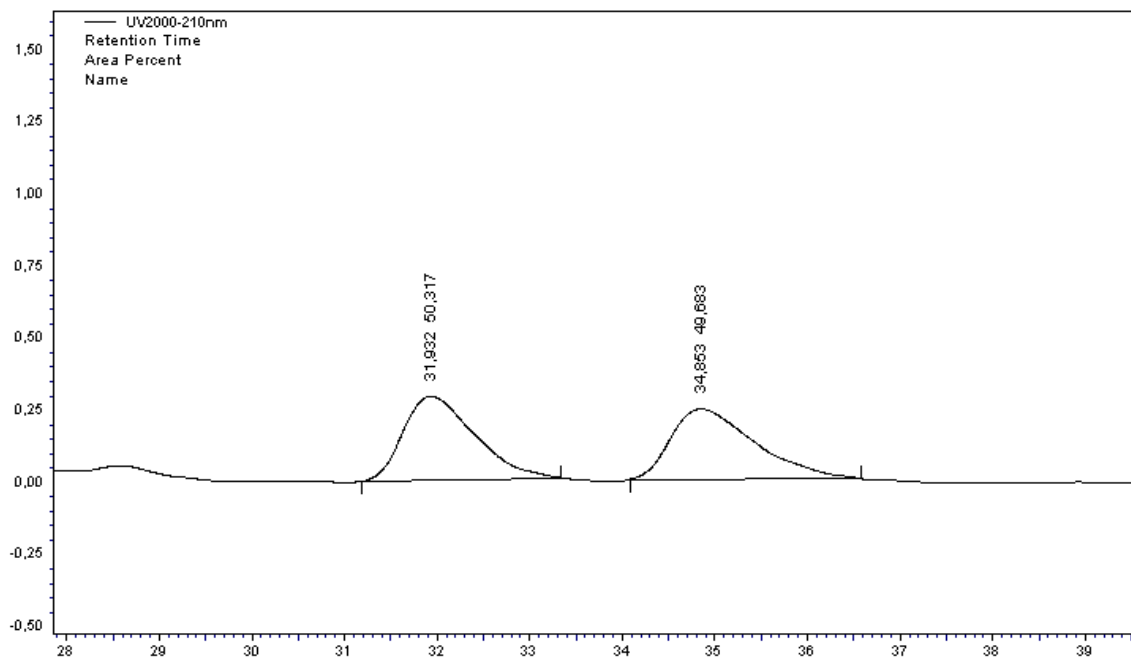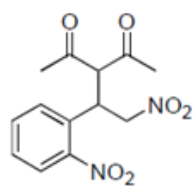
Figure B 7. HPLC chromatogram of *rac*-**72a**
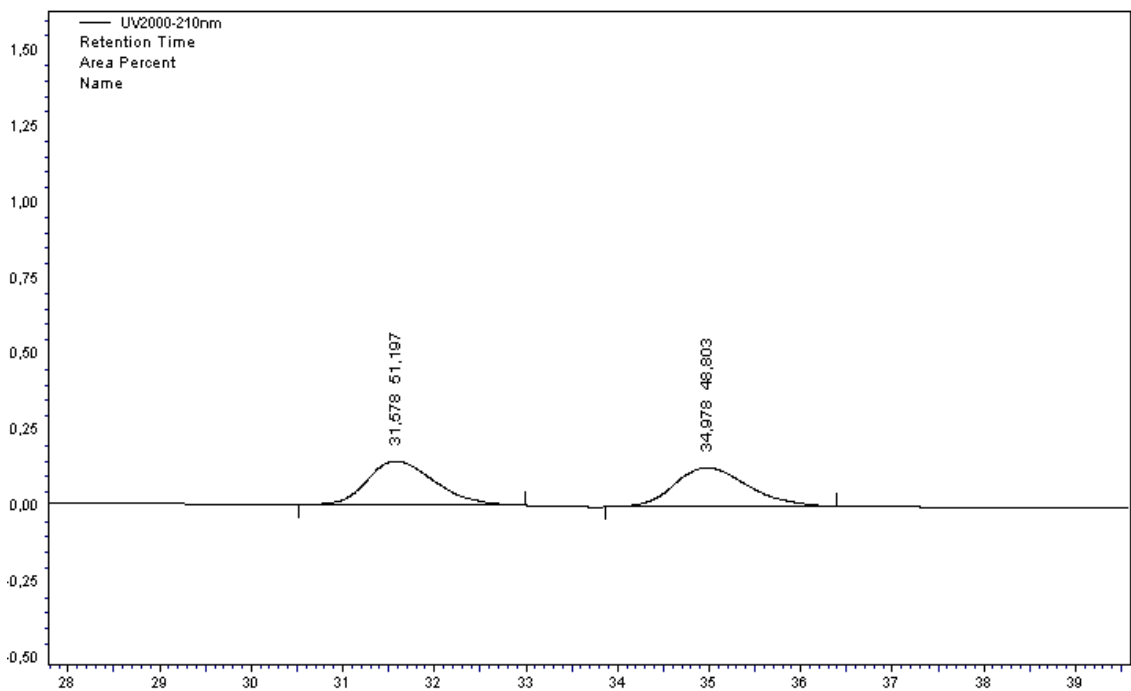
Figure B 8. HPLC chromatogram of *ent*-**72a**

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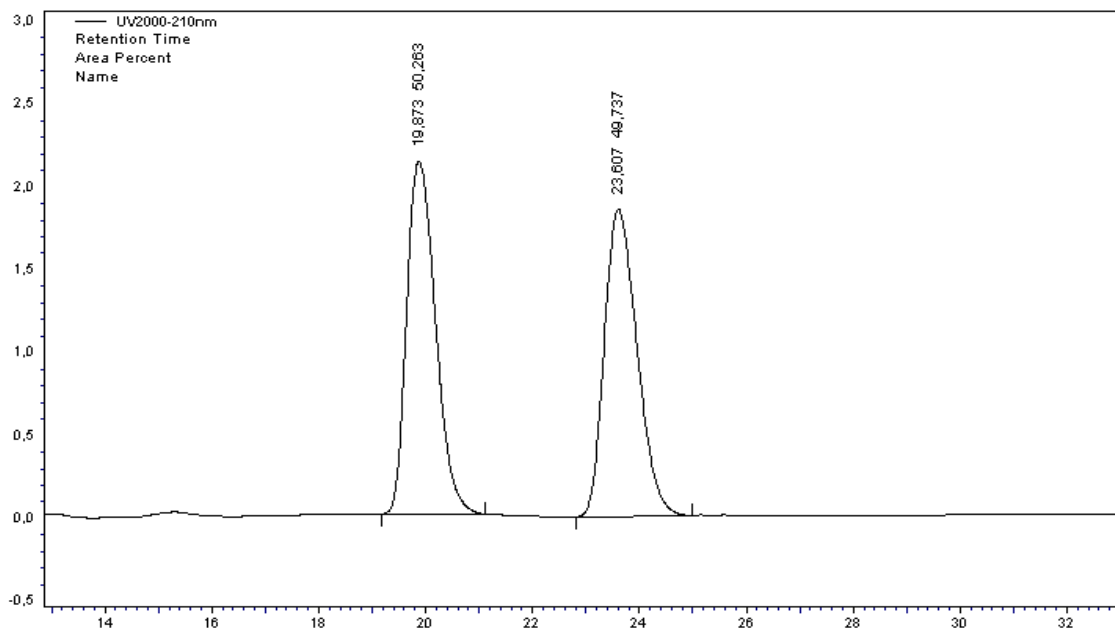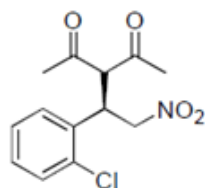
Figure B 9. HPLC chromatogram of *rac*-**72b**
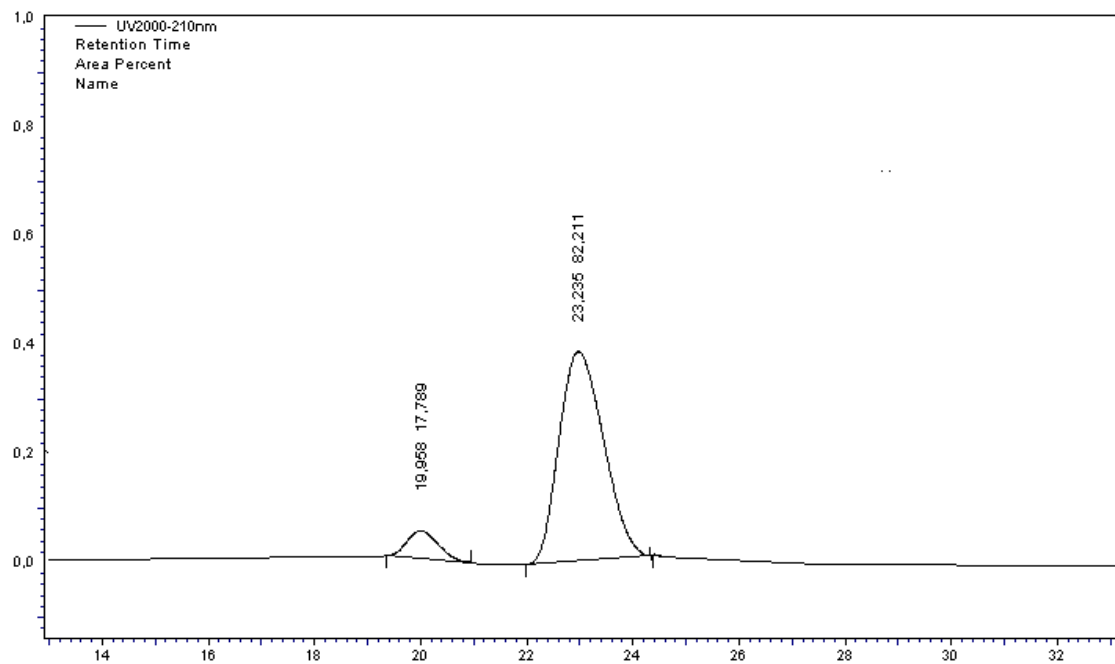
Figure B 10. HPLC chromatogram of *ent*-**72b**
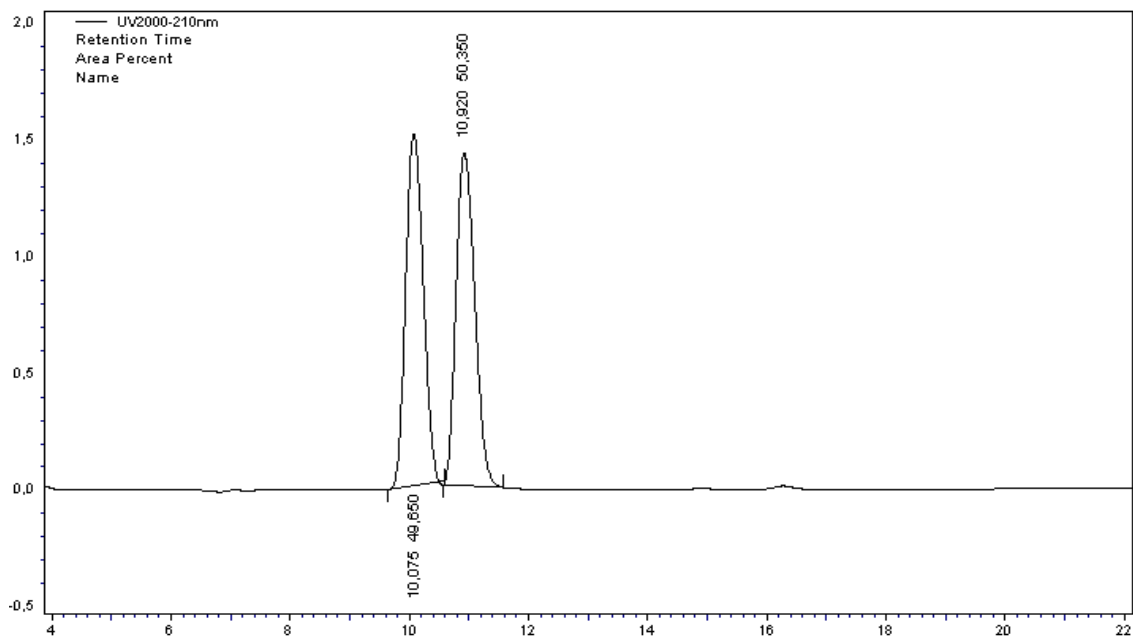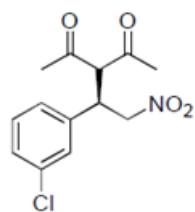
Figure B 11. HPLC chromatogram of *rac*-**72c**
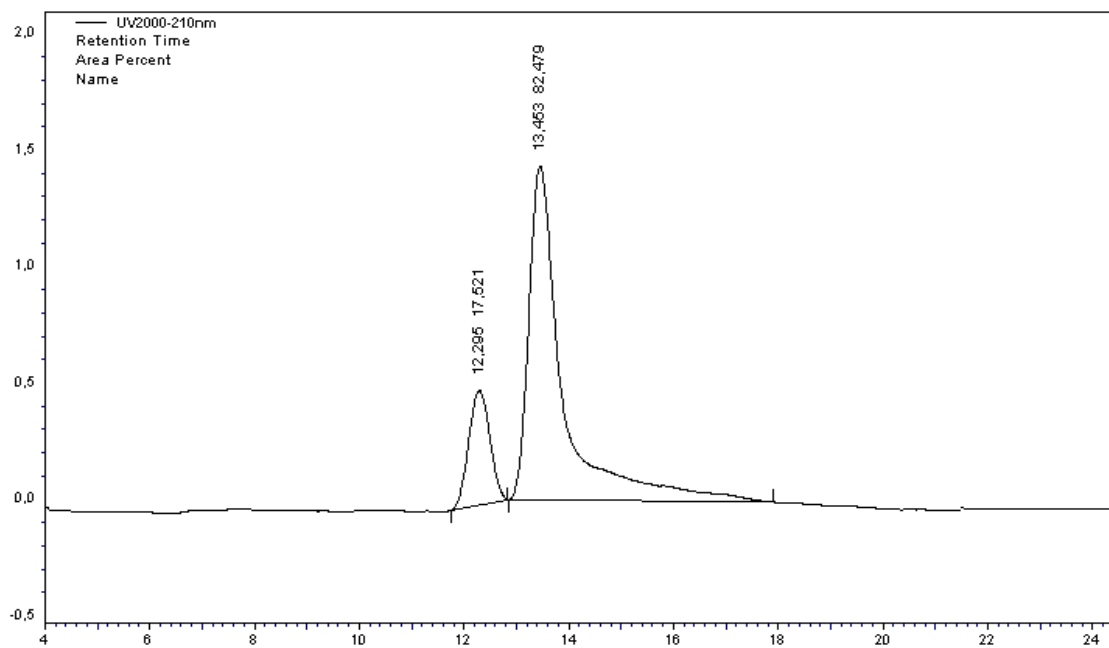
Figure B 12. HPLC chromatogram of *ent*-**72c**

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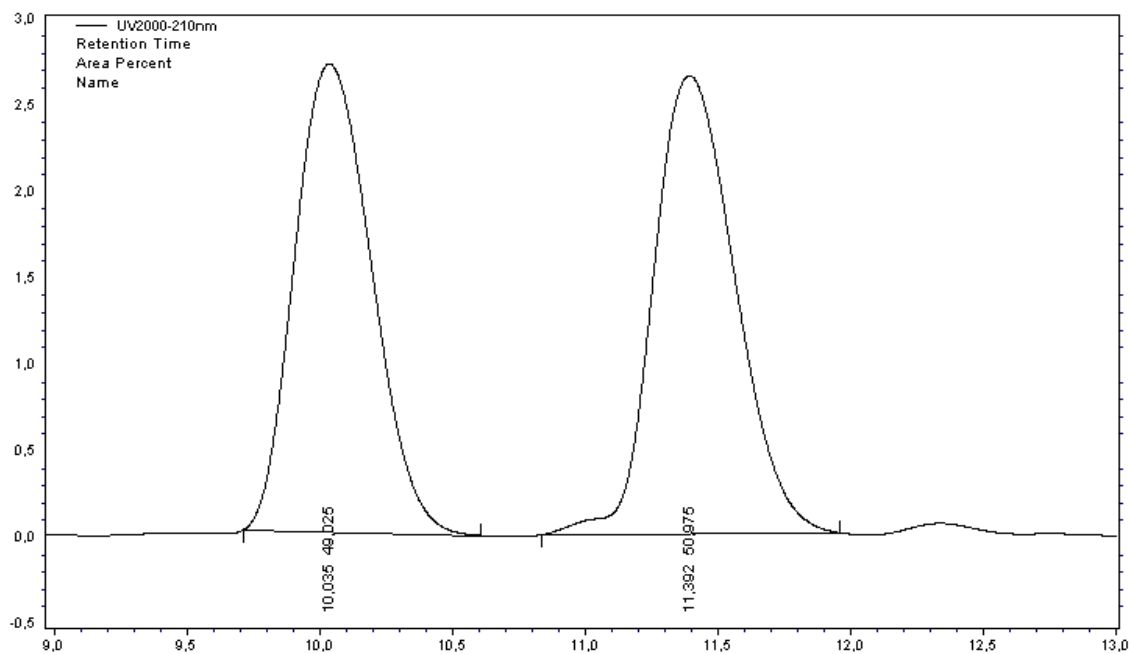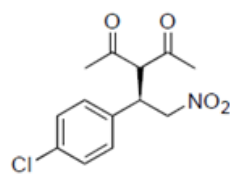
Figure B 13. HPLC chromatogram of *rac*-**72d**
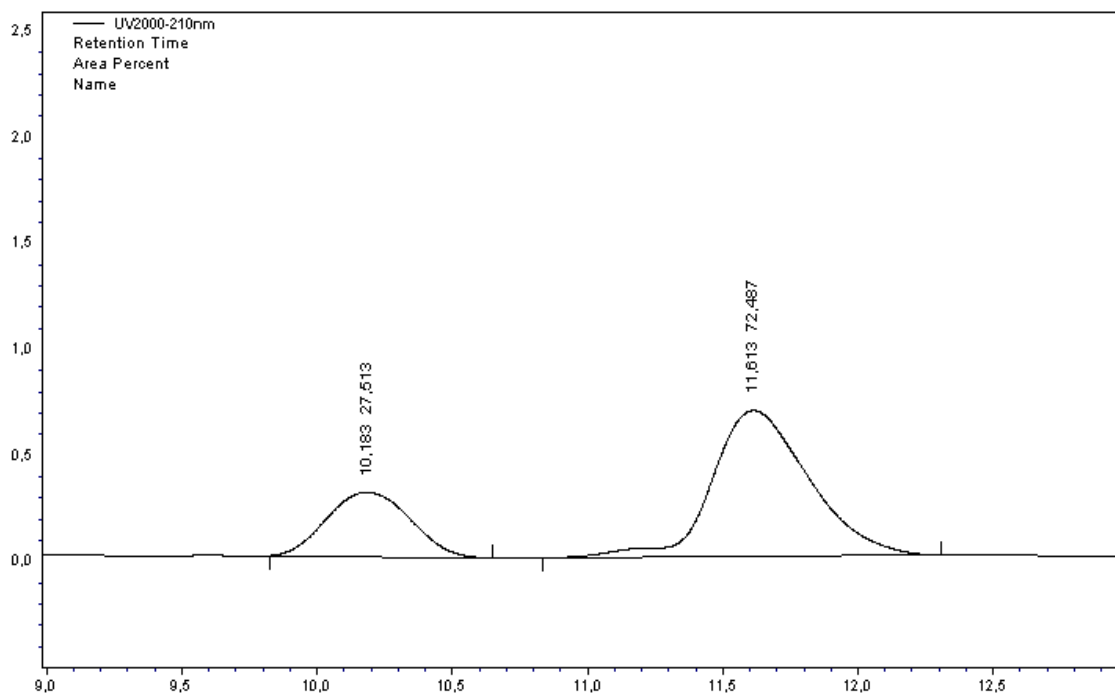
Figure B 14. HPLC chromatogram of *ent*-**72d**
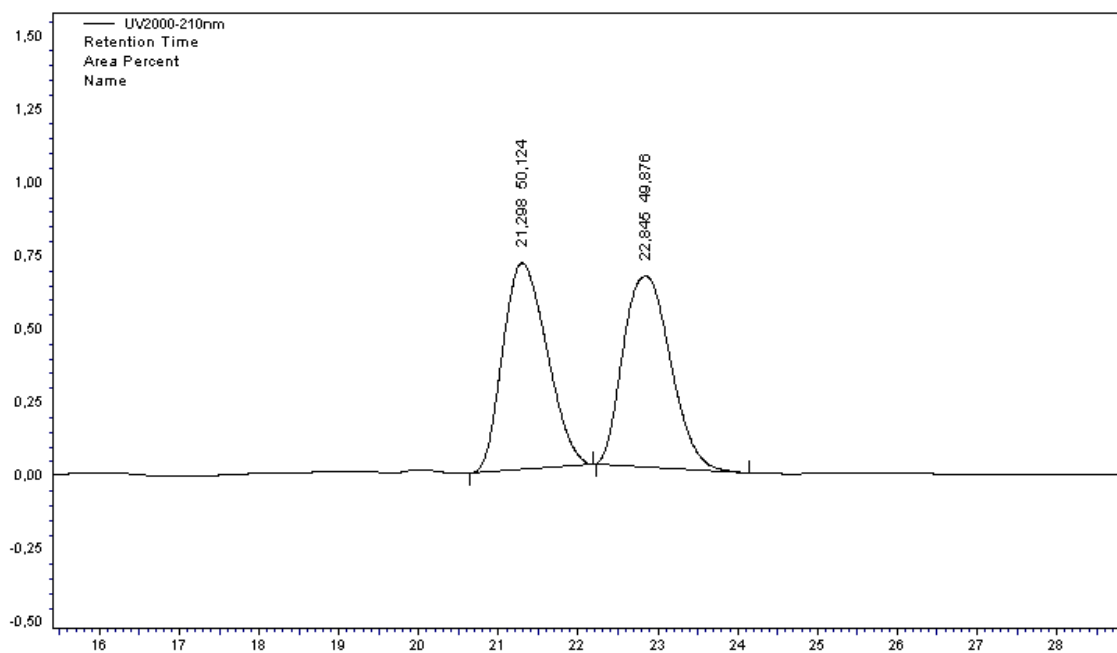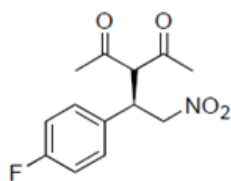
Figure B 15. HPLC chromatogram of *rac*-**72e**
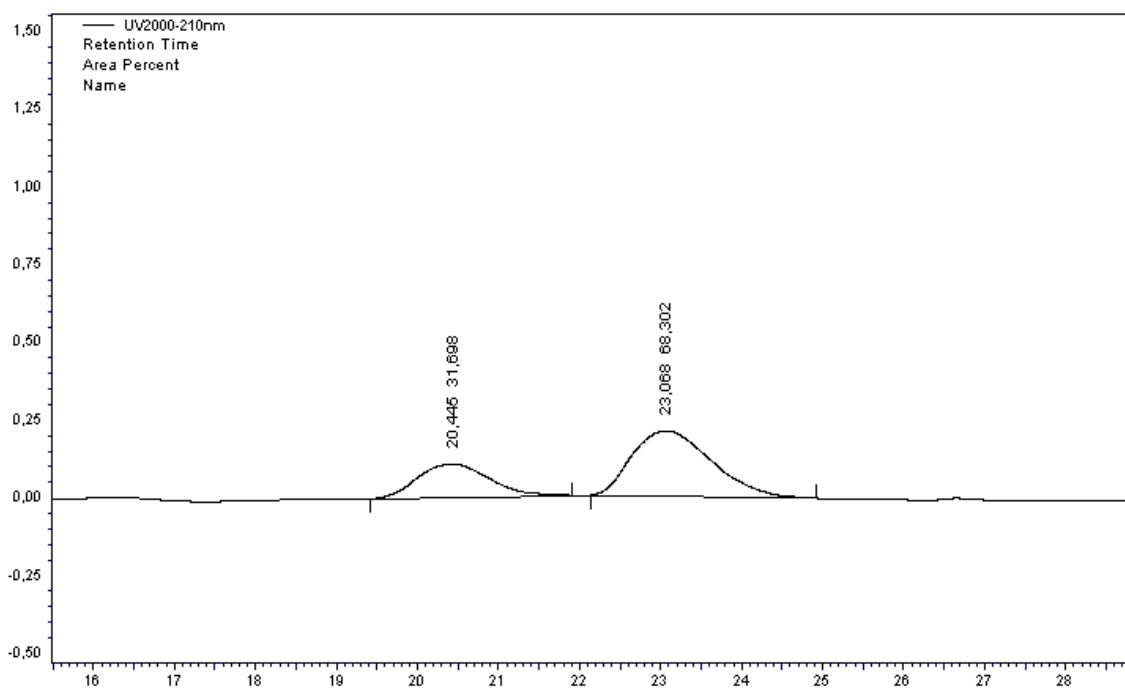
Figure B 16. HPLC chromatogram of *ent*-**72e**
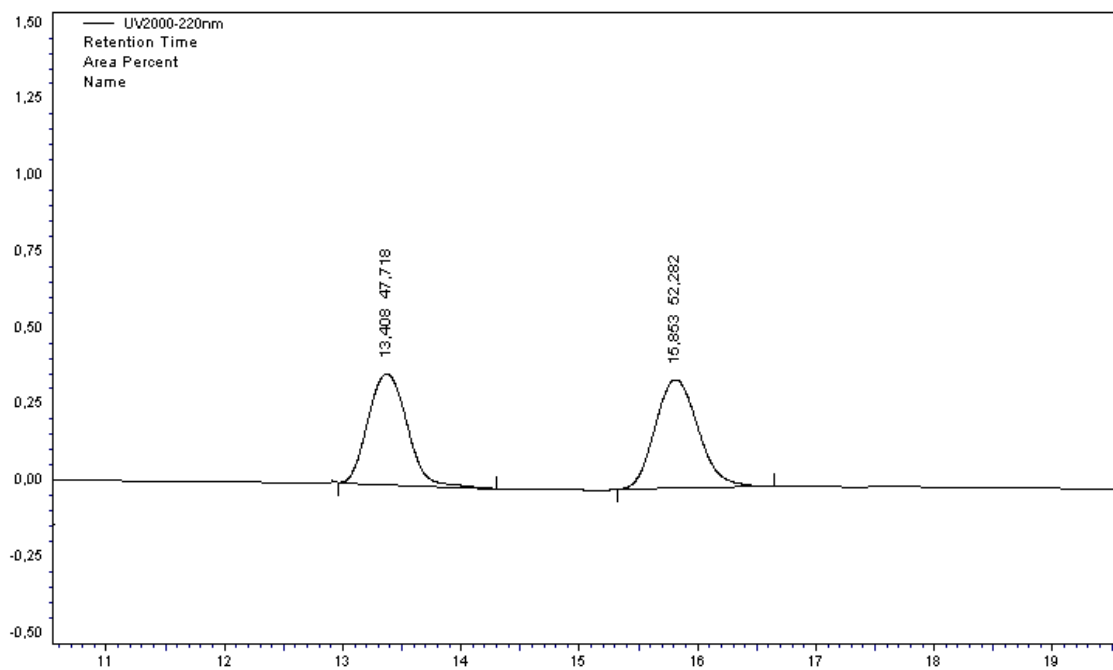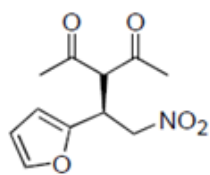
Figure B 17. HPLC chromatogram of *rac*-**72f**
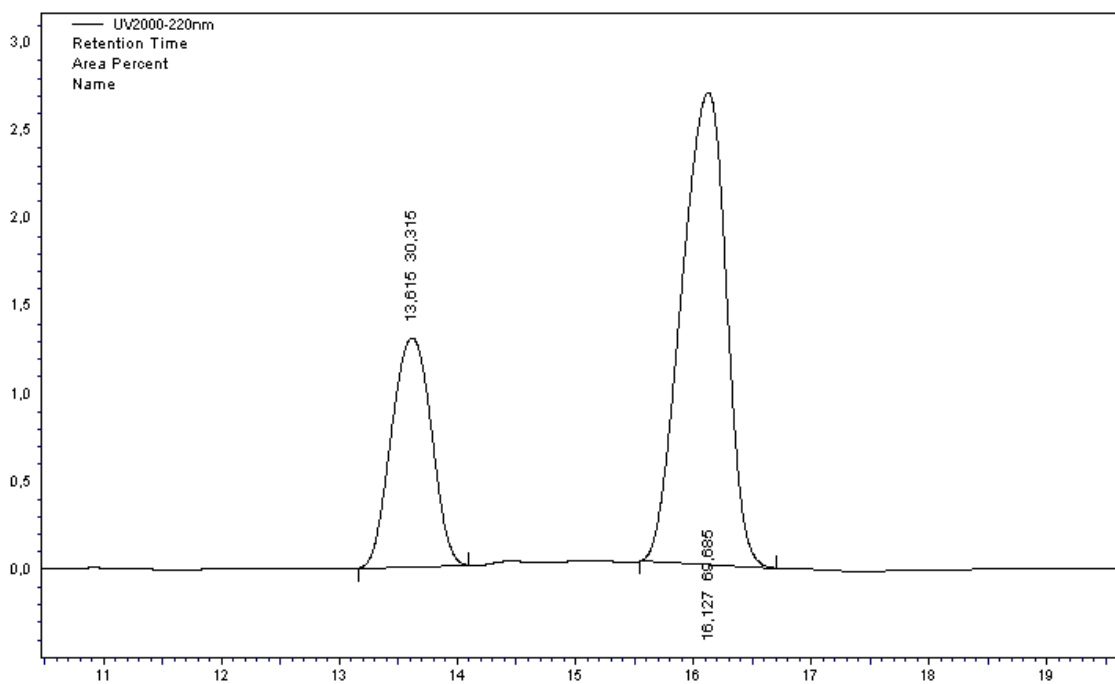
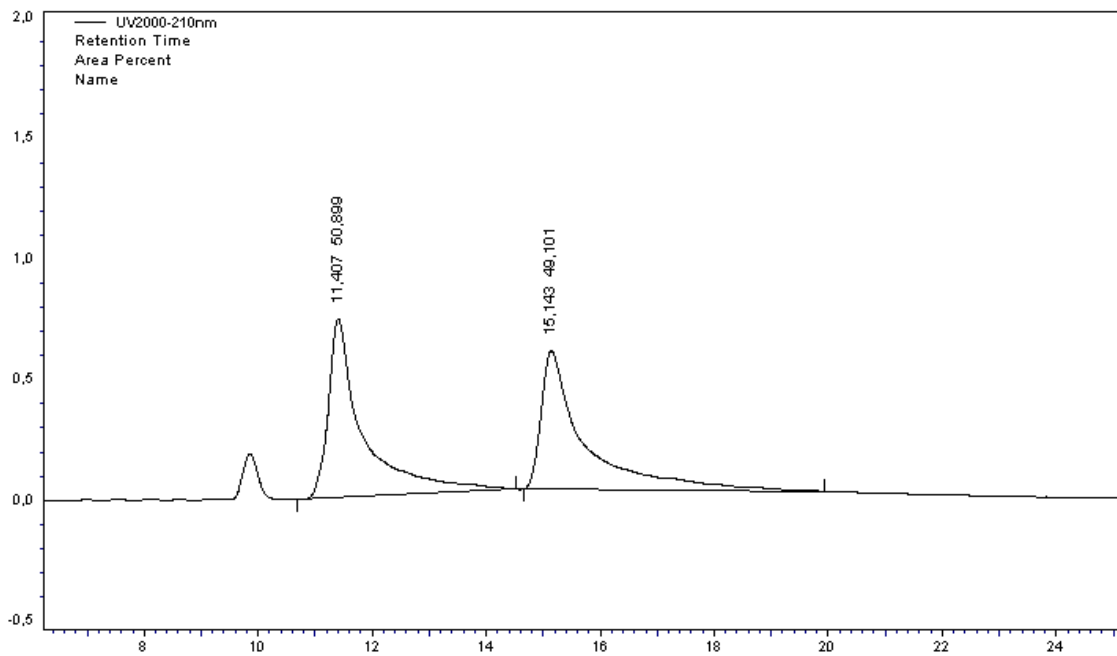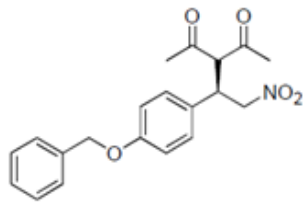**Figure B 18.** HPLC chromatogram of *ent*-**72f**
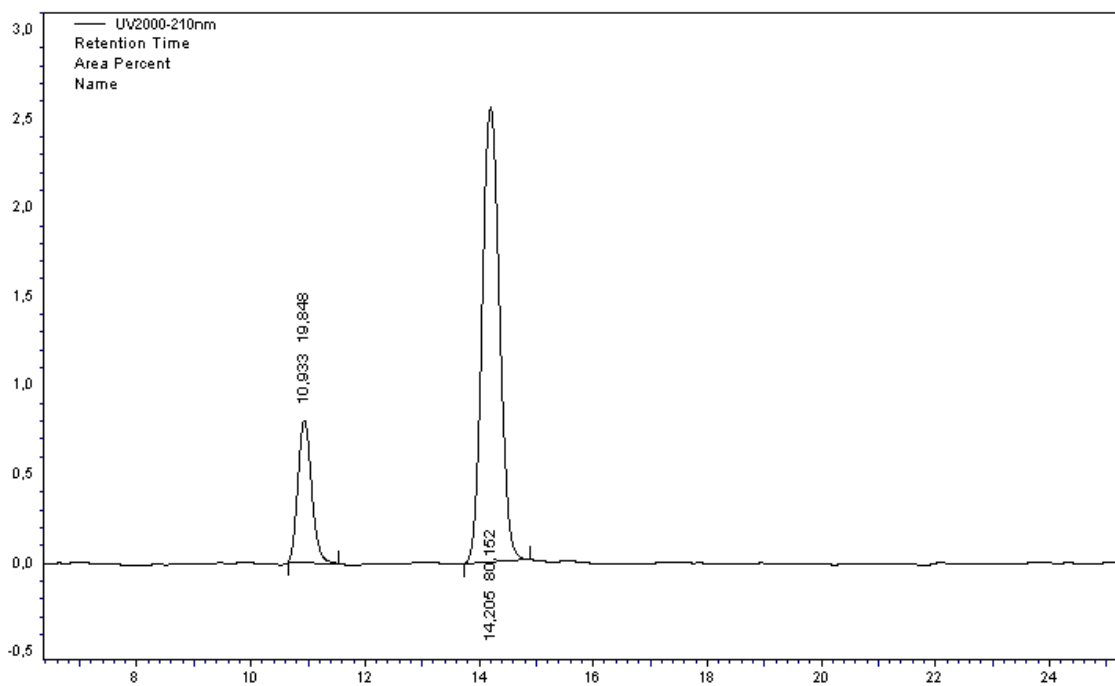
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Figure B 19. HPLC chromatogram of *rac*-**72g**

Figure B 20. HPLC chromatogram of *ent*-**72g**