T.C.

DİCLE ÜNİVERSİTESİ

FEN BİLİMLERİ ENSTİTÜSÜ

AMİNO ALKOL İMİT ESASLI KİRAL SOLVATLAYICI REAKTİFLER: SENTEZLERİ VE NMR İLE KARBOKSİLLİ ASİTLERİN ENANTİOMERİK YARILMA UYGULAMALARI

Basam JAMEEL

YÜKSEK LİSANS TEZİ

KİMYA ANABİLİM DALI

DİYARBAKIR

2017

T.C.

DİCLE ÜNİVERSİTESİ

FEN BİLİMLERİ ENSTİTÜSÜ MÜDÜRLÜĞÜ

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Basam JAMEEL tarafından yapılan "**Amino Alkol İmit Esaslı Kiral Solvatlayıcı Reaktifler: Sentezleri ve NMR ile Karboksilli Asitlerin Enantiomerik Yarılma Uygulamaları**" konulu bu çalışma, jürimiz tarafından Kimya Anabilim Dalında YÜKSEK LİSANS tezi olarak kabul edilmiştir.

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ÖZET

AMİNO ALKOL İMİT ESASLI KİRAL SOLVATLAYICI REAKTİFLER: SENTEZLERİ VE NMR İLE KARBOKSİLLİ ASİTLERİN ENANTİOMERİK YARILMA UYGULAMALARI

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Kiral tanıma, kiralitenin biyoloji, ilaç kimyası ve asimetrik katalizdeki öneminden dolayı son yıllarda önem arz kazanmaya başlamıştır. Kiralite ve ilgili alanlarda mutlak konfigurasyonların yarılması ve enatiomerik saflıklarının belirlenmesi bir kiral bileşik için vazgeçilmez bir zorunluluktur.

Kiral moleküllerin önemi biyolojik moleküllerle sınırlı değildir. Bunlar; ilaç, tat ve koku verici maddelerde olduğu gibi materyal bilimi ve moleküler tanıma gibi diğer alanlarda da önem arz ederler. Bu tür moleküllerin birçok özelliği, sistemin kiralitesiyle açık bir şekilde bağlı olması sebebiyle test numunelerinde mevcut izomerin bileşiminin

bilinmesi hayati bir zorunluluktur. Bu nedenle, hızlı ve doğru ve güvenilir bir teknikle kiral numunelerdeki enantiyomer oranının belirlemesini gerekli kılar. Kiral karışımlarda enantiomer oranının belirlenmesi yöntemlerinden biri molekülü diastereomer türevlerine dönüştürmektir. Test numunelerini diastereomerlere dönüştürmek iki yöntemle mümkündür. Bunlardan biri, numunenin kiral türevlendirici bir reaktif (chiral derivatizing agents (CDA)) ile kovalent bağ oluşturmasını, diğer alternatif ise bir kiral solvatlayıcı reaktif (KSR) ile geçici supramoleküler etkileşimini sağlamaktır.

Bu projenin amacı, biyolojik açıdan önemli çeşitli kiral karboksilli asitlerin enantiyomerik yarılmalarında kullanmak üzere çeşitli kiral solvatlayıcı reaktifler sentezleyerek ve NMR spektroskopisi yardımıyla bu konudaki potansiyellerini araştırmaktır. Bu amaçla, başlangıçta bir seri amino alkol veya amino alkol imit (**2-8**), çeşitli kiral aminlerin (*R*)-*N*-(2,3-epoksipropil)ftalimit'in regioselektif epoksit halka açılması tepkimesi ile sentezlendi. Amino alkol veya amino alkol imit fonksiyonlu kiral bileşikler **2-8**, mandelik asit (**A**), *o*-kloromandelik asit (**B**), α-fenil-α-metoksiasetik asit (**C**), ibuprofen (**D**) ve naproksen (**E**) analitleri için potansiyel kiral solvatlayıcı reaktif özelliklerini incelemek üzere kullanıldılar.

Bu çalışmada, C_2-Simetrik (*S*,*R*,*S*,*R*)-**3,** 24.8 Hz'lik yarılma değeri ile mandelik asit için en iyi reaktif olarak tespit edilmiştir. Aynı reaktifin α-Fenil-α-metoksiasetik asit, *o*-kloromandelik asit için bulunan değerleri sırasıyla 16.6 ve 8 Hz'dir. α-Fenil-α-metoksiasetik asidin en iyi yarılması ise 32 Hz'lik değerle **KSR 5** ile elde edildi. **KSR 5**'in *o*-kloromandelik asit, ibuprofen and naproksen'e karşı elde edilen yarılma değerleri sırasıyla 7.2, 4.4, 2 ve 3 Hz'dir.

Anahtar Kelimeler: Kiral solvatlayıcı reaktifler, Enantiyomerik saflık, Enantiyomerik yarılma, Kiral tanıma.

ABSTRACT

AMINO ALCOHOL IMIDE BASED CHIRAL SOLVATING AGENTS: SYNTHESIS AND APPLICATIONS IN THE NMR ENANTIODISCRIMINATION OF CARBOXYLIC ACIDS

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Chiral recognition has received considerable attention in recent years due to the significant importance of chirality in biology, pharmaceutical chemistry, and asymmetric catalysis. In the field of chirality and related research, the discrimination of the absolute configuration and the determination of the enantiomeric purity are indispensable to a chiral compound.

The significance of chiral molecules is not restricted to bioactive molecules such as pharmaceuticals, flavouring agents, and fragrances, but has covered many other areas of molecular recognition and material science. Many properties of such molecules are clearly linked to the chirality of the system and hence it is vital to know the composition of the present isomers in a test sample. This has necessitated a need for quick, accurate, and reliable techniques to establish the ratio of enantiomers in chiral samples. The transform of enantiomers to their diastereomer derivatives is one of the determining of enantiomeric ratio in the mixture. Converting the test sample to diastereomers can be carried out in two ways, by forming covalent bonds with chiral derivatised agents or

alternatively by forming temporary supramolecular interactions with chiral solvating (or complexing) agents.

The target of this project is to prepare chiral solvating agents (CSA) in order to use in enantiomeric discrimination of biological important chiral carboxylic acids (**A-D**) by NMR spectroscopy. For this purpose, initially, a series of amino alcohol imids **2-8** were synthesized by regioselective ring opening reaction of (*R*)-*N*-(2,3-epoxypropyl)phthalimide with various chiral amines. Amino alcohol or amino alcohol amides **2-8** were tested as potential chiral solvating agents to the enantiomeric discrimination of mandelic acid (**A**), *o*-chloromandelic acid (**B**), α-phenyl-α-metoxyacetic acid, (**C**), ibuprophen (**D**) and naproxen (**E**).

C_2-Symmetric (*S,R,S,R*)-**3** found to be the best reagent for enantiomeric discrimination for mandelic acid with ΔΔδ of 24.8 Hz. The values for α-phenyl-α-metoxyacetic acid and *o*-chloro mandelic acid were found to be 16.6 and 8 Hz respectively. CSA **5** exhibited the best enantiomeric discrimination for α-phenyl-α-methoxyacetic acid with ΔΔδ of 32 Hz. Enantiomeric differentiated values found for mandelic acid, *o*-chloro mandelic acid, ibuprophen and naproxen are 7.2, 4.4, 2 and 3 Hz respectively.

Keywords: Chiral solvating agents, Enantiomeric purity, Enantiodiscrimination, Chiral recognition.

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KISALTMALAR

AcOH: Asetik Asit

ACE: Affinite Kılcal Elektroforezi

BINOL: 1,1'-Bi(2-naftol)

CDA: Kiral Türevlendirici Reaktif

CGE: Kılcal Jel Elektroforezi

CIEF: Kılcal İzoelektronik Odaklanma

CIP: Kılcal İzotakoforez

CZE: Kılcal Bölge Elektroforezi

DCC: Disiklohegzilkarbodiimid

DME: Dimetoksietan

DSC: Diferansiyel Taramalı Kalorimetri

EC: Kılcal Elektroforez

EtOH: Etanol

FTIR: Fourier Transform İnfrared Spektroskopi

GC: Gaz Kromatografisi

HPLC: Yüksek Performanslı Sıvı Kromatografisi

KSR: Kiral Solvatlayıcı Reaktif

MS: Kütle Spektrometresi

NEP: (*R*)-*N*-(2,3-epoksipropil)ftalimid

NMR: Nükleer Manyetik Rezonans

THF: Tetrahidrofuran

TLC: İnce Tabaka Kromatografisi

PPh_3: Trifenilfosfin

EtOAc: Etilasetat

TEA: Trietilamin

NEP: (*R*)-N-(2,3-epoksipropil)ftalimit

H: Heksan

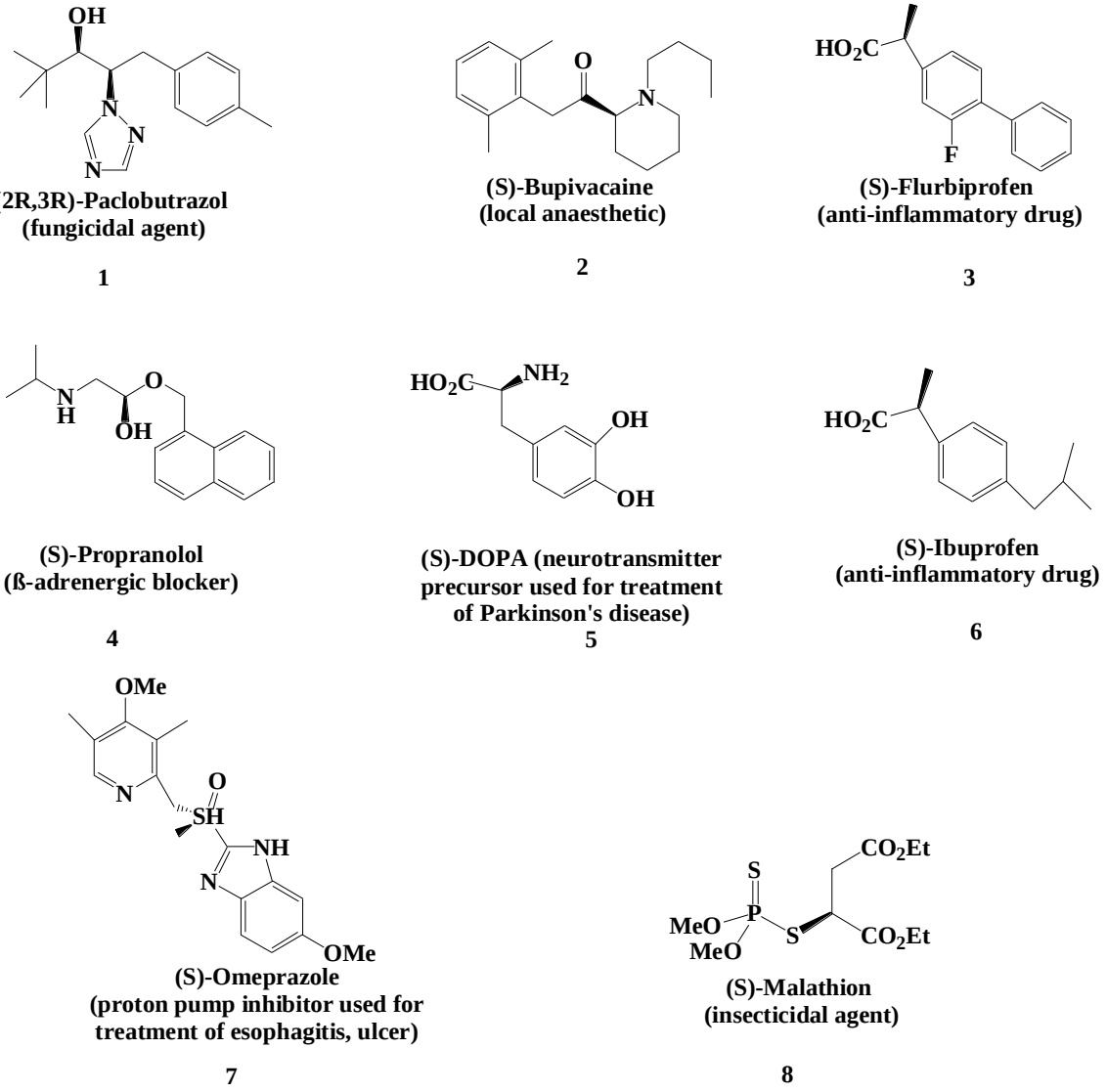
1. GİRİŞ

1.1. Kiralitenin Tarihi ve Önemi

'Kiralite' terimi 1870'lerden beri kimyada bilinmektedir ve kimyacıların bu terimi kullanmalarından önce yaklaşık yüzyıl öncesine dayanmaktadır (Eliel, 1962). Kiral sözcüğü ise bilinmemesine rağmen sonraki versiyonlarda ortaya çıkmıştır (Eliel ve Wilen, 1994). Basitçe bir anlatımla kiralite hem sağ hem de sol elin var olması ancak sadece birinin kullanılması gibidir. Örneğin, sağ ve sol elin ayna görüntüleri birbirleri ile üstüste çakışmazlar ve bu özellik nedeniyle ellerimiz 'kiral' olarak adlandırılır. Kiral sözcüğü Yunancada kullanılan ve el anlamına gelen 'kheir' kelimesinden gelmektedir (Kelvin, 1904).

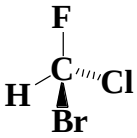
Stereokimyanın öncüsü Louis Pasteur, 1848 yılında yayınlanan ünlü makalesinde kiralitenin önemini vurgulamıştır (Pasteur, 1848). Günümüzde kiraliteye doğanın her alanında karşılaşılan bir şey olduğunu biliyoruz. Örneğin; helezonik nötrino ve DNA, doğal kiral proteinler, bitkilerdeki karbohidratlar, sarmal bakteriler ve deniz kabuklularının hepsi kiraldir. Pasteur'e göre kiral maddeler birbirleriyle üst üste çakışmayan ayna görüntülerine sahip enantiyomer çiftleri şeklinde bulunmakta ve bu ilişki tıpkı sağ ve sol ele uyumlu olan eldivenler arasındaki gibidir. Kiral bir ortamda birbirinden çok farklı kimyasal ve fiziksel özellikler gösteren enantiyomerler, moleküler düzeyde kiralitenin öneminin artmasını sağlar. Başlıca biyolojik aktif karışımlar kiraldir ve bunlara örnek olarak; zirai kimyasallar, güzel kokular, tatlandırıcılar, ilaçlar ve besin maddeleri verilebilir. Bunların yarısından fazlası günümüzde en çok satılan ilaçları da içermektedir. Bu ilaçlardan; Lipitor (kolesterol düşürücü, 2004 yılı küresel satış 12 Milyar ABD Doları), Zocor (kolesterol düşürücü, 5,9 Milyar ABD Doları), Plavix (antitrombotik, 5,0 Milyar ABD Doları) ve Nexium (antiülser ilacı, 4,8 Milyar ABD Doları) tek bir enantiyomer şeklinde ticari olarak piyasaya sürülmektedir.

Pasteur 1853 yılında optikçe aktif chinchonidine alkaloidi ile rasemik tartarik asitin diastereomerik tuzlarını oluşturup kristallendirme yoluyla iki enantiyomerini birbirinden ayırmayı başardı (Pasteur, 1853). Diastereomerik tuzlardan (-)- tartarik asit tuzu kristallenirken (+)- tartarik asit tuzu ise çözelti fazında kalmıştı.



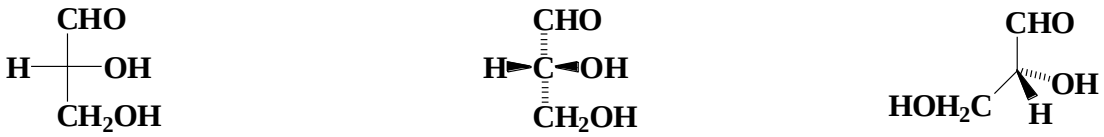
Şekil 1.1 Ticari olarak satılan bazı ilaç ve zirai kimyasallar

1874 yılında Fransız kimyacı Le Bel ve Hollandalı kimyacı van't Hoff birbirlerinden bağımsız olarak beş atomlu bir molekülde bu atomlardan biri olan karbon atomunun diğer dört atomla bağ yaptığını ve bu yapının da dört açılı ve düzgün dört yüzlü bir yapı oluşturduğunu varsaymışlardı. Bu nedenle merkez karbon atomu kiral karbon ya da stereojenik merkez olarak adlandırılmış ve bu özelliklere sahip molekül de kiral olarak belirtilmiştir. Le Bel ve van't Hoff'un bu kabulleri gerçekten de doğruydu. Şimdi bilinen en basit optikçe aktif molekül CHFClBr'dir (Franks ve ark. 2004).



Şekil 1.2 Optikçe Aktif Molekül

Fischer'in 1919'da stereo kimyasal adlandırmada sürekliği sağlamak üzere glikozun D-enantiyomerinin beşinci karbonu başlangıç noktası olarak seçildi. Fischer projeksiyonunda ilk defa Gliseraldehit molekülü çizildi (Şekil 1.3).



Fischer izdösüm **Kama kesikli kama** **Üçboyutlu**

Şekil 1.3 D-Gliseraldehid'in çeşitli gösterimleri

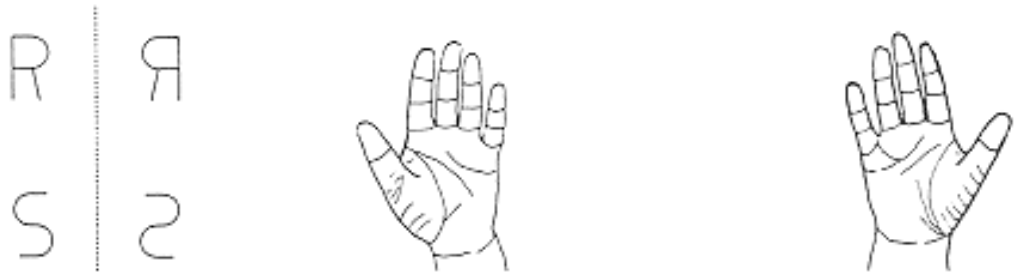
Bu gösterimlerde, düz çizgilerle gösterilen bütün bağlar için düşey olanlar; bakılan düzlemden geriye doğru, yatay olanlar ise bakan kişiye yönelmiş sübstitüentleri göstermektedir. Çizilen molekülde en uzun karbon zinciri dikey olarak yazılır ve en yukarı uçta da yükseltgenme basamağı yüksek karbon atomu bulunur. Fischer, (+)-glikoz molekülünü sadece (+)-glikozun C-5'deki sterejenik merkez kalıntısına sahip (+)- gliseraldehite bozundurdu. Fischer Şekil 1.3'te gösterildiği gibi (+)-gliseraldehidi göstermiş ve stereojenik merkezdeki sübstitüe OH grubu sağ tarafta bulunduğu için D-(+)-gliseraldehit olarak adlandırmıştı.

Fischer izdöşümlerinin bir diğer gösterim yolu, dolgulu ve kesikli kama gösterimleridir. Burada dolgulu kama ile gösterilenler gözlemciye taraf, kesikli kama ise gözlemciden arkaya doğru olan bağları gösterir (Şekil 1.3). Alternatif olarak perspektif gösterim de ise bağlar düzgün dört yüzlü bir şekilde düzenlenmiş olup gözlemciye doğru yönelmiş bağ dolgulu kama, gözlemciden arkaya doğru olan bağ ise kesikli kama ile gösterilmiştir (Cahn ve ark. 1956, Cahn ve ark. 1966).

1.2. Stereokimyanın Prensipleri

Organik kimya bilimi, moleküler yapı ile karbon karışımların özellikleri arasındaki bağlantı ile başlıca ilgilidir. Organik bileşiklerin üç boyutlu yapılarla ilgilenen bölümü stereokimya olarak adlandırılmaktadır. Bu alan stereokimya olarak adlandırılmakta ve yapıların stereoizomerizm, stereokimyada kullanılan bir terimdir. İzomerlerin her biri için üç boyutlu uzayda atomların yönelimlerinin birbirinden farklı olduğu yapılar, stereoizomer olarak adlandırılır. İki ya da daha çok boyut ile orantı (ya da eksikliği) geometrik şekillerin özelliklerini arttıran bir şeydir.

Oran (veya orantısızlık) iki veya daha fazla boyutuyla geometrik şekillerin canlandırıcı özelliklerinden biridir. Örneğin, alfabe simetrik ve simetrik olmayan iki boyutlu harflerden oluşmaktadır. Bir reflektör taklit edildiklerinde sonradan farklı görünüm arz ederler. Böylece, simetrik olmayan harflerin ayna görüntüleri ters dönmüş olarak görünür. Ayna görüntülerinin özdeş olmama özelliği maddenin üç boyutlu yapısında da mevcuttur. Bununla birlikte, bir önemli değişik durum; R ve S'nin ayna görüntüsü kâğıt düzleminden kaldırılıp takla attırılıp tekrar yerine yerleştirilirse orijinal harf ile aynı görüntü elde edilir. Bunun tam tersi olarak elin iki tarafının (avuç içi ve sırt) birbirine eş olmamasından dolayı sağ elin ayna görüntüsü gerçek görüntüyle tam olarak üst üste çakışmaz. Sağ elin ayna görüntüsü, sol el ile çakışır ve özdeştir.



Şekil 1.4. Asimetrik şekillerin iki ve üç boyuttaki ayna görüntüsü ilişkileri

1.2.1. Kiralite Nedir?

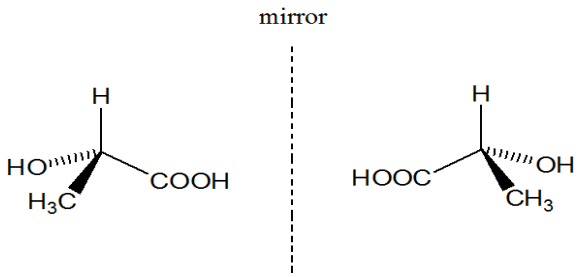
Kiralite geometrik bir niteliktir ve bir objenin ayna görüntüsüyle üst üste çakışmaması durumunda o nesneye kiral denirken, ayna görüntüsüyle üst üste çakışan objeye ise akiral denir. Kiral objelere örnek olarak sağ ve sol eller, saat yönünün tersine

işlenmiş vidalar, deniz kabukları verilebilir. İki boyutlu harfler kiral değildirler çünkü bir simetri düzlemi olan sayfa düzlemi üzerinde bulunurlar. Kiralite için diğer bir açıklama ise simetri özellikleri üzerine kurulmuş olup, kiral bir obje yansıyan bir simetriden yoksundur.

Moleküler yapılar için olduğu gibi makroskopik nesneler için de uzaysal düzenlenmeler vardır. Sonuç olarak, bir molekül kiral ise ayna görüntüsü ile çakışmaz. Kiralitenin molekülün tamamına ait bir özellik olduğunu vurgulamak da önemlidir. Molekülün içinde bir kiral merkez bulunduğunu söylemek de doğru olmayacaktır. Bunu asimetrik merkez ya da stereojenik merkez olarak adlandırmak daha iyi olacaktır (Mislow ve Siegel 1984). Mislow ve Siegel bir stereojenik atomu; birkaç grup bağlı olan ve bu gruplardan herhangi ikisinin yer değiştirmesiyle bir stereoizomer oluşturan atom olarak tanımladılar. Asimetrik merkez terimi yaygınlaşarak daha fazla kullanılmaktadır. Benzer şekilde birden fazla stereojenik merkez içeren bir moleküle multikiral denilmesi de yanlış olacaktır, yani bir molekül ya kiraldir ya da akiraldir.

1.2.2. Enantiyomerler

En yaygın kullanıldığı şekliyle tetrahedral bir karbon atomuna dört farklı grup bağlıysa bu karbon atomu molekülün stereojenik (asimetrik) merkezidir. Bir molekül; aynı kimyasal özelliklere sahip stereoizomerleri içeren akiral (dengeli) şartlarda iki farklı karışımdan meydana gelebilir. Bu kombinasyonların yapıları üst üste çakışmazlar ve birbirlerinin ayna görüntüsüdürler.



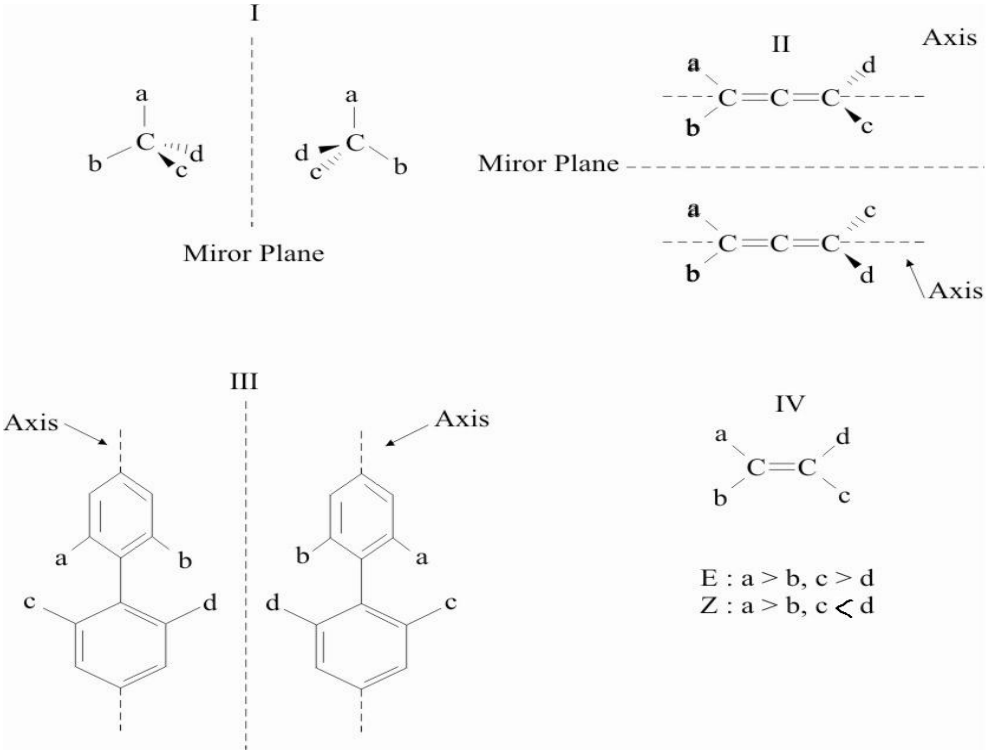
Şekil 1.5 Laktik asit enantiyomerleri

Böyle stereoizomerler enantiyomer olarak adlandırılırlar (Yunanca; enantio: zıt, karşıt). Örneğin, laktik asit kiral bir moleküldür ve bir enantiyomer çifti oluşturmaktadır. Şekil 1.5'te bu laktik asit stereoizomerlerin gösterimleri verilmiştir.

Görsel olarak ya da daha ileri gözlemler açısından kiral bir molekülün enantiyomerine dönüşümünün gözlemlenebilmesi ya da ayrımın olabilmesi için enerji bariyerinin 80 kJ/mol'den daha fazla olması gereklidir. Trisübstitüe azot atomunun hızlı bir şekilde ters çevrilmesi, stereojenik azot içeren moleküllerde izomerlerin birbirinden ayrımını engeller. (Bijvoet ve ark. 1951).

1.3. Moleküllerin Kiralitesi

Kiralite, çok az sayıdaki organik moleküllere özgü bir olgudur. Bazı moleküllerde karbon atomu dört farklı grup ya da atom bulundurmaktadır. Asimetrik bu tür moleküller, üç boyutlu şekilleri itibariyle farklı olup, üst üste çakışmayan birbirlerinin ayna görüntüleridir (Federsei, 1994). Birbirinin ayna görüntüsü olup üst üste çakışmayan bu izomerler enantiomer olan stereoizemerler olarak adlandırılırlar. Farklı enantiyomerlerin varlığı stereoizomerizm veya kiralite olgusunu oluşturur. Enantiyomerlerin 1:1 orandaki karışımına rasemik karışım denir. Allenler ve kümülenlerde merkez kiraliteye ek olarak aksiyal kiralite meydana gelebilir. Dönme simetrisini kaybeden ikinci çift bağdaki C2'den dolayı birinci sınıfta yer alan türde sübstitüentlerin farklı olması gerekmez. İkinci türde ise tek sayıda karbon atomu içerenler, potansiyel olarak kiraldir fakat çift sayıda karbon bulunduranlar E/Z izomerisi (geometrik izomerizm) ile sonuçlanır (Federsei, 1994). Aksiyal kiraliteye bir diğer örnek olarak konformasyonel kiralite gösteren atropizomerler olarak nitelendirilirler. Orto pozisyonlarında hacimli grupların olduğu tetra sübstitüe biaril yapılarda C-C tekli bağı etrafında dönme engellendiği için iki formun birbirine dönüşümü de engellenmiş olacaktır. Son olarak atomların ya da atom gruplarının bir stereojenik düzleme göre düzenlenmesinden kaynaklı düzlemsel bir kiralite vardır. Bununla birlikte, bu kiralite türü oldukça nadirdir (Federsei, 1994). Helikal (sarmal) yapılarda görülen kiralite sıra dışı bir kiralitedir ve biyopolimerler, proteinler ve polisakkaritler gibi makromoleküllerde çoğunlukla görülmektedir (Ma ve Ark. 2009). Bir sarmal yapı ya sağ el (saat yönünde) ya da sol el (saat yönünün tersi) gibi düzenlendiği için kiral özellik gösterir. Bir stereoizomer birden fazla stereojenik merkeze (örneğin; n tane) sahip olduğu durumda teorik olarak 2^n sayıda enantiyomeri vardır. Stereoizomerliğin dört türü Şekil 1.6'da verilmiştir.



Şekil 1.6. Stereoizomerlerin sınıflandırılması: I, kiral merkez; II, kiral eksen; III, atrop.izomerizm; IV, E-/Z- geometrik izomerler

1.4. Biyolojik Sistemlerde Kiralitenin Önemi

Birçok biyolojik uygulama alanında kiralitenin rolü nedeniyle moleküler uyum ve stratejiler açısından kiral reseptörlerin sentezi daha da önem kazandırmıştır. Birçok biyolojik hayati yanıtın özgüllüğü ve iyi organizasyonu; kiral bir host (konukçu) molekülün seçici olarak enantiyomerlerden birine uyumluluğu ve böylece kiralliğin tanınması üzerine kurulmuştur. Karboksilik asitlerin kiral uyumluluğunu taklit eden reseptörlerin, biyolojik sistemlerde ve kiralite temelinde organik çalışmalardaki önemlerinden dolayı enantiyomerlerin ayrılması, planlanması ve araştırılması büyük önem taşımaktadır. Konuk-konukçu çalışmalarının kökenine ve enantiyomerik saflığın belirlenmesine yönelik taklit reseptörlerin hazırlanması ve stratejisine dair sayısız çalışma bulunmaktadır. Günümüzde, kiral tanıma ve enantiyomerik saflığın belirlenmesi için kütle spektrumu, gaz kromatografisi, kapiler elektroforez, yüksek performanslı sıvı kromatografisi, absorbans spektrometresi, infrared spektroskopisi, sirkular dikroizm, X-ışını dağılımı, nükleer magnetik rezonans (NMR) gibi birçok seçenek ve metod mevcuttur (Bozkurt ve ark. 2011).

Üç yerden aynı anda ve tam olarak uyum gösteren aktif enantiyomer 'eutomer' ve aynı anda üç noktadan daha az yerle uyumlu olan inaktif enantiyomer ise 'distomer' olarak adlandırılır (Srinivasu ve ark. 2005). Bu nedenle biyolojik sistemlerde meydana gelen düzenleyici ve metabolik işlemler stereokimyaya duyarlıdır ve bir enantiyomer çiftinin etkilerine paralel olarak farklı reaksiyonlar görülebilir. Bu farklılıklar boşaltım, dağılım oranları, metabolizma, birbirine karşı antagonist özellikler gösterme ya da toksikoloji özellikleri şeklinde söylenebilir. Aktif olmayan enantiyomerin varlığı dikkat çekicidir, hem eutomerin varlığına karşıt etkisi hem de kütlesiyle. Hatta bazen toksik özellikte de olabilmektedir. Eudismik oran, enerjisi daha yüksek olan enantiyomerin etkinliğinin daha az aktif olana olan orandır. (Waldeck 1993, Jalba ve ark. 2004). Bu nedenle bugünkü tıbbi gelişmenin ana anahtarı daha fazla eutomer keşfetmektir. Tıpta kullanılan kiral ilaçlarla tam olarak ilgilenmek için, toksikolojik klinik veya terapötik ilaçların izlenmesinde rasemik karışımdaki optikçe aktif saf bileşenler bilinmelidir.

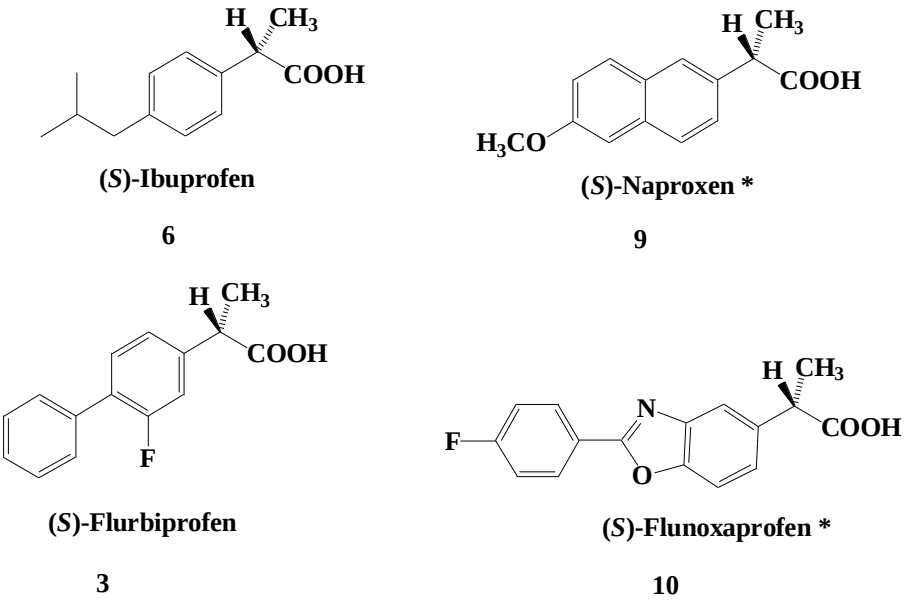
1.5. Kiralitenin Gelişimi ve İlaçlar

Rasemik bir ilaçın enatiyomerleri, aktif yapının farmakolojik etkilerinin aksine etkiler gösterebilir (Jalba ve ark. 2004). Birçok kiral ilaç içeren biyoaktif biyosentetik karışımlar, genellikle rasemat şekindedirler (Kostyanovsky ve ark. 2002). Açıkçası bir ilaç molekülünde stereojenik merkez sayısının artması işi oldukça zorlaştıran bir durumdur. Doku/organ hasarları ya da yan etkiler, insana belli bir enatiyomerin verilmesiyle durdurulamaz. Çünkü; güvenli olmayan metabolitler, kiral inversiyon veya rasemleşme in vivo olarak gerçekleşebilir. Öte yandan ideal terapötik etkisinin gösterilmesi adına eutomerin üzerinde durulması uygun olabilir. Örneğin, ibuprofen bir yan etki göstermeden kiral inversiyona uğrar ve aktif olmayan (*R*)-enantiyomeri aktif (*S*)-enantiyomerine enzimatik bir mekanizma üzerinden dönüşmektedir (Rentsch 2002). 1960'lı yıların sonunda rasemik karışım şeklinde piyasaya çıkan Talidomid olumsuz bir örnek olarak verilebilir. Hamile kadınların bulantılarını gidermek için onaylanan bu ilacın tedavi eden ve zararsız (+)-izomeri vücutta fetusun korkunç bir deformasyonuna sebep olan (-)-izomerine dönüştüğü ortaya çıktı. (Federsei 1994, Knoche ve Blaschke 1994, Robin 1995). Bununla birlikte diüretik olarak kullanılan Indacrinone'da distomerin varlığı eutomerin etkisini arttırıcı etkisi sebebiyle uygundu (Kubinyi, 2002). Talidomid felaketinden sonra ortaya çıkanlar her yeni ilaca genel bir dikkat

oluştu ve yeni ilaç önerileri dikkatle gözden geçirildi. Hastaları enantiyomerlerin istenmeyen yan etkilerinden korumak adına her bir enantiyomerin toksikolojik ve farmakolojik etkisi hesaba katılmalıdır (Witte ve ark. 1993, Rauws ve Groen 1994, Rentsch 2002). Son zamanlarda artık endüstri haline gelen ilaç üretimi, seçkin profesyonellerin kontrol ve onayından sorumlu olduğu ABD, Japonya ve bazı Avrupa ülkelerinde ilaç endüstrisindeki kiral ilaçların prestijini yeniden doğru yola soktu (hem kiral hem de kiral olmayan ilaçların tümünde). Amerika Birleşik Devletlerinde gıda ve ilaç idaresi (FDA) yeni ilaç taleplerini almakta ve bunların kimyasal prosedürleri, uygun etiketleme, safsızlık verileri, farmakokinetik, toksikolojik aktivite ve stabilite testleri gibi testlerin sonuçlarını değerlendirip bir veri haline getirmektedir. Eğer ilaç bir rasemat ise her bir enantiyomerin farmakolojik, toksikolojik ve stereokimyasal verilerini de içermelidir. Rasematın mevcut bilgierine bağlı olarak, her bir enantiyomer için toksikolojik ve farmakolojik değerlendirme yapılmalıdır. Dahası incelenen eutomerin distomere dönüşümüyle ilgili bilgileri de içermelidir (Birleşik Devletler Gıda ve İlaç İdaresi (US FDA, 1992).

1.5.1. Arilpropiyonik Asit Esaslı Anti-inflamatuar İlaçlar:

Şekil 1.7'de ibuprofen ve naproksen gibi ilaçlarla gösterilen α-arilpropiyonik asitler, romatoid inflamasyonun tedavisinde ve genel olarak analjezik türü ilaç gruplarında kullanılan en büyük grubu oluşturmaktadır. Örneğin, ibuprofen baş ağrısı başta olmak üzere hafif şiddetteki ağrılarda yaygın olarak verilen bir ilaçtır. Bu ilaçların tümü kiral olmakla beraber tedavi edici özellikteki enantiyomer (*S*) enantiyomeridir (örn. Naproksen için ER 30). Dikkat çekici bir şekilde ibuprofenin aktif olmayan *(R)*-enantiyomeri metabolizmada konfigürasyon inversiyonuna uğrar ve aktif (*S*) izomerine dönüşür (Williams, 1990).

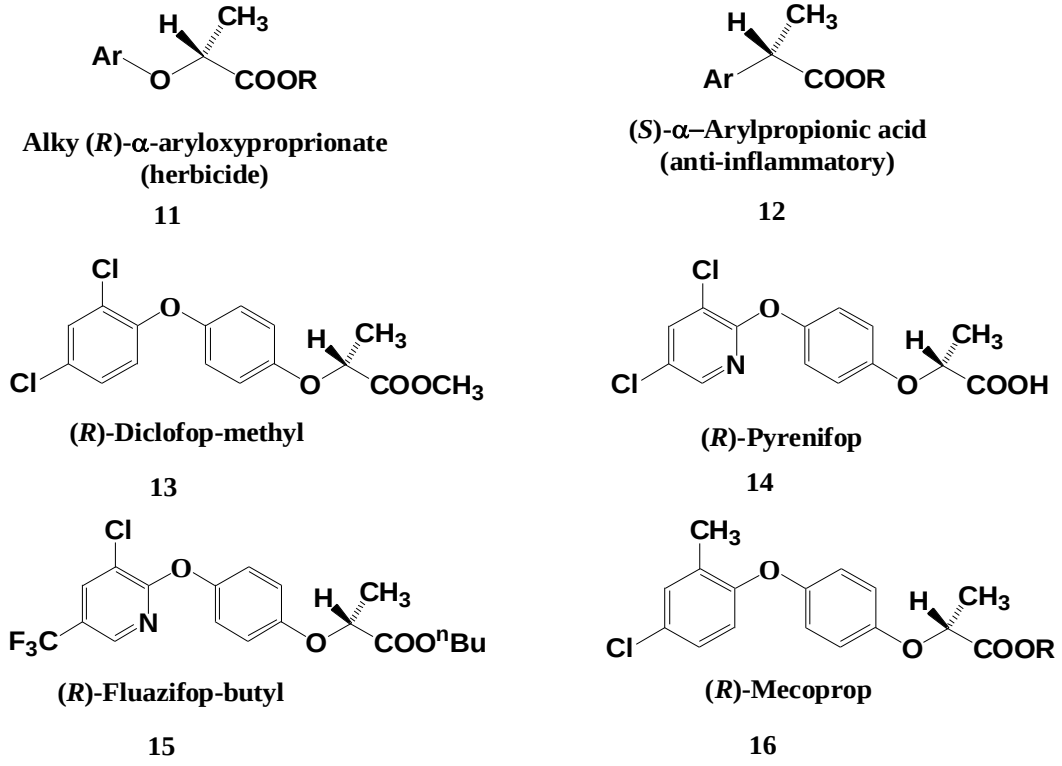


Şekil 1.7. Nonsteroidal anti-inflamatuar α-arilpropiyonik asitlerin yapıları

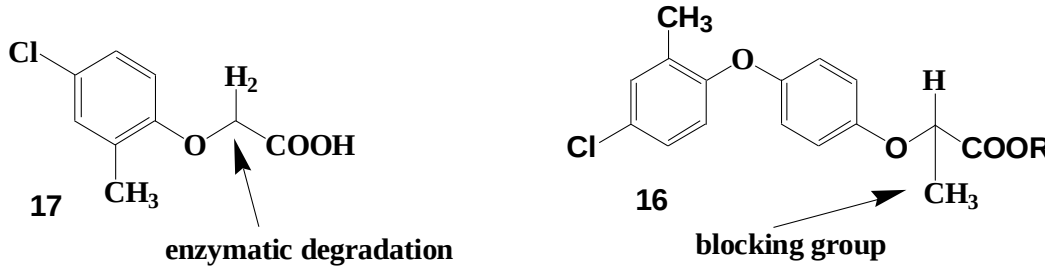
1.5.2. α-Ariloksipropiyonik Herbisitler

Pyrenifop, mecoprop, diclofop ve fluazifop gibi α-arilpropiyonik asitler, ticari olarak satılmakta olan herbisitler arasında önemli bir sınıfı oluştururlar (Şekil 1.8). Bunlar kiral moleküllerdir ve herbisidal etkinlikleri (bitki büyüme hormone aktivitesinin inhibisyonu, indol-3-asetik asit) neredeyse sadece (*R*) enatiyomerde bulunmaktadır (Ariëns ve ark.1988, Naber ve ark. 1988). α-Ariloksipropiyonik asitlerin (*R*)-enantiyomeri, α-arilpropiyonik asitlerin antiinflamatuar özellik gösteren (S) enantiyomerine yapısal olarak benzerlik göstermektedir (konfigürasyon aynı fakat grup öncelikleri değişmiştir). Hem asit herbisitler hem de α-arilpropiyonik asit ilaçların mantıksal çizgisi aynı yönde ilerlemektedir. Her iki durumda da benzer yapıdaki asetik asitin yerdeğişimi ilk olarak bulundu. Fakat bu ilk karışımlar in vivo olarak biyolojik bozunma ile aktif olmayan metabolitlere dönüştüler. Böyle durumlarda sıklıkla kullanılan yöntem, molekülün metabolik olarak hassas olduğu durumda çoğunlukla bir substituent takmaktır ki bu grup da çoğunlukla bir metil grubudur (Ariëns ve ark.1988). Böylelikle hedef organizmada bulunan enzimler tarafından molekülün bozunması inhibe edilebilir ve böylece etki süresi uzarken muhalefeti de azaltır. Dolayısıyla bir α-metil grubuyla aktif herbisitlerin ve antiinflamatuar ilaçların iyileşmesi sağlanmıştır. Bu durum mecocrop için Şekil.1.9'da gösterilmektedir.

α-Metil grubu ile başlanması hem moleküle bir kiralite getirmiş hem de enzimatik saldırının sterik olarak engellenmesini sağlayarak iki enantiyomerden biri için daha önemli olmasını sağlamıştır. Bazı durumlarda bu isomer yine de enzyme bağlanabilir fakat değiştirilemez ve böylece diğer enantiyomerin bozunması önlenir. α-Arilpropiyonik asit ilaçlar ile birlikte bazı α-ariloksipropiyonik asit herbisitler metabolizmada inversiyona uğrarlar. Örneğin, fluazifop bütilin (*S*)-enantiyomerinin (*R*)-enantiyomerine inversiyonu herbisitle tedavi edilen toprakta meydana gelirken dezenfekte toprakta bu dönüşüm olamamaktadır. Bu biyodönüşümün pratik önemi herbisitin gerekliliğine bağlıdır ve köklü ürünlerde (*S*)-enantiyomerin pestisit olarak kullanılmasının çiçeklenme sonrası yapılması avantajlı olacağı bildirilmiştir (Ariëns ve ark. 1988).



Şekil 1.8 Çeşitli α-ariloksipropiyonik asit esaslı herbisit eutomerlerin yapıları



MCPA= 4-chloro-2-methylphenoxyacetic acid
rapid biodegradation (not resistant)

(R)-Mecoprop
slow iodegradation (not resistant)

Şekil 1.9 Metabolik bozunmaya karşı stabilizasyon yoluyla herbisitlerde direnç kontrolü

1.6. Stereoizomerlerin Rezülusyonu

Enantiyomerler, hem preparatif hem de analitik ölçekte bir yöntemle rezole edilmektedir. Bunlar iki farklı anabaşlık altında sınıflandırılacak olunursa; bunlardan geleneksel metod ile enantiyomerlerden biri enzimatik bozunma, modern teknolojik metot ise kromatografik yaklaşımları, elektroforetik ve spektroskopi içerikli tercihli kristalizasyon kullanılır.

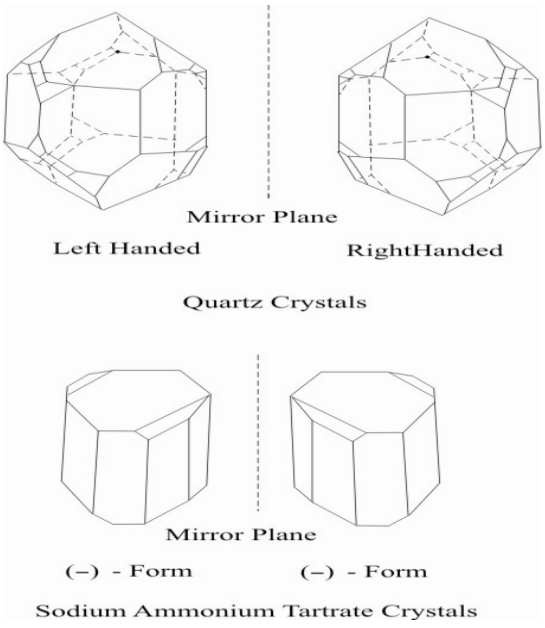
1.6.1. Geleneksel Metodlar

Biyokimyasal işlemlerde, bir enantiyomerik formun tamamını enzim aracılığıyla kinetik rezülüsyona tabii tutulur. Bakteri, maya ve küfler gibi mikroorganizmaların rasemik karışımlar içerisinde büyümesine fırsat verildiğinde, bunlar seçici olarak bir form ile birleşirken diğer form ise çözücü içerisinde çözünür. Örneğin, penicillium glaucum'un rasemik amonyum tartarat çözeltisine eklenmesiyle dekstrorotator form biter ve bundan dolayı levorotator enantiomer ortaya çıkar (Pasteur, 1858). Kristallendirme, her iki enantiyomerlerin ayrılmasında başvurulan bir başka metottur. Kristallendirmede ilke olarak her iki enantiyomerin optikçe kirletilmemiş diastereomerik tuzları oluşturulup bu diastereomerik tuzların basitçe birbirinden ayrılması sağlanır. Bu metotta kural, çözücü reaktiflerin optikçe saf olmaları önem arzeder. Birçok durumda çözücü, istenen enantiyomerler diastereomerik tuzdan ayrıldıktan sonra reaktif saflaştırılarak tekrar kullanılır (Tolman ve Šimek 2000). Mekanik yöntemlerle ayırma (cımbız, pens vb. kullanarak), sodyum amonyum tartarat

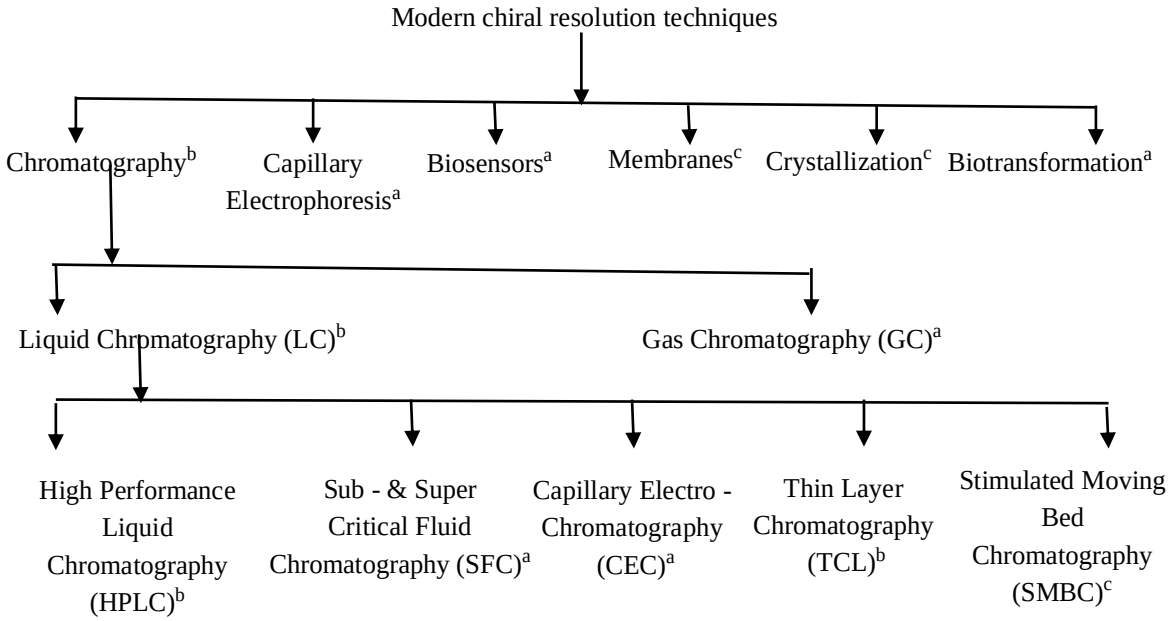
ve kuvarz gibi kristallenen rasemik bileşiklerin enantiyomerik kristallerinin ayrılmasında kullanılabilir. Çünkü bunların kristalleri birbirlerinin ayna görüntüleri gibidir (Şekil 1.10). Bu tipik teknikler, enzimatik süreçlerde enantiyomerlerden birinin bozunması ve kristallendirme işlemlerinin sınırlı örneğe uygulaması gibi dezavantajlar nedeniyle rutin laboratuvar işlemlerinde belli bir prestije erişilememiştir. Bunlara ilaveten, bu yöntemler; normal örneklerde bu işlemler analitik ölçeklere uygulanamamaktadır (Layh ve ark. 1994).

1.6.2. Modern Metodlar

Günümüzde en pratik yöntemler kromatografi, biyosensör, elektroforetik, spektroskopi ve membran yöntemleridir (Pirkle ve ark. 1994, Cilurzo ve ark. 2010). (Şekil 1.11). Spektroskopik metotlar arasında; optik çevirme açılarını belirleme (polarimetri), İnfrared ve Nükleer Manyetik Rezonans (NMR) spektorskopileri kullanılmaktadır. Diferansiyel Tarama Kalorimetresi (DSC) ile de sadece rasemik karışımlar ve farklı enantiyomerler ayırt edilebilir. NMR spektroskopisinde kiral solvatlaştıcı reaktifler (KSR) kullanılarak kiral karbon atomlarının kimyasal kaymalarının değişmesi sağlanabilir.



Şekil 1.10 Kuartz ve sodyum amonyum tartarat kristallerinin stereoyapıları

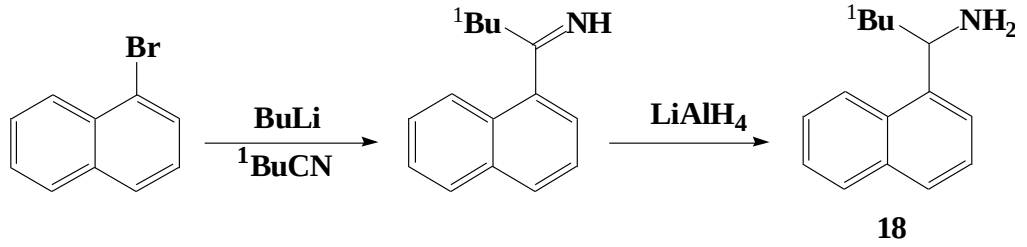


Şekil 1.11 Kiral rezulüsyonun farklı yolları: a, analitik; b, analitik ve preparatif; c, preparatif

Bunlara ilaveten, diferansiyel taramalı kalorimetri (DSC) ve spektroskopik yöntemler, model olarak kiral ve non-kiral safsızlıkları belirlemede duyarlıdırlar. Bunun dışında, hem izomer hem de enantiyomer karışımlarının küçük varyasyonlarında bile hassaslık ve duyarlılık gösterebilirler. Bu yöntemler, günümüzde hazırlık aşamasında başarısız olabilmektedir. 1994 yılında kiral bir membran kullanılarak enantiyomerler ayrıştırılmıştır (Pirkle ve Bowen 1994). Ancak bu yöntem henüz tam olarak gelişmemiştir. Kiral çözünür elektroforetik teknikler arasında kılcal izotakoforez (CIP), kılcal izoelektrik odaklama (CIEF), kılcal bölge elektroforezi (CZE), kılcal jel elektroforezi (CGE), affinite kılcal elektroforezi (ACE) ve mikroişlemciler üzerinde ayırma gibi çeşitli kapiler elektroforez yöntemler kullanılmaktadır. Diğerlerinden farklı olarak CZE tekniği, bu amaçla düzenli olarak kullanılmaktadır (Eeckhaut ve ark. 2009). Başka bir deyişle elektroforetik metotlardaki dezavantajlar, kiral alanlardaki çalışmaları kısıtlamış ve yeterince büyümesine engel olmuştur. Ayrıca, elektroforetik yöntemler, kiral ayırma teknikleri için çok gerekli iken preparatif ölçeklerde kullanılmamalıdır.

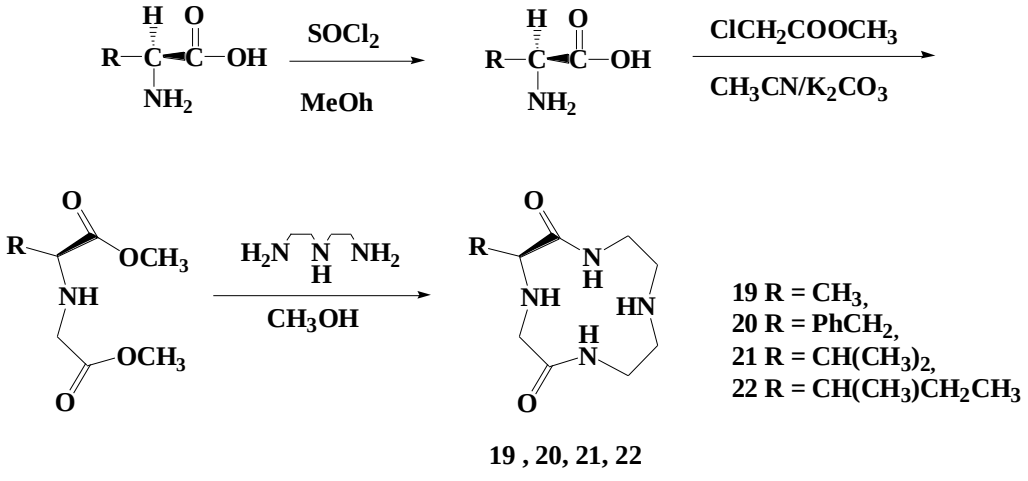
2. KAYNAK ÖZETLERİ

Port ve arkadaşları, rasemik olarak sentezledikleri bileşik **18**'i kromatografik yöntemle enantiyomerlerine ayırdılar (Port ve ark. 2000). Bu bileşiği, çeşitli karboksilik asitler ve alkoller (1-fenil-1-metoksiasetik asit, 1-fenil-1,2-etandiol, 3-fenilbütanoik asit, ibuprofen, α-bromoasetik asit vb.) için kiral solvatlayıcı reaktif (KSR) olarak denediler. 400 MHz NMR ile yaptıkları denemelerinde yüksek bir enantiyomerik yarılma sağladılar. (Port ve ark. 2000). NOE (Nuclear Overhauser Effect) yöntemi ve diğer yöntemlerle kompleksleşme oranı ve türünü araştırdılar. Oluşan diastereomerdeki benzer bir geometriyi bu komplekslerdeki π–π ve hidrojen bağlarıyla açıkladılar.



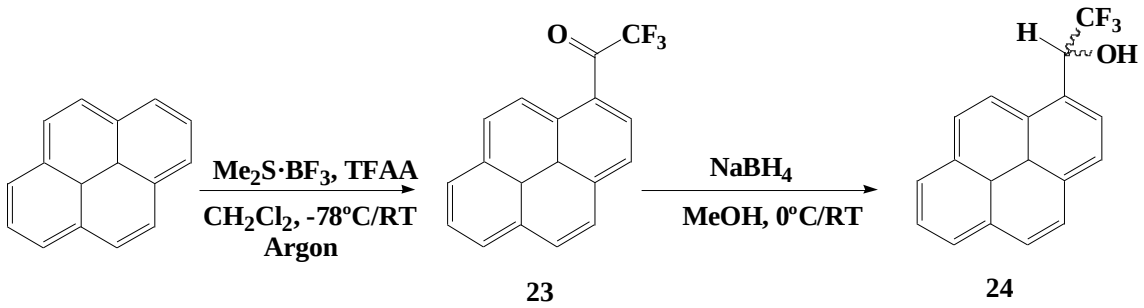
Şekil 2.1. KSR **18**'in sentezi

Yuan ve arkadaşları, kiral amino asitlerden yola çıkarak makrosiklik yapıda dioksosiklinler **19-22** sentezlediler (Yuan ve ark. 2002). Bu bileşiklerin mandelik asit ve türevlerinde enantiyomerik ayrım (1.2 ile 8.4 Hz arasında) sağladığı bildirilmiştir (Şekil 2.2).

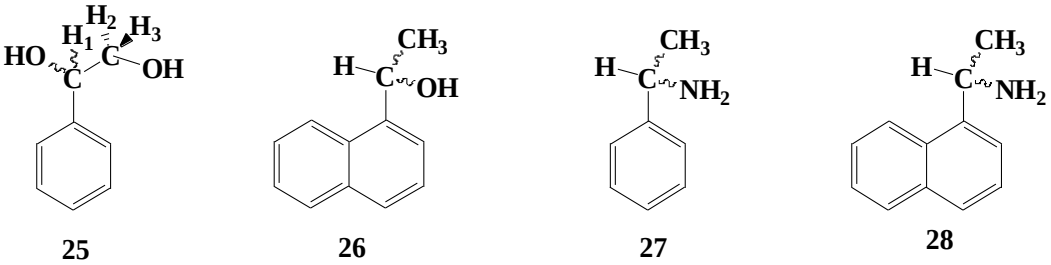


Şekil 2.2. Dioksosiklen**19-22**'nin aminoasitlerden sentezi

Munoz ve Virgili (2002) rasemik formda sentezledikleri bileşik **24'**ü preparatif HPLC ile enantiomerik rezolüsyonunu gerçekleştirdiler. Bileşik **24,** çeşitli aromatik amin ve alkollerin enantiyomerik yarılmasında KSR olarak kullanıldı (Şekil 2.3). Çalışmada, piren halkasının enantiomerik yarılmayı arttırıcı etkisi olduğu belirtildi (0.003-0.012 ppm).

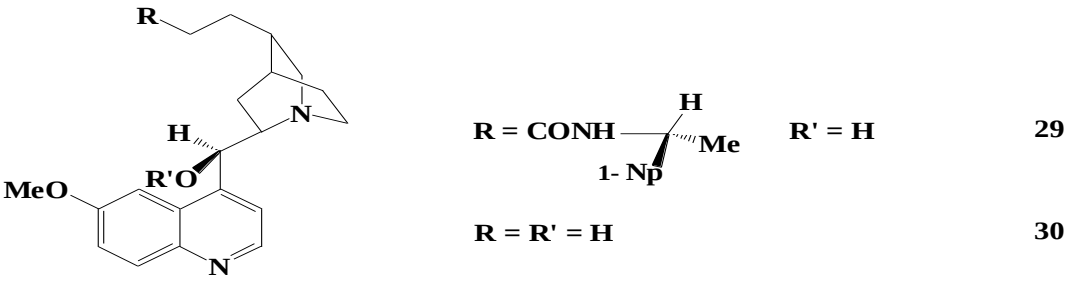


Şekil 2.3. Piren halkalı KSR **24**'ün sentez basamakları



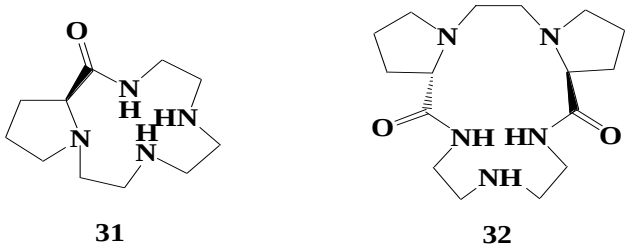
Şekil 2.4. KSR **24**'ün enantiyomerik yarılmalarında kullanıldığı analitler

Benzer amaçlarla Uccello-Barretta ve arkadaşları (2003) kinin çift bağlarını türevlendirmek suretiyle kinin karbamoil türevli bileşik **29 ve 30'**u sentezlediler. Bu bileşikleri NMR spektroskopisi vasıtasıyla çok sayıda kiral amin, eter, keton, karboksilik asit ve esterin enantiomerik yarılmasında KSR olarak denediler. Onlar, kinin türevi bileşiklerin de kendisine benzer enantiyomerik yarılma (90 Hz'e kadar) özellikleri olduğunu gösterdiler.

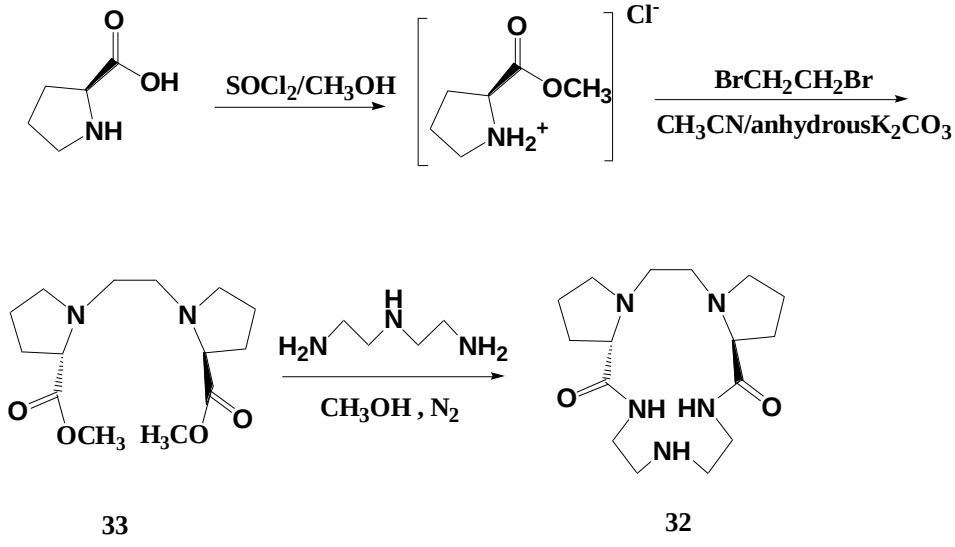


Şekil 2.5. KSR **29** ve **30** bileşiklerinin yapısı

Yang ve çalışma arkadaşları (2004), L-prolinden türetilen kiral rijit dioksopoliamin makrosiklik **31** ve **32**'yi mandelik asit ve türevleri, dibenzoiltartarik asit ve naproksen gibi analitlerin enantiomerik yarılmasını incelemek üzere sentezlediler. Bu çalışmada, 1:2 KSR/Analit oranı kullanıldığında en iyi seçiciliği 13.2 Hz ile mandelik asit ile gösterdiği rapor edildi.

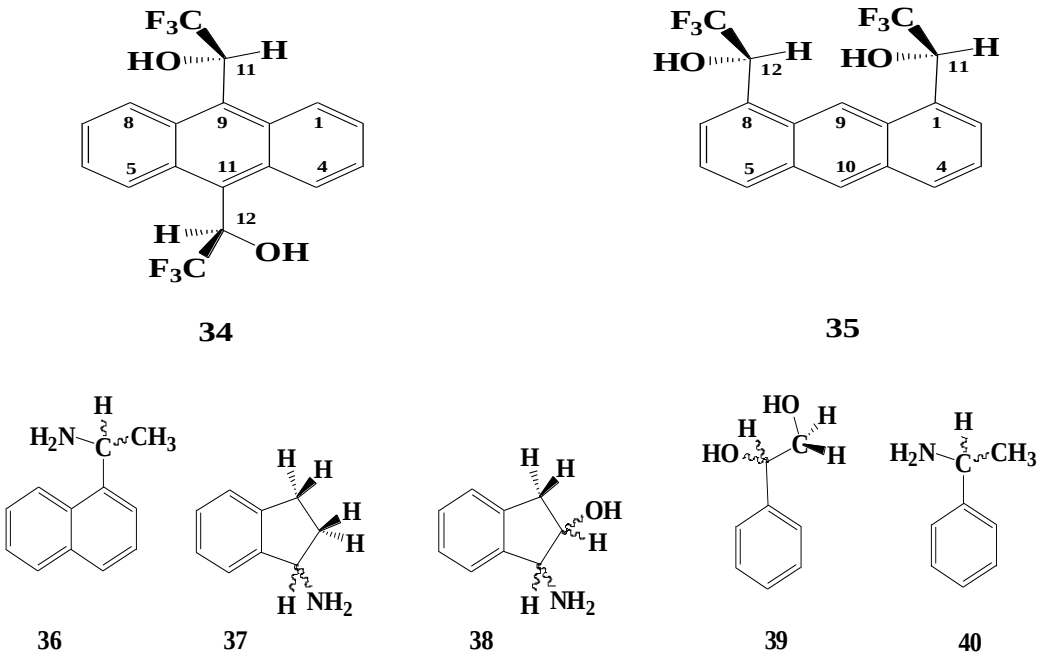


Şekil 2.6 Kiral makrosiklik dioksopoliamin **31** ve **32**'nin yapıları.



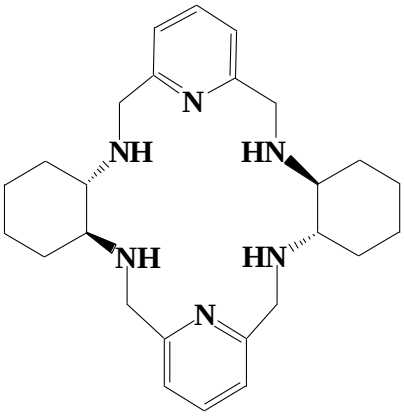
Şekil 2.7. KSR **32** bileşiğinin sentezi

Pe´rez-Trujillo ve arkadaşları (2005) **34** ve **35** yapılarının enantiyomerlerinin sentezini ve konformasyonel davranışlarını araştırarak, onları KSR olarak kiral amin, alkol ve diolleri analitlere (**36-40)** karşı test ettiler (Şekil 2.8). Yazarlar, bu KSR'lerle NMR spektroskopisi kullanarak 0.007-0.034 ppm değerlerinde iyi bir seçicilik gösterildiğini rapor ettiler.

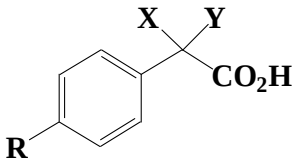


Şekil 2.8. Analit **34-40** yapıları

Poliazamakrosiklik **41** yapısı, mandelik asit ve benzer yapıdaki çeşitli karboksilik asitlerin (**42-45**) enantiyomerik fazlalığının belirlenmesi amacıyla kiral solvatlaştırıcı reaktif olarak kullanılmıştır (Şekil 2.9). KSR **41**'in düşük miktar (0.125 ekivalent) kullanılarak yüksek enantiyomerik yarılma ($\Delta\Delta\delta$ = 0.20 ppm'e kadar) değerleri elde edildi.



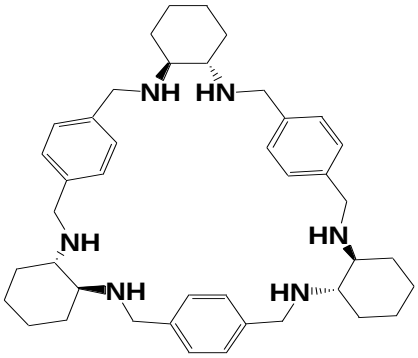
(S,S,S,S)-41



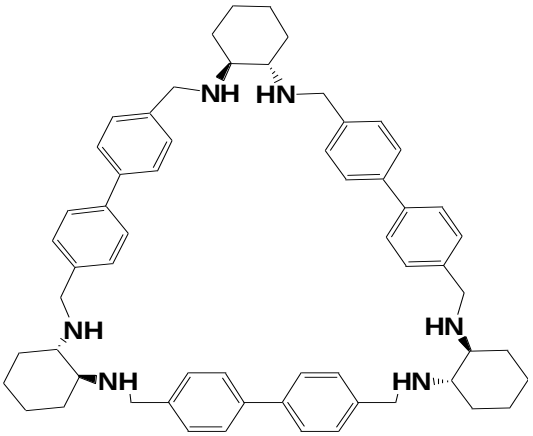
42 (R=H, X=OH, Y=H)
43 (R=Cl, X=OH, Y=H)
44 (R=OMe, X=OH, Y=H)
45 (R=H, X=OMe, Y=H)

Şekil 2.9. KSR **41** ve kiral karoksilli asit analitlerin (**42–45**) yapısı

Üçgen yapıdaki kiral **46** ve **47** makrosiklikler, kondensasyon reaksiyonu ile sentezlenerek bazı alkol, siyanohidrin ve proparjil alkolllerin konformasyonlarını belirlemek üzere NMR spektroskopisinde kiral kaydırıcı reaktif olarak kullanıldı (Tanaka ve ark. 2007). Yazarlar, bu KSR'lerle 30 Hz değerlerine varan enantiyomerik yarılma değerleri elde etmeyi başardılar.



(S,S,S,S,S,S)-(+)-46

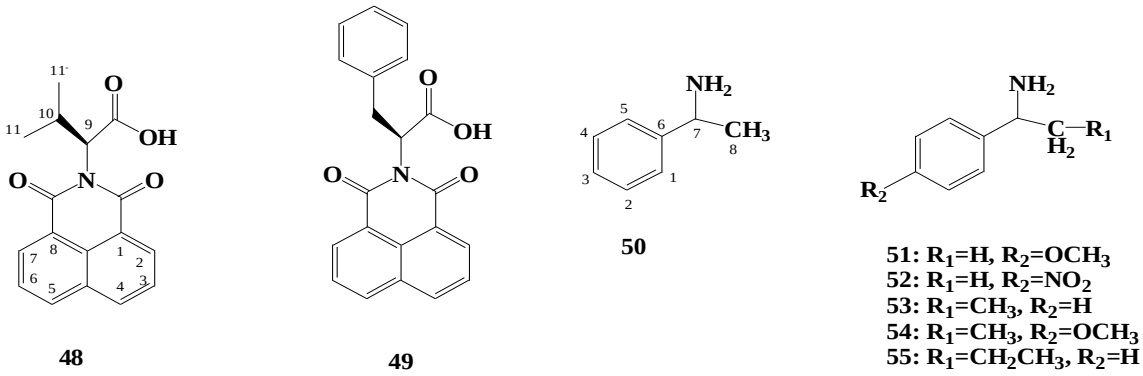


(S,S,S,S,S,S)-(+)-47

Şekil 2.10. KSR **46** ve KSR **47'**nin yapıları

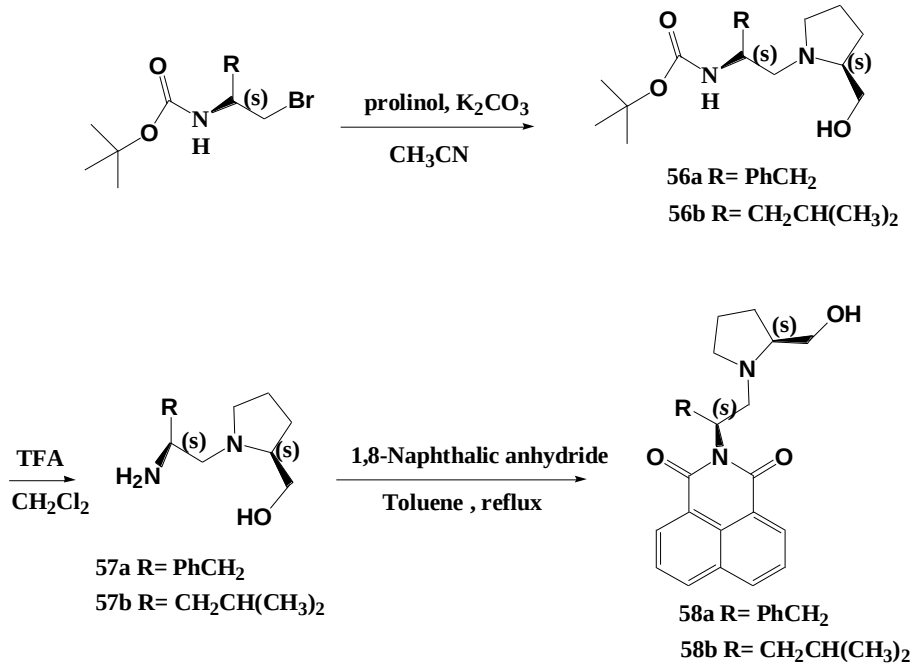
^{1}H NMR spektroskopisi kullanılarak **51-55** analitlerin enantiyomerik yarılmaları **48** ve **49** yapısındaki benzo[de]izokinolin-1,3-dion amino asitlerle gerçekleştirildi. Tek stereojenik merkezli basit yapılarılarıyla özellikle KSR-**48** yapısının 66.0 Hz'e kadar

olan değerlerde iyi bir yarılma gösterdiği belirlendi. İlave çalışmalarında, kompleksleşme oranı ve bağlanma sabitleri araştırılmıştır (Luo ve ark. 2007).



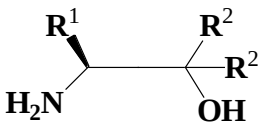
Şekil 2.11. KSR **48-49** ve analit **50-55**'in yapıları

Luo ve arkadaşları yukardaki çalışmadan aldıkları ilhamla 2008 yılında tasarladıkları iki adet amfifilik kiral reseptör **58a ve 58b**'yi sentezlediler (Şekil 2.12). Onlar, bu bileşikleri mandelik asit ve türevleri için enantiyomerik yarıcı reaktif olarak kullandılar. Çalışmadan elde edilen sonuçlara göre, KSR **58a**'nın sadece apolar analitlere karşı iyi bir enantiomerik yarılma özelliği (6.9-85 Hz) sergilemediği aynı zamanda polar çözücülerde polar analitlere karşı da benzer davranış gösterdiği tespit edildi (Luo ve ark, 2008).

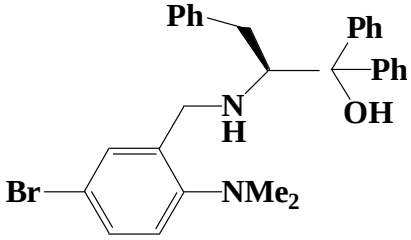


Şekil 2.12. KSR **58a** ve **58b** için sentez yöntemi

Bir çok amino alkol **59-62** bir seri kiral karboksilli asidin kiral solvatize edici reaktifi olarak kullanmak üzere sentezlendi. Bu çalışmada KSR **62**'nin özellikle test edilen karboksilli asitlerin tosil türevlerine karşı etkin bir enantio ayrıştırmaya sahip olduğu tespit edildi. Elde edilen sonuçlar itibari ile bazı amino asitlerin mutlak konfigurasyonunun tespitinin mümkün olabileceği gösterildi (Wang ve ark. 2008).



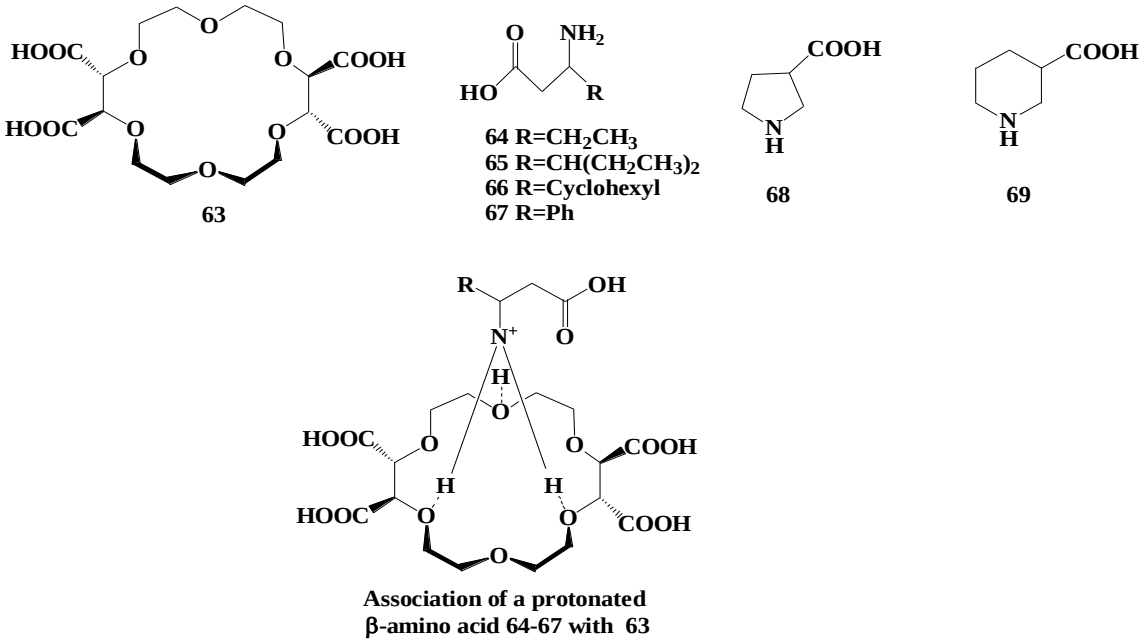
59 : R^1 = Me_2CH, R^2 = Ph
60 : R^1 = $PhCH_2$, R^2 = Ph
61 : R^1 = $PhCH_2$, R^2 = H



62

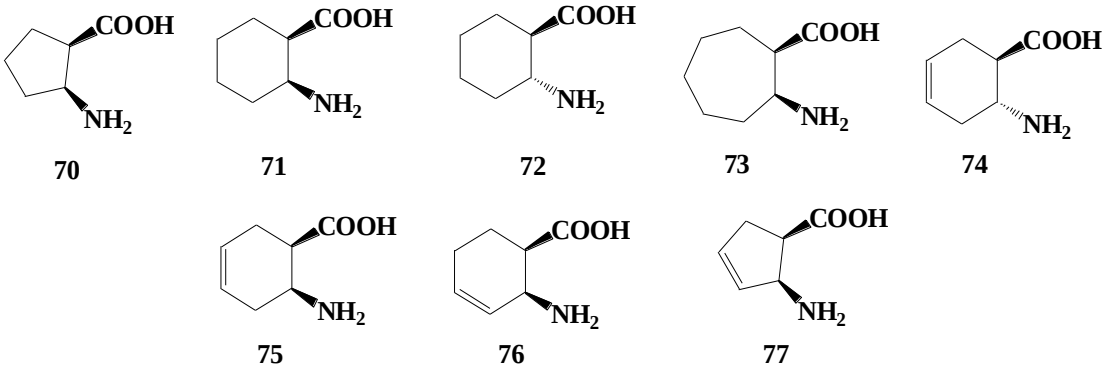
Şekil 2.13. Amino alkol KSR **59**–**62** yapıları

Amino asit **64-69** analitlerin α-metilene ve β-metin hidrojen atomlarının kimyasal kaymaları ölçülerek taç eter **63**'ün iyi bir KSR olduğu gösterildi. Böylece, bu sonuçlarla bazı analitler için mutlak konfigurasyonlarının tespitinin mümkün olduğu tespit edildi (Wenzel ve ark. 2009).



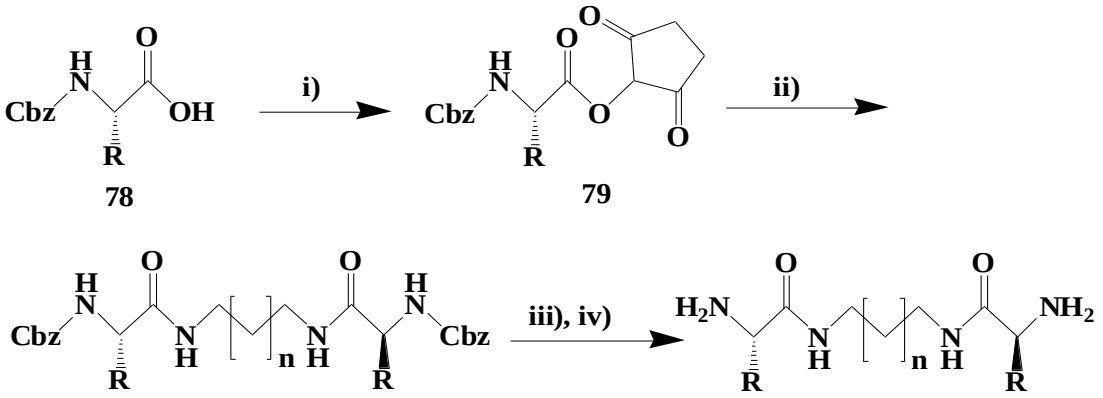
Şekil 2.14. KSR **63** ve protonlanmış β-amino asit ile kompleksleşmesinin yapısı

Benzer şekilde taç eter **63** kullanılarak β-aminoasitler **70-77**'nin mükemmel bir enantiomerik ayrıştıması sağlandı. Amino asitlerin bu etkin ayrıştırmasının; amin protonlanması neticesinde oluşan amonyum iyonu ile taç eter halkası arasında meydana gelen üç ayak şeklindeki hidrojen bağından kaynaklandığı ifade edildi (Wenzel ve Ark. 2010). Bu çalışmada, methanol-*d*4 içinde taç eter ve β-amino asit çözülerek, taç eter ile β-amino asitler arasında nötralleşme sonucunda amonyum iyonları oluşur. β-amino asitlerin iki stereojenik merkezine bağlı α-hydrojenlerinin enantiomerik farklılandırılması ile ölçümler yapılmıştır.



Şekil 2.15. KSR **63** ile test edilen *β*-amino asitler

Şekil 2.16'dan görüleceği üzere yaygın amino asitlerden çıkılarak çeşitli bis(amino amides) sentezlenerek bazı amino asitlerin enantiomerik yarılmasında kullanılmıştır (Altava ve ark. 2010). Bu çalışmada, amino asidin yan kollarının enantiomerik ayrıştıma işleminde önemli bir role sahip oldukları tespit edildi. Analitlerle KSR'ler arasındaki bağlanmayı incelemek amacıyla ESI-MS, NMR, DSC, and molecular modelleme gibi yöntemlere başvurulmuştur. Veriler amino asitten protonun KSR'ye tranferi neticesinde oluşan iyon çifti ile farklandırma işleminin gerçekleştiği ifade edilmektedir.

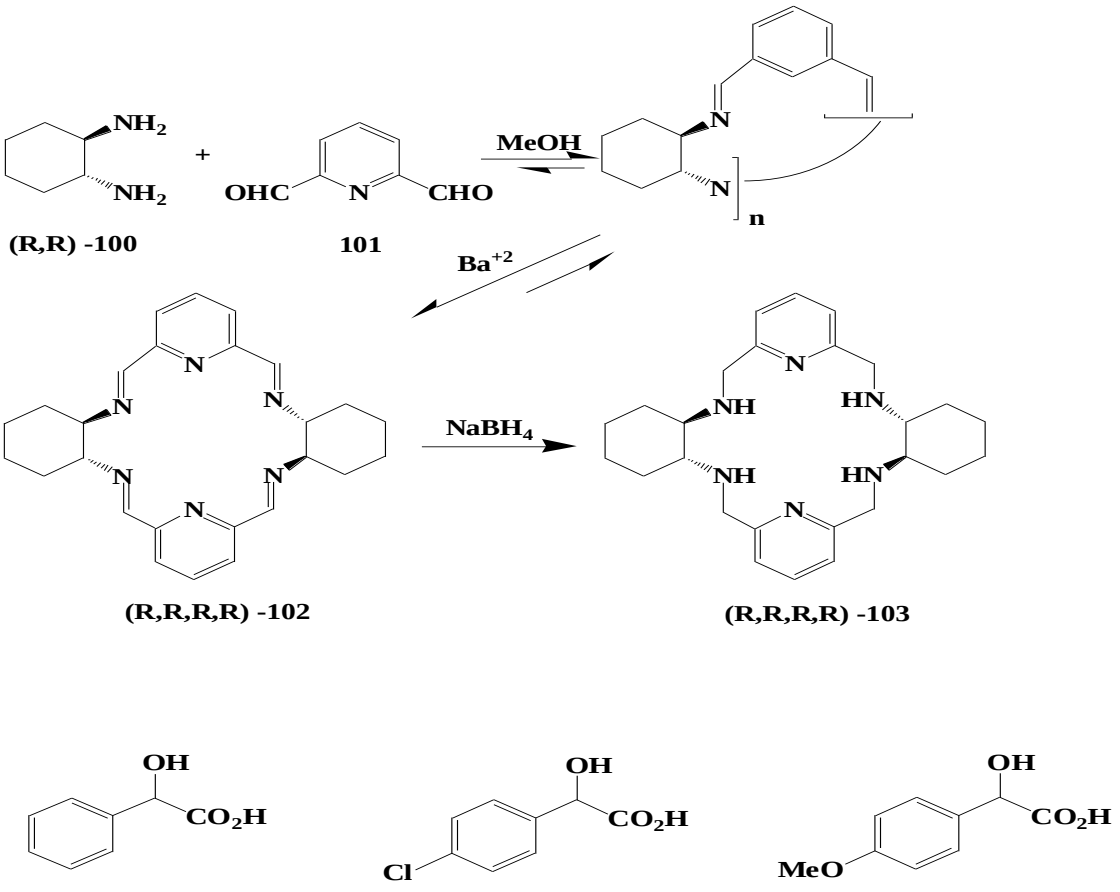


80-83; n = 0, 2, 4, 6; R = $CH(CH_3)_2$
84-89; n = 0, 1, 2, 3, 4, 6; R = CH_2Ph

90-93; n = 0, 2, 4, 6; R = $CH(CH_3)_2$
94-99; n = 0, 1, 2, 3, 4, 6; R = CH_2Ph

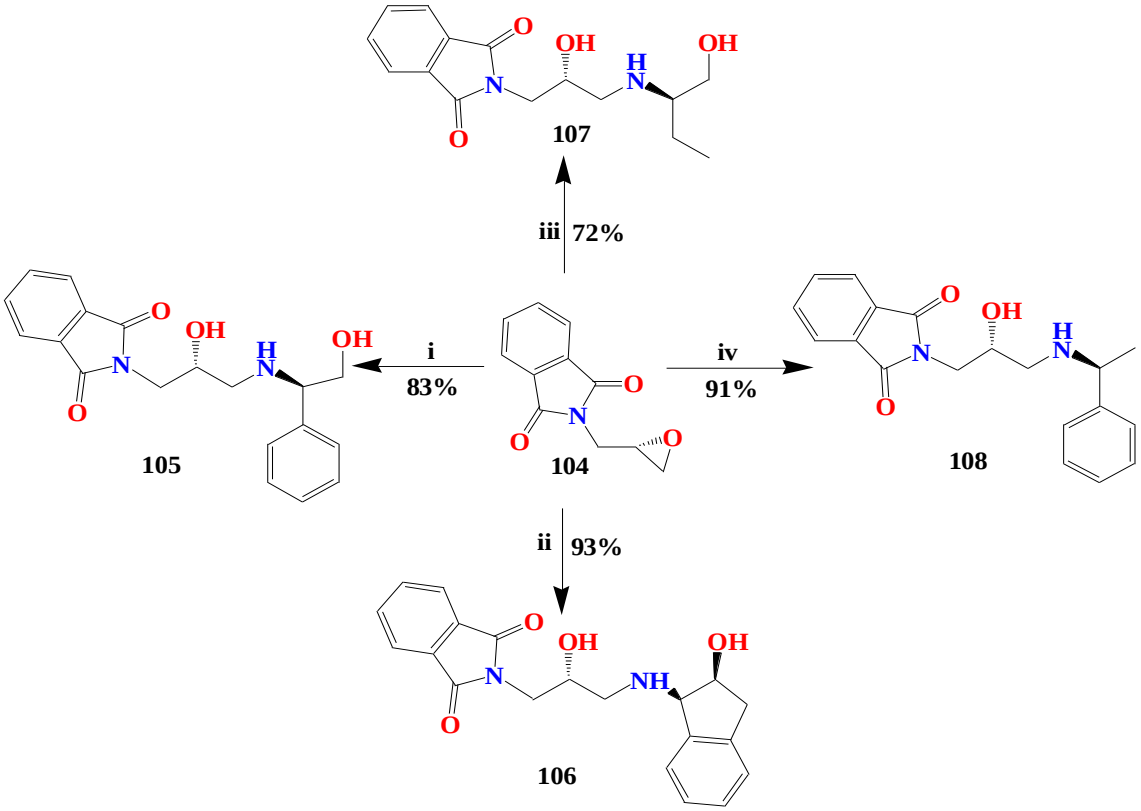
Şekil 2.16. Kiral bis(amino amit) ligandların sentezi. [Reaktifler ve şartlar: (i) DCC, N-hydroksisüksinimid, THF, rt; (ii) $H_2NCH_2(CH_2)nCH_2NH_2$, DME, rt; (iii) HBr/AcOH; (iv) $NaOH_{aq}$]

KSR **103**, kiral 1,2-diaminosikloheksan ile piridin esaslı dialdehitin kondensasyon tepkimesini takiben Ba^{2+} iyonunun template etkisi ile dimerik halkalaşmayi izleyen $NaBH_4$ indirgemesi sonucunda sentezlenmiştir (Şekil 2.17). Bu çalışmada; mandelik asit, *p*-kloro- and *p*-metoksimandelik asit'lerden oluşan anilitlerin (Şekil 2.17) KSR **103** ile 1:1 oranındaki kiral solvatlama deneylerinde 0.13 ppm'e varan kiral farklandırma değerleri elde edilmiştir (Busto ve ark. 2010).



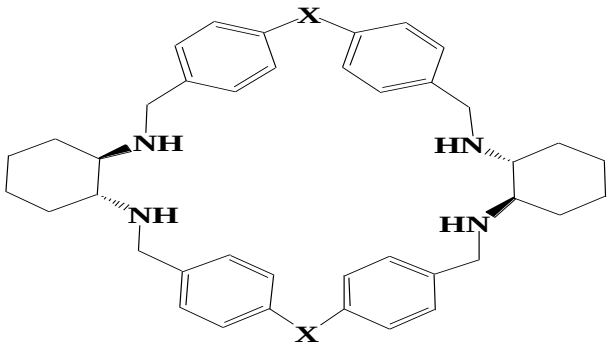
Şekil 2.17 KSR **102** ve **103**'ün sentezi ve kiral yarılması gerçekleştirilen analitler

KSR **106-108;** (*R*)-*N*-(2,3-epoksipropil) ftalimit (NEP)'in çeşitli kiral aminler ve amino alkol ile regiseçici halka açılması tepkimesi ile sentezlendiler (Şekil 2.18). Bu reaktiflerin mandelik asit ve türevlerine yönelik kiral solvatlayıcı özelikleri araştırılmış olup özellikle KSR 108 ile 30 Hz'e varan kiral yarılma değerleri elde edildi (Bozkurt ve ark. 2011).



Şekil 2.18. KSR **105** ve **108**'in sentezi [(i)-(iv): Çözücü: 2-propanol, ve kiral amin ya da amino alkol, refluks]

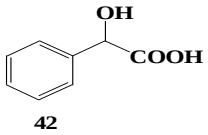
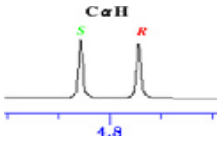
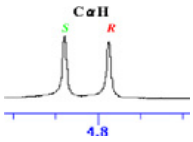
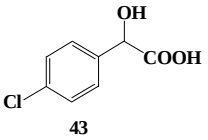
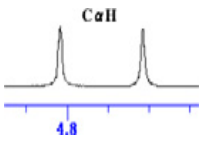
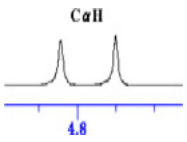
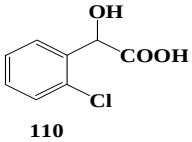
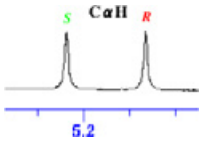
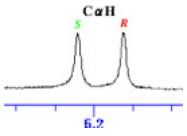
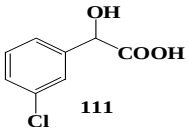
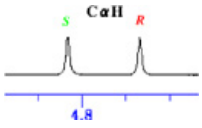
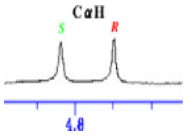
Tanaka ve arkadaşları, (*R*,*R*)-1,2-diaminosikloheksan ile ekivalent dialdehidlerin [2+2] siklokondensasyonundan kiral makrosiklik aminler **109a** ve **109b**'yi hazırladılar. Onlar, bu makrosikliklerin mandelik asit ve türevlerinin enantiomerik oranlarının belirlenmesi için uygun birer kiral solvatlayıcı reaktif olduğunu gösterdiler (Tablo 2.1), (Tanaka ve ark. 2011).



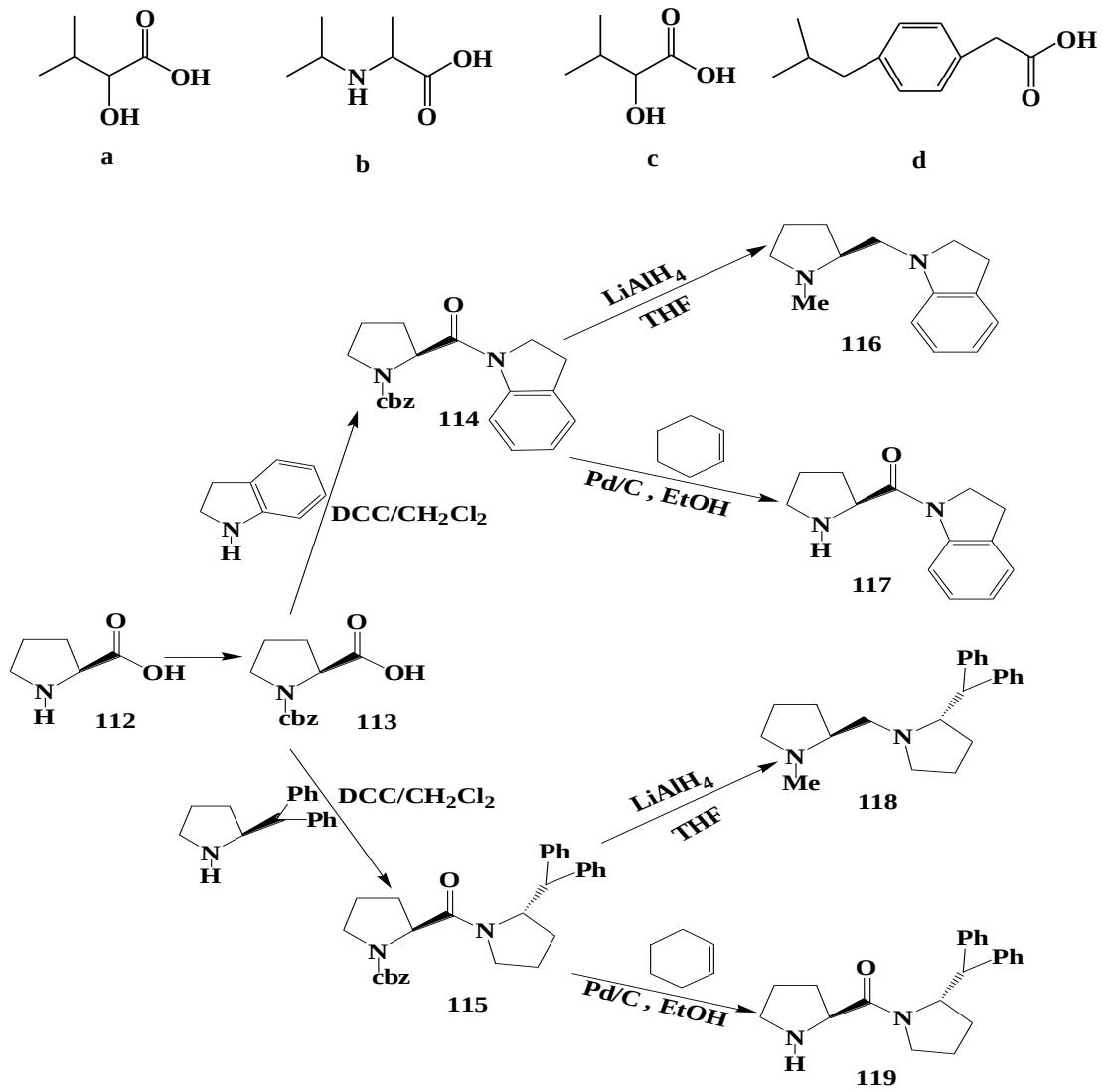
(R,R,R,R)-109 **a: X = CH_2**
b: X = O

Şekil 2.19. KSR **109a** ve **109b**'nin yapısı

Tablo 2.1 Rasemik mandelik asit ve türevlerinin KSR **109a** ve **109b'**nin 0.25 mol oranı ile 400 MHz, $CDCl_3$ içinde alınmış kısmi ^{1}H NMR spektrumları

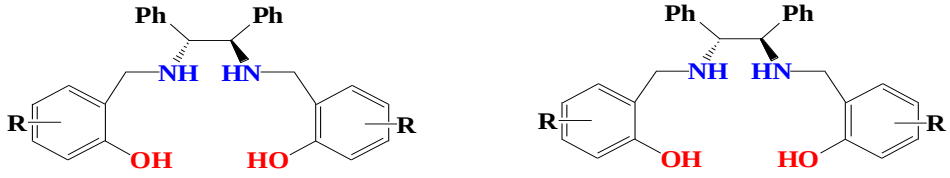
		109a		**109b**	
No	K. Asit	Spektrum	ΔΔδ^b (ppm)	Spektrum	ΔΔδ^b (ppm)
1	 **42**		0.058		0.052
2	 **43**		0.101		0.066
3	 **110**		0.085		0.059
4	 **111**		0.083		0.071

Naziroğlu ve arkadaşları, L-prolin türevi dört adet kiral reseptör **116-119** sentezlediler (Şekil 2.20). ^{1}H NMR spektroskopi yöntemi ile bu kiral reseptörleri çeşitli karboksilli asitlerin enantiomerik fazlalıklarını değerlendirmek üzere KSR olarak kullandılar. En iyi kiral solvatlayıcı reaktif **117** ile karboksilli asitlerin enantiomerik fazlalıklarını ölçmenin mümkün olabileceğini gösterdiler (Naziroglu ve ark. 2011).

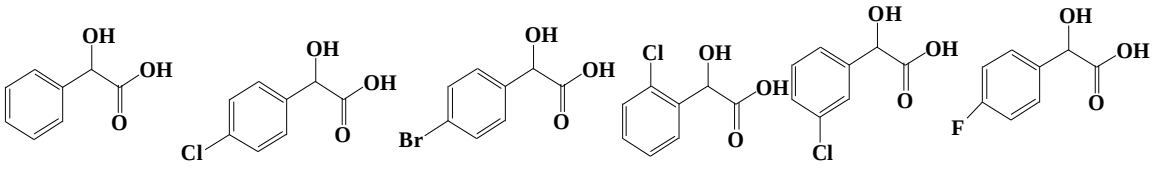


Şekil 2.20. L-prolin türevi kiral KSR **116-119** sentezi

Lu ve arkaşları (2011) C_2-Simetrik salen ligand temelli yeni bir seri aminofenol bileşiği **120-123,** kiral 1,2-diaminoetanın türevlerinden sentezlediler (Şekil 2.21). Hazırladıkları kiral bileşikleri değişik kiral karboksilli asitler **42, 43, 53, 110, 111, 124** için kiral solvatlayıcı reaktif olarak denediler. İlgi çekici sonuçlar tabloda verilmiştir (Tablo 2.2).

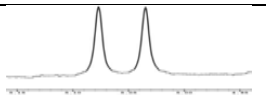
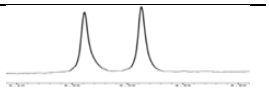
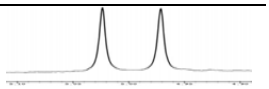
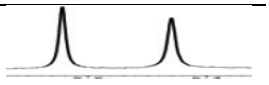
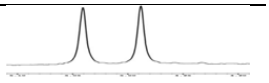
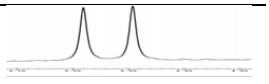


Şekil 2.21. Kiral solvatlayıcı reaktif **120-123**'ün yapıları



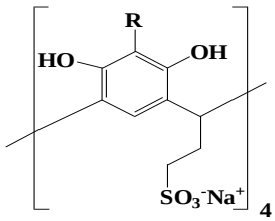
Şekil 2.22. KSR **120-123** ile test edilen kiral karboksilli asitlerin yapıları

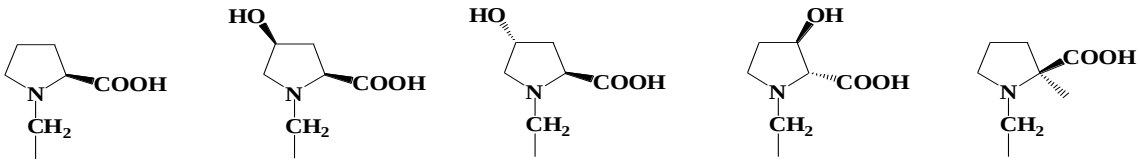
Tablo 2.2. Karboksilli asitlerin KSR **120** varlığında ^{1}H NMR spektroskopisi (500 MHz) ile $CDCl_3$ ve 25 ^{o}C'deki eşdeğer olmayan kimyasal kayma (ΔΔδ) değerleri.[a]

Entry	Carboksilli asit	ΔΔδ (ppm)	ΔΔδ (Hz)	Spektrumlar
1	42	0.042	21.02	
2	43	0.051	25.74	
3	53	0.052	26.21	
4	110	0.092	46.08	
5	111	0.053	26.27	
6	124	0.042	21.20	

[a] Örnekler; 1:3 KSR/ karboksilli asit oranı, 0.6 mL toplam hacimde son konsantrasyon 15 ve 5 mM olarak $CDCl_3$ içinde alınmıştır.

Suda çözünebilir α-metil-*L*-prolinilmetil ünitesi taşıyan kaliks[4]resorsinaren dizayn edilerek; fenil veya indol halkası, piridilli amonyum iyonu, indan veya dihidroindol halkası içeren çeşitli amino asit türevlerine karşı NMR'da kiral solvatlayıcı reaktif olarak kullanıldı (Şekil 2.23). Çalışmada, prolin ünitesinin seçiciliği araştırılarak önceki çalışmalarla karşılaştırması yapılmıştır. Araştırmacılar, α-methyl-L-prolinilmetil türevli kaliksarenin enantiomerik ayrımının bir çok benzer ünite içeren reaktiften daha üstün olduğunu gösterdiler (Pham ve Wanzel, 2011).

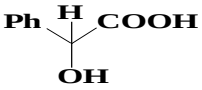
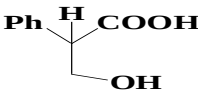
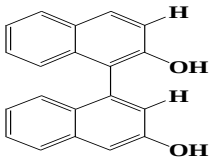




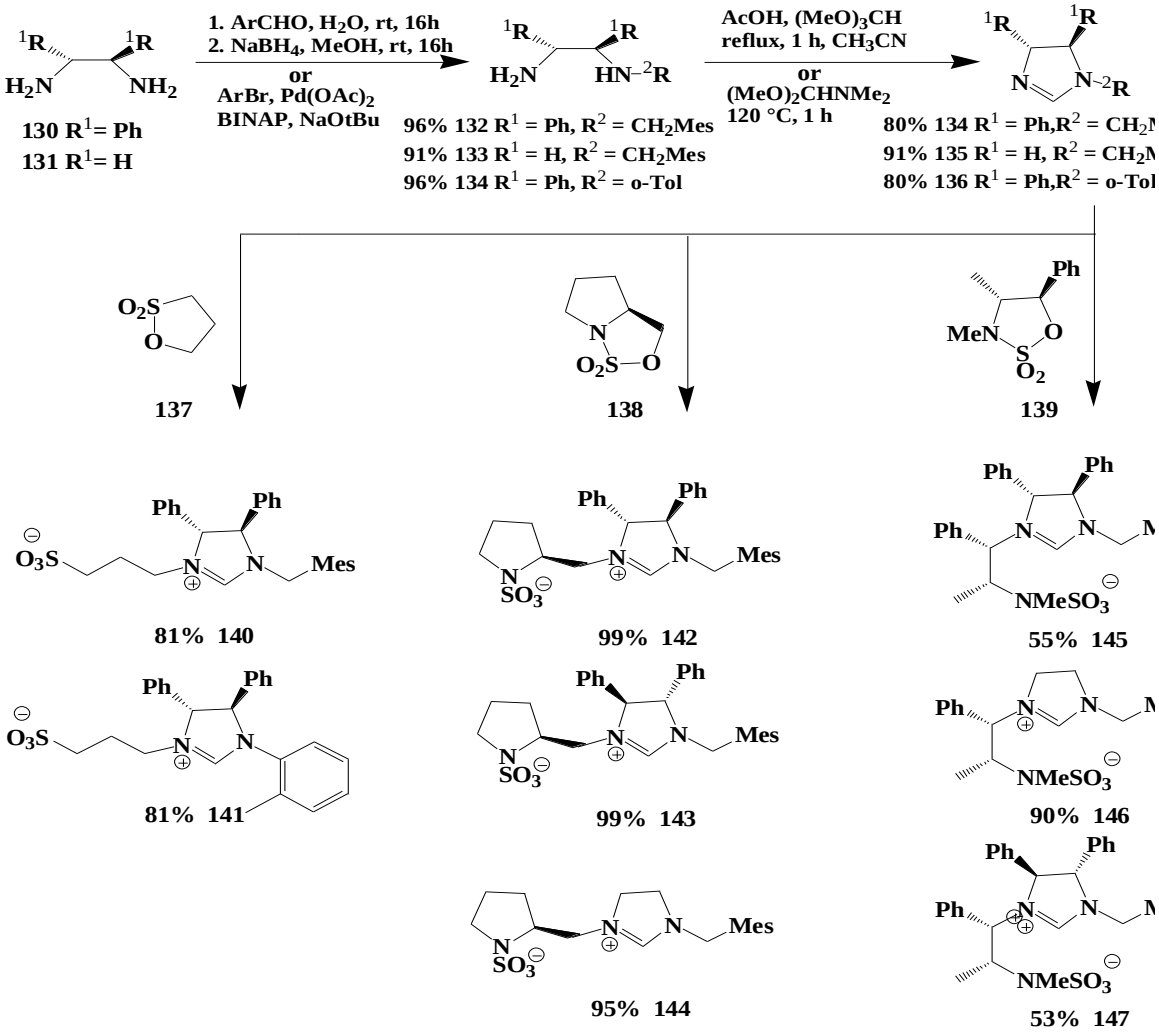
125 126 127 128 129

Şekil 2.23. α-Metil-*L*-prolinilmetil ünitesi taşıyan kaliks[4]resorsinaren KSR **125–129'**un yapıları

Table 2.3 Zwitter iyon **147** varlığında ^{1}H NMR (400 MHz $CDCl_3$ içinde çeşitli analitleri kimyasal kayma farklılıkları (ΔΔδ)

No	Bileşik	δ (ppm)	δ (ppm) **19** ile	^{1}H ΔΔδ (Hz)
1	 **42**	5.19	5.00/4.85	60 (CH)
2	 **148**	4.06	3.98/3.93	20 (CH)
3	 **149**	8.00	8.03/8.01	8.0 (CH)

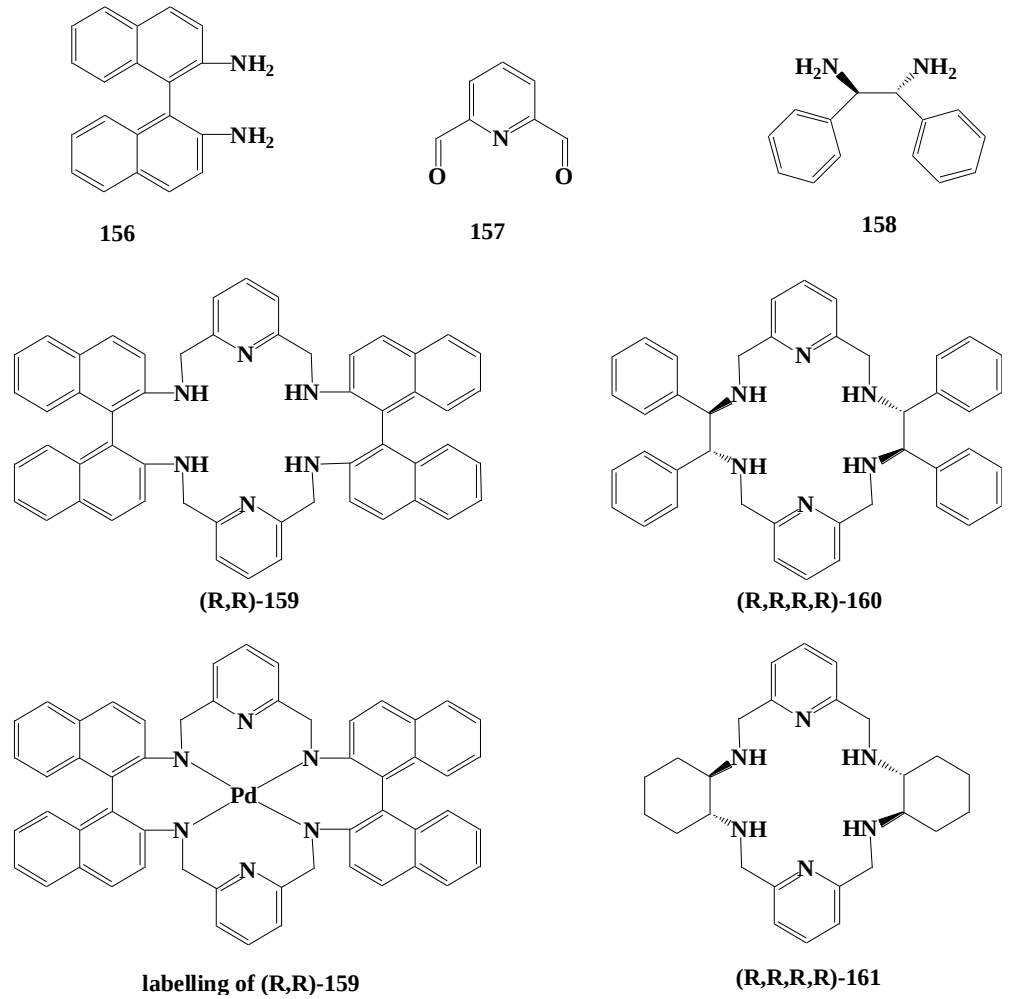
Alkoller, amino alkoller, tiyoller, nitro alkoller, siyanohidrinler, Mosher asidi, ve karboksilli asitler içeren bir çok analitin enantiomerik ayrıştırması, alkilsülfonat, sülfamat ve imidalinyum gruplu zwitter iyonlar taşıyan simetrik olmayan heterosiklik bileşiklerle incelendi (Şekil 2.24). Analitlere ait Cα-H'nine ait kimyasal kayma farklılık değerleri Tablo 2.3'te verilmiştir.



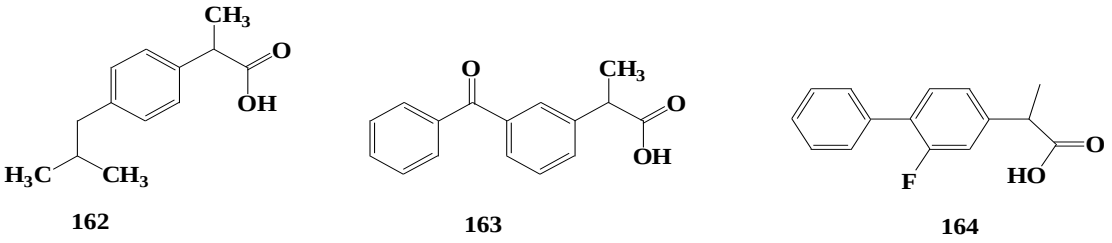
Şekil 2.24. İmidazolyum ve alkil sülfonat veya sülfamat içeren zwitter iyonik yapılar

Poliazamakrosiklik *R,R*)-**159** (*R,R,R,R*)-**160** bileşikleri kiral bir amin bileşiğinin kurşun (II) veya lantanit (III) metallerinin template etkisi halkalaştırıldıktan sonra sodyum bor hidrür ile indirgenmesini izleyen demetalleştirme gibi adımlar izlenerek sentezlendi (Şekil 2.25). Poliazamakrosiklik *R,R*)-**159** (*R,R,R,R*)-**160;** steroid olmayan

ilaçlar **162-164**'ün kiral ayrıştırma reaktifi olarak kullanımına yönelik yapılmış NMR deneylerinde 0.1 ppm değerlerde kimyasal kayma değerleri elde edildiği ifade edilmektedir (Gospodarowicz ve ark. 2012).

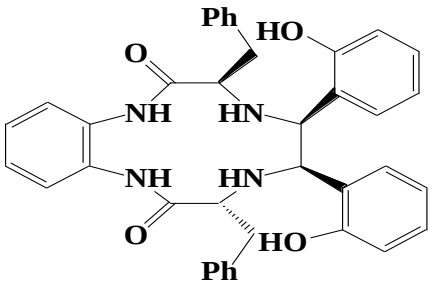


Şekil 2.25. KSR **156-161**'in yapısı ve **(*R*,*R*)-159** kompleksi

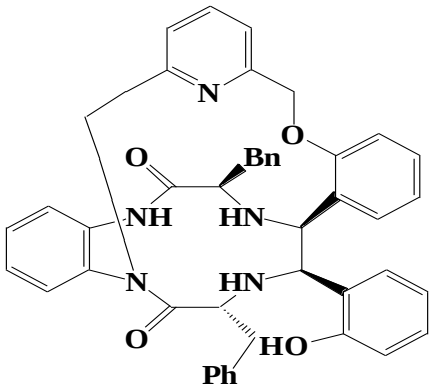


Şekil 2.26 Enantiomerik ayrıştırması yapılan analitler **162-164.**

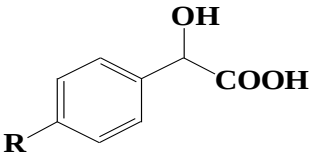
Birden fazla bağlanma yüzüne sahip kiral makrosiklik **165** ve **166;** analitler **167-173'**ün enantiomerik saflıklarını ölçmek üzere KSR olarak sentezlendiler. Elde edilen ^{1}H NMR eşdeğer olmayan kimyasal kayma değerleri (36 Hz'e varan) bu bileşiklerin bu amaçla kullanımlarının uygun olduğunu göstermektedir (Guo ve ark. 2013).



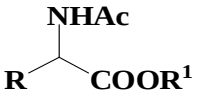
165



166



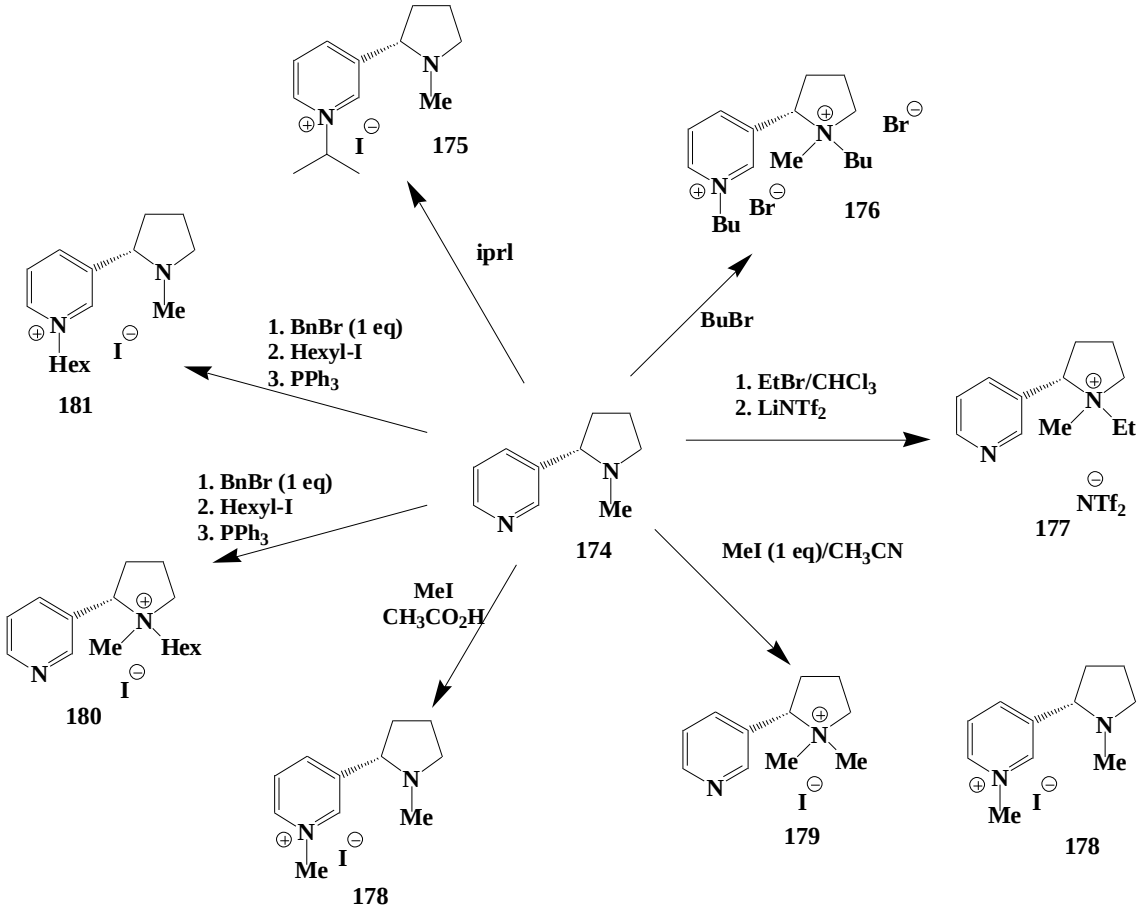
167: R = H
168: R = CH_3O



169: R =$H_3CSCH_2CH_2$, R^1 = H
170: R = Ph,R^1 = H
171: R =CH_3, R^1 = H
172: R = $(CH_3)_2CHCH_2$, R^1 = H
173: R = $(CH_3)_2CH$,R^1 = H

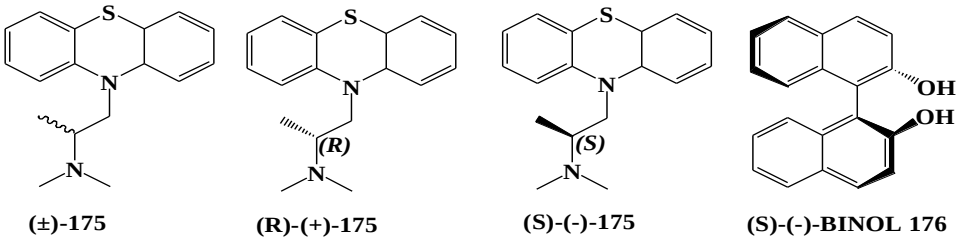
Şekil 2.27. Kiral makrosiklikler **165, 166'**nın ve karboksilli asit ve α-aminoasit **167-173** yapısı

Heckel ve arkadaşları, (-)-nikotin esaslı bir çok iyonik sıvı **175-181** sentezleyerek onları uygun alkil halojenürlerle kuaterner tuzlarına dönüştürdüler (Şekil 2.28). Anyon değişimi sonrası bu iyonik sıvılar KSR olarak ^{19}F and ^{1}H NMR spektroskopi yöntemleri ile Mosher ve mandelik asit gibi asitlerin enantiomerik diskriminasynonunda denendiler. Onlar, bu deneyleri polar olmayan çözücü ortamında metanol ilavesi ile yapılabileceğini gösterdiler (Heckel ve ark. 2013).



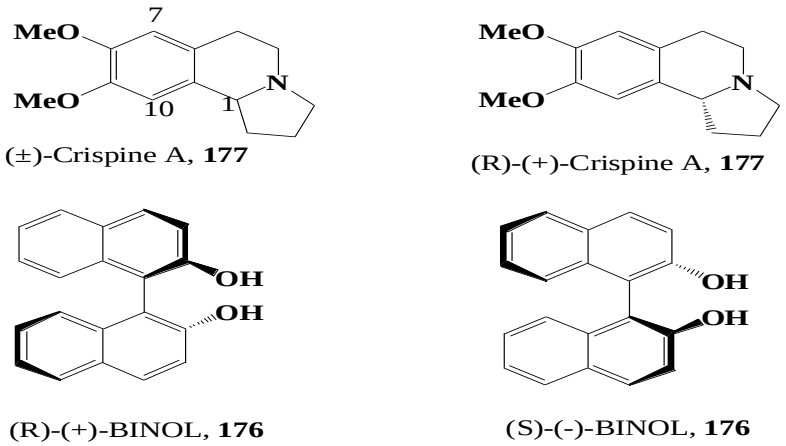
Şekil 2.28. (-)-Nikotin **174** esaslı iyonik sıvı **175-181** sentezi

Prometazin **175'**in enantiomerik saflığı ilk defa **KSR** (*S*)-**BINOL 176** kullanılarak ^{1}H NMR spektroskopi yöntemi ile ölçüldü. Aynı amaçla Chiralcel® OJ dolgulu HPLC kolonu kulanıldığında elde edilen sonuçlarla NMR verilerinin birbiriyle uyumlu olduğu görüldü (Borowiecki 2014).



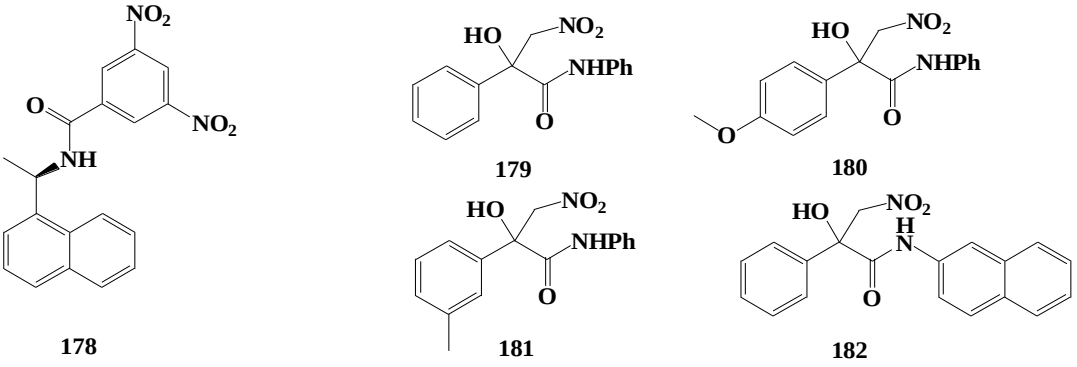
Şekil 2.29. Prometazin **175** ve (*S*)-BINOL **176**'nın kimyasal yapısı

Yuste ve arkadaşları KSR (*R*)- and (*S*)-BINOL **176'yı** kullanarak antitümör crispine A **177**'nin enatiomerik saflığını tespit etmek üzere kullandılar (Şekil 2.29). Döterokloroform veya perdöterobenzen içinde KSR **176** ile crispine A **177** enantiomerlerinin arasında oluşan diastereomerik konuk-konukçu komplekslerin ^{1}H NMR sinyalleri ile crispine A'nın enantiomerik saflığını hızlı ve kolay bir şekilde ölçülebileceğini gösterdi.



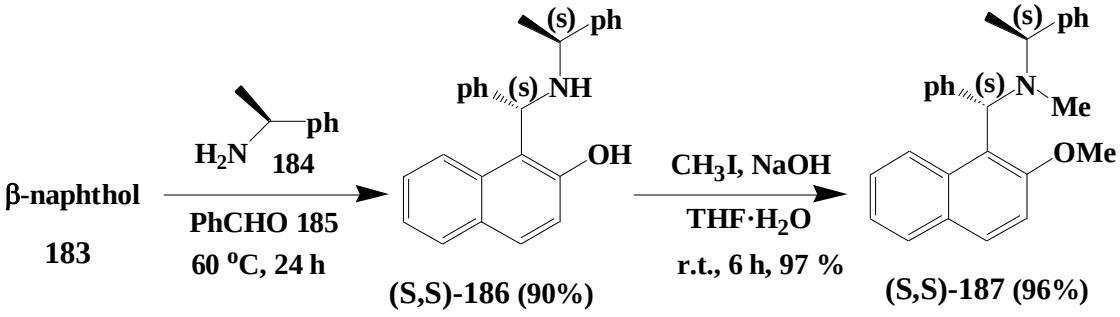
Şekil 2.30. Bileşik **176 ve 177**'nin yapısı

Wolff ve arkadaşları çok fonsiyonlu tersiyer alkoller için Whelk-O tipi KSR **178** kullandılar (Şekil 2.31). KSR'nin kristalografik analizinde iki conformasynun mevcut olduğu, bunların çözelti fazında da birlikte oldukları öne sürüldü. Bu konformasyonlardan birinin sadece bir enantiomerle π–π stacking, C-H/π etkileşimi and hydrojen bağı ile bağlanarak ekivalent olmayan NMR sinyallerine yol açtığı ve bu sayede **179-182** benzeri on sekiz analitin stokiyometrik oranlardaki kullanımlarıyla rezolüsyonları rapor edildi (Wolf ve ark. 2014).



Şekil 2.31. KSR **178** ve tersiyer alkoller **179–182**'nin yapısı

Chaudhary ve arkadaşları, 2-naftol'ün Mannich tepkimesi ile bir seri optikçe aktif aminonaftol hazırlayarak NMR ile rasemik mandelik asidin Cα-H sinyal ayrıştırılmasında KSR olarak kullandılar (Şekil 2.32). Kovalent olmayan etkileşimlerde aminonaftol türevi yapılarla seçicilik üzerine ilişki kurulumu amaçlanmış olup, alınan sonuçlarda; teorik ile deneysel enantiomerik saflık değerleri arasında lineer bir ilişki olduğu saptanmıştır. Bu sebeple, KSR **187** ile bilinmeyen herhangi bir mandelik asit numunesinin enantiomerik saflığının tespit edilebileceği sonuçlardan anlaşılmaktadır (Tablo 2.4), (Chaudhary ve ark. 2014).



Şekil 2.32. KSR **186** ve **187**'nin sentezi

Tablo 2.4. Aminonaftil türevi KSR **186** ve **187**'nin rasemik mandelik asit Cα-H sinyal kaymaları (Δδ = Kimyasal kayma farkı, ΔΔδ = Eşdeğer olmayan kimyasal kayma farkı)

No	KSR	Sinyal PhCH(OH)COOH	
		Δδ(ppm)	**ΔΔδ (ppm)**
1	(S,S)-**186**	-0.22	0.005
2	(S,S)-**187**	-0.24	0.012

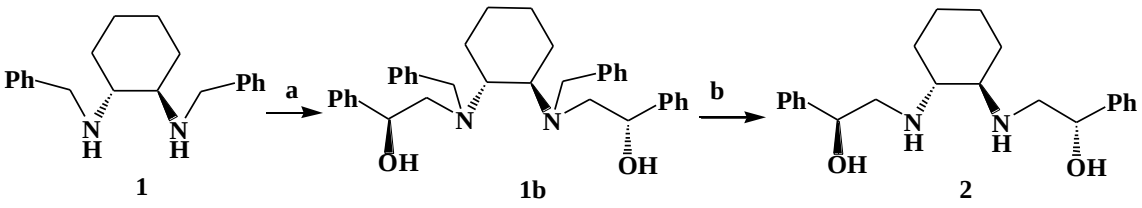
3. MATERYAL VE METOT

3.1. Ekipman ve Kimyasallar

Erime noktası, GALLENKAMP Model erimenoktası cihazı ile açık kapiler ile tespit edilmiştir. IR spektrumları MATTSON 1000 FTIR Model spektrometreyle, Element analizleri CARLO-ERBA 1108 model cihazla, ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{1}H NMR titrasyon ve iki boyutlu NMR (DEPT, COSY, HETCOR) spektrumları BRUKER DPX-400 High Performance Digital FT-NMR spektrometreyle, Spesifik çevirme açıları ($[\alpha]^{t}_{D}$) PERKİN ELMER 341 model polarimetre cihaz ile alınmıştır. Kullanılan kimyasallar ve çözücüler Merck ya da Sigma Aldrich olup, ayrıca saflaştırılmaksızın kullanılmıştır. Kolon kromatografisi ve ince tabaka kromatografisi için Silika jel 60 (Merck, 0.040-0.063 mm) ve silika jel / TLC kart (F_{254}) kullanıldı. Kimyasal kayma (δ) ve kapling sabitleri (J) sırasıyla ppm (parts per million) ve Hertz olarak hesaplandı.

3.2. Sentez

3.2.1. (*1R,2R*)-bis[(*R*)-2-hidroksi(2-fenil)etil]-1,2-diaminosikloheksan (2):



1 1b 2

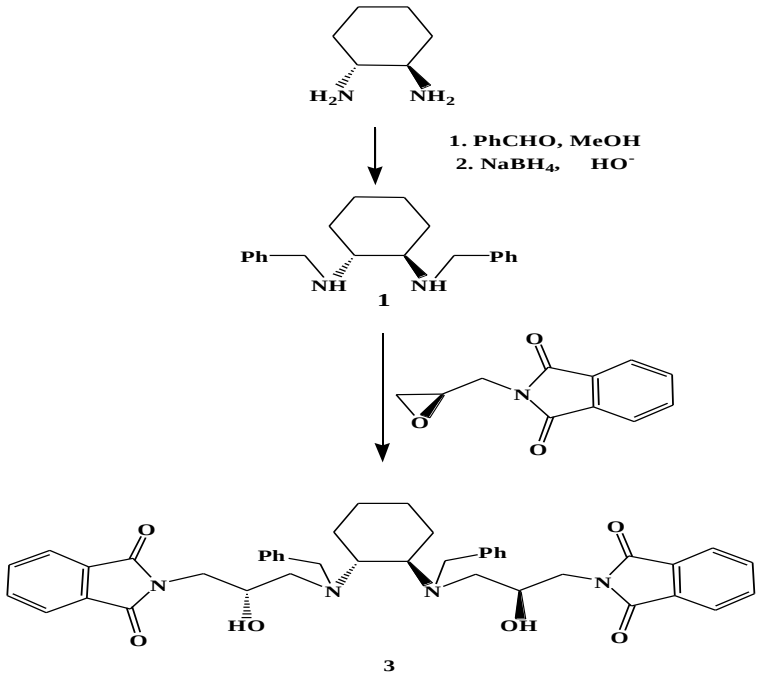
1b bileşiği, literatür yöntemine göre (*R*)-stiren oksit ile **1** bileşiğinden çıkılarak sentezlendi **(**Karakaplan ve ark. 2013). Bileşik **2**, uygun literature yönemi ile **1b** bişeşiğinin hidrojen atmosferinde $Pd(OH)_2/C$ ile debenzilasyonu ile hazırlandı (Xu ve ark. 2008). Bu amaçla, $Pd(OH)_2/C$ (20%, 75 mg) bir defada **1b** (400 mg, 0.75 mmol) metanoldeki (10 mL) çözeltisine ilave edildi. Karışımdan iki saat süreyle hidrojen gazı geçirilerek reaksiyon TLC ile takip edildi. Reaksioyn sona erdikten sonar ortama sodium karbonat (80 mg, 0.75 mmol) ilave edildikten sonra 1 saat oda koşullarında magnetic karıştıcı ile karıştırıldı. Çözelti süzüldü ve methanol ile tekrar yıkandıktan sonra vakumda çözücüsü uçuruldu. Ham ürün silika jel dolgulu kolonda H: EA: EtOH: TEA (4: 1: 1: 0.5 as eluent) ile saflaştırıldı. Elde edilen ürün vizkos sıvı olup, verimi

190 mg'dır (% 71.7). IR (cm^{-1}): 3346, 3250, 3057, 3030, 2926, 2860, 1493, 1453, 1348, 1310, 1195, 1139, 1056, 924, 893, 854, 791, 756, 701. ^{1}H NMR ($CDCl_3$) δ: 7.41-7.27(m, 10H), 4.55 (dd, 4, 8.12Hz, 2H), 2,90-2,71(m, 8H), 2,32-2,27(m, 2H), 2.12-1.99 (m, 2H), 1.38-1.37(m, 2H); 1.28-1.05 (m, 4H). ^{13}C NMR ($CDCl_3$): 142,55, 128,39, 127.48, 125.90, 72.00, 60.32, 53.84, 31.87, 25,01. $C_{22}H_{30}N_2O_2$ için hesaplanan: C: 74.57, ; H: 8.47 ; N: 7.90 . Bulunan: C: 74.89; H: 8.36; N: 7.82.

3.2.2. Bileşik 3–7 için Genel Sentez Yöntemi:

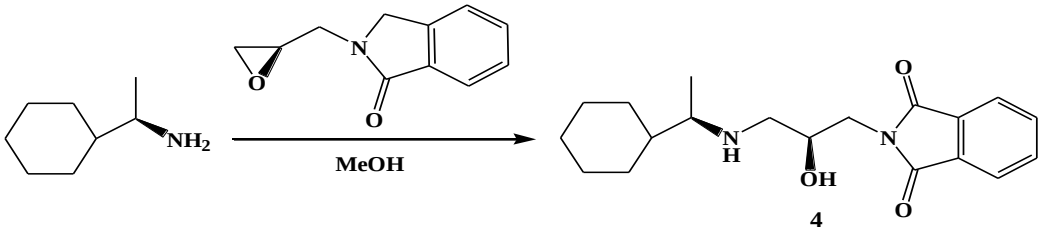
Bileşik **3-7'**nin original sentez yöntemi Roehrig ve arkadaşları tarafından rapor edildi **(**Roehrig ve ark. 2005). Buna göre, kiral amin veya amino alkol'ün (0.6 mmol, 1.2 kat.) 10 mL *i*-propanol'deki çözeltisi (*R*)-*N*-(2,3-epoksipropil)ftalimid'in (**NEP**) (102 mg, 0.50 mmol) 10 mL *i*-propanol'deki buzla soğutulmuş çözeltisine ilave edildi. Buzlu ortamda bir saat karıştırıldıktan sonra 12 saat riflaks edildi. Reaksiyonun ilerleyişi TLC ile takip edilerek reaksiyonun tamamlanması ile çözücü döner buharlaştırıcıda vakum uygulanarak uçurulur. Ham ürün uygun yöntemle saflaştırılır.

3.2.3. *N,N'*-Dibenzil-*N,N'*-bis[(*S*)-2-hidroksi-3-ftalimit]-(*R,R*)-1,2-diaminosikloheksan (3):



Bileşik **(*S,R,S,R*)-3,** NEP (2.04 g, 5 mmol) ve **1** (0.73 g, 5 mmol) bileşikleriyle genel sentez yöntemine uygun olarak sentezlendi. Ham ürün metanolden kristallendirilerek saflaştırıldı. Verim 2.45 g olup, % 70'dir. E.n.: 164-165 ^{o}C, $[\alpha]_D^{20}$ = -14.2^{o} (c=1, $CHCl_3$). IR (cm^{-1}): 3434.6, 3384.5, 3332.4, 3053.75, 2931.3, 2859.9, 1771.3, 1709.6, 1612.2, 1434.97, 1393.3, 1147.4, 1083.8, 1011.5, 842.7, 626.0, 619.0. ^{1}H NMR ($CDCl_3$): 7.84 (d, 2.4Hz, 2H); 7.713 (d, 2.8 Hz, 2H); 7.468-7335(m, 10H); 4.34-3.27 (m, 10H); 2.86- 2.14(m, 6H); 1.69-1.67(m, 6H); 1.05 (m, 4H). ^{13}C NMR ($CDCl_3$): 168.33, 138.08, 133.80, 132.17, 128.33, 127.35, 123.24, 66.58, 58.86, 56.28, 53.08, 42.21, 25.40, 23.76. $C_{42}H_{44}N_4O_6$ için hesaplanan: C: 72.00., H: 6.28; N: 8.0. Bulunan: C: 71.58; H: 6.12; N: 7.78.

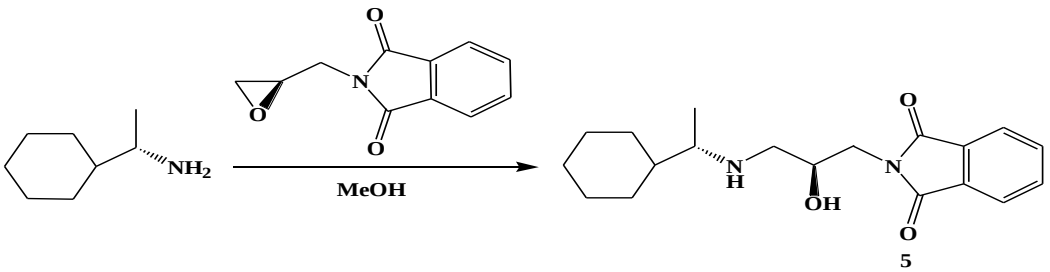
3.2.4. 1-[(*R*)-1-Sikloheksiletiamin)]-3-ftalimit-(*S*)-2-propanol (4):



4

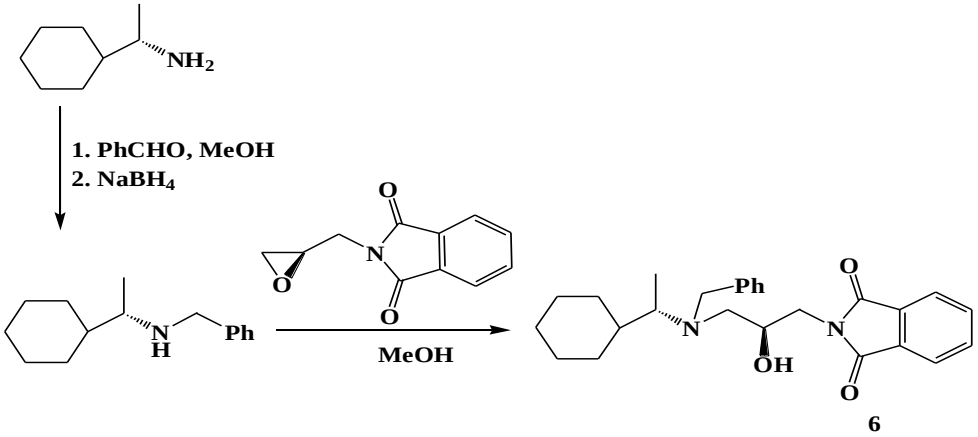
Bileşik **4, NEP** (767 mg, 3.77 mmol) ve (*R*)-1-sikloheksiletilamin (0.4 g, 3.15 mmol) bileşikleriyle genel sentez yöntemi kullanılarak hazırlandı. Ham ürün silica jel dolgulu kolonda H: EA (1:4 eluent) kullanılark saflaştırıldı. Verim 0.707 g olup, % 68'dir. E.n.: 136-138 ^{o}C, $[\alpha]_D^{20}$ = 14^{o} (c=1, $CHCl_3$). IR (cm^{-1}): 3460.7, 3453.6, 3319.8, 3262.9, 3032.5, 2911.0, 2848.3, 2760.6, 2697.9, 1769.3, 1709.6, 1439.6, 1393.3, 1318.1, 1163.8, 1112.74, 1094.42, 1024.0, 898.9, 836.9, 789.7, 717.7. ^{1}H NMR ($CDCl_3$): 7.88-7.86 (m, 2H); 7.75-7.73 (m, 2H); 4.04-4.01(m, 1H); AB sistemi; A kısmı: 3.808 (dd, 24.8Hz, 13.6Hz, -CH_2- 1H); B kısmı: 3.793(dd, 23.2 Hz, 14Hz, -CH2-, 1H); 2.83(dd, 9.2Hz, 3.2Hz, 1H); 2.69(dd, 12.4 Hz, 7.2Hz, 1H); 2.572-2.542(m, 1H): 1.77-1.69 (m, 5H); 1.26-1.01 (m, 9H). ^{13}C NMR ($CDCl_3$): 168.64, 134.07, 132.03, 123.41, 66.99, 58.19, 49.38, 42.24, 41.60, 29.61, 28.20, 26.54, 26.40, 26.29, 16.29. $C_{19}H_{26}N_2O_3$ için hesaplanan: C: 69.09, H: 7.87; N: 8.48. Bulunan: C: 68.87; H: 7.69; N: 7.79.

3.2.5. 1-[(*S*)-1-Sikloheksiletilamin)]-3-ftalimit-(*R*)-2-propanol (5):



Bileşik **5, NEP** (767 mg 3,77 mmol) ve (*S*)-1-sikloheksiletilamin (0.4 g, 3.15 mmol) bileşikleriyle genel sentez yöntemi kullanılarak hazırlandı. Ham ürün silica jel dolgulu kolonda H: EtOAc (3:2 as eluent) kullanılark saflaştırıldı. Vizkoz ürün 760 mg olup, verim % 73.07'dir. $[\alpha]_D^{20}$ = + 7.2 ^{o} (c=1, $CHCl_3$). IR (cm^{-1}): 3386.5, 3380.5, 3378, 3156.29, 3142.3, 3130.4, 3125.5, 2918.75, 2850.3, 1710.65, 1614.14, 1429.0, 1394.29, 1329.69, 1189.8, 1127.2, 1087.67, 1029.8, 982.5, 917.0, 722.2^{1}H NMR ($CDCl_3$): 7.86-7.71 (m, 4H); 3.96-3.93 (m, 1H); AB sistem; A kısmı: 3.78(dd, 22.8Hz, 17.6Hz, -CH2-, 1H); B kısmı: 3.76(dd, 21.2Hz, 14 Hz, -CH2-1H); 3.103(m, 2H): 2.86(dd, 12.4 Hz, 4Hz. 1H); 2.536-2.449(m, 1H); 1.75-1.65 (m, 5H); 1.22-0.98(m, 10 H). ^{13}C NMR ($CDCl_3$): 168,64, 134.01, 132.02, 123.35, 67.98, 58.45, 50.20, 42.69,41.89, 29.75, 27.95, 26.66, 26.54, 26.40, 16.93. Anal. Cald. for $C_{19}H_{26}N_2O_3$ C: 69.09, H: 7.87; N: 8.48. Found: C: 68.72; H: 7.7.62; N: 7.92.

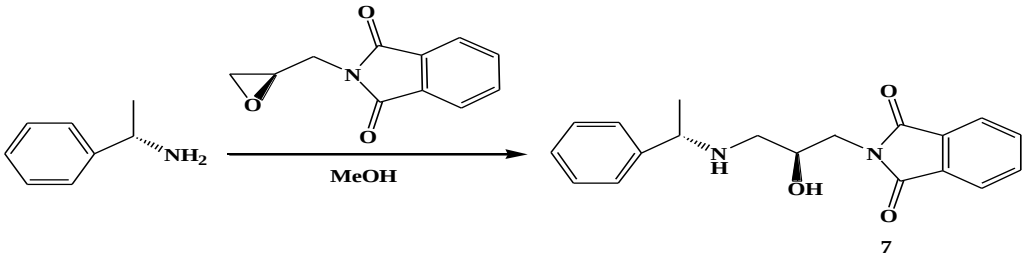
3.2.6. *N*-Benzil-1-[(*S*)-*α*-sikloheksiletilamino)]-3-ftalimit-(*R*)-2-propanol (6):



Bileşik **6** için öncelikle (*S*)-*N*-benzill-***α***-sikloheksiletilamin sentezlendi. Bu amaçla, (S)-***α***-cyclohexylethylamine (1 mL, 6.82 mmol) literature yöntemine göre benzillenerek 1.42 g (% 96) (*S*)-*N*-benzil-α- sikloheksiletilamin elde edildi (Tye ve ark. 2001). (IR (cm^{-1}): 3321.8, 3161.7, 3067.2, 2940.12, 1643.9, 1582.3, 1483.0, 1431.9, 1378.8, 1332.8, 1224.5, 1189.8, 1068.3, 981.6, 838.8. ^{1}H NMR ($CDCl_3$): δ: 7.38-7.29(m, 5H), 3.89(d, 1H, J=13.2 Hz), 3.75(d, 1H, J=13.2 Hz), 2.58-2.51(m, 1H), 1.82-1.71(m, 6H), 1.44-1.14(m, 4H), 1.09-1.01(m, 5H). ^{13}C NMR ($CDCl_3$): 141.16, 128.34, 128.12, 126.75, 57.12, 51.62, 43.02, 29.89, 28.13, 26.84, 26.72, 26.59, 16.79).

Bileşik **6,** NEP (655 mg 3,22 mmol) ve (*S*)-*N*-benzill-***α***-sikloheksiletilamin (0.7 g, 3.22 mmol) bileşikleriyle genel sentez yöntemi kullanılarak hazırlandı. Ham ürün silica jel dolgulu kolonda H: EtOAc (2:1 as eluent) kullanılark saflaştırıldı. Vizkoz ürün 1.05 g olup, verim % 77.66'dir. $[\alpha]_D^{20}$ = +9.8^o (c=1, $CHCl_3$). IR (cm^{-1}): 3564, 3514, 3476, 3434, 3086, 2913, 2859, 1772, 1712, 1611, 1429, 1393, 1327, 1262, 1151, 1086, 1027, 960, 722. ^{1}H NMR ($CDCl_3$): 7.78-7.76 (m, 2H); 7.76-7.63 (m, 2H); 7.31-7.16 (m, 5H); 3.85-3.76 (m, 2H): 3.70-3.69 (m, 1H); 3.47-3.35 (m, 2H): 3.17 (s, 1H); 2.61-2.23 (m, 4H); 1.73-1.64 (m, 4 H); 1.23-1.14(m, 1H). ^{13}C NMR ($CDCl_3$): 168.57, 140.08, 133.88, 132.03, 129.10, 128.29, 126.98, 123.20, 68.29, 61.89, 55.79, 54.78, 42.71, 41.08, 31.45, 30.54, 26.57, 26.48, 26.33, 11.09. $C_{26}H_{32}N_2O_3$ için hesaplanan: C: 74.28; H: 7.62; N: 6.66; Bulunan: C: 74.86; H: 7.29; N: 7.41.

3.2.7. [(*R*)-Feniletilamino)]-3-ftalimit-(*R*)-2-propanol (7):

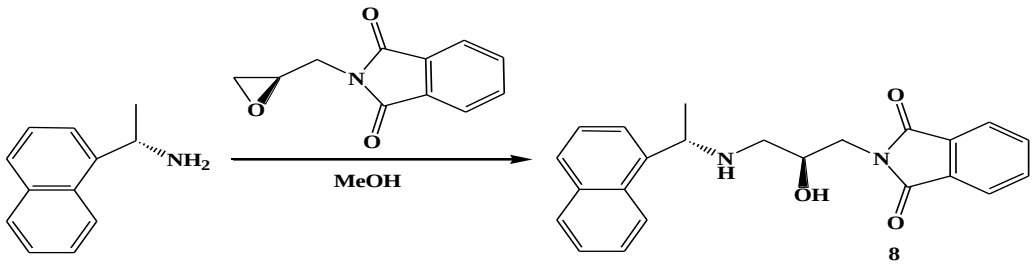


7

Bileşik **7, NEP** (500 mg 2.46 mmol) ve (*S*)-α-feniletilamin (298 mg, 2.46 mmol) bileşikleriyle genel sentez yöntemi kullanılarak hazırlandı. Ham ürün silica jel dolgulu kolonda H: EtOAc: TEA (1:0.5:0.1 eluent) kullanılark saflaştırıldı. Vizkoz ürün 612 mg olup, verim % 76.69'dur. $[\alpha]_D^{20}$ = 10.7^o(c =1, $CHCl_3$). IR (cm^{-1}): 3264, 2921,

2851, 1773, 1714, 1566, 1463, 1395, 1085, 1023, 918, 627. ^{1}H NMR ($CDCl_3$) δ: 7.84-7.81(m, 2H); 7.72-7.69(m, 2H); 7.31-7.22(m, 5H); 3.912-3.87 (m, 1H); 3.807- 3.689 (m, 3H); 2.71 (bs, 1H); 2.62-2.56(m, 2H); 1.39-1.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.70, 145.14, 134.05, 131.98, 128.53, 127.08, 126.57, 123.37, 68.47, 58.52, 50.50, 42.00, 24.14. $C_{19}H_{20}N_2O_3$ için hesaplanan: C: 70.37; H: 6.17; N: 8.64; Bulunan: C: 70.56; H: 6.10; N: 8.54.

3.2.8. 1-[(*S*)-(α-naftil)etilamin]-3-ftalimit-(*R*)-2-propanol (8):



8

Bileşik **8, NEP** (528 mg 2.6 mmol) ve (*S*)-1-(α-naphthyl)ethylamine (442.45 mg, 2.6 mmol) bileşikleriyle genel sentez yöntemi uygulanarak hazırlandı. Ham ürün silica jel dolgulu kolonda *n*-heksan: EtOH (4:1 eluent) kullanılark saflaştırıldı. Vizkoz ürün 698 mg olup, verim % 72'dir. E.n:. 249-250^{o}C. $[\alpha]_D^{20}$ = +16.9^{o} (c =0.5, DMSO). IR (cm^{-1}): 3492, 3468, 3421, 3352, 3290.9, 3051.8, 2952.5, 2843,5, 2796.3, 2689.2, 2622.7, 2526.3, 1773.2, 1711.5, 1588.1, 1433.8, 1395.2, 1345.1, 1296.9, 1092.5, 1008.6, 964.2, 801.3, 779.1, 723.2. ^{1}H NMR ($DMSD_6$): 9.78 (bs, 1H); 9.08(bs, 1H): 8.20-8.18 (m, 1H); 8.00- 7.56 (m, 8H); 5.86 (s, 1H); 5.36 (s, 1H); 4.20(s, 1H); 3.57-3.12(m, 3H); 2.67 (s, 1H): 2.47(s, 1H); 1.68-1.67(d, 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 168.28, 134.81, 134.10, 133.80, 132.12, 130.83, 129.37, 127.41, 126.60, 126.60, 124.74, 123.50, 122.96, 64.36, 52.76, 49.40, 41.97, 20.55. $C_{23}H_{22}N_2O_3$ için hesaplanan: C, 73.80; H, 5.88; N, 7.49. Bulunan: C, 73.36; H: 6.10; N, 7.84.

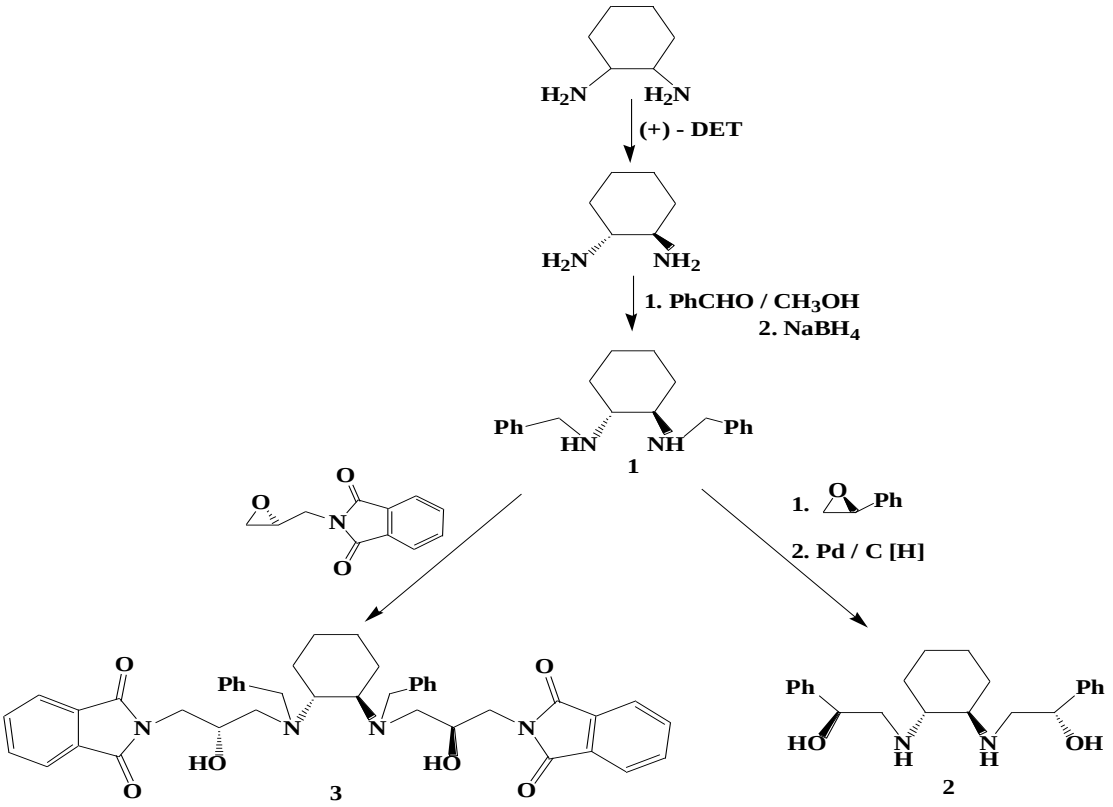
3.2.9. Kompleksleşme Stokiyometri Oranının Belirlenmesi (Job plot):

KSR **3** ile mandelik asit enantiomerleri arasında kompleksleşme oranını belirlenmesi Job plot yöntemi kullanıldı (Job, P. 1928). Bu amaçla, eş molar miktardaki KSR **3** ve analit $CDCl_3$ içinde çözüldü. Çözeltiler 9 adet NMR tüpüne molar konsantrasyon 01-0.9 olacak şekilde hazırlandı. Herbir çözeltideki mandelik asidin Cα-H ait kimyasal kayma (Δδ) ölçüldü. Mol oranına karşın moloranı.kimyasal kayma farkı X.(Δδ) grafiğe edildi.

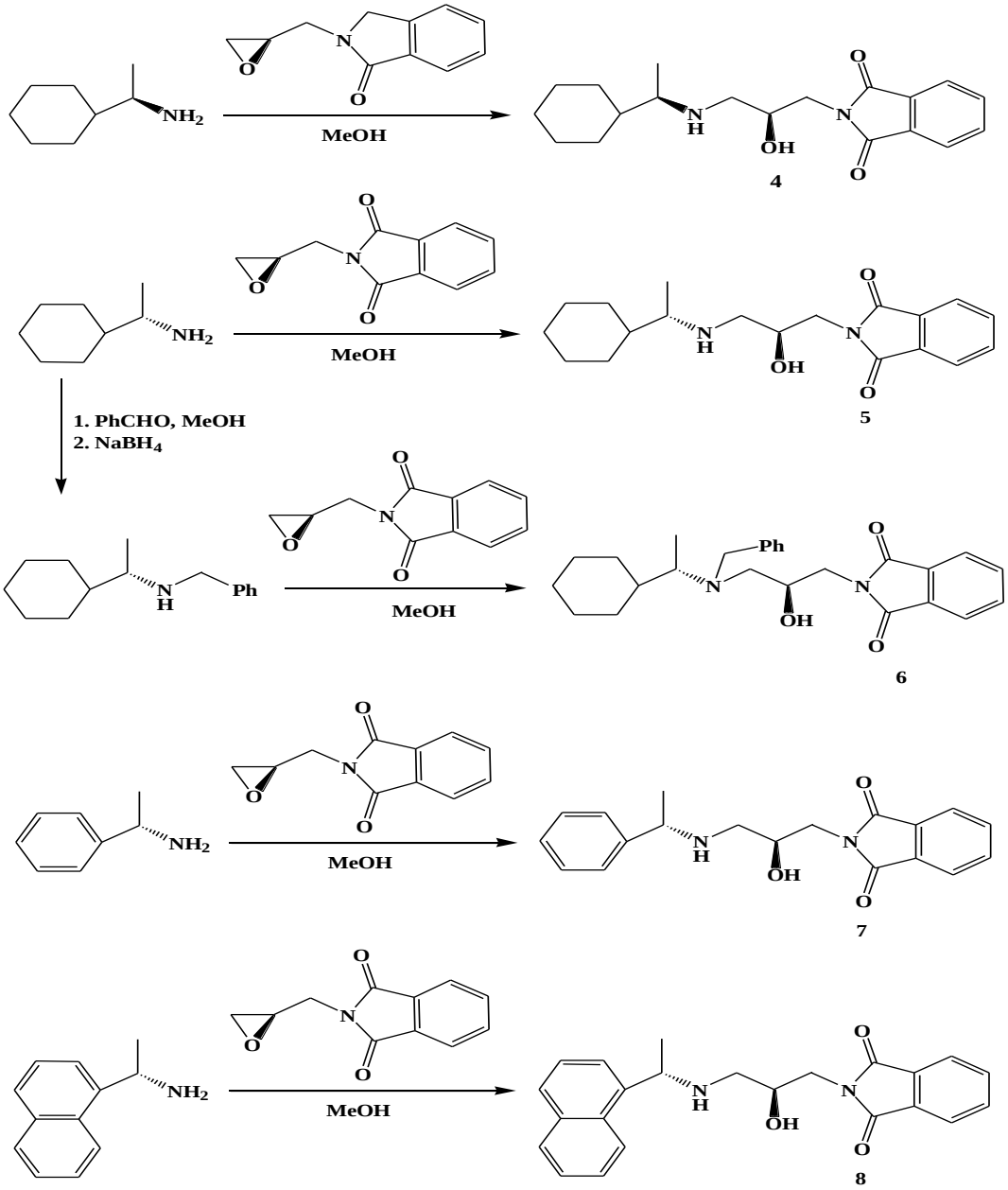
4. SONUÇLAR ve TARTIŞMA

Amino alkol imit fonksiyonel birimi çeşitli aminlerin *N*-(2,3-epoksipropil)ftalimid ile regioseçici halka açma tepkimesi sonucunda oluşturuldu (Şekil 4.1 ve 4.2). Bu sistemin seçilmesinin nedeni kolay temin edilebilir, kısmen ucuz giriş maddeleri ve stereojenik merkeze yakın hidroksil, amin ve imid gibi çoklu fonksiyonel gruplar içermesidir.

Burada, öncelikle bir çok asimetrik katalizörün iskeletini oluşturan *N,N'*-dibenzil-1,2-diamnosikloheksan **1**'in farklı türevlerinin hazırlanması planlandı (Song ve ark. 2014). İmit fonksiyonalitesi bulunmayan (*R*,*R*,*R*,*R*)-**2** bileşiği, önce (*R*,*R*)-**1** ile (*R*)-stiren oksid'in tepkimesinden elde edilen ürünün daha sonra $Pd(OH)_2/C$ katalizörlüğünde debenzilasyonundan % 71.7 verimle hazırlandı. Tersiyer amin fonksiyonlu C_2-simetrik (*S*,*R*,*S*,*R*)-**3,** kiral amin (*R*,*R*)-**1** ile kiral epoksit'in regioseçici halka açılması tepkimesinden yüksek bir verimle elde edildi (% 70).



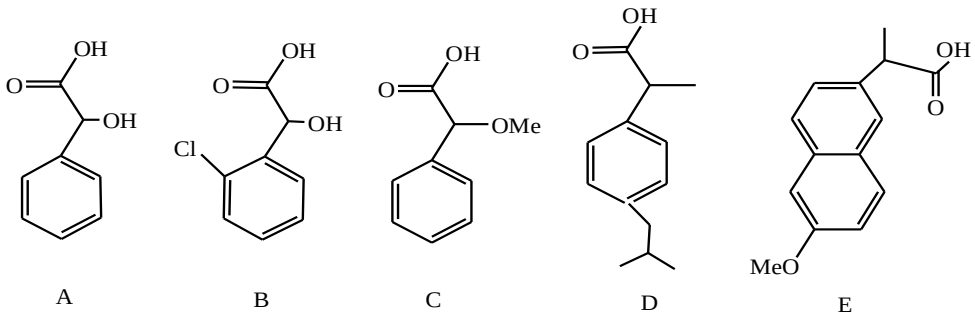
Şekil 4.1. Amino alkol KSR **2** and amino alkol imit KSR **3** sentezi



Şekil 4.2. Amino alkol imit KSR **3-8** sentezi

Kiral bileşikler (*R,R*)-**4** ve (*S,R*)-**5;** **NEP** epoksitin sırayla **(***R)*- and *(S)-(1)*-sikloheksiletilamin ile halka açılması tepkimesinden % 68 ve 73 verimle elde edildiler. Bunları takiben, (*S,R*)-**5'**in NH fonksiyonalitesini bloke etmek ve dolayısıyla hidroksil ve imit fonksiyonalitesinin analit etkileşiminini incelemek üzere; *(S)-(1)*-sikloheksiletiamin benzaldehit ile uygun iminine dönüştürüldükten sonra $NaBH_4$ ile indirgenmesi neticesinde elde edilen kiral sekonder amin **NEP** ile halka açılması tepkimesinden oldukça yüksek bir verimli (*S,R*)-**6** hazırlandı (Şekil 4.2). Bunlarla

birlikte, çalışmanın boyutunu genişletmek maksadıyla aromatik ünite içeren sübstituentler bu sisteme dahil edildi. Bunun için fenil ve naftil ünitesi içeren (*S*,*R*)-**7** ve (*S*,*R*)-**8;** kiral epoksit **NEP**'in sırasıyla (*S*)-α-feniletilamini ve (*S*)-1-(1-nafthil)etilamin ile regioseçici halka açılması tepkimesi ile yüksek verimlerle sentezlendiler.



Şekil 4.3. Enantiomerik yarılmaları test edilen analitler

Amino alkol veya amino alkol imit fonksiyonlu kiral bileşikler **2-8**, mandelik asit (**A**), *o*-kloromandelik acit (**B**), α-fenil-α-metoksiasetik asit (**C**), ibuprofen (**D**) ve naproksen (**E**) analitleri için potansiyel kiral solvatlayıcı reaktif etkileri ^{1}H NMR spektroskopisi yardımıyla incelemek üzere kullanıldılar (Şekil 4.1). Bu çalışmadan elde edilen sonuçlar aşağıda verilmiştir.

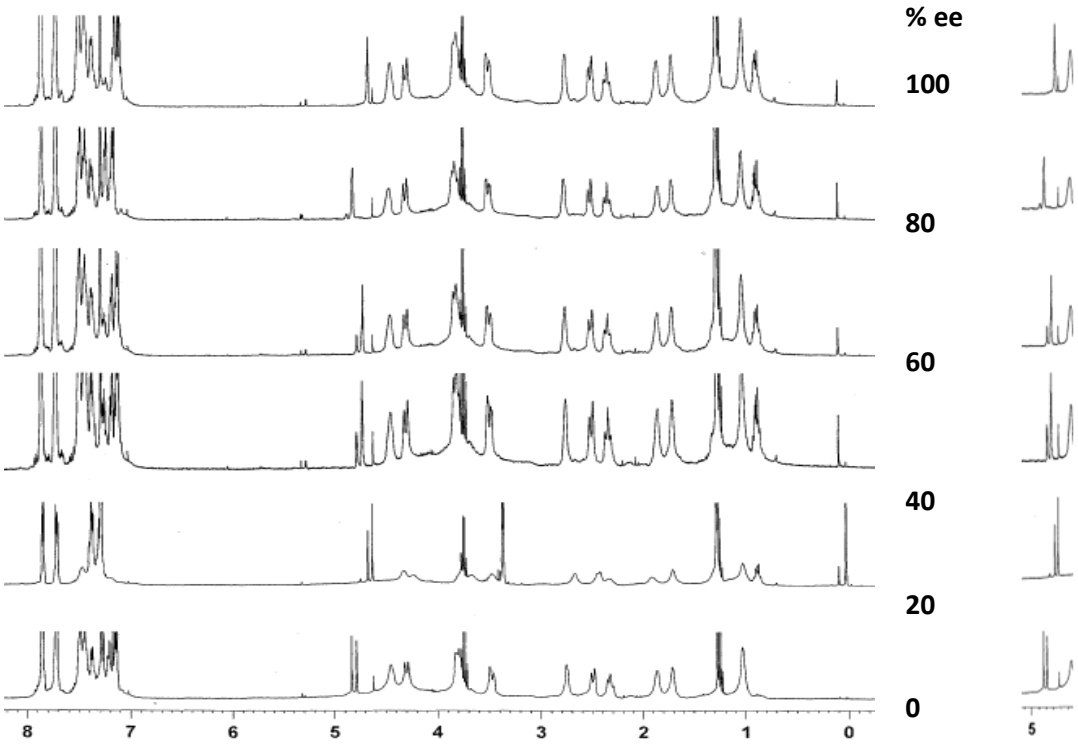
1. Sekonder alkol fonksiyonlu amino alkol (*R*,*R*,*R*,*R*)-**2,** düşük enantomerik ayrıştırma sağlarken bütün analitlerde C-α-H sinyalinin yüksek alana kaymasına (0.02-0.3 ppm) yol açmıştır. En iyi ayrıştırma (ΔΔδ) 10 Hz değerle mandelik asit ile elde edilmiştir (Tablo 4.1 ve 4.2).

2. C_2-Simetrik amino alkol imid (*S*,*R*,*S*,*R*)-**3,** mandelik asitin enantiomerik ayrıştırmasında (ΔΔδ) 24.8 Hz değeri ile en iyi reaktif olarak tespit edilmiştir. α-Fenil-α-metoksiasetik acit (**C**) ve *o*-kloromandelik acit (**B**) için bu değerler sırasıyla 16.6 and 8 Hz'dir. Bu sebeple analit mandelik asit için (*S*,*R*,*S*,*R*)-**3'**ü model pratik uygulanabilir KSR olduğunu gösterdik (Şekil 4.4.).

Tablo 4.1. KSR **2-5** varlığında karboksilli asitler **A-D'**nin 5 mM $CDCl_3$ ve 25 ^oC'deki analitin Cα-H ait kimyasal kayma farkı (Δδ, ppm) ve yarılma değerleri (ΔΔδ, ppm)

	Asit	Sinyal	KSR (δ: ppm)							
			2		3		4		5	
			$\Delta\delta^a$	ΔΔδ	$\Delta\delta^a$	ΔΔδ	$\Delta\delta^a$	ΔΔδ	$\Delta\delta^a$	ΔΔδ
1	A	CαH	-0.300	0.025	-0.513	0.062	0.489	0.022	-0.474	0.018
2	B	CαH	-0.247	0.011	-0.514	0.020	-0.456	0.014	-0.452	0.011
3	C	CαH	-0.002	0.00	-0.164	0.042	-0.242	0.009	-1.117	0.080
4	D	CαH	0.015	0.002	-0.020	0.000	-0.384	0.003	-0.147	0.005
5	E	CαH	-0.013	0.000	-0.045	0.000	-0.236	0.008	-0.110	0.006

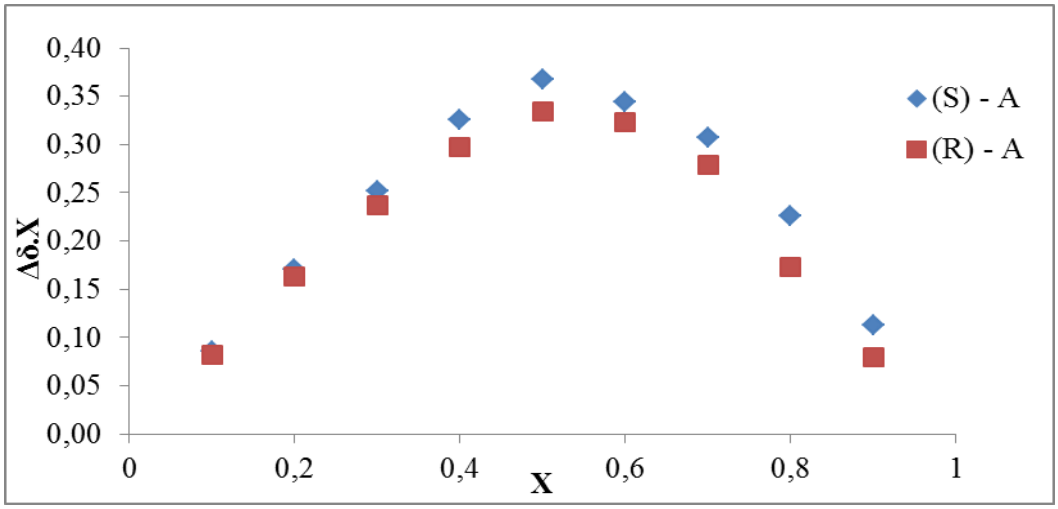
[a]: Her iki enantiomerin sinyal ortalaması.



Şekil 4.4. KSR **(*S,R,S,R*)-3**'ün değişik enantiomerik saflıktaki mandelik asit çözeltilerine ait ^1H NMR spektrumları (5 mM , 1:2 KSR/A)

Kiral solvatlayıcı reaktifler ile analitler arasındaki kompleksleşmeyi daha detaylı incelemek amacıyla (*S,R,S,R*)-**3** ile analit **A** arasındaki kompleksleşme oranları Job plot

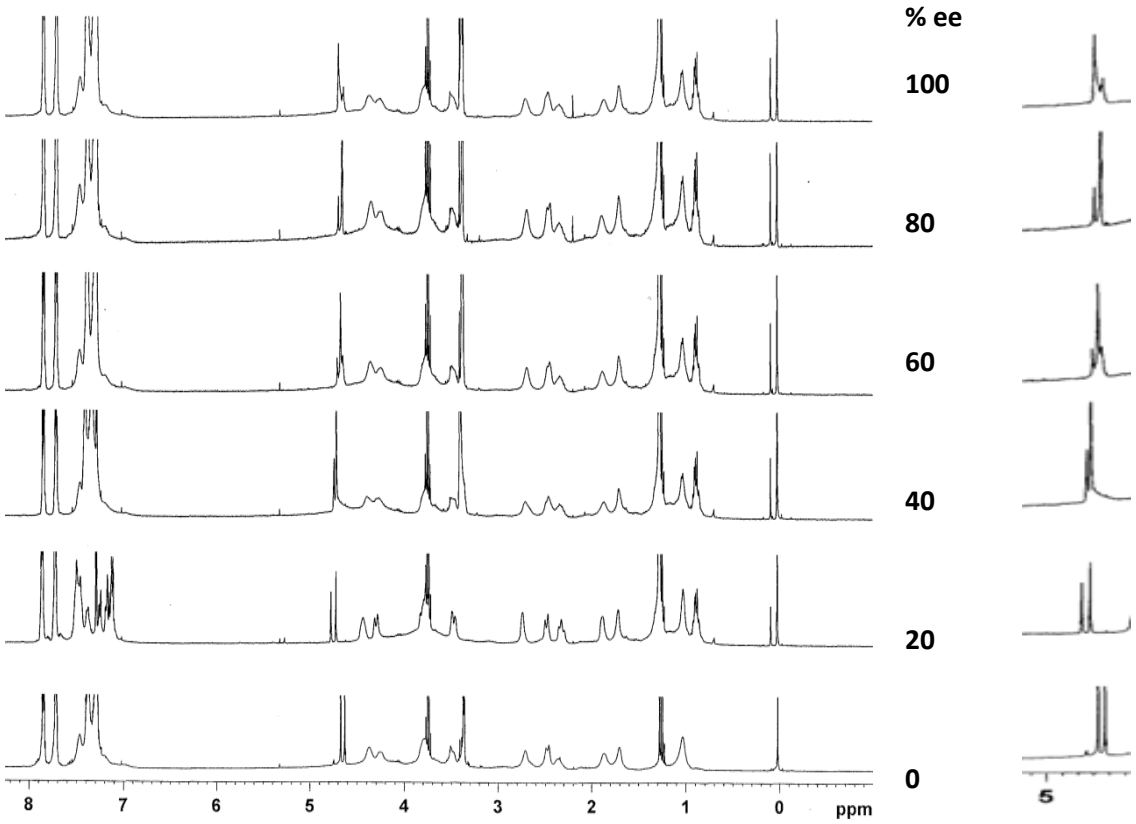
yöntemi ile araştırıldı. Buna göre, (*S*,*R*,*S*,*R*)-**3** mandelik asidin her iki enantiomeriyle 1:1 kompleksleştiği görüldü (Şekil 4.5.).



Şekil 4.5. (*S*)- ve (*R*)-**A** ile KSR (*R*,*R*,*R*,*R*)-**3**'ün Job plotu

3. (*S*)-1-Sikloheksiletilamin'den türeyen amino alkol imit (*S*,*R*)-**5,** (*R*,*R*)-**4**'den daha iyi bir enantiomerik ayırma sağladığı; buradan aminin S konfigürasyonun analit **C** ile daha uygun bir bağlanma cebi oluşturduğunu işaret etmektedir. (*S*,*R*)-**5** ΔΔδ 32 Hz değeri ile en iyi ayırmayı α-fenil-α-metoksiasetik asit (**C**) analitine karşı göstermiştir. Mandelik asit (**A**), o-kloromandelik asit (**B**), ibuprofen (**D**) ve naproksen (**E**) için elde edilen ayrıştırma değerleri sırasıyla 7.2, 4.4, 2.0 and 3.0 Hz dir.

KSR (*S*,*R*)-**5'in** etkin ayırımsal sonuçları bizi α-fenil-α-metoksiasetik asit (**C**) analitinin farklı enantiomerik saflıktaki (0-100 %) çözeltileri hazırlamamızı yönlendirmiştir. Tatmin edici deneysel ayırımlar elde edildiği Şekil 4.6'da görülmektedir.



Şekil 4.6. KSR (*S,R*)-**5**'in değişik enantiomerik saflıktaki α-fenil-α-metoksiasetik asit (**C**) çözeltilerine ait ^{1}H NMR spektrumları (20 mM , 1:1 KSR/A)

4. (*S,R*)- **5**'in benzil türevi, amino alkol imid KSR **6** düşük enantomerik ayrıştırma sergilemiştir. KSR **6** mandelik asit, *o*-kloromandelik aside karşı sırasıyla ΔΔδ = 2.4 and 3 Hz'lik bir bir ayrıştırma sağlamıştır (Tablo 4.2).

5. Sürpriz bir şekilde, fenil ve naftil substituent taşıyan KSR (*S,R*)-**7** ve (*S,R*)-**8** ise test edilen tüm analitlerin enantiomerlerine karşı en düşük ayrıştırma sergilediği; bu durum (*S,R*)-**7** ve (*S,R*)-**8** reaktiflerin düşük polariteleri nedeniyle düşük çözünürlükleri ve/veya düzlemsel aromatic sübstitüentlerin kompleksleşmeye sterik bir engel oluşturduğu dolayısıyla bunun da enantiyomerik ayrıştırmayı önemli ölçüde ortadan kaldırdığı düşünülmektedir.

Tablo 4.2. KSR **6-8** varlığında karboksilli acitler **A-D'**nin 5 mM $CDCl_3$ ve 25 ^oC'deki analitin Cα-H ait kimyasal kayma farkı (Δδ, ppm) ve yarılma değerleri (ΔΔδ, ppm)

	Asit	Sinyal	KSR 6		KSR 7		KSR 8	
			Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ
6	**A**	CαH	-0.153	0.06	-0.136	0.019	-0.006	0.00
7	**B**	CαH	-0.167	0.05	-0.173	0.00	0.015	0.00
8	**C**	CαH	-0.007	0.00	-0.059	0.00	0.002	0.00
9	**D**	CαH	-0.067	0.00	+0.093	0.00	-0.002	0.00
10	**E**	CαH	-0.007	0.00	-0.166	0.013	0.013	0.00

[a]: Her iki enantiyomerin sinyalleri arasındaki ortalama.

Sonuç olarak, bu çalışmada yeni bir amino alkol ve altı amino alkol imit fonksiyonlu bileşik sentezlendi. Bu bileşikleri potansiyel KSR olarak biyolojik önemi olan kiral karboksilli asitler (**A-E**)'nin C-α-H sinyallerine ait yarılmalar ^1H NMR spektroskopisi kullanılarak incelendi. (*S,R,S,R*)-**3** ve (*S,R*)-**5,** sırasIyla mandelik asit **ve** α-fenil-α-metoksiasetik asite karşı önemli ölçüde ayrıştırma özelliklerinin olduğu belirlendi. Bu da sözkonusu analitler için (*S,R,S,R*)-**3** ve (*S,R*)-**5'**in potansiyel birer KSR oludğunu göstermektedir. Sonuçlar, iyi bir ayrıştırma için; kiral sekonder veya tersiyer amine fonksiyonalitesi yanında aynı zamanda reaktif ve analit polaritesinin gerekli olduğunu göstermektedir.

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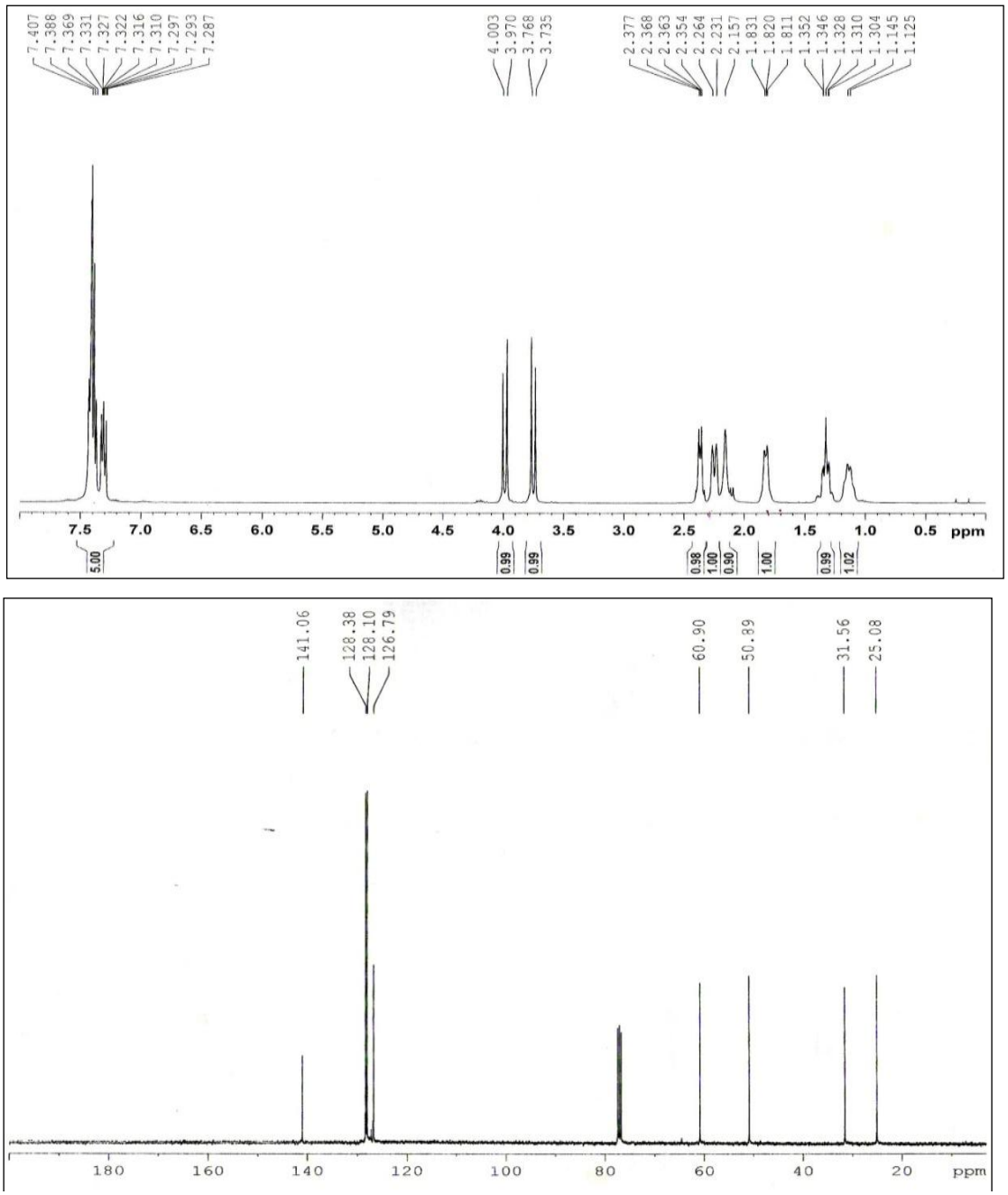
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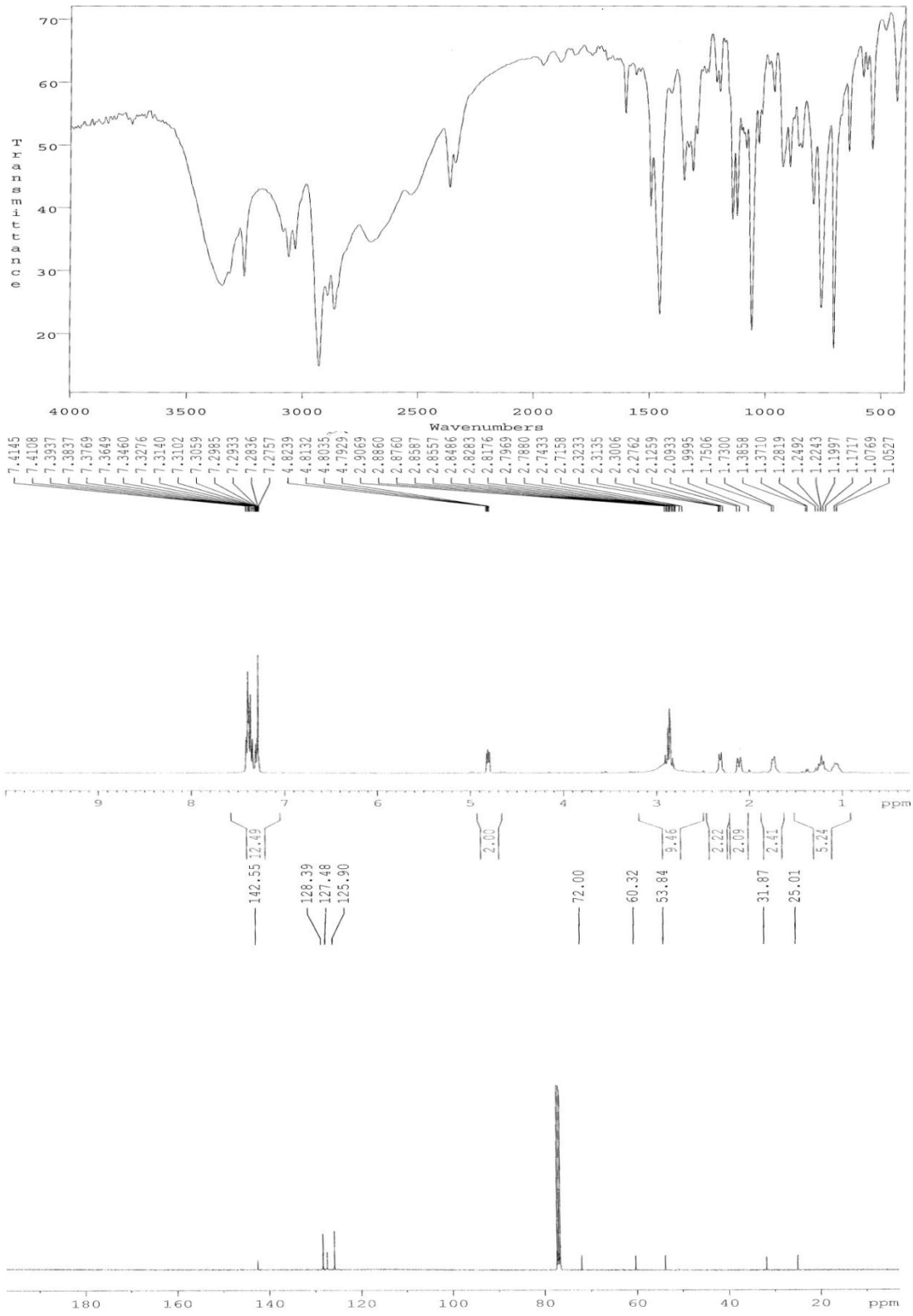
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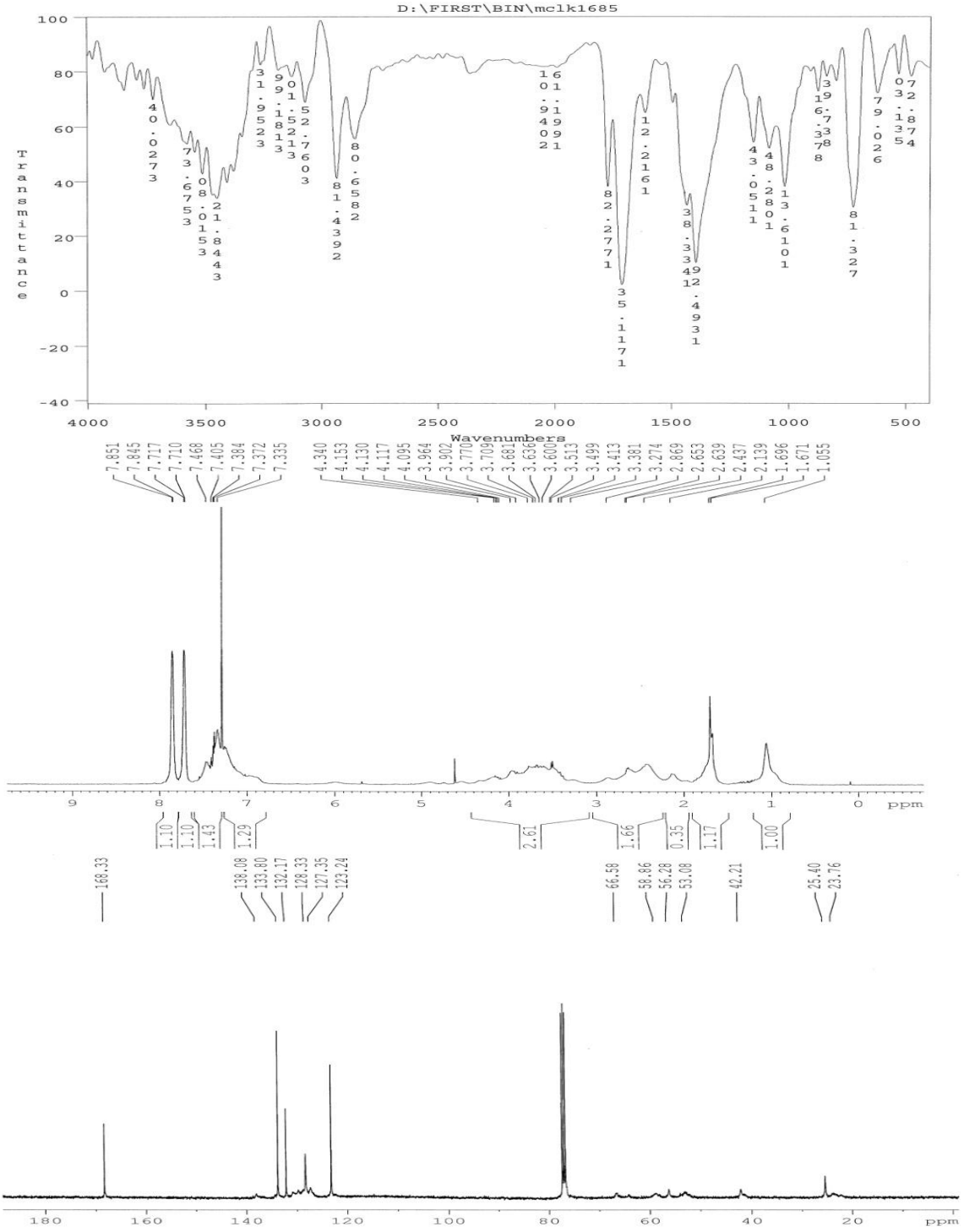
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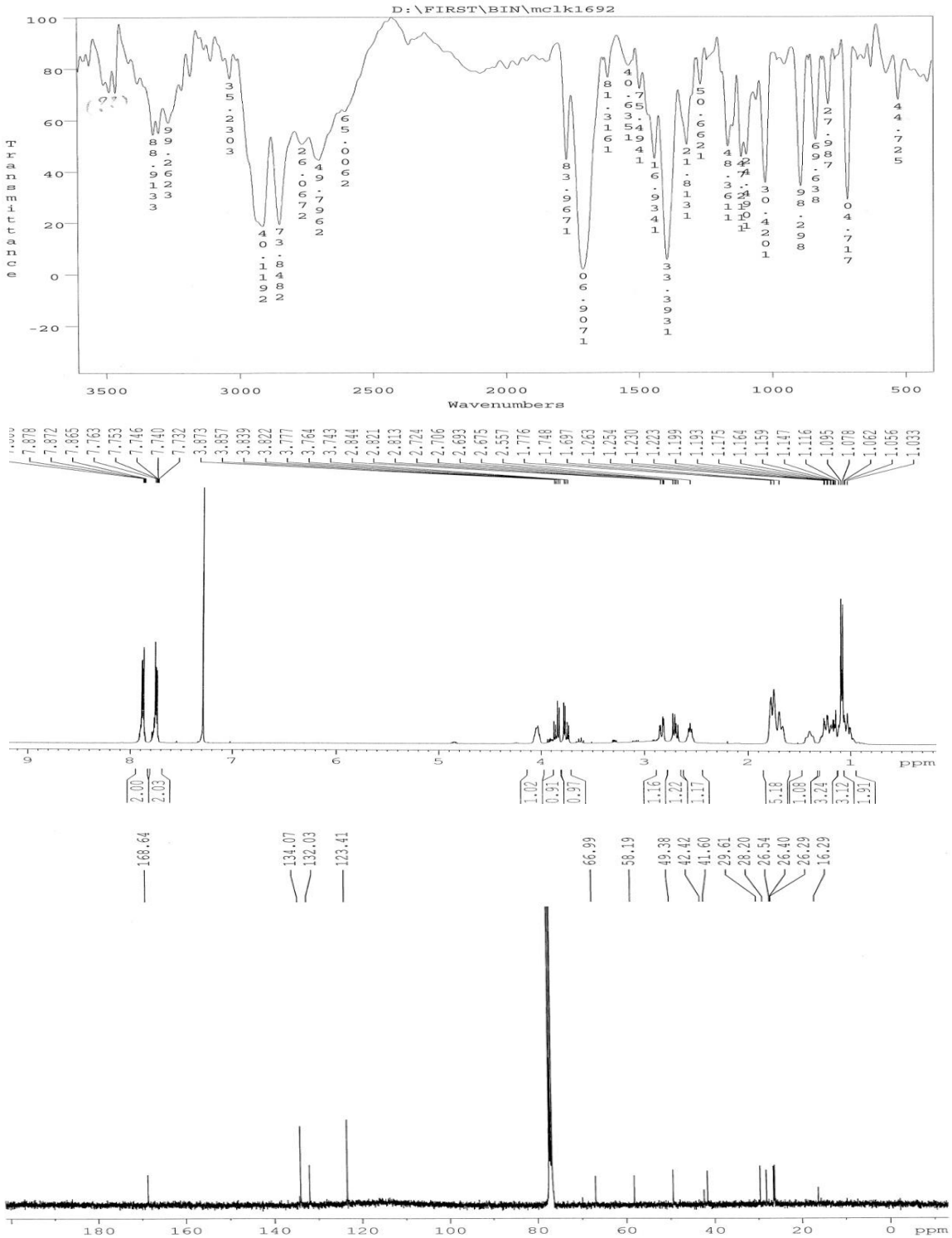
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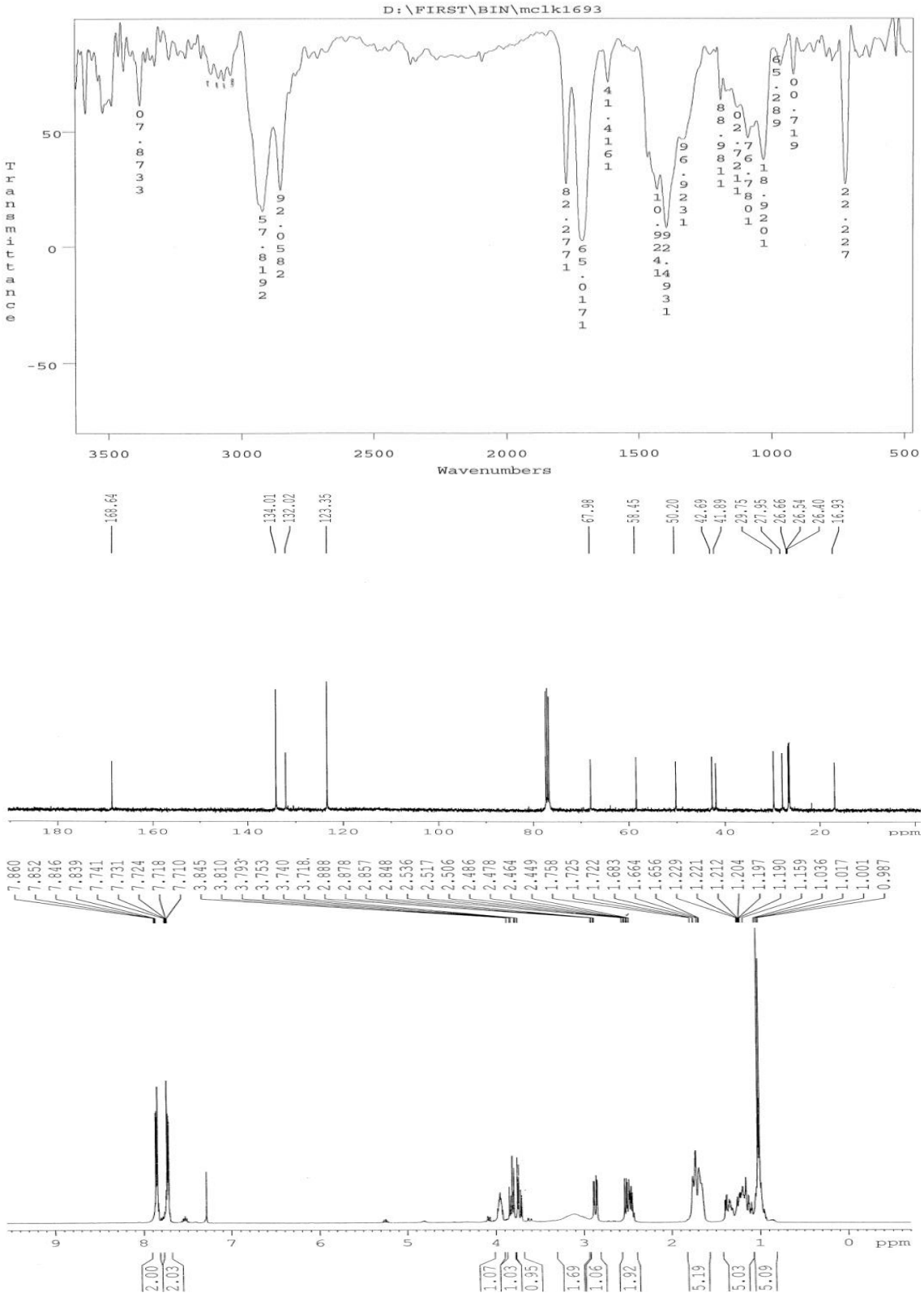
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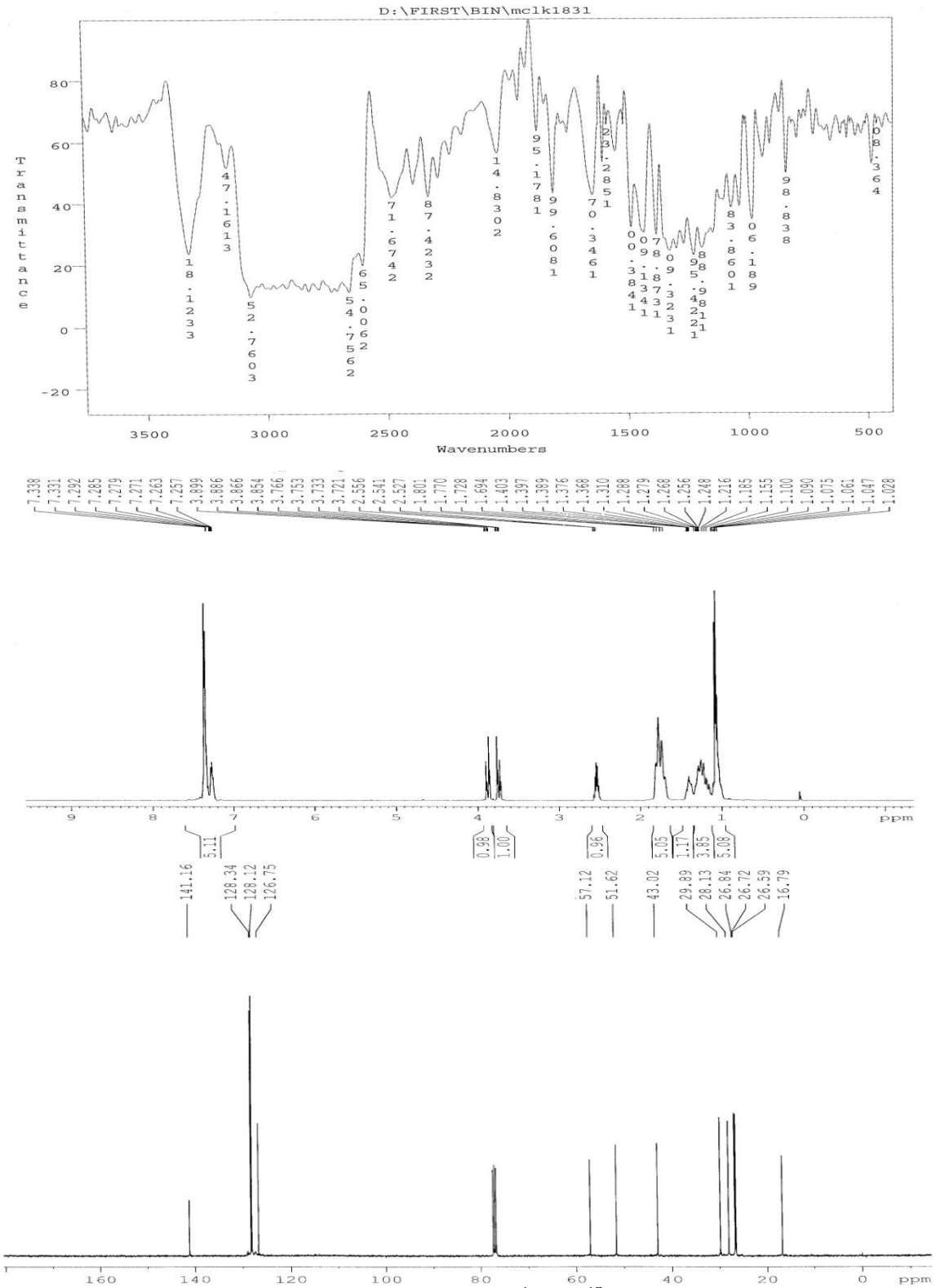
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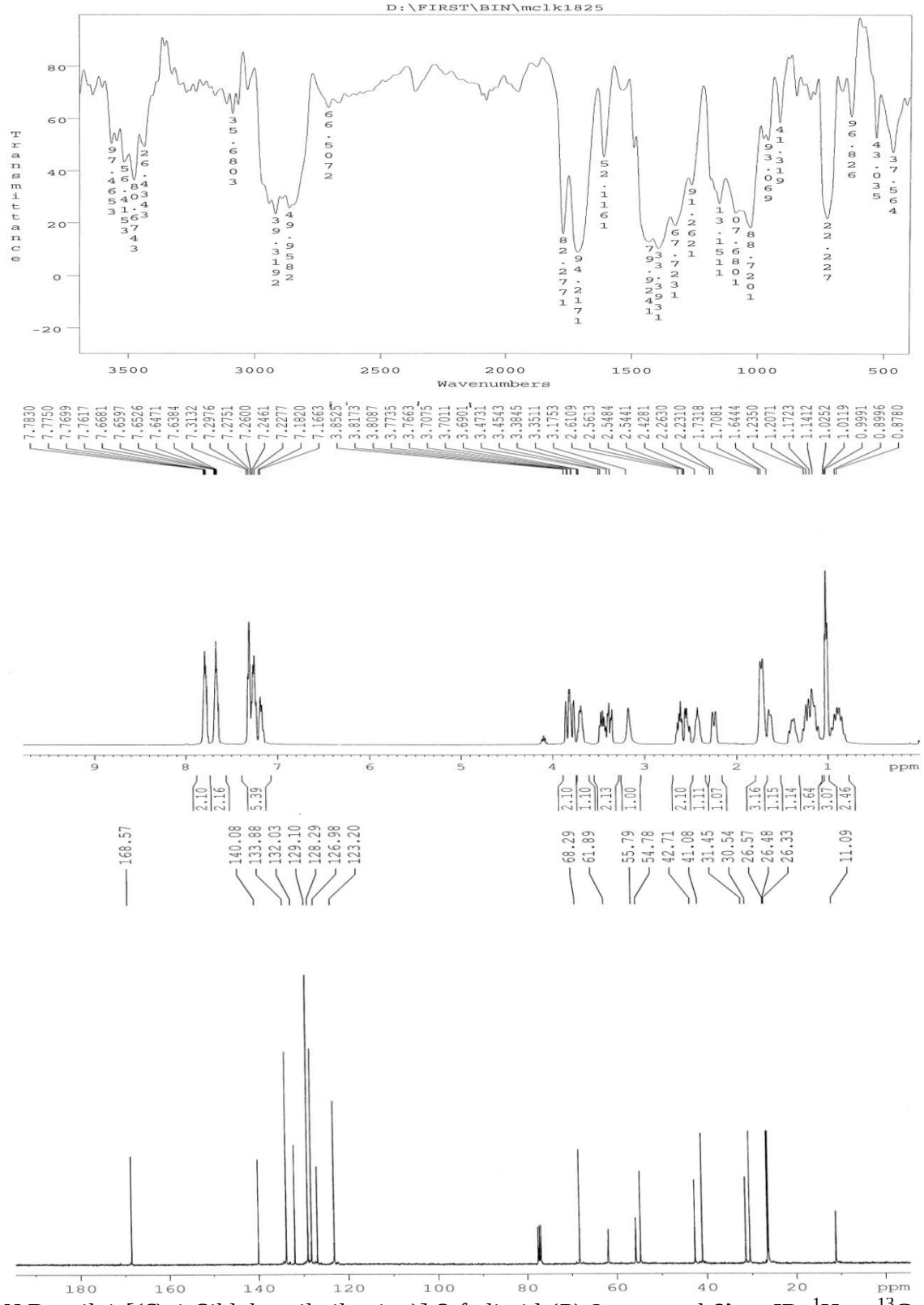
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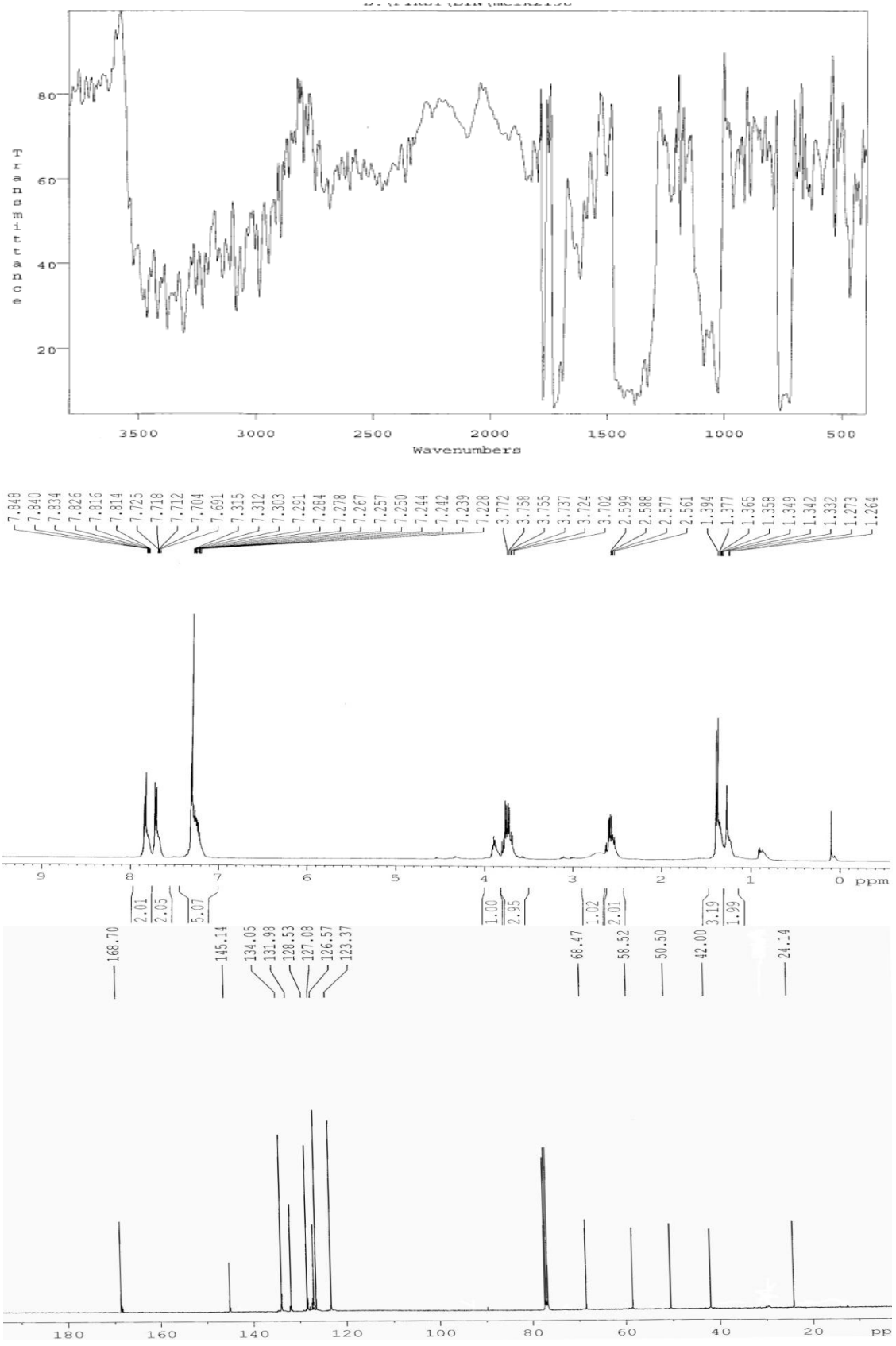
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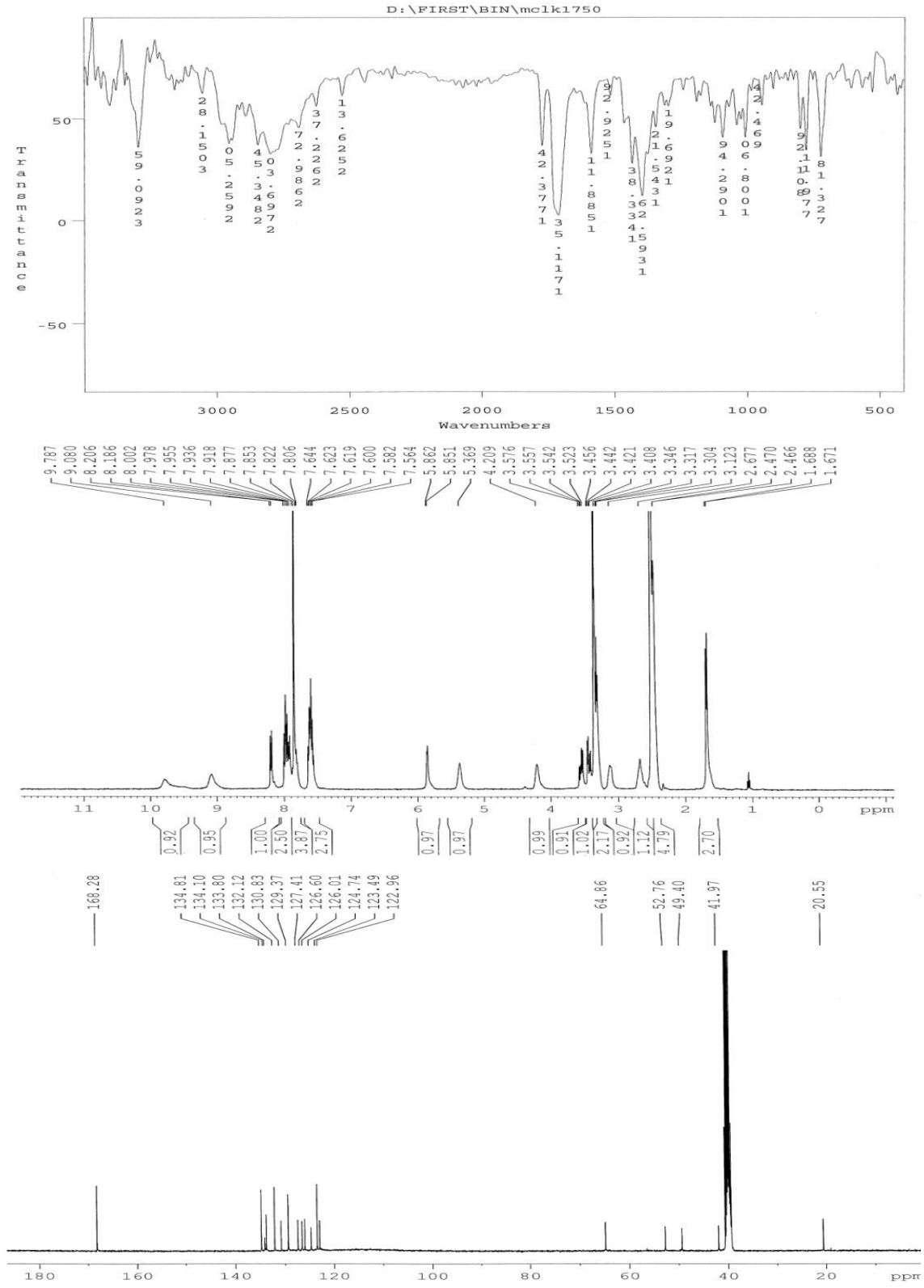
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ÖZGEÇMİŞ

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AMINO ALCOHOL IMIDE BASED CHIRAL SOLVATING AGENTS:

SYNTHESIS AND APPLICATIONS IN THE NMR ENANTIODISCRIMINATION OF CARBOXYLIC ACIDS

Basam JAMEEL

M.Sc. THESIS

DEPARTMENT OF CHEMISTRY

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ABSTRACT

AMINO ALCOHOL AMIDE BASED CHIRAL SOLVATING AGENTS: SYNTHESIS AND APPLICATIONS IN THE NMR ENANTIODISCRIMINATION OF CARBOXYLIC ACIDS

M.Sc. THESIS

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Chiral recognition has received considerable attention in recent years due to the significant importance of chirality in biology, pharmaceutical chemistry, and asymmetric catalysis. In the field of chirality and related research, the discrimination of the absolute configuration and the determination of the enantiomeric purity are indispensable to a chiral compound.

The significance of chiral molecules is not restricted to bioactive molecules such as pharmaceuticals, flavoring agents, and fragrances, but has covered many other areas of molecular recognition and material science. Many properties of such molecules are clearly linked to the chirality of the system and hence it is vital to know the composition of the present isomers in a test sample. This has necessitated a need for quick, accurate, and reliable techniques to establish the ratio of enantiomers in chiral samples. The transform of enantiomers to their diastereomer derivatives is one of the determining of enantiomeric ratio in the mixture. Converting the test sample to diastereomers can be carried out in two ways, by forming covalent bonds with chiral derivatizing agents

(CDA) or alternatively by forming temporary supramolecular interactions with chiral solvating (or complexing) agents (CSA).

The target of this project is to prepare chiral solvating agents (CSA) in order to use in enantiomeric discrimination of biological important chiral carboxylic acids (**A-D**) by NMR spectroscopy. For this purpose, initially, a series of amino alcohol imids **2-8** were synthesized by regioselective ring opening reaction of (*R*)-*N*-(2,3-epoxypropyl)phthalimide with various chiral amines. Amino alcohol or amino alcohol amides **2-8** were tested as potential chiral solvating agents to the enantiomeric discrimination of mandelic acid (**A**), *o*-chloromandelic acid (**B**), α-phenyl-α-metoxyacetic acid, (**C**), ibuprophen (**D**) and naproxen (**E**).

C_2-Symmetric (*S,R,S,R*)-**3** found to be the best reagent for enantiomeric discrimination for mandelic acid with ΔΔδ of 24.8 Hz. The values for α-phenyl-α-metoxyacetic acid and *o*-chloro mandelic acid were found to be 16.6 and 8 Hz respectively. CSA **5** exhibited the best enantiomeric discrimination for α-phenyl-α-methoxyacetic acid with ΔΔδ of 32 Hz. Enantiomeric differentiated values found for mandelic acid, *o*-chloro mandelic acid, ibuprophen and naproxen are 7.2, 4.4, 2 and 3 Hz respectively.

Keywords: Chiral solvating agents, Enantiomeric purity, Enantiodiscrimination, Chiral recognition.

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ABBREVIATIONS

ACE: Affinity Capillary Electrophoresis

BINOL: 1,1'-Bi(2-naphthol)

CD: Circular Dichroism

CDA: Chiral Derivatization Agent

CGE: Capillary Gel Electrophoresis

CIEF: Capillary İsoelectric Focusing

CIP: Capillary Isotachophoresis

CSA: Chiral Solvating Agent

CZE: Capillary Zone Electrophoresis

DCC: Dicyclohexylcarbodiimide

DME: Dimethoxyethane

DSC: Differential Skimming Calorimetry

EC: Capillary Electrophoresis

EtOH: Ethanol

FTIR: Fourier Transform Infrared Spectroscopy

GC: Gas Chromatography

HPLC: High-Performance Liquid Chromatoghraphy

MS: Mass Spectrometry

NEP: (*R*)-*N*-(2,3-epoxypropyl)phthalimide

NMR: Nuclear Magnetic Resonance

NOE: Nuclear Overhauser Effect

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

ESI-MS: Electrospray Ionisation Mass Spectrometry

PPh_3: Triphenylphosphine

EtOAc: Ethylacetate

TEA: Triethylamine

NEP: (*R*)-N-(2,3-epoxypropyl)phthalimide

H: *n*-Hexane

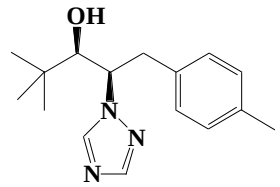
1. INTRODUCTION

1.1. History of Chirality and Its Importance

The idea of "chirality" has been known in chemistry since the 1870's however it would be about a hundred years before chemists started to use this term (Eliel 1962). The word chiral is not acknowledged, though it would be protruding in later versions (Eliel and Wilen 1994). In chiefly simple terms, chirality is "handedness," - that is, being of right/left opposition. For instance, the mirror images right and left hand are not superimposed, for his reason our hands called "chiral". The word "chiral" is came from the Greek called kheir (Kelvin 1904).

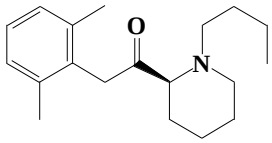
Louis Pasteur, as a pioneering stereochemists, pointed the significance of chirality in 1948 with his famous report (Pasteur 1848). Nowadays, we understand that chirality must be encountered at all stages in nature. For example; the helical neutrino and DNA, inherently chiral proteins, or plants carbohydrates, helical bacteria and sea shells all of them are chiral. He realized that chiral substances exist like a pair of enantiomorphous mirror images that are nonsuperimposable and related to each other like a left- and right-handed glove. At the molecular level, chirality brings rise to enantiomers that can expose awfully different chemical and physical properties in a chiral setting. Several biologically active mixtures, for instance agrochemicals, scents, flavors, medications and nutrients are chiral and more than fifty percent of today's top-selling medicines containing Lipitor (cholesterol reducer, global sales in 2004: $12.0 billion), Zocor (cholesterol reducer, $5.9 billion), Plavix (antithrombic, $5.0 billion) and Nexium (antiulcerant, $4.8 billion) are traded as single enantiomers.

In 1853 Pasteur prospered in separating the two enantiomers of racemic tartaric acid by crystallization of the diastereomeric salts formed with the optically active alkaloid cinchonidine (Pasteur 1853). The diastereomeric salt which crystallized out contained (-)-tartaric acid while the (+)-tartrate salt remained in solution.



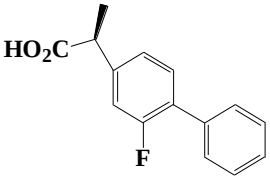
(2R,3R)-Paclobutrazol (fungicidal agent)

1



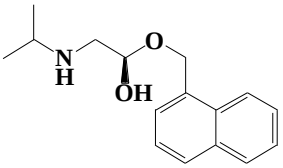
(S)-Bupivacaine (local anaesthetic)

2



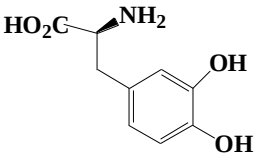
(S)-Flurbiprofen (anti-inflammatory drug)

3



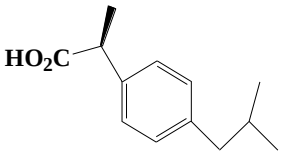
(S)-Propranolol (ß-adrenergic blocker)

4



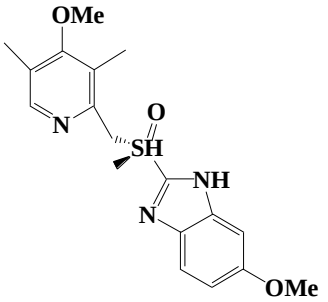
(S)-DOPA (neurotransmitter precursor used for treatment of Parkinson's disease)

5



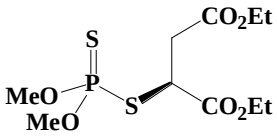
(S)-Ibuprofen (anti-inflammatory drug)

6



(S)-Omeprazole (proton pump inhibitor used for treatment of esophagitis, ulcer)

7



(S)-Malathion (insecticidal agent)

8

Figure 1.1 Some of trade pharmaceuticals and agrochemicals.

Individualistically the French chemist Le Bel and the Dutch chemist Van‘t Hoff both of them, in 1874 regarded that the molecule consist of five atoms one of atom it is carbon formed chemical bonds to four other atoms at the four angles of a tetrahedron. Therefore, the central carbon atom is called chiral or stereogenic center and the molecule is known as the chiral. This offer of Le Bel and Van’t Hoff as it changes out, absolutely correct; indeed, now the simplest molecule known as optically active molecule it is CHFClBr (Franks et al. 2004).

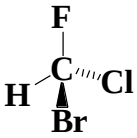
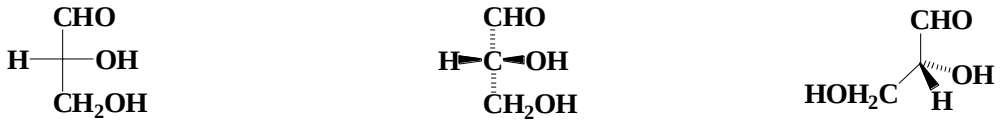


Figure 1.2 An optically active molecule

The necessity for permanency in stereo chemical designation encouraged Fischer to use the C-5 of the D-enantiomer of glucose as a beginning point in 1919. The molecule is first drawn as a Fischer projection (Figure 1.3).



Fischer projection **Flying-Wedge representations** **Perspective representations**

Figure 1.3 Various representations of D-glyceraldehyde

Where all links are drawn as solid lines with the understanding that vertical bonds point away and horizontal bonds point in the direction of the onlooker. Additionally, the molecule is drawn with the longest carbon chain vertical and exceedingly oxidized end of the chain is at the top. (+)-Glucose was corrupted by Fischer to (+)-glyceraldehyde, in which the only residual stereogenic center invents from the C-5 of glucose. Personally, Fischer allocated the structure shown in Figure 1.3 to (+) glyceraldehyde and named it D-(+)-glyceraldehyde, because of the position of the OH substituent on the right-hand side of the stereogenic center.

In a different way of explanation Fischer projections is the ostensible flying-wedge illustration in which bonds pointing towards the observer are represented by a wedge, bonds pointing distant by a wrecked line (Figure 1.3). In the perception illustration, alternatively, the bonds are organized in a tetrahedral arrangement, with the bonds pointing towards and away from the observer designated by a wedge and a broken line, individually, and bonds in the plane of the paper by a constant line (Figure 1.3) (Cahn et al. 1956, 1966).

1.2. Principles of Stereochemistry

The science of organic chemistry is chiefly involved with the connection between the molecular structure and properties of carbon mixtures. That part of the science which deals with construction in three dimensions is termed stereochemistry. One typical of stereochemistry is stereoisomerism; isomers that not look like from every last one only in the way that the atoms are oriented in three dimensional space are called stereoisomers. Proportion (or the lack of it) is one of the exhilarating features of geometric figures with two or more dimensions. For example, the alphabet has both unsymmetrical and symmetrical two-dimensional letters. The later have different existences when they are imitated in a reflector. So, the mirror-images of the unsymmetrical letters R and S look overturned (Figure 1.4). The property of nonidentical mirror-images also happens for substances with three dimensions. However, there is one significant variance. The mirror-image of the letter R or S can be lifted out of the place of the paper, turned over, and located exactly on top of the original letter. The mirror-image of a right hand, in contrast, is not superimposable on the real right hand because the two sides of the hand (palm and back) are not equal. The mirror-image of a right hand is, however, identical with and superimposable on a left hand.

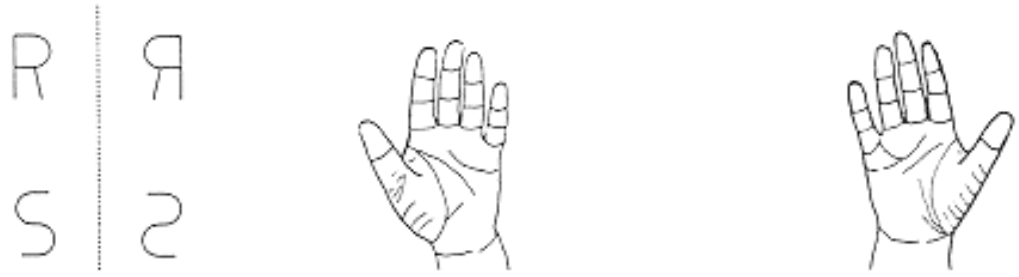


Figure 1.4 Mirror image connections of asymmetrical figures in two and three dimensions.

1.2.1. What Is Chirality

Chirality is a geometrical attribute; an object that is not superimposable upon its mirror-image is said to be chiral while an achiral object is one that is superimposable on

its own mirror-image. Normal samples of chiral objects are an individual's left and right hands, counterclockwise-threaded screws, seashells - and dice and clockwise. The two-dimensional letters are not chiral like the plane of the paper in which they lie is a plane of symmetry. An substitute explanation of chirality is established on symmetry features: a chiral object lacks reflectional symmetry.

The spatial preparations that exist for macroscopic objects also exist at the molecular level. As a result, a molecule is chiral when it is not superimposable on its mirror-image (i.e., when it lacks reflectional symmetry). It is important to stress that chirality is a property of the molecule as a whole. It is incorrect, therefore, to say that a molecule contains a chiral center. It is better to refer to asymmetric centers or even better, stereogenic centers. Mislow and Siegel have defined a stereogenic atom as: an atom bearing several groups of such nature that an exchange of two groups will create a stereoisomer (Mislow and Siegel 1984). However, we shall from time to time use the more commonly established term asymmetric center. Similarly, it is not correct to describe a molecule constituting more than one stereogenic center as multichiral; a molecule is either chiral or achiral.

1.2.2. Enantiomers

The most common kind of chiral particle has a tetrahedral carbon atom committed to four diverse groups; the carbon atom is the stereogenic (asymmetric) center of the molecule. A molecule having four diverse groups occurs as two different mixtures that are stereoisomers and have the same chemical properties in an achiral (balanced) condition. The structures of these combinations are nonsuperimposable. They are images of each other.

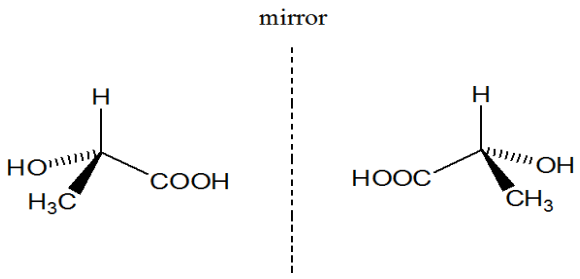


Figure 1.5 Enantiomers of lactic acid.

Such stereoisomers are named enantiomers (Greek: enantio, opposite). Lactic acid, for instance, is a chiral molecule and happens by way of a double of enantiomers. The current method of describing such stereoisomers is exposed in Figure 1.5. It must be renowned that a further condition that has to be attained in order to sign visual action is that the energy barrier for change of a chiral molecule into its enantiomer must be high enough (> 80 kJ/mol) to allow separation or at least observation. The rapid inversion of trisubstituted nitrogen is a familiar phenomenon that precludes the separation of stable visual isomers of molecules with stereogenic nitrogen atoms (Bijvoet et al. 1951).

1.3. Chirality of molecules

Chirality it is the phenomenon that subsists in organic compounds. Although it has also been established in few organic molecules. In some compounds, the carbon atoms stay committed to four different groups or atoms. Asymmetric this sort of compounds are different in their exist and three-dimensional in shape into two methods, both of them are mirror of each other, but nonsuperimposable (Federsei 1994). It doesn't difficulty what balance method is practical to each compound, it is impossible for both mirror images to superimpose upon each other. These mirror images are called chiral molecules or enantiomers or stereoisomers (Federsei 1994). The subsistence of variety of enantiomers contains the phenomenon of chirality, or stereoisomerism. A racemic mixture is a 50:50 ratio of enantiomers. Besides central chirality, axial chirality can be found in cumulenes and allenes. The substituents are not necessarily different in the former class. The loss of the C_2 rotational symmetry group is caused by the second double bond. In the former class, an even number of carbon atoms results in E/Z isomerism (i.e. geometrical isomerism), whereas only some with an odd number of gathered carbon atoms are possibly chiral (Federsei 1994). The rotation around a carbon-carbon single bond will not be hindered, avoiding the two forms from interconverting unless the ortho substituents in tetra substituted biaryls are large enough. Lastly, there occurs a planar chirality that rises in the arrangement of atoms or it's groups qualified to a stereogenic plane. Though, this shape of chirality is quite infrequent (Federsei 1994).

The extraordinary system of chirality usually occurs in macromolecules like polysaccharides, proteins and biopolymers are called helicity (Ma et al. 2009). Left-handed (counterclockwise) or right-handed (clockwise) arrangement that constantly chiral are owed by helix. The number of theoretically possible enantiomers will be resulting in the 2^n formula as a stereoisomer has more than one stereogenic center (e.g., n). Figure **1.6**. offers four kinds of stereoisomerism.

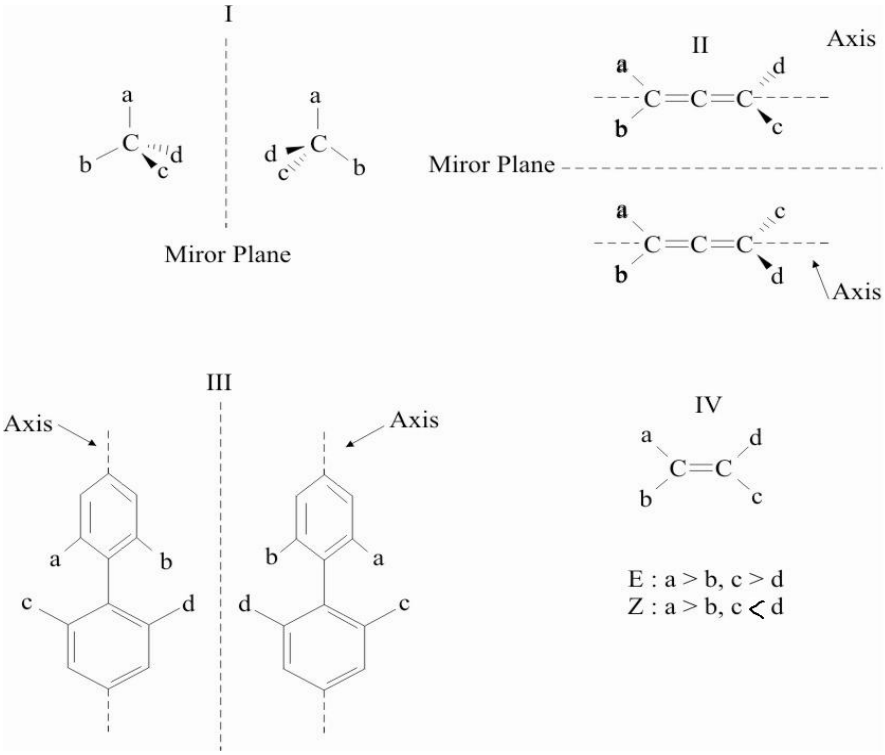


Figure 1.6 The classifications of stereoisomerism: I, chiral center; II, chiral axis; III, atropisomerism and IV, E-/Z- geometrical (isomerism).

1.4. The Significances of Chirality in the Systems of Biology

Because of the role of chirality in many biological practices the synthesis of chiral receptors for molecular agreement and the strategy have reached farther importance. The specificity and good organization of many biologically vital responses are built on recognition of chiral, one of the two enantiomers is fixed by the method in which a chiral host molecule selectively. The chiral agreement of carboxylic acids by pretended receptors is of serious significance in the departure, planning, and exploration of enantiomers because of their significance in the systems of biology and practicality

as a basis of chirality in organic preparations, in current ages unlimited determination has been given, to the strategy and preparation of pretended receptors for discrimination of enantiomeric pureness and to distinguish the roots of the method of host–guest appearances. Currently, there are a choice of ways (e.g., mass spectrometry, gas chromatography, capillary electrophoresis, high-performance liquid chromatography, absorbance spectrometry, infrared transmission spectrometry, circular dichroism, X-ray anomalous scattering, nuclear magnetic resonance) available for chiral recognition and the determination of enantiomeric purity (Bozkurt et al. 2011).

The eutomer (active enantiomer) is the enantiomer that communicates immediately with entirely three places, but the distomer (inactive enantiomer) that ties to less than three sites at the same time (Srinivasu et al. 2005). For that reason, regulatory and metabolic methods mediated by systems of biology are sensitive to stereochemistry, and dissimilar reactions usually could be seen upon paralleling the actions of a couple of enantiomers. These varieties could be uttered in excretion, distribution rates, metabolism, antagonistic actions relative to each other, or in properties of toxicology. The annotation of the inactive enantiomer is very stimulating; it might be not only antagonistic to the action of the eutomer but also weight, or sometimes even toxic. The eudismic ratio is the relative of the influence of the energetic enantiomer to that of the fewer active one (Waldeck 1993, Jalba et al. 2004). Thus nowadays the main significance in the progress of a new medicine is focused to discover the eutomer. To exactly deal with chiral dr ugs in medicine progress, in toxicological clinic or their apeutic drug monitoring, the optically ac tive pure types of the racemic compound must be recognized.

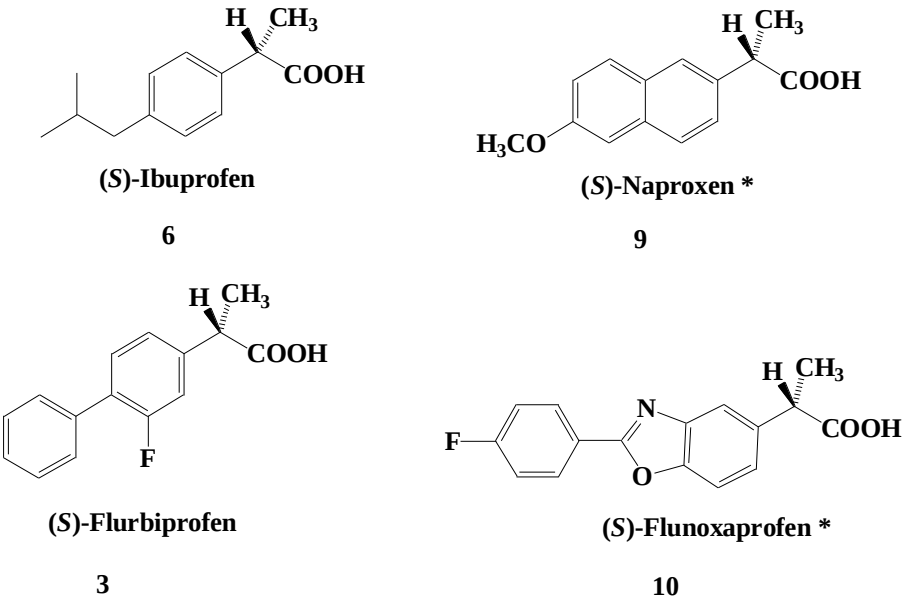
1.5. The Developments of Chirality and Drug

Though the enantiomers of a racemic drug can reveal unlike pharmacological actions in active structure (Jalba et al. 2004). Bioactive synthetic mixtures, that include many of the chiral drugs, are often directed as racemates (Kostyanovsky et al. 2002). Clearly, the more chiral centers existing in a drug compound, the more difficult in condition. The tissue/organ harm or side effects, are not stopped by applying a particular enantiomer to humans ever since, for instance, the construction of unsafe metabolites, also chiral inversion or racemization, can take place in vivo. On the other

hand, for proving the ideal therapeutic influence, it could look to be appropriate to manage the eutomer. For instance, ibuprofen provides chiral inversion without negative side effects, an enzymatic mechanism transforms the inactive *R*-(-)-isomer into the active *S*-(+)-enantiomer (Rentsch 2002). In the end of 1960s a negative sample is thalidomide that was announced to the bazaar as a relaxing, in the racemic form. Even as practiced in the therapeutic and not hurtful (+)-isomer, in vivo inter conversion into the hurtful (-)-isomer was offered for being in charge of terrible deformity of fetus while thalidomide was approved for pregnant women. (Federsei 1994, Knoche et al. 1994, Robin 1995). In the diuretic indacrinon, though, the distomer attendance was appropriate, as it supported the healing efficiency eutomer by provoking a side of its effects (Kubinyi 2002). Besides making a general attention, the thalidomide calamity lead to a severer resistor, and the approving new medicines advices were reviewed. For keeping patients from unsolicited and hurtful effect sides of enantiomers, the probability of a different single enantiomer action with concern to toxicology and pharmacology ought to be used into account (Witte et al. 1993, Rauws and Groen 1994, Rentsch, 2002). revised the regulation prestige of chiral medicinal produces on the industries of pharmacy in the United States, Japan and some European countries where chosen professionals are in charge of the controlling and consent of lately industrialized drugs (chiral and non-chiral). Chemistry as well as industrial and control data, such as procedures and stipulations, proper labeling, impurity limits, pharmacokinetic profile, toxicology, pharmacological activity, and results of stability tests are new drug requests which are acquiesced to the food and drug administration (FDA) in the United States. As long as the drug includes a racemate, the data of all toxicology and pharmacology and the stereochemistry of the single enantiomer should be contained. An evaluative toxicology and pharmacology must be conducted for single enantiomer, depending on on the existing information of the race mate. Moreover, the assessment must contain data regarding the interconversion of the studied eutomer into the distomer (US Food and Drug Administration 1992).

1.5.1. The Arylpropionic Acid Antiinflammatory Drugs

The α-arylpropionic acids, typified by ibuprofen and naproxen (Figure 1.7), constitute the biggest particular group of medicines used in the cure of rheumatoid inflammation and as general analgesics; ibuprofen, for example, is an extensively used over-the-counter drug for headache and minor pains. These medicines are all chiral molecules and it is the (*S*)-enantiomer that is reponsible for the preferred healing effect (e.g., the ER for naproxen is 30). Interestingly, the inactive (*R*)-enantiomers undergo an unidirectional metabolic inversion of configuration to give the active (*S*)-enantiomer (Williams 1990).



(*S*)-Ibuprofen **6**

(*S*)-Naproxen * **9**

(*S*)-Flurbiprofen **3**

(*S*)-Flunoxaprofen * **10**

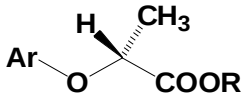
Figure 1.7. Structures of α-arylpropionic acid nonsteroidal antiinflammatory drugs.

1.5.2. α-Aryloxypropionic Herbicides

The α-aryloxypropionic acidssuch as pyrenifop, mecoprop, diclofop, and fluazifopconstitute a commercially important class of herbicides (Figure 1.8). They are chiral molecules and the herbicidal activity (inhibition of the plant growth hormone activity, indole-3-acetic acid) resides virtually entirely in the (*R*)-enantiomer (Ariëns et al. 1988, Naber et al. 1988). The (*R*)-enantiomer of α-aryloxyproprionic acid tolerates a arresting structural resemblance to the active (*S*)-enantiomer of the α-arylpropionic acid antiinflammatory medicines. (Note: the configuration is the same but that the

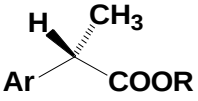
significance of the groups has reformed). Interestingly, both the α-aryloxyproprionic acid herbicides and the α-arylproprionic acid drugs were progressed next the same line of reasoning. In both cases, the action was first discovered in the corresponding exchanged acetic acid. Unfortunately, these first mixtures born quick in vivo biodegradation to sedentary metabolites. A frequently used method in such cases is to present a suitable substituent, often a methyl group, at the metabolically susceptible situation in the molecule (Ariëns et al. 1988). This tends to inhibit degradation of the molecule by enzymes present in the target organism, thereby extending the period of action and decreasing opposition. Hence, starter of an α-methyl group led to the improvement of the active herbicides and antiinflammatory medicines, correspondingly. This is explained in (Figure 1.9) for mecoprop.

The introduction of the α-methyl group also introduces chirality into the molecule and the steric blocking of enzymatic attack could only be important for one of the two enantiomers. In some cases, this isomer may still bind to the enzyme but not be changed, thus inhibiting degradation of the other isomer. In common with the α-arylpropionic acid drugs, some of the α-aryloxypropionic acid herbicides also undergo metabolic inversion of alignment. For example, inversion of the inactive (*S*)-enantiomer of fluazifop-butyl to the active (*R*)-acid is perceived in soil cured with this herbicide no inversion takes place when the soil is disinfected. The practical significances of this bioinversion are reliant on the method of demand of the herbicide and it has been suggested (Ariëns et al.1988). that postemergence spurting of deep-rooted crops with the (*S*)-enantiomer as a 'propesticide' may be advantageous.



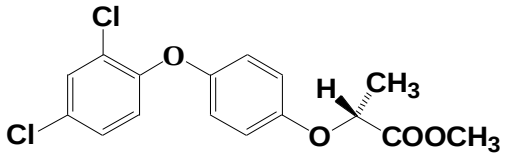
Alky (*R*)-α-aryloxyproprionate (herbicide)

11



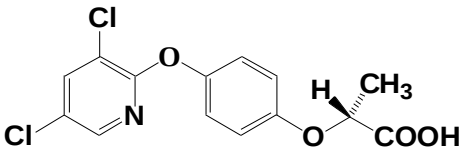
(*S*)-α–Arylpropionic acid (anti-inflammatory)

12



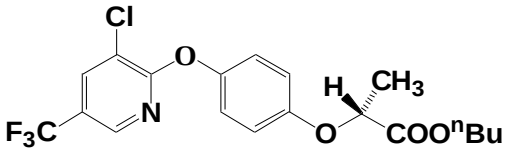
(*R*)-Diclofop-methyl

13



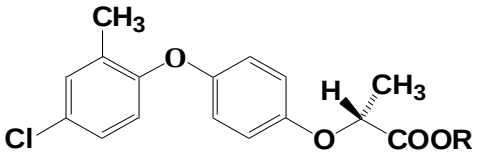
(*R*)-Pyrenifop

14



(*R*)-Fluazifop-butyl

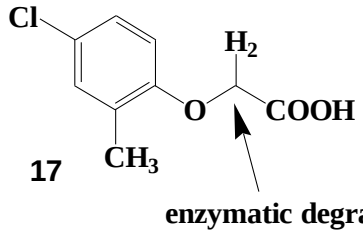
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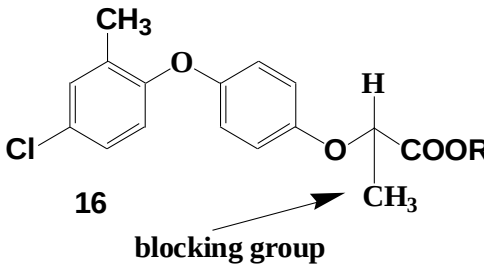
(*R*)-Mecoprop

16

Figure 1.8 Structures of the eutomers of α-aryloxypropionic acid herbicides.



MCPA= 4-chloro-2-methylphenoxyacetic acid
rapid biodegradation (not resistant)



(R)-Mecoprop
slow iodegradation (not resistant)

Figure 1.9 Control of resistance in herbicides by stabilization to metabolic degradation.

1.6. Resolution of Stereoisomers

A lot of procedures have been used for the resolve of the enantiomers on both preparative scales and analytical. The dissimilar ways may be categorized into two

classes; the traditional method, using enzymatic degradation of one of the enantiomers and the modern technologies of preferential crystallization include chromatographic approaches, electrophoretic and spectroscopic.

1.6.1. Traditional Methods

The resources of biochemical processes affect kinetic resolve in the enzymatic method which finishes an enantiomeric form. As assured microorganism like bacteria, yeast and molds are permitted to grow in mixtures of racemic solution; they integrate a selective form, leaving the other one in solution. For example, the resolution converts levorotatory owing to obliteration of the dextrorotatory form as the usual mold Penicillium glaucum is added to a solution of racemic ammonium tartrate (Pasteur 1858). Crystallization is another process of enantiomer separation. The crystallization principle is founded on the formation by two enantiomers of the diastereomeric salts of an optically unpolluted composite, and these diastereomeric salts could be parted simply In this method, the optically active solving agent should be of great ocular cleanliness. In many situations, the agent of resolving is convalesced and converts accessible for reusing after the wanted enantiomers have been parted from the diastereomeric salt (Tolman and Šimek 2000). The separation of mechanical methods (by tweezers, etc.) could be applied for the enantiomeric crystals separation of racemic composites which crystallize as conglomerates, such as sodium ammonium tartrate and quartz, as their crystals are mirror images of each other (Figure 1.10). These typical techniques certainly not attained the prestige of routine laboratory practising owed to definite drawback, as the very limited number of requests of the crystalization process and the degradation of one of the enantiomers in the enzymatic process, additionally, in normal samples these procedures could not be used at the analytical scale (Layh et al. 1994).

1.6.2. Modern Methods

At this time, the most generally practical methods are the chromatographic, biosensor, electrophoretic, spectroscopic and membrane (Figure 1.11) (Pirkle and Bowen 1994, Cilurzo et al. 2010). Among the spectroscopic methods, detectives use ocular gyration measurements, infrared (IR) and nuclear magnetic resonance (NMR) spectroscopies, and the last as differential scanning calorimetry (DSC), can differentiate

only racemic mixture (+) and distinct enantiomer. In NMR spectroscopy, chiral solvating agent (CSA) can be applied for promoting a conversion in the chemical shift of the chiral carbon atoms.

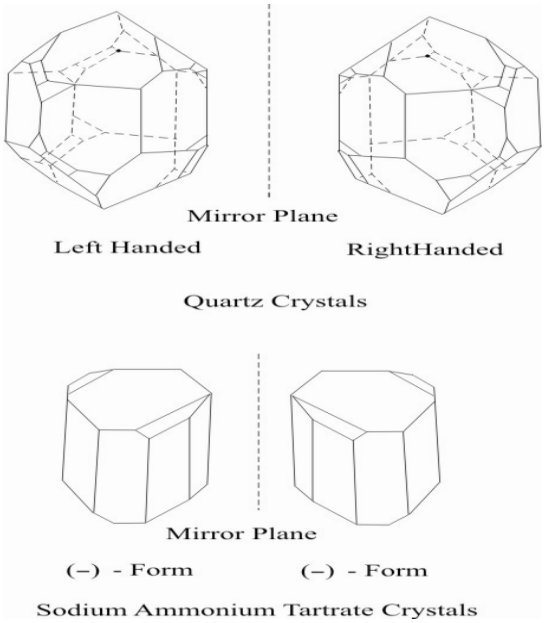


Figure 1.10 The stereostructures of quartz and sodium ammonium tartrate crystals.

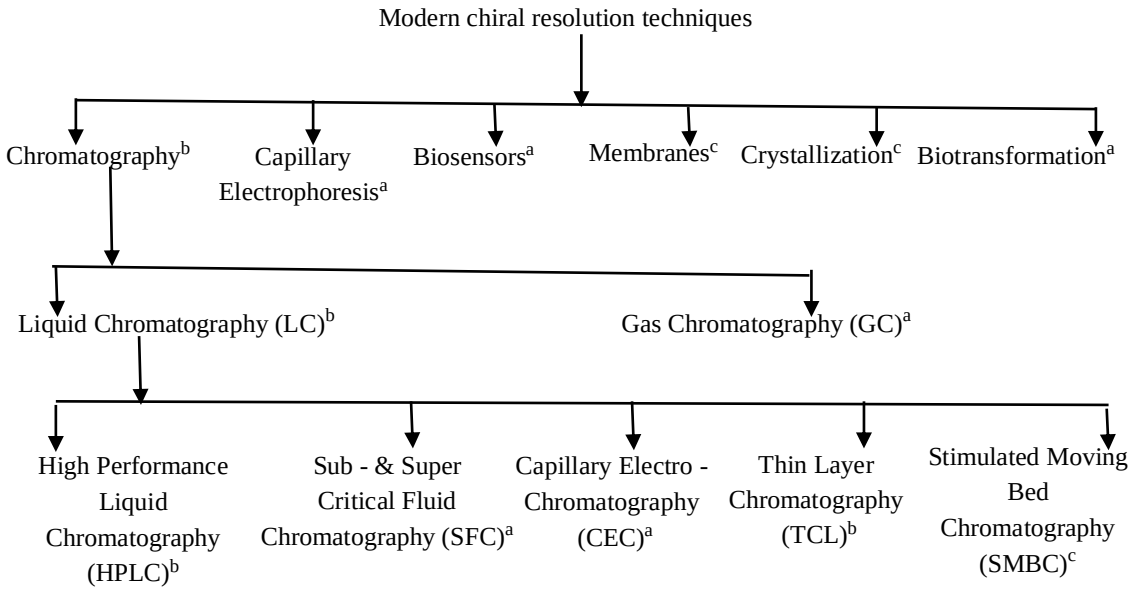


Figure 1.11 The different ways of chiral resolve: a, analytical; b, analytical and preparative; c, preparative.

In addition, the DSC (differential scanning calorimetry) and the spectroscopic methods are sensible to meddling in nonchiral and chiral scums in the model. Moreover,

they could accurateness and sensibility, meanwhile the variances in both mixtures isomer and enantiomers might be tiny. Also, these procedures are unsuccessful these days at the preparative gage. To discrete the enantiomers at the preparative gage, membranes of chiral were used in 1994 (Pirkle and Bowen 1994). But the method has not completely developed yet. Among the chiral resolve electrophoretic techniques, several capillary electrophoresis forms like capillary isotachophoresis (CIP), capillary isoelectric focusing (CIEF), capillary zone electrophoresis (CZE), capillary gel electrophoresis (CGE), affinity capillary electrophoresis (ACE), and separation on microprocessors have been used. For this aim, the CZE technique has been used regularly in contrast to others (Eeckhaut and Michotte 2009). In another way, disadvantages related to the method of electrophoretic lead to the deficiency growth of contemporary chiral stages have restricted the requests of these approaches. Furthermore, the methods of electrophoretic must not be used at the preparative gage that is very necessary for chiral separation sciences.

2. PREVIOUS STUDIES

Compound **18** was synthesized by Port et al. (2000) as racemic form then separated into the two enantiomers by chromatography. They tested compound **18** as CSA by using some chiral alcohol and carboxylic acids (1-phenyl-1-metoxyacetic acid, 1-Phenyl-1,2-ethanediol, 3-phenylbutanoic acid, ibuprofen, α-bromoacetic acid etc.). They achieved high enantiomeric discrimination (0.02-0.29 ppm) by using NMR (400 MHz) (Port et al. 2000). Complexation ratio and species investigated by continuous variations and nuclear overhauser effect (NOE). Similar geometry of two diastereoisomers formed indicate the π–π-stacking and by hydrogen bonding of the functional groups.

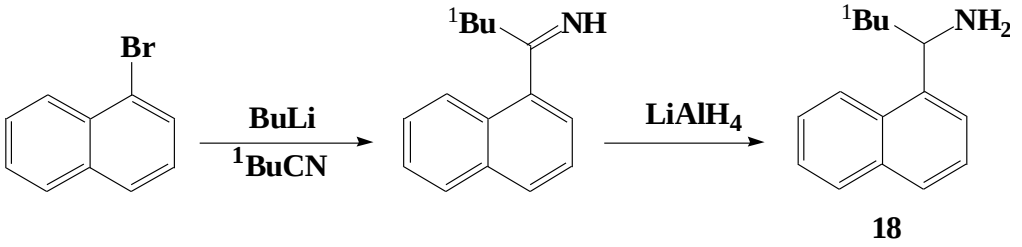


Figure 2.1 Synthesis of CSA **18**

The synthesis of dioxocyclen macrocles **19-22** were achieved from chiral amino acids by Yuan et al. (2002). They exhibit promising enantiodiscrimination (from 1.2 to 8.4 Hz) towards mandelic acid and its derivatives (Figure 2.2).

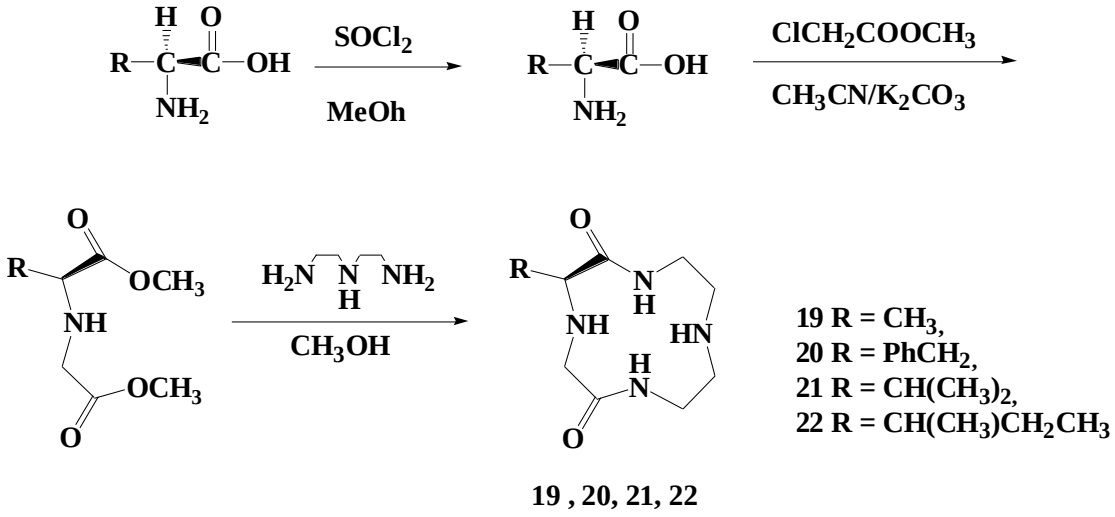


Figure 2.2 The synthesis of dioxocyclens **19-22** starting from amino acids

Racemic form of compound **24** has been reported by Munoz and Virgili (2002). They discriminated this compound by preparative HPLC to its pure enantiomers and used for enantiodiscrimination of several aromatic amines and alcohols as a CSA (Figure 2.3). It was shown that pyrene ring of **24** increases the enantiodiscrimination (up to the 0.003-0.012 ppm).

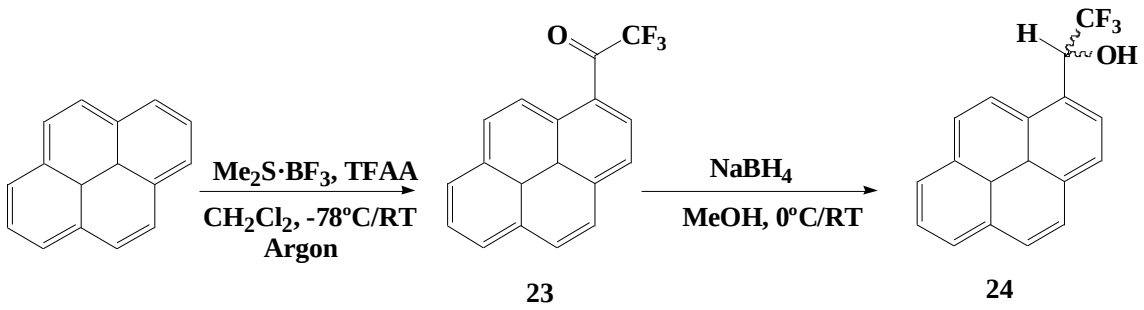


Figure 2.3 Preparation of compound **24** from pyrene **22**

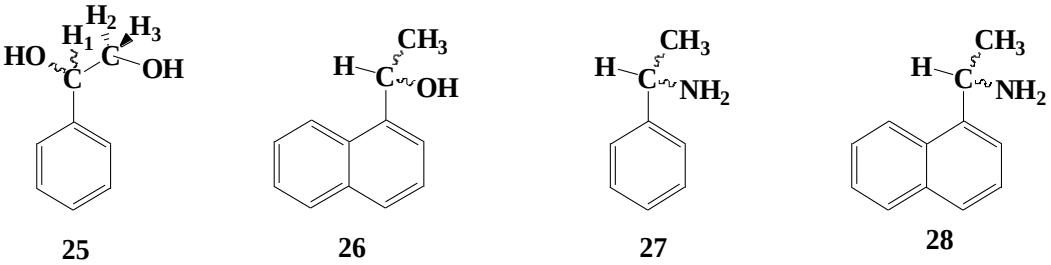


Figure 2.4 Chiral compounds used for discriminating experiments

Uccello-Barretta et al. (2003) synthesized carbamoyl derivatives of quinine (**29, 30**) by derivatization of its double bond and used as CSAs by NMR spectroscopy. They used several analytes including chiral amines, ethers, ketons, carboxylic acids, esters, groups. Derivatized quinine exhibit similar enantiodiscrimination properties (up to the 90 Hz).

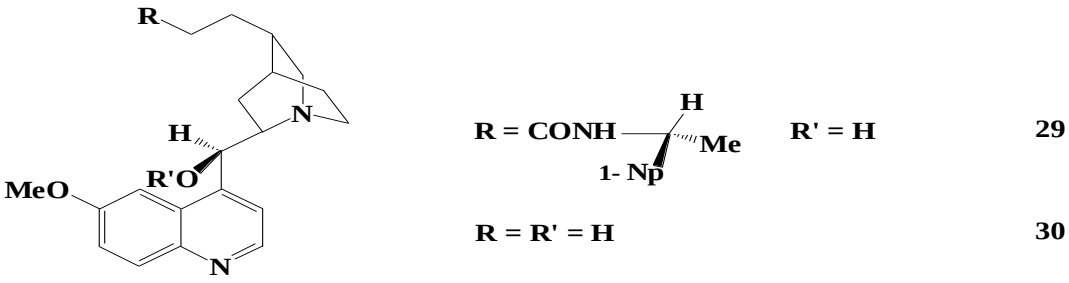


Figure 2.5 Structures of CSAs **29, 30**

Chiral rigid novel macrocyclic dioxopolyamines **31** and **32** which were derived from L-Proline have been prepared in order to investigate the enantiodiscrimination of mandelic acid and its derivatives, dibenzoyltartaric acid and naproxen (Yang et al. 2004). In their report, the best selectivity was obtained in the case of mandelic acid with 13.2 Hz by using ratio of 1:2 CSA: Analytes.

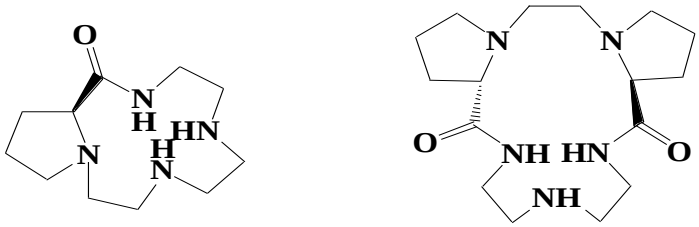


Figure 2.6 Structures of the chiral macrocyclic dioxopolyamines **31** and **32**.

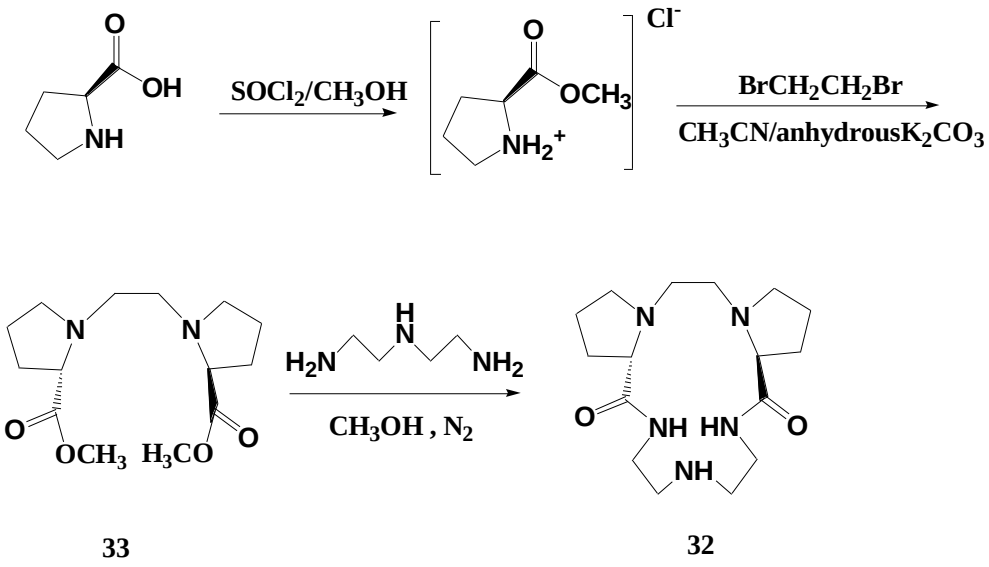


Figure 2.7 The synthetic route of compound **32**.

Pe´rez-Trujillo et al. (2005) described the preparation enantiomers of **34** and **35** and their conformational behaviours. Their chiral solvating agents' ability has been tested by using chiral amine, amino alcohol and diol compounds **36-40**(Figure 2.8). They showed a good selectivity with 0.007-0.034 ppm by ^{1}H NMR spectroscopy.

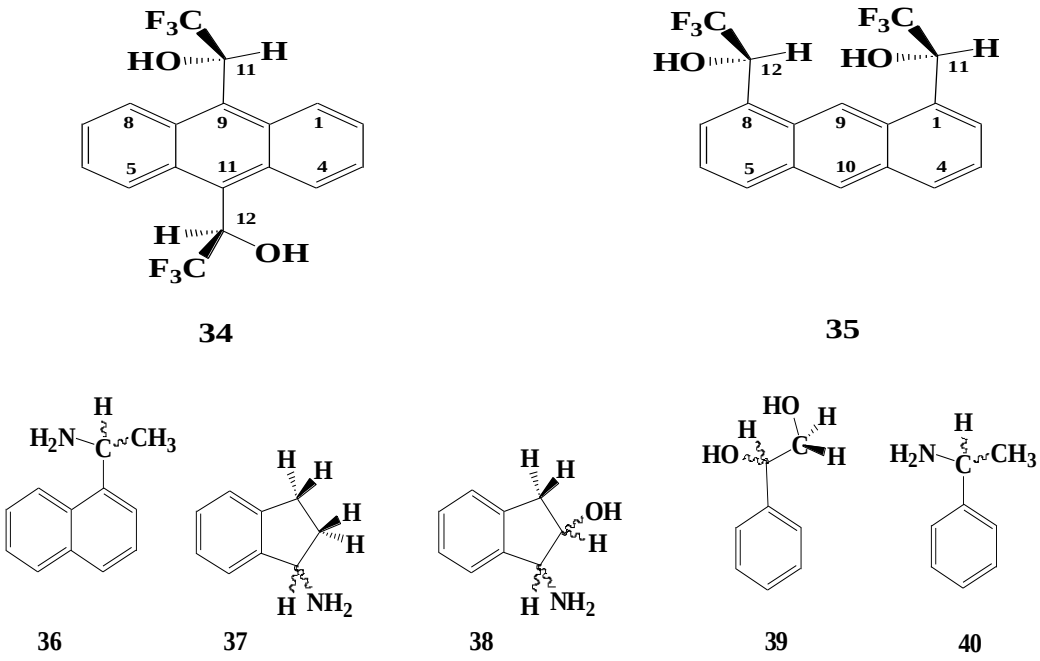
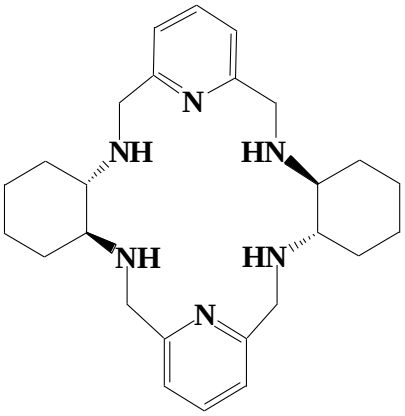
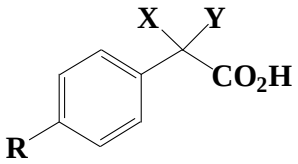


Figure 2.8 Structures of **34-40**

Polyazamacrocycle **41** has been used as chiral solvating agent for the enantiomeric excess determination of different carboxylic acids including mandelic acid and its derivatives **42-45** (Figure 2.5). High enantiomeric differentiated (up to $\Delta\Delta\delta$ = 0.20 ppm) values obtained by using a low amount (even 0.125 equiv) of the CSA **41**.



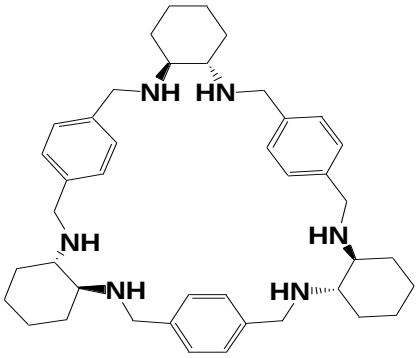
(S,S,S,S)-41



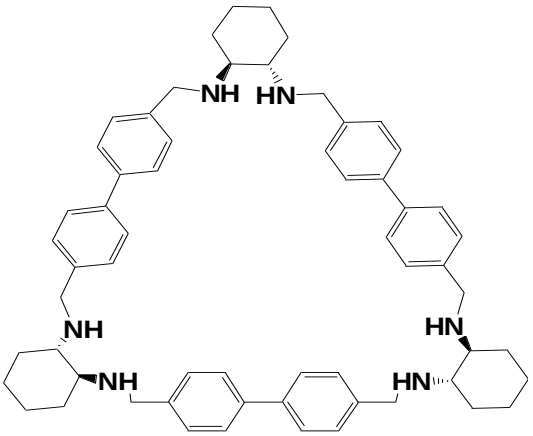
42 (R=H, X=OH, Y=H)
43 (R=Cl, X=OH, Y=H)
44 (R=OMe, X=OH, Y=H)
45 (R=H, X=OMe, Y=H)

Figure 2.9. Chemical structures of CSA **41** and the carboxylic acids (**42–45**)

Chiral trianglamines **46** and **47** have been synthesized by condensation reaction in order to using as NMR chiral shift reagents for enantiomeric excess resolution and complete conformation of some alcohols, cyanohydrins, and propargyl alcohols (Tanaka et al. 2007). They achieved good enantiodifferentiated values up to the 30 Hz.



(S,S,S,S,S,S,S)-(+)-46



(S,S,S,S,S,S,S)-(+)-47

Figure 2.10. Structures of CSA **46** , CSA **47**

Enantiodiscriminating ability of two benzo[de]isoquinoline-1,3-dione amino acids **48** and **49** have been tested for analytes **51-55** by ^{1}H NMR spectroscopy. They showed that simple structure and with a stereogenic center CSA **48** exhibit a good ability to separate the multiplet of analytes up to the 66.0 Hz. Their binding constant and complexation ratio were investigated as further studies (Luo et al. 2007).

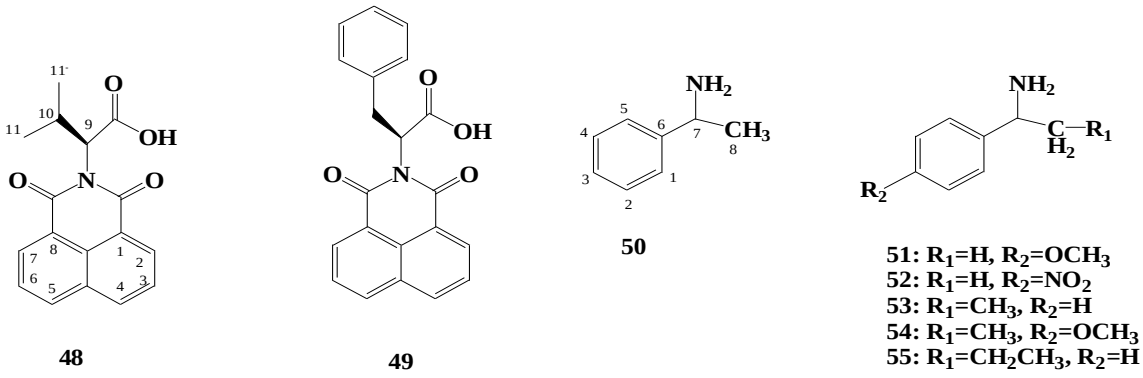


Figure 2.11. The structures of CSAs **48** and **49** and analytes **50-55**

Luo et al. (2008) synthesized and designed two amphiphilic chiral receptors **58a** and **58b** used enantiodiscriminating reagent against enantiomers of mandelic acid and its derivatives. It has been shown that CSA **58a** not anly exhibit good enantio differentiated values (6.9-85 Hz) towards lipophilic analytes but also as the first example to determine some hydrophilic analytes in polar solvent as well (Luo et al. 2008).

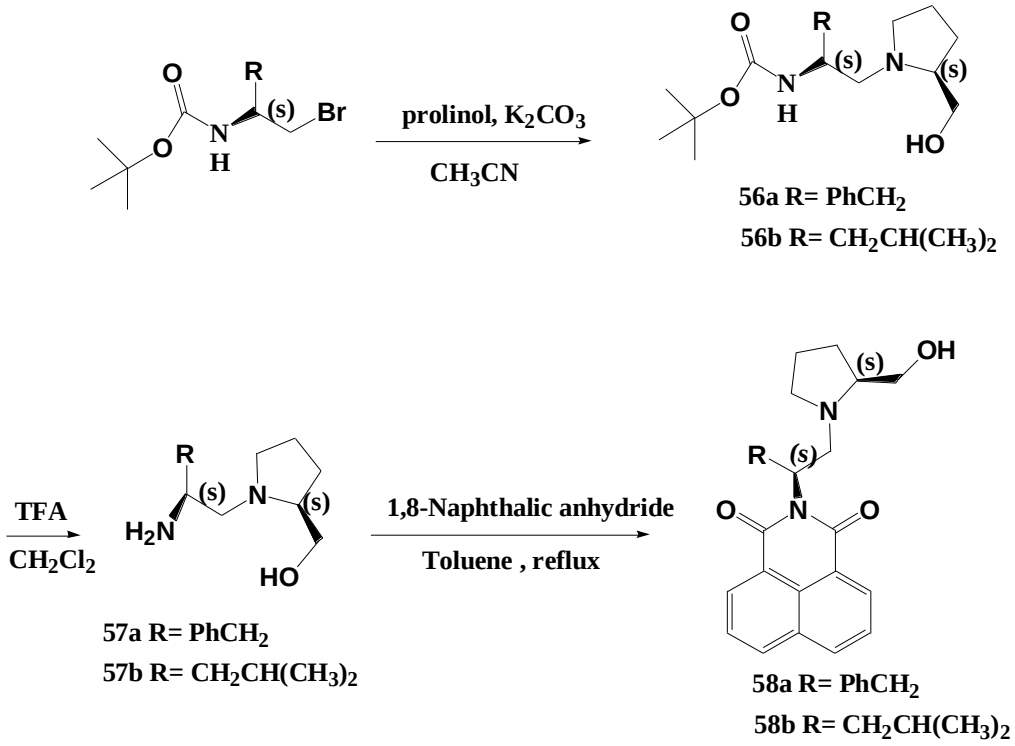
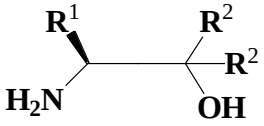
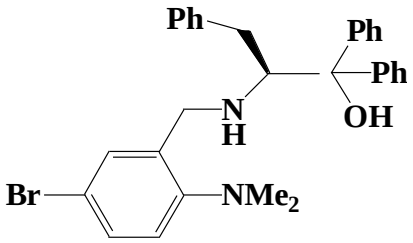


Figure 2.12. The synthesis route of compounds **58a** and **58b**

Several chiral amino alcohols **60-62** have been synthesized in order to investigate their chiral solvating ability against a series of chiral acids (Figure 2.13). It was demonstrated that CSA **62** show good differenentieted ability for especially Ts-derivative of amino acids tested. Therefore, the results indicate that it is possible to achive the absulate configuration of some analytes by these CSAs (Wang et al. 2008).



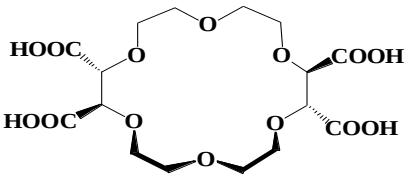
59 : R^1 = Me_2CH, R^2 = Ph
60 : R^1 = $PhCH_2$, R^2 = Ph
61 : R^1 = $PhCH_2$, R^2 = H



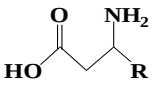
62

Figure 2.13. The structures of amino alcohols **59**–**62**

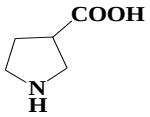
It was shown that crown ether **63** have a good NMR solvating agent against amino acid **64-69** by mesurement of chemical shifts of α-methylene and *β*-methine hydrogen atoms. It was demonstrated that absolute configuration of some analytes can be determined by using these CSAs (Wenzel et al. 2009).



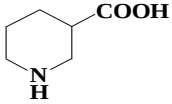
63



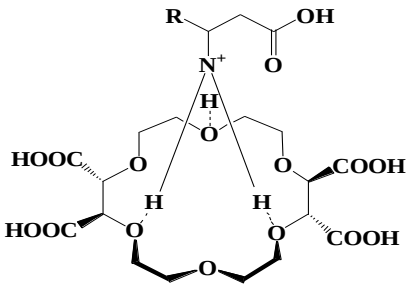
64 R=CH_2CH_3
65 R=$CH(CH_2CH_3)_2$
66 R=Cyclohexyl
67 R=Ph



68



69



Association of a protonated β-amino acid 64-67 with 63

Figure 2.14. Structure of CSA **63** and the association of a protonated *β*-amino acid with **63**

Wenzel et al. (2010) were also reported that an excellent enantiodiscrimination of *β*-aminoacids **70-77** were achieved by CSA **63** (Figure 2.14). Effective discrimination of amino acids were attributed to the diastereoselective complexation occurs by protonated amine groups to ammonium form and crown ring formed hydrogen bonding as a tripodal shape of interactions. In methanol d_4 the crown ether was added to the neutral *β*-amino acids. The ammonium ion is forms by the neutralization reaction between *β*-amino acid and crown ether. The two hydrogen atoms α enantiomeric discrimination to the carboxylic acid and amine moieties of the *β*-amino acid were noticed with each studied substance.

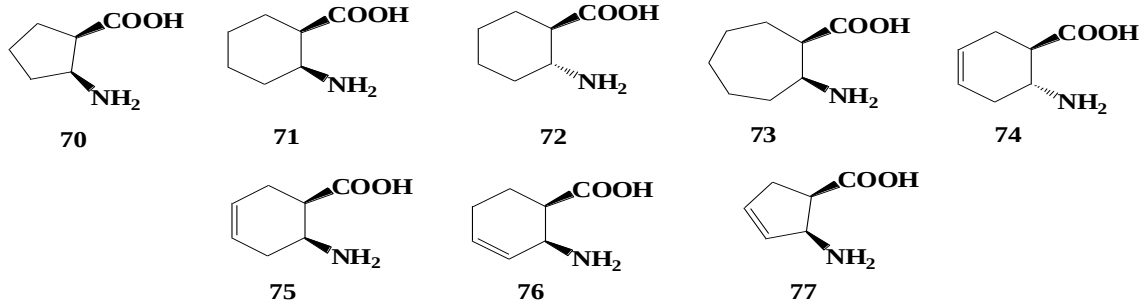


Figure 2.15. *β*-amino acids tested as analytes for CSA **63**

NMR enantiodiscrimination of some carboxylic acids were achieved by synthesized several bis(amino amides) which are derivative from regular amino acids (Figure 2.16). It was shown that the side arm of amino acid is important on the differentiated process to make them as good chiral solvating agents. ESI-MS, NMR, DSC, and molecular modelling have been used in order to investigate the binding between CSAs and analytes. The data showed that the complication includes the establishment of an ionic pair after proton transfer from the acids to the CSA (Altava et al. 2010).

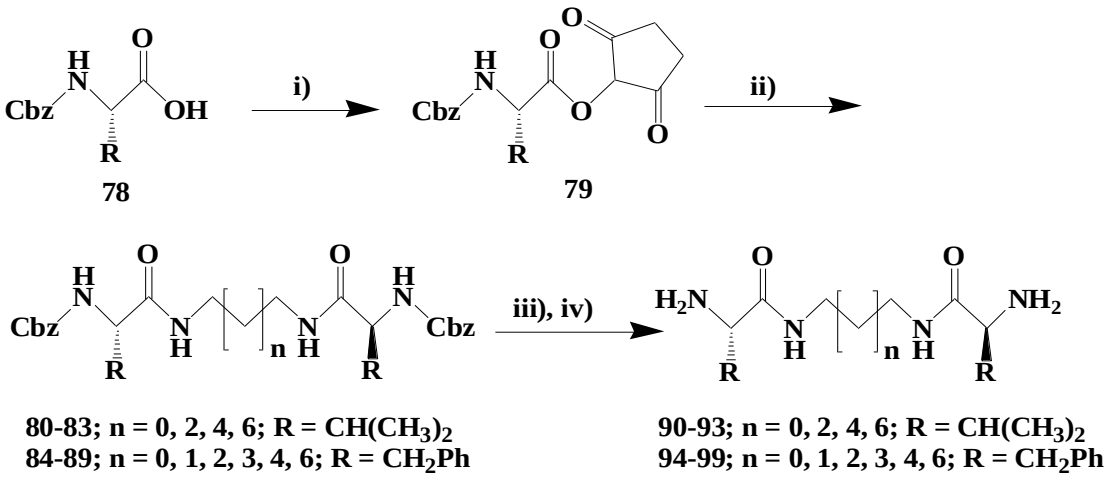
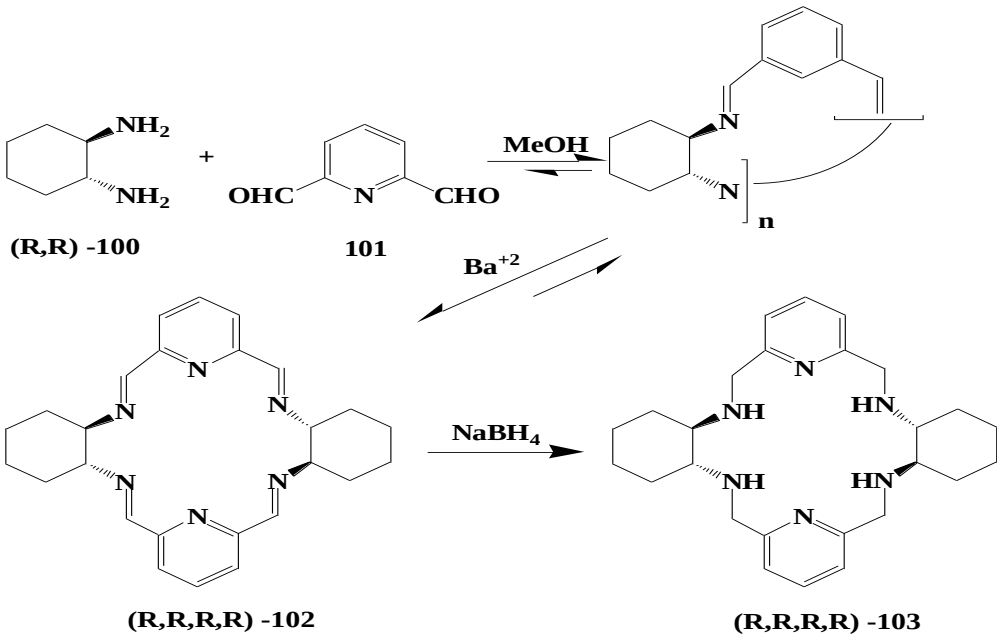


Figure 2.16. Synthesis of chiral bis(amino amide) CSAs. Reagents and conditions: (i) DCC, N-hydroxysuccinimide, THF, rt; (ii) $H_2NCH_2(CH_2)nCH_2NH_2$, DME, rt; (iii) HBr/AcOH; (iv) $NaOH_{aq}$.

CSA **103** was synthesized by starting from condensation of chiral 1,2-diamnocyclohexane with pyridine based dialdehydes then converted to the dimer ring by template effect of Ba^{2+} ions followed by reduction with $NaBH_4$ (Figure 2.17). It was shown that CSA was differentiated mandelic acid, *p*-chloro- and *p*-metoxymandelic acids (Figure 2.17) up to the $\Delta\Delta\delta$ = 0.13 ppm by using 1:1 ratio of CSA/Analyte and using NMR signals (Busto et al. 2010).



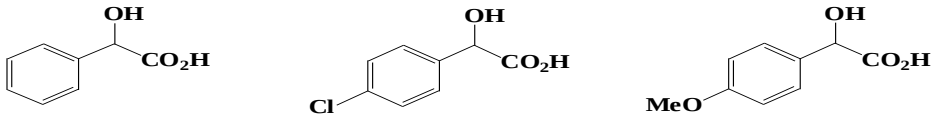


Figure 2.17. Synthesis of CSAs **102-103** and analytes herein

CSA **105-108** were designed by ring opening of (*R*)-*N*-(2,3-epoxypropyl) phthalimide (**NEP**) with several chiral primary amines (Figure 2.18). It has been shown that these CSAs especially CSA **108** exhibit a good selectivity towards mandelic acid and its derivatives (up to the 30.0 Hz), (Bozkurt et. al. 2011).

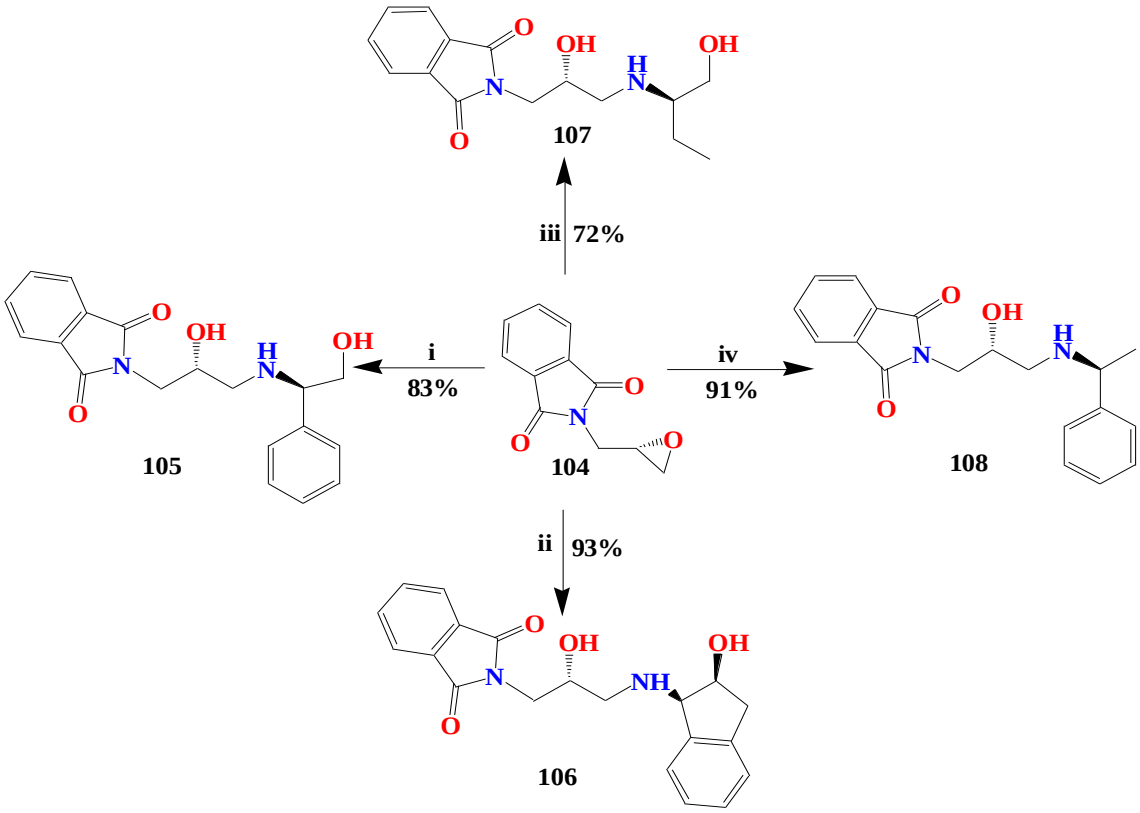
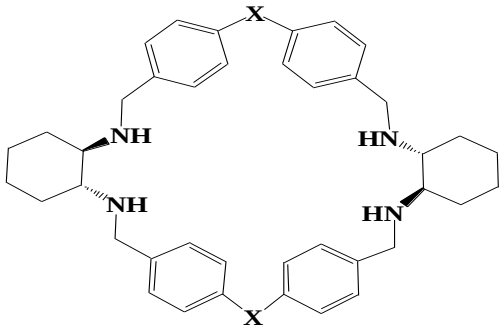


Figure 2.18. Synthesis of CSAs **105-108** (i)-(iv) Solvent: 2-propanol, and suitable chiral amine or aminoalcohol, reflux.

Tanaka et al. (2011) prepared chiral macrocyclic amines **109a** and **109b** by the reaction of [2+2] cyclocondensation of (*R*,*R*)-1,2-diaminocyclohexane with equivalent dialdehydes. They discovered that chiral rhombamine macrocycle **109** has presented to

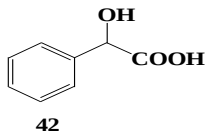
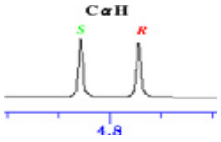
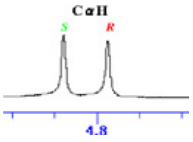
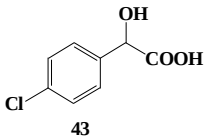
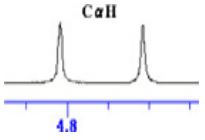
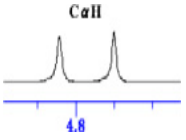
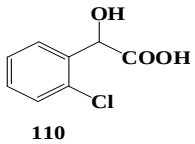
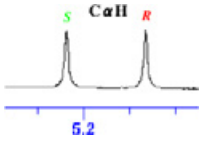
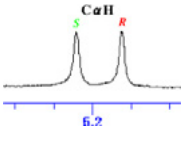
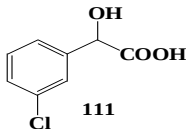
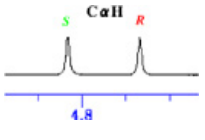
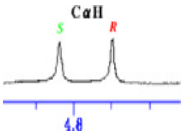
be a very suitable chiral shift substance for the easy and quick resolve of both complete configuration and enantiomer excess of an extensive carboxylic acids range (at Table 2.1.) (Tanaka et al. 2011).



(R,R,R,R)-109 **a: X = CH_2**
b: X = O

Figure 2.19 Structures of CSA **109a** and **109b**

Table 2.1 Partial ^{1}H NMR (400 MHz in $CDCl_3$) spectra of rac-mandelic acid derivatives in the presence of 0.25 equiv of **109a** and **109b.**

		109a		**109b**	
Entry	C. Acid	Spectrum	$\Delta\Delta\delta^b$ (ppm)	Spectrum	$\Delta\Delta\delta^b$ (ppm)
1	 **42**		0.058		0.052
2	 **43**		0.101		0.066
3	 **110**		0.085		0.059
4	 **111**		0.083		0.071

Naziroglu et al. (2011) have been synthesized four proline-derived chiral CSAs **116–119** from L-proline. They used ^{1}H NMR spectroscopy to examine the enantiomeric

recognition ability of various carboxylic acids (**a-d**) as CSAs. Different selectivities have been obtained by this CSAs with racemic analytes tested. The best chiral shift reactivity was found with prolinamide **117.** They show that the resolve of the ee of chiral carboxylic acids could be possible with CSA **117**.

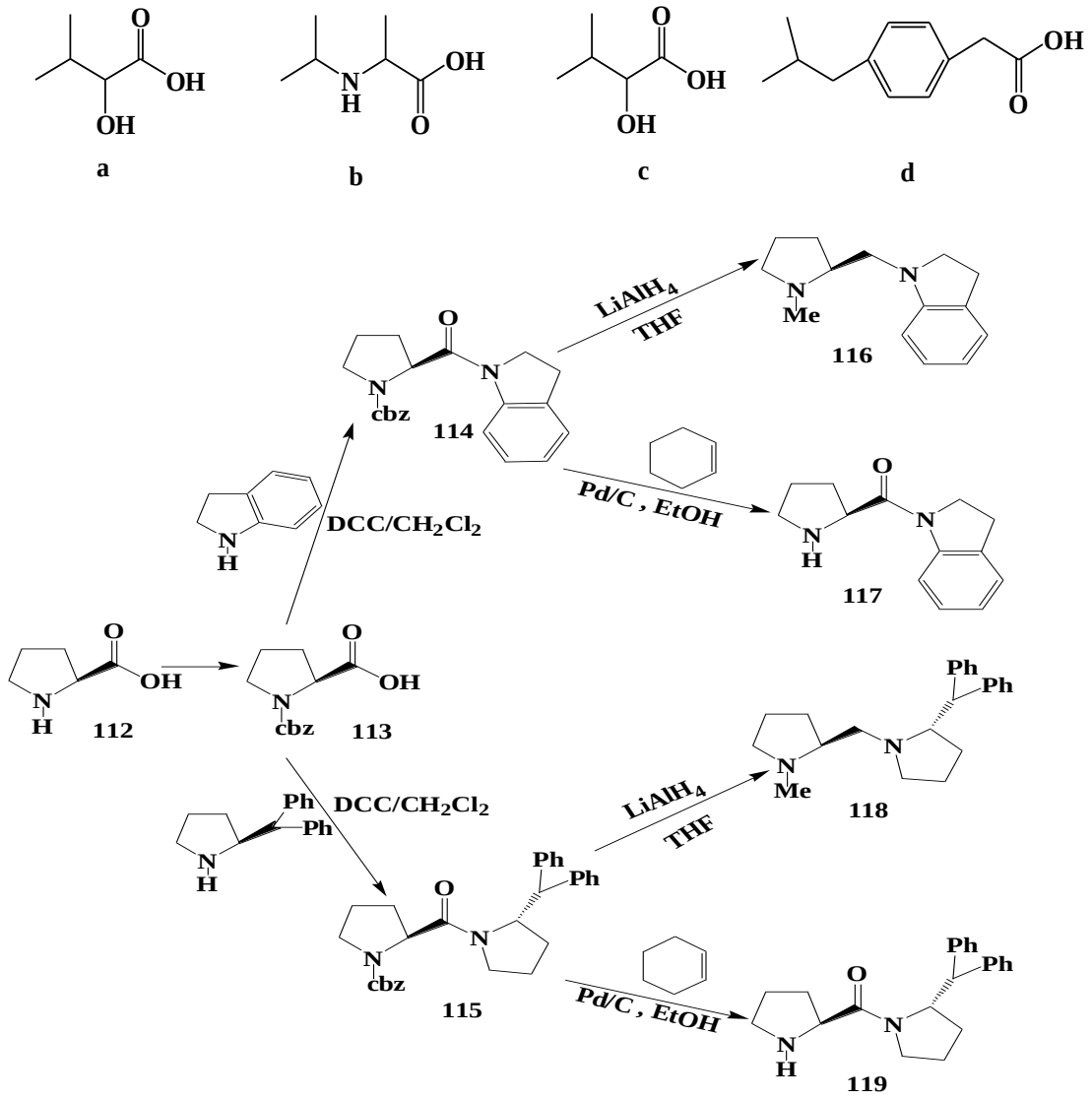


Figure 2.20. Synthesis of L-proline derived CSAs **116–119**

A series of new chiral C_2-symmetric salen ligand-based aminophenol compounds **120-123** have been prepared from chiral derivatives of 1,2-diaminoethane (Figure 2.21). They achieved an operative discernment in the ^{1}H NMR spectra between the enantiomers of a great variation of carboxylic acids **42, 43, 53, 110, 111, 124** when used these composites as CSAs (Table 2.4.),(Lu et al. 2011).

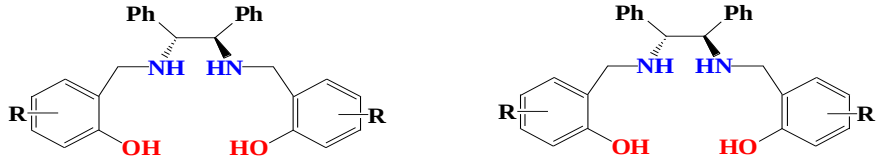


Figure 2.21. Structures of CSAs **120-123.**

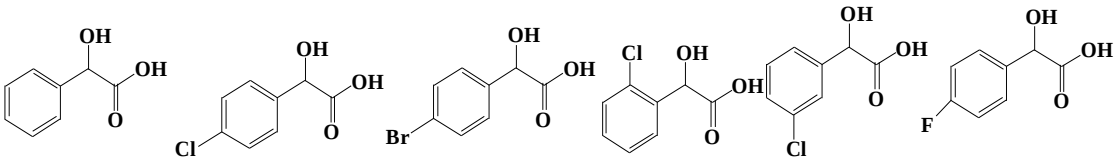
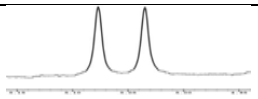
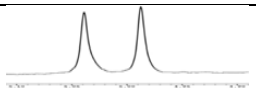
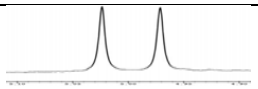
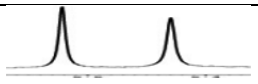
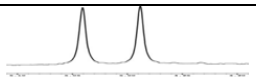
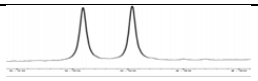


Figure 2.22. Structures of carboxylic acids tested with CSAs **120-123**

Table 2.2. Measurements of ^{1}H NMR chemical shift in nonequivalencies (ΔΔδ) of the carboxylic acids in the presence of CSA **120** by ^{1}H NMR spectroscopy (500 MHz) in $CDCl_3$ at 25 ^{o}C.[a]

Entry	Carboxylic acids	ΔΔδ (ppm)	ΔΔδ (Hz)	Spectra
1	42	0.042	21.02	
2	43	0.051	25.74	
3	53	0.052	26.21	
4	110	0.092	46.08	
5	111	0.053	26.27	
6	124	0.042	21.20	

[a] All samples were prepared by mixing 3 equiv of CSA and 1 equiv of acids in NMR tubes, the final concentrations were 15 and 5 mM in 0.6 mL of $CDCl_3$.

Water soluble calix[4]resorcinarene bearing α-methyl-*L*-prolinylmethyl substituents has been designed and used as chiral NMR solvating agent against several amino acid derivatives including phenyl or indole rings, ammonium ions with pyridyl, indane or dihydroindole rings (Figure 2.23). The effect of proline moieties on selectivity have been investigated and compared with previously proline included reports. They show that the α-methyl-L-prolinylmethyl derivatives lead larger enantiomeric discrimination of one or more ^{1}H resonances than the previous systems for most of the substrates (Pham and Wanzel 2011).

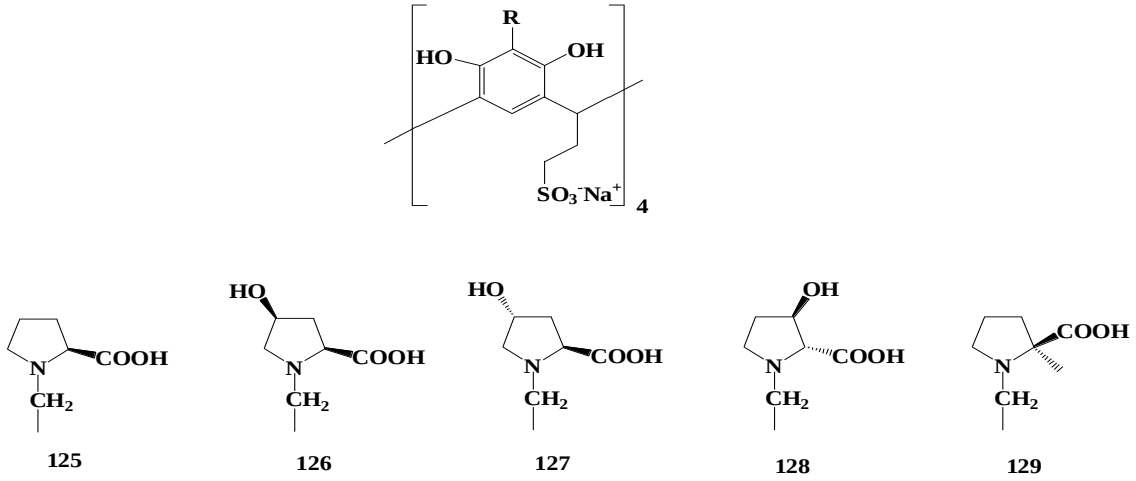
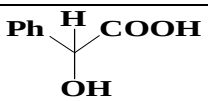
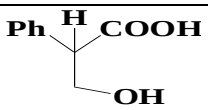
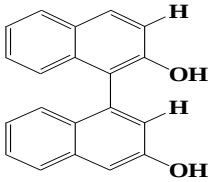


Figure 2.23. Structures of CSA **125–129** bearing α-methyl-L-prolinylmethyl moieties

Enantiodiscriminaton of several analytes including alcohols, amino alcohols, thiols, nitro alcohols, cyanohydrins, Mosher's acid, and carboxylic acids have been reported by using nonsymmetric heterocyclic subunit bearing zwitterions including alkylsulfonate or sulfamate and imidazolinium groups. Significant result can be seen in Table 2.3. (Tabassum et al. 2011).

Table 2.3. ^{1}H NMR (400 MHz) of racemic compounds in the presence of enantiopure zwitterion **147** in $CDCl_3$.

Entry	Compounds	δ (ppm)	δ (ppm) with **19**	^{1}H ΔΔδ (Hz)
1	 **42**	5.19	5.00/4.85	60 (CH)
2	 **148**	4.06	3.98/3.93	20 (CH)
3	 **149**	8.00	8.03/8.01	8.0 (CH)

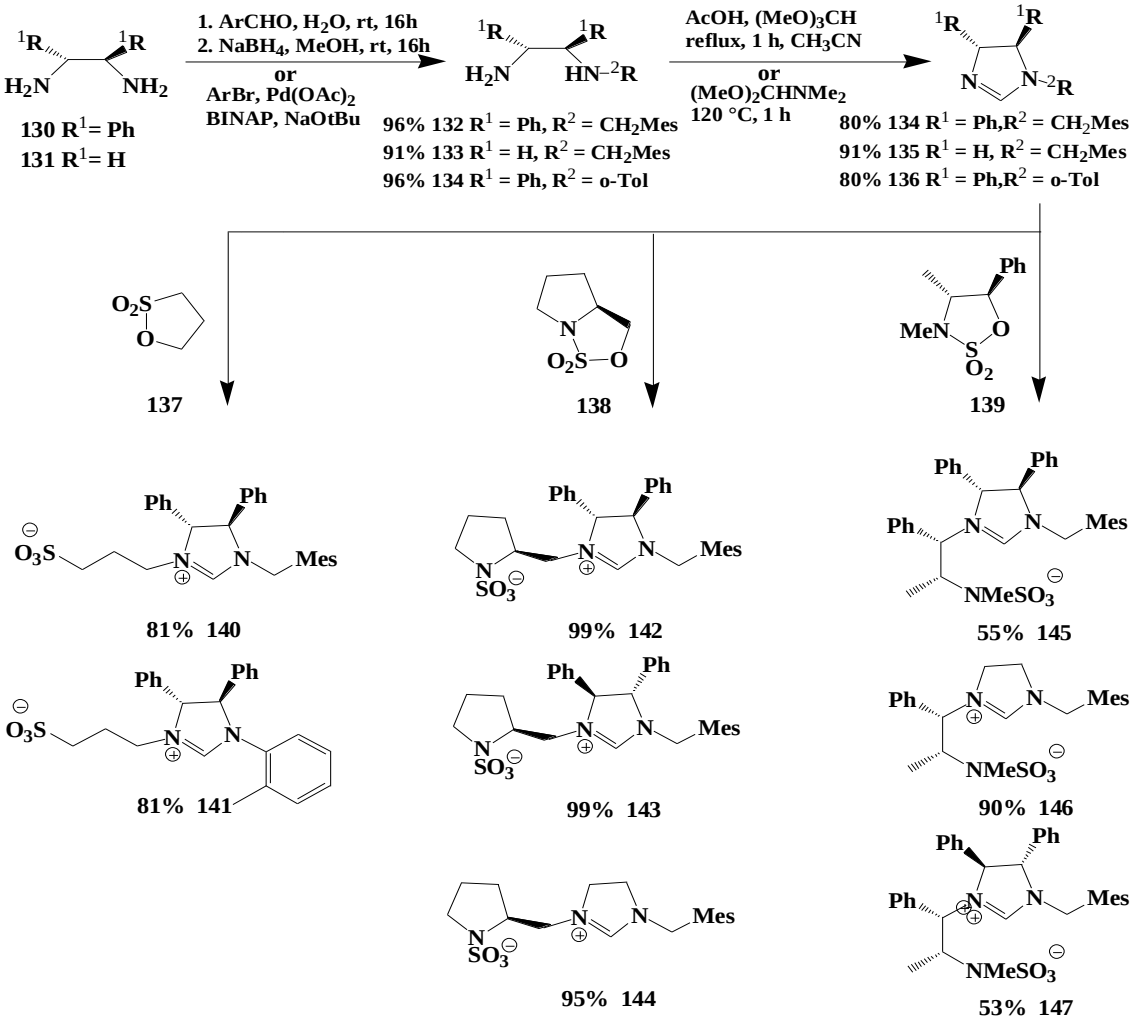
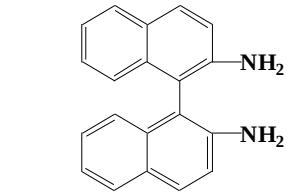
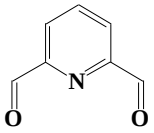


Figure 2.24. Synthesis of zwitterions incorporating imidazolinium and alkylsulfonate or sulfamate groups

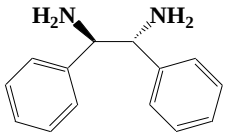
Polyazamacrocycles(*R*,*R*)-**159** (*R*,*R*,*R*,*R*)-**160** was synthesized by using (*R*,*S*)-**156**, (*S*,*S*)-**158** as starting chiral amines with template effect of lead (II) or lantanide III ions, and then reduction with $NaBH_4$ and subsequent demetallation (Figure 2.25.). Enantiodiscrimaination of nonstereoidal drugs **162-164** were investigated by using polyaza macrocycles (*R*,*R*)-**159** and (*R*,*R*,*R*,*R*)-**160** as CSAs (Figure 2.25.). It was found that nonequivalence values of up to 0.1 ppm were obtained by NMR data (Gospodarowicz et al. 2012).



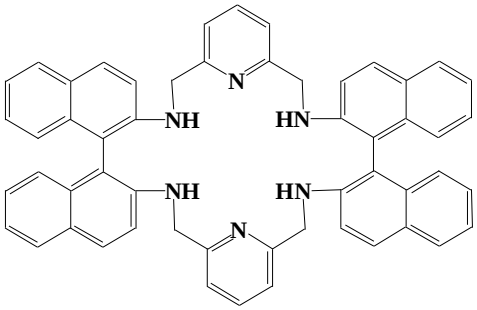
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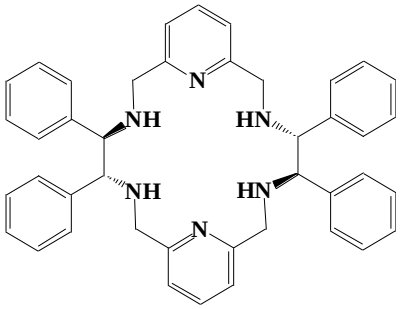
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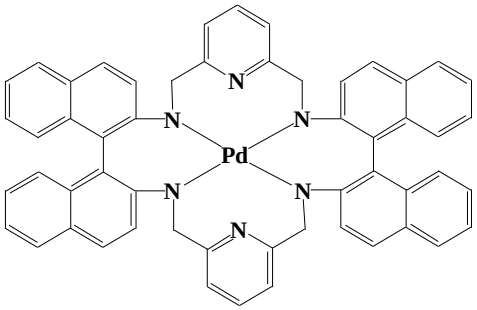
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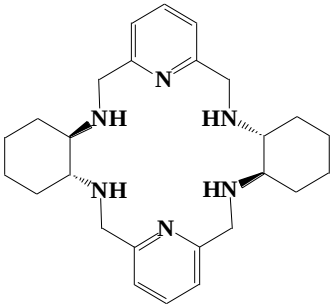
(R,R)-159



(R,R,R,R)-160

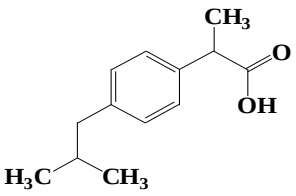


labelling of (R,R)-159

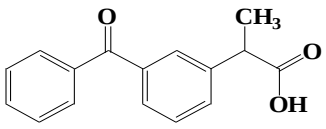


(R,R,R,R)-161

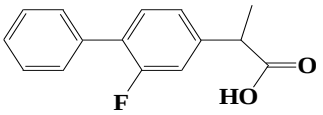
Figure 2.25. Structures of compound **156-158,** structures of macrocyclic compounds **159-161** and the labelling of **(*R,R*)-159**



162



163

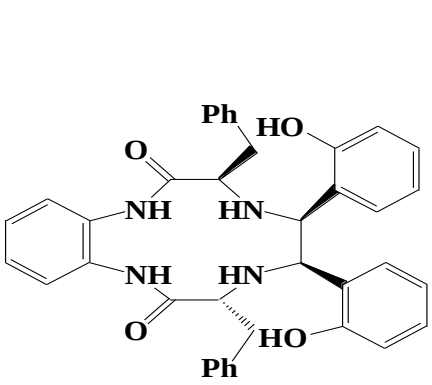


164

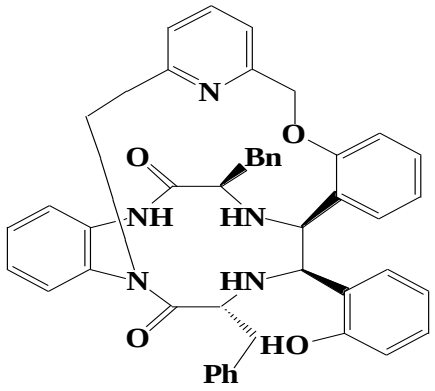
Figure 2.26. Analytes **162-164** used in enantiodiscrimination studies.

Chiral macrocycles **165** and **166** having several binding face have been designed in order to using enantiopurity of analytes **167-173** as CSAs. ^{1}H NMR chemical shift

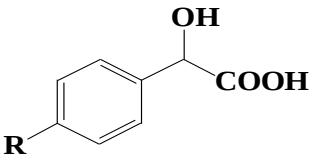
nonequivalence (ΔΔδ) were indicate that macrocycles **165** and **166** are effective CSAs towards the analytes tested up to the 36 Hz (Guo et al. 2013).



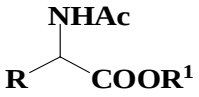
165



166



167: R = H
168: R = CH_3O



169: R =$H_3CSCH_2CH_2$, R^1 = H
170: R = Ph,R^1 = H
171: R =CH_3, R^1 = H
172: R = $(CH_3)_2CHCH_2$, R^1 = H
173: R = $(CH_3)_2CH$,R^1 = H

Figure 2.27. Structures of the chiral macrocycles **165**, **166** and structures of the carboxylic acids and α-amino acid derivatives **167-173**

Heckel et al. (2013) synthesized several ionic liquids **175-181** based on (-)-nicotine in high yields. Heterocycles were converted to quaternization by appropriate alkyl halides (Figure 2.28.). After anion metathesis the ionic liquids were examined as CSAs and presented a discriminate of the indications of mandelic acid and Mosher's acid by the ^{19}F and ^{1}H NMR spectroscopies. Adding to non-protic solvents it was also probable to use methanol in the experimentations (Heckel et al. 2013).

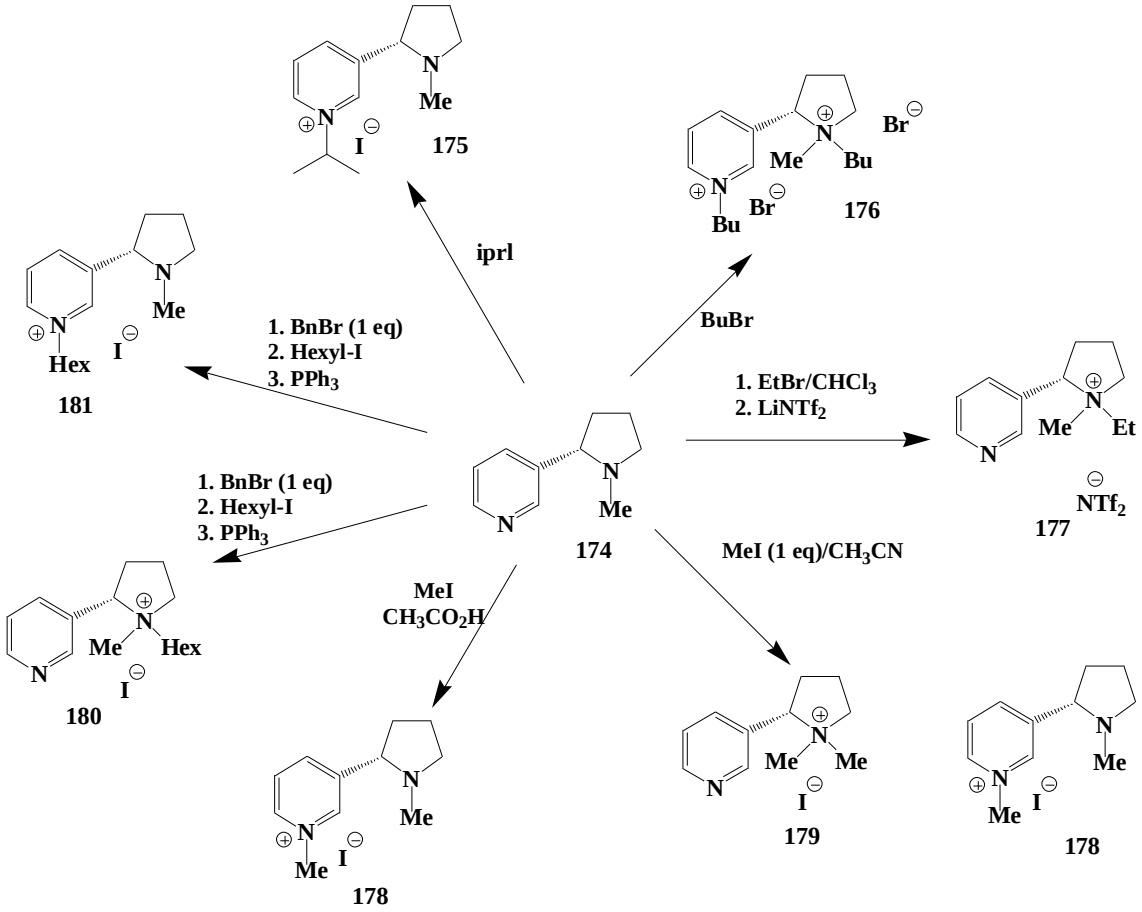


Figure 2.28. Synthesis of enantiopure ionic liquids **175-181** based on (-)-nicotine **174**.

Enantio purity of promethazine **175** was measured for the first time by means of ^{1}H NMR spectroscopy using (*S*)-BINOL **176** (1,1-bi(2-naphthol)) as a chiral CSA. Optimal conditions for the resolution of the promethazine enantiomers were also established by HPLC using a Chiralcel® OJ column. It was shown that both results were consistent with each other (Borowiecki 2014).

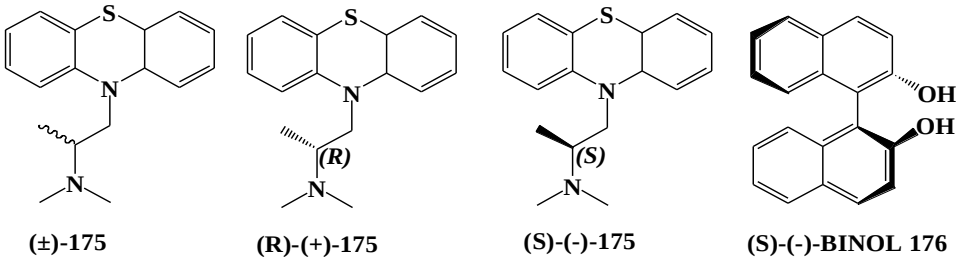


Figure 2.29. Chemical structures of promethazine **175** and (*S*)-BINOL **176**.

Yuste et al. (2014) investigated the use of (*R*)- and (*S*)-BINOL **176** as chiral CSA in order to determine the enantiomeric purity of the antitumor alkaloid crispine A **177**. The formation of diasteromeric host–guest complexes between the CSA and (±)-crispine A **177** produced significant ^{1}H NMR signal splitting which allowed the accurate and rapid determination of its enantiomeric composition in $CDCl_3$ or C_6D_6 solution (Figure 2.30.).

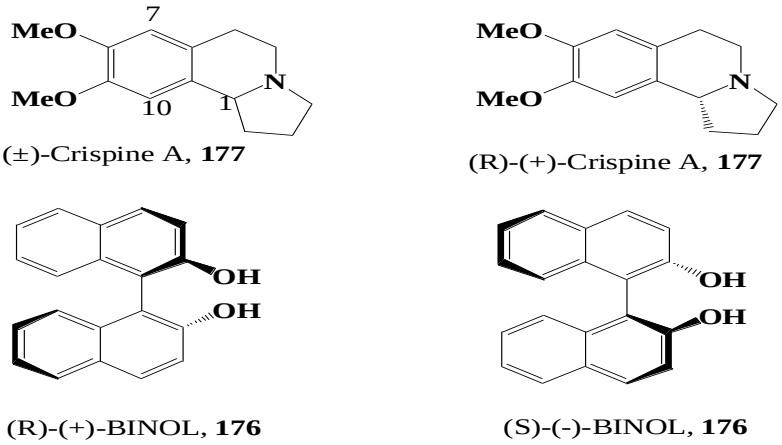


Figure 2.30. Chemical structures of compounds **177** and **176.**

Wolf et al. (2014) used NMR enantioresolution of multifunctional tertiary alcohols by a Whelk-O type chiral solvating agent **178** (Figure 2.31.). Crystallographic analysis of the CSA revealed two conformers, which can be expected to coexist in solution. One conformation affords a chiral cleft that can engage a single enantiomer in simultaneous π–π stacking, C-H/π interactions and hydrogen bonding. This chiral recognition process yields non-equivalent NMR signals for the enantiomers of eighteen substrates such as **179-182** even when substoichiometric amounts of the CSA are used.

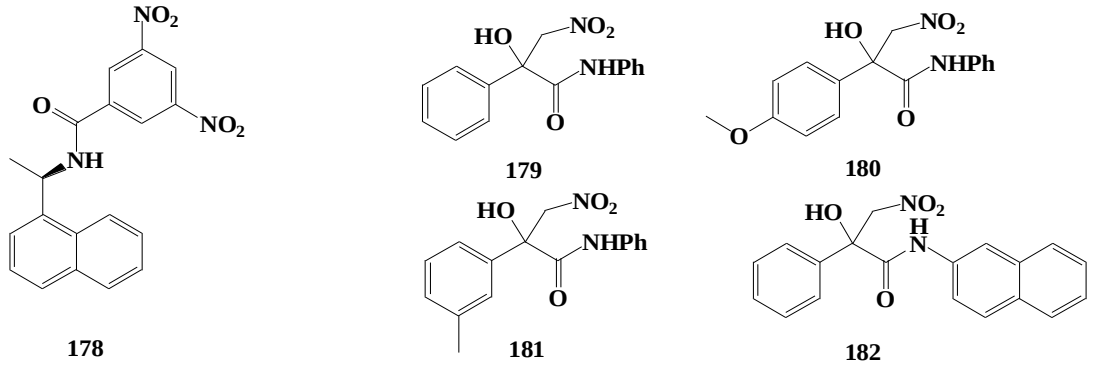


Figure 2.31. Structure of CSA **178** and tertiary alcohols **179–182.**

Chaudhary et al. (2014) prepared an optically active a series of aminonaphthol derivatives by aromatic Mannich reaction of 2-naphthol and screened as CSA to discriminate the Cα-H of racemic mandelic acid by ^{1}H NMR analysis. An effort was made to establish a correlation of the structure of aminonaphthol derivatives and the selectivity in this non-covalent interaction. A linear relationship between the experimental and calculated enantiomeric purity was established. The results indicate that the enantiomeric purity of unknown mandelic acid could be determined by CSA **187**.

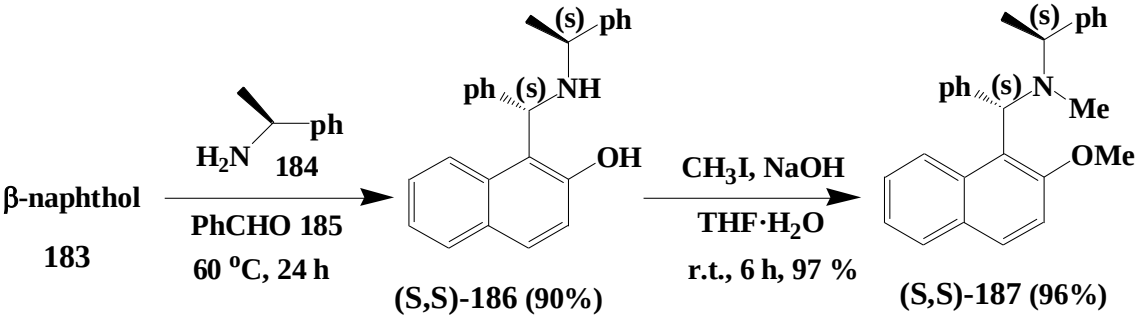


Figure 2.32. Synthesis of enantiopure aminoalkylnaphthol (*S,S*)-**186** by a solvent free asymmetric Mannich reaction then synthesis the dialkyl derivative (*S,S*)-**187**.

Table 2.4. Effect of aminonaphthyl derivatives as CSAs on the α-proton of racemic mandelic acid. [Δδ = Induced chemical shift;[a] ΔΔδ = chemical shift non-equivalences.]

No	CSA	Probe signal PhCH(OH)COOH	
		Δδ (ppm)	**ΔΔδ (ppm)**
1	(*S*,*S*)-**186**	-0.22	0.005
2	(*S*,*S*)-**187**	-0.24	0.012

[a]: The difference between the signals of DL-mandelic acid in $CDCl_3$ solution and the average of the signals of the two enantiomers after the addition of the CSA.

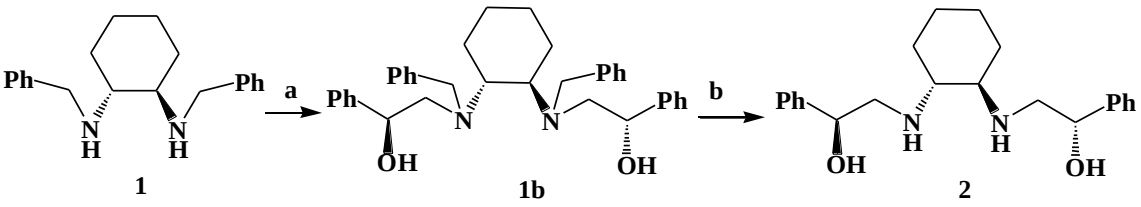
3. MATERIALS AND METHODS

3.1. Apparatus and Chemicals

Melting points were determined with GALLENKAMP Model apparatus with open capillaries. Infrared spectra were recorded on a MİDAC-FTIR Model 1700 spectrophotometer. The Basic analyses were got with CARLO-ERBA Model 1108 apparatus. ^{13}C NMR (100 MHz) and ^{1}H NMR (400 MHz) spectra were recorded on BRUKER DPX-400 high performance digital FT-NMR spectrometer, with tetramethylsilane as the interior standard solutions in deuteriochloroform. Optical rotations were recorded using PERKIN ELMER Model 341 polarimeter. All chemicals were purchased from Sigma Aldrich and Merck and reagent grade unless otherwise specified.

3.2. Synthesis

3.2.1. (*1R,2R*)-bis[(*R*)-2-hydroxy(2-phenyl)ethyl]-1,2-diaminocyclohexane (2):



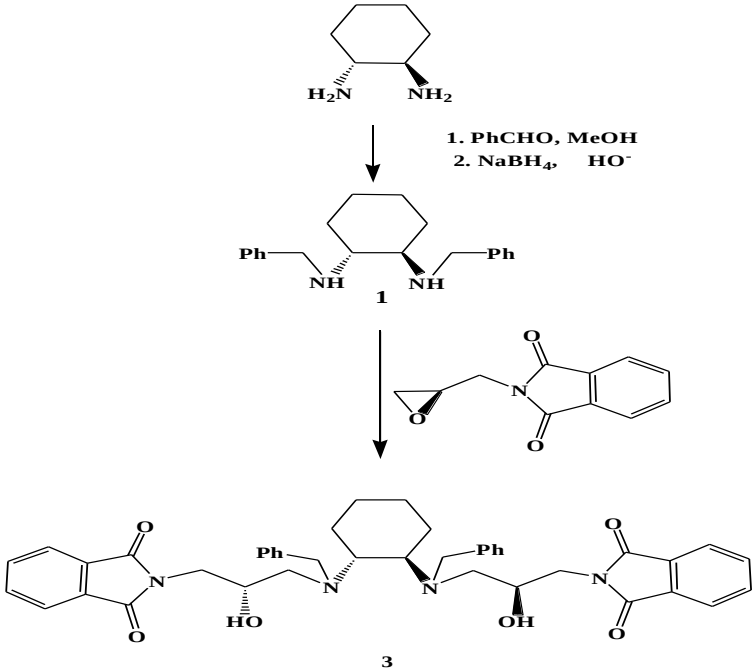
Compound **1b** has been synthesized by starting from compound **1** and (*R*)-styrene oxide as the method described **(**Karakaplan et al. 2013). Compound **2** was prepared by debenzylation of compound **1b** with $Pd(OH)_2/C$ in hydrogen atmosphere as the method described previously (Xu et al. 2008). Therefore, $Pd(OH)_2/C$ (20%, 75 mg) was added in one portion to a solution of the appropriate amount of compound **1b** (400 mg, 0.75 mmol) in methanol (10 mL). The mixture was stirred under hydrogen at room temperature and then the reaction was monitored by TLC. Sodium carbonate (80 mg, 0.75 mmol) was added and stirred for 1 hr. by the completion of the reaction. The solution was filtrated and washed with methanol, then concentrated in vacuum. The crude product was purified by column chromatography on silica gel H: EA: EtOH: TEA

(4: 1: 1: 0.5 as eluent) to give 190 mg % 71.7 of compound **2** as a viscous oil. IR (cm^{-1}): 3346, 3250, 3057, 3030, 2926, 2860, 1493, 1453, 1348, 1310, 1195, 1139, 1056, 924, 893, 854, 791, 756, 701. ^{1}H NMR ($CDCl_3$) δ: 7.41-7.27(m, 10H), 4.55 (dd, 4, 8.12Hz, 2H), 2,90-2,71(m, 8H), 2,32-2,27(m, 2H), 2.12-1.99 (m, 2H), 1.38-1.37(m, 2H); 1.28-1.05 (m, 4H). ^{13}C NMR ($CDCl_3$): 142,55, 128,39, 127.48, 125.90, 72.00, 60.32, 53.84, 31.87, 25,01. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C: 74.57, ; H: 8.47 ; N: 7.90 . Found: C: 74.89; H: 8.36; N: 7.82.

3.2.2. General procedure for the synthesis of compounds 3–7.

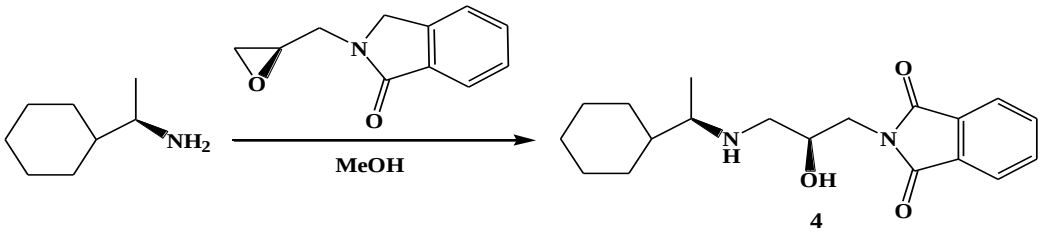
Compounds **3-7** have been synthesized using a procedure originally reported by Roehrig et al. **(**2005). Chiral amine or amino alcohol (0.6 mmol, 1.2 equiv.) in 10 mL isopropanol was added to the solution of (*R*)-*N*-(2,3-epoxypropyl)phthalimide (**NEP**) (102 mg, 0.50 mmol) in 10 mL of isopropanol at in an ice bath and stirred for 1 h then refluxed for 12 hours. The reaction monitorized by TLC. The solvent was removed by rotary evoparatore under reduced pressure after completion off the reaction. Crude product is purified by appropriate method.

3.2.3. *N,N'*-Dibenzyl-*N,N'*-bis[(*S*)-2-hydroxy-3-phthalimide]-(*R,R*)-1,2-diamino-cyclohexane (3):



Compound (*S,R,S,R*)-**3** was synthesized by reacting **NEP** (2.04 g, 5 mmol) and **1** (0.73 g, 5 mmol) as the method described above. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by crystallization with MeOH to give 2.45 g 70 % as a white crystals. M.p.: 164-165 ^{o}C, $[\alpha]_D^{20}$ = -14.2^{o} (c=1, $CHCl_3$). IR (cm^{-1}): 3434.6, 3384.5, 3332.4, 3053.75, 2931.3, 2859.9, 1771.3, 1709.6, 1612.2, 1434.97, 1393.3, 1147.4, 1083.8, 1011.5, 842.7, 626.0, 619.0. ^{1}H NMR ($CDCl_3$): 7.84 (d, 2.4Hz, 2H); 7.713 (d, 2.8 Hz, 2H); 7.468-7335(m, 10H); 4.34-3.27 (m, 10H); 2.86- 2.14(m, 6H); 1.69-1.67(m, 6H); 1.05 (m, 4H). ^{13}C NMR ($CDCl_3$): 168.33, 138.08, 133.80, 132.17, 128.33, 127.35, 123.24, 66.58, 58.86, 56.28, 53.08, 42.21, 25.40, 23.76. Anal. Calcd for $C_{42}H_{44}N_4O_6$ C: 72.00., H: 6.28; N: 8.0. Found: C: 71.58; H: 6.12; N: 7.78.

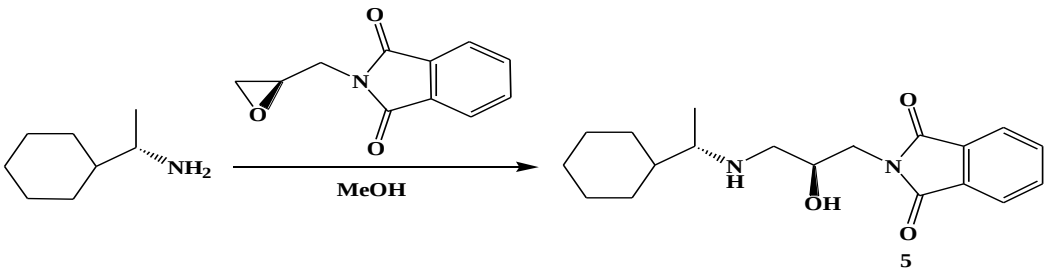
3.2.4. 1-[(*R*)-1-Cyclohexylethylamino)]-3-phthalimide-(*S*)-2-propanol (4):



4

Compound **4** was synthesized by reacting **NEP** (767 mg, 3.77 mmol) and (*R*)-1-cyclohexylethylamine (0.4 g, 3.15 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by column chromatography on silica gel with H: EA (1:4 as eluent) to give 0.707 mg % 68 yield as white powder crystals. M.p.: 136-138 ^{o}C, $[\alpha]_D^{20}$ = 14^{o} (c=1, $CHCl_3$). IR (cm^{-1}): 3460.7, 3453.6, 3319.8, 3262.9, 3032.5, 2911.0, 2848.3, 2760.6, 2697.9, 1769.3, 1709.6, 1439.6, 1393.3, 1318.1, 1163.8, 1112.74, 1094.42, 1024.0, 898.9, 836.9, 789.7, 717.7. ^{1}H NMR ($CDCl_3$): 7.88-7.86 (m, 2H); 7.75-7.73 (m, 2H); 4.04-4.01(m, 1H); AB system; A part: 3.808 (dd, 24.8Hz, 13.6Hz, -CH_2- 1H); B part: 3.793(dd, 23.2 Hz, 14Hz, -CH2-, 1H); 2.83(dd, 9.2Hz, 3.2Hz, 1H); 2.69(dd, 12.4 Hz, 7.2Hz, 1H); 2.572-2.542(m, 1H): 1.77-1.69 (m, 5H); 1.26-1.01 (m, 9H). ^{13}C NMR ($CDCl_3$): 168.64, 134.07, 132.03, 123.41, 66.99, 58.19, 49.38, 42.24, 41.60, 29.61, 28.20, 26.54, 26.40, 26.29, 16.29. Anal. Cald for $C_{19}H_{26}N_2O_3$ C: 69.09, H: 7.87; N: 8.48. Found: C: 68.87; H: 7.69; N: 7.79.

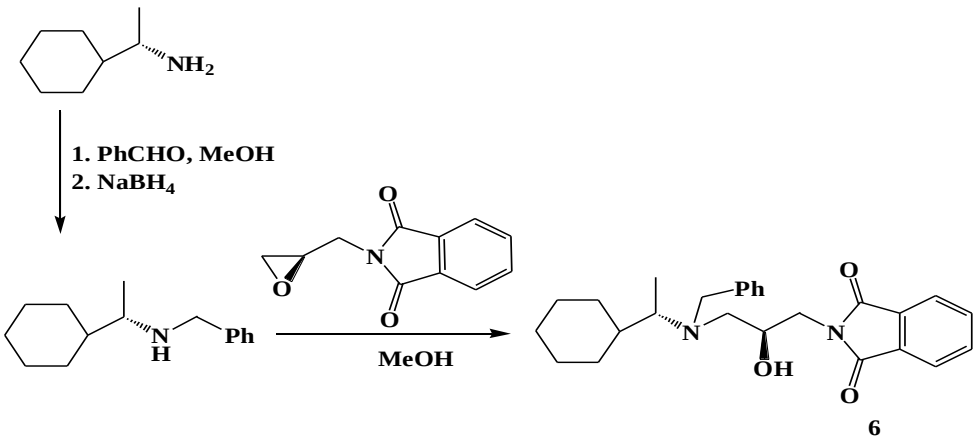
3.2.5. 1-[(*S*)-1-Cyclohexylethylamino)]-3-phthalimide-(*R*)-2-propanol (5):



5

Compound **5** was synthesized by reacting **NEP** (767 mg 3,77 mmol) and (*S*)-α-cyclohexylethylamine (0.4 g, 3.15 mmol) as usual manner**.** Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by column chromatography on silica gel H: EtOAc (3:2 as eluent) to give 0.76 mg 73.07 % as viscous oil. $[\alpha]_D^{20}$ = + 7.2 ^{o} (c=1, $CHCl_3$). IR (cm^{-1}): 3386.5, 3380.5, 3378, 3156.29, 3142.3, 3130.4, 3125.5, 2918.75, 2850.3, 1710.65, 1614.14, 1429.0, 1394.29, 1329.69, 1189.8, 1127.2, 1087.67, 1029.8, 982.5, 917.0, 722.2^{1}H NMR ($CDCl_3$): 7.86-7.71 (m, 4H); 3.96-3.93 (m, 1H); AB system; A part: 3.78(dd, 22.8Hz, 17.6Hz, -CH2-, 1H); B part: 3.76(dd, 21.2Hz, 14 Hz, -CH2-1H); 3.103(m, 2H): 2.86(dd, 12.4 Hz, 4Hz. 1H); 2.536-2.449(m, 1H); 1.75-1.65 (m, 5H); 1.22-0.98(m, 10 H). ^{13}C NMR ($CDCl_3$): 168,64, 134.01, 132.02, 123.35, 67.98, 58.45, 50.20, 42.69,41.89, 29.75, 27.95, 26.66, 26.54, 26.40, 16.93. Anal. Cald. for $C_{19}H_{26}N_2O_3$ C: 69.09, H: 7.87; N: 8.48. Found: C: 68.72; H: 7.7.62; N: 7.92.

3.2.6. *N*-Benzyl-1-[(*S*)-1-Cyclohexylethylamino)]-3-phthalimide-(*R*)-2-propanol (6):

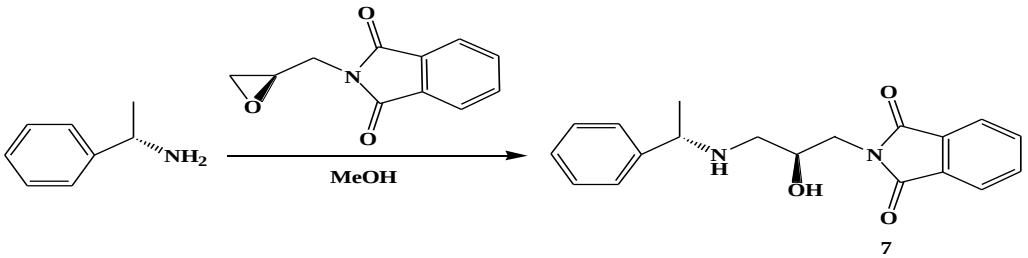


6

(*S*)-*N*-benzyl-***α***-cyclohexylethylamine was prepared as a precursor of compound **6**. Therefore, (S)-***α***-cyclohexylethylamine (1 mL, 6.82 mmol) was benzylated according to the lit. method to give 1.42 g 96 % of (*S*)-*N*-benzyl-α-cyclohexylethylamine (Tye et al. 2001). (IR (cm^{-1}): 3321.8, 3161.7, 3067.2, 2940.12, 1643.9, 1582.3, 1483.0, 1431.9, 1378.8, 1332.8, 1224.5, 1189.8, 1068.3, 981.6, 838.8. ^{1}H NMR ($CDCl_3$): δ: 7.38-7.29(m, 5H), 3.89(d, 1H, J=13.2 Hz), 3.75(d, 1H, J=13.2 Hz), 2.58-2.51(m, 1H), 1.82-1.71(m, 6H), 1.44-1.14(m, 4H), 1.09-1.01(m, 5H). ^{13}C NMR ($CDCl_3$): 141.16, 128.34, 128.12, 126.75, 57.12, 51.62, 43.02, 29.89, 28.13, 26.84, 26.72, 26.59, 16.79).

Compound **6** was synthesized by using **NEP** (655 mg, 3.22 mmol) and (*S*)-*N*-benzyl-cyclohexylethylamine (0.7 g, 3.22 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by flash chromatography on silica gel H: EtOAc (2:1 as eluent) to give compound **6** as viscous oil (1.05g, 77.66 %). $[\alpha]_D^{20}$ = +9.8^o (c=1, $CHCl_3$). IR (cm^{-1}): 3564, 3514, 3476, 3434, 3086, 2913, 2859, 1772, 1712, 1611, 1429, 1393, 1327, 1262, 1151, 1086, 1027, 960, 722. ^{1}H NMR ($CDCl_3$): 7.78-7.76 (m, 2H); 7.76-7.63 (m, 2H); 7.31-7.16 (m, 5H); 3.85-3.76 (m, 2H): 3.70-3.69 (m, 1H); 3.47-3.35 (m, 2H): 3.17 (s, 1H); 2.61-2.23 (m, 4H); 1.73-1.64 (m, 4 H); 1.23-1.14(m, 1H). ^{13}C NMR ($CDCl_3$): 168.57, 140.08, 133.88, 132.03, 129.10, 128.29, 126.98, 123.20, 68.29, 61.89, 55.79, 54.78, 42.71, 41.08, 31.45, 30.54, 26.57, 26.48, 26.33, 11.09. Anal. Cald for $C_{26}H_{32}N_2O_3$ C: 74.28; H: 7.62; N: 6.66; found: C: 74.86; H: 7.29; N: 7.41.

3.2.7. [(*R*)-Phenyethylamino)]-3-phthalimide-(*R*)-2-propanol (7):

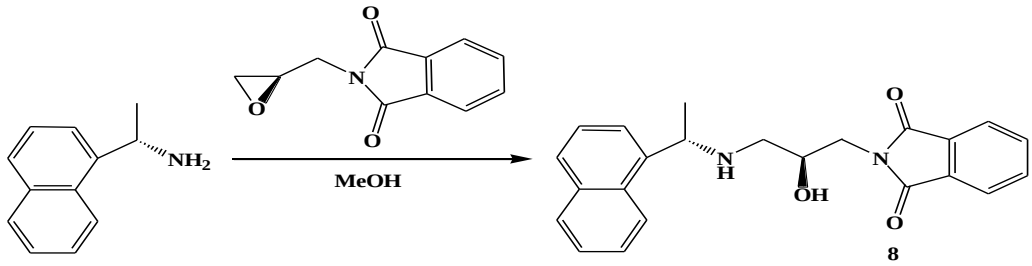


7

Compound **7** was synthesized by reacting **NEP** (500 mg, 2.46 mmol) and (*S*)-α-phenylethylamine (298 mg, 2.46 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by

column chromatography on silica gel H: EtOAc: TEA (1:0.5:0.1 as eluent) to afford pure compound **7** (612 mg, 76.69 %) as a viscous oil. $[\alpha]_D^{20}$ = 10.7°(c =1, $CHCl_3$). IR (cm^{-1}): 3264, 2921, 2851, 1773, 1714, 1566, 1463, 1395, 1085, 1023, 918, 627. ^1H NMR ($CDCl_3$) δ: 7.84-7.81(m, 2H); 7.72-7.69(m, 2H); 7.31-7.22(m, 5H); 3.912-3.87 (m, 1H); 3.807- 3.689 (m, 3H); 2.71 (bs, 1H); 2.62-2.56(m, 2H); 1.39-1.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.70, 145.14, 134.05, 131.98, 128.53, 127.08, 126.57, 123.37, 68.47, 58.52, 50.50, 42.00, 24.14. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C: 70.37; H: 6.17; N: 8.64; Found: C: 70.56; H: 6.10; N: 8.54.

3.2.8. 1-[(S)-1-Naphthylethylamino)]-3-phthalimide-(*R*)-2-propanol (8):



8

Compound **8** was synthesized by reacting **NEP** (528 mg 2.6 mmol) and (*S*)-1-(1-naphthyl)ethylamine (442.45 mg, 2.6 mmol) as usual manner. Solvent was removed under reduced pressure by completion of the reaction and the crude product was purified by column chromatography on silica gel with H: EtOH (4:1 as eluent) to give pure compound **8** (698 mg, 72 %) as a white solid. M.p.: 249-250 °C. $[\alpha]_D^{20}$ = +16.9° (c =0.5, DMSO). IR (cm^{-1}): 3492, 3468, 3421, 3352, 3290.9, 3051.8, 2952.5, 2843,5, 2796.3, 2689.2, 2622.7, 2526.3, 1773.2, 1711.5, 1588.1, 1433.8, 1395.2, 1345.1, 1296.9, 1092.5, 1008.6, 964.2, 801.3, 779.1, 723.2. ^1H NMR ($DMSD_6$): 9.78 (bs, 1H); 9.08(bs, 1H): 8.20-8.18 (m, 1H); 8.00- 7.56 (m, 8H); 5.86 (s, 1H); 5.36 (s, 1H); 4.20(s, 1H); 3.57-3.12(m, 3H); 2.67 (s, 1H): 2.47(s, 1H); 1.68-1.67(d, 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 168.28, 134.81, 134.10, 133.80, 132.12, 130.83, 129.37, 127.41, 126.60, 126.60, 124.74, 123.50, 122.96, 64.36, 52.76, 49.40, 41.97, 20.55. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.80; H, 5.88; N, 7.49. Found: C, 73.36; H: 6.10; N, 7.84.

3.2.9. Evaluation of the stoichiometric ratio of CSA-3 and mandelic acid enantiomers (Job plots):

The stoichiometry of the complexes between CSA **3** and enantiomers of mandelic acid was clarified Job plot (Job 1928). Therefore, equimolar amounts of CSA and analytes were dissolved in $CDCl_3$. The solution distributed among nine NMR tubes that molar raction of that solutions was keept from 0.1-0.9. Chemical shifts differences ($\Delta\delta$) C-α-H of mandelic acid was determined. Mol fraction (X) of these nine tubes ploted against X.($\Delta\delta$) itself.

4. RESULTS AND DISCUSSIONS

The basic unit amino alcohol imide functionality was created by the regioselective ring opening reaction of (*R*)-*N*-(2,3-epoxypropyl)phthalimide (**NEP**) with various chiral amines (Figure 4.1 and 4.2). We chose this system due to the simplicity of its preparation from readily available substances and connected with three functional groups of hydroxyl, secondary or tertiary amine and imide groups which are closely to the stereocenters.

Herein we planned to make different derivatives of enantiomerically pure *N,N'*-dibenzyl-1,2-diamnocyclohexane **1** which is used as many asymmetric catalyst scaffold (Song et al. 2014). C_2-symmetric compound (*R,R,R,R*)-**2** with the lacks of the imid functionalty, was synthesized via two steps whereas at the first step compound (*R,R*)-**1** reacted with (*R*)-styrene oxide to give an amino alcohol followed by the debenzylation with $Pd(OH)_2/C$ to give (*R,R,R,R*)-**2** in 71.7 % yield. C_2-symmetric (*S,R,S,R*)-**3** with tertiary amine functionality was easily prepared by regioselective ring opening of **NEP** with chiral amine (*R,R*)-**1** in high yield (70 %).

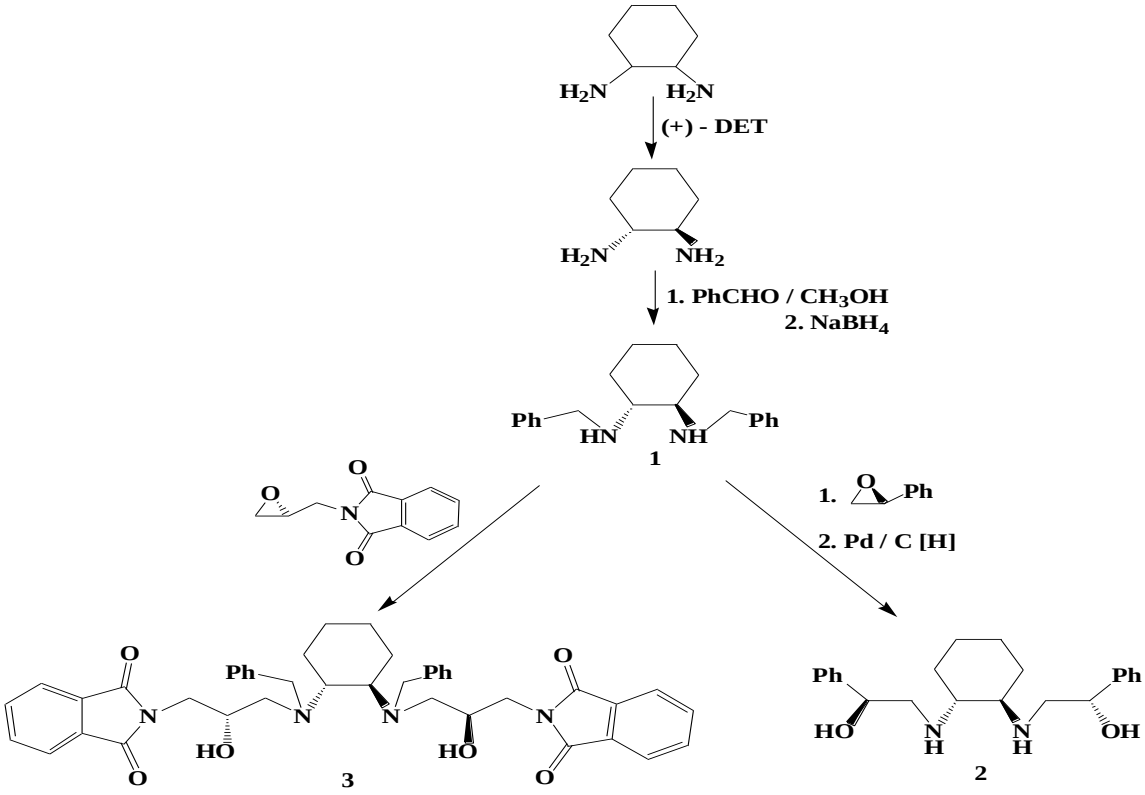


Figure 4.1. Synthesis of amino alcohol CSA **2** and amino alcohol imide CSA **3**

Chiral compound (*R*,*R*)-**4** and (*S*,*R*)-**5** were prepared by the ring opening reaction of **NEP** with *(R)*- and *(S)*-cyclohexylethylamine in 68 and 73 % yield respectively. We next tried to block the N–H functionality of (*S*,*R*)-**5** in order to investigate the effect of hydroxyl and imide groups to interactions with the analyte. With this aim *(S)*-cyclohexylethylamine was condensed with benzaldehyde to imine intermediate and followed by reduction formed benzylated product. It was then converted to the (*S*,*R*)-**6** by used epoxide with excellent conversion (Figure 4.2). Extended studies were focused on the introducing aromatic substituents to this system. Therefore, (*S*,*R*)-**7** and (*S*,*R*)-**8** bearing phenyl and naphthyl substituents have been prepared in high yields by regioselective ring opening of **NEP** with (*S*)-α-phenylethlamine and (*S*)-1-(1-naphthyl)ethylamine respectively.

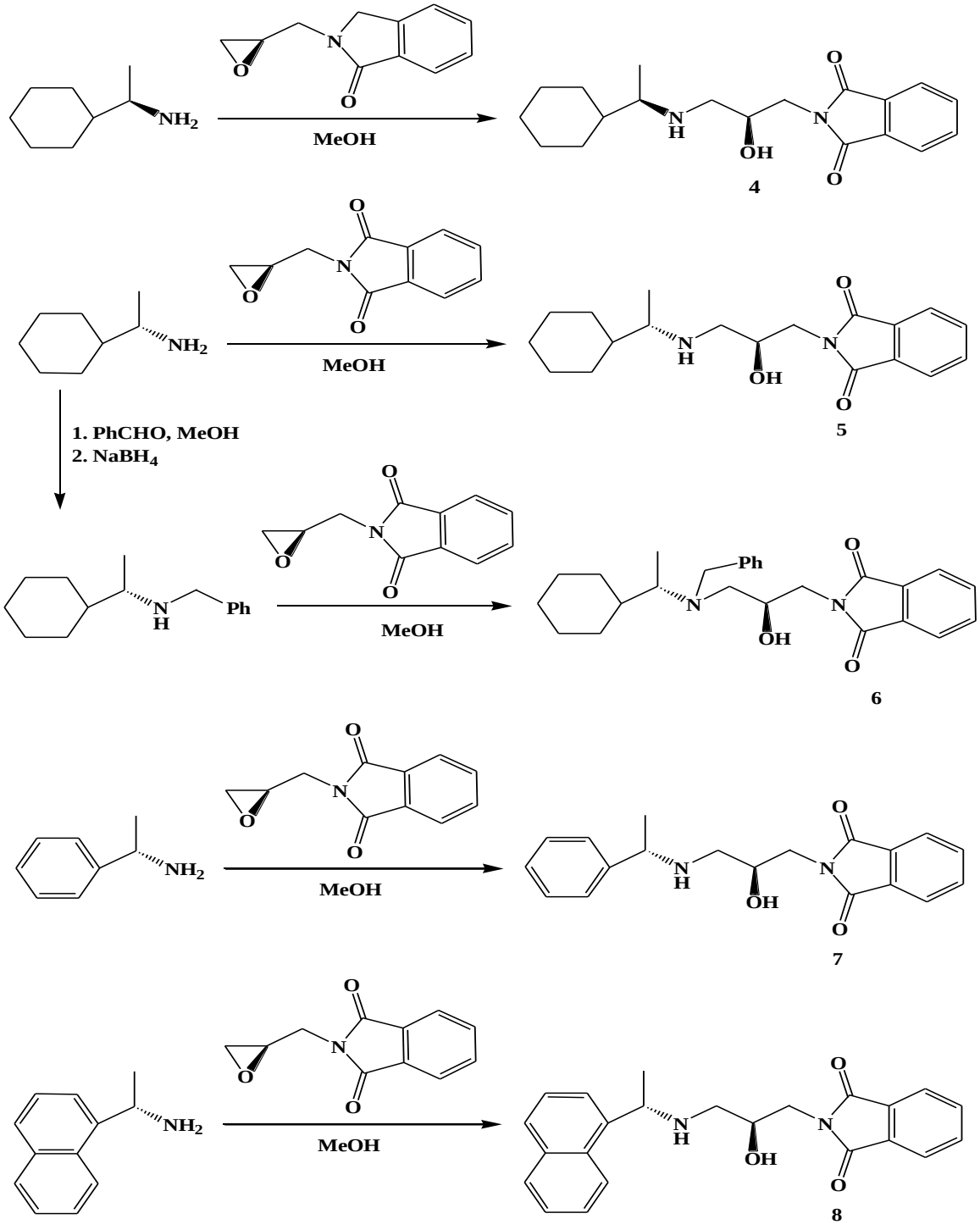


Figure 4.2. Synthesis of amino alcohol imide CSAs **3-8**

Amino alcohol or amino alcohol imide functionalized molecules **2-8** were used as potential CSAs for chiral discrimination of mandelic acid (**A**), *o*-chloromandelic acid (**B**), α-phenyl-α-metoxyacetic acid (**C**), ibuprofen (**D**) and naproxen (**E**) as analytes in ^{1}H NMR spectroscopy (Figure 4.3.).

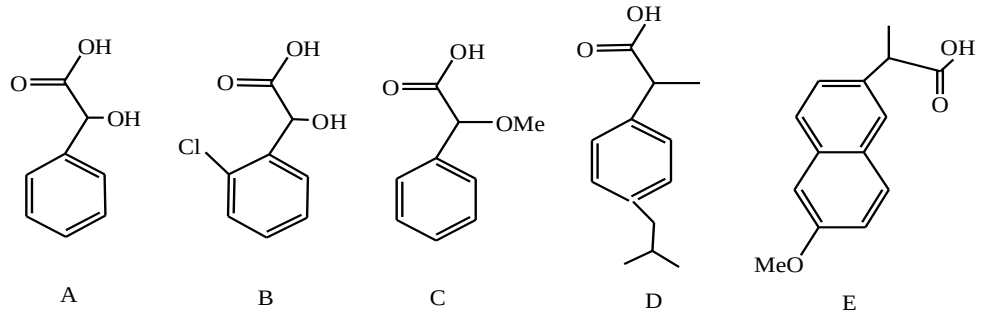


Figure 4.3. Structure of analytes tested herein

The results obtained by this work are as follows:

1. Amino alcohol (*R,R,R,R*)-**2** with secondary alcohol functionality shifted the C-α-H of analytes to the high magnetic field (0.02-0.3 ppm) and exhibited low enantomeric discriminations. The best differentiated value was obtained in the case of mandelic acid with ΔΔδ of 10 Hz (Table 4.1. and 4.2.).

2. C_2-Symmetric amino alcohol imide (*S,R,S,R*)-**3** was found to be the best reagent for enantiomeric discrimination for mandelic acid with ΔΔδ of 24.8Hz. The values for α-phenyl-α metoxyacetic acid and *o*-chloromandelic acid were found to be 16.6 and 8 Hz respectively. Therefore, we have shown the practically applicable of the (*S,R,S,R*)-**3** as a satisfactory CSA for the measurement of mandelic acid as a model analyte (Figure 4.4.).

Table 4.1. Induced shifts (Δδ, ppm) and splitting (ΔΔδ, ppm) for the signal of the carboxylic acids **A-E** in the presence of CSA **2-5** (400 MHz, 5 mM in $CDCl_3$ at 25 ^oC).

			CSA (δ: ppm)							
	Acid	**Signal**	**2**		**3**		**4**		**5**	
			Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ
1	A	CαH	-0.300	0.025	-0.513	0.062	0.489	0.022	-0.474	0.018
2	B	CαH	-0.247	0.011	-0.514	0.020	-0.456	0.014	-0.452	0.011
3	C	CαH	-0.002	0.00	-0.164	0.042	-0.242	0.009	-1.117	0.080
4	D	CαH	0.015	0.002	-0.020	0.000	-0.384	0.003	-0.147	0.005
5	E	CαH	-0.013	0.000	-0.045	0.000	-0.236	0.008	-0.110	0.006

[a]: Averaged between signals from both enantiomers.

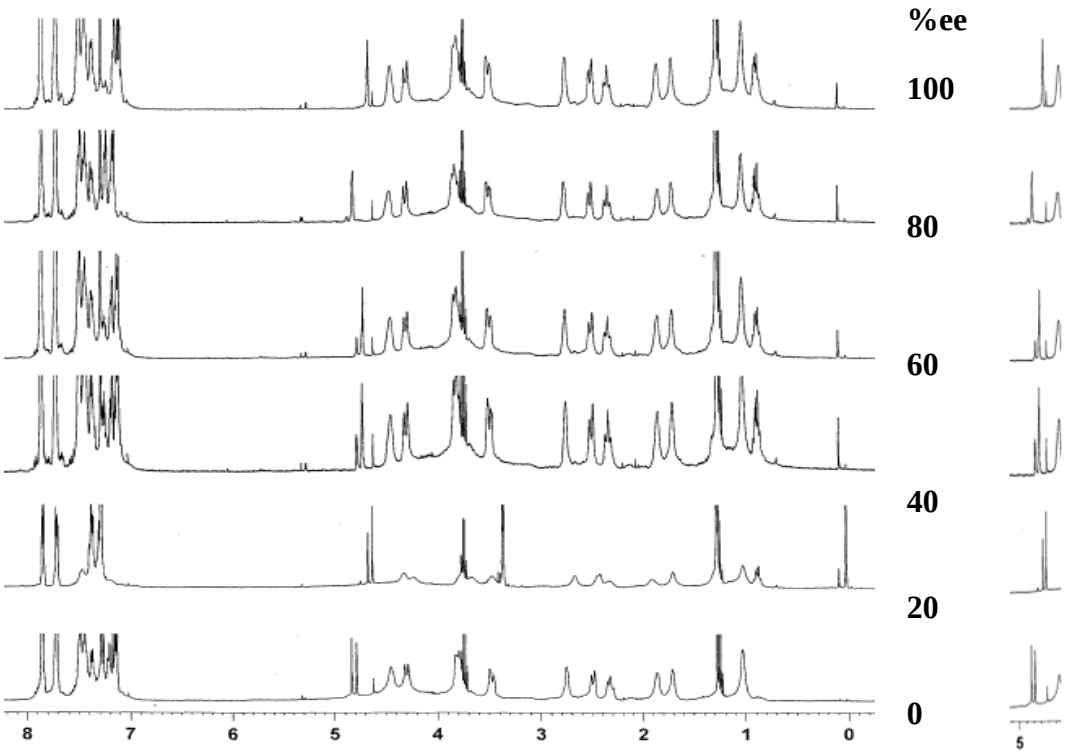


Figure 4.4. ^{1}H NMR spectra of the CSA (*S*,*R*,*S*,*R*)-**3** with different enantiomeric purities in the presence of mandelic acid (5 mM , 0.5:1 CSA/A)

We have also tried to get a deeper knowledge about inclusion complexes formed in solution. Therefore, we focused on the species formed between (*S*,*R*,*S*,*R*)-**3** and analyte **A**. Job plots for both enantiomers of mandelic acid indicate 1:1 CSA/A stoichiometry (Figure 4.5).

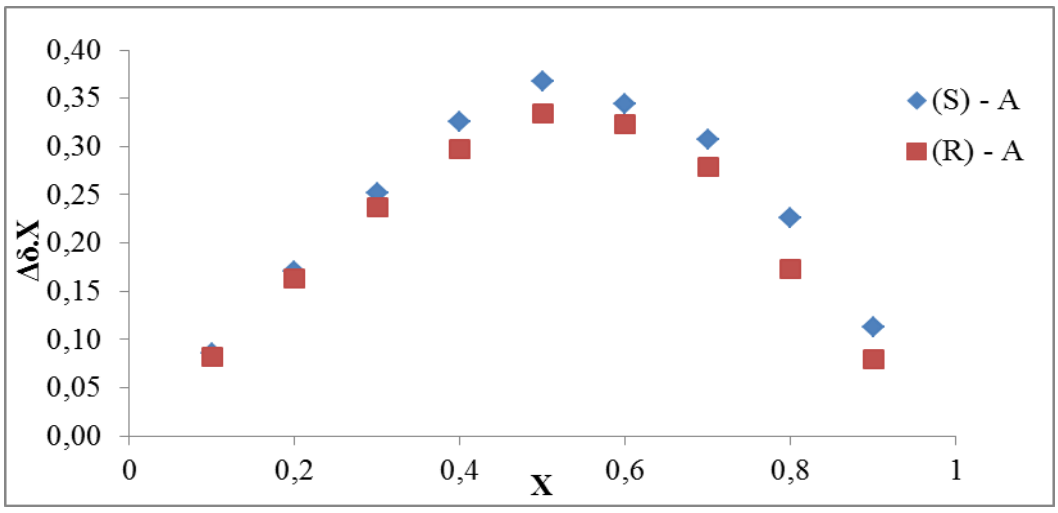


Figure 4.5. Job plots for (*S*)- and (*R*)-**A** with CSA (*R*,*R*,*R*,*R*)-**3**.

3. Amino alcohol amide (*S*,*R*)-**5** which derived from (*S*)-1-cyclohexylethylamine was also showed better enantiomeric discrimination than (*R*,*R*)-**4** indicate that the *S* configuration of amine leading the better enantiomeric discrimination by creating better pocket sides to binding one of the enantiomer of the analyte **C**. The best discrimination was found to be for α-phenyl-α-methoxyacetic acid with ΔΔδ of 32 Hz. Enantiomeric differentiated values found for mandelic acid, *o*-chloromandelic, ibuprofen and naproxen are 7.2, 4.4, 2.0 and 3.0 Hz respectively.

Reasonable good CSA activity of (*S*,*R*)-**5** lead us to prepare samples of different enantiomeric purity (0-100 %) of α-phenyl-α-methoxyacetic acid and it showed a satisfactory experimentally enantiomeric discriminaton (Figure 4.6.).

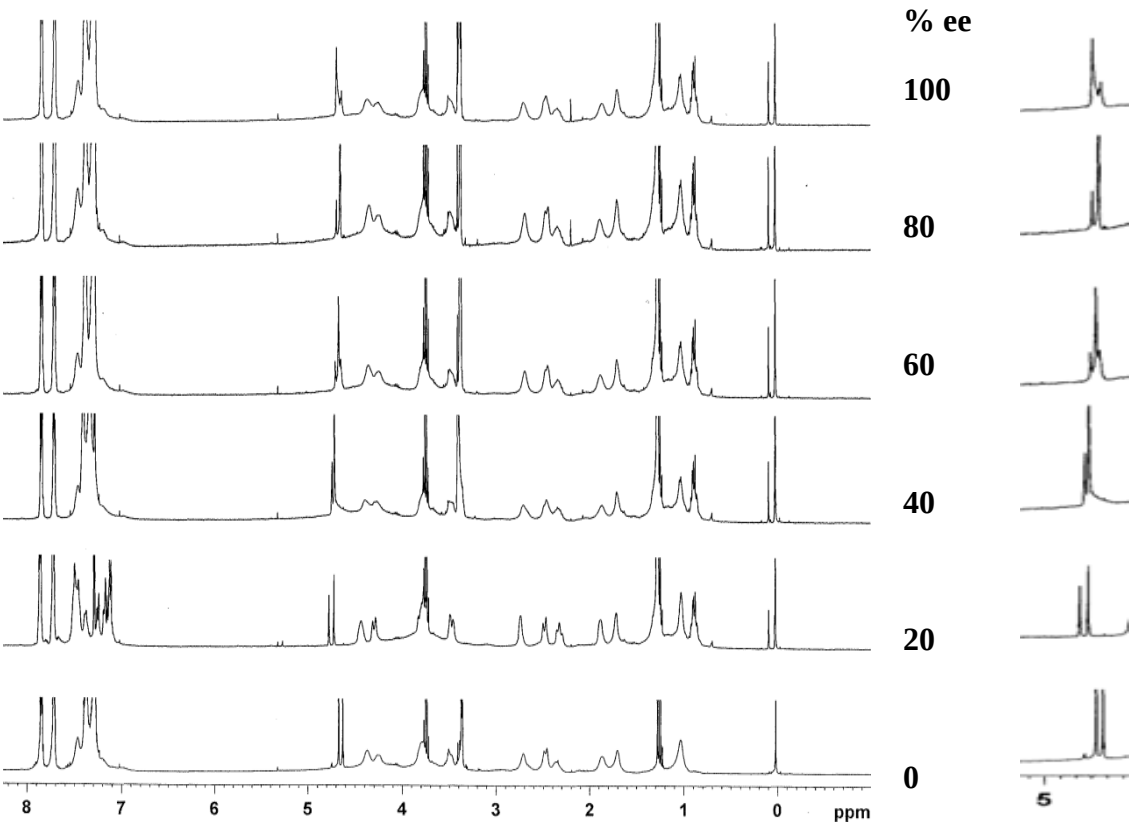


Figure 4.6. ^{1}H NMR spectra of the CSA **5** with different enantiomeric purities in the presence of α-phenyl-α-methoxyacetic acid (C) (20 mM ,Ratio: 1: 1 CSA/C)

4. Tertiary amine functionality of (S,R)-6 as a benzyl derived from (S,R)-5 exhibited low enantiomeric differentiated values. It showed only towards mandelic acid, *o*-chloro mandelic acid with ΔΔδ of 2.4 and 3 Hz respectively (Table 4.2.).

5. Surprisingly, it was found that amino alcohol imide (*S,R*)-**7** and (*S,R*)-**8** which bearing phenyl and naphthyl substituents exhibit lowest enantiomeric differentiated values towards all analytes. This is attributed to the lower polarity or planar shape of side arm of CSA (*S,R*)-**7** and (*S,R*)-**8** caused low solubility to form inclusion complexes.

Table 4.2. Induced shifts (Δδ, ppm) and splitting (ΔΔδ, ppm) for the signal of the carboxylic acids **A-E** in the presence of CSA **6-8** (400 MHz, 5 mM in $CDCl_3$ at 25 ^oC).

	Acid	**Signal**	**CSA**					
			6		**7**		**8**	
			Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ	Δδ[a]	ΔΔδ
6	A	CαH	-0.153	0.06	-0.136	0.019	-0.006	0.00
7	B	CαH	-0.167	0.05	-0.173	0.00	0.015	0.00
8	C	CαH	-0.007	0.00	-0.059	0.00	0.002	0.00
9	D	CαH	-0.067	0.00	+0.093	0.00	-0.002	0.00
10	E	CαH	-0.007	0.00	-0.166	0.013	0.013	0.00

[a]: Averaged between signals from both enantiomers.

In conclusion, we have synthesized novel an amino alcohol and six amino alcohol imide functionalized compounds and investigated their potential CSAs by ^1H NMR spectroscopy to discriminate the C-α-H of biological important chiral carboxylic acids (**A-E**). (*S,R,S,R*)-**3** and (*S,R*)-**5** showed satisfactory discrimination towards mandelic acid and α-phenyl-α-methoxyacetic acid respectively. This indicate that (*S,R,S,R*)-**3** and (*S,R*)-**5** are potential CSAs for analytes tested. The results also indicate that not only secondary or tertiary classes of chiral amine but also polarity of reagent and analyte are also effective in the chiral discrimination in ^1H NMR analysis.

5. REFERENCES

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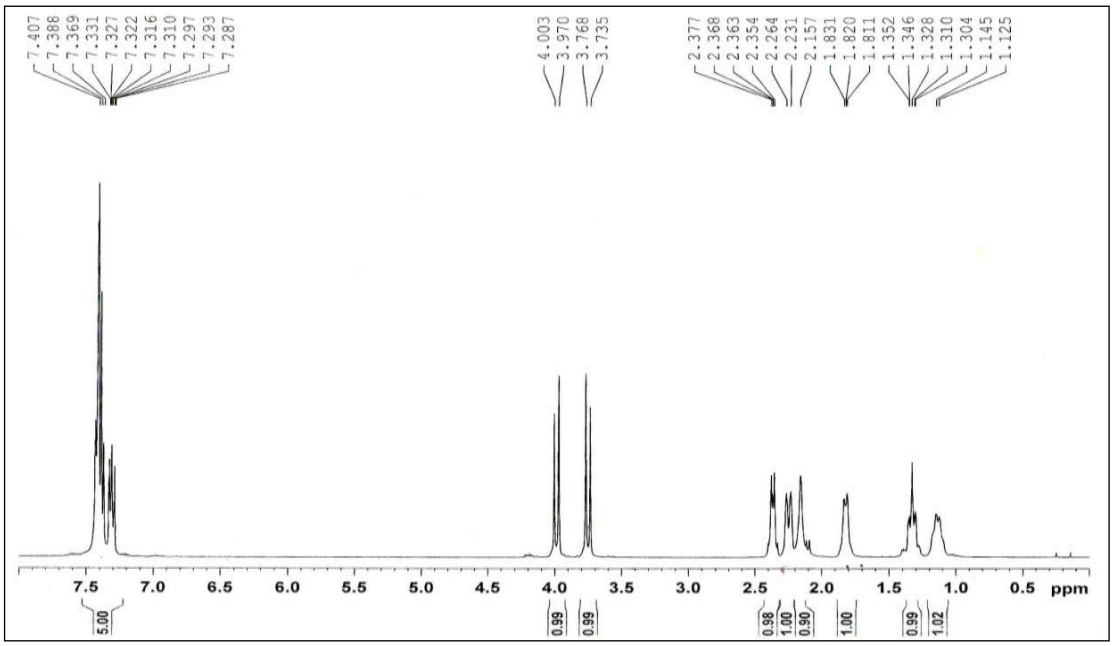
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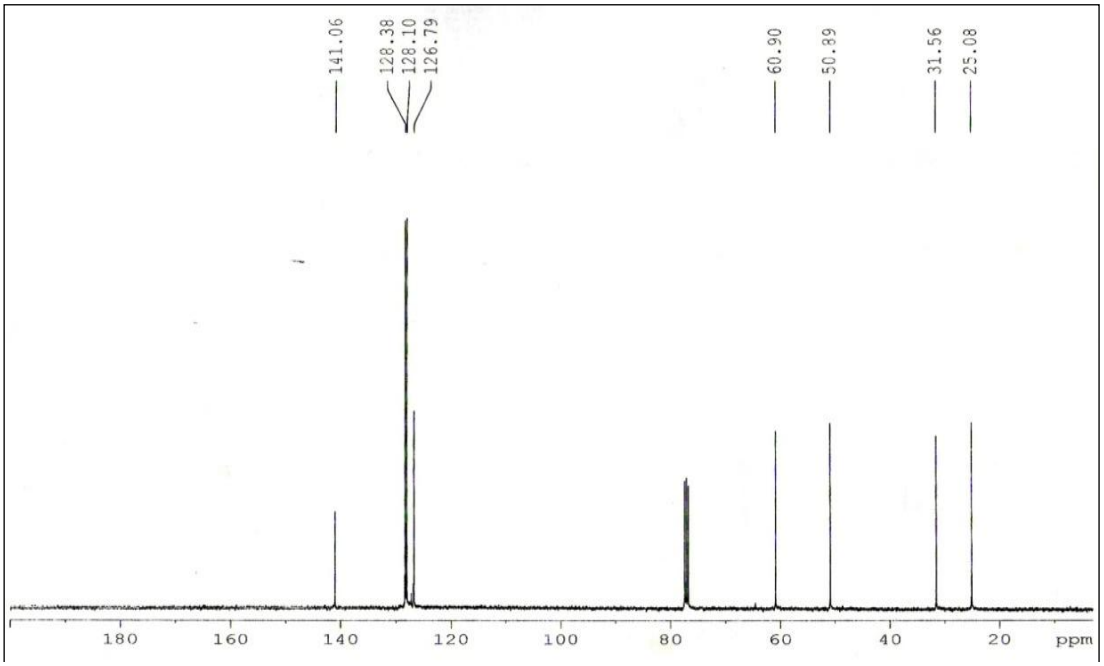
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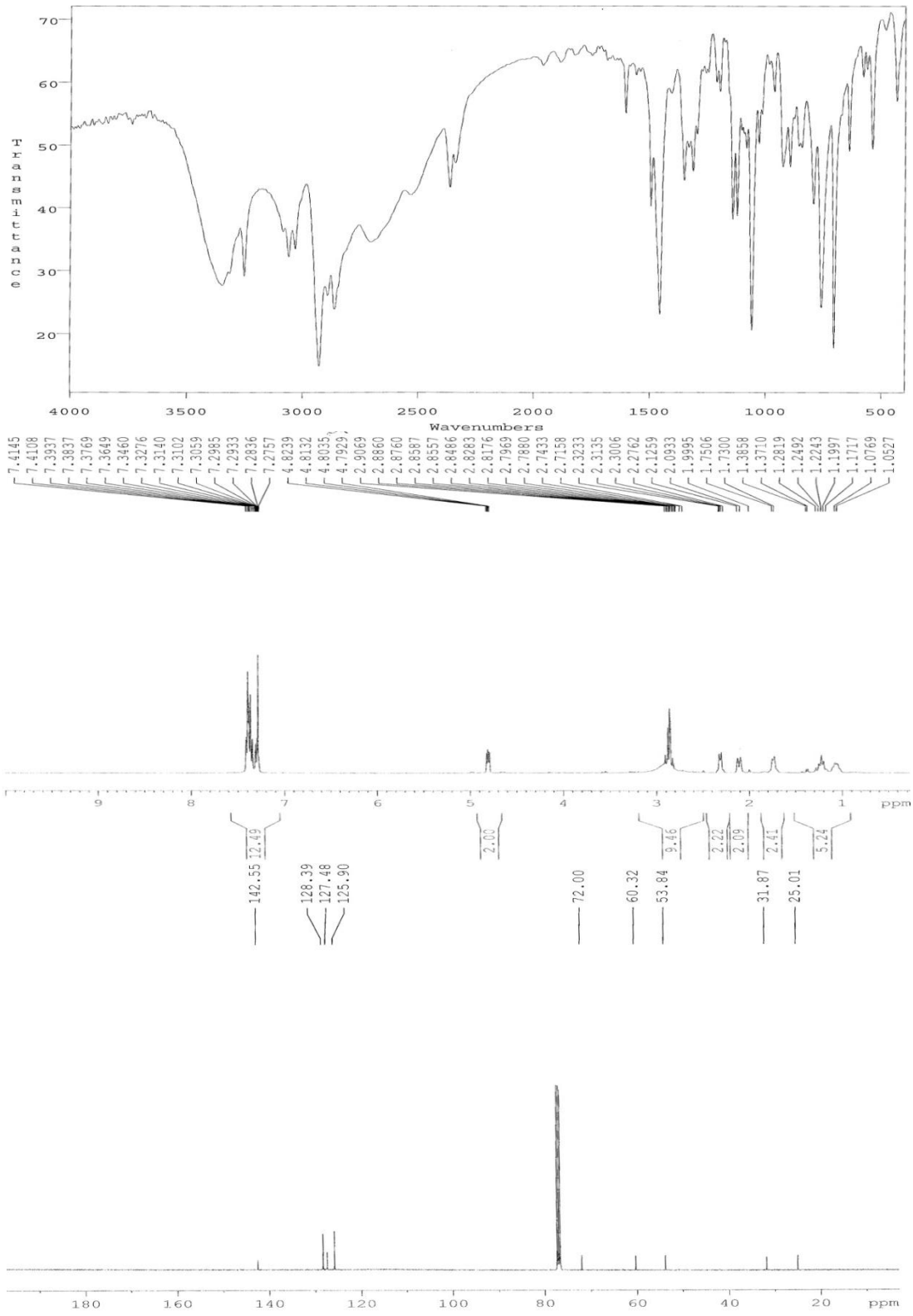
APPENDICES

SPECTRA

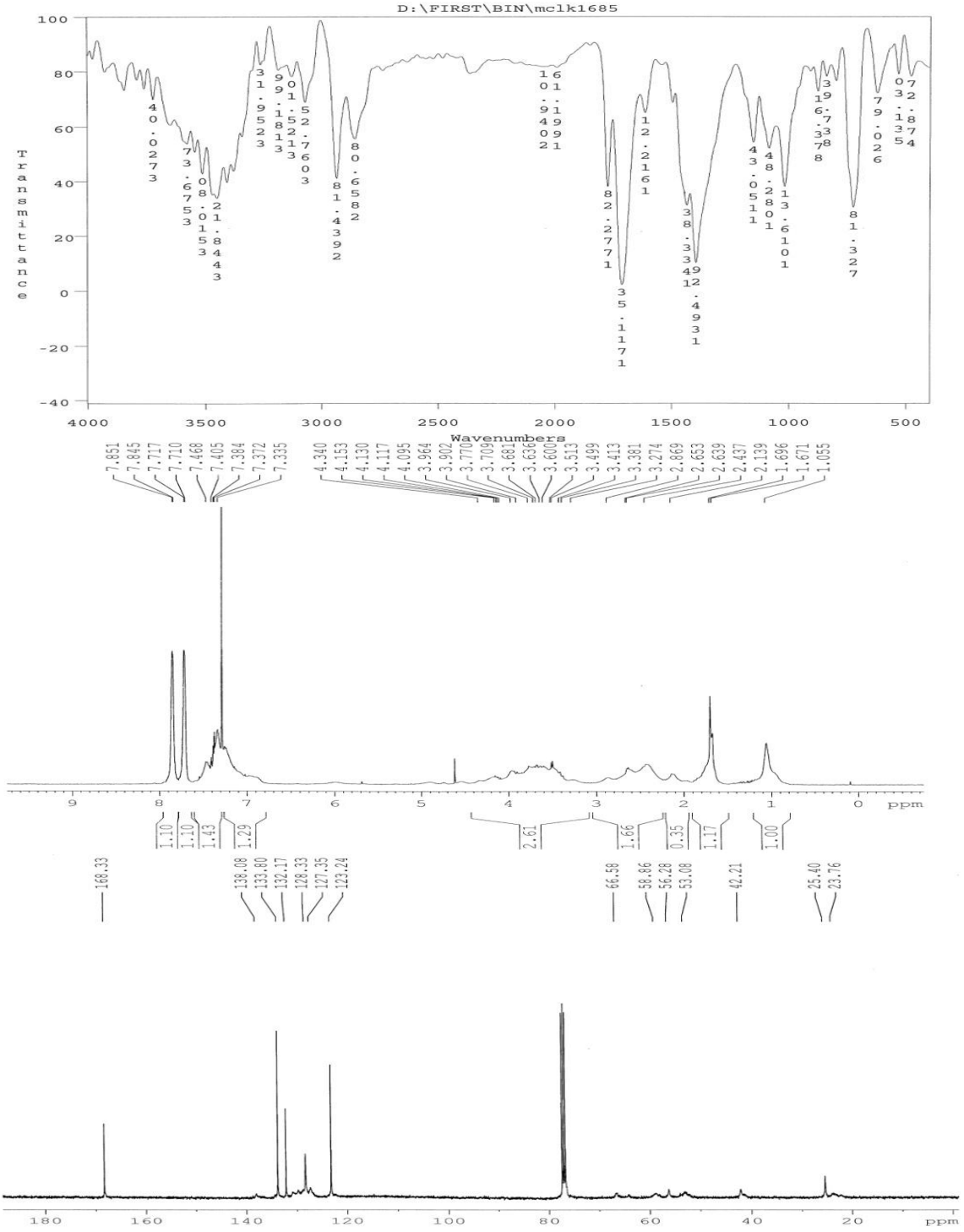




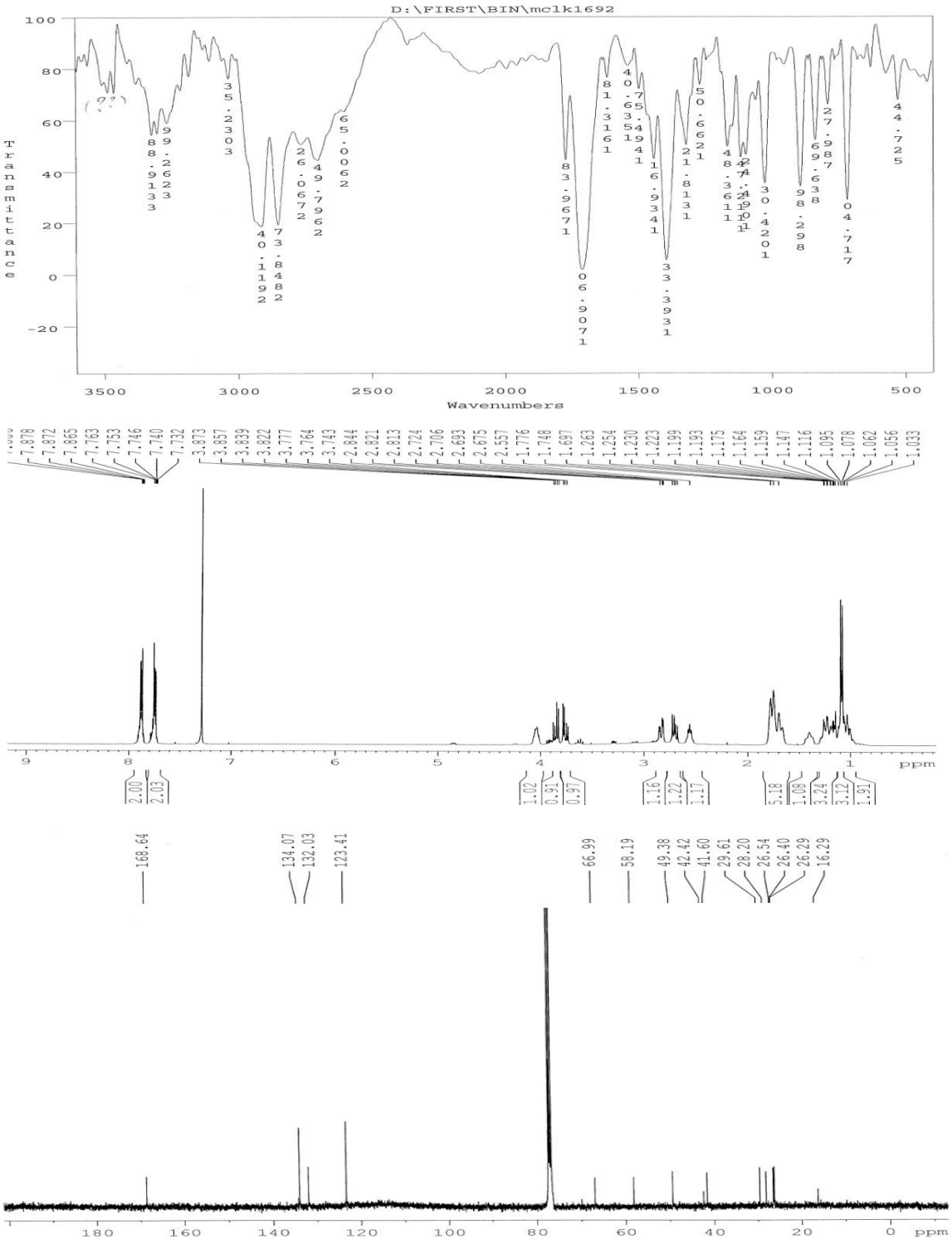
^{1}H and ^{13}C NMR spectra of (*R*,*R*)-*N,N'*-Dibenzyl-1,2-diaminocyclohexane **1**



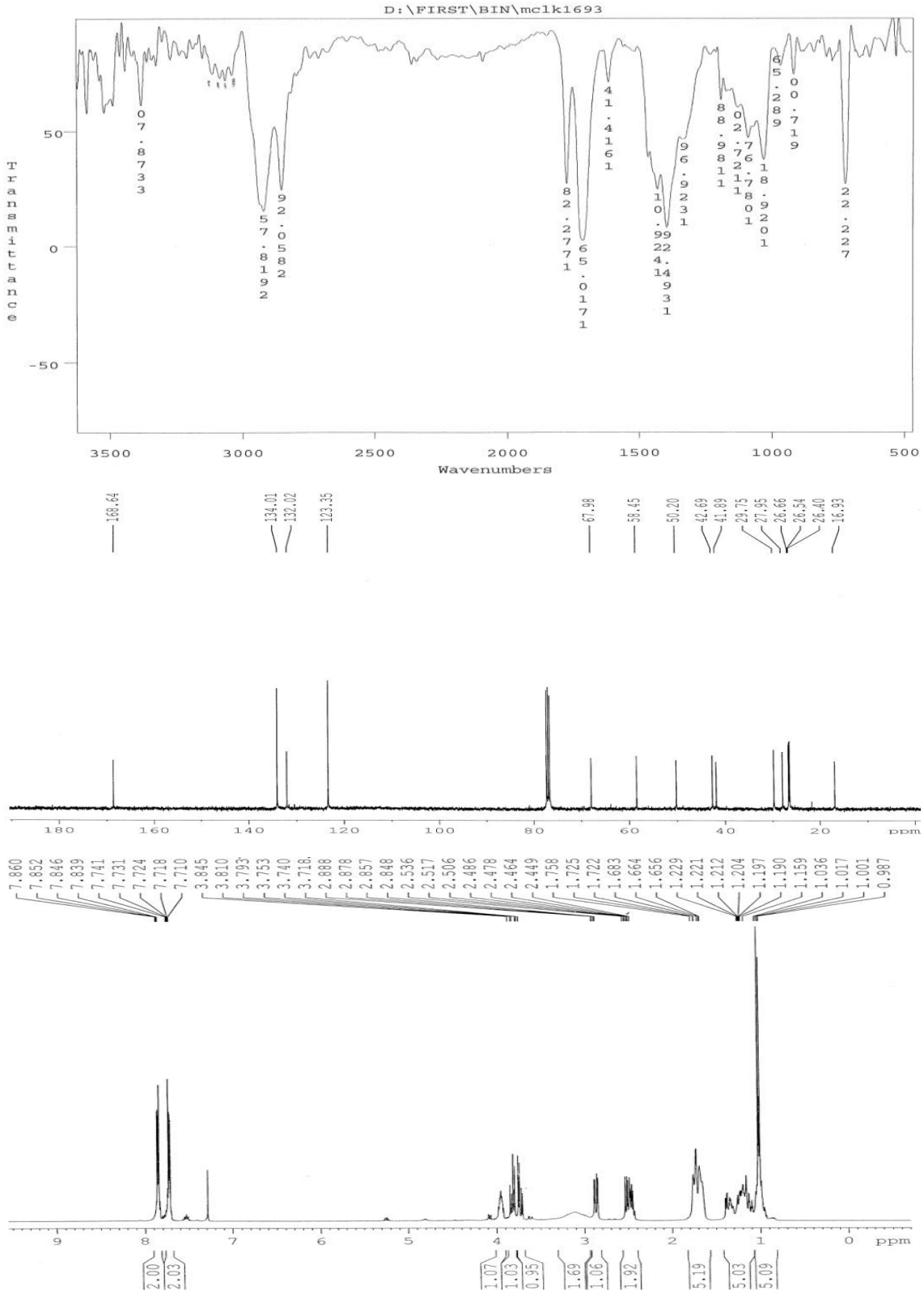
IR, ^{1}H and ^{13}C NMR Spectra of (*R*,*R*)-bis[(*R*)-2-hydroxy(2-phenyl)ethyl]-1,2-diaminocyclohexane **2**



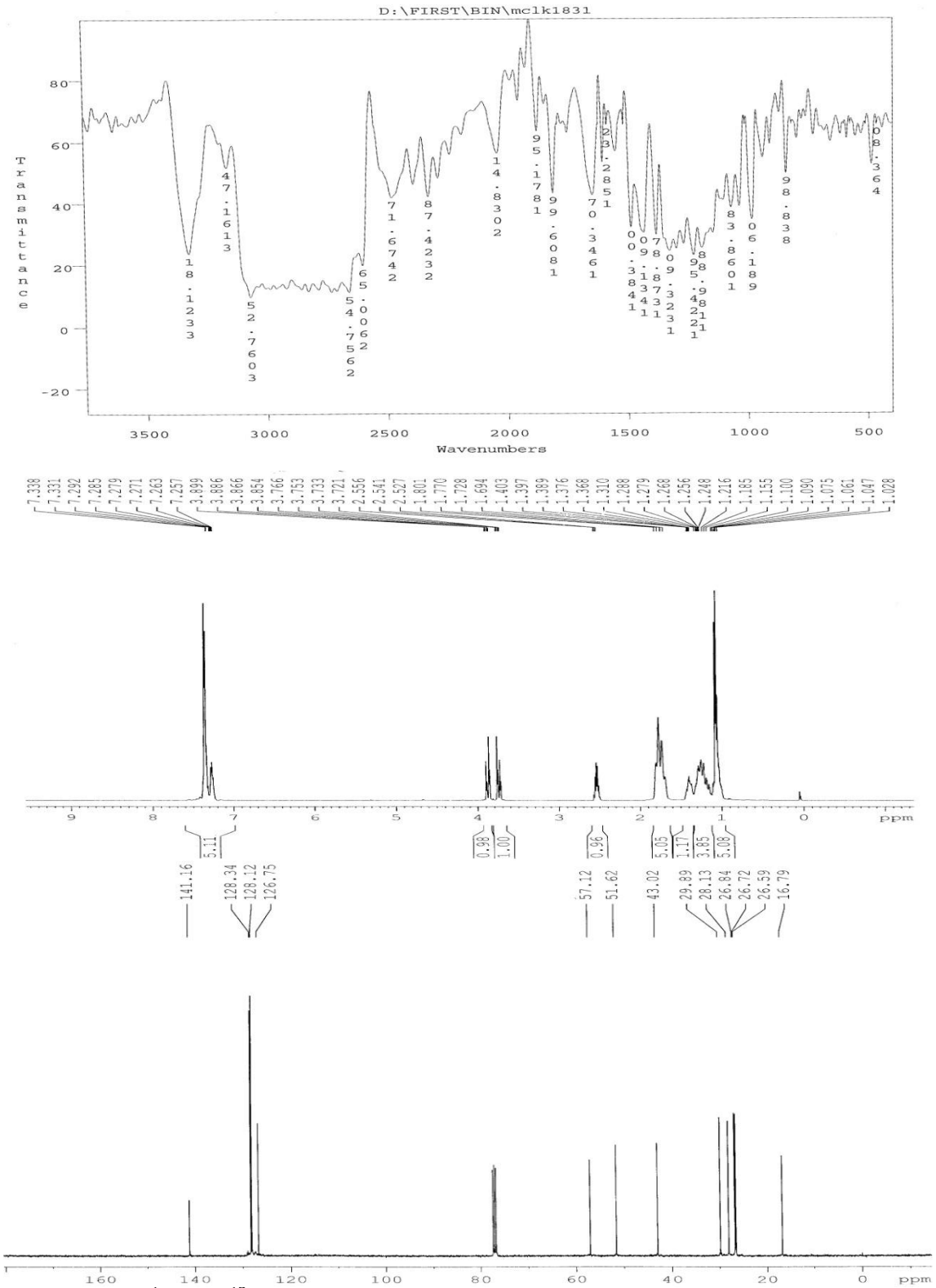
IR, ^{1}H and ^{13}C NMR Spectra of *N,N'*-Dibenzyl-*N,N'*-bis[(*S*)-2-hydroxy-3-phtalimide]-(*1R,2R*)-diaminocyclohexane **3**



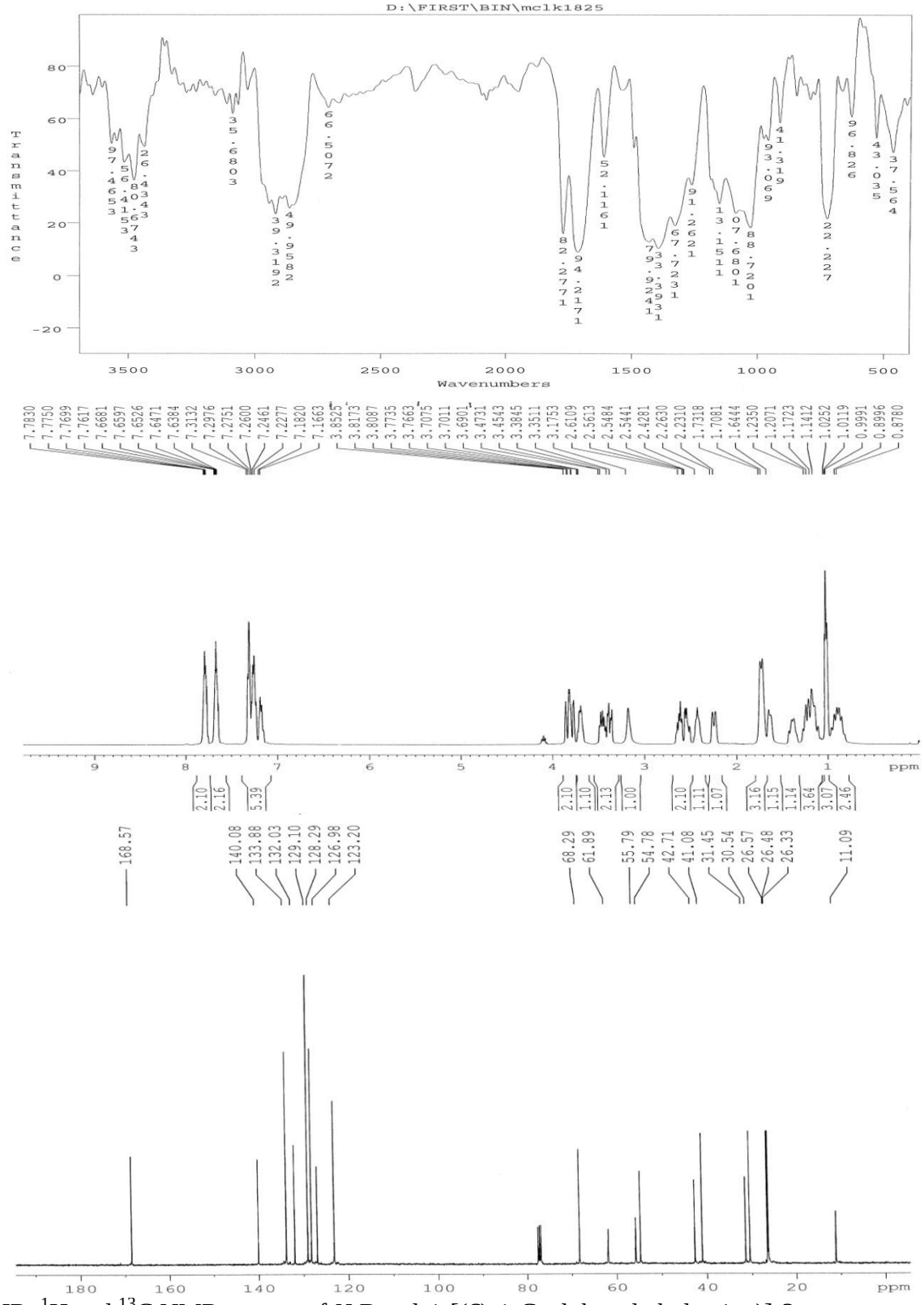
IR, ^{1}H and ^{13}C NMR spectra of 1-[(*R*)-1-cyclohexylethylamino)]-3-phtalimide-(*S*)-2-propanol **4**



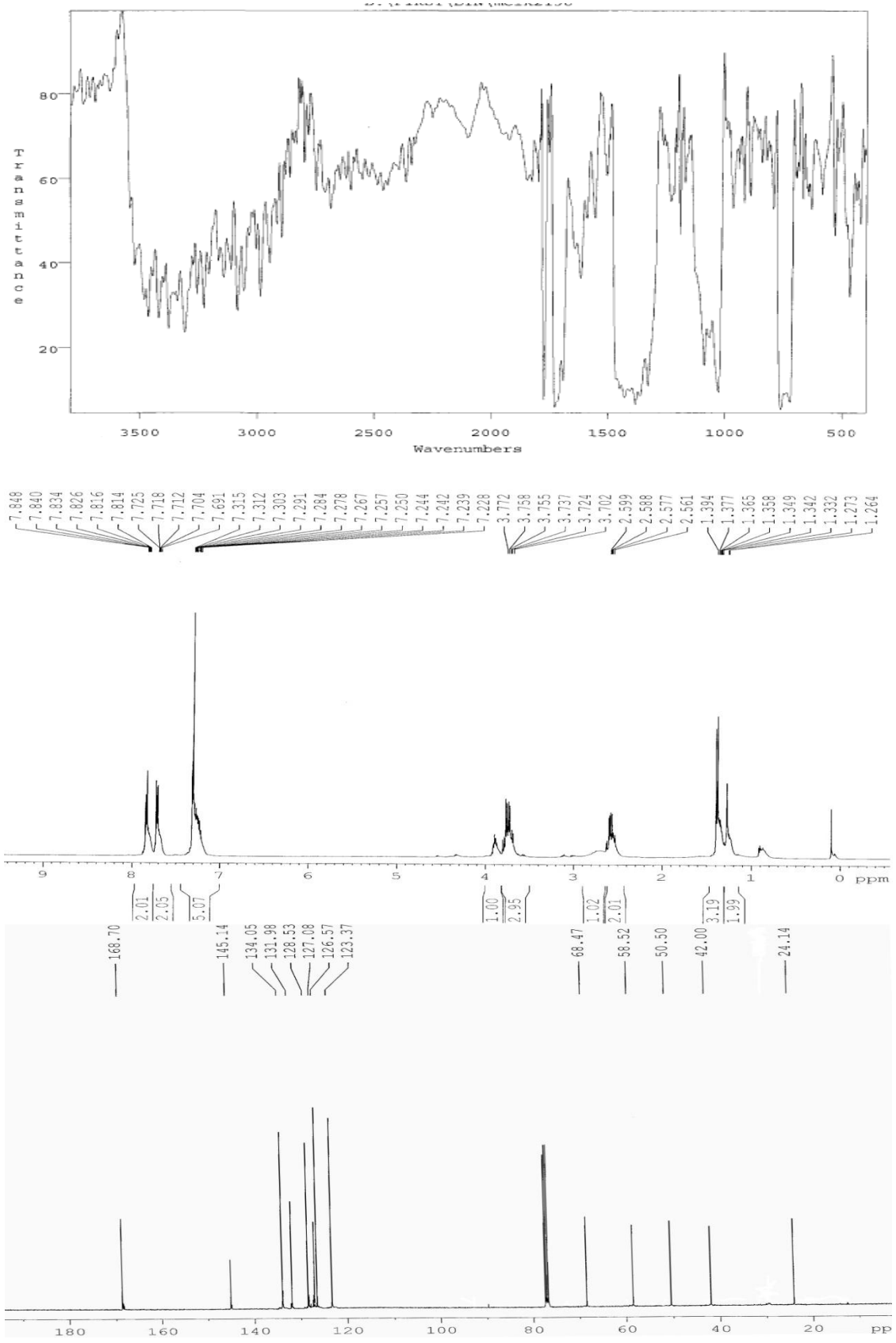
IR, ^{1}H and ^{13}C NMR spectra of 1-[(*S*)-1-cyclohexylethylamino)]-3-phtalimide-(*R*)-2-propanol **5**



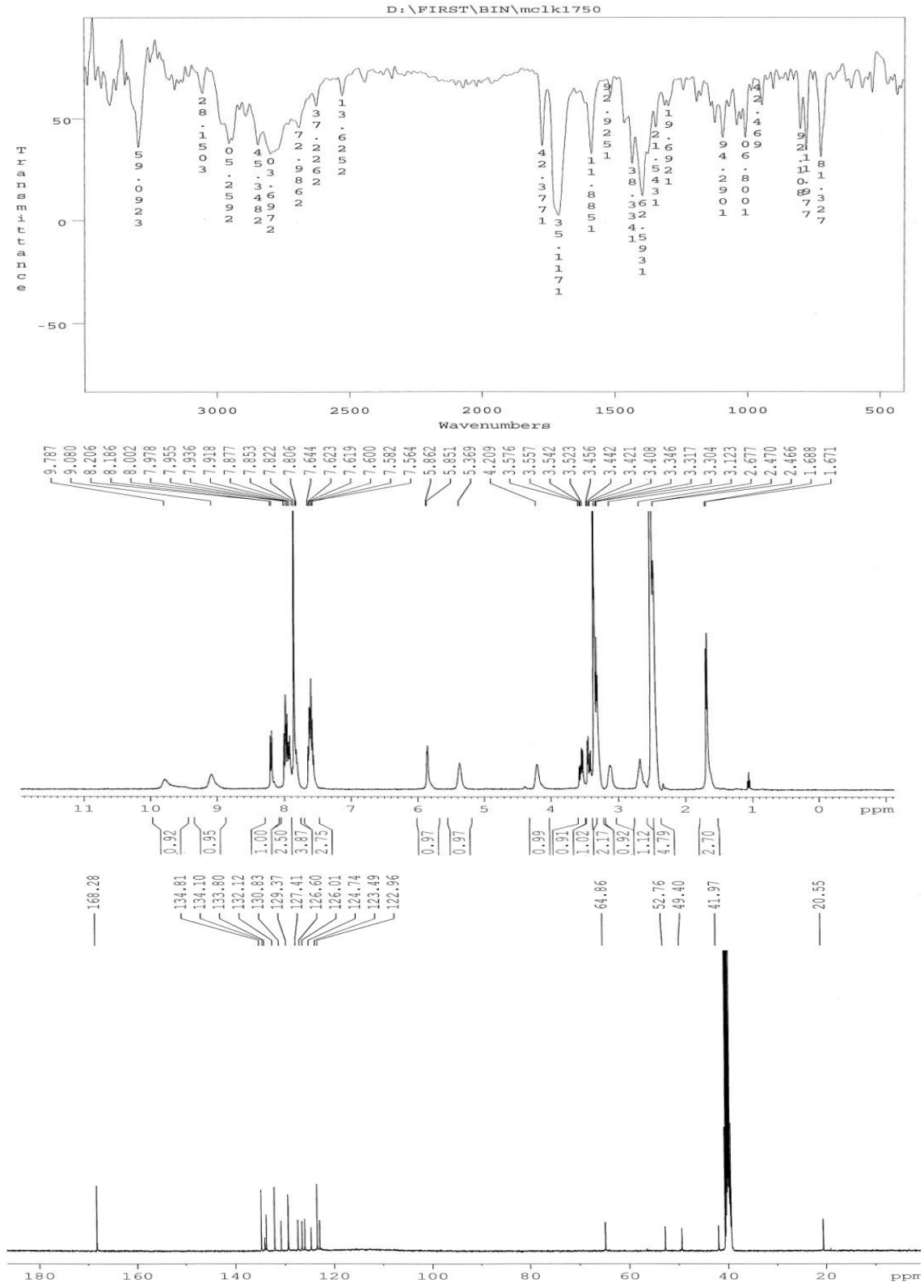
IR, ^{1}H and ^{13}C NMR spectra of (*S*)-*N*-benzyl-cyclohexylethylamine



IR, ^{1}H and ^{13}C NMR spectra of *N*-Bezyl-1-[(*S*)-1-Cyclohexylethylamino)]-3-phtalimide-(*R*)-2-propanol **6**



IR, ^{1}H and ^{13}C NMR spectra of [(*R*)-Phenylethylamino)]-3-phtalimide-(*R*)-2-propanol **7**



IR, ^{1}H and ^{13}C NMR spectra of 1-[(*S*)-1-Naphthylethylamino)]-3-phtalimide-(*R*)-2-propanol **8**

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FEN BİLİMLERİ ENSTİTÜSÜ
YÜKSEK LİSANS TEZ ÇALIŞMASI İNTİHAL RAPORU FORMU

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TEZ KONUSU	Amino Alcohol Imide Based Chiral Solvating Agents: Synthesis and Applications in the NMR Enantiodiscrimination of Carboxylic Acids
İNTİHAL RAPORU BİLGİLERİ	
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BENZERLİK ORANI	% 21
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Yukarıda başlığı/konusu gösterilen tez çalışmamın kapak sayfası, giriş, ana bölümler, sonuç ve tartışma kısımlarından oluşan toplam 71 sayfalık kısmına ilişkin, 27/ 02 / 2017 tarihinde şahsım/tez danışmanım tarafından TURNİTİN adlı intihal tespit programından aşağıda belirtilen filtrelemeler uygulanarak alınmış olan intihal raporuna göre, tezimin benzerlik oranı % 21'dir.

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☒ Kaynakça hariç
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X % 13'u bu tezden üretilen makaleyi göstermektedir.

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Gereğini saygılarımla arz ederim.

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