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ปีการศึกษา 2549

SYNTHESIS OF PROLINAMIDE DERIVATIVES AS ORGANOCATALYSTS FOR ASYMMETRIC SYNTHESIS

Mr. Sornpranart Sathapornvajana

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Chemistry

Department of Chemistry
Faculty of Science
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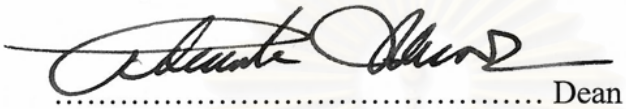
Thesis Title	Synthesis of Prolinamide Derivative as Organocatalysts for Asymmetric Synthesis
By	Mr. Sornpranart Sathapornvajana
Field of Study	Chemistry
Thesis Advisor	Associate Professor Tirayut Vilaivan, D. Phil.

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for Master's Degree



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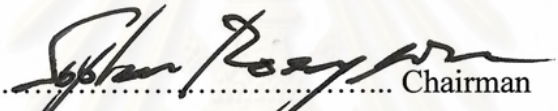

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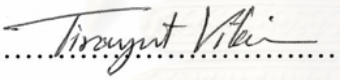

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สรประนาท สถาพรวจนา : การสังเคราะห์อนุพันธ์ของโพรลินาไมด์เพื่อเป็นออร์แกโนคะตะลิสต์สำหรับการสังเคราะห์แบบอสมมาตร (SYNTHESIS OF PROLINAMIDE DERIVATIVES AS ORGANOCATALYSTS FOR ASYMMETRIC SYNTHESIS) ที่ปรึกษา : รศ. ดร. ธีรยุทธ วิไลวัลย์; 210 หน้า.

งานวิจัยนี้ได้สังเคราะห์อนุพันธ์ของโพรลินาไมด์จากโพรลีน และ2-อะมิโนฟีนอลโดยมีวัตถุประสงค์ที่จะอาศัยการเพิ่มหมู่ที่สามารถสร้างพันธะไฮโดรเจนบอนด์ ในการเร่งปฏิกิริยาแอลดอลแบบอสมมาตร ปฏิกิริยาแอลดอลระหว่างแอโรมาติกแอลดีไฮด์ชนิดต่างๆและไซโคลเฮกซาโนนโดยมีตัวเร่งปฏิกิริยาที่ดีที่สุดให้ผลิตภัณฑ์แอลดอลที่มีไดแอสเตอเมอริกเรโช (dr) สูงถึง 95:5 และอิแนนชิโอเมอริก เอ็กเซส (*ee*) สูงถึง 95 เปอร์เซ็นต์ นอกจากนี้ยังได้ทดลองประเมินประสิทธิภาพของคะตะลิสต์ในการเร่งปฏิกิริยาในน้ำ พบว่าจากปฏิกิริยาแอลดอลระหว่างแอโรมาติกแอลดีไฮด์ชนิดต่างๆและไซโคลเฮกซาโนนให้ผลิตภัณฑ์แอลดอลที่มีไดแอสเตอเมอริกเรโช (dr) 94:6 และอิแนนชิโอเมอริก เอ็กเซส (*ee*) 97 เปอร์เซ็นต์ สูงกว่าเมื่อเปรียบเทียบกับการทำปฏิกิริยาในตัวทำละลายอินทรีย์ นอกจากนี้ยังได้เสนอแบบจำลองสถานะแทรนซิชัน เพื่ออธิบายซีเล็กติวิตี้ของปฏิกิริยา

ภาควิชา เคมี ลายมือชื่อนิสิต .....

สาขาวิชา เคมี ลายมือชื่ออาจารย์ที่ปรึกษา .....

ปีการศึกษา 2549

##4772510323 : MAJOR CHEMISTRY

KEY WORD : ASYMMETRIC ALDOL REACTION/ PROLINE

SYNTHESIS OF PROLINAMIDE DERIVATIVES AS ORGANOCATALYSTS FOR ASYMMETRIC SYNTHESIS. THESIS ADVISOR : ASSOC. PROF. TIRAYUT VILAIVAN, D.Phil. 210 pp.

L-Prolinamide derivatives were synthesized from L-proline and 2-aminophenols with the objective to utilize additional H-bonding from the aminophenol in catalyzing asymmetric aldol reactions. Aldol reactions between various aromatic aldehydes and cyclohexanone in the presence of the best prolinamide derivatives afforded the aldol product with diastereoselectivity up to 95:5 (*anti*:*syn*) and enantioselectivity up to 95 % (*anti*). Furthermore, the catalyst performance was evaluated in the direct aldol reaction in water. Reactions of aromatic aldehydes and cyclohexanone gave the aldol products with higher diastereoselectivity up to 94:6 (*anti*:*syn*) and enantioselectivity over 97 % (*anti*) compared to reactions in organic solvents. A transition state model to explain the selectivity was also proposed.

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Department……Chemistry……Student's signature……Sornprannart Sathapornvajana……

Field of study……Chemistry……Advisor's signature……Tirayut Vilaivan……

Academic year……2006……

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LIST OF ABBREVIATIONS

δ	chemical shift
μL	microliter
$[\alpha]_D$	specific rotation
AcOH	acetic acid
Ar	aromatic
aq	aqueous
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
br	broad (NMR)
Bu	butyl
calcd	calculated
CAN	cerium (IV) ammonium nitrate
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
d	doublet (NMR)
dd	doublet of doublets (NMR)
dr	diastereomeric ratio
D_2O	deuterium oxide
DCM	dichloromethane
DMF	*N*,*N*′ dimethylformamide
DMSO-d_6	deuterated dimethylsulfoxide
EDC.HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride
EtOH	ethanol
ee	enantiomeric excess
equiv	equivalent (s)
g	gram
h	hour
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
HNO_3	nitric acid
H_2	hydrogen gas

J	coupling constant
m	multiplet (NMR)
MeCN	acetonitile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mM	millimolar
mmol	millimole
mp.	melting point
MS	mass spectrometry
$NaHCO_3$	sodium hydrogencorbonate
NMR	nuclear magnetic resonance
^oC	degree celcius
Pd/C	palladium/charcoal activated
Ph	phenyl
q	quartet (NMR)
R_f	retention factor
Sn	tin
s	singlet (NMR)
t	triplet (NMR)
td	triplet of doublets (NMR)
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time
Ts	*p*-toluenesulfonyl (=tosyl)

CHAPTER I

INTRODUCTION

1.1 Chirality

Chirality is a fundamental symmetry property of three-dimensional objects. An object is said to be chiral if there is no internal plane of symmetry, and the object and its mirror image are not superimposable, i.e.: they are related like our left and right hands. Hence this property is called chirality, from the Greek word for hand.

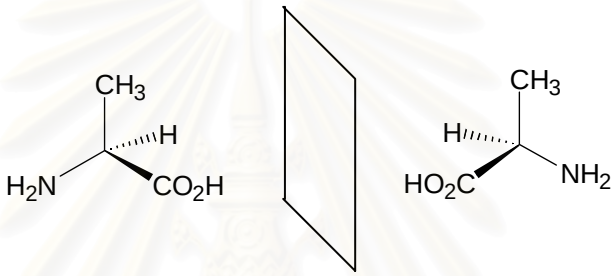


Figure 1-1. A simple molecule as enantiomers

In chemistry, chirality is applied to the three-dimensional structure of molecules. A pair of chiral molecules is constitutionally identical but differs in the three-dimensional arrangement of atoms such that they are related as mirror images. A chiral molecule and its mirror image molecule are called stereoisomers or enantiomers (from the Greek word for opposite). Enantiomers have identical chemical and physical properties, such as melting point, solubility, chromatographic retention time, IR and NMR spectra. However, they differ in their ability to rotate the plane of polarized light and the way they interact with another chiral molecule. One enantiomer will rotate the plane of polarized light in equal amount but in opposite direction to the other. For this reason, stereoisomers are also called optical isomers.

If a molecule contains more than one (n) chiral center, the possible configurations are up to 2^n and they cannot all be mirror images of each other, in which case they are called diastereomers. An example is provided by the four possible stereoisomers of the amino acid threonine (Figure 1-2).

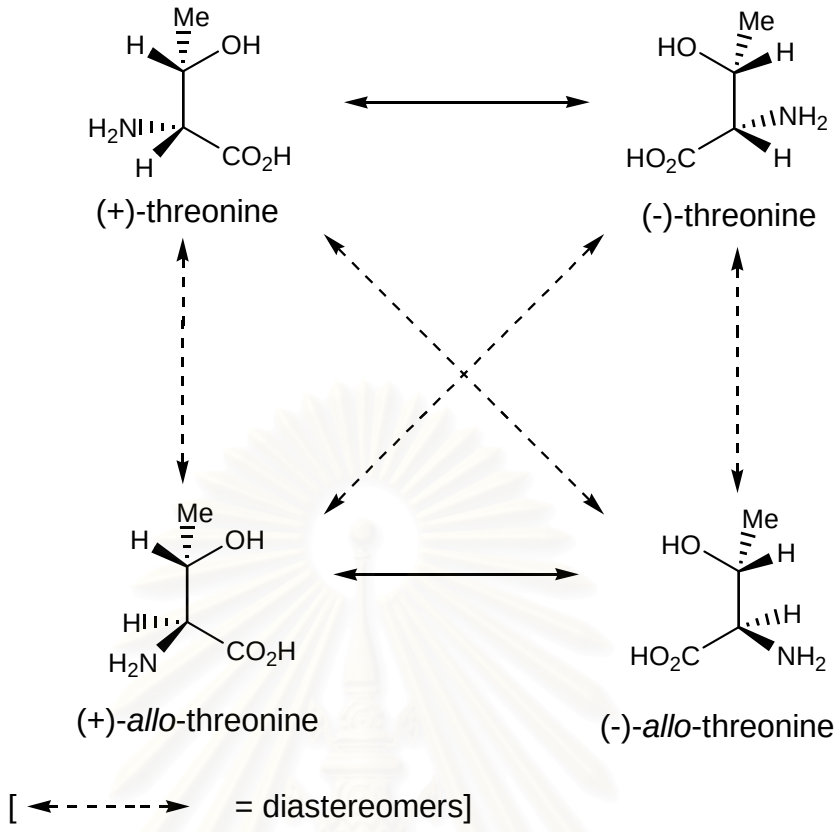


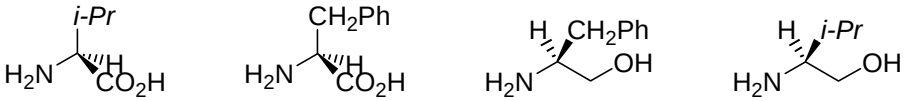
Figure 1-2. The amino acid threonine certain one more stereogenic center

1.2 Asymmetric synthesis

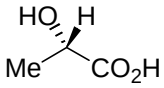
Since the early 1970s, there has been a dramatic increase in research on new methods for the preparation of chiral compounds in the form of single enantiomers. This method is called “asymmetric synthesis”. Asymmetric synthesis [1] involves the formation of a new stereogenic unit in the substrate under the influence of a chiral group in the form of chiral starting materials, auxiliaries, reagents or catalysts

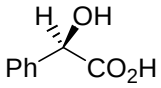
The ultimate source of starting materials for chiral compounds in all asymmetric synthesis is Nature. Naturally occurring chiral compounds provide an enormous range and diversity of possible starting materials. They can be classified in to five major classes.

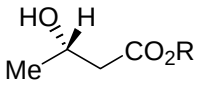
1 Amino acids and amino alcohols

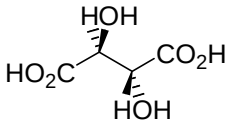


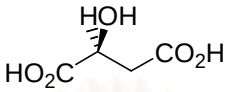
2. Hydroxy acids



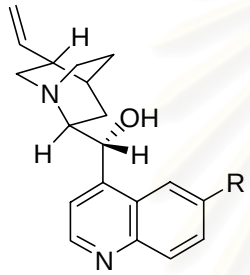


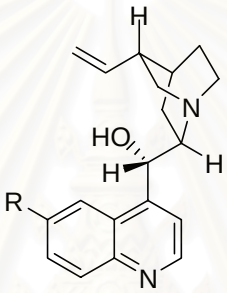




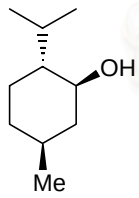


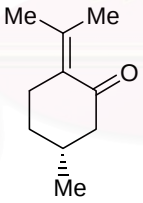
3. Alkaloids and other amines

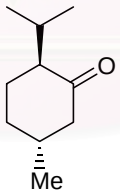


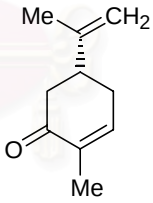


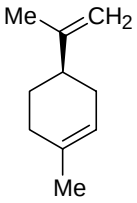
4. Terpenes



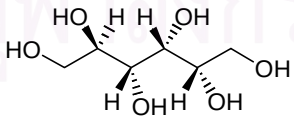


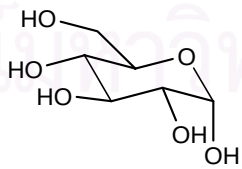






5. Carbohydrates



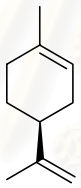


Asymmetric synthesis may be classified into two types – diastereoselective and enantioselective synthesis. In diastereoselective synthesis products are obtained as mixture of diastereomers resulting form creation of new stereogenic centers while the pre-existing stereogenic center is still covalently

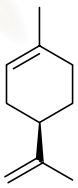
attached to the products. On the other hand, enantioselective synthesis refers to reactions whereby products are obtained as mixture of unequal amounts of enantiomers. In these cases, the pre-existing chirality does not appear in the final products.

1.2.1 The importance of enantioselective synthesis

Chiral compounds occur in Nature are optically active due to the inherent chirality of the enzymes that are responsible for their production. Receptor sites in biological systems, which are also optically active, have the ability to differentiate between two enantiomers of a specified molecule. It is not surprising the biologically active chiral molecules such as drugs and hormones will have only one enantiomer that can perfectly interact with their specific receptors. It is more often than not that the other enantiomer will not interact in the same way to produce the same effect. In certain cases the other form may even be harmful (for example, by interacting with a different receptor).

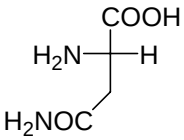


(*S*)-limonene

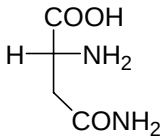


(*R*)-limonene

The following examples illustrate the fact that the interaction at the receptor in a biological system depends fundamentally on the structure of the molecule. *Limonene,* for example, is chiral and the receptors in our nose are sensitive enough to tell the difference between the two enantiomers of limonene. (*S*)-Limonene has the lemon odour, (*R*)-Limonene has the odour of orange.

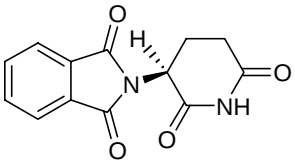


(*R*)-asparagine



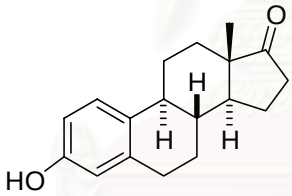
(*S*)-asparagine

Taste receptors on our tongues can also differentiate enantiomers. (*R*)-Asparagine tastes sweet, whereas the (*S*)-enantiomer has a bitter taste.

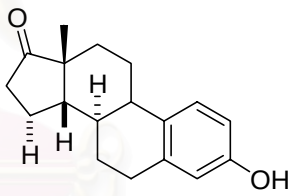


thalidomide

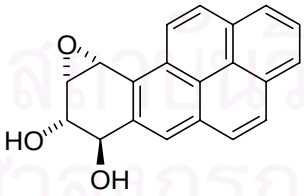
Whenever a compound is introduced into the body, either as a food additive or a drug, the question of toxicity always arises. This was the case, for example, with the drug thalidomide. It was used clinically as a racemate in the 1960s [2] to suppress morning sickness in pregnant women. Unfortunately, it was only discovered later that only one of the enantiomers of thalidomide helped against nausea, while the other one could cause fetal damage. Another example is the naturally occurring hormone-Estrone. (+)-Estrone has the well-known estrogenic hormone effect, while the (-) enantiomer is completely inactive. The (+)-form of the hydroxylated metabolites of benzo[a]pyrene is extremely carcinogenic, but the carcinogenic property is completely absent in the (-)-form.



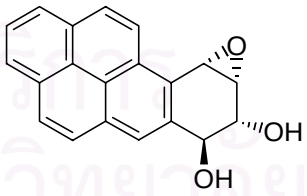
(+)-Estrone



(-)-Estrone



(+)-benzo[a]pyrene metabolite



(-)-benzo[a]pyrene metabolite

1.2.2 Catalytic asymmetric reaction

Catalytic asymmetric synthesis has been first developed around early 1980s and since then has progressed rapidly. In catalytic asymmetric reactions, achiral substrates and reagents react in the presence of chiral catalysts to give enantiomerically enriched products. The most prominent advantage over other

methods of asymmetric synthesis is that the enantiomerically pure compounds necessary to create the new stereogenic centers are required only in catalytic amounts. This class of reaction is obviously very attractive from the industrial perspective and is therefore presently the subject of intensive research.

Generally, the field of asymmetric synthesis was dominated mainly by two types of catalysts namely transition metal complexes and enzymes. Both types of catalysts do not only catalyze a wide range of transformations with useful level of enantioselectivity, but often do so with high predictability. However, during the past few years a significant new movement in organic synthesis has emerged: the use of small, purely organic compounds as catalysts for a wide range of asymmetric reactions. Organocatalyst have several advantages over metal based catalysts. They are usually more stable, less expensive, non-toxic, and readily available.

In metal-mediated enantioselective catalytic reactions, the metal plays an organizational role by translating chiral information and activating the substrates. In the absence of the metal, hydrogen bonding between catalysts and substrates at the reaction center plays a crucial role in the determination of the stereoselectivity of the reaction. Although this represents an energy contribution of only 1-6 kcal mol^{-1} to the interactions, hydrogen bonding influences the conformational preferences by forming rigid three-dimensional structures and contributes to the affinity and selectivity of molecular recognition.

The growing interest in the field of asymmetric organocatalysis is evidenced by the sharply increasing number of publications in recent years. Furthermore, already several monographs dedicated to this topic only have already appeared as published book [3] and several reviews [4-6].

1.3 Asymmetric organocatalysis

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound, which does not contain a metal atom [3-5]. This type of catalysis is complementary with the metal-complex mediated, and also, with biocatalytic transformations. These catalysts are often more stable than enzymes or other bioorganic catalysts. Also, these small organic molecules can be anchored to solid support and reused more conveniently than organometallic/bioorganic analogues. Usually organocatalytic reactions can be

performed under an aerobic atmosphere, without the requirement for strictly anhydrous solvents and in many cases protection of functional groups is not required.

The area of organocatalysis is not entirely new. In the early 1970s, Hajos [7-8] and Parrish at Hoffmann La Roche reported a proline-catalyzed intramolecular aldol reaction of a triketone. It is the intramolecular version of a now well-known L-proline catalyzed aldol reactions. The reaction is a desymmetrization reaction that discriminates between two enantiotopic carbonyl groups. The achiral triketone (1) cyclized to give the aldol product (2), with good enantioselectivity. The reaction proceeds *via* temporary formation of an enamine from the remote ketone, which is sufficiently reactive to affect the cyclization. This is a particularly powerful reaction because it offers a simple and effective way to produce a quite complex product in single step *via* a highly organized chiral transition state.

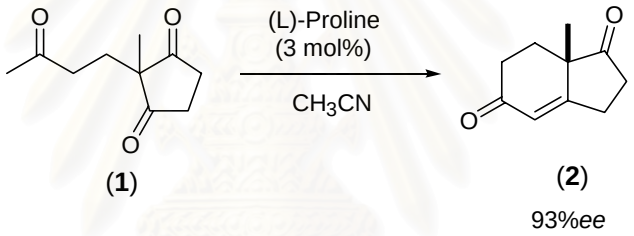


Figure 1-3. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

The field of asymmetric organocatalysis developed later was dominated by covalent catalysis of amine-based reactions with carbonyl compounds (Figure 1-4) [9]. Most of these reactions proceed by the generalized enamine cycle or as charge-accelerated reactions through the formation of iminium intermediates. Iminium catalysis directly utilizes the higher reactivity of the iminium ion in comparison to the carbonyl species. Enamine catalysis involves catalytically generated enamine intermediates that are formed via deprotonation of an iminium ion, and react with various electrophiles or undergo pericyclic reactions.

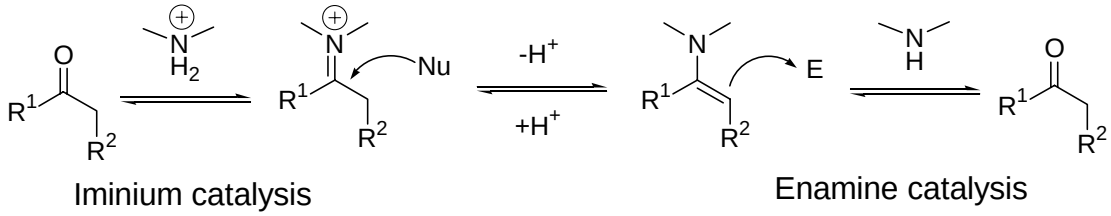


Figure 1-4. Activation of a carbonyl group by the formation of iminium ion or enamine intermediates

1.3.1 Proline-catalyzed asymmetric reactions

Proline is a very attractive catalyst because it is inexpensive, readily available in both enantiomeric forms, non-toxic, and typically its reactions require no stringent reaction conditions such as low temperatures, inert atmosphere etc. L-Proline (**B**) is one of the twenty proteinogenic amino acids which is used in living organisms as the building blocks of proteins. The other nineteen amino acids possess primary amino groups (general structure **A**), but due to the linkage between the α-carbon and the amino group through a three carbon side chain, proline has a unique secondary amino functional group.

A **B**

Figure 1-5. General structure of α-amino acid (**A**) and α-imino acid (**B**)

The distinctive cyclic structure of proline side chain locks its φ backbone dihedral angle at approximately -75°, giving proline an exceptional conformational rigidity compared to other amino acids. The extra degree of rigidity in the cyclic amino acid L-proline makes it particularly useful in directing many asymmetric processes [10].

Although the L-proline-mediated Robinson annulation mentioned above offers practical and enantioselective route to the Wieland-Miescher ketone, which is an important building block for total synthesis, the power of proline-catalyzed asymmetric synthesis has still been largely neglected for the next 30 years. Renewed interest in this reaction was awakened by the observation that proline is able to

catalyze not only intramolecular but also intermolecular reactions with high selectivity and in high yield [11-12].

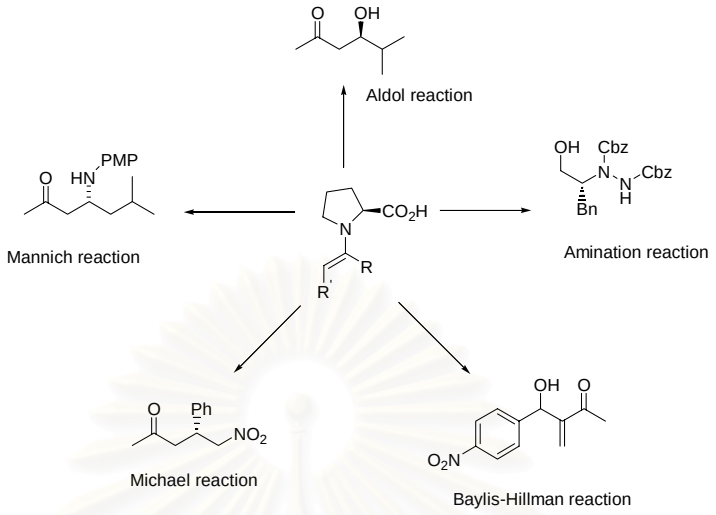


Figure 1-6. The proline-catalyzed asymmetric reaction

It should be noted that although proline and its derivatives such as (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) have been used for a long time in asymmetric synthesis [1], their uses had been limited to stoichiometric quantities. The catalytic potential of proline has been the subject of extensive studies in recent years after List and Barbas revealed report in pioneering studies on proline-catalyzed intermolecular aldol reactions. The reaction of *p*-nitrobenzaldehyde with acetone furnished the aldol product (3) in 76% *ee* [13]. The remarkable chemo- and enantioselectivies observed by List et al. triggered massive further research activities in the field of proline-catalyzed aldol, Mannich [14-15], Michael [16-17], α-amination [18] and many other related reactions [19] (Figure 1-6).

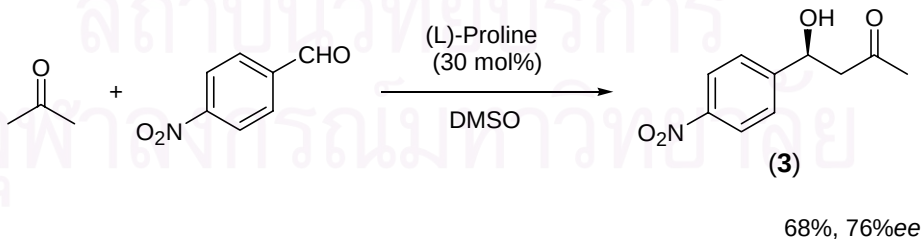
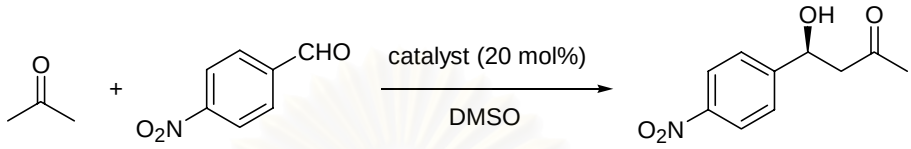


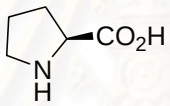
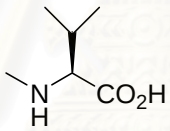
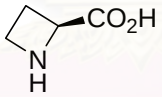
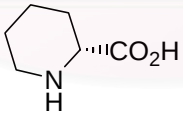
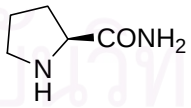
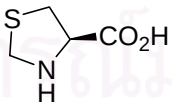
Figure 1-7. The first proline-catalyzed asymmetric intermolecular aldol reaction

Proline is bifunctional, with carboxylic acid and amine functionalities. These two functional groups can both act as acid or base and can also facilitate chemical transformations in concert. Pervious reports suggested that all basic structural features

of proline, e.g. the five-membered pyrrolidine ring, the free carboxyl and the secondary amine function proved essential for effective catalysis (Table 1-1) [20].

Table 1-1. Exploration of various amino acid and commercially available derivatives as catalysts of the direct asymmetric aldol reaction of acetone and 4-nitrobenzaldehyde



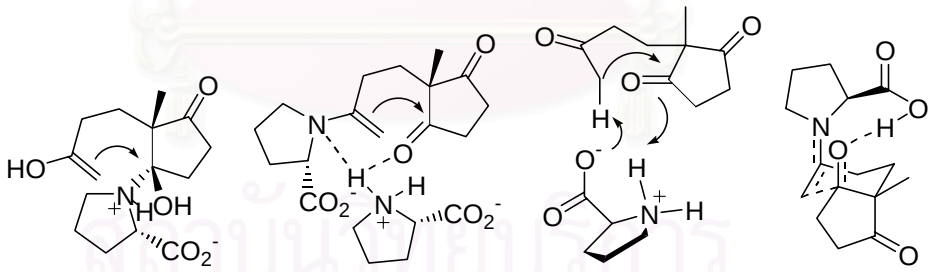
Entry	Catalyst	Yield (%)	*ee* (%)
1	(*L*)-His, (*L*)-Val, (*L*)-Tyr, (*L*)-Phe	<10	n.d.
2		68	76
3		<10	n.d.
4		55	40
5		<10	n.d.
6		<10	n.d.
7		67	73

Among several natural amino acids, L-proline (Table 1-1, entries 1 and 2) was the only effective catalyst for the model reaction. Also both *N*-methylvaline (Table 1-1, entries 3) bearing acyclic secondary amine functionality and L-prolinamide (Table 1-1, entries 6) were not effective catalysts. This result clearly demonstrated that the cyclic secondary amine structure as well as an acidic proton is essential for efficient

catalysis to occur. Further, comparison of 2-azetidinecarboxylic acid, pipecolic acid (Table 1-1, entries 4 and 5) and L-proline showed that the five-membered pyrrolidine ring is best suited as the secondary cyclic amine moiety. This is confirmed by the good catalytic activity of thiazolidine-2-carboxylic acid (entry 7).

1.3.2 Mechanism of the proline-catalyzed aldol reaction

The mechanisms of the proline-catalyzed aldol reaction have been the subject of intense investigation. For example, Hajos [8] suggested a mechanism that involves the activation of the carbonyl groups as a carbinol amine (**A**, Figure 1-8). Agami and colleagues [21] have led to the proposal of a side-chain enamine mechanism that involves two proline molecules in the C–C bond forming transition state, one engaged in enamine formation and the other as a proton transfer mediator (**B**, Figure 1-8). Swaminathan *et al.* [22] favored a heterogeneous aldolization mechanism on the surface of crystalline proline (**C**, Figure 1-8), despite the fact that many proline-catalyzed aldolizations are completely homogenous. On the basis of density functional theory calculations, Houk *et al.* [23] subsequently proposed a very similar mechanism for the intramolecular variant (**D**, Figure 1-8). The Houk model is now widely accepted as the most likely mechanism for the proline-catalyzed aldol reaction.



A Hajos Model **B** Agami Model **C** Swaminathan Model **D** Houk Model

Figure 1-8. Proline-catalyzed proposed mechanisms (transition states).

List and Houk have proposed that proline-catalyzed intermolecular aldol reactions follow an enamine mechanism, in which proline carboxylic group fulfils a number of crucial roles in the catalytic cycle (Figrure 1-9). It may facilitate each individual step of the mechanism, including the nucleophilic attack of the amino group (I) and the dehydration of the carbinol amine intermediate (II) following the

deprotonation of the iminium species generate enamine intermediate (III). In the transition state carbon—carbon bond formation was achieved by nucleophilic attack of the aldehyde with the intermediate enamine. In this bimolecular complex (IVa), the carboxylic acid proton forms hydrogen bonding between the reaction partners thereby brings them in a close proximity. As a result, the iminium-aldol intermediate is generated stereoselectively (*re*-facial attack). Subsequent hydrolysis of the intermediate then releases the aldol adduct and regenerates the catalyst.

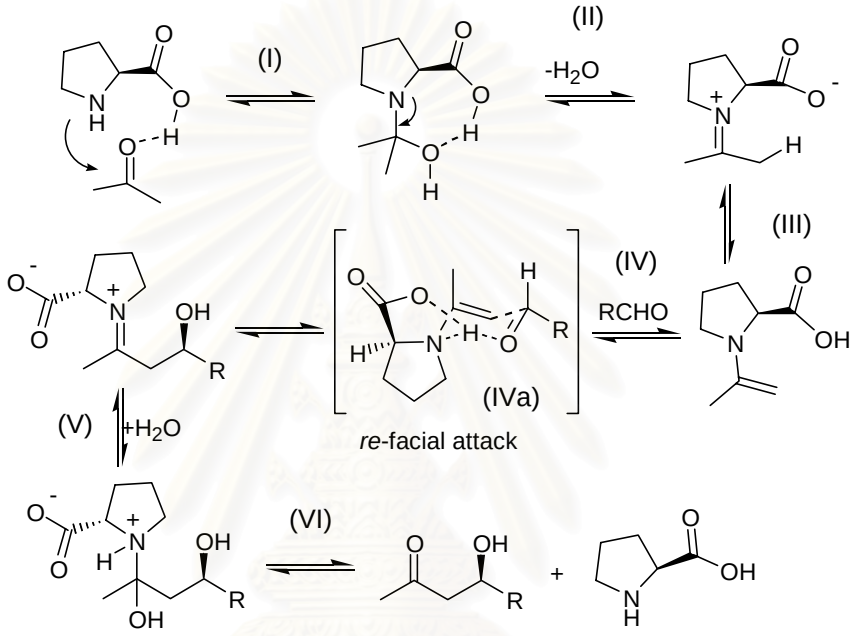


Figure 1-9. A proposed mechanism of the proline-catalyzed aldol reaction

1.4 Asymmetric Aldol reaction

The aldol reaction is an important carbon-carbon bond forming reaction in organic chemistry. It involves the addition of an enol or enolate anion to an aldehyde or ketone to form β-hydroxy carbonyl compounds (“aldols”). This structural unit is found in many naturally occurring molecules and pharmaceuticals. [24-25] Sometime, the aldol addition product loses a molecule of water during the reaction to from an α,β-unsaturated ketone (or aldehyde). This is called an aldol condensation. In the field of organic synthesis and natural product chemistry, the aldol reaction is one of the most efficient methods for extending the carbon framework of an organic synthon. Since the discovery of the Lewis acid-catalyzed asymmetric aldol reaction with enolsilanes by Mukaiyama, [26] numerous extensions of this type of reaction have been reported. [27-28]

The aldol reaction is used widely in the large scale production of commodity chemicals such as pentaerythritol [29] and in the pharmaceutical industry for the synthesis of optically pure drugs. For example, the heart disease drug atorvastatin (Lipitor) employed two aldol reactions, allowing access to multigram quantities of the drug.[30]

In the usual aldol addition, the carbonyl compound is deprotonated to form the enolate. The enolate is then added to another molecule of aldehyde or ketone to forms the aldol product as an alkoxide, which is then protonated on workup. In many cases, the enolate is first trapped as silyl enol ether. However, a direct aldol reaction between two carbonyl compounds without having to go through the enolate or enol ether preparation should be more desirable.

Recent methodologies allow a much wider variety of aldol reaction to be conducted, often with a catalytic amount of chiral ligand. Amongst the first catalytic aldol reactions were the tin triflate-catalyzed reactions reported by Kobayashi and co-workers. The tin complex of ligand (**4**) catalyses the addition of reactive silyl enol ethers, such as compound (**5**), to give very good enantioselectivity in some cases (Figure 1-10). [31]

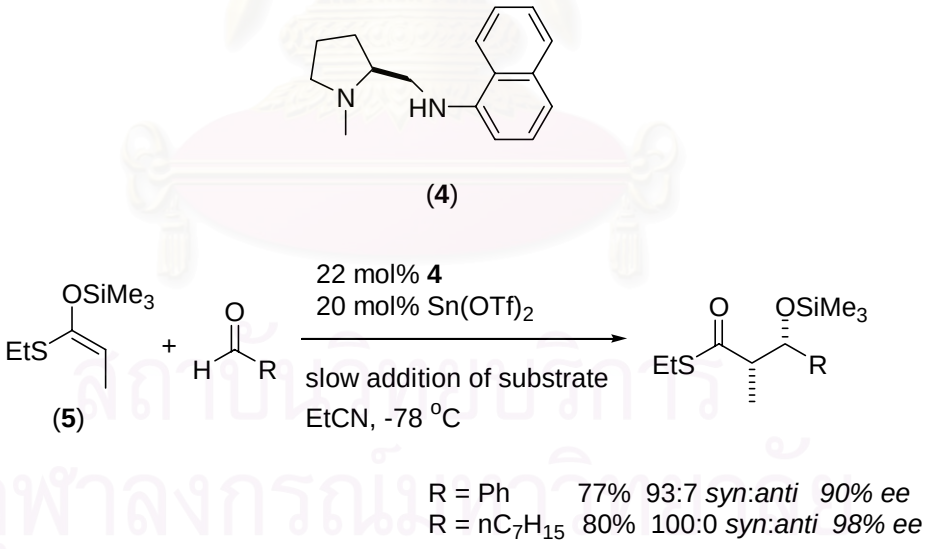
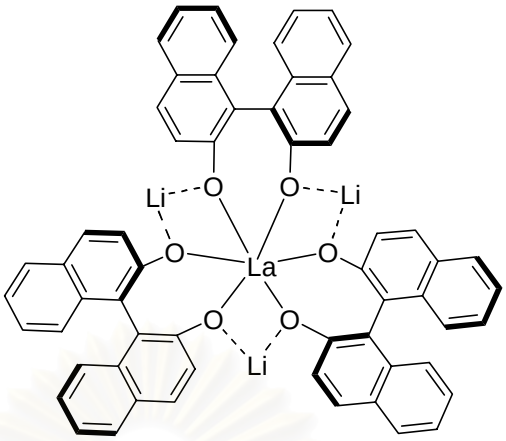


Figure 1-10. The first catalytic asymmetric aldol reaction

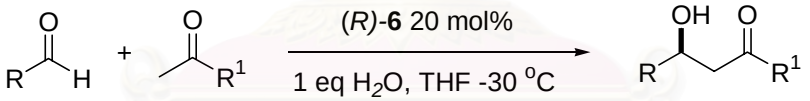
Shibasaki has reported aldol reactions between unmodified aldehydes and ketones using his famous heterobimetallic complexes. The reaction of aromatic or aliphatic aldehydes and methylketones gave β-hydroxyketones as the major product with high yield and enantioselectivities.



(**6**)

Figure 1-11. Heterobimetallic complexes developed by Shibasaki

The first example of a direct asymmetric aldol reaction catalyzed by heterobimetallic complexes has been reported by Shibasaki in 1997. [32] The reaction between aromatic or aliphatic aldehydes and methylketones gave β-hydroxyketones as the major products with high yields and enantioselectivities (Figure 1-12).

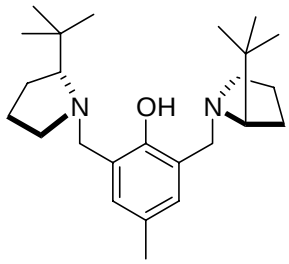


> 80%, up to 90% *ee*

R = *t*-Bu, *i*-Pr, c-Hex, $Ph(CH_2)_2$
R^1 = Ph, 1-naphthyl, Me, Et

Figure 1-12. The first asymmetric direct aldol reaction catalyzed by heterobimetallic complex (**6**)

In 2000, Trost has designed a zinc complex for the direct catalytic asymmetric aldol reaction with high enantioselectivities. Complex of chiral ligand (**7**) with diethylzinc (Et_2Zn) was used as the catalyst and the addition of molecular sieves increased the turnover frequency (Figure 1-13). [33]



(**7**)

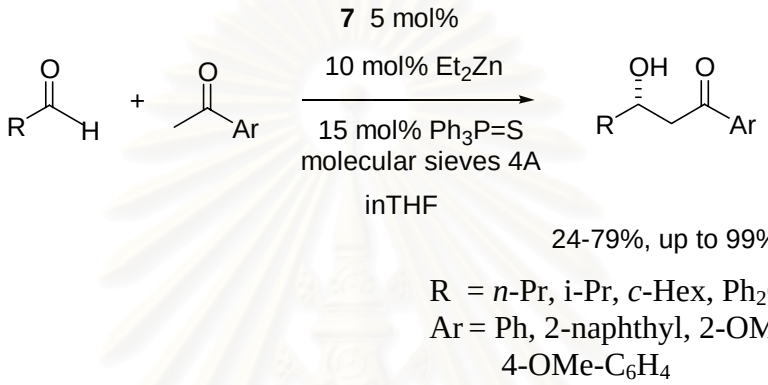


Figure 1-13. Asymmetric aldol reaction catalyzed by zinc complex catalyst

In a more recent example, biomimetic approach was used by Shair employing beta-thioketoacids as the nucleophile. [34] Interestingly, aromatic and branched aliphatic aldehydes are typically poor substrates (Figrure 1-14).

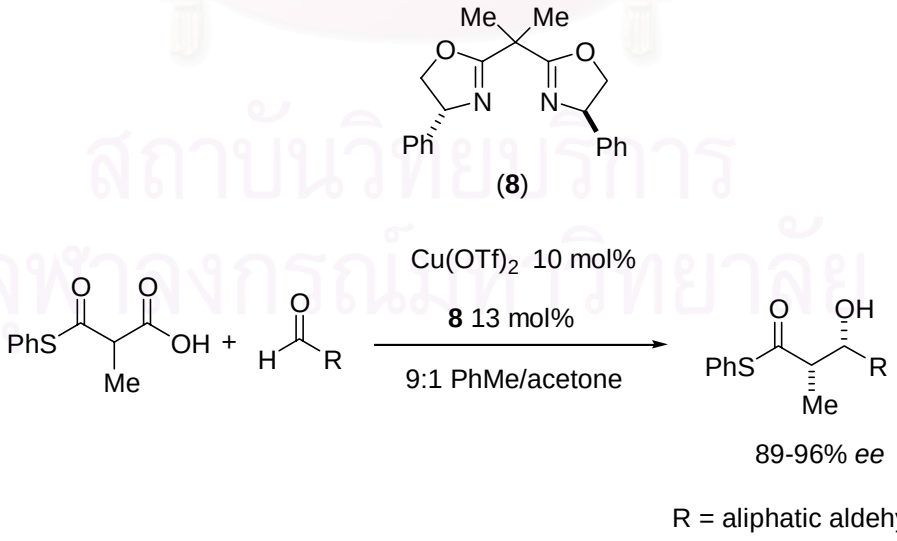


Figure 1-14. Asymmetric thioester aldol reaction catalyzed by bis(oxazoline) catalyst

In 2006, Hoveyda developed amino acid-base chiral ligands with transition metal [Ag(II)] to promote enantioselective Mukaiyama aldol addition to α-ketoesters. [35] The combination of AgF_2 and **9** can be used to catalyze enantioselective aldol reactions between enolsilanes and a variety of α-ketoesters in high yield and enantioselectivities up to 96% *ee* (Figrure 1-15).

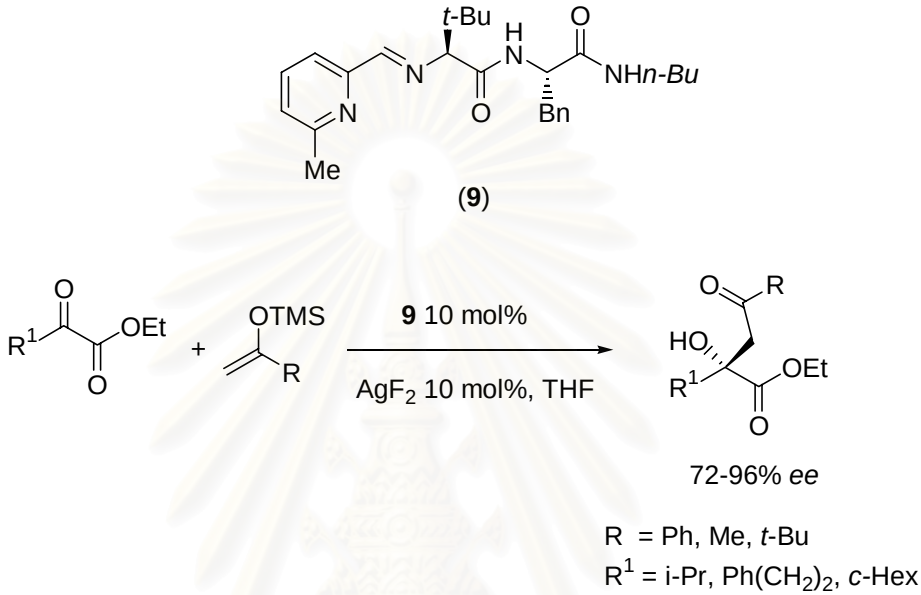


Figure 1-15. Asymmetric aldol reaction catalyzed by Ag-catalyst to α-ketoesters

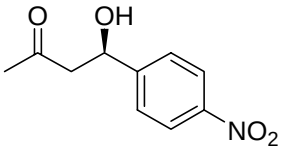
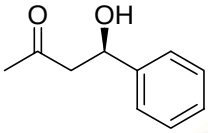
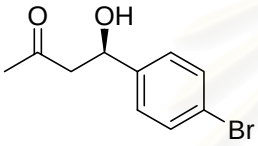
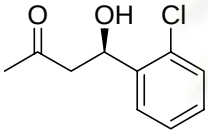
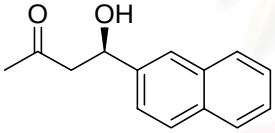
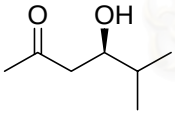
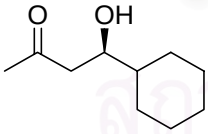
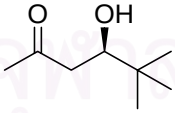
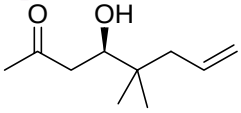
Aldol reaction under organocatalytic conditions have been the focus of extensive studies. Since the pioneering finding by List and Barbas III that L-proline could work as a catalyst in the intermolecular direct aldol reaction (Figure 1-6).

1.6 Review of asymmetric direct aldol reactions catalyzed by proline and analogues

1.6.1 proline-catalyzed asymmetric direct aldol reaction

In general, aldol reactions of acetone with aliphatic and aromatic aldehydes affords the aldol products with moderate enantioselectivities. α-Substituted aliphatic aldehydes gave significantly higher enantioselectivities of the aldol products (Table 1-2).

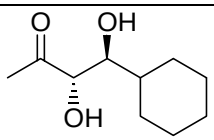
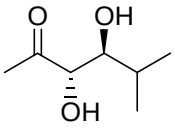
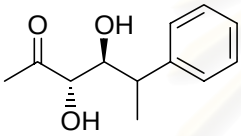
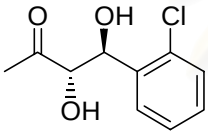
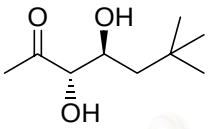
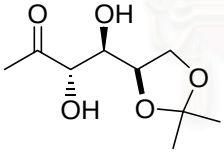
Table 1-2. Proline-catalyzed direct asymmetric aldol reactions using acetone as the donor with select aromatic and aliphatic aldehydes [20]

Product	Yield (%)	ee (%)
	68	76
	62	60
	74	65
	94	69
	54	77
	97	96
	63	84
	81	>99
	85	>99

Furthermore, the direct aldol reactions also worked with other ketones such as butanone, cyclopentanone and cyclohexanone. Unfortunately, some important ketones, including acetophenone and 3-pentanone failed in these reactions. Excellent

results were obtained with hydroxyacetone (Table 1-3). [36] In this case, *anti*-diols are formed in high regioselectivities, diastereoselectivities and enantioselectivities.

Table 1-3. The proline-catalyzed intermolecular aldol reaction using hydroxyacetone as the donor

Product	Yield (%)	dr	ee (%)
	60	>20:1	>99
	62	>20:1	>99
	51	>20:1	>95
	95	1.5:1	67
	38	1.7:1	>97
	40	2:1	>97

Recently, the proline-catalyzed intermolecular aldol reaction with acetone has been applied to the highly diastereoselective synthesis of complex sugar derivatives (Figure 1-16). [37]

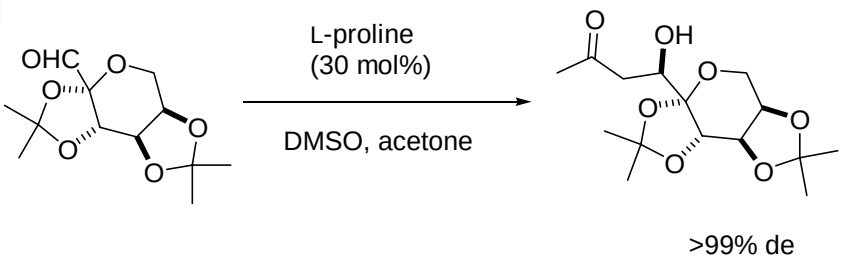


Figure 1-16. The proline-catalyzed intermolecular aldol reaction in the synthesis of complex sugars

1.6.2 proline derivative catalyzed asymmetric direct aldol reactions

Although impressive results were observed for α-branched aliphatic aldehydes, only moderate enantioselectivities were observed for the reactions of aromatic aldehydes with acetone catalyzed by L-proline. Thus far, substrate scope for the proline-catalyzed direct asymmetric aldol reactions between aldehydes and ketones are still relatively narrow. Several developments of proline derivatives were attempted in order to improve the catalytic efficiency and expand the substrate range.

In 2004, Yamamoto reported a proline-derived tetrazole catalyst for direct aldol reaction in the water. Catalyst **10** showed high activities and efficiency even at 5 mol% loading to provide aldol products in high enantioselectivities and diastereoselectivities (Figure 1-17). [38]

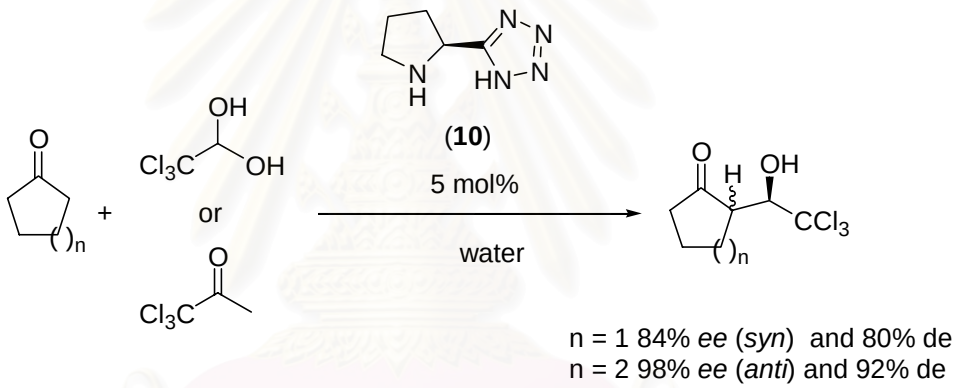


Figure 1-17. The proline-tetrazole catalyzed direct asymmetric aldol reaction

In 2004, Li and co-worker discovered that *N*-terminal dipeptides containing proline were efficient catalysts for direct aldol reactions between acetone and various aldehydes. The reaction proceeded efficiently at 0 °C, in the presence of *N*-methylmorpholine (NMM) and polyethylene glycol monomethyl ether 5000 (PGME 5000) in DMSO to give the aldol products in excellent yield (62-96%) and good enantioselectivity (up to >99 %*ee*) (Figure 1-18). [39]

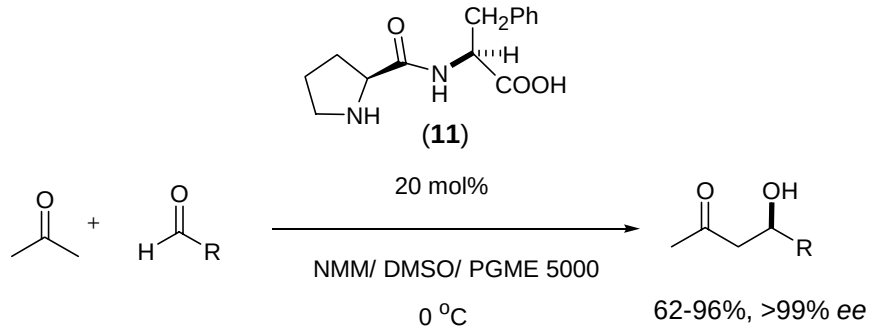


Figure 1-18. The dipeptide-catalyzed direct asymmetric aldol reaction

In 2004, Berkessel and co-worker introduced a new class of proline-derived acylsulfonamide catalysts. *N*-Sulfonylcarboxamides are known to be of similar acidity as carboxylic acids. The catalytic performance of *N*-arylsulfonylproline amide derivatives was evaluated in the direct aldol reaction between acetone to 4-nitrobenzaldehyde which resulted in high enantioselectivities (up to 98%*ee*) at low catalyst loadings (5-10 mol%) (Figure 1-19). [40]

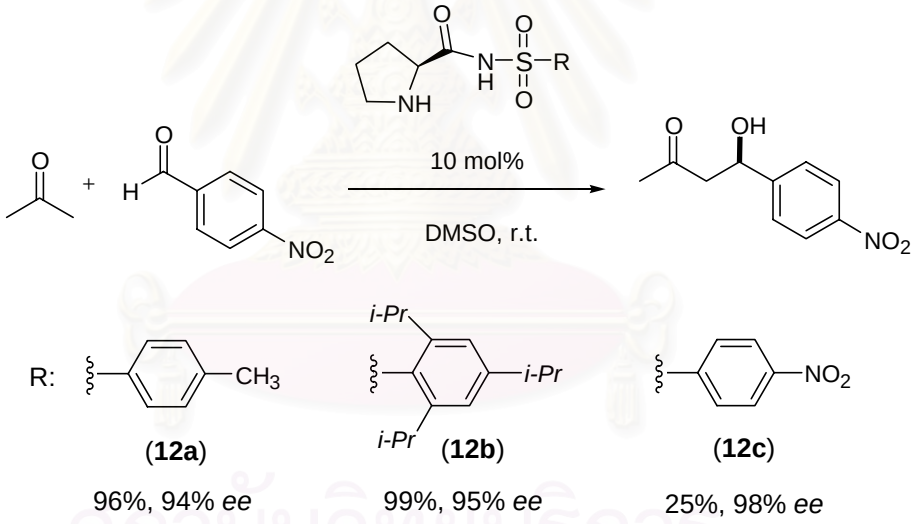


Figure 1-19. The direct aldol reaction catalyzed by *N*-arylsulfonylproline amide derivatives

In the same year, Vincent employed [41] new chiral benzoimidazole–pyrrolidine ligand (BIP) in the presence of a Brönsted acid (eg. AcOH, TFA) to catalyze aldol reactions. The aldol products were obtained in high yield and enantioselectivity when stronger acid additive (TFA) was used (Figure 1-20).

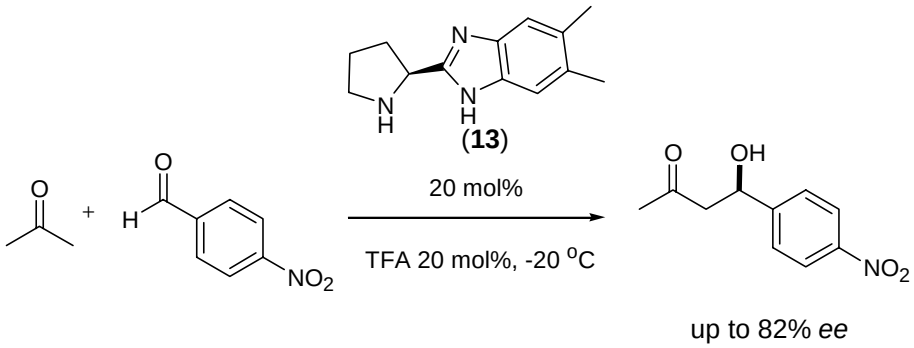


Figure 1-20. Benzoimidazole-pyrrolidine catalyzed for the direct aldol reaction

In 2004, Tanimori reported new C2- symmetric proline diamide catalysts and was obtained in asymmetric direct aldol reaction. The best result (up to 80% *ee*) with prolinamide **16** (Figure 1-21). [42]

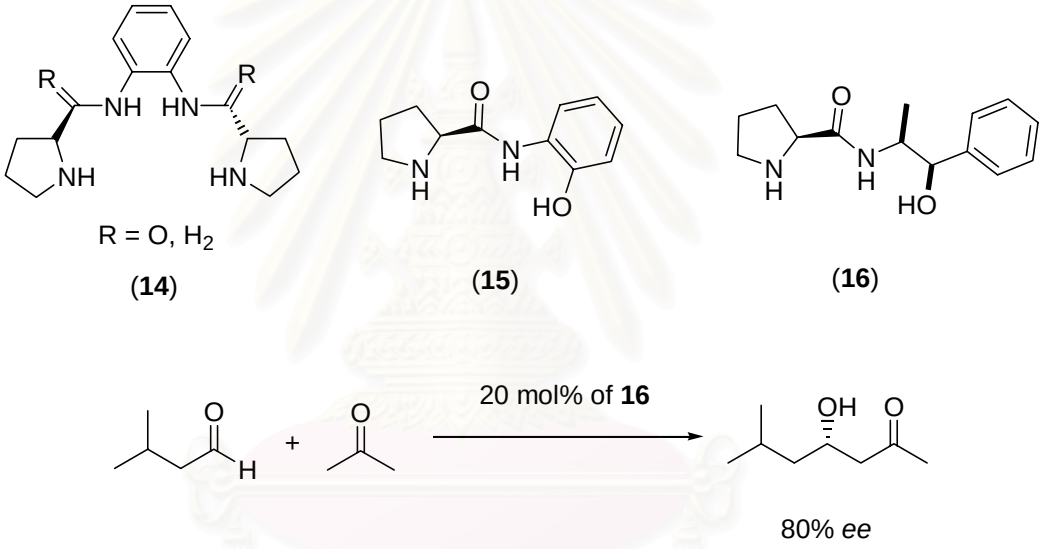


Figure 1-21. The C2- symmetric diamides and diamine and prolinamide catalyst for the direct aldol reaction

In 2004, Tang and co-worker developed L-prolinamide **17**, prepared from L-proline and simple aliphatic and aromatic amines, and L-prolinamide **18**, prepared from of L-proline and β-aminoalcohols as catalysts for asymmetric direct aldol reactions. L-Prolinamide **17** gave a moderate enantioselectivites of up to 46 % *ee* at room temperature for a model reaction between 4-nitrobenzaldehyde with neat acetone. L-prolinamide **18** exhibited higher enantioselectivities of up to 93% *ee* for aromatic aldehydes and up to > 99% *ee* for aliphatic aldehydes at -25 °C (Figure 1-22). [43-44]

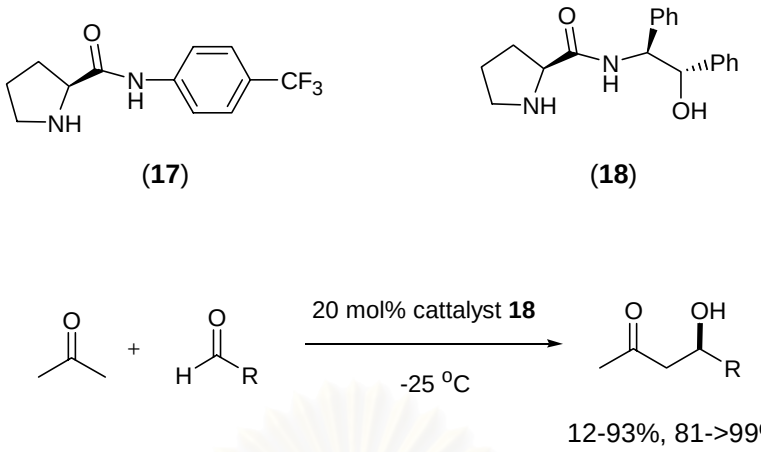


Figure 1-22. The prolinamide catalyst for a highly enantioselective direct aldol reaction

One year later Gong has successfully extended the range of organocatalyst for direct aldol reaction. The catalyst **19** at 2 mol% loading significantly catalyzes the aldol reactions of a wide range of aldehydes with acetone and butanone with very high enantioselectivities ranging from 96% to >99% *ee* (Figure 1-23). [45]

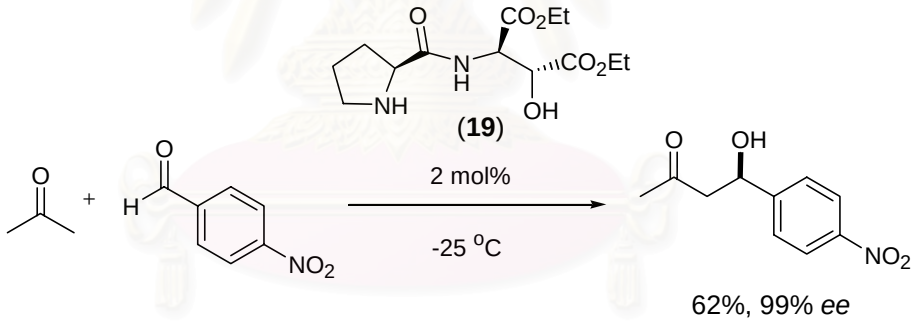


Figure 1-23. The highly efficient prolinamide-catalyzed for direct aldol reaction

In 2005, Xiao and co-worker presented a readily tunable and bifunctional L-prolinamide as another novel organocatalyst for direct asymmetric aldol reaction. Among the catalytic systems examined, **20** with 20 mol% of acetic acid (AcOH) exhibited good catalytic efficiency in the direct aldol reaction asymmetric aldol reactions between various aromatic aldehydes and cyclohexanone. The aldol products were obtained in high yields (up to 94%), enantioselectivities (up to 96% *ee*), and diasteroselectivities (up to 99:1) (Figure 1-24). [46]

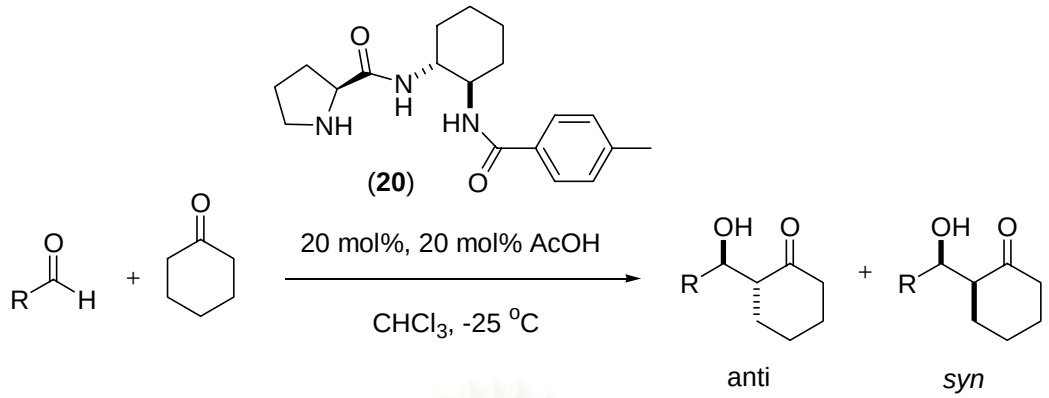


Figure 1-24. Bifunctional prolinamide derivatives for direct aldol reaction

A report by Barbas III and co-worker in 2005 emphasized the importance of acid additive once again in proline catalyzed asymmetric aldol reactions. The diamine **21**/TFA bifunctional catalyst system catalyze aldol reactions in water without addition of organic solvent with excellent reactivity (up to 99% yield), diastereoselectivity (up to 91:1) and enantioselectivity (up to 99%*ee*) (Figure 1-25). [47]

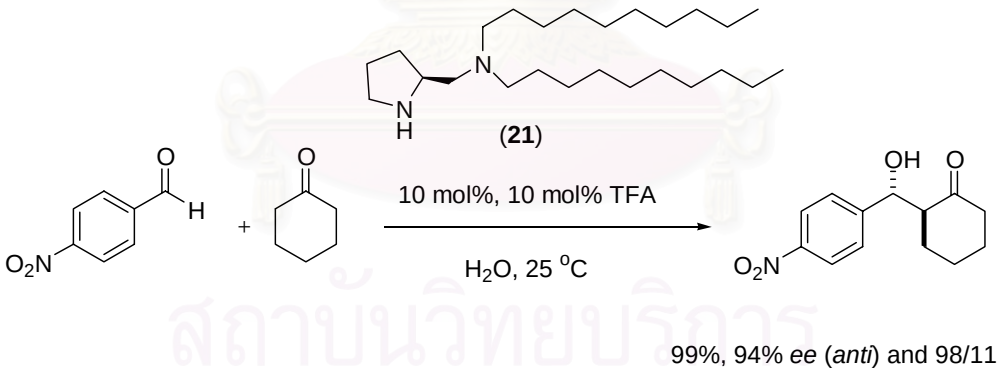


Figure 1-25. Diamine-catalyzed for direct aldol reactions in water

Next, Gong has designed a combination of pyrrolidine-2-carboxamide and aminopyrodine in a single catalyst. The asymmetric direct aldol reaction of ketones with aryl and alkyl α-keto acids, affording *α*-hydroxyl carboxylic acids with a tertiary stereogenic center with excellent enantioselectivities up to 98% *ee* (Figure 1-26). [48]

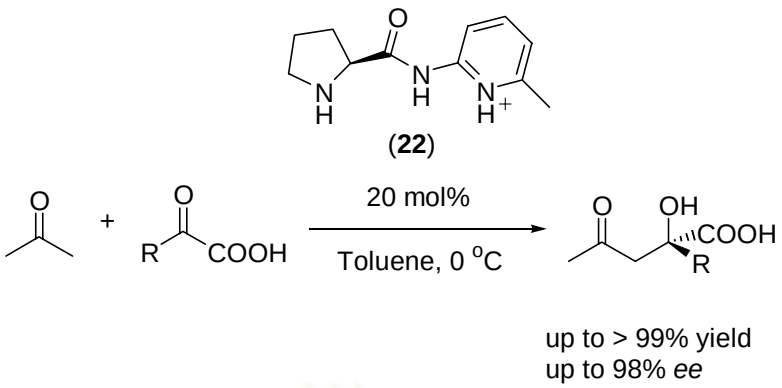


Figure 1-26. The asymmetric aldol reactions to α-ketoacid

Recently, Singh and co-worker reported another highly enantioselective direct aldol reaction catalyzed by L-prolinamides with *gem*-diphenyl groups. The reactions were efficient at 5-10 mol% catalyst loading, and excellent enantioselectivity (97-99 %*ee*) were obtained for both aromatic and aliphatic aldehydes. The presence of the gem-diphenyl group at the β-carbon is necessary for high enantioselectivity (Figure 1-27). [49]

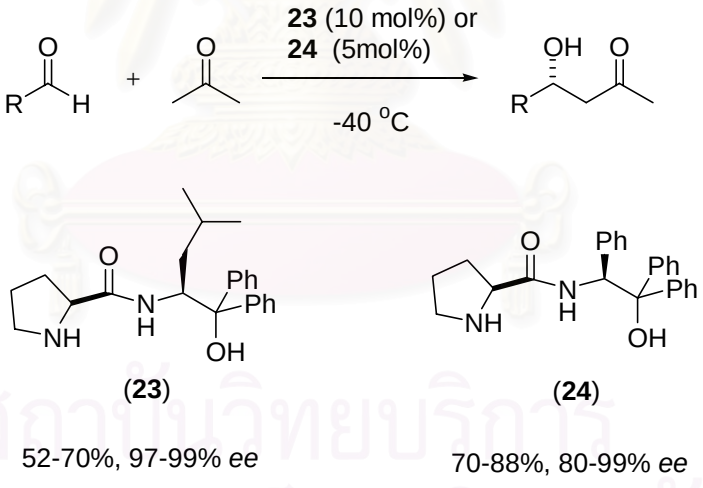


Figure 1-27. The prolinamide-catalyzed for direct aldol reaction

In 2006, Wang and co-worker have developed a very efficient *N*-prolylsulfonamide based dendritic proline catalyst for the asymmetric direct aldol reaction in water. Aldol reactions catalyzed by the dendritic catalyst gave the products in high isolated yields (up to 99%) with excellent *anti* diastereoselectivities (up to

>99:1) and enantioselectivities (up to >99%*ee*). Furthermore, these dendritic catalysts may be recovered and reused without loss of reactivities (Figure 1-28). [50]

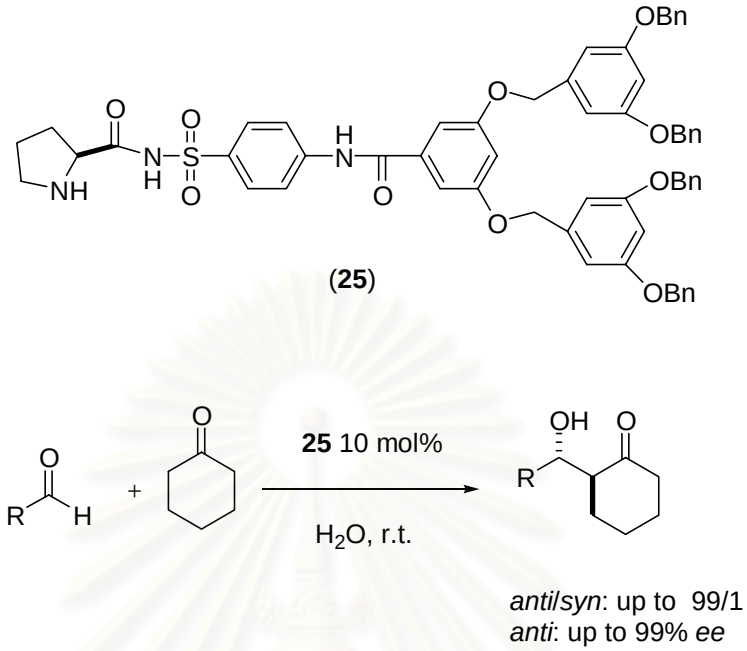


Figure 1-28. The highly efficient the catalyst asymmetric direct aldol reaction in water

Recently, 4-hydroxyproline anchored to a polystyrene resin has been applied to the direct aldol reaction in water by Pericas. The result showed that the immobilized catalyst in the presence of catalytic amounts of DiMePEG catalyzed the reactions with high *anti*-diastereoselectivities (up to >98:2) and enantioselectivities (up to >97%*ee*). It should be noted that in this particular case, the immobilized proline gave better enantioselectivity than free proline (Figure 1-29). [51]

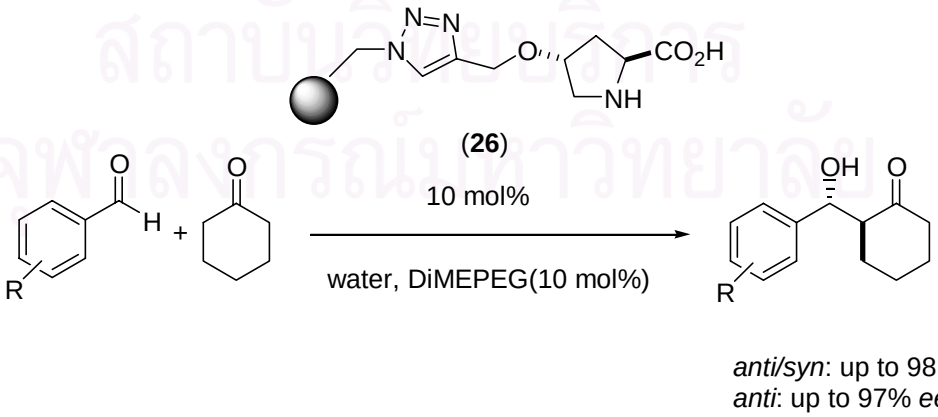


Figure 1-29. The polystyrene-supported hydroxyproline catalyst asymmetric direct aldol reaction in water

CHAPTER II

EXPERIMENTAL SECTION

2.1 Measurement

The weight of all substances chemical was determined on a Metler Toledo electrical balance. Evaporation of solvents was carried out on Büchi Rotavapor R-200 with a water aspirator model B-490 or a Refco Vacubrand pump. The magnetic stirrers were of Nuova II. The progress of the reaction was followed by thin layer chromatography (TLC) performed on Merck D.C. silica gel 60 F_{254} 0.2 mm. precoated aluminium plates cat. no. 1.05554 and visualized by using short wavelength UV light (254 nm), $KMnO_4$ solution or ninhydrin solution. Column chromatography was performed on silica gel 230-400 mesh for flash column chromatography.

Chiral high performance liquid chromatography (HPLC) experiments were performed on Water 600^{TM} equipped with UV/Vis detector in normal phase mode using hexanes:^{i}PrOH as eluent. A Daicel Chiralpak AD column and a Chiralcel OJ column were used for the separation enantiomers. The optical rotations were measured at the ambient temperature with a Jasco P-1010 Polarimeter. Elemental analysis results were analyzed on CHNS/O Analyzer (Perkin Elmer PE2400 Series II) at Scientific and Technological Research Equipment Centre, Chulalongkorn University.

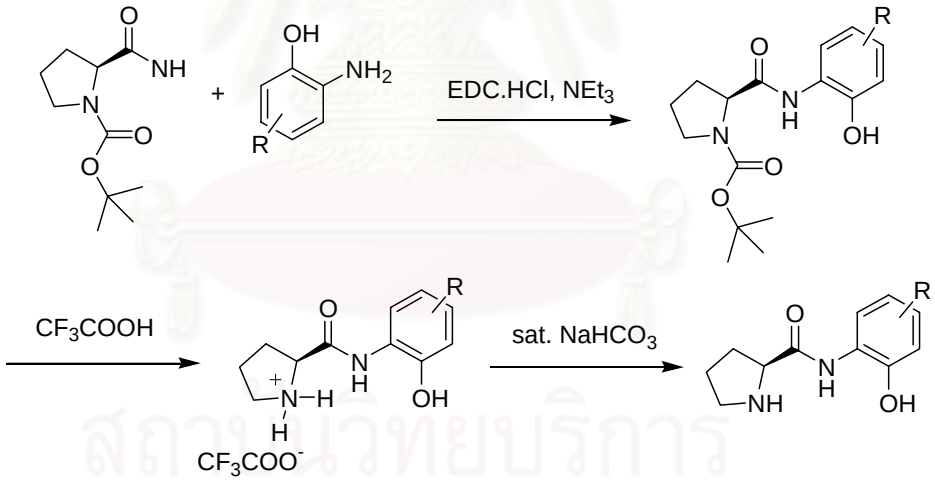
Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-400 plus operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or using the residual protonated solvent signal as a reference. Coupling constant (*J*) are proton-proton coupling unless otherwise noted and reported in hertz (Hz). Multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

2.2 Materials

All chemicals were purchased from Fluka, Merck or Aldrich Chemical Co., Ltd., and were used as received without further purification. Commercial grade solvents were distilled before use for column chromatography. Chloroform for the reactions was distilled under an atmosphere of dry nitrogen with calcium hydride (CaH_2) and dried over activated 3Å molecular sieves. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl radical prior to use. HPLC grade hexanes and 2-propanol for HPLC experiments on a chiral column were obtained from Merck and filtered through a membrane filter before use. Other solvents for the reactions were AR grade and used without furher purification. High purity nitrogen and hydrogen gas for the experiments were purchased from TIG.

2.3 General procedure for the synthesis of organocatalysts

2.3.1 Synthesis L-prolinamides from 2-aminophenols

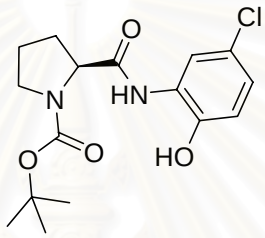


Step 1 2-aminophenol (1.5 mmol) and *N*-Boc-L-proline (1.5 mmol) was dissolved in 10 mL dichloromethane. After the solution was stirred for 5 min, EDC.HCl (1.6 mmol) was added and the reaction mixture was stirred overnight. The resulting solution was washed with water and the solvent removed under reduced pressure. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent.

Step 2 *N*-Boc-L-prolinamide derivatives (0.7 mmol) prepared from step 2 was dissolved in a mixture of trifluoroacetic acid/dichloromethane (1:1) 2 mL. After standing for 2 hours without stirring at room temperature, the organic solvent was removed by evaporation to afford the crude products as trifluoroacetate salt.

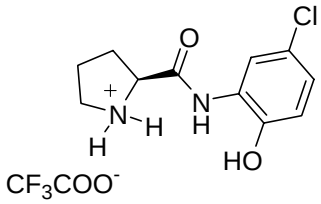
Conversion to the free amine: the trifluoroacetate salt was treated with saturated aqueous solution, $NaHCO_3$ then extracted with ethyl acetate. The organic solvent was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

2.3.1.1 2-(5´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(27)**



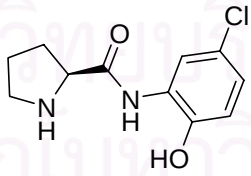
2-(5´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 1 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 2-amino-4-chlorophenol (0.2154 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a brown solid (0.4550 g, 89%); $[\alpha]^{25}_D$ = -104.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, C$\underline{H}_3$ Boc), 1.92-2.28 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.41 and 3.53 (brs, 2H, C$\underline{H}_2$N), 4.35 and 4.80 (brs, 1H, C$\underline{H}$N), 6.81 (brs, 1H, C$\underline{H}$ Ar), 6.92 (brs, 1H, C$\underline{H}$ Ar), 7.37 (brs, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 and 24.5 (rotamer) (C$\underline{H}_2$(4)), 28.3 (C$\underline{H}_3$ Boc), 28.9 and 31.2 (rotamer) (C$\underline{H}_2$(3)), 47.3 (C$\underline{H}_2$N), 60.4 and 61.9 (rotamer) (C$\underline{H}$N), 81.5 (C$\underline{(CH_3)}_3$ Boc), 116.9 and 118.5 (rotamer) (C$\underline{H}$ Ar), 120.2 and 121.5 (rotamer) (C$\underline{H}$ Ar), 124.7 (C$\underline{}$ Ar), 124.9 and 125.6 (rotamer) (C$\underline{H}$ Ar), 126.5 (C$\underline{}$ Ar), 145.5 and 146.3 (rotamer) (C$\underline{}$ Ar), 155.1 and 156.1 (rotamer) (C$\underline{O}$ Boc), 171.7 (C$\underline{O}$ amide).

2.3.1.2 Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28a·TFA)**



Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 2 using 2-(5´-chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.3408 mg, 1 mmol) and TFA (1 mL). The product was obtained as a brown solid (0.3192 g, 90%); m.p. 155.7-158.9 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -28.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.35 (m, 1H, CH$_a$$\underline{H}_b$(3)), 3.26 (m, 2H, C$\underline{H}_2$N), 4.52 (m, 1H, C$\underline{H}$N), 6.91 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.01 (dd, *J* = 8.8, 2.0 Hz, 1H, C$\underline{H}$ Ar), 7.93 (d, *J* = 2.0 Hz, 1H, C$\underline{H}$ Ar), 9.97 and 10.57 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 (C$\underline{H}_2$(4)), 30.4 (C$\underline{H}_2$(3)), 46.4 (C$\underline{H}_2$N), 60.0 (C$\underline{H}$N), 117.6 (q, $^{1}J_{C\text{-}F}$ = 298.4 Hz, C$\underline{F}_3$ TFA), 116.9 (C$\underline{H}$ Ar), 122.1 (C$\underline{H}$ Ar), 122.4 (C$\underline{}$ Ar), 125.0 (C$\underline{H}$ Ar), 126.9 (C$\underline{}$ Ar), 147.5 (C$\underline{}$ Ar), 158.8 (q, $^{2}J_{C\text{-}F}$ = 30.9 Hz, C$\underline{O}$ TFA), 168.0 (C$\underline{O}$ amide); Anal. Calcd for $C_{13}H_{14}ClF_3N_2O_4$: C, 44.02; H, 3.98; N, 7.90. Found: C, 44.05; H, 3.92; N, 7.93 %.

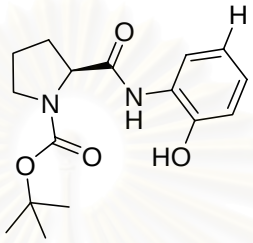
2.3.1.3 Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide **(28a)**



Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide was converted to free amine using pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate (0.1774 mg, 0.5 mmol). The product was obtained as a white solid (0.1083 g, 95%); m.p. 158.5-160.1 ^{o}C; $[\alpha]^{25}_{D}$ = -56.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62 (5, *J* = 6.8 Hz, 2H, C$\underline{H}_2$(4)), 1.78 (6, *J* = 6.4 Hz, 1H, C$\underline{H}_a$H$_b$(3)), 2.04 (m, 1H, CH$_a$$\underline{H}_b$(3)), 2.77 (m, 1H, C$\underline{H}_aH_b$N), 2.96 (m, 1H,

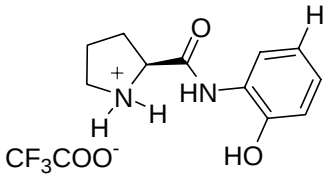
$CH_a\underline{H}_bN$), 3.76 (m, 1H, C<u>H</u>N), 6.85(d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1H, C<u>H</u> Ar), 8.25 (d, *J* = 2.4 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.4 (<u>C</u>H_2(4)), 30.7 (<u>C</u>H_2(3)), 47.1 (<u>C</u>H_2N), 61.2 (<u>C</u>HN), 116.1 (<u>C</u>H Ar), 118.5 (<u>C</u>H Ar), 122.8 (<u>C</u> Ar), 123.2 (<u>C</u>H Ar), 128.0 (<u>C</u> Ar), 145.6 (<u>C</u> Ar), 173.7 (<u>C</u>O amide).

2.3.1.4 2-(2´-Hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(29)**



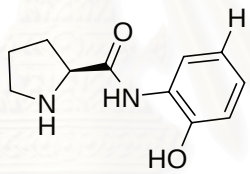
2-(2´-Hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 1 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 2-aminophenol (0.1637 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.3355 g, 73%); $[\alpha]^{25}_D$ = -151.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H, C<u>H</u>$_3$ Boc), 1.94-2.43 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.48 (brs, 2H, C<u>H</u>$_2$N), 4.54 (brs, 1H, C<u>H</u>N), 6.82 (brs, 1H, C<u>H</u> Ar), 6.97-7.08 (brs, 2H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 and 24.5 (rotamer) (<u>C</u>H_2(4)), 28.3 (<u>C</u>H_3 Boc), 31.3 (<u>C</u>H_2(3)), 47.2 (<u>C</u>H_2N), 60.2 and 61.7 (rotamer) (<u>C</u>HN), 81.3 (<u>C</u>$(CH_3)_3$ Boc), 117.5 and 118.7 (rotamer) (<u>C</u>H Ar), 120.2 (rotamer) (<u>C</u>H Ar), 121.1 and 122.3 (rotamer) (<u>C</u>H Ar), 125.6 (<u>C</u> Ar), 126.1 and 126.6 (rotamer) (<u>C</u> Ar), 147.7 and 148.2 (rotamer) (<u>C</u>H Ar), 155.0 and 156.3 (rotamer) (<u>C</u>O Boc), 172.0 (<u>C</u>O amide).

2.3.1.5 Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide trifluoroacetate **(28b·TFA)**



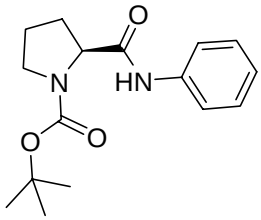
Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 2 using 2-(2´-Hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2145 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a white solid (0.1749 g, 78%); m.p. 150.1-151.9 ^{o}C (dec); $[\alpha]^{27}_{D}$ = -33.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.39 (m, 1H, CH$_a\underline{H}_b$(3)), 3.26 (m, 2H, C$\underline{H}_2$N), 4.52 (m, 1H, C$\underline{H}$N), 6.79 (m, 1H, C$\underline{H}$ Ar), 6.91 (m, 1H, C$\underline{H}$ Ar), 6.95 (m, 1H, C$\underline{H}$ Ar), 7.78 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 9.82 and 10.06 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.1 ($\underline{C}$H$_2$(4)), 30.5 ($\underline{C}$H$_2$(3)), 46.2 ($\underline{C}$H$_2$N), 60.0 ($\underline{C}$HN), 117.6 (q, $^{1}J_{C\text{-}F}$ = 297.4 Hz, $\underline{C}$F$_3$ TFA), 116.0 ($\underline{C}$H Ar), 119.1 ($\underline{C}$H Ar), 123.2 ($\underline{C}$H Ar), 125.5 ($\underline{C}$H Ar), 125.8 ($\underline{C}$ Ar), 148.9 ($\underline{C}$ Ar), 158.8 (q, $^{2}J_{C\text{-}F}$ = 31.2 Hz, $\underline{C}$O TFA), 167.6 ($\underline{C}$O amide); Anal. Calcd for $C_{13}H_{14}ClF_3N_2O_4$: C, 44.02; H, 3.98; N, 7.90. Found: C, 44.05; H, 3.92; N, 7.93 %.

2.3.1.6 Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide **(28b)**



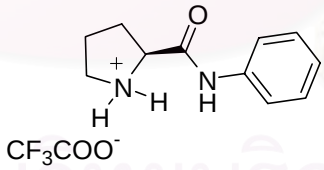
Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide was converted to free amine using pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide trifluoroacetate (0.1601 g, 0.5 mmol). The product was obtained as a white solid (0.1000 g, 97%); m.p. 163.4-164.9 ^{o}C; $[\alpha]^{25}_{D}$ = -44.5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.61 (m, 2H, C$\underline{H}_2$(4)), 1.78 (m, 1H, C$\underline{H}_a$H$_b$(3)), 2.02 (m, 1H, CH$_a\underline{H}_b$(3)), 2.75 (m, 1H, C$\underline{H}_2$N), 2.94 (m, 1H, C$\underline{H}_2$N), 3.70 (m, 1H, C$\underline{H}$N), 6.74 (m, 1H, C$\underline{H}$ Ar), 6.84 (brs, 2H, 2 x C$\underline{H}$ Ar), 8.16 (d, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 10.09 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5 ($\underline{C}$H$_2$(4)), 30.8 ($\underline{C}$H$_2$(3)), 47.1 ($\underline{C}$H$_2$N), 61.3 ($\underline{C}$HN), 115.1 ($\underline{C}$H Ar), 119.2 ($\underline{C}$H Ar), 119.5 ($\underline{C}$H Ar), 123.8 ($\underline{C}$H Ar), 126.9 ($\underline{C}$ Ar), 146.6 ($\underline{C}$ Ar), 173.4 ($\underline{C}$O amide).

2.3.1.7 2-Phenylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(30)**



2-Phenylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 1 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), aniline (0.1397 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.4138 g, 95%); $[\alpha]^{27}_{D}$ = -137.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, C<u>H</u>$_3$ Boc), 1.88-2.43 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.36 and 3.45 (brs, 2H, C<u>H</u>$_2$N), 4.48 (brs, 1H, C<u>H</u>N), 7.02 (brs, 1H, C<u>H</u> Ar), 7.24 (brs, 2H, C<u>H</u> Ar), 7.48 (d, *J* = 8 Hz, 2H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (<u>C</u>H$_2$(4)), 27.7 (<u>C</u>H$_2$(3)), 28.5 (<u>C</u>H$_3$ Boc), 47.2 (<u>C</u>H$_2$N), 60.5 and 62.0 (rotamer) (<u>C</u>HN), 80.7 (<u>C</u>(CH$_3$)$_3$ Boc), 119.6 (2 x <u>C</u>H Ar), 123.7 (<u>C</u>H Ar), 128.8 (2 x <u>C</u>H Ar), 138.4 (<u>C</u> Ar), 156.3 (<u>C</u>O Boc), 170.2 (<u>C</u>O amide).

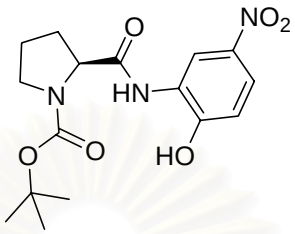
2.3.1.8 Pyrrolidine-2-carboxylic acid phenylamide trifluoroacetate **(31)**



Pyrrolidine-2-carboxylic acid phenylamide trifluoroacetate was prepared according to step 2 using 2-Phenylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2033 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a colorless oil (0.2087 g, 98%); $[\alpha]^{25}_{D}$ = -26.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 1.90 (m, 2H, C<u>H</u>$_2$(4)), 2.04 (m, 1H, C<u>H</u>$_a$H$_b$(3)), 2.42 (m, 1H, CH$_a$<u>H</u>$_b$(3)), 3.30 (brs, 2H, C<u>H</u>$_2$N), 4.75 (brs, 1H, C<u>H</u>N), 7.07 (t, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 7.22 (t, *J* = 8.0 Hz, 2H, C<u>H</u> Ar), 7.46 (d, *J* = 8.0 Hz, 2H, C<u>H</u> Ar), 10.33 (s, 1H, CON<u>H</u>); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 24.3 (<u>C</u>H$_2$(4)), 30.1 (<u>C</u>H$_2$(3)), 46.5 (<u>C</u>H$_2$N), 60.2 (<u>C</u>HN), 116.5 (q,

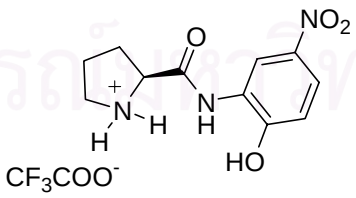
$^{1}J_{C\text{-}F}$ = 291.0 Hz, CF_3 TFA), 120.4 (2 x CH Ar), 125.0 (CH Ar), 125.9 (2 x CH Ar), 137.2 (C Ar), 162.5 (q, $^{2}J_{C\text{-}F}$ = 36.3 Hz, CO TFA), 167.0 (CO amide).

2.3.1.9 2-(2´-Hydroxy-5´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(32)**



2-(2´-Hydroxy-5´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 1 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 2-amino-4-nitrophenol (0.2312 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a yellow solid (0.4164 g, 79%); $[\alpha]^{27}_{D}$ = -97.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (brs, 9H, CH_3 Boc), 1.97-2.25 (brs, 4H, CH_2(3) and CH_2(4)), 3.46 and 3.58 (brs, 2H, CH_2N), 4.48 (brs, 1H, CHN), 6.84 (brs, 1H, CH Ar), 7.80 (brs, 1H, CH Ar), 8.44 (brs, 1H, CH Ar), 9.17 and 10.23 (NH and OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4 (CH_2(4)), 28.4 (CH_3 Boc), 29.4 and 31.1 (rotamer) (CH_2(3)), 47.4 (CH_2N), 60.6 and 62.0 (rotamer) (CHN), 81.8 (C$(CH_3)_3$ Boc), 116.4 (CH Ar), 117.0 (CH Ar), 121.4 (CH Ar), 125.8 (C Ar), 140.4 (C Ar), 153.0 (C Ar), 156.1 (CO Boc), 172.0 (CO amide).

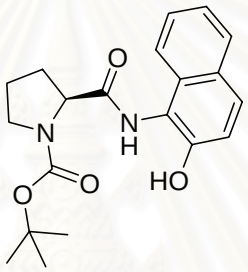
2.3.1.10 Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-nitro-phenyl)-amide trifluoroacetate **(28g)**



Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-nitro-phenyl)-amide trifluoroacetate was prepared according to step 2 using 2-(2´-Hydroxy-5´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2460 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a yellow solid (0.2148 g, 84%); m.p.

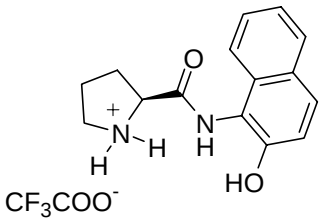
205.8-208.2 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -25.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (m, 3H, C$\underline{H}_a\underline{H}_b$(3) and C$\underline{H}_2$(4)), 2.36 (m, 1H, CH$_a\underline{H}_b$(3)), 3.27 (m, 2H, C$\underline{H}_2$N), 4.56 (m, 1H, C$\underline{H}$N), 7.07 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.95 (dd, *J* = 8.8, 2.4 Hz, 1H, C$\underline{H}$ Ar), 8.91 (d, *J* = 2.4 Hz, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 (C$\underline{H}_2$(4)), 30.4 (C$\underline{H}_2$(3)), 46.4 (C$\underline{H}_2$N), 60.0 (C$\underline{H}$N), 115.4 (C$\underline{H}$ Ar), 117.5 (q, $^{1}J_{C\text{-}F}$ = 297.3 Hz, C$\underline{F}_3$ TFA), 117.7 (C$\underline{H}$ Ar), 122.0 (C$\underline{H}$ Ar), 126.1 (C$\underline{}$ Ar), 139.3 (C$\underline{}$ Ar), 155.1 (C$\underline{}$ Ar), 158.9 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz, C$\underline{}$O TFA), 168.4 (C$\underline{}$O amide); Anal. Calcd for $C_{13}H_{14}F_3N_3O_6$: C, 42.75; H, 3.86; N, 11.50. Found: C, 42.77; H, 3.89; N, 11.55 %.

2.3.1.11 2-(2´-Hydroxy-naphthalen-1´-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(33)**



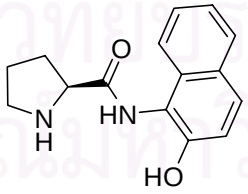
2-(2´-Hydroxy-naphthalen-1´-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 1 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 1-amino-2-naphthol hydrochloride (mg, mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a brown solid (0.4277 g, 80%); $[\alpha]^{25}_{D}$ = -130.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H, C$\underline{H}_3$ Boc), 2.00-2.55 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.46 (brs, 2H, C$\underline{H}_2$N), 4.70 (brs, 1H, C$\underline{H}$N), 7.25 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.35 (t, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 7.45 (t, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar); 7.68 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.77 (d, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 7.87 (brs, 1H, C$\underline{H}$ Ar), 9.62 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (C$\underline{H}_2$(4)), 28.0 (C$\underline{H}_2$(3)), 28.4 (C$\underline{H}_3$ Boc), 47.4 (C$\underline{H}_2$N), 60.3 (C$\underline{H}$N), 81.5 (C$\underline{}$(CH$_3$)$_3$ Boc), 117.1 (C$\underline{H}$ Ar), 120.3 (C$\underline{H}$ Ar), 121.2 (C$\underline{H}$ Ar), 123.7 (C$\underline{H}$ Ar), 126.8 (C$\underline{H}$ Ar), 128.3 (C$\underline{H}$ Ar), 128.5 (C$\underline{H}$ Ar), 128.7 (C$\underline{H}$ Ar), 129.0 (C$\underline{H}$ Ar), 148.1 (C$\underline{H}$ Ar), 156.7 (C$\underline{}$O Boc), 172.4 (C$\underline{}$O amide).

2.3.1.12 Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide trifluoroacetate **(28e·TFA)**



Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide trifluoroacetate was prepared according to step 2 using 2-(2´-Hydroxy-naphthalen-1´-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2495 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a brown oil (0.2592 g, 100%); $[\alpha]^{25}_{D}$ = -84.0 (*c* 0.2, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (m, 2H, C$\underline{H}_2$(4)), 2.17 (m, 1H, CH$_a\underline{H}_b$(3)), 2.53 (m, 1H, C$\underline{H}_a$H$_b$(3)), 3.28 (m, 2H, C$\underline{H}_2$N), 4.54 (m, 1H, C$\underline{H}$N), 7.23 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.30 (t, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 7.44 (t, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar); 7.65 (d, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 7.75 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.80 (d, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 8.65, 9.66 and 10.03 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.1 (C$\underline{H}_2$(4)), 30.3 (C$\underline{H}_2$(3)), 46.2 (C$\underline{H}_2$N), 60.0 (C$\underline{H}$N), 116.6 (q, $^{1}J_{C\text{-}F}$ = 298.0 Hz, C$\underline{F}_3$ TFA), 115.3 (C$\underline{}$ Ar), 119.0 (C$\underline{H}$ Ar), 122.0 (C$\underline{H}$ Ar), 123.4 (C$\underline{H}$ Ar), 126.9 (C$\underline{H}$ Ar), 128.3 (C$\underline{H}$ Ar), 128.4 (C$\underline{}$ Ar), 128.9 (C$\underline{H}$ Ar), 131.9 (C$\underline{}$ Ar), 151.2 (C$\underline{}$ Ar), 159.0 (q, $^{2}J_{C\text{-}F}$ = 35.5 Hz, C$\underline{O}$ TFA), 168.5 (C$\underline{O}$ amide).

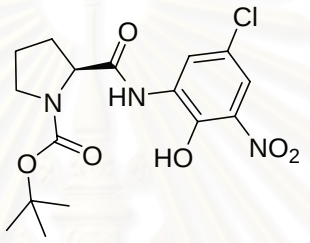
2.3.1.13 Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide **(28e)**



Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide was converted to free amine using pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide trifluoroacetate (0.1852 g, 0.5 mmol). The product was obtained as a brown solid (0.1256 g, 98 %); $[\alpha]^{25}_{D}$ = -21.6 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.73 (m, 2H, C$\underline{H}_2$(4)), 1.90 (m, 1H, CH$_a\underline{H}_b$(3)), 2.10 (m, 1H, C$\underline{H}_a$H$_b$(3)),

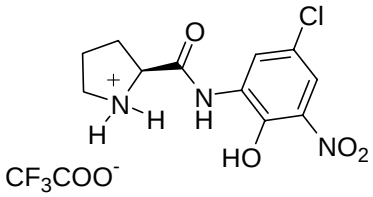
2.96 (m, 2H, C<u>H</u>$_2$N), 3.86 (m, 1H, C<u>H</u>N), 7.17 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 7.30 (t, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 7.43 (t, *J* = 8.0 Hz, 1H, C<u>H</u> Ar); 7.60 (d, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 7.70 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 7.79 (d, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 9.76 (N<u>H</u> or O<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.4 (<u>C</u>H$_2$(4)), 31.1 (<u>C</u>H$_2$(3)), 47.3 (<u>C</u>H$_2$N), 60.0 (<u>C</u>HN), 117.0 (<u>C</u> Ar), 119.3 (<u>C</u>H Ar), 122.1 (<u>C</u>H Ar), 123.3 (<u>C</u>H Ar), 126.7 (<u>C</u>H Ar), 128.0 (<u>C</u>H Ar), 128.3 (<u>C</u>H Ar), 128.5 (<u>C</u> Ar), 131.2 (<u>C</u> Ar), 149.9 (<u>C</u> Ar), 175.0 (<u>C</u>O amide).

2.3.1.14 2-(5´-Chloro-2´-hydroxy-3´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(34)**



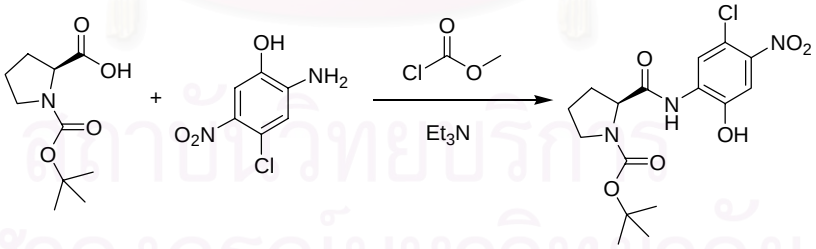
2-(5´-Chloro-2´-hydroxy-3´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 1 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 2-amino-4-chloro-6-nitrophenol (0.2829 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a yellow oil (0.3588 g, 62%); $[\alpha]^{25}_D$ = -46.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H, C<u>H</u>$_3$ Boc), 1.95-2.49 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.43 (brs, 2H, C<u>H</u>$_2$N), 4.51 (brs, 1H, C<u>H</u>N), 7.79(s, 1H, C<u>H</u> Ar), 8.78 (s, 1H, C<u>H</u> Ar), 9.76 and 10.92 (N<u>H</u> and O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (<u>C</u>H$_2$(4)), 27.6 (<u>C</u>H$_2$(3)), 28.6 (<u>C</u>H$_3$ Boc), 47.4 (<u>C</u>H$_2$N), 61.0 (<u>C</u>HN), 81.4 (<u>C</u>(CH$_3$)$_3$ Boc), 117.7 (<u>C</u>H Ar), 125.7 (<u>C</u> Ar), 126.7 (<u>C</u>H Ar), 130.8 (<u>C</u> Ar), 133.2 (<u>C</u> Ar), 143.8 (<u>C</u> Ar), 156.7 (<u>C</u>O Boc), 171.1 (<u>C</u>O amide).

2.3.1.15 Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-3´-nitro-phenyl)-amide trifluoroacetate **(28p)**



Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-3´-nitro-phenyl)-amide trifluoroacetate was prepared according to step 2 using 2-(5´-Chloro-2´-hydroxy-3´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2701 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a yellow solid (0.2798 g, 100%); m.p. 230.2-232.8 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -37.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (m, 2H, C$\underline{H}_2$(4)), 1.99 (m, 1H, C$\underline{H}_a$H$_b$(3)), 2.35 (m, 1H, CH$_a\underline{H}_b$(3)), 3.26 (m, 2H, C$\underline{H}_2$N), 4.55 (m, 1H, C$\underline{H}$N), 7.80(d, *J* = 2.0 Hz, 1H, C$\underline{H}$ Ar), 8.18 (d, *J* = 2.0 Hz, 1H, C$\underline{H}$ Ar), 9.555 and 10.39 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 ($\underline{C}$H$_2$(4)), 30.2 ($\underline{C}$H$_2$(3)), 46.4 ($\underline{C}$H$_2$N), 60.0 ($\underline{C}$HN), 117.1 (q, $^{1}J_{C\text{-}F}$ = 296.8 Hz, $\underline{C}$F$_3$ TFA), 120.3 ($\underline{C}$H Ar), 122.4 ($\underline{C}$ Ar), 127.4 ($\underline{C}$H Ar), 130.6 ($\underline{C}$ Ar), 138.0 ($\underline{C}$ Ar), 144.0 ($\underline{C}$ Ar), 158.8 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz, $\underline{C}$O TFA), 168.7 ($\underline{C}$O amide).

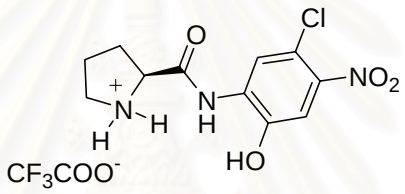
2.3.1.16 2-(5´-Chloro-2´-hydroxy-4´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(35)**



N-Boc-L-proline (0.3229 g, 1.5 mmol) and TEA (0.1518 g, 1.5 mmol) were dissolved in THF. To the solution was added dropwise methylchloroformate (g, 1.5 mmol) at 0 °C over a period of 15 min. After the solution was stirred for 30 min at 0 °C, 2-amino-4-chloro-5-nitrophenol (0.2829 g, 1.5 mmol) was added dropwise over a period of 15 min. The resulting solution was stirred at 0 °C for 1 h, and at room temperature for overnight. The solution was diluted with ethyl acetate and washed with water, any solids were filtered off, and the residue was evaporated to dryness.

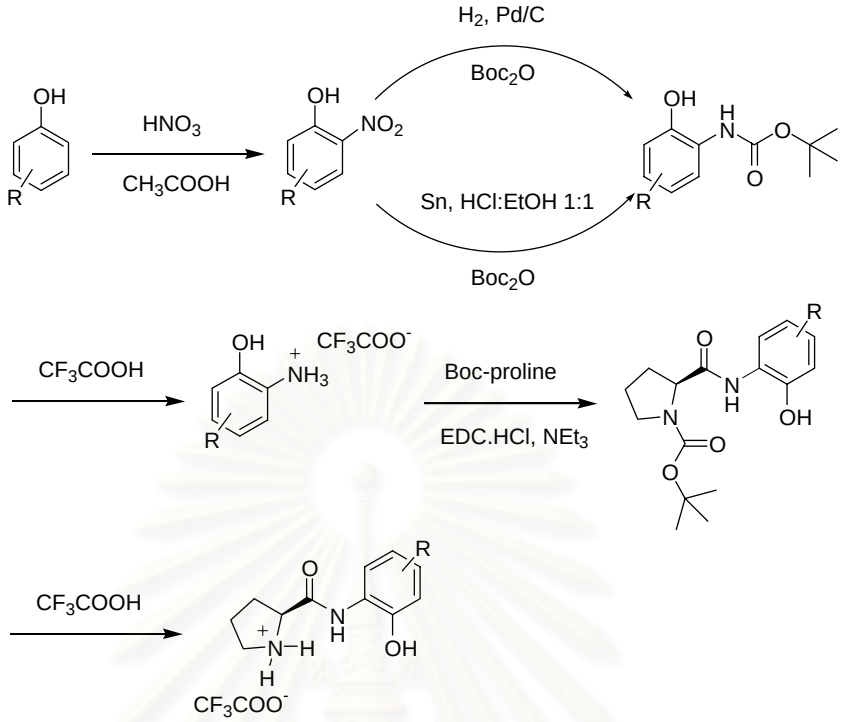
The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent. The product was obtained as a yellow oil (0.4514 g, 78%); $[\alpha]^{25}_{D}$ = -79.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 and 1.52 (brs, 9H, C$\underline{H}_3$ Boc), 1.98-2.25 (brs, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.47 and 3.59 (brs, 2H, C$\underline{H}_2$N), 4.44 (brs, 1H, C$\underline{H}$N), 7.48 (brs, 1H, C$\underline{H}$ Ar), 7.97 (s, 1H, C$\underline{H}$ Ar) 9.00 and 9.95 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3 (C$\underline{H}_2$(4)), 28.4 (C$\underline{H}_3$ Boc), 29.3 and 31.1 (rotamer) (C$\underline{H}_2$(3)), 47.4 (C$\underline{H}_2$N), 60.7 and 62.3 (rotamer) (C$\underline{H}$N), 82.2 (C$\underline{(CH_3)}_3$ Boc), 113.1 (C$\underline{H}$ Ar), 120.0 (C$\underline{}$ Ar), 122.0(C$\underline{H}$ Ar), 131.0 (C$\underline{}$ Ar), 142.3 (C$\underline{}$ Ar), 144.8 (C$\underline{}$ Ar), 156.2 (C$\underline{O}$ Boc), 171.1 (C$\underline{O}$ amide).

2.3.1.17 Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-4´-nitro-phenyl)-amide trifluoroacetate **(28o)**



Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-4´-nitro-phenyl)-amide trifluoroacetate was prepared according to step 2 using 2-(5´-chloro-2´-hydroxy-4´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2701 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a yellow solid (0.2630 g, 94%); m.p. 206.1-208.9 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -33.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.35 (m, 1H, CH$_a\underline{H}_b$(3)), 3.26 (m, 2H, C$\underline{H}_2$N), 4.61 (m, 1H, C$\underline{H}$N), 7.61 (s, 1H, C$\underline{H}$ Ar), 8.33 (s, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 (C$\underline{H}_2$(4)), 30.6 (C$\underline{H}_2$(3)), 46.7 (C$\underline{H}_2$N), 60.4 (C$\underline{H}$N), 117.8 (q, $^1J_{C\text{-}F}$ = 297.3 Hz, C$\underline{F}_3$ TFA), 112.6 (C$\underline{H}$ Ar), 116.1 (C$\underline{}$ Ar), 123.1 (C$\underline{H}$ Ar), 131.9 (H Ar), 142.7 (C$\underline{}$ Ar), 147.6 (C$\underline{}$ Ar), 159.2 (q, $^2J_{C\text{-}F}$ = 31.7 Hz, C$\underline{O}$ TFA), 169.2 (C$\underline{O}$ amide); Anal. Calcd for $C_{13}H_{14}ClF_3N_3O_6$: C, 39.06; H, 3.28; N, 10.51. Found: C, 39.18; H, 3.23; N, 10.52 %.

2.3.2 Synthesis L-prolinamides from phenol



Step 1 Phenol derivative (30 mmol) was dissolved in glacial acetic acid (10 mL) and the mixture was cooled down to 0 ^{o}C. Concentrated nitric acid (45 mmol) was added dropwise and the reaction mixture was stirred until the starting material was completely consumed (monitored by TLC). The reaction mixture was quenched with water then ethyl acetate (30 mL) was added. After extraction with water (2 x 20 mL), the organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography using hexanes and ethyl acetate as eluent.

Step 2 Method A: The 2-nitrophenol derivatives (5 mmol) prepared in step 1 was dissolved in 10 mL of absolute methanol. Then 10% Pd/C (100 mg/g of substrate) and di-*tert*-butyl dicarbonate (5 mmol) was added. The reaction mixture was stirred under hydrogen atmosphere (1 atm) until the starting material completely disappeared (monitored by TLC). The reaction mixture was filtered through celite to remove the catalyst. The organic solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent.

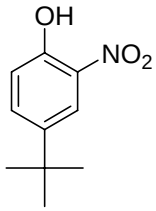
Method B: 2-nitrophenol derivatives (10 mmol) prepared from step 1 was stirred in 10 mL of hydrochloric acid (conc.)/ethanol (1:1). Then excess of tin powder was added and the reaction mixture was stirred for 15-30 minutes. The mixture was adjusted to pH 10 with $NaHCO_3$ and filtered through celite to remove the tin (II) chloride. After removal of solvent, the residue was dissolved in 10 mL of absolute methanol and then di-*tert*-butyl dicarbonate (10 mmol) was added. The reaction mixture was stirred until the starting material was completely consumed (monitored by TLC). The organic solvent was removed by evaporation. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent.

Step 3 *N*-Boc-aminophenol derivatives (3 mmol) prepared from step 2 was dissolved in mixture of trifluoroacetic acid/dichloromethane (1:1) 2 mL for 2 hours without stirring. The organic solvent was removed by evaporation to afford the crude products as trifluoroacetate salt. The residue was purified by recystlization with diethyl ether or dichloromethane

Step 4 2-aminophenol (1.5 mmol) prepared from step 3 was dissolved in 10 mL dichloromethane then drop triethylanime (1.5 mmol). After the solution was stirred for 5 min, *N*-Boc-L-proline (1.5 mmol) and EDC.HCl (1.6 mmol) were added and the reaction mixture was stirred overnight. The resulting solution was washed with water and the solvent removed at reduced pressure. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent.

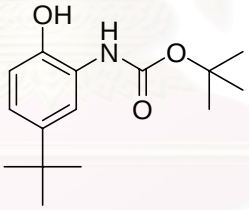
Step 5 *N*-Boc-L-prolinamide derivatives (0.7 mmol) prepared from step 2 was dissolved in mixture of trifluoroacetic acid/dichloromethane (1:1) 2 mL for 2 hours without stirring. The organic solvent was removed by evaporation to afford the crude products as trifluoroacetate salt.

2.3.2.1 4-*tert*-Butyl-2-nitro-phenol **(36)**



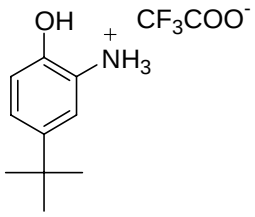
4-*tert*-Butyl-2-nitro-phenol was prepared according to step 1 using 4-*tert*-butyl-phenol (g, 30 mmol) and nitric acid (2 mL, 45 mmol). The product was obtained as a yellow solid (5.1538 g, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H, 3 x C<u>H</u>$_3$), 6.95 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 7.54 (dd, *J* = 8.8, 2.4 Hz, 1H, C<u>H</u> Ar), 7.94 (d, *J* = 2.4 Hz, 1H, C<u>H</u> Ar), 10.32 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1 (3 x <u>C</u>H$_3$), 34.4 (<u>C</u>(CH$_3$)$_3$), 119.6 (<u>C</u>H Ar), 120.8 (<u>C</u>H Ar), 133.1 (<u>C</u> Ar), 135.5 (<u>C</u>H Ar), 143.7 (<u>C</u> Ar), 153.1 (<u>C</u> Ar).

2.3.2.2 (5-*tert*-Butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(37)**



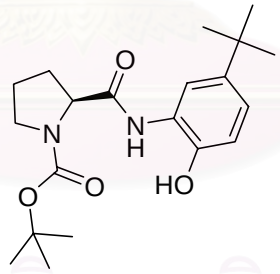
(5-*tert*-Butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method A) using 4-*tert*-butyl-2-nitro-phenol (1.9522 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol) and Pd/C (0.1952 g). The product was obtained as a white solid (2.4943 g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H, 3 x C<u>H</u>$_3$), 1.57 (s, 9H, C<u>H</u>$_3$ Boc), 6.92 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.03 (dd, *J* = 8.4, 2.0 Hz, 1H, C<u>H</u> Ar) , 7.21 (N<u>H</u> Boc), 7.40 (brs, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (3 x <u>C</u>H$_3$), 31.4 (<u>C</u>H$_3$ Boc), 34.1 (<u>C</u>(CH$_3$)$_3$), 82.0 (<u>C</u>(CH$_3$)$_3$ Boc), 117.4 (<u>C</u> Ar), 118.1 (<u>C</u>H Ar) , 121.9 (<u>C</u>H Ar), 125.2 (<u>C</u>H Ar), 143.8 (<u>C</u> Ar), 144.3 (<u>C</u> Ar), 155.2 (<u>C</u>O Boc).

2.3.2.3 4-*tert*-butyl-2-aminophenol trifluoroacetate salt **(38)**



4-*tert*-Butyl-2-aminophenol trifluoro acetate salt was prepared according to step 3 using (5-*tert*-butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (1.3268 g, 5 mmol) and TFA (1 mL). The product was obtained as a white solid (1.2206 g, 92%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 9H, 3 x C$\underline{H}_3$), 6.90 (d, J = 8.4 Hz, 1H, C$\underline{H}$ Ar), 7.17 (d, J = 8.4 Hz, 1H, C$\underline{H}$ Ar), 7.25 (s, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.6 (3 x $\underline{C}H_3$), 34.2($\underline{C}(CH_3)_3$), 117.4 (q, $^{1}J_{C\text{-}F}$ = 296.5 Hz, $\underline{C}F_3$ TFA), 116.1 ($\underline{C}$H Ar), 120.1 ($\underline{C}$ Ar), 120.5 ($\underline{C}$H Ar), 125.4 ($\underline{C}$H Ar), 142.3 ($\underline{C}$ Ar), 148.4 ($\underline{C}$ Ar), 158.9 (q, $^{2}J_{C\text{-}F}$ = 31.9 Hz, $\underline{C}$O TFA).

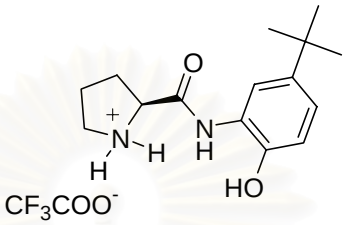
2.3.2.4 2-(5´-*tert*-Butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(39)**



2-(5´-*tert*-Butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 5-*tert*-butyl-2-hydroxy-phenyl-ammonium trifluoroacetate (0.4189 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.4893 g, 90%); $[\alpha]^{25}_{D}$ = -141.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, 3 x C$\underline{H}_3$), 1.51 (s, 9H, CH_3 Boc), 1.93-2.40 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.43 (brs, 2H, C$\underline{H}_2$N), 4.58 (brs, 1H, C$\underline{H}$N), 6.90 (s, 1H, C$\underline{H}$ Ar), 6.94 (d, J = 8.4 Hz, 1H, C$\underline{H}$ Ar), 7.13 (d, J = 8.4 Hz, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 ($\underline{C}H_2$(4)), 28.1 ($\underline{C}H_2$(3)), 28.4 ($\underline{C}H_3$ Boc), 31.3 (3 x

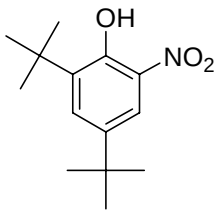
$\underline{C}H_3$), 33.9 ($\underline{C}(CH_3)_3$), 47.2 ($\underline{C}H_2N$), 59.9 ($\underline{C}HN$), 81.3 ($\underline{C}(CH_3)_3$ Boc), 119.0 ($\underline{C}H$ Ar), 119.3 ($\underline{C}H$ Ar), 124.0 ($\underline{C}H$ Ar), 124.8 ($\underline{C}$ Ar), 143.5 ($\underline{C}$ Ar), 146.2 ($\underline{C}$ Ar), 156.4 ($\underline{C}O$ Boc), 171.9 ($\underline{C}O$ amide).

2.3.2.5 Pyrrolidine-2-carboxylic acid (5´-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate **(28c)**



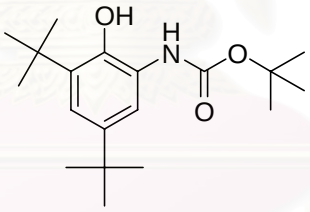
Pyrrolidine-2-carboxylic acid (5´-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(5´-*tert*-butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.1812 g, 0.5 mmol) and TFA (1 mL). The product was obtained as a white solid (0.1694 g, 90%); m.p. 120.2-123.8 ^oC; $[\alpha]^{25}_D$ = -23.8 (*c* 1.0, MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 9H, 3 x $C\underline{H}_3$), 1.92 (m, 3H, $C\underline{H}_aH_b$(3) and $C\underline{H}_2$(4)), 2.37 (m, 1H, $CH_a\underline{H}_b$(3)), 3.24 (m, 2H, $C\underline{H}_2N$), 4.48 (m, 1H, $C\underline{H}N$), 6.81 (d, *J* = 8.4 Hz, 1H, $C\underline{H}$ Ar), 6.99 (dd, *J* = 8.4, 2.4 Hz, 1H, $C\underline{H}$ Ar), 7.87 (d, *J* = 2.4 Hz, 1H, $C\underline{H}$ Ar), 9.77 and 9.79 ($N\underline{H}$ and $O\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 ($\underline{C}H_2CH_2N$), 30.4 ($\underline{C}H_2CHN$), 31.8 (3 x $\underline{C}H_3$), 34.3 ($\underline{C}(CH_3)_3$), 46.4 ($\underline{C}H_2N$), 60.1 ($\underline{C}HN$), 117.7 (q, $^1J_{C\text{-}F}$ = 298.8 Hz, $\underline{C}F_3$ TFA), 115.3 ($\underline{C}H$ Ar), 120.1 ($\underline{C}H$ Ar), 122.5 ($\underline{C}H$ Ar), 124.9 ($\underline{C}$ Ar), 141.5 ($\underline{C}$ Ar), 146.4 ($\underline{C}$ Ar), 158.5 (q, $^2J_{C\text{-}F}$ = 30.8 Hz, $\underline{C}O$ TFA), 167.6 ($\underline{C}O$ amide); Anal. Calcd for $C_{17}H_{23}F_3N_2O_4$: C, 54.25; H, 6.16; N, 7.44. Found: C, 54.08; H, 6.18; N, 7.45 %.

2.3.2.6 2,4-Di-*tert*-butyl-6-nitro-phenol **(40)**



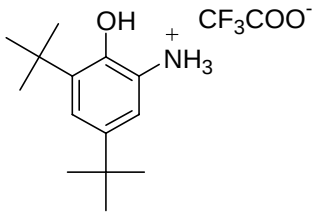
2,4-Di-*tert*-butyl-6-nitro-phenol was prepared according to step 1 using 2,4-di-*tert*-butyl-phenol (6.1896 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol). The product was obtained as a yellow solid (4.5992 g, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H, 3 x C<u>H</u>$_3$), 1.45 (s, 9H, 3 x C<u>H</u>$_3$), 7.65 (s, 1H, C<u>H</u> Ar), 7.96 (s, 1H, C<u>H</u> Ar), 11.45 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3 (3 x <u>C</u>H$_3$), 31.1 (3 x <u>C</u>H$_3$), 34.5 (<u>C</u>(CH$_3$)$_3$), 35.7 (<u>C</u>(CH$_3$)$_3$), 118.8 (<u>C</u>H Ar), 132.6 (<u>C</u>H Ar), 133.6 (<u>C</u> Ar), 139.8 (<u>C</u> Ar), 141.9 (<u>C</u> Ar), 153.0 (<u>C</u> Ar).

2.3.2.7 (3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(41)**



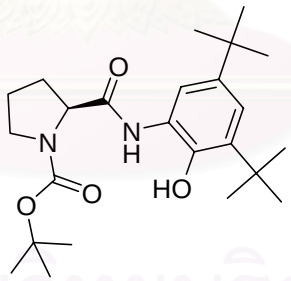
(3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method A) using 2,4-di-*tert*-butyl-6-nitro-phenol (2.5132 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol), and Pd/C (0.2513 g). The product was obtained as a white solid (3.1502 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H, 3 x C<u>H</u>$_3$), 1.45 (s, 9H, 3 x C<u>H</u>$_3$), 1.53 (s, 9H, C<u>H</u>$_3$ Boc), 6.55 (s 1H, CON<u>H</u> Boc), 6.79 (s, 1H, C<u>H</u> Ar), 7.17 (s, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (3 x <u>C</u>H$_3$), 29.8 (3 x <u>C</u>H$_3$), 31.5 (<u>C</u>H$_3$ Boc), 34.2 (<u>C</u>(CH$_3$)$_3$), 35.4 (<u>C</u>(CH$_3$)$_3$), 82.0 (<u>C</u>(CH$_3$)$_3$ Boc), 117.7 (<u>C</u>H Ar), 121.2 (<u>C</u>H Ar), 125.3 (<u>C</u> Ar), 139.5 (<u>C</u> Ar), 142.4 (<u>C</u> Ar), 145.6 (<u>C</u> Ar), 155.7 (<u>C</u>O Boc).

2.3.2.8 2,4-Di-*tert*-butyl-6-aminophenol trifluoroacetate salt **(42)**



3,5-Di-*tert*-butyl-2-hydroxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (3,5-di-*tert*-butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (0.9644 g, 3 mmol) and TFA (1 mL). The product was obtained as a white solid (0.9558 g, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H, 3 x C$\underline{H}_3$), 1.40 (s, 9H, 3 x C$\underline{H}_3$), 7.20 (s, 1H, C$\underline{H}$ Ar), 7.40 (s, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4 (3 x $\underline{C}H_3$), 29.8 (3 x $\underline{C}H_3$), 30.9 ($\underline{C}(CH_3)_3$), 34.7 ($\underline{C}(CH_3)_3$), 114.9 (q, $^{1}J_{C\text{-}F}$ = 285.0 Hz, $\underline{C}F_3$ TFA), 118.2 ($\underline{C}$H Ar), 119.8 ($\underline{C}$ Ar), 125.3 ($\underline{C}$H Ar), 134.0 ($\underline{C}$ Ar), 144.4 ($\underline{C}$ Ar), 146.0 ($\underline{C}$ Ar), 161.1(q, $^{2}J_{C\text{-}F}$ = 40.4 Hz, $\underline{C}$O TFA).

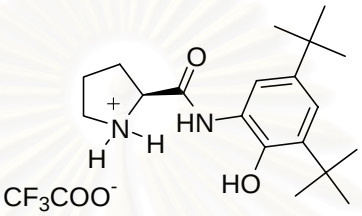
2.3.2.9 2-(3´,5´-Di-*tert*-butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(43)**



2-(3´,5´-Di-*tert*-butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 3,5-di-*tert*-butyl-2-hydroxy-phenyl-ammonium trifluoroacetate (0.5030 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.5023 g, 80%); $[\alpha]^{25}_{D}$ = -108.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H, 3 x C$\underline{H}_3$), 1.42 (s, 9H, 3 x C$\underline{H}_3$), 1.48 (s, 9H, C$\underline{H}_3$ Boc), 2.04-2.37 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.41 and 3.54 (brs, 2H, C$\underline{H}_2$N), 4.64 (brs, 1H, C$\underline{H}$N), 6.71 (s, 1H, C$\underline{H}$ Ar), 7.14 (s, 1H, C$\underline{H}$ Ar), 9.79 (

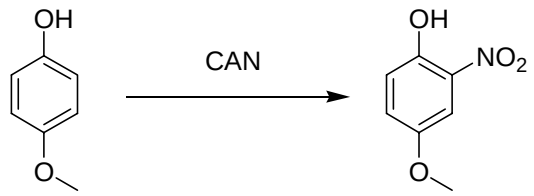
NH or OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (CH_2(4)), 28.4 (3 x CH_3), 28.6 (CH_2(3)), 29.8 (3 x CH_3), 31.4 (CH_3 Boc), 34.1 ($C(CH_3)_3$), 35.4 ($C(CH_3)_3$), 47.2 (CH_2N), 59.8 and 61.3 (rotamer) (CHN), 81.0 ($C(CH_3)_3$ Boc), 117.9 (CH Ar), 122.1 (CH Ar), 126.1 (C Ar), 139.5 (C Ar), 142.2 (C Ar), 145.9 (C Ar), 156.0 (CO Boc), 171.2 (CO amide).

2.3.2.10 Pyrrolidine-2-carboxylic acid (3´,5´-di-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate **(28d)**



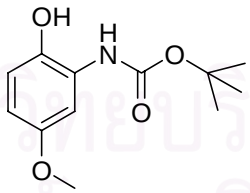
Pyrrolidine-2-carboxylic acid (3´,5´-di-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(3´,5´-di-*tert*-butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2930 g, 0.7 mmol and TFA (1 mL). The product was obtained as a white solid (0.3027 g, 100%); $[\alpha]^{25}_D$ = -40.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, 3 x CH_3), 1.39 (s, 9H, 3 x CH_3), 2.01 (m, 2H, CH_2(4)), 2.16 (m, 1H, CH_aH_b(3)), 2.46 (m, 1H, CH_aH_b(3)), 3.37 (m, 2H, CH_2N), 4.90 (m, 1H, CHN), 7.00 (s, 1H, CH Ar), 7.25 (s, 1H, CH Ar), 9.45 (NH and OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (CH_2(4)), 29.7 (3 x CH_3), 30.3 (CH_2(3)), 31.3 (3 x CH_3), 34.3 ($C(CH_3)_3$), 35.3 ($C(CH_3)_3$), 47.0 (CH_2N), 60.2 (CHN), 115.6 (q, $^1J_{C\text{-}F}$ = 392.9 Hz, CF_3 TFA), 119.0 (CH Ar), 123.0 (CH Ar), 124.4 (C Ar), 139.5 (C Ar), 143.4 (C Ar), 145.7 (C Ar), 161.6 (q, $^2J_{C\text{-}F}$ = 39.2 Hz, CO TFA), 168.3 (CO amide).

2.3.2.11 4-Methoxy-2-nitro-phenol **(44)**



CAN (3.2894 g, 6 mmol) was added to a stirred mixture containing hydroquinone monomethyl ether (0.4966g, 4 mmol), $NaHCO_3$ (1 g) and 10 mL of anhydrous MeCN at rt. The resulting mixture was stirred for 30 min during which time the yellow color of CAN was discharged. The mixture was filtered, washed with water, and extracted with $CHCl_3$ (3 x 20 mL). The combined $CHCl_3$ extracts were dried, and the solvent evaporated in *vacuo* to give the corresponding 2-nitrophenol. The residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent. The product was obtained as a orange solid (0.0725 g, 11%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H, OC<u>H</u>$_3$), 7.06 (d, *J* = 9.2 Hz, 1H, C<u>H</u> Ar), 7.20 (dd, *J* = 9.2, 2.8 Hz, 1H, C<u>H</u> Ar), 7.47 (d, *J* = 2.8 Hz, 1H, C<u>H</u> Ar), 10.31 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0 (O<u>C</u>H$_3$), 105.6 (<u>C</u>H Ar), 120.8 (<u>C</u>H Ar), 127.2 (<u>C</u>H Ar), 132.9 (<u>C</u> Ar), 150.0 (<u>C</u> Ar), 152.6 (<u>C</u> Ar).

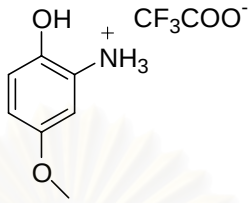
2.3.2.12 (2-Hydroxy-5-methoxy-phenyl)-carbamic acid tert-butyl ester **(45)**



(2-Hydroxy-5-methoxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method A) using 4-methoxy-2-nitro-phenol (0.2030 g, 1.2 mmol), di-*tert*-butyl dicarbonate (0.2619 g, 1.2 mmol) and Pd/C (0.0203 g). The product was obtained as a orange oil (0.2652 g, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H, C<u>H</u>$_3$ Boc), 3.69 (s, 3H, OC<u>H</u>$_3$), 6.48 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 6.79 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 7.22 (brs, 1H, N<u>H</u> Boc). 7.27 (brs, 1H C<u>H</u> Ar); ^{13}C NMR (100 MHz,

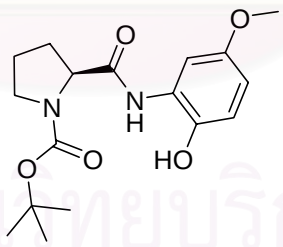
$CDCl_3$) δ 28.3 (CH_3 Boc), 55.8 (OCH_3), 81.4 (C$(CH_3)_3$ Boc), 106.0 (CH Ar), 109.6 (CH Ar), 117.1 (C Ar), 126.9 (CH Ar), 139.9 (C Ar), 153.5 (C Ar), 154.3 (CO Boc).

2.3.2.13 4-Methoxy-2-aminophenol trifluoroacetate salt **(46)**



2-Hydroxy-5-methoxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (2-hydroxy-5-methoxy-phenyl)-carbamic acid *tert*-butyl ester violet solid (0.2632 g, 1.1 mmol) and TFA (1 mL). The product was obtained as a (0.2534 g, 91%); ^{1}H NMR (400 MHz, methanol-d_4) δ 3.73 (s, 3H, OCH_3), 6.85 (m, 3H, 3 x CH Ar); ^{13}C NMR (100 MHz, methanol-d_4) δ 54.9 (OCH_3), 116.7 (q, $^1J_{C\text{-}F}$ = 290.9 Hz, CF_3 TFA), 109.0 (CH Ar), 114.6 (CH Ar), 116.4 (CH Ar), 118.7 (C Ar), 144.4 (C Ar), 153.0 (C Ar), 161.6 (q, $^2J_{C\text{-}F}$ = 34.6 Hz, CO TFA).

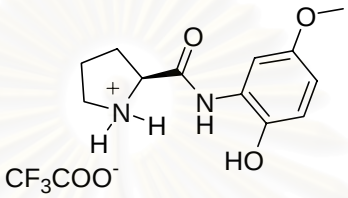
2.3.2.14 2-(2´-Hydroxy-5´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(47)**



2-(2´-Hydroxy-5´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.2153 g, 1 mmol), 2-hydroxy-5-methoxy-phenyl-ammonium trifluoroacetate (0.2532 g, 1 mmol), TEA (0.1012 g, 1 mmol) and EDC.HCl (0.2109 g, 1.1 mmol). The product was obtained as a violet solid (0.2395 g, 80%); $[\alpha]^{25}_D$ = -110.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H, CH_3 Boc), 1.90-2.26 (brs, 4H, CH_2(3) and CH_2(4)), 3.40 and 3.52 (brs, 2H, CH_2N), 3.61 (s, 3H, OCH_3), 4.33 and 4.54 (brs, 1H, CHN), 6.54 (s, 1H, CH Ar), 6.82 (brs, 1H, 2 x CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8

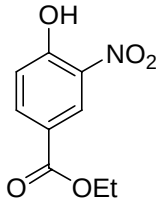
and 24.5 (rotamer) (CH_2(4)), 28.3 (CH_3 Boc), 28.9 and 31.3 (rotamer) (CH_2(3)), 47.2 (CH_2N), 55.7 (OCH_3), 60.3 and 61.8 (rotamer) (CHN), 81.2 (C$(CH_3)_3$ Boc), 106.7 (CH Ar), 111.1 and 112.5 (rotamer) (CH Ar), 117.3 and 119.0 (rotamer) (CH Ar), 126.0 (C Ar), 141.2 and 141.5 (rotamer) (C Ar), 153.2 (C Ar), 154.8 and 155.9 (rotamer) (CO Boc), 172.0 (CO amide).

2.3.2.15 Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-methoxy-phenyl)-amide trifluoroacetate **(28f)**



Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-methoxy-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(2´-hydroxy-5´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.1682 g, 0.5 mmol) and TFA (1 mL). The product was obtained as a dark bule oil (0.1541 g, 100%); $[\alpha]^{25}_D$ = -52.0 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, methanol-d_4) δ 2.10 (brs, 3H, CH_aH_b(3) and CH_2(4)), 2.51 (brs, 1H, CH_aH_b(3)), 3.38 and 3.44 (brs, 2H, CH_2N), 3.71 (s, 3H, OCH_3), 4.53 (brs, 1H, CHN), 6.60 (d, *J* = 8.4 Hz, 1H, CH Ar), 6.79 (d, *J* = 8.4 Hz, 1H, CH Ar), 7.51 (s, 1H, CH Ar); ^{13}C NMR (100 MHz, methanol-d_4) δ 23.7 (CH_2(4)), 30.0 (CH_2(3)), 46.1(CH_2N), 54.8 (OCH_3), 60.3 (CHN), 116.8 (q, $^1J_{C\text{-}F}$ = 289.7 Hz, CF_3 TFA), 108.4 (CH Ar), 110.5 (CH Ar), 115.3 (CH Ar), 125.4 (C Ar), 141.9 (C Ar), 152.7 (C Ar), 161.8 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, CO TFA), 166.9 (CO amide).

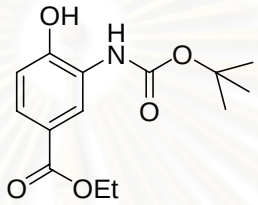
2.3.2.16 Ethyl-4-hydroxy-3-nitro benzoate **(48)**



Ethyl-4-hydroxy-3-nitro benzoate was prepared according to step 1 using ethyl-4-hydroxy benzoate (4.9851 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol).

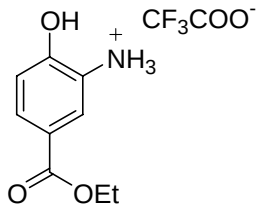
The product was obtained as a yellow solid (5.5749 g, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 4.39 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 7.20 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 8.23 (dd, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 8.80 (s, 1H, C<u>H</u> Ar), 10.86 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 ($OCH_2\underline{C}H_3$), 61.6 ($O\underline{C}H_2CH_3$), 120.2 (<u>C</u>H Ar), 123.1 (<u>C</u> Ar), 127.2 (<u>C</u>H Ar), 133.2 (<u>C</u> Ar), 137.9 (<u>C</u>H Ar), 158.0 (<u>C</u> Ar), 164.3 (<u>C</u>O ester).

2.3.2.17 Ethyl-3-(N-tertbutorycarbonylamino)-4-hydroxy benzoate **(49)**



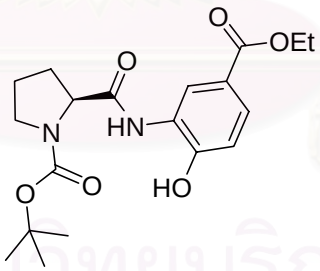
Ethyl-3-(N-tertbutorycarbonylamino)-4-hydroxy benzoate was prepared according to step 2 (method A) using ethyl-4-hydroxy-3-nitro benzoate (2.1117 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol), and Pd/C (0.2112 g). The product was obtained as a orange oil (2.7567 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.51 (s, 9H, $C\underline{H}_3$ Boc), 4.31 (q, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 6.96 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.18 (s 1H, CON<u>H</u> Boc), 7.67 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 8.09 (s, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 ($OCH_2\underline{C}H_3$), 28.2 ($\underline{C}H_3$ Boc), 61.1 ($O\underline{C}H_2CH_3$), 81.2 ($\underline{C}(CH_3)_3$ Boc), 116.3 (<u>C</u> Ar), 121.8 (<u>C</u>H Ar), 122.1 (<u>C</u>H Ar), 126.1 (<u>C</u>H Ar), 126.4 (<u>C</u> Ar), 150.9 (<u>C</u> Ar), 154.4 (<u>C</u>O Boc), 167.2 (<u>C</u>O ester).

2.3.2.18 Ethyl-4-hydroxy-3-aminobenzoate trifluoroacetate salt **(50)**



Ethyl-3-amino-4-hydroxy benzoate trifluoroacetate was prepared according to step 3 using ethyl-3-(N-tertbutorycarbonylamino)-4-hydroxy benzoate (0.8439 g, 3 mmol) and TFA (1 mL). The product was obtained as a brown solid (0.7958 g, 95%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 4.22 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 7.02 (d, J = 8.4 Hz, 1H, C<u>H</u> Ar), 7.67 (dd, J = 8.4, 2.0 Hz, 1H, C<u>H</u> Ar), 7.78 (d, J = 2.0 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.6 ($OCH_2\underline{C}H_3$), 60.9 ($O\underline{C}H_2CH_3$), 116.0 (<u>C</u>H Ar), 116.9 (q, $^{1}J_{C\text{-}F}$ = 293.5 Hz, $\underline{C}F_3$ TFA), 121.2 (<u>C</u> Ar), 123.4 (<u>C</u> Ar), 123.6 (<u>C</u>H Ar), 128.8 (<u>C</u>H Ar), 154.6 (<u>C</u> Ar), 159.3 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, <u>C</u>O TFA), 165.5 (<u>C</u>O ester).

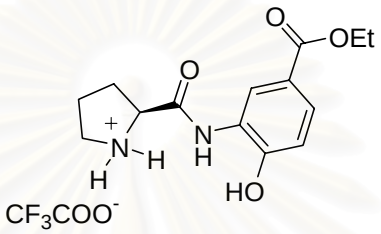
2.3.2.19 2-(2´-Hydroxy-5´-ethoxycarbonyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(51)**



2-(2´-Hydroxy-5´-ethoxycarbonyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), ethyl-3-amino-4-hydroxy benzoate trifluoroacetate (0.4188 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.4938 g, 87%); $[\alpha]^{25}_{D}$ = -51.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.62(s, 9H, $C\underline{H}_3$ Boc), 1.97-2.47 (brs, 4H, $C\underline{H}_2$(3) and $C\underline{H}_2$(4)), 3.48 (brs, 2H, $C\underline{H}_2N$), 4.32 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.56 (brs, 1H, C<u>H</u>N), 7.01 (d, J = 8.4 Hz, 1H, C<u>H</u> Ar), 7.26 (s,

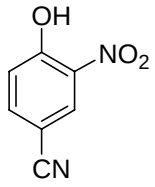
1H, C<u>H</u> Ar), 7.80 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 ($OCH_2\underline{C}H_3$), 24.5 ($\underline{C}H_2$(4)), 28.3 ($\underline{C}H_3$ Boc), 31.2 ($\underline{C}H_2$(3)), 47.3 ($\underline{C}H_2N$), 60.1 and 61.7 (rotamer) (<u>C</u>HN), 60.8 ($O\underline{C}H_2CH_3$), 81.5 ($\underline{C}(CH_3)_3$ Boc), 118.6 (<u>C</u> Ar), 122.3 (<u>C</u>H Ar), 124.1 (<u>C</u> Ar), 125.4 (<u>C</u>H Ar), 128.4 (<u>C</u>H Ar), 152.7 (<u>C</u> Ar), 156.4 (<u>C</u>O Boc), 166.1 (<u>C</u>O ester), 172.3 (<u>C</u>O amide).

2.3.2.20 Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-ethoxycarbonyl-phenyl)-amide trifluoroacetate **(28h)**



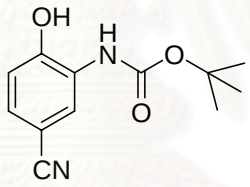
Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-ethoxycarbonyl-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(2´-hydroxy-5´-ethoxycarbonyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2649 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a white solid (0.2527 g, 92%); m.p. 179.8-181.6 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -22.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (t, *J* = 6.8 Hz, 3H, $OCH_2C\underline{H}_3$), 1.96 (m, 3H, $C\underline{H}_aH_b$(3) and $C\underline{H}_2$(4)), 2.38 (m, 1H, $CH_a\underline{H}_b$(3)), 3.28 (m, 2H, $C\underline{H}_2N$), 4.23 (q, *J* = 6.8 Hz, 2H, $OC\underline{H}_2CH_3$), 4.54 (m, 1H, C<u>H</u>N), 7.02 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.62 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 8.52 (s, 1H, C<u>H</u> Ar), 10.00 (N<u>H</u> and O<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.7 ($OCH_2\underline{C}H_3$), 24.0 ($\underline{C}H_2$(4)), 30.4 ($\underline{C}H_2$(3)), 46.3 ($\underline{C}H_2N$), 60.0 (<u>C</u>HN), 60.7 ($O\underline{C}H_2CH_3$), 117.5 (q, $^{1}J_{C\text{-}F}$ = 296.6 Hz, $\underline{C}F_3$ TFA), 115.5 (<u>C</u>H Ar), 117.5 (q, *J* = 296.6 Hz, $\underline{C}F_3$ TFA), 120.7 (<u>C</u> Ar), 124.1 (<u>C</u>H Ar), 125.6 (<u>C</u> Ar), 127.5 (<u>C</u>H Ar), 153.4 (<u>C</u> Ar), 159.3 (q, $^{2}J_{C\text{-}F}$ = 31.1 Hz, <u>C</u>O TFA), 165.9 (<u>C</u>O ester), 168.0 (<u>C</u>O amide); Anal. Calcd for $C_{16}H_{19}ClF_3N_2O_6$: C, 48.98; H, 4.88; N, 7.14. Found: C, 48.99; H, 4.88; N, 7.12 %.

2.3.2.21 4-Hydroxy-3-nitro-benzonitrile **(52)**



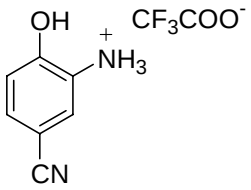
4-Hydroxy-3-nitro-benzonitrile was prepared according to step 1 using 4-hydroxybenzonitrile (3.5736 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol). The product was obtained as a yellow solid (2.4618 g, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.82 (dd, *J* = 8.4, 2.0 Hz, 1H, C<u>H</u> Ar), 8.46 (d, *J* = 2.0 Hz, 1H, C<u>H</u> Ar), 10.89 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.7 (<u>C</u> Ar), 116.8 (<u>C</u>N), 122.0 (<u>C</u>H Ar), 130.3 (<u>C</u>H Ar), 133 (<u>C</u> Ar), 139.8 (<u>C</u>H Ar), 158.0 (<u>C</u> Ar).

2.3.2.22 (5-Cyano-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(53)**



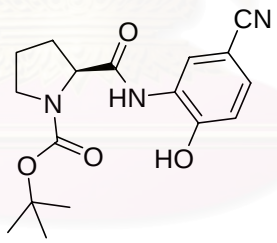
(5-Cyano-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method A) using 4-hydroxy-3-nitro-benzonitrile (1.6412 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol), and Pd/C (0.1641 g). The product was obtained as a white solid (1.0776 g, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H, C<u>H</u>$_3$ Boc), 6.94 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.20 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 8.12 (s, 1H, C<u>H</u> Ar), 8.77 (s, 1H, CON<u>H</u> Boc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (<u>C</u>H$_3$ Boc), 82.2 (<u>C</u>(CH$_3$)$_3$ Boc), 102.6 (<u>C</u> Ar), 116.2 (<u>C</u>H Ar), 119.5 (<u>C</u>N), 122.9 (<u>C</u>H Ar), 127.7 (<u>C</u> Ar), 128.3 (<u>C</u>H Ar), 150.1 (<u>C</u> Ar), 153.8 (<u>C</u>O Boc).

2.3.2.23 4-Hydroxy-3-aminobenzonitrile trifluoroacetate salt **(54)**



5-Cyano-2-hydroxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (5-cyano-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (0.7028 g, 3 mmol) and TFA (1 mL). The product was obtained as a white solid (0.7296 g, 98%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 (d, J = 8.8 Hz, 1H, C<u>H</u> Ar), 7.18 (brs, 1H, C<u>H</u> Ar), 7.20 (brs, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 101.5 (<u>C</u> Ar), 116.3 (q, $^{1}J_{C\text{-}F}$ = 290.2 Hz, <u>C</u>F$_3$ TFA), 116.0 (<u>C</u>H Ar), 120.0 (<u>C</u>N), 121.3 (<u>C</u>H Ar), 127.0 (<u>C</u>H Ar), 131.1 (<u>C</u> Ar), 151.8 (<u>C</u> Ar), 159.0 (q, $^{2}J_{C\text{-}F}$ = 34.9 Hz, <u>C</u>O TFA).

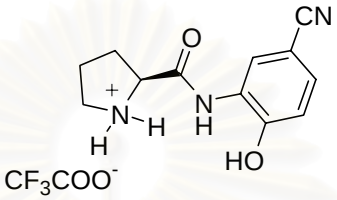
2.3.2.24 2-(5´-Cyano-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(55)**



2-(5´-Cyano-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 5-cyano-2-hydroxy-phenyl-ammonium trifluoroacetate (0.3723 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a brown solid (0.2982 g, 60%); $[\alpha]^{25}_{D}$ = -82.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 and 1.44 (s, 9H, C<u>H</u>$_3$ Boc), 1.90-2.18 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.41 and 3.51 (brs, 2H, C<u>H</u>$_2$N), 4.33 and 4.43 (brs, 1H, C<u>H</u>N), 6.92 (brs, 1H, C<u>H</u> Ar), 7.26 (brs, 1H, C<u>H</u> Ar), 7.70 (brs, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 and 24.4 (rotamer) (<u>C</u>H$_2$(4)), 28.3 (<u>C</u>H$_3$ Boc), 29.5 and 31.2 (rotamer) (<u>C</u>H$_2$(3)), 47.0 and 47.4 (rotamer) (<u>C</u>H$_2$N), 60.7 and 61.8 (rotamer) (<u>C</u>HN), 81.4

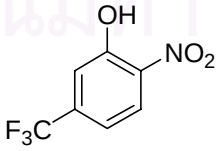
(C(CH$_3$)$_3$ Boc), 102.5 and 102.7 (rotamer) (C Ar), 116.2 and 116.5 (rotamer) (CH Ar), 119.2 (CN), 123.8 and 124.3 (rotamer) (CH Ar), 126.7 (C Ar), 129.3 (CH Ar), 150.6 and 150.9 (rotamer) (C Ar), 154.8 and 155.8 (rotamer) (CO Boc), 171.6 and 172.0 (rotamer) (CO amide).

2.3.2.25 Pyrrolidine-2-carboxylic acid (5´-cyano-2´-hydroxy-phenyl)-amide trifluoroacetate **(28i)**



Pyrrolidine-2-carboxylic acid (5´-cyano-2´-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(5´-cyano-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2320 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a borwn solid (0.2175 g, 90%); m.p. 133.4-135.9 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -28.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (m, 3H, CH$_a$H$_b$(3) and CH$_2$(4)), 2.35 (m, 1H, CH$_a$H$_b$(3)), 3.25 (m, 2H, CH$_2$N), 4.51 (m, 1H, CHN), 7.06 (d, *J* = 8.0 Hz, 1H, CH Ar), 7.46 (d, *J* = 8.0 Hz, 1H, CH Ar), 8.25 (s, 1H, CH Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 (CH$_2$(4)), 30.6 (CH$_2$(3)), 46.6 (CH$_2$N), 60.2 (CHN), 101.2 (C Ar), 116.9 (CH Ar), 117.8 (q, $^{1}J_{C\text{-}F}$ = 297.0 Hz, CF$_3$ TFA), 120.0 (CN), 126.3 (CH Ar), 126.8 (C Ar), 130.6 (CH Ar), 153.5 (C Ar), 159.4 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz, CO TFA), 168.5 (CO amide).

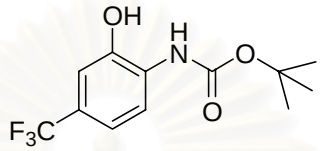
2.3.2.26 2-Nitro-5-trifluoromethyl-phenol **(56)**



2-Nitro-5-trifluoromethyl-phenol was prepared according to step 1 using alpha,alpha,alpha-trifluoro-m-cresol (1.6211 g, 10 mmol) and nitric acid (0.66 mL, 15 mmol). The product was obtained as a yellow solid (0.3393 g, 16%); ^{1}H NMR (400

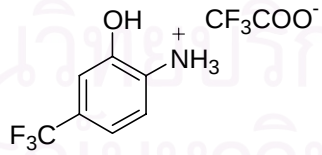
MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 7.42 (s, 1H, C<u>H</u> Ar), 8.22 (d, *J* = 8.8 Hz, 1H, C<u>H</u> Ar), 10.56 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.7 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, <u>C</u>H Ar), 117.9 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, <u>C</u>H Ar), 122.4 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, <u>C</u>F_3), 126.1 (<u>C</u>H Ar), 135.2 (<u>C</u> Ar), 138.5 (q, $^2J_{C\text{-}F}$ = 33.5 Hz, <u>C</u>CF_3 Ar), 154.8 (<u>C</u> Ar).

2.3.2.27 (2-Hydroxy-4-trifluoromethyl-phenyl)-carbamic acid *tert*-butyl ester **(57)**



(2-Hydroxy-4-trifluoromethyl-phenyl)-carbamic acid *tert*-butyl esterwas prepared according to step 2 (method A) using 2-nitro-5-trifluoromethyl-phenol (0.2485 g, 1.2 mmol), di-*tert*-butyl dicarbonate (0.2619 g, 1.2 mmol), and Pd/C (0.0249 g). The product was obtained as a white solid (0.2335 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H, C<u>H</u>$_3$ Boc), 6.89 (s, 1H, CON<u>H</u>), 7.01 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.17 (s, 1H, C<u>H</u> Ar), 7.36 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (<u>C</u>H_3 Boc), 82.7 (<u>C</u>$(CH_3)_3$ Boc), 115.3 (<u>C</u>H Ar), 117.8 (q, $^3J_{C\text{-}F}$ = 3.9 Hz, <u>C</u>H Ar), 120.7 (<u>C</u>H Ar), 123.8 (q, $^1J_{C\text{-}F}$ = 270.1 Hz, <u>C</u>F_3), 126.9 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, <u>C</u>CF_3 Ar), 129.0 (<u>C</u> Ar), 146.6 (<u>C</u> Ar), 154.5 (<u>C</u>O amide).

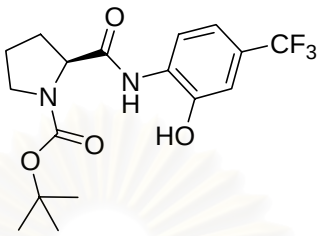
2.3.2.28 5-trifluoromethyl-2-aminophenol trifluoroacetate salt **(58)**



2-Hydroxy-4-trifluoromethyl-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (2-hydroxy-4-trifluoromethyl-phenyl)-carbamic acid *tert*-butyl ester (0.2218g, 0.8 mmol) and TFA (1 mL). The product was obtained as a white solid (0.2259 g, 97%); ^{1}H NMR (400 MHz, D_2O) δ 7.11 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar), 7.13 (s, 1H, C<u>H</u> Ar), 7.26 (d, *J* = 8.4 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, D_2O) δ 113.1 (<u>C</u>H Ar), 116.3 (q, $^1J_{C\text{-}F}$ = 290.1 Hz, <u>C</u>F_3 TFA), 117.1 (<u>C</u>H Ar), 121.5 (<u>C</u> Ar),

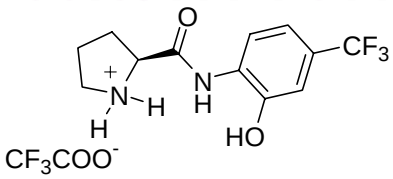
123.2 (q, $^{1}J_{C\text{-}F}$ = 270.3 Hz, <u>C</u>F_3), 124.4 (<u>C</u>H Ar), 131.2 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz, <u>C</u>CF_3 Ar), 149.9 (<u>C</u> Ar), 158.8 (q, $^{2}J_{C\text{-}F}$ = 31.1 Hz, <u>C</u>O TFA).

2.3.2.29 2-(2´-Hydroxy-4´-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(59)**



2-(2´-Hydroxy-4´-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.1208 g, 0.7 mmol), 2-hydroxy-4-trifluoromethyl-phenyl-ammonium trifluoroacetate (0.2045g, 0.7 mmol), TEA (0.0708 g, 0.7 mmol) and EDC.HCl (0.1534 g, 0.8 mmol). The product was obtained as a white solid (0.2227 g, 85%); $[\alpha]^{25}_{D}$ = -118.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H, C<u>H</u>$_3$ Boc), 1.95-2.34 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.42 and 3.55 (brs, 2H, C<u>H</u>$_2$N), 4.39 and 4.53 (brs, 1H, C<u>H</u>N), 6.99 (brs, 1H, C<u>H</u> Ar), 7.14(brs, 1H, C<u>H</u> Ar), 7.39 (brs, 1H, C<u>H</u> Ar), 7.97, 8.51 and 9.54 (N<u>H</u> and O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (<u>C</u>H$_2$(4)), 28.3 (<u>C</u>H$_3$ Boc), 28.6 (<u>C</u>H$_2$(3)), 47.3 (<u>C</u>H$_2$N), 60.3 and 62.1 (rotamer) (<u>C</u>HN), 81.6 (<u>C</u>(CH$_3$)$_3$ Boc), 113.3 and 115.1 (rotamer) (<u>C</u>H Ar), 117.0 (<u>C</u>H Ar), 120.2 and 121.6 (rotamer) (<u>C</u>H Ar), 123.8 (q, $^{1}J_{C\text{-}F}$ = 270.2 Hz, <u>C</u>F_3), 127.5 (q, $^{2}J_{C\text{-}F}$ = 25.1 Hz, <u>C</u>CF_3 Ar), 128.8 (<u>C</u> Ar), 146.7 and 147.5 (rotamer) (<u>C</u> Ar), 156.3 (<u>C</u>O Boc), 171.8 (<u>C</u>O amide).

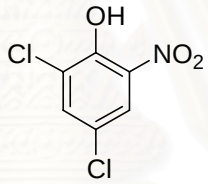
2.3.2.30 Pyrrolidine-2-carboxylic acid (2´-hydroxy-4´-trifluoromethyl-phenyl)-amide trifluoroacetate **(28j)**



Pyrrolidine-2-carboxylic acid (2´-hydroxy-4´-trifluoromethyl-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(2´-hydroxy-4´-

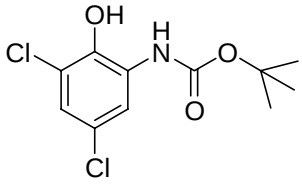
trifluoromethyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.1872 g, 0.5 mmol) and TFA (1 mL). The product was obtained as a white solid (0.1864 g, 96%); m.p. 205.5-207.7 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -35.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (m, 3H, C$\underline{H}_a\underline{H}_b$(3) and C$\underline{H}_2$(4)), 2.37 (m, 1H, CH$_a\underline{H}_b$(3)), 3.25 (m, 2H, C$\underline{H}_2$N), 4.54 (m, 1H, C$\underline{H}$N), 7.16 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 7.18 (s,1H, C$\underline{H}$ Ar), 8.11 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 10.10 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.1 ($\underline{C}$H$_2$(4)), 30.4 ($\underline{C}$H$_2$(3)), 46.4 ($\underline{C}$H$_2$N), 60.1 ($\underline{C}$HN), 111.8 ($\underline{C}$H Ar), 116.2 ($\underline{C}$H Ar), 117.3 (q, $^{1}J_{C\text{-}F}$ = 129.1 Hz, $\underline{C}$F$_3$ TFA), 122.5 ($\underline{C}$H Ar), 124.5 (q, $^{1}J_{C\text{-}F}$ = 270.0 Hz, $\underline{C}$F$_3$), 125.4 (q, $^{2}J_{C\text{-}F}$ = 31.7 Hz, $\underline{C}$CF$_3$ Ar), 129.6 ($\underline{C}$ Ar), 148.6 ($\underline{C}$ Ar), 158.8 (q, $^{2}J_{C\text{-}F}$ = 31.1 Hz, $\underline{C}$O TFA), 168.3 ($\underline{C}$O amide); Anal. Calcd for $C_{14}H_{14}F_6N_2O_4$: C, 43.31; H, 3.63; N, 7.22. Found: C, 43.52; H,3.68; N, 7.14 %.

2.3.2.31 2,4-Dichloro-6-nitro-phenol **(60)**



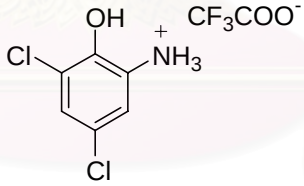
2,4-Dichloro-6-nitro-phenol was prepared according to step 1 using 2,4-dichloro-phenol (4.8900 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol). The product was obtained as a yellow solid (5.9904 g, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H, C$\underline{H}$ Ar), 8.05 (s, 1H, C$\underline{H}$ Ar); 10.91 (s, 1H, O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.0 ($\underline{C}$H Ar), 124.6 ($\underline{C}$ Ar), 125.7 ($\underline{C}$ Ar), 134.2 ($\underline{C}$ Ar), 137.3 ($\underline{C}$H Ar), 150.3 ($\underline{C}$ Ar).

2.3.2.32 (3,5-Dichloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(61)**



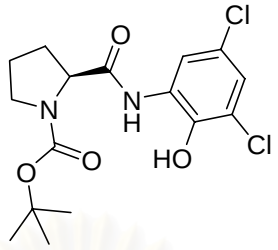
(3,5-Dichloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method B) 2,4-dichloro-6-nitro-phenol using (2.0800 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol), tin powder (excess) and hydrochloric acid (conc.)/ethanol (1:1) (10 mL). The product was obtained as a brown solid (1.2516 g, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H, C$\underline{H}_3$ Boc), 6.97 (s, 1H, CON$\underline{H}$ Boc), 7.01 (s, 1H, C$\underline{H}$ Ar), 7.84 (s, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (C$\underline{H}_3$ Boc), 81.8 ($\underline{C}(CH_3)_3$ Boc), 117.8 ($\underline{C}$H Ar), 120.3 ($\underline{C}$ Ar), 122.1 ($\underline{C}$H Ar), 125.8 ($\underline{C}$ Ar), 128.3 ($\underline{C}$ Ar), 139.4 ($\underline{C}$ Ar), 152.9 ($\underline{C}$O Boc).

2.3.2.33 2,4-Dichloro-6-aminophenol trifluoroacetate salt **(62)**



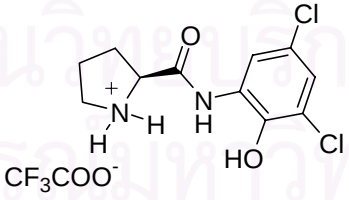
3,5-Dichloro-2-hydroxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (3,5-dichloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (0.8344 g, 3 mmol) and TFA (1 mL). The product was obtained as a brown solid (0.7798 g, 89%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (s, 1H, C$\underline{H}$ Ar), 6.76 (s, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.0 ($\underline{C}$ Ar), 115.9 (q, $^{1}J_{C\text{-}F}$ = 288.4 Hz, $\underline{C}F_3$ TFA), 118.6 ($\underline{C}$H Ar), 121.9 ($\underline{C}$ Ar), 124.1 ($\underline{C}$ Ar), 137.0 ($\underline{C}$H Ar), 140.6 ($\underline{C}$ Ar) 159.0 (q, $^{2}J_{C\text{-}F}$ = 37.2 Hz, $\underline{C}$O TFA).

2.3.2.34 2-(3′,5′-Dichloro-2′-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(63)**



2-(3′,5′-Dichloro-2′-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 3,5-dichloro-2-hydroxy-phenyl-ammonium trifluoroacetate (0.4381 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.4616 g, 82%); $[\alpha]^{25}_{D}$ = -111.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, C$\underline{H}_3$ Boc), 1.93-2.36 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.40 and 3.49 (brs, 2H, C$\underline{H}_2$N), 4.53 (brs, 1H, C$\underline{H}$N), 7.08 (brs, 1H, C$\underline{H}$ Ar), 7.45 (brs, 1H, C$\underline{H}$ Ar), 9.66 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (C$\underline{H}_2$(4)), 28.4 (C$\underline{H}_3$ Boc), 31.2 (C$\underline{H}_2$(3)), 47.3 (C$\underline{H}_2$N), 60.4 and 61.9 (rotamer) (C$\underline{H}$N), 81.3 (C$\underline{(CH_3)}_3$ Boc), 119.5 (C$\underline{H}$ Ar), 120.1 (C$\underline{}$ Ar), 122.7 (C$\underline{H}$ Ar), 125.0 (C$\underline{}$ Ar), 127.7 (C$\underline{}$ Ar), 142.2 (C$\underline{}$ Ar), 156.3 (C$\underline{O}$ Boc), 172.0 (C$\underline{O}$ amide).

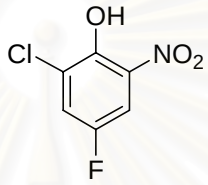
2.3.2.35 Pyrrolidine-2-carboxylic acid (3′,5′-dichloro-2′-hydroxy-phenyl)-amide trifluoroacetate **(28k)**



Pyrrolidine-2-carboxylic acid (3′,5′-dichloro-2′-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(3′,5′-dichloro-2′-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2627 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a white solid (0.2588 g, 95%); m.p. 150.2-152.3 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -34.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.90 (m, 2H, C$\underline{H}_2$(4)), 2.00 (m, 1H, C$\underline{H}_a$H$_b$(3)), 2.33 (m, 1H, CH$_a$$\underline{H}_b$(3)), 3.24 (m,

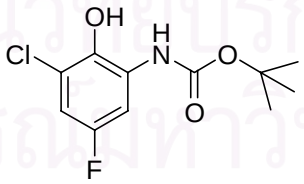
2H, C<u>H</u>$_2$N), 4.49 (m, 1H, C<u>H</u>N), 7.34 (s, 1H, C<u>H</u> Ar), 7.82 (s, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 (<u>C</u>H$_2$(4)), 30.2 (<u>C</u>H$_2$(3)), 46.4 (<u>C</u>H$_2$N), 60.0 (<u>C</u>HN), 117.6 (q, $^1J_{C\text{-}F}$ = 298.1 Hz, <u>C</u>F$_3$ TFA), 122.1 (<u>C</u>H Ar), 122.5 (<u>C</u> Ar), 123.3 (<u>C</u> Ar), 125.5 (<u>C</u>H Ar), 128.9 (<u>C</u> Ar), 144.5 (<u>C</u> Ar), 158.8 (q, $^2J_{C\text{-}F}$ = 31.1 Hz, <u>C</u>O TFA), 168.5 (<u>C</u>O amide); Anal. Calcd for $C_{13}H_{13}Cl_2F_3N_2O_4$: C, 40.12; H, 3.37; N, 7.20. Found: C, 40.18; H, 3.37; N, 7.30 %.

2.3.2.36 2-Chloro-4-fluoro-6-nitro-phenol **(64)**



2-Chloro-4-fluoro-6-nitro-phenol was prepared according to step 1 using 2-chloro-4-fluoro-phenol (4.3965 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol). The product was obtained as a yellow solid (0.5287 g, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, $^3J_{H\text{-}F}$ = 8.0 Hz, $^4J_{H\text{-}H}$ = 2.8 Hz, 1H, C<u>H</u> Ar), 7.77 (dd, $^3J_{C\text{-}F}$ = 8.0 Hz, $^4J_{H\text{-}H}$ = 2.8 Hz, 1H, C<u>H</u> Ar), 10.76 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.7 (d, $^2J_{C\text{-}F}$ = 27.0 Hz, <u>C</u>H Ar), 125.6 125.9 (d, $^3J_{C\text{-}F}$ = 9.9 Hz, <u>C</u> Ar), (d, $^2J_{C\text{-}F}$ = 26.1 Hz, <u>C</u>H Ar), 133.6 (<u>C</u> Ar), 148.4 (d, $^3J_{C\text{-}F}$ = 2.3 Hz, <u>C</u> Ar), 153.6 (d, $^1J_{C\text{-}F}$ = 244.7 Hz, <u>C</u> Ar).

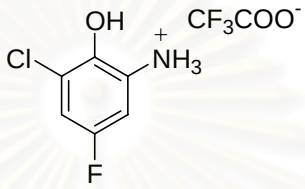
2.3.2.37 (3-Chloro-5-fluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(65)**



(3-Chloro-5-fluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method B) using 2-chloro-4-fluoro-6-nitro-phenol (1.9154 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol), tin powder (excess) and hydrochloric acid (conc.)/ethanol (1:1) (10 mL). The product was obtained as a brown oil (1.3585 g, 52%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H,

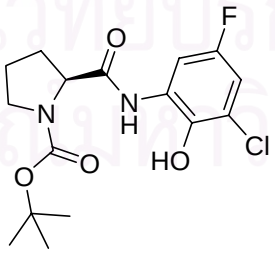
C<u>H</u>$_3$ Boc), 6.73 (d, $^3J_{H\text{-}F}$ = 8.0 Hz, 1H, <u>C</u>H Ar), 7.03 (s, 1H, CON<u>H</u> Boc), 7.69 (d, $^3J_{H\text{-}F}$ = 9.6 Hz, 1H, <u>C</u>H Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (<u>C</u>H$_3$ Boc), 81.6 (<u>C</u>(CH$_3$)$_3$ Boc), 105.4 (d, $^2J_{C\text{-}F}$ = 28.9 Hz, <u>C</u>H Ar), 108.39 (d, $^2J_{C\text{-}F}$ = 26.7 Hz, <u>C</u>H Ar), 119.4 (d, $^3J_{C\text{-}F}$ = 12.6 Hz, <u>C</u> Ar), 128.1 (d, $^3J_{C\text{-}F}$ = 12.5 Hz, <u>C</u> Ar), 136.8 (<u>C</u> Ar), 153.8 (d, $^1J_{C\text{-}F}$ = 233.5 Hz, <u>C</u> Ar), 157.4 (<u>C</u>O Boc).

2.3.2.38 2-Chloro-4-fluoro-6-aminophenol trifluoroacetate salt **(66)**



3-Chloro-5-fluoro-2-hydroxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (3-chloro-5-fluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (0.7850 g, 3 mmol) and TFA (1 mL). The product was obtained as a brown solid (0.7468 g, 90%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.56 (m, 2H, C<u>H</u> Ar), ^{13}C NMR (100 MHz, DMSO-d_6) δ 102.2 (d, $^2J_{C\text{-}F}$ = 25.9 Hz, <u>C</u>H Ar), 105.5 (d, $^2J_{C\text{-}F}$ = 26.1 Hz, <u>C</u>H Ar), 115.9 (q, $^1J_{C\text{-}F}$ = 288.6 Hz, <u>C</u>F$_3$ TFA), 112.5 (d, $^3J_{C\text{-}F}$ = 13.7 Hz, <u>C</u> Ar), 137.1 (d, $^3J_{C\text{-}F}$ = 12.6 Hz, <u>C</u> Ar), 138.1 (<u>C</u> Ar), 156.0 (d, $^1J_{C\text{-}F}$ = 234.7 Hz, <u>C</u> Ar), 159.0 (q, $^2J_{C\text{-}F}$ = 36.9 Hz, <u>C</u>O TFA).

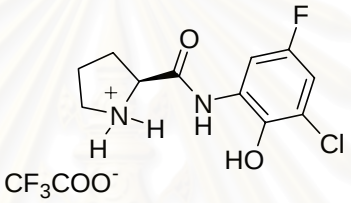
2.3.2.39 2-(3´-Chloro-5´-fluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(67)**



2-(3´-Chloro-5´-fluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 3-chloro-5-fluoro-2-hydroxy-phenyl-ammonium trifluoroacetate (0.4134 mg, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl

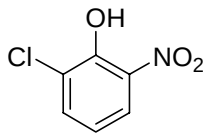
(0.3067 g, 1.6 mmol). The product was obtained as a brown solid (0.4016 g, 75%); $[\alpha]^{25}_{D}$ = -127.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, C$\underline{H}_3$ Boc), 1.93-2.40 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.89 and 3.48 (brs, 2H, C$\underline{H}_2$N), 4.36 and 4.51 (brs, 1H, C$\underline{H}$N), 6.83 (brs, 1H, C$\underline{H}$ Ar), 7.40 (brs, 1H, C$\underline{H}$ Ar), 9.60 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (C$\underline{H}_2$(4)), 28.3 (C$\underline{H}_3$ Boc), 31.1 (C$\underline{H}_2$(3)), 47.5 (C$\underline{H}_2$N), 60.5 and 62.0 (rotamer) (C$\underline{H}$N), 81.4 (C$\underline{(CH_3)}_3$ Boc), 107.2 (C$\underline{H}$ Ar), 111.9 (C$\underline{H}$ Ar), 121.7 (C$\underline{}$ Ar), 127.5 (C$\underline{}$ Ar), 139.4 (C$\underline{}$ Ar), 154.4 (C$\underline{}$ Ar), 156.8 (C$\underline{O}$ Boc), 171.6 (C$\underline{O}$ amide).

2.3.2.40 Pyrrolidine-2-carboxylic acid (3´-chloro-5´-fluoro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28l)**



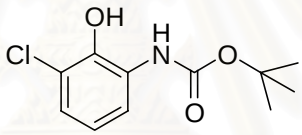
Pyrrolidine-2-carboxylic acid (3´-chloro-5´-fluoro-2´-hydroxy-phenyl)-amide trifluoroacetate was prepared according to step 5 using 2-(3´-chloro-5´-fluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2512 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a brown solid (0.2400 g, 92%); m.p. 151.9-154.1 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -44.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.35 (m, 1H, CH$_a$$\underline{H}_b$(3)), 3.25 (m, 2H, C$\underline{H}_2$N), 4.55 (m, 1H, C$\underline{H}$N), 7.16 (d, $^3J_{H\text{-}F}$ = 8.0 Hz, 1H, C$\underline{H}$ Ar), 7.67 (d, $^3J_{H\text{-}F}$ = 10.0 Hz, 1H, C$\underline{H}$ Ar), 10.23 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 (C$\underline{H}_2$(4)), 30.3 (C$\underline{H}_2$(3)), 46.3 (C$\underline{H}_2$N), 60.0 (C$\underline{H}$N), 109.0 (d, $^2J_{C\text{-}F}$ = 27.2 Hz, C$\underline{H}$ Ar), 112.6 (d, $^2J_{C\text{-}F}$ = 26.1 Hz, C$\underline{H}$ Ar), 117.5 (q, $^1J_{C\text{-}F}$ = 297.0 Hz, C$\underline{F}_3$ TFA), 122.2 (d, $^3J_{C\text{-}F}$ = 12.9 Hz, C$\underline{}$ Ar), 128.9 (d, $^3J_{C\text{-}F}$ = 12.3 Hz, C$\underline{}$ Ar), 141.7 (C$\underline{}$ Ar), 154.8 (d, $^1J_{C\text{-}F}$ = 235.6 Hz, C$\underline{}$ Ar), 159.0 (q, $^2J_{C\text{-}F}$ = 33.7 Hz, C$\underline{O}$ TFA), 168.5 (C$\underline{O}$ amide); Anal. Calcd for $C_{13}H_{13}ClF_4N_2O_4$: C, 41.89; H, 3.52; N, 7.52. Found: C, 41.90; H, 3.57; N, 7.52 %.

2.3.2.41 2-Chloro-6-nitro-phenol **(68)**



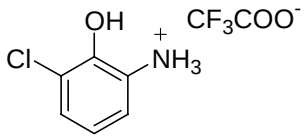
2-Chloro-6-nitro-phenol was prepared according to step 1 using 2-chloro-phenol (5.1424 g, 40 mmol) and nitric acid (2.64 mL, 60 mmol). The product was obtained as a yellow solid (2.2276 g, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (t, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 7.54 (d, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 8.03 (d, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 10.99 (s, 1H, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6 (<u>C</u>H Ar), 123.6 (<u>C</u>H Ar), 124.6 (<u>C</u> Ar), 134.5 (<u>C</u> Ar), 137.5 (<u>C</u>H Ar), 151.4 (<u>C</u> Ar).

2.3.2.42 (3-Chloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(69)**



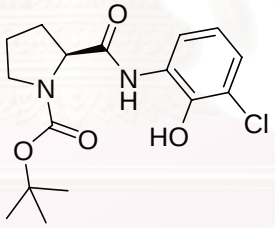
(3-Chloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester was prepared according to step 2 (method B) using 2-chloro-6-nitro-phenol (1.7555 g, 10 mmol), di-*tert*-butyl dicarbonate (2.1825 g, 10 mmol), tin powder (excess) and hydrochloric acid (conc.)/ethanol (1:1) (10 mL). The product was obtained as a white solid (1.1941 g, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H, C<u>H</u>$_3$ Boc), 6.80 (t, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 6.99 (d, *J* = 8.0 Hz, 1H, C<u>H</u> Ar), 7.68 (d, *J* = 8.0 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (<u>C</u>H$_3$ Boc), 81.6 (<u>C</u>(CH$_3$)$_3$ Boc), 118.4 (<u>C</u>H Ar), 120.8 (<u>C</u> Ar), 121.2 (<u>C</u>H Ar), 123.4 (<u>C</u>H Ar), 127.8 (<u>C</u> Ar), 141.4 (<u>C</u> Ar), 153.6 (<u>C</u>O Boc).

2.3.2.43 2-Chloro-6-aminophenol trifluoroacetate salt **(70)**



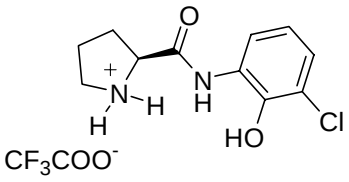
3-Chloro-2-hydroxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (3-chloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (0.7311 g, 3 mmol) and TFA (1 mL). The product was obtained as a white solid (0.6723 g, 87%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (t, J = 8.0 Hz, 1H, C<u>H</u> Ar), 7.06 (d, J = 8.0 Hz, 1H, C<u>H</u> Ar), 7.21 (d, J = 8.0 Hz, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.6 (q, $^{1}J_{C\text{-}F}$ = 292.7 Hz, <u>C</u>F$_3$ TFA), 119.6 (<u>C</u> Ar), 121.1 (<u>C</u>H Ar), 121.7 (<u>C</u> Ar), 125.0 (<u>C</u>H Ar), 129.1 (<u>C</u>H Ar), 144.5 (<u>C</u> Ar), 159.0 (q, $^{2}J_{C\text{-}F}$ = 34.3 Hz, <u>C</u>O TFA).

2.3.2.44 2-(3´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(71)**



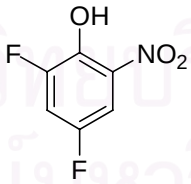
2-(3´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 3-chloro-2-hydroxy-phenyl-ammonium trifluoroacetate (0.3879 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.3823 g, 75%); $[\alpha]^{25}_{D}$ = -135.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H, C<u>H</u>$_3$ Boc), 1.91-2.35 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.44 (brs, 2H, C<u>H</u>$_2$N), 4.45 (brs, 1H, C<u>H</u>N), 6.72 (brs, 1H, C<u>H</u> Ar), 7.08 (brs, 1H, C<u>H</u> Ar), 7.21 (d, J = 8 Hz, 1H, C<u>H</u> Ar), 7.65, 8.40 and 9.67 (N<u>H</u> and O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (<u>C</u>H$_2$(4)), 28.6 (<u>C</u>H$_3$ Boc), 31.4 (<u>C</u>H$_2$(3)), 47.5 (<u>C</u>H$_2$N), 60.5 and 62.0 (rotamer) (<u>C</u>HN), 81.4 (<u>C</u>(CH$_3$)$_3$ Boc), 120.7 (2 x <u>C</u>H Ar), 123.0 (<u>C</u> Ar), 126.3 (<u>C</u>H Ar), 127.3 (<u>C</u> Ar), 144.1 (<u>C</u> Ar), 156.5 (<u>C</u>O Boc), 172.3 (<u>C</u>O amide).

2.3.2.45 Pyrrolidine-2-carboxylic acid (3´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28m)**



Pyrrolidine-2-carboxylic acid (3´-chloro-2´-hydroxy-phenyl)-amide was prepared trifluoroacetate according to step 5 using 2-(3´-chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2386 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a white solid (0.2384 g, 96%); m.p. 110.3-113.2 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -39.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.36 (m, 1H, CH$_a\underline{H}_b$(3)), 3.25 (m, 2H, C$\underline{H}_2$N), 4.47 (m, 1H, C$\underline{H}$N), 6.85 (t, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 7.19 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 7.60 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 10.08 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.1 (C$\underline{H}_2$(4)), 35.2 (C$\underline{H}_2$(3)), 51.4 (C$\underline{H}_2$N), 65.0 (C$\underline{H}$N), 117.9 (q, $^{1}J_{C\text{-}F}$ = 298.2 Hz, C$\underline{F}_3$ TFA), 125.5 (C$\underline{H}$ Ar), 126.7 (C$\underline{H}$ Ar), 128.1 (C$\underline{H}$ Ar), 131.7 (C$\underline{H}$ Ar), 132.7 (C$\underline{H}$ Ar), 160.7 (C$\underline{H}$ Ar), 163.5 (q, $^{2}J_{C\text{-}F}$ = 30.7 Hz, C$\underline{O}$ TFA), 173.2 (C$\underline{O}$ amide); Anal. Calcd for $C_{13}H_{14}ClF_3N_2O_4$: C, 44.02; H, 3.98; N, 7.90. Found: C, 44.03; H, 4.00; N, 7.94 %.

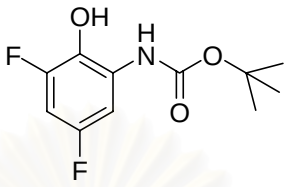
2.3.2.46 2,4-Difluoro-6-nitro-phenol **(72)**



2,4-Difluoro-6-nitro-phenol was prepared according to step 1 using 2,4-difluoro-phenol (3.9030 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol). The product was obtained as a yellow solid (3.6088 g, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H, C$\underline{H}$ Ar), 7.65 (m, 1H, C$\underline{H}$ Ar), 10.32 (s, 1H, O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.4 (dd, $^{2}J_{C\text{-}F}$ = 27.1 Hz, $^{4}J_{C\text{-}F}$ = 4.3 Hz, C$\underline{H}$ Ar), 113.0 (dd, $^{2}J_{C\text{-}F}$ = 27.2 Hz, $^{2}J_{C\text{-}F}$ = 21.3 Hz, C$\underline{H}$ Ar), 134.1 (C$\underline{H}$ Ar), 142.2 (dd, $^{2}J_{C\text{-}F}$ = 15.0 Hz, $^{4}J_{C\text{-}F}$ = 3.3 Hz,

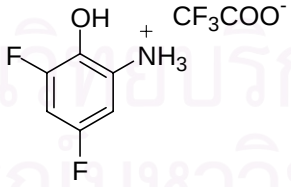
C Ar), 151.8 (dd, $^{1}J_{C\text{-}F}$ = 86.0 Hz, $^{3}J_{C\text{-}F}$ = 11.1 Hz, C Ar), 154.3 (dd, $^{1}J_{C\text{-}F}$ = 76.8 Hz, $^{3}J_{C\text{-}F}$ = 10.9 Hz, C Ar).

2.3.2.47 (3,5-Difluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(73)**



(3,5-Difluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl esterwas prepared according to step 2 (method B) using 2,4-difluoro-6-nitro-phenol (1.7509 g, 10 mmol), di-*tert*-butyl dicarbonate 2.1825 g, 10 mmol), tin powder (excess) and hydrochloric acid (conc.)/ethanol (1:1) (10 mL). The product was obtained as a brown solid (1.2016 g, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H, CH_3 Boc), 6.21 (brs, 1H, CH Ar), 6.24 (brs, 1H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6 (CH_3 Boc), 84.9 (C$(CH_3)_3$ Boc), 93.8 (dd, $^{2}J_{C\text{-}F}$ = 27.5 Hz, $^{2}J_{C\text{-}F}$ = 23.1 Hz, CH Ar), 98.5 (dd, $^{2}J_{C\text{-}F}$ = 26.3 Hz, $^{4}J_{C\text{-}F}$ = 2.8 Hz, CH Ar), 122.9 (dd, $^{2}J_{C\text{-}F}$ = 15.2 Hz, $^{4}J_{C\text{-}F}$ = 3.8 Hz, C Ar), 141.5 (dd, $^{3}J_{C\text{-}F}$ = 13.6, 4.8 Hz, C Ar), 150.8 (CO Boc), 155.3 (dd, $^{1}J_{C\text{-}F}$ = 246.0 Hz, $^{3}J_{C\text{-}F}$ = 15.7 Hz, C Ar), 160.6 (dd, $^{1}J_{C\text{-}F}$ = 241.9 Hz, $^{3}J_{C\text{-}F}$ = 14.2 Hz, C Ar).

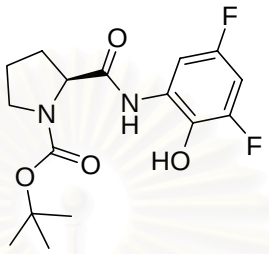
2.3.2.48 2,4-Difluoro-6-aminophenol trifluoroacetate salt **(74)**



3,5-Difluoro-2-hydroxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (3,5-difluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester (0.7357 g, 3 mmol) and TFA (1 mL). The product was obtained as a brown solid (0.6763 g, 87%); ^{1}H NMR (400 MHz, D_2O) δ 6.84 (m, 1H, CH Ar), 6.92 (m, 1H, CH Ar); ^{13}C NMR (100 MHz, D_2O) δ 104.5 (dd, Hz, $^{2}J_{C\text{-}F}$ = 26.9 Hz, $^{2}J_{C\text{-}F}$ = 23.0 Hz, CH Ar), 106.4 (dd, $^{2}J_{C\text{-}F}$ = 26.6 Hz, $^{4}J_{C\text{-}F}$ = 3.7 Hz, CH Ar), 116.1 (q, $^{1}J_{C\text{-}F}$ =

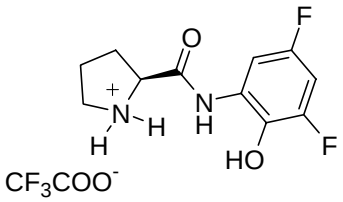
290.0 Hz, $\underline{C}F_3$ TFA), 120.5 (m, $\underline{C}$ Ar), 134.9 (dd, $^2J_{C\text{-}F}$ = 17.7 Hz, $^4J_{C\text{-}F}$ = 3.7 Hz, $\underline{C}$ Ar), 151.4 (dd, $^1J_{C\text{-}F}$ = 241.0 Hz, $^3J_{C\text{-}F}$ = 13.5 Hz, $\underline{C}$ Ar), 154.5 (dd, $^1J_{C\text{-}F}$ = 238.7 Hz, $^3J_{C\text{-}F}$ = 12.3 Hz, $\underline{C}$ Ar), 162.9 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, $\underline{C}$O TFA).

2.3.2.49 2-(3´,5´-Difluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(75)**



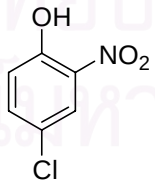
2-(3´,5´-Difluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 3,5-difluoro-2-hydroxy-phenyl-ammonium trifluoroacetate (0.3887 mg, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.3903 g, 76%); $[\alpha]^{27}_D$ = -101.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, C$\underline{H}_3$ Boc), 1.92-2.31 (brs, 4H, C$\underline{H}_2$(3) and C$\underline{H}_2$(4)), 3.40 and 3.51 (brs, 2H, C$\underline{H}_2$N), 4.36 and 4.51 (brs, 1H, C$\underline{H}$N), 6.57 (brs, 1H, C$\underline{H}$ Ar), 7.08 (brs, 1H, C$\underline{H}$ Ar), 8.53 and 9.55 (N$\underline{H}$ and O$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 and 24.5 (rotamer) ($\underline{C}H_2$(4)), 28.2 ($\underline{C}H_3$ Boc), 31.2 ($\underline{C}H_2$(3)), 47.3 ($\underline{C}H_2$N), 60.5 and 61.9 (rotamer) ($\underline{C}$HN), 81.4 ($\underline{C}(CH_3)_3$ Boc), 100.0 ($\underline{C}$H Ar), 103.6 ($\underline{C}$H Ar), 127.9 (brs, $\underline{C}$ Ar), 131.1 and 132.2 (rotamer) (brs, $\underline{C}$ Ar), 150.1 and 150.7 (rotamer), 152.5 and 153.1 (rotamer), 154.0 and 154.8 (rotamer) (brs, 2 x $\underline{C}$ Ar), 156.2 ($\underline{C}$O Boc), 171.8 ($\underline{C}$O amide).

2.3.2.50 Pyrrolidine-2-carboxylic acid (3´,5´-difluoro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28n)**



Pyrrolidine-2-carboxylic acid (3´,5´-difluoro-2´-hydroxy-phenyl)-amide trifluoroacetate according to step 5 using 2-(3´,5´-difluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2396 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a white solid (0.2195 g, 88%); m.p. 166.7-168.8 ^{o}C (dec); $[\alpha]^{25}_{D}$ = -40.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.90 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.36 (m, 1H, CH$_a\underline{H}_b$(3)), 3.25 (m, 2H, C$\underline{H}_2$N), 4.54 (m, 1H, C$\underline{H}$N), 7.03 (m, 1H, C$\underline{H}$ Ar), 7.63 (m, 1H, C$\underline{H}$ Ar), 10.21 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 ($\underline{C}$H$_2$(4)), 30.4 ($\underline{C}$H$_2$(3)), 46.4 ($\underline{C}$H$_2$N), 60.0 ($\underline{C}$HN), 100.4 (dd, $^{2}J_{C\text{-}F}$ = 27.0 Hz, $^{2}J_{C\text{-}F}$ = 23.5 Hz, $\underline{C}$H Ar), 104.9 (dd, $^{2}J_{C\text{-}F}$ = 27.3 Hz, $^{4}J_{C\text{-}F}$ = 2.8 Hz, $\underline{C}$H Ar), 117.7 (q, $^{1}J_{C\text{-}F}$ = 298.0 Hz, $\underline{C}$F$_3$ TFA), 128.8 (m, $\underline{C}$ Ar), 132.8 (dd, $^{2}J_{C\text{-}F}$ = 16.5 Hz, $^{4}J_{C\text{-}F}$ = 2.4 Hz, $\underline{C}$ Ar), 151.5 (dd, $^{1}J_{C\text{-}F}$ = 237.9 Hz, $^{3}J_{C\text{-}F}$ = 14.9 Hz, $\underline{C}$ Ar), 154.2 (dd, $^{1}J_{C\text{-}F}$ = 233.4 Hz, $^{3}J_{C\text{-}F}$ = 12.3 Hz, $\underline{C}$ Ar), 158.6 (q, $^{2}J_{C\text{-}F}$ = 30.8 Hz, $\underline{C}$O TFA), 168.3 ($\underline{C}$O amide); Anal. Calcd for $C_{13}H_{13}ClF_5N_2O_4$: C, 43.83; H, 3.68; N, 7.86. Found: C, 44.03; H, 3.99; N, 7.94 %.

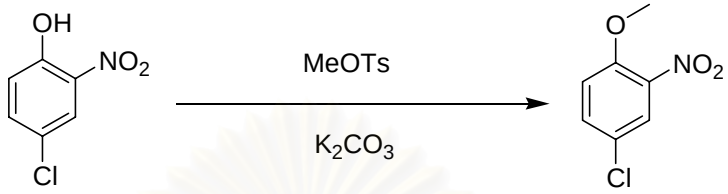
2.3.2.51 4-Chloro-2-nitro-phenol **(76)**



4-Chloro-2-nitro-phenol was prepared according to step 1 using 4-chloro-phenol (3.8568 g, 30 mmol) and nitric acid (1.98 mL, 45 mmol). The product was obtained as a yellow solid (5.1024 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.53 (dd, *J* = 8.8, 2.4 Hz, 1H, C$\underline{H}$ Ar), 8.09 (d, *J* = 2.4 Hz, 1H,

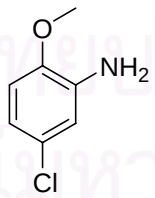
CH Ar), 10.46 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6 (CH Ar), 124.5 (CH Ar), 125.4 (C Ar), 133.8 (C Ar), 137.8 (CH Ar), 153.9 (C Ar).

2.3.2.52 4-Chloro-1-methoxy-2-nitro-benzene **(77)**



4-Chloro-2-nitro-phenol (1.7355 g, 10 mmol) was dissolved in MeCN (10 mL). Then potassium carbonate (3.4553 g, 25 mmol) (2.5 eq) and methyl-4-toluene sulfonate (2.7935 g, 1.5 mmol) (1.5 eq) were added and the resulting mixture was reflux for 6 hr. The mixture was added water (20 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined CH_2Cl_2 extracts were dried, and the solvent evaporated in *vacuo*. The product was obtained as a yellow solid (1.8383 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H, OCH_3), 7.03 (d, *J* = 9.2 Hz, 1H, CH Ar), 7.45 (dd, *J* = 9.2, 2.8 Hz, 1H, CH Ar), 7.75 (d, *J* = 2.8 Hz, 1H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.8 (OCH_3), 114.9 (CH Ar), 125.1 (C Ar), 125.4 (CH Ar), 134.1 (CH Ar), 139.5 (C Ar), 151.7 (C Ar).

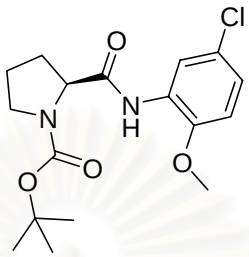
2.3.2.54 5-Chloro-2-methoxy-phenyl-ammonium trifluoroacetate **(78)**



5-Chloro-2-methoxy-phenyl-ammonium trifluoroacetate was prepared according to step 3 using (5-chloro-2-methoxy-phenyl)-carbamic acid tert-butyl ester (0.9379 g, 5 mmol), tin powder (excess) and hydrochloric acid (conc.)/ethanol (1:1) (10 mL). The product was obtained as a white solid (0.7697 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H, OCH_3), 3.90 (s, 2H, NH_2 Ar), 6.67 (s, 3H, 3 x CH Ar);

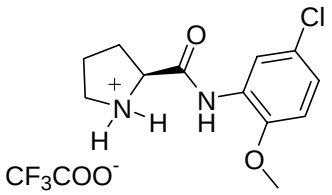
^{13}C NMR (100 MHz, $CDCl_3$) δ 56.8 (O<u>C</u>H$_3$), 111.1 (<u>C</u>H Ar), 114.5 (<u>C</u>H Ar), 117.6 (<u>C</u>H Ar), 125.8 (<u>C</u> Ar), 137.4 (<u>C</u> Ar), 145.9 (<u>C</u> Ar).

2.3.2.55 2-(5´-Chloro-2´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(79)**



2-(5´-Chloro-2´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester was prepared according to step 4 using *N*-Boc-L-proline (0.3229 g, 1.5 mmol), 5-chloro-2-methoxy-phenyl-ammonium trifluoroacetate (0.2364 g, 1.5 mmol), TEA (0.1518 g, 1.5 mmol) and EDC.HCl (0.3067 g, 1.6 mmol). The product was obtained as a white solid (0.4631 g, 87%); $[\alpha]^{25}_D$ = -130.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 and 1.46 (s, 9H, C<u>H</u>$_3$ Boc), 1.88-2.41 (brs, 4H, C<u>H</u>$_2$(3) and C<u>H</u>$_2$(4)), 3.40 and 3.50 (brs, 2H, C<u>H</u>$_2$N), 3.80 (s, 3H, OC<u>H</u>$_3$), 4.26 and 4.44 (brs, 1H, C<u>H</u>N), 6.71 (brs, 1H, C<u>H</u> Ar), 6.92 (brs, 1H, C<u>H</u> Ar), 8.41 (brs, 1H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 and 24.5 (rotamer) (<u>C</u>H$_2$(4)), 28.3 (<u>C</u>H$_3$ Boc), 31.2 (<u>C</u>H$_2$(3)), 47.1 (<u>C</u>H$_2$N), 55.9 (O<u>C</u>H$_3$), 60.8 and 62.1 (rotamer) (<u>C</u>HN), 80.6 (<u>C</u>(CH$_3$)$_3$ Boc), 110.7 (<u>C</u>H Ar), 119.5 (<u>C</u>H Ar), 122.9 and 123.3 (rotamer) (<u>C</u>H Ar), 125.8 (<u>C</u> Ar), 127.9 and 128.8 (rotamer) (<u>C</u> Ar), 146.7 (<u>C</u> Ar), 155.8 (<u>C</u>O Boc), 170.6 (<u>C</u>O amide).

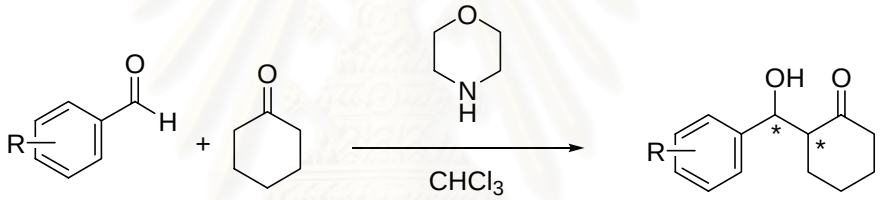
2.3.2.56 Pyrrolidine-2-carboxylic acid (5´-chloro-2´-methoxy-phenyl)-amide trifluoroacetate **(28q)**



Pyrrolidine-2-carboxylic acid (5´-chloro-2´-methoxy-phenyl)-amide trifluoroacetate according to step 5 using 2-(5´-chloro-2´-methoxy-phenylcarbamoyl)-

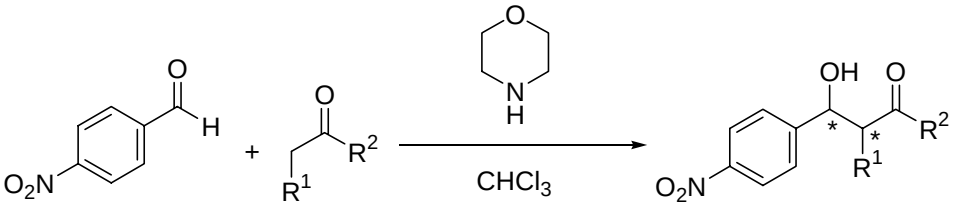
pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.2483 g, 0.7 mmol) and TFA (1 mL). The product was obtained as a white solid (0.2426 g, 94%); m.p. 185.5-186.9 ^{o}C (dec); $[\alpha]^{27}_{D}$ = -28.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (m, 3H, C$\underline{H}_a$H$_b$(3) and C$\underline{H}_2$(4)), 2.35 (m, 1H, CH$_a\underline{H}_b$(3)), 3.26 (m, 2H, C$\underline{H}_2$N), 3.83 (s, 3H, OC$\underline{H}_3$), 4.55 (m, 1H, C$\underline{H}$N), 7.08 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$ Ar), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1H, C$\underline{H}$ Ar), 7.99 (d, *J* = 2.4 Hz, 1H, C$\underline{H}$ Ar), 10.09 (N$\underline{H}$ or O$\underline{H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0 ($\underline{C}$H$_2$(4)), 30.4 ($\underline{C}$H$_2$(3)), 46.3 ($\underline{C}$H$_2$N), 56.6 (O$\underline{C}$H$_3$), 60.0 ($\underline{C}$HN), 113.3 ($\underline{C}$H Ar), 117.6 (q, $^{1}J_{C\text{-}F}$ = 296.6 Hz, $\underline{C}$F$_3$ TFA), 122.0 ($\underline{C}$H Ar), 124.2 ($\underline{C}$H Ar) , 125.1 ($\underline{C}$ Ar), 127.9 ($\underline{C}$ Ar), 149.2 ($\underline{C}$ Ar), 158.9 (q, $^{2}J_{C\text{-}F}$ = 27.3 Hz, $\underline{C}$O TFA), 168.2 ($\underline{C}$O amide); Anal. Calcd for $C_{14}H_{16}ClF_3N_2O_4$: C, 45.60; H, 4.37; N, 7.60. Found: C, 45.67; H, 4.35; N, 7.61 %.

2.4 General procedure for the preparation of racemic aldol products from aldehydes and cyclohexanone



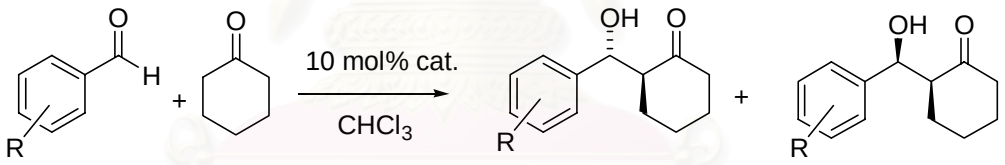
To the 1:1 chlorofrom/cyclohexanone mixture (2 mL) was added the corresponding aldehyde at 30 ^{o}C. Then 1 equiv of morpholine was added with vigorous stirring. The mixture treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate (2 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed *in vacuo*. The residue was purified through flash column chromatography with hexanes-ethyl acetate to afford the racemic aldol products as mixture of all four diastereomers.

2.5 General procedure for the preparation of racemic aldol products from 4-nitrobenzaldehyde and ketones



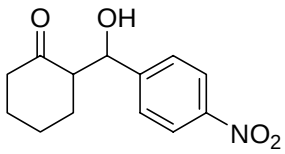
To the 1:1 chlorofrom/corresponding ketone (2 mL) was added the 4-nitrobenzaldehyde at 30 ^{o}C. Then 1 equiv of morpholine was added with vigorous stirring. The mixture treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate (2 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed *in vacuo*. The residue was purified through flash column chromatography with hexanes-ethyl acetate to afford the racemic aldol products as mixture of diastereomers.

2.6 General procedure for the direct Aldol reaction



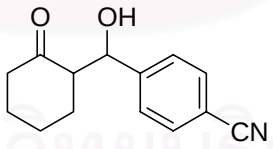
The L-prolinamide derivatives (0.05 mmol) and corresponding aldehyde (0.5 mmol) were stirred in 2 mL of chlorofrom/cyclohexanone (1:1) at 30 ^{0}C. The reaction mixture was stirred for 29–72 hours. The mixture treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate (2x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed *in vacuo*. The residue was purified by flash column chromatography with hexanes-ethyl acetate to afford the pure adducts.

2.6.1 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(80a)**



2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone was prepared according to the general procedure using 4-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cyclohexanone (1 mL) and purified by column chromatography to give the product as a white solid (0.1159 g, 93%). *anti*/*syn* = 91:9,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.42 (m, 1H, C$\underline{H}_2$), 1.54 -1.84 (m, 4H , C$\underline{H}_2$), 2.09-2.14 (m, 1H, C$\underline{H}_2$), 2.38 (dd, *J* = 12.8, 6.4 Hz, 1H, C$\underline{H}$), 2.48-2.52 (m, 1H, C$\underline{H}_2$), 2.55-2.62 (m, 1H, C$\underline{H}_2$), 4.90 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$OH), 7.50 (d, *J* = 8.8 Hz, 2H, C$\underline{H}$ Ar), 8.21 (d, *J* = 8.8 Hz, 2H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (C$\underline{H}_2$), 27.6 (C$\underline{H}_2$), 30.6 (C$\underline{H}_2$), 42.6 (C$\underline{H}_2$), 57.1 (C$\underline{H}$), 73.7 (C$\underline{H}$OH), 123.4 (C$\underline{H}$ Ar), 127.9 (C$\underline{H}$ Ar), 147.4 (C$\underline{}$ Ar), 148.6 (C$\underline{}$ Ar), 214.7 (C$\underline{}$O); HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 70.9 min and t_R(major) 95.2 min, 96 %*ee*; $[\alpha]^{20}_{D}$ = + 1.9 (*c* 1.0, $CHCl_3$).

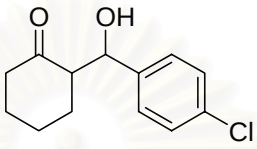
2.6.2 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(80b)**



4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile was prepared according to the general procedure using 4-cyano-benzaldehyde (65.6 mg, 0.5 mmol) and cyclohexanone (1mL) and purified by column chromatography to give a white solid (0.1101 g, 96%). *anti*/*syn*= 86/14,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.32 (m, 1H, C$\underline{H}_2$), 1.748-1.61 (m, 3H, C$\underline{H}_2$), 1.73-1.76 (m, 1H, C$\underline{H}_2$), 2.01-2.04 (m, 1H, C$\underline{H}_2$), 2.30 (td, *J* = 13.2, 6.0 Hz, 1H, C$\underline{H}$), 2.39-2.42 (m, 1H, C$\underline{H}_2$), 2.51-2.58 (m, 1H, C$\underline{H}_2$), 4.79 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$OH), 7.39 (d, *J* = 8.4 Hz, 2H, C$\underline{H}$ Ar), 7.57 (d, *J* = 8.4 Hz, 2H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (C$\underline{H}_2$), 27.6 (C$\underline{H}_2$), 30.6 (C$\underline{H}_2$),

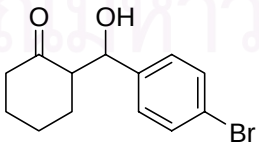
42.5 (CH_2), 57.0 (CH), 73.9 (CHOH), 111.4 (C Ar), 118.7 (CN), 127.8 (CH Ar), 132.1 (CH Ar), 146.5 (C Ar), 214.8 (CO); HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 230 nm) t_R(minor) 55.3 min and t_R(major) 70.4 min, 91 %*ee*; $[\alpha]^{20}_D$ = +9.2 (*c* 1.0, $CHCl_3$).

2.6.3 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(80c)**



2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone was prepared according to the general procedure using 4-chloro-benzaldehyde (70.3 mg, 0.5 mmol) and cyclohexanone (1mL) and purified by column chromatography to give a white solid (0.0895 g, 75%). *anti*/*syn*= 89/11,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.31 (m, 1H, CH_2), 1.50-1.68 (m, 3H, CH_2), 1.78-1.79 (m, 1H, CH_2), 2.04-2.08 (m, 1H, CH_2), 2.32 (td, *J*= 13.2, 6.0 Hz, 1H, CH), 2.43-2.47 (m, 1H, CH_2), 2.50-2.57 (m, 1H, CH_2), 4.74 (d, *J* = 8.4 Hz, 1H, CHOH), 7.26 (dd, *J* = 24.4, 8.4 Hz, 4H, CH Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (CH_2), 27.7 (CH_2), 30.7 (CH_2), 42.6 (CH_2), 57.3 (CH), 74.0 (CHOH), 128.4 (CH Ar), 128.5 (CH Ar), 133.5 (C Ar), 139.5 (C Ar), 215.2 (CO); HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 230 nm) t_R(minor) 33.5 min and t_R(major) 39.3 min, 88 %*ee*; $[\alpha]^{20}_D$ = +19.9 (*c* 1.0, $CHCl_3$).

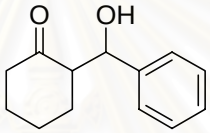
2.6.4 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(80d)**



2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone was prepared according to the general procedure using 4-bromo-benzaldehyde (92.5 mg, 0.5 mmol) and cyclohexanone (1mL) and purified by column chromatography to give a white solid (0.1175 g, 83%). *anti*/*syn*= 88/12,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.31 (m,

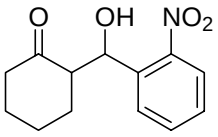
1H), 1.49-1.67 (m, 3H, C<u>H</u>$_2$), 1.75-1.78 (m, 1H, C<u>H</u>$_2$), 2.03-2.08 (m, 1H, C<u>H</u>$_2$), 2.32 (td, *J* = 13.2, 6.0 Hz, 1H, C<u>H</u>), 2.43- 2.46 (m, 1H, C<u>H</u>$_2$), 2.49- 2.56 (m, 1H, C<u>H</u>$_2$), 4.72 (d, *J* = 8.4 Hz, 1H, C<u>H</u>OH), 7.17 (d, *J* = 8.4 Hz, 2H, C<u>H</u> Ar), 7.44 (d, *J* = 8.4 Hz, 2H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (<u>C</u>H$_2$), 27.7 (<u>C</u>H$_2$), 30.7 (<u>C</u>H$_2$), 42.6 (<u>C</u>H$_2$), 57.3 (<u>C</u>H), 74.1 (<u>C</u>HOH), 121.6 (<u>C</u> Ar), 128.7 (<u>C</u>H Ar), 131.4 (<u>C</u>H Ar), 140.0 (<u>C</u> Ar), 215.2 (<u>C</u>O); HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 230 nm) t_R(minor) 33.3 min and t_R(major) 39.1 min, 89 %*ee*; $[\alpha]^{20}_D$ = +15.7 (*c* 1.0, $CHCl_3$).

2.6.5 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(80e)**



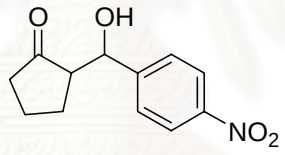
2-(Hydroxy-phenyl-methyl)-cyclohexanone was prepared according to the general procedure using benzaldehyde (102 μl, 0.5 mmol) and cyclohexanone (1mL) and purified by column chromatography to give a colorless oil (0.0725 g, 71%). *anti*/*syn*= 81/19,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.34 (m, 1H, C<u>H</u>$_2$), 1.52-1.79 (m, 4H, C<u>H</u>$_2$), 2.06-2.10 (m, 1H, C<u>H</u>$_2$), 2.36 (td, *J* = 12.8, 6.0 Hz, 1H, C<u>H</u>$_2$), 2.46-2.50 (m, 1H, C<u>H</u>$_2$), 2.59-2.62 (m, 1H, C<u>H</u>$_2$), 4.78 (d, *J* = 8.8 Hz, 1H, C<u>H</u>OH), 7.29-7.35 (m, 5H, C<u>H</u> Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (<u>C</u>H$_2$), 27.8 (<u>C</u>H$_2$), 30.8 (<u>C</u>H$_2$), 42.7 (<u>C</u>H$_2$), 57.4 (<u>C</u>H), 74.8 (<u>C</u>HOH), 127.0 (<u>C</u>H Ar), 127.9 (<u>C</u>H Ar), 128.4 (<u>C</u>H Ar), 140.9 (<u>C</u> Ar), 215.7 (<u>C</u>O); HPLC analyzed with a Chiralpak OJ-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(major) 18.2 min and t_R(minor) 22.9 min, 81 %*ee*.

2.6.6 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(80f)**



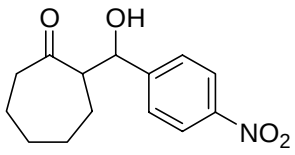
2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone was prepared according to the general procedure using 2-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cyclohexanone (1mL) and purified by column chromatography to give a colorless oil (0.1022 g, 82%). *anti*/*syn*= 95/5,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.68 (m, 4H, C$\underline{H}_2$), 1.77-1.81 (m, 1H, C$\underline{H}_2$), 2.03-2.07 (m, 1H, C$\underline{H}_2$), 2.30 (td, *J* = 13.2, 6.0 Hz, 1H, C$\underline{H}_2$), 2.38-2.42 (m, 1H, C$\underline{H}_2$), 2.70-2.76 (m, 1H, C$\underline{H}_2$), 5.40 (d, *J* = 7.2 Hz, 1H, C$\underline{H}$OH), 7.39 (t, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 7.59 (t, *J* = 7.6 Hz, 1H, C$\underline{H}$ Ar), 7.72 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar), 7.78 (d, *J* = 8.0 Hz, 1H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (C$\underline{H}_2$), 27.8 (C$\underline{H}_2$), 31.1 (C$\underline{H}_2$), 42.8 (C$\underline{H}_2$), 57.3 (C$\underline{H}$), 69.6 (C$\underline{H}$OH), 124.0 (C$\underline{H}$ Ar), 128.4 (C$\underline{H}$ Ar), 129.0 (C$\underline{H}$ Ar), 133.1 (C$\underline{H}$ Ar), 136.5 (C$\underline{}$ Ar), 148.7 (C$\underline{}$ Ar), 214.9 (C$\underline{}$O); HPLC analyzed with a Chiralpak OJ-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 38.4 min and t_R(major) 43.5 min, 95 %*ee*; $[\alpha]^{20}_{D}$ = +7.3 (*c* 1.0, $CHCl_3$).

2.6.7 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **(80g)**



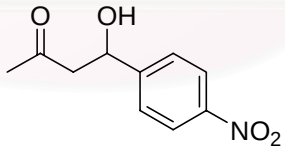
2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone was prepared according to the general procedure using 4-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cyclopentanone (1mL) and purified by column chromatography to give a white solid (0.1129 g, 96%). *anti*/*syn*= 33/67,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.75 (m, 2H, C$\underline{H}_2$), 1.93-2.01 (m, 2H, C$\underline{H}_2$), 2.04-2.44 (m, 3H, C$\underline{H}_2$), 4.82 (d, *J* = 8.8 Hz, 1H, C$\underline{H}$OH), 7.48 (d, *J* = 8.0 Hz, 2H, C$\underline{H}$ Ar), 8.12 (d, *J* = 8.4 Hz, 2H, C$\underline{H}$ Ar); HPLC analyzed with a Chiralpak AD-H column (95:5 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 104.1 min and t_R(major) 111.5 min, 79 %*ee*; $[\alpha]^{20}_{D}$ = +76.9 (*c* 1.0, $CHCl_3$).

2.6.8 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cycloheptanone **(80h)**



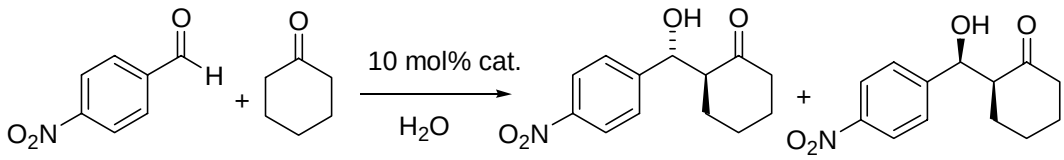
2-[Hydroxy-(4-nitro-phenyl)-methyl]-cycloheptanone was prepared according to the general procedure using 4-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cycloheptanone (1mL) and purified by column chromatography to give a brown oil (0.0395 g, 30%). *anti*/*syn*= 61/39,^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.42 (m, 2H, C$\underline{H}_2$), 1.54-1.87 (m, 4H, C$\underline{H}_2$), 2.21 (m, 2H, C$\underline{H}_2$), 2.35-2.62 (m, 2H, C$\underline{H}_2$), 2.84 (m, 1H, C$\underline{H}_2$), 4.91 (d, *J* = 7.6 Hz, 1H, C$\underline{H}$OH), 7.52 (d, *J* = 8.0 Hz, 2H, C$\underline{H}$ Ar), 8.19 (d, *J* = 8.8 Hz, 2H, C$\underline{H}$ Ar); HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 45.4 min and t_R(major) 102.5 min, 37 %*ee*; $[\alpha]^{20}_{D}$ = +2.9 (*c* 1.0, $CHCl_3$).

2.6.9 4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one **(80i)**



4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one was prepared according to the general procedure using 4-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and acetone (1mL) and purified by column chromatography to give a white solid (0.0680 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, C$\underline{H}_3$), 2.84 (d, *J* = 6.4 Hz, 2H, C$\underline{H}_2$), 5.24 (t, *J* = 6.0 Hz, 1H, C$\underline{H}$OH), 7.51 (d, *J* = 8.8 Hz, 2H, C$\underline{H}$ Ar), 8.16 (d, *J* = 8.8 Hz, 2H, C$\underline{H}$ Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7 (C$\underline{H}_3$), 51.5 (C$\underline{H}_2$), 68.9 (C$\underline{H}$OH), 123.7 (C$\underline{H}$ Ar), 126.4 (C$\underline{H}$ Ar), 147.2 (C$\underline{}$ Ar), 150.1 (C$\underline{}$ Ar), 208.6 (C$\underline{O}$); HPLC analyzed with a Chiralcel OJ-H column (85:15 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 48.0 min and t_R(major) 55.2 min, 69 %*ee*; $[\alpha]^{20}_{D}$ = +39.1 (*c* 1.0, $CHCl_3$).

2.7 General procedure for the direct Aldol reaction in water



The L-prolinamide derivatives (0.05 mmol) and corresponding aldehyde (0.5 mmol) were stirred in 1 mL of water at 30 ^{0}C, then cyclohexanone (1.0 mmol). The reaction mixture was stirred for 24–72 hours. The mixture extracted with ethyl acetate (2x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed *in vacuo*. The residue was purified by flash column chromatography with hexanes-ethyl acetate to afford the pure adducts.

2.7.1 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(80a)**

2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone was prepared according to the general procedure using 4-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cyclohexanone (104.0 µl, 1 mmol) and purified by column chromatography to give a white solid (0.1196 g, 96%). *anti*/*syn*= 94:6, HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 51.9 min and t_R(major) 79.3 min, 97%*ee*; $[\alpha]^{20}_D$ = +5.7 (*c* 1.0, $CHCl_3$).

2.7.2 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(80b)**

4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile was prepared according to the general procedure using 4-cyano-benzaldehyde (65.6 mg, 0.5 mmol) and cyclohexanone (104.0 µl, 1 mmol) and purified by column chromatography to give a white solid (0.1043 g, 91%). *anti*/*syn*= 91:9, HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 230 nm) t_R(minor) 55.0 min and t_R(major) 69.6 min, 96 %*ee*; $[\alpha]^{20}_D$ = +11.5 (*c* 1.0, $CHCl_3$).

2.7.3 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(80c)**

2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone was prepared according to the general procedure using 4-chloro-benzaldehyde (70.3 mg, 0.5 mmol) and cyclohexanone (104.0 µl, 1 mmol) and purified by column chromatography to

give a white solid (0.0847 g, 70%). *anti*/*syn*= 88:12, HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 230 nm) t_R(minor) 32.3 min and t_R(major) 37.7 min, 94 %*ee*; $[\alpha]^{20}_D$ = +18.7 (*c* 1.0, $CHCl_3$).

2.7.4 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(80d)**

2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone was prepared according to the general procedure using 4-bromo-benzaldehyde (92.5 mg, 0.5 mmol) and cyclohexanone (104.0 µl, 1 mmol) and purified by column chromatography to give a white solid (0.1005 g, 71 %). *anti*/*syn*= 90:10, HPLC analyzed with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 230 nm) t_R(minor) 33.9 min and t_R(major) 40.6 min, 93 %*ee*; $[\alpha]^{20}_D$ = +14.0 (*c* 1.0, $CHCl_3$).

2.7.5 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(80e)**

2-(Hydroxy-phenyl-methyl)-cyclohexanone was prepared according to the general procedure using benzaldehyde (102 µl, 0.5 mmol) and cyclohexanone (104.0 µl, 1 mmol) and purified by column chromatography to give a colorless oil (0.0694 g, 68%). *anti*/*syn*= 88/12, HPLC analyzed with a Chiralpak OJ-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(major) 18.2 min and t_R(minor) 22.9 min, 90 %*ee*.

2.7.6 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(80f)**

2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone was prepared according to the general procedure using 2-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cyclohexanone (104.0 µl, 1 mmol) and purified by column chromatography to give a colorless oil (0.0810 g, 65%). *anti*/*syn*= 95:5, HPLC analyzed with a Chiralpak OJ-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) 43.7 min and t_R(major) 47.9 min, 97 %*ee*; $[\alpha]^{20}_D$ = +10.4 (*c* 1.0, $CHCl_3$).

2.7.7 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **(80g)**

2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone was prepared according to the general procedure using 4-nitro-benzaldehyde (75.6 mg, 0.5 mmol) and cyclopentanone (88.8 µl, 1 mmol) and purified by column chromatography to give a white solid (0.0917 g, 78%). *anti*/*syn*= 49/51, HPLC analyzed with a Chiralpak AD-H

column (95:5 hexanes:isopropanol, 0.5 mL/min, 245 nm) t_R(minor) min and t_R(major) min, 79 %*ee*; $[\alpha]^{20}_D$ = +7.2 (*c* 1.0, $CHCl_3$).

2.8 Determination of enantiomeric excess and diastereoisomeric ratio

2.8.1 Determination of enantiomeric excess by Normal phase chiral HPLC

The enantiomeric excess was determined by High performance liquid chromatography (HPLC) using chiral column. A Chiralpak AD column and a Chiralcel OJ column were selected for the enantiomeric separation of aldol product. The percent enantiomeric excess (enantiomeric purity) can be calculated by equation (1) by using the peak areas of the (*R*) and (*S*) enantiomers.

$$\%ee = \frac{|A_R - A_S| \times 100}{|A_R + A_S|} \qquad (1)$$

%*ee* = percent enantiomeric excess

A_R = peak area of *R* enantiomer

A_S = peak area of *S* enantiomer

Figure 2-1. HPLC chromatograms of separated by a column

2.8.2 ^{1}H-NMR spectroscopy for determination of diastereoisomeric ratio

The most useful alternative measure of diastereoselectivity is the diastereomer ratio (d.r.). If the same proton of a pair of diastereomers is shown difference chemical shift in NMR spectra and give baseline resolution. ^{1}H-NMR spectroscopy can be measure the diastereomer ratio from compare an integration of the appropriate singles.

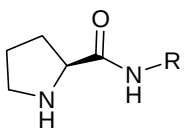
CHAPTER III

RESULTS AND DISCUSSION

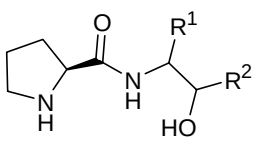
The development of metal-free organocatalysts has emerged as a new frontier in asymmetric catalysis. [4-5] Since the pioneering finding by List and Barbas and their co-workers [13] that L-proline could work as a catalyst in the intermolecular direct aldol reaction, the concept of small organic molecules as catalysts has received great attention. Shortly after that, L-proline and derivatives have been continuously developed for aldol and many other reactions. In recent years, several kinds of efficient organocatalysts have been discovered for the directed asymmetric aldol reactions including L-proline, 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) [20], L-prolinol [52], L-prolinamides [20,43], and certain peptides. [53] Recently, Tang and co-worker [43] discovered a new highly efficient organocatalyst derived from L-prolinamide for catalytic asymmetric aldol reactions. This research aims to develop conceptually similar, but less structurally complicated prolinamide derivatives as catalysts for asymmetric aldol reaction.

3.1 Catalyst design

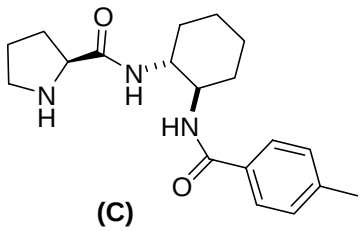
According to the Houk-List model, [23] proline-based catalysts firstly form an enamine intermediate with a carbonyl compound containing α-hydrogen. This enamine then reacts with another carbonyl compound through a highly ordered transition state. The catalyst is believed to stabilize the transition state through hydrogen bonding. Therefore, the acid side-chain of proline is critical for the reactivity and stereoselectivity of the proline-catalyzed direct aldol reaction.



(A)



(B)



(C)

L-Prolinamides were reported as poor catalyst for asymmetric aldol reaction. In 2004, Tang [44-45] reported that proline *N*-alkylamides provided lower enantioselectivities than *N*-arylamides **(A)**. In particular, the enantioselectivity increases as the aryl substituent varies from electron-donating to electron-withdrawing groups due to the increased acidity of the amide NH. However, the best stereoselectiveties obtained for these simple proline arylamides were still only moderate. Better results were obtained with proline secondary amides with a terminal hydroxyl group **(B)**. This catalyst possesses two functional groups which act as hydrogen bond donors (amide and hydroxyl groups) contributing to high enantioselectivities of the catalyst. It appears that the presence of double hydrogen bonding can help fixing the transition state more efficiently compared to only one hydrogen bonding in proline (Figure 3-1). In recent year, other examples of catalyst capable of forming double hydrogen bonding which gave rise to high enantioselectivities have been demonstrated. In 2005, Xiao and co-workers describe a new series of bifunctional L-prolinamide **(C)** which can catalyze the direct asymmetric aldol reaction with high efficiency.

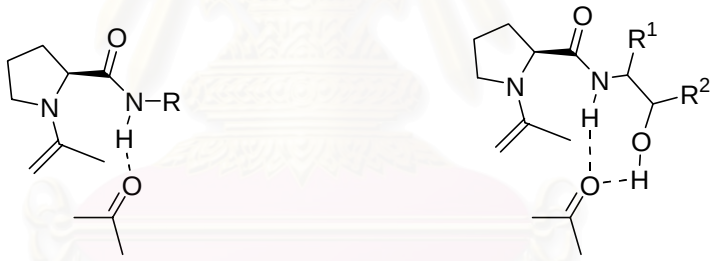


Figure 3-1. Possible stabilize the transition state by mono and double hydrogen bonding

These earlier results inspired a new design for praline-based catalysts in this work (Figure 3-2). The catalysts are prolinamides derived from aminophenols bearing two hydrogen bond donors, namely the amide NH and hydroxyl groups. The hydrogen bonding ability of these catalysts can be fine tuned by adjusting electronic properties of the substituents on the aromatic ring.

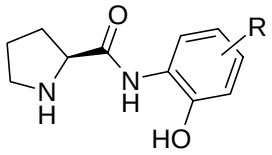


Figure 3-2. The new L-prolinamide for catalytic asymmetric reactions

3.2 Synthesis of the catalyst

The proposed L-prolinamide-based organocatalysts could be synthesized form coupling of L-proline with 2-aminophenol derivatives. Some of these aminophenols are commercially available but many have to be prepared from phenols. A retrosysthetic plan is shown in Figure 3-3.

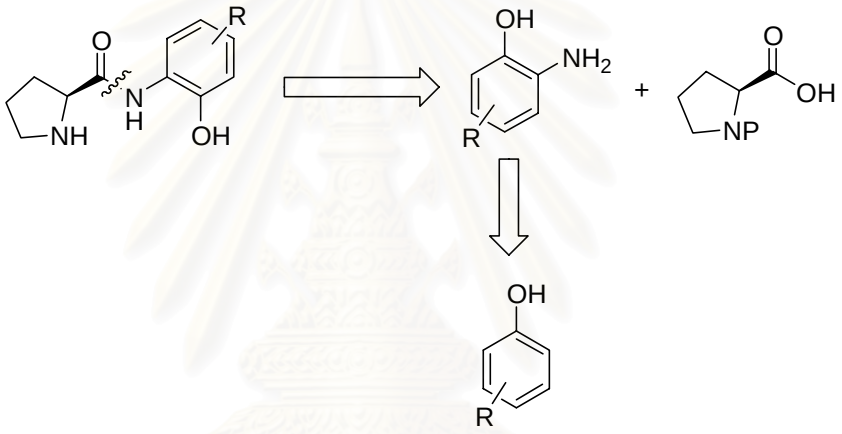


Figure 3-3. Retrosynthesis of L-prolinamide organocatalyst (P = protecting group)

3.2.1 Synthesis of 2-aminophenol

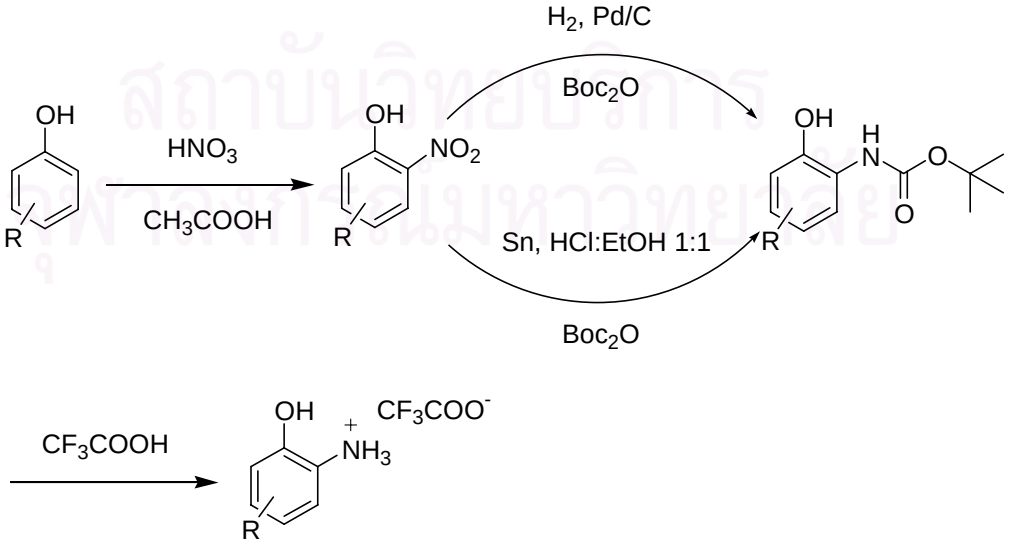


Figure 3-4. General synthetic plan of 2-aminophenols

The synthetic plan for non-comercially available 2-aminophenols is shown in Figure 3-4. *o*-Nitrophenol derivatives were synthesized through the classical of phenols nitration under mild condition. [54] In addition to the desired *o*-nitrophenol derivatives, *p*-nitro phenols and/or dinitration products were also obtained if the structures pemit their formation. The reactions carried out at 0 °C gave *o*-nitrophenols in synthetically useful yield with all substrates except for 4-cyanophenol, which required heating at 40 °C for 10 hour. In this case the electrophile (NO_2^+) attacked the aromatic ring with difficulty because of the electron withdrawing effect the cyano group. Nitration of 2-chlorophenol gave both *o*-nitrophenol (32 %) and *p*-nitrophenol. The product mixture was purified by column chromatography. The identity of each product was confirmed by ^{1}H-NMR spetra (Figure 3-5).

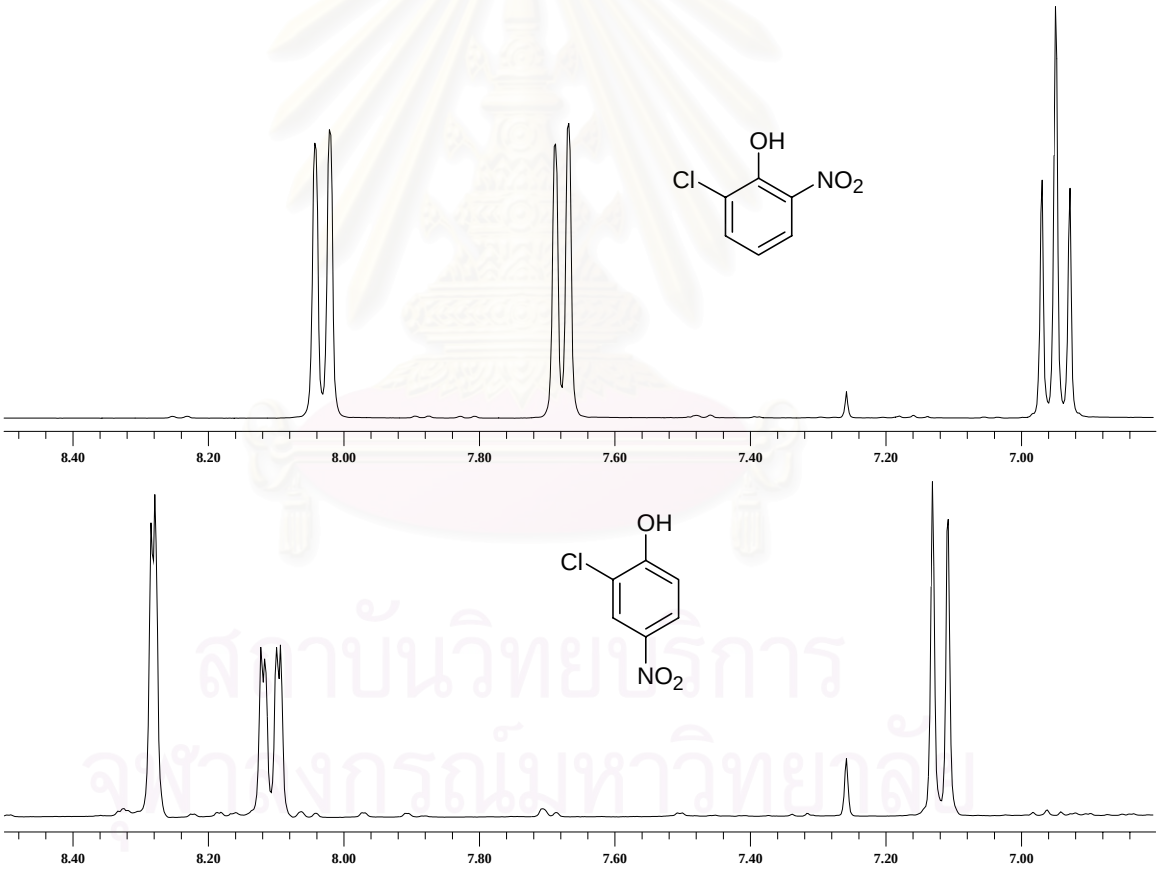


Figure 3-5. ^{1}H-NMR spectra of 6-chloro-2-nitrophenol (top); and ^{1}H-NMR spectra of 2-chloro-4-nitrophenol (bottom);

Three possible products were obtained from nitration of *m*-trimethylfluorophenol. The desired product containing the nitro group at the C-6

position was obtained in only 16% yield. ^{1}H-NMR spectra confirmed the *ortho*-(C-6) substitution pattern according to the presence of a proton peak of phenolic-OH at an unusually downfield position of 10.5 ppm as a result of intramolecular hydrogen bonding with the nitro group (Figure 3-7).

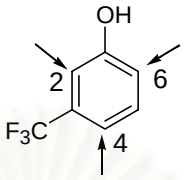


Figure 3-6. Three possible sites for nitration of 3-trifluoromethylphenol

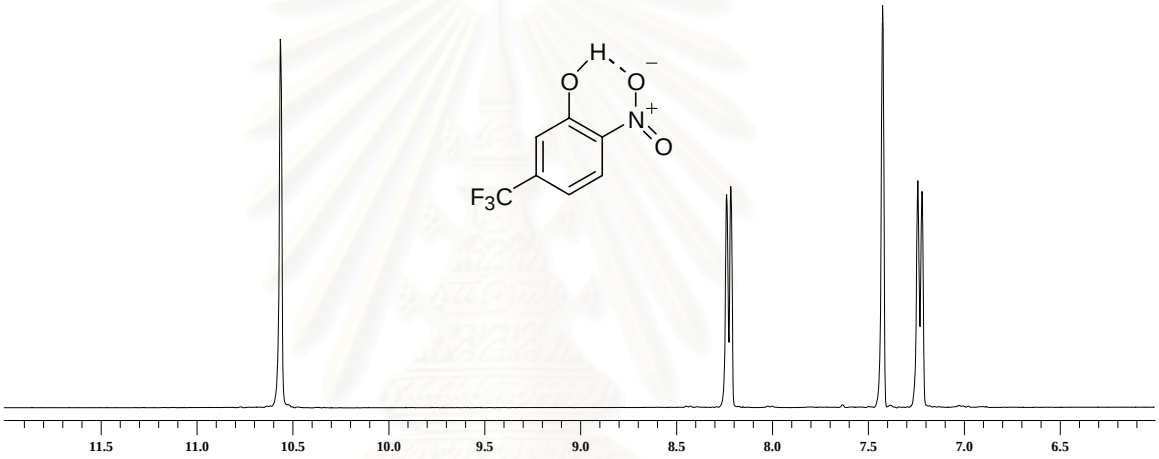


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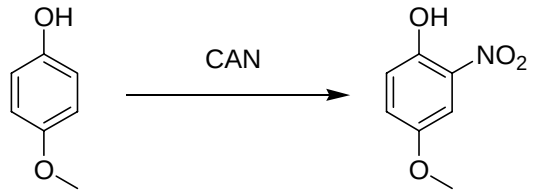
Figure 3-7. ^{1}H-NMR spectra of 2-nitro-5-trimethylfluorophenol

This general method worked with all phenols except 4-methoxyphenol (hydroquinone monomethyl ether). Nitration of this compound with HNO_3 gave the desired *o*-nitrophenol in very poor yield because both the hydroxy and methoxy group directed the nitration to different positions. Furthermore, both groups are strongly activating groups therefore it was difficult to obtain mononitration products. Consequently, a more efficient method for the regioselective introduction of the *ortho* nitro group onto 4-methoxyphenol was desirable. A survey of the literature showed that cerium (IV) ammonium nitrate (CAN) in the presence of $NaHCO_3$ have been used for selective *ortho*-nitration of phenols. The high *ortho* regioselectivity observed in the CAN nitration suggested that a Fries type rearrangement may be involved in the nitration. In our hands, the *ortho*-nitration product was obtained in only 11% yield.

Although the yield was poor, this method was clearly better than direct nitration by HNO_3. [55]



Reduction of the nitro group to amino group can be facilitated by many different reagents under a variety of conditions. One general method for reducing aromatic nitro compounds to aromatic amines was to use hydrogenation reaction in the presence of Pd/C catalyst. Hydrogenation of *o*-nitrophenol derivatives catalyzed by Pd/C in the presence Boc_2O afforded *N*-Boc-2-aminophenols in high yield. [56] Although there are possibilities of *N*- and *O*-butoxycarbonylation, the *N*-Boc derivatives were obtained as the only products. Subsequent deprotection of the Boc group by TFA gave the desired 2-aminophenols as TFA salts. Temporary protection of the amino group in aminophenols by Boc or salt formation was vital for their successful preparation since these compounds are unstable in the free base forms under oxygen atmosphere and darkened rapidly in solution upon contact with air.

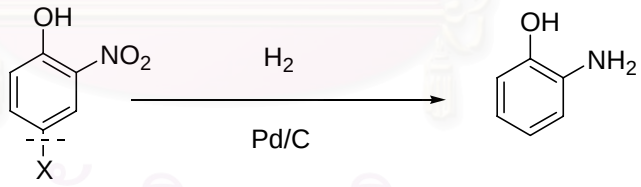
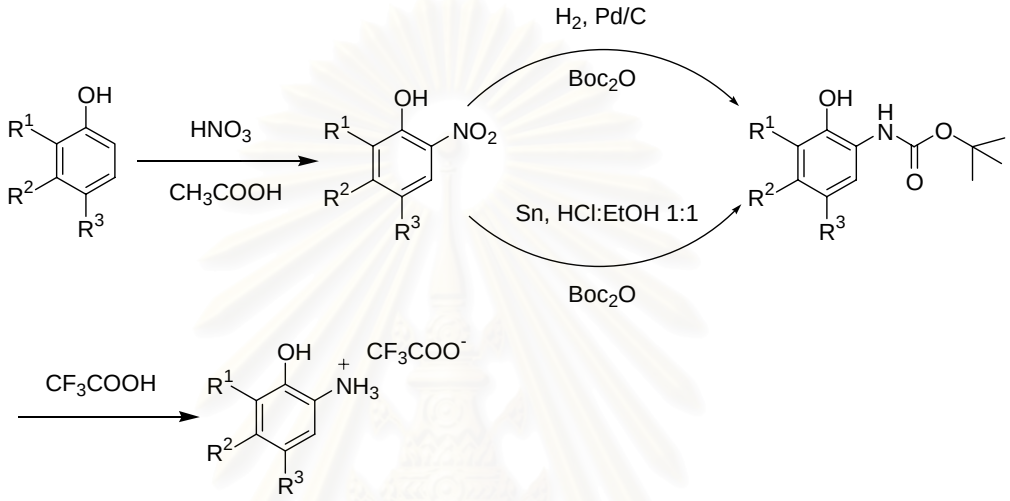


Figure 3-8. Aromatic C-X bond cleavage under hydrogenation conditions (X = Cl**)**

Nonetheless, the hydrogenation method for the synthesis of 2-aminophenol derivatives described above was not completely satisfactory for all substrates. Hydrogenation of *o*-nitrophenols bearing halogen substituents (eg. Cl) gave products derived from cleavage of the C—X bond. Therefore, a more general reduction method was required. Among alternative methods for the synthesis of aromatic amine from aryl nitro compounds [57] including iron or tin in acid media, sodium hydrosulfite, titanium(III) chloride etc, our choice was tin reduction on account of its good reactivity and clean conversion. The tin reduction of *o*-nitrophenol bearing halogen

substituents provided the desired aminophenols in moderate yield which was isolated as their *N*-Boc derivatives. This method generally provided lower yield than hydrogenation reaction partly because the reduction and *N*-Boc protection could not be performed in one pot. TFA deprotection of *N*-Boc-protecting group was then carried out as described previously to give the trifluoroacetate salts in high yield.

Table 3-1. Synthesis 2-aminophenols from phenols derivative



Entry	R^1	R^2	R^3	%Yield			
				Nitration	reduction		Boc-deprotection
					H_2/Pd	Tin	
1	H	H	*tert*-butyl	88	94	-	92
2	*tert*-butyl	H	*tert*-butyl	61	98	-	95
3	H	H	OMe	11	92	-	91
4	H	H	CO_2Et	88	98	-	85
5	H	H	CN	50	46	-	98
6	H	CF_3	H	16	70	-	97
7	Cl	H	Cl	96	-	45	89
8	Cl	H	F	92	-	50	90
9	F	H	F	69	-	57	96
10	Cl	H	H	32	-	49	87

The *O*-methylated derivative of 2-amino-4-chlorophenol was also synthesized following the route shown in Figure 3-9. Nitration of 4-chlorophenol under the standard conditions afforded the *o*-nitrophenol in 98% yield. *O*-Methylation was accomplished by refluxing with methyl-4-toluenesulfonate/K_2CO_3 in 98% yield. Reduction of the nitro group was carried out by tin reduction in 98% yield.

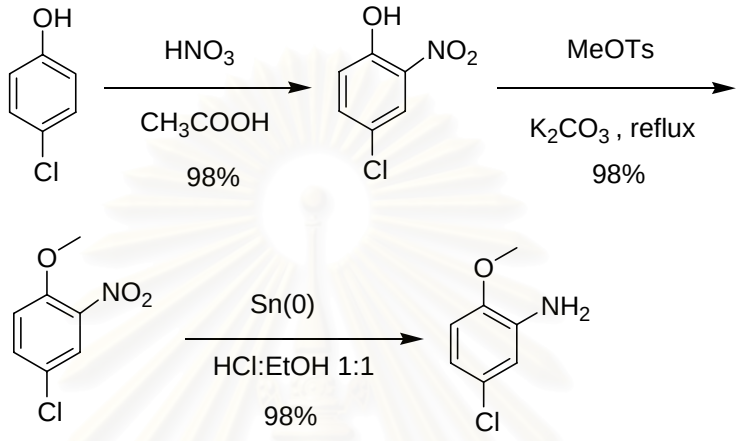


Figure 3-9. The systhesis of the *O*-methylated derivative of 2-amino-4-chlorophenol

3.2.2 Synthesis of catalyst

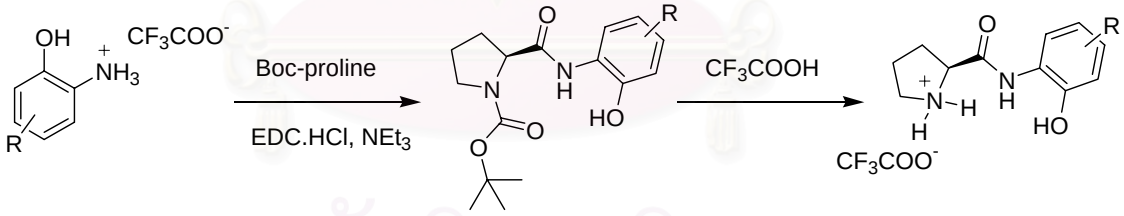
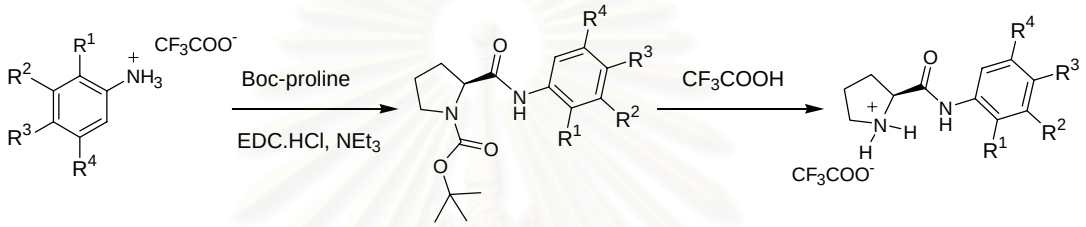


Figure 3-10. General synthetic of L-prolinamide catalysts

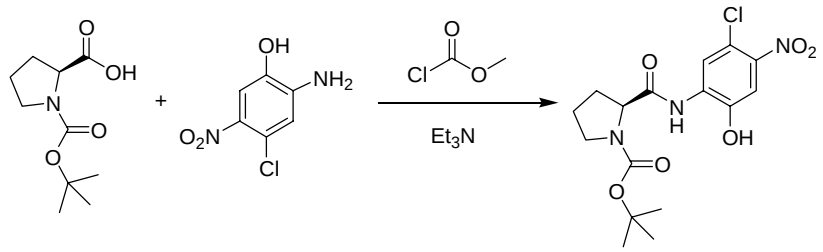
Coupling reaction of 2-aminophenol with *N*-Boc-proline was mediated by a classical peptide coupling reagent EDC·HCl. [58-59] Other peptide coupling reagents such as DCC has also been used, but EDC·HCl was found to be the most convenient due to the formation of a water soluble urea by-product. During the coupling reaction, protection of the proline nitrogen atom was necessary. The common nitrogen protecting groups Boc and Z. Boc-proline was used because the TFA cleavage in the final step gave the desired products as trifluoroacetate salts. On the other hand, Z-

proline derivatives gave the final products in free base form after hydrogenation. 2-Aminophenols react with Boc-proline in the presence of stoichiometric amounts of EDC·HCl to give the Boc-protected amides in 60-95 %yield. Addition of triethylamine (1 equiv.) was required when the aminophenols were in the form of TFA salts. The prolinamides as trifluoroacetate salts were obtained after removal of the *N*-Boc-protecting group in high yield.

Table 3-2. Synthesis of L-prolinamide catalysts from 2-aminophenols and Boc-proline



Entry	Catalyst	R				%Yield	
		R^1	R^2	R^3	R^4	coupling	deprotection
1	**28a**	OH	H	H	Cl	89	90
2	**28b**	OH	H	H	H	73	78
3	**28c**	OH	H	H	*t*-butyl	90	90
4	**28d**	OH	*t*-butyl	H	*t*-butyl	80	100
5	**28e**	1-amino-2-naphtol				73	100
6	**28f**	OH	H	H	OMe	80	100
7	**28g**	OH	H	H	NO_2	79	84
8	**28h**	OH	H	H	CO_2Et	87	92
9	**28i**	OH	H	H	CN	60	90
10	**28j**	OH	H	CF_3	H	85	96
11	**28k**	OH	Cl	H	Cl	82	95
12	**28l**	OH	Cl	H	F	75	92
13	**28m**	OH	Cl	H	H	75	96
14	**28n**	OH	F	H	F	76	88
15	**28o**	OH	H	NO_2	Cl	78	94
16	**28p**	OH	NO_2	H	Cl	62	100
17	**28q**	OMe	H	H	Cl	87	94
18	**31**	H	H	H	H	95	98



Coupling reaction of 2-amino-4-chloro-5-nitrophenol using peptide EDC·HCl would not be successful due to the electron-withdrawing effect of the nitro group at *para* position of the amino group. To acylate this poorly nucleophilic amine, it was necessary to activate the Boc-L-proline with methyl chloroformate. [58-59]

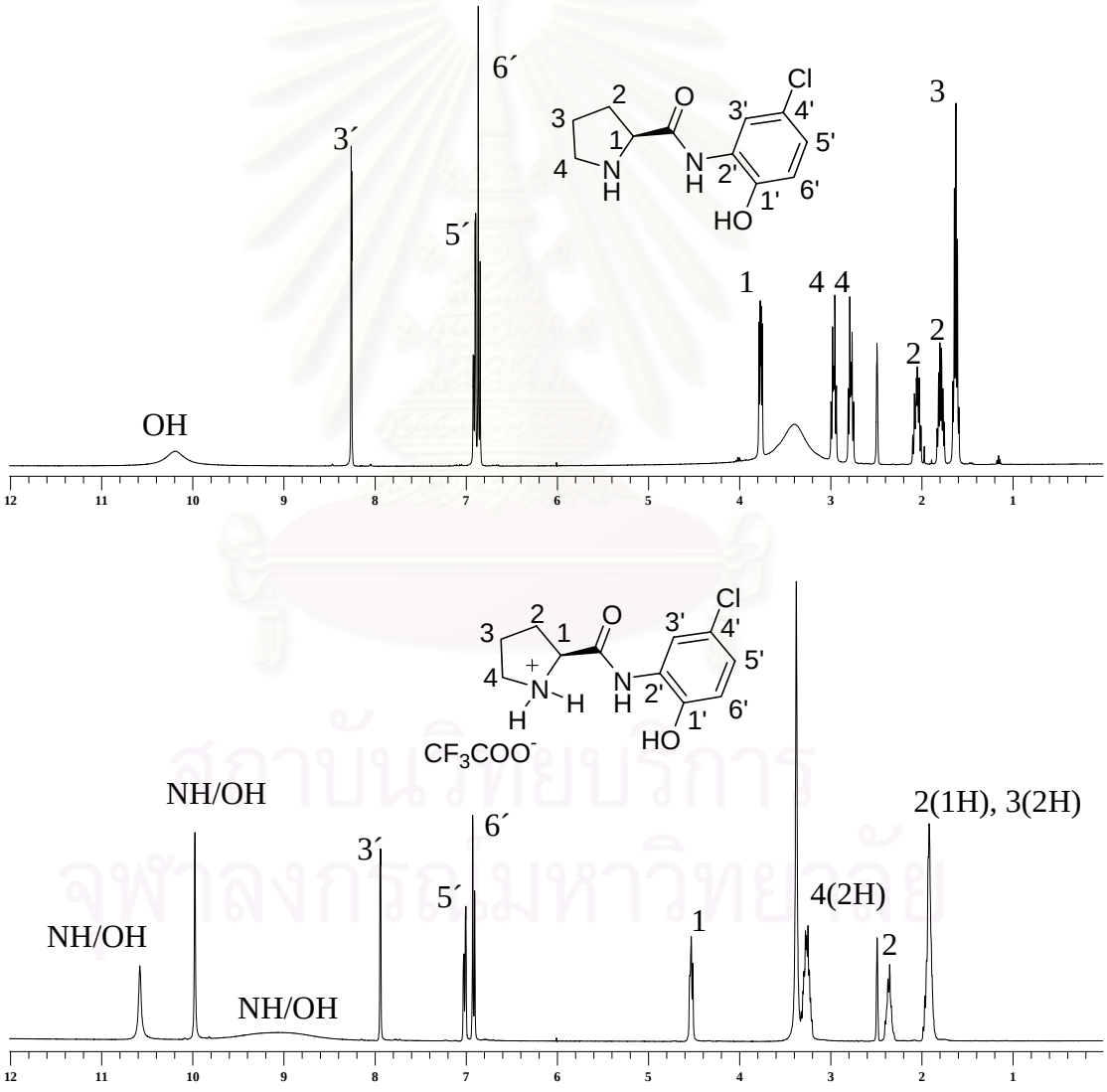


Figure 3-11. ^{1}H-NMR spectra of L-prolinamide **28a** (top); and ^{1}H-NMR spectra of L-prolinamide salt acetate **28a·TFA** (bottom);

Most L-prolinamide derivatives in this work were prepared as TFA salt, although some have also been prepared as free bases (**28a**, **28b** and **28e**) for comparison. NMR spectra of the two types of catalyst were quite different. ^{1}H NMR of **28a** in the free base form showed CHC$\underline{H_2}$C$\underline{H_2}$CH$_2$ signals at 1.62, 1.78 and 2.04 ppm, NC$\underline{H_2}$CH$_2$ signals at 2.77 and 2.96 ppm, NC$\underline{H}$CH$_2$ signal at 3.76 ppm, and C$\underline{H}$ Ar signals at 6.85, 6.90 and 8.25 ppm. ^{1}H NMR spectrum of **28a·TFA** showed CHC$\underline{H_2}$C$\underline{H_2}$CH$_2$ signals at 1.91 and 2.35 ppm, NC$\underline{H_2}$CH$_2$ signals at 3.26 ppm, NC$\underline{H}$CH$_2$ 4.52 ppm, C$\underline{H}$ Ar signals at 6.91, 7.01 and 7.93 ppm, CON$\underline{H}$ and O$\underline{H}$ signal at 9.97 and 10.57 ppm. The ^{1}H-NMR chemical shifts of the pyrrolidine ring protons of the TFA salts are deshielded compared to the free base owing to influence of the protonated ring nitrogen atom.

3.3 Determination of the enantiomeric excess and diastereomeric ratio

3.3.1 Determination of enantiomeric excess

The most commonly used parameter to describe the degree of enantioselectivity is enantiomeric excess (*ee*). The term enantiomeric excess was introduced in 1971 by Morrison and Mosher. [60] This is defined as the proportion of the major enantiomer less that of the minor enantiomer and is commonly expressed as a percentage. The value of the enantiomeric excess can range from 0% to 100%. For a compound containing a single chiral center, a racemic mixture consists of 50% of the *R* enantiomer and 50% of the *S* enantiomer. The enantiomeric excess in this case is 0. A sample that contains 100% of one enantiomer has an enantiomeric excess of 100%. General techniques for determining enantiomeric excess include nuclear magnetic resonance (NMR) spectroscopy, high performance liquid chromatography (HPLC), and gas chromatography (GC). High performance liquid chromatography (HPLC) using chiral columns have been extensively used for determination of enantiomeric purity of aldol condensation products in many reports. Enantiomer separation on chiral stationary phase depends upon formation of transient diastereomeric complexes of differing free energy between the analyze and the support. As a result, the two enantiomers differentially adsorbs on the chiral support, resulting in different retention time. The compound which forms the most stable diastereoisomer will be most retained, whereas the opposite enantiomer will form a less stable diastereoisomer and will elute first.

In our work, chromatographic analysis for the optically purity of aldol adduct were carried out using HPLC method on chiral column ChiralPak AD-H®, Daicel ChiralCel OJ-H® and Daicel ChiralCel OD®.

3.3.2 Determination of diastereomeric ratio

In comparing any two of these stereoisomers two possibilities: they may be mirror images of each other, in which case they are enantiomers, otherwise they are diastereomers. While compounds that are enantiomers have identical chemical and physical properties and equal but opposite optical rotations, compounds which are diastereomeric with each other can have completely different chemical and physical properties including optical rotations. The measure of diastereoselectivity is expressed as the diastereomeric ratio (dr). The most useful alternative mean to measure diastereoselectivity is nuclear magnetic resonance (NMR) spectroscopy. If the same protons of a pair of diastereomers appear at different chemical shift in NMR spectra at sufficient resolution, the dr can be measured by comparing the integrals of the appropriate signals. Alternatively chromatographic techniques such as GC and HPLC may be used. In this study, chiral HPLC is used for measuring both *ee* and dr.

3.4 L-Prolinamide-catalyzed direct Aldol reaction

L-Prolinamide catalysts synthesized were explored for reactivity and stereoselectivity in direct asymmetric aldol reaction. The catalytic activity of these new catalysts for the asymmetric direct aldol reaction was investigated using a model reaction between 4-nitrobenzaldehyde and cyclohexanone. Reaction of this pair of substrates is well documented, [46] hence enabling comparison with other catalysts reported in the literature. In addition, the conditions for determining %*ee* and dr were previously established (chiral HPLC on ChiralPak AD-H®). The aldol adduct contains four possible stereoisomers because of the presence of two new stereogenic centers. One pair of enantiomers is *anti*-product and the other pair of enantiomers is *syn*-product (Figure 3-12). Under optimal condition, all four stereoisomers could be separated by chiral HPLC (Figure 3-13).

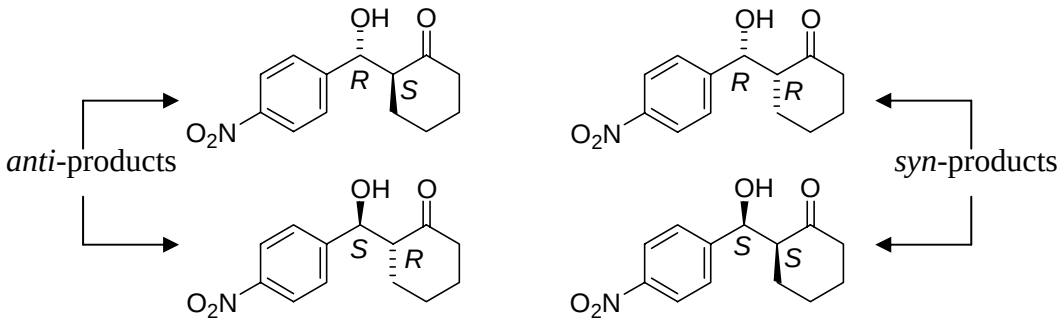


Figure 3-12. Four possible aldol adducts formed from 4-nitrobenzaldehyde and cyclohexanone

Initially, the L-prolinamide derivative **28a**, which was easily prepared from commercially available 2-amino-4-chlorophenol, was studied by employing 10 mol% of this catalyst in chloroform at room temperature (30 °C). The result was encouraging since the expected aldol product was obtained in 93 % yield. The identity and purity of the product was confirmed by NMR-spectra. In ^{1}H-NMR (Figure 3-13) the aldol adduct showed peak of CHOH at chemical shift (δ) 4.84 (*anti*) and 5.40 (*syn*). The dr (*anti*:*syn*) as determined by chiral HPLC was 85:15 with the *anti* diastereomers predominantly formed. Furthermore the *ee* of the *anti* product was as high as 84% while that of the *syn* product was only 61%. Optimization of the reaction conditions and effects of various parameters were then investigated.

3.4.1 Optimization of the reaction conditions

3.4.1.1 Optimize catalyst loading

Loading of the catalyst is a very important aspect of catalytic asymmetric synthesis. The lower the loading, the more efficient the catalyst. Proline based catalysts are not usually very efficient in terms of catalyst loading or turnover. Many previous reports [36, 40, 43, 44] used catalyst loading as high as 20 or 30 mol%. Nevertheless, in some of these reports the catalyst loading could be decreased to 5 mol% [45] or lower. It is therefore important to investigate how little catalyst may be used while acceptable reactivity and diastereo- and enantio-selectivities can still be achieved.

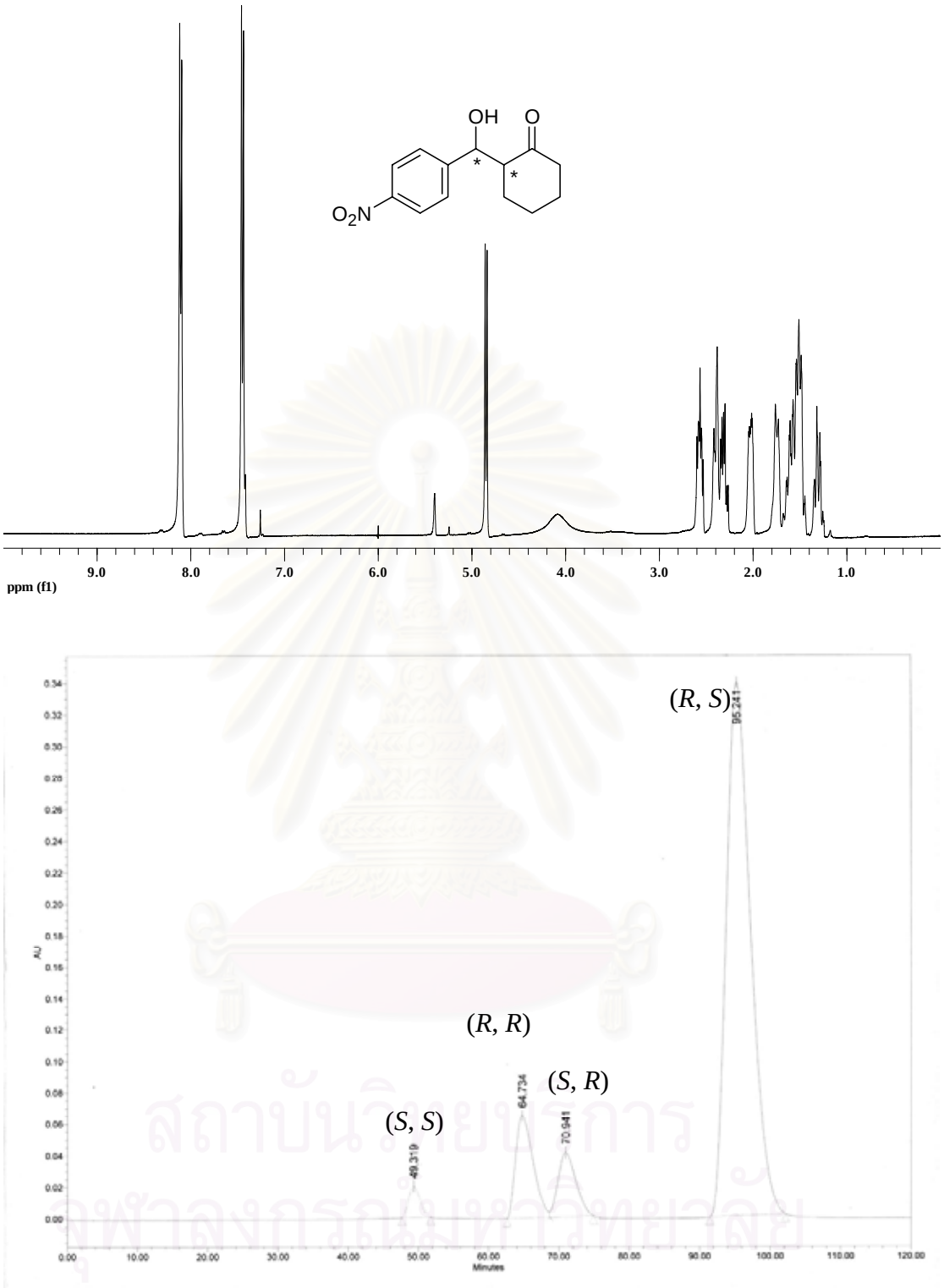
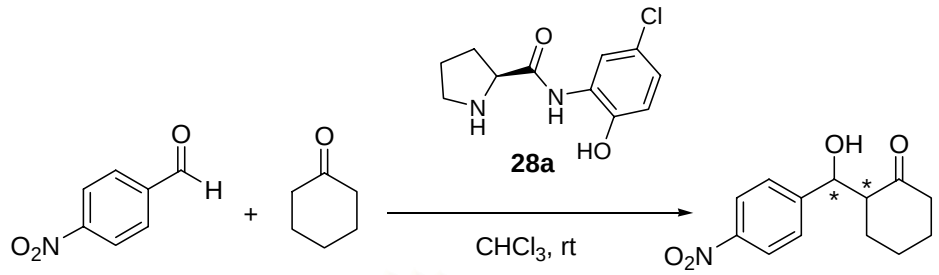


Figure 3-13. ^{1}H-NMR spectra (CDCl , 400 MHz) of aldol product **80a** (top); and HPLC chromatrogram of aldol product **80a** with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.5 mL/min, 245 nm) (bottom);

Table 3-3 Optimize catalyst loading on the aldol reaction of 4-nitrobenzaldehyde cyclohexanone catalyzed by **28a**



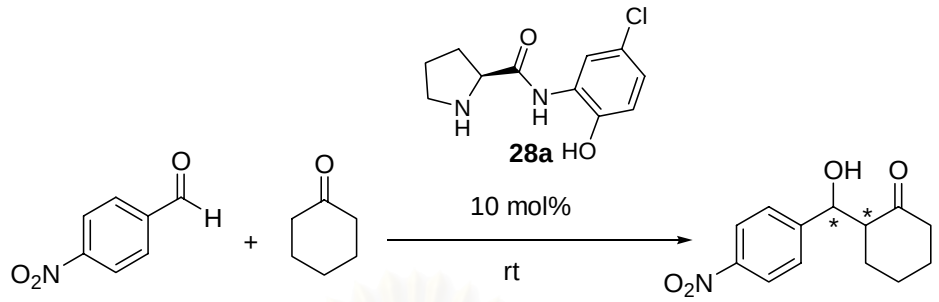
Entry	Loading (mol%)	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	20	15	93	75 (59)	85:15
2	10	29	93	84 (61)	85:15
3	5	67	91	88 (63)	86:14

For the catalyst **28a**, the catalyst loading of 20 and 10 mol% provided good reactivies and selectivities for the model aldol reaction. When the reaction was performed with 5 mol% of catalyst, the reactivity noticeably declined. Surprisingly, the enantioselectivity appeared to increase slightly at lower catalyst loading. Nevertheless, the difference is not large enough to justify its benefits considering that the reaction proceeded quite slowly. The results showed that the catalyst amount at 10 mol% was the most appropriate for further studies.

3.4.1.2 Study of solvent effects

Polarity of solvents can have dramatic effects to both reactivity and selectivities of asymmetric reactions. To test the effect of solvents, representative solvents which covered all of types including polar-protic solvent (ethanol), polar-aprotic solvent (*N*,*N*-dimethylformamide), aprotic coordinating solvent (tetrahydrofuran) and aprotic non-coordinating solvent (chloroform). The results are shown in Table 3-4.

Table 3-4 Effect of solvent on the aldol reaction of 4-nitrobenzaldehyde cyclohexanone catalyzed by **28a**



Entry	Solvent	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	$CHCl_3$	29	93	84 (61)	85:15
2	THF	44	92	75 (50)	80:20
3	DMF	48	63	70 (50)	73:27
4	EtOH	48	78	74 (34)	79:21

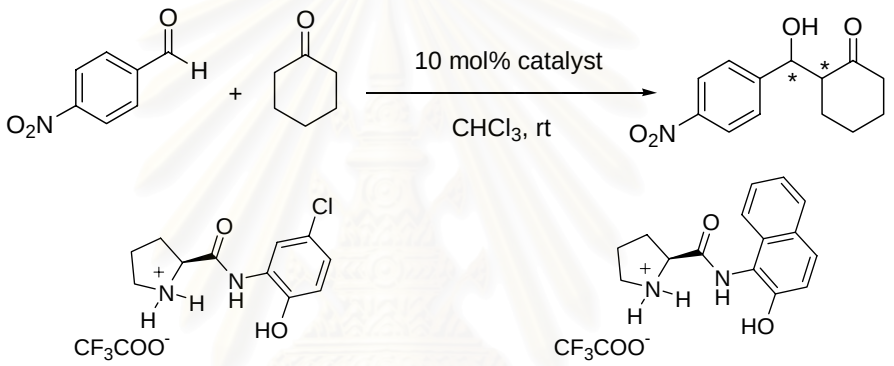
The reactions carried out in polar and coordinating solvents afford lower enantioselectivity compare to non-polar/non-coordinating solvents. The results confirmed that the type of solvent played a crucial role for direct aldol reaction. The best result was obtained in chloroform solvent for both yield and %*ee*. In this work, prolinamide-catalyzed in the catalytic aldol reaction requires non-polar solvent to induce the high stereoselectivity. This can be explained by the transition state for proline-catalyzed aldol reactions, in which hydrogen bonding between proline or prolinamide side-chain and C=O of the aldehyde is required. In polar or coordinating solvents, this interaction is diminished due to solvent competition in the formation of hydrogen bonding.

3.4.2 Type of catalysts (free bases and TFA salts)

The direct aldol reactions first studied with catalyst **28a**. The reactions were carried out under the optimized condition with 10 mol% of catalyst in chloroform at room temperature. The L-prolinamide **28a** promoted the reaction with a high yield of 93 % and good enantionselectivity of 84 %*ee*. Previous reports have shown that an acid additive (eg. AcOH, TFA) can improve enantioselectivity. [46] Nevertheless, the aldol reaction with L-prolinamide **28a** free base in the presence of trifluoroacetic acid

(TFA) (1 eguiv) afforded the aldol adduct with lower enantioselectivity of 80%*ee*. Controlling the amount of TFA turned out to be crucial to obtain high enantioselectivity. The best result was obtained using the trifluoroacetate salt of **28a** (prepared by deprotection of Boc-**28a** with TFA). Trifluoroacetate salts of other L-prolinamide catalysts (**28b** and **28e**) also performed better than the corresponding free bases thereby confirming the previous results. Further screening was therefore carried out on the trifluoroacetate salts rather than the free bases. The results are summarized in Table 3-5.

Table 3-5 Effect of type of catalysts on the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone

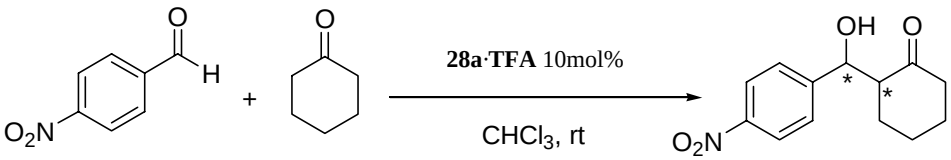


28a·TFA **28e·TFA**

Entry	Catalyst	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	**28a**	29	93	84 (61)	85:15
2	**28a·TFA**	29	95	91 (7)	90:10
3	**28b**	72	92	68 (47)	76:24
4	**28b·TFA**	72	93	89 (36)	86:14
5	**28e**	72	75	53 (40)	74:26
6	**28e·TFA**	72	68	79 (17)	78:22

Because of its good reactivity, the catalyst **28a·TFA** was next chosen for attempt to decrease the catalyst loading. The reaction was performed with 5 and 1 mol% of the catalyst. The results showed that lowering the catalyst loading provided only slightly lower enantioselectivity but significantly decreased reactivity. Therefore the catalyst loading was chosen at 10 mol% for further studies.

Table 3-6 Optimize catalyst loading on the aldol reaction of 4-nitrobenzaldehyde and cyclohexanone catalyzed by **28a·TFA**



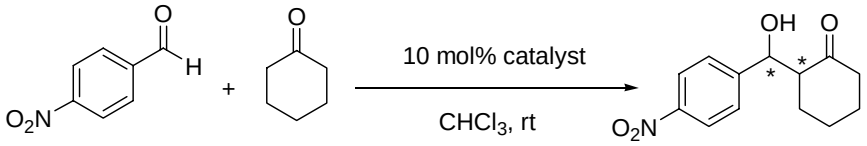
Entry	Loading	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	10	29	95	91 (7)	90:10
2	5	48	89	94 (24)	93:7
3	1	48	41	93 (5)	88:12

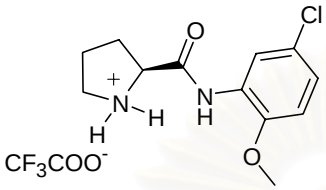
3.4.3 The role of hydroxyl group of phenol

To ascertain the essential role of the phenolic-OH group in this type of organocatalyst for aldol reactions, the catalyst **28a**, **28b, 28q** and **31** were prepared and evaluated in the same model aldol reaction of 4-nitrobenzaldehyde and cyclohexanone under the optimized condition obtained above.

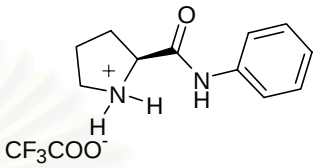
The result showed that both L-prolinamide catalysts with the phenolic-OH group (**28a** and **28b**) consistently afforded better yield and enantioselectivity than L-prolinamide catalysts **28q** and **31** lacking this OH group. The results confirmed our previous hypothesis that double hydrogen bonding can improve the performance of prolinamide catalysts for aldol reaction.

Table 3-7. Effect of the phenolic hydroxyl group on the aldol reaction of 4-nitrobenzaldehyde and cyclohexanone





28q·TFA



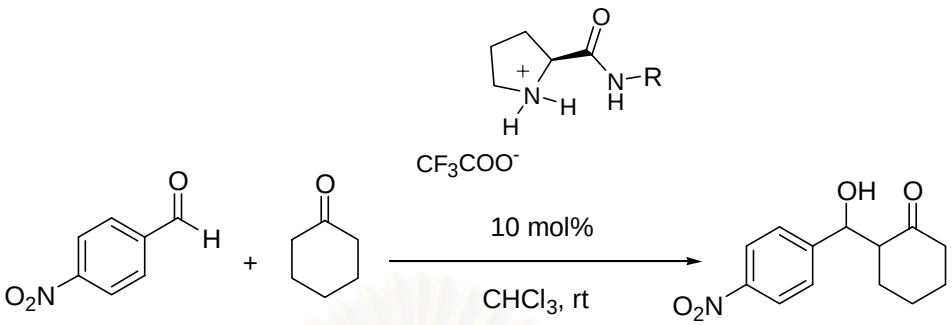
31·TFA

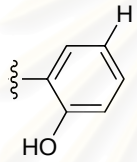
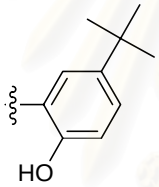
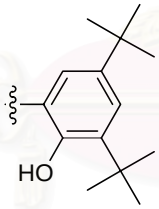
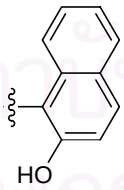
Entry	Catalyst	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	**28a·TFA**	29	95	91 (7)	90:10
2	**28b·TFA**	72	93	89 (36)	86:14
3	**28q·TFA**	29	47	65 (13)	86:14
4	**31·TFA**	72	41	66 (6)	77:23

3.4.4 Effect of catalyst structure

Next the effect of catalyst structure was studied using the TFA salt under the optimized conditions obtained previously. Several prolinamides derived from various substituted aminophenols (**28b**-**28l**) and one aminonaphthol (**28e**) were prepared. The substituents were chosen so that they provide different steric and eletronic effects. In many reported catalytic asymmetric reactions, the presence of bulky substituents in the substrates or catalysts is essential to obtain good enantioselectivites. On the other hand, electronic effects can affect the acid strength of the OH group thus the H-bond donor properties of the catalyst.

Table 3-8. Effect of bulky groups in catalysts on the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone

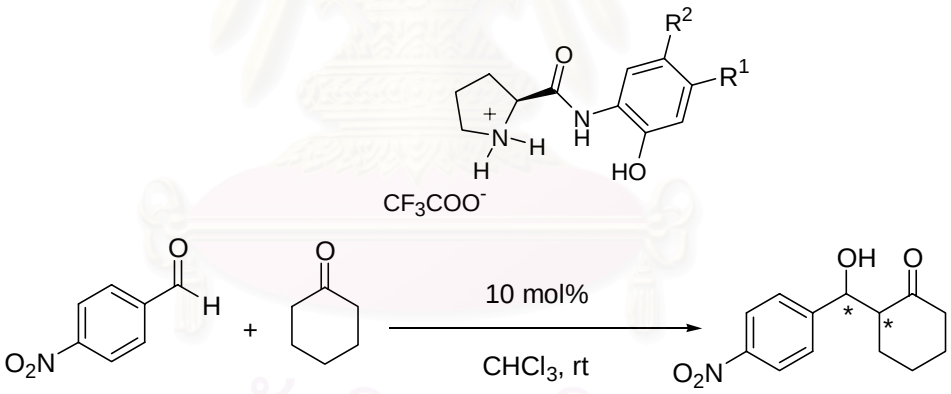


Entry	catalyst	R	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	**28b**		72	93	89 (36)	86:14
2	**28c**		72	87	89 (34)	86:14
3	**28d**		72	75	78 (27)	80:20
4	**28e**		72	68	79 (17)	78:22

To study steric effects, catalyst **28b**, **28c**, **28d** and **28e** were compared using the same model aldol reaction under the optimized conditions. The result is shown in Table 3-8. Catalysts **28c**, **28d** and **28e** were designed to have bulky groups on the aromatic rings. The negative effects on increasing steric effect is clearly seen when compare catalysts **28b** with **28c** and **28d**. The presence of one or more *tert*-butyl groups resulted in lower yield and enantioselectivity while diastereoselectivity was

not much affected. The same trend can be observed when the catalysts **28e** and **28b** were compared. The results suggested that the presence of bulky substituents was not tolerated and therefore the catalyst should not have large substituents. Next electronic effects of substituents were investigated with catalyst **28f**-**28j**. Disappointingly no definite trend could be observed. Similar yields, enantioselectivities and diastereoselectivities were obtained regardless of the type of substituents (electron-donating group vs electron-withdrawing group). Consequently, it was not possible to conclusively describe the influence of substituent on aromatic ring. The reaction catalyzed by **28g** was slow because the catalyst was insoluble during the reaction. However, the catalyst **28a** with chloro substitution, having both electron-donating (by resonance effect) and electron-withdrawing (by inductive effect) properties, afforded the best enantioselectivity for this class of catalyst. Therefore the catalyst **28a** was chosen for further optimization.

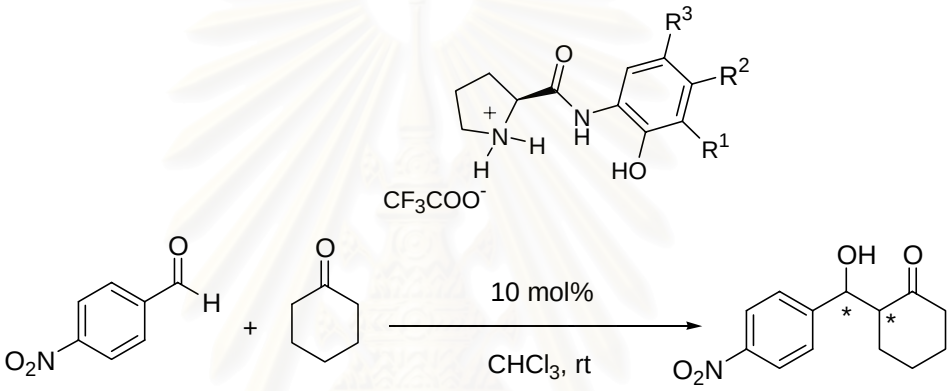
Table 3-9. Effect of electronic group in catalysts on the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone



Entry	Catalyst	R		Time(h)	%yield	%*ee*	dr
		R^1	R^2			*anti*(*syn*)	(*anti*:*syn*)
1	**28a**	H	Cl	29	95	91 (7)	90:10
2	**28f**	H	OMe	44	92	93(22)	92:8
3	**28g**	H	NO_2	144	90	92(23)	87:13
4	**28h**	H	CO_2Et	42	86	90(12)	90:10
5	**28i**	H	CN	48	90	91(10)	91:9
6	**28j**	CF_3	H	40	92	92(10)	93:7

The prolinamide **28o** were prepared based on prolinamide **28a** with an additional nitro group, in the hope that the nitro group might increase the hydrogen bond donor properties of the OH and NH groups so that the catalytic activity and enantioselectivity might be increased. The result of prolinamide **28o** was disappointing since lower enantioselectivities were obtained compared with prolinamide **28a**. Similar with catalyst **28p** provided both lower reactivity and enantioselectivity.

Table 3-10 Effect of addition of more than one halogens to the catalysts on the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone



Entry	Catalyst	R			Time(h)	%yield	%*ee*	dr
		R^1	R^2	R^3			*anti*(*syn*)	(*anti*:*syn*)
1	**28a**	H	H	Cl	29	95	91 (7)	90:10
2	**28k**	Cl	H	Cl	29	90	92 (13)	91:9
3	**28l**	Cl	H	F	29	93	95 (30)	91:9
4	**28m**	Cl	H	H	29	91	95 (7)	93:7
5	**28n**	F	H	F	29	93	94 (7)	93:7
7	**28o**	H	NO_2	Cl	29	89	90 (1)	91:9
8	**28p**	NO_2	H	Cl	48	82	84 (39)	89:11

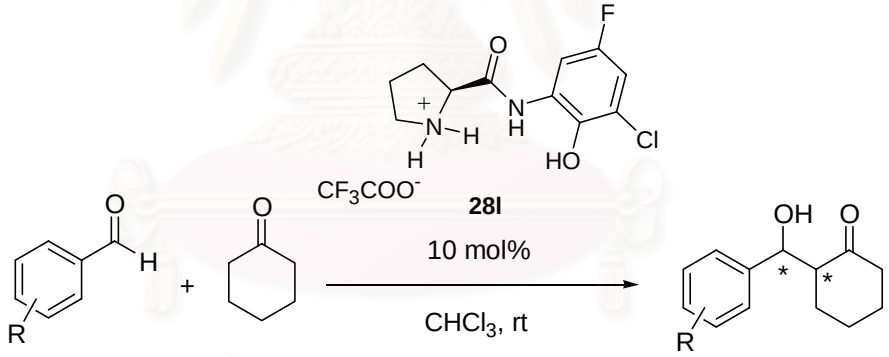
Since the best catalyst obtained so far contained Cl as subtituent, it was reasonable to investigate the effect of addition of more than one halogen atoms to the catalyst. The prolinamide **28k** with two chloro groups provided lower enentioselectivity than the catalyst **28l** in which one chloro group was replaced by fluoro group. This result suggested that catalysts carrying fluoro groups might be

better than chloro groups. However, the prolinamide **28n** with two fluoro groups provided lower enentioselectivity than the catalyst **28l**. It was also found that the presence of chloro group at *ortho*-position (**28m**) resulted in better enentioselectivity than at *para*-position **28a**. The best results were obtained with the catalyst **28l** containing chloro group at *ortho*-position and fluoro or hydrogen at *para*-position with 93%, 91:9 (*anti*:*syn*) and 95% *ee*(*anti*).

3.4.4 Scope and limitation

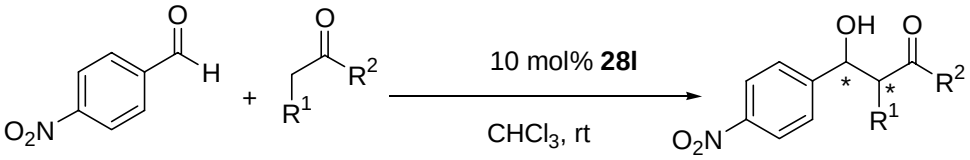
The scope and limitations of the direct aldol reaction catalyzed by **28l** were also examined. The direct aldol reaction was tested with a series of aromatic aldehyde acceptors (Table 3-11) and ketone donors (Table 3-12). Reactions afforded *anti*-aldol products with highly diastereoselectivities and enantioselectivities with most aromatic aldehydes acceptors. However, ketones donors other than cyclohexanone gave rather poor enantioselectivities and diastereoselectivities.

Table 3-11. Aldol reactions of various aldehydes with cyclohexanone catalyzed by **28l**



Entry	R	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	4-CN	48	96	91 (16)	86:14
2	4-Cl	72	75	88 (10)	89:11
3	4-Br	72	83	89 (3)	88:12
4	4-H	72	71	81 (7)	81:19
5	2-NO_2	48	82	95 (75)	95:5

Table 3-12. Aldol reactions of various ketones with 4-nitrobenzaldehyde catalyzed by **1l**



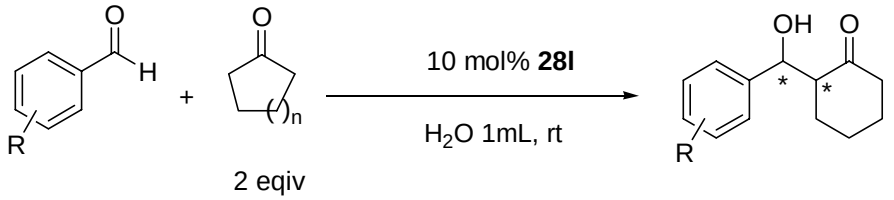
Entry	R^1	R^2	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1	$-(CH_2)_3-$		29	96	79(67)	33:67
2	$-(CH_2)_6-$		72	30	37(22)	61:39
3	Me	H	48	65	69	-

3.4.5 The aldol reaction in water

Water is one of the most desirable solvent in the field of organic synthesis especially on an industrial scale in respect to environmental concerns, safety, and cost. The developments of catalytic asymmetric reactions that can be performed in water are widely interested. Initially, the model aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was performed in water in the presence of 10 mol% of **28l** without co-solvents. The aldol product was obtained in good yield and enantioselectivity. Most interestingly, there was a slight increase in both diastereoselectivity and enantioselectivety compared to the reaction in chloroform.

The scope of prolinamide **28l**-catalyzed aldol reactions in water was then examined with a series of arylaldehyde acceptors and ketone donors (Table 3-13). The resulted showed that in all cases the enantioselectivitives and diastereoselectivitives were superior to the same reactions performed in chloroform. Although the reason is not yet understood, this appears to be consistent with previous literature work concerning proline-catalyzed aldol reactions in water [47,50,51] and the results should be of interest for process chemists. A control experiment using neat cyclohexanone and 4-nitrobenzaldehyde without water gave the *anti* aldol product in 96% yield but only 89% *ee* and 90:10 dr indicating the essential role of water.

Table 3-13. Aldol reaction of various aldehydes with cyclohexanone catalyzed by **28l** in water

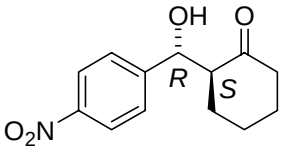


Entry	R	n	Time(h)	%yield	%*ee* *anti*(*syn*)	dr (*anti*:*syn*)
1[a]	4-NO_2	2	29	93	95 (30)	91:9
2[b]	4-NO_2	2	24	96	93 (39)	90:10
3	4-NO_2	2	24	91	97 (35)	94:6
4	4-CN	2	48	91	96 (59)	91:9
5	4-Cl	2	72	70	94 (24)	88:12
6	4-Br	2	72	71	93 (55)	90:10
7	4-H	2	72	68	90 (29)	88:12
8	2-NO_2	2	48	65	97 (67)	95:5
9	4-NO_2	1	48	78	79 (33)	49:51

a The reaction perform in chloroform. b The reaction perform in neat cyclohexanone

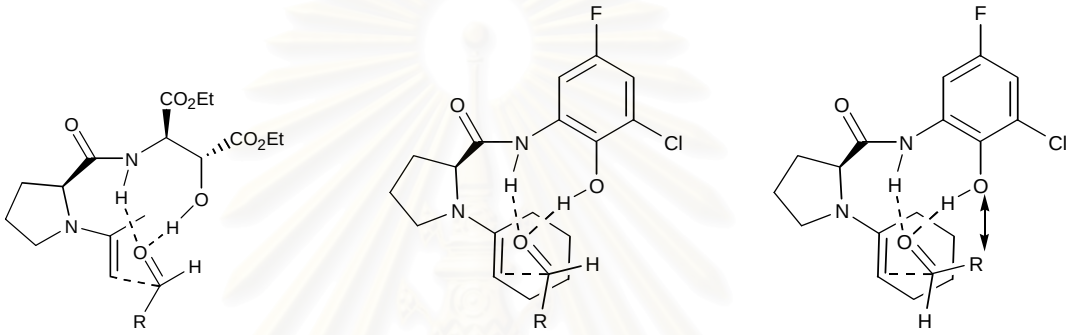
3.5 Transition state consideration

The transition state model to predict or explain the stereochemical courses of aldol reactions is well documented. [46, 47, 50] By comparing the chiral HPLC chromatogram with the literature, the absolute configuration of the major product was determined to be anti "*R,S*". Models proposed in the literature have been successfully used to explain the stereochemical outcome.



The organocatalyst **28l** showed much better ability at controlling the stereochemical outcome of the aldol reaction. Gong [45] proposed that a related prolinamide catalyst **19** worked as a bifunctional catalyst *via* the transition state TS1.

Therefore, the prolinamide **28l** is assumed to catalyze the direct aldol reaction *via* a similar transition state (TS2). The pyrrolidine reacted with the donor carbonyl compound to from an enamine intermediate and the aldehyde substrate is held in close proximity to the reaction center through double hydrogen bonding with the enamine intermediate. The enamine attacked the aldehyde from the more accessible *re*–face to afford the product, which is consistent with the experimental results. The transition state TS3 is less favorable because the larger group (R) of the aldehyde substrate may interact with hydroxyl group or *ortho*-substituent of the catalyst.

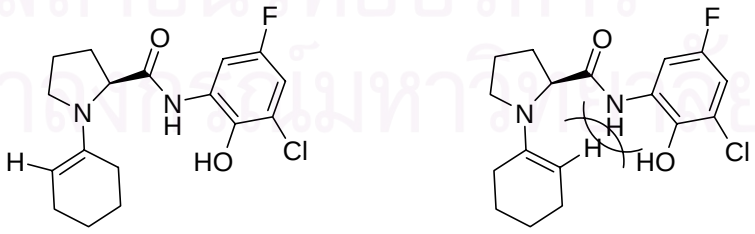


TS1 TS2 (Favored) TS3 (Unfavored)

(*R*,*S*) (*S*,*S*)

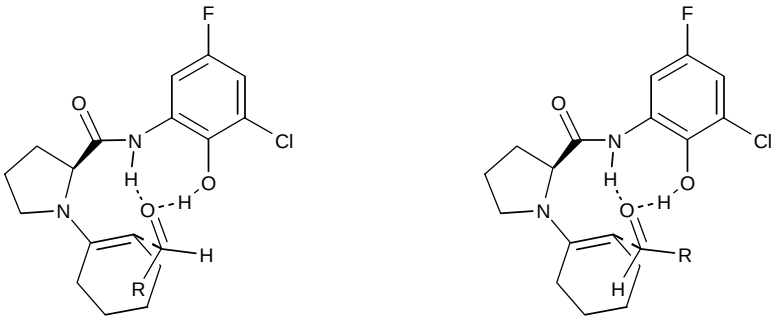
Figure 3-14. The proposed transition state model of asymmetric direct aldol reaction

To explain the face selectivity in attacking by the eanamine intermediate, two conformations must be considered. Formation of enamine **1** is more favored compared to **2** due to the presence of greater 1,3-allylic strain in **2** therefore TS4 and TS5 are expected to have higher activation energy.



1 **2**

In conclusion, the standard models for proline or prolinamide catalyzed aldol reactions have been successfully employed to explain the stereochemical outcome of the direct aldol reaction catalyzed by **28l**.



TS4 TS5

(*R*,*R*) (*S*,*R*)

Figure 3-15. The transition state model of asymmetric direct aldol reaction with enamine **2**

During the preparation of this thesis, a similar prolinamide catalyst has been reported by Tang and co-workers as a catalyst direct aldol reaction (published in Jan 2007). Only a limited structural variation has been made and limited reaction parameters have been studied. Up to 99:1 dr and 99% *ee* were obtained. The results are in good agreement with this work. [61]

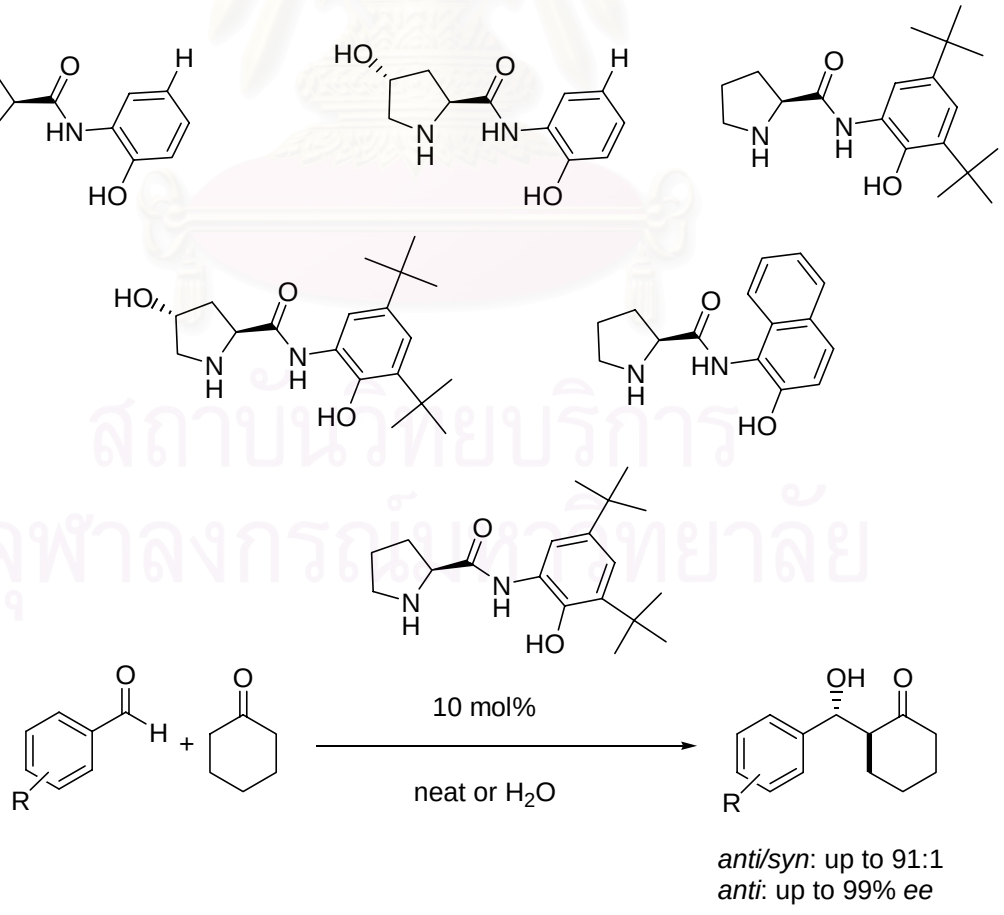


Figure 3-16. Asymmetric direct aldol reaction with prolinamide-catalyzed

CHAPTER IV

CONCLUSION

New L-prolinamide catalysts were explored for the asymmetric direct aldol reaction. L-Prolinamides derived form L-proline and 2-aminophenols were found to be effective catalysts for the direct aldol reaction between 4-nitrobenzaldehyde and cyclohexanone at room temperature. A series of L-prolinamide prepared as the trifluoroacetate salt exhibited higher enantioselectivity and diastereoselectivity compared to the free base forms. Effects of substituents on the catalyst were investigated. Comparable yields, enantioselectivites and diastereoselectivities were obtained regardless of the type of substituents (electron-donating group vs electron-withdrawing group). However, the catalyst with 2-chloro, 4-fluoro substitution on the aminophenol, which has both electron-donating (by resonance effect) and electron-withdrawing (by inductive effect), afforded the best enantioselectivity. Up to 95% *ee* and up to 95:5 (*anti*:*syn*) diastereoselectivity were obtained wit this catalyst.

The direct aldol reactions have been extended to other substrates with a series of aromatic aldehydes and cyclohexanone to afford the aldol products with high enantioselectivities and diastereoselectivies. However, replacing of cyclohexanone with other ketones such as cyclopentanone, cycloheptanone and acetone provided only moderate to poor enantioselectivities. In addition, the prolinamide catalyst system provided excellent diastereoselectivity, and enantioselectivity for direct aldol reactions between aromatic aldehydes and cyclohexanone in water (up to 97% *ee* and up to 94:6).

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APPENDICES

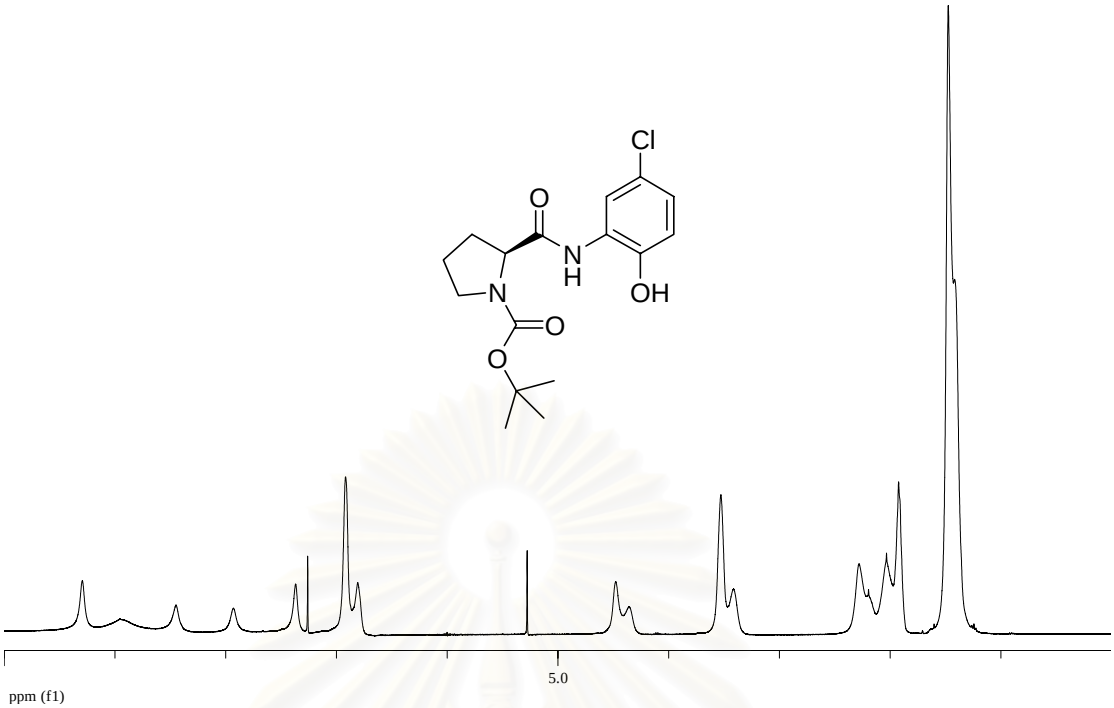


Figure 1 ^{1}H-NMR of 2-(5´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(27)**

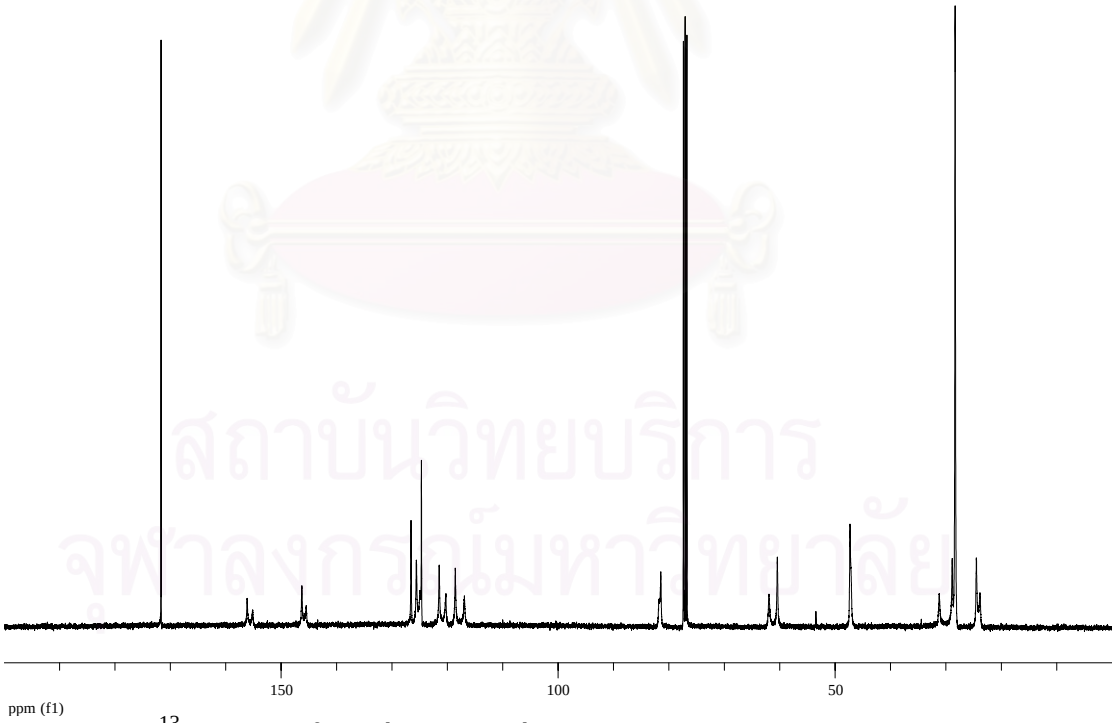


Figure 2 ^{13}C-NMR of 2-(5´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(27)**

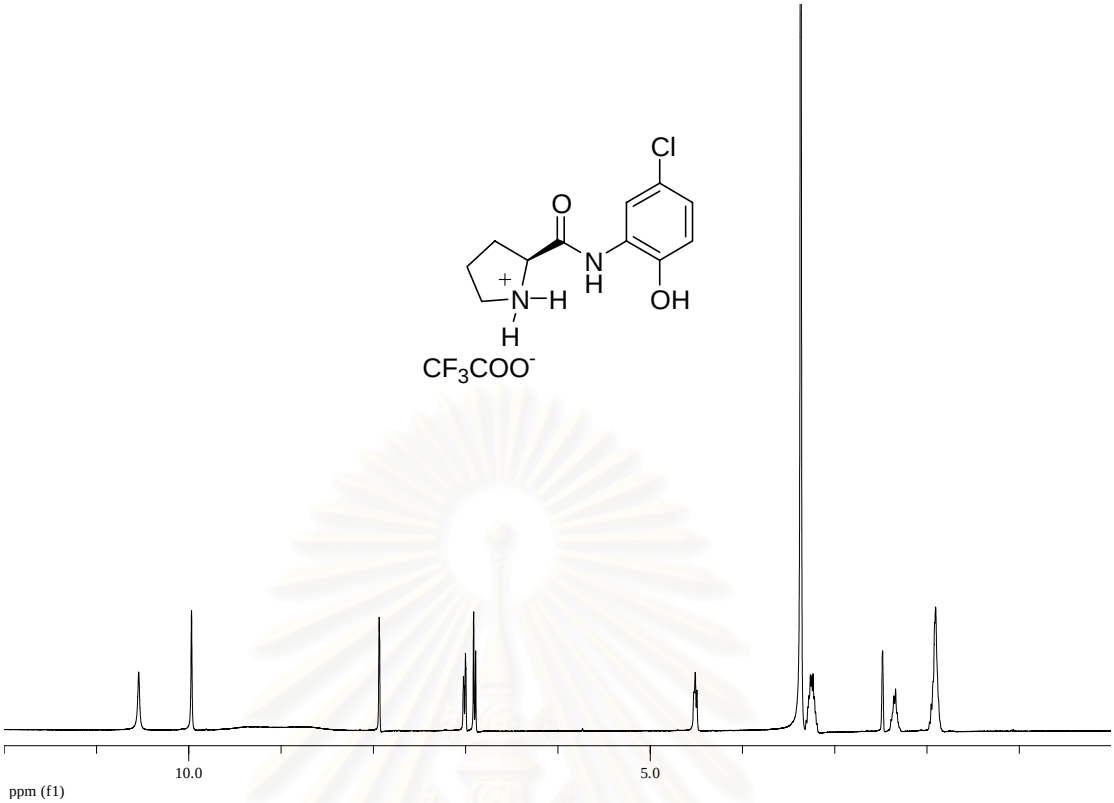


Figure 3 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28a·TFA)**

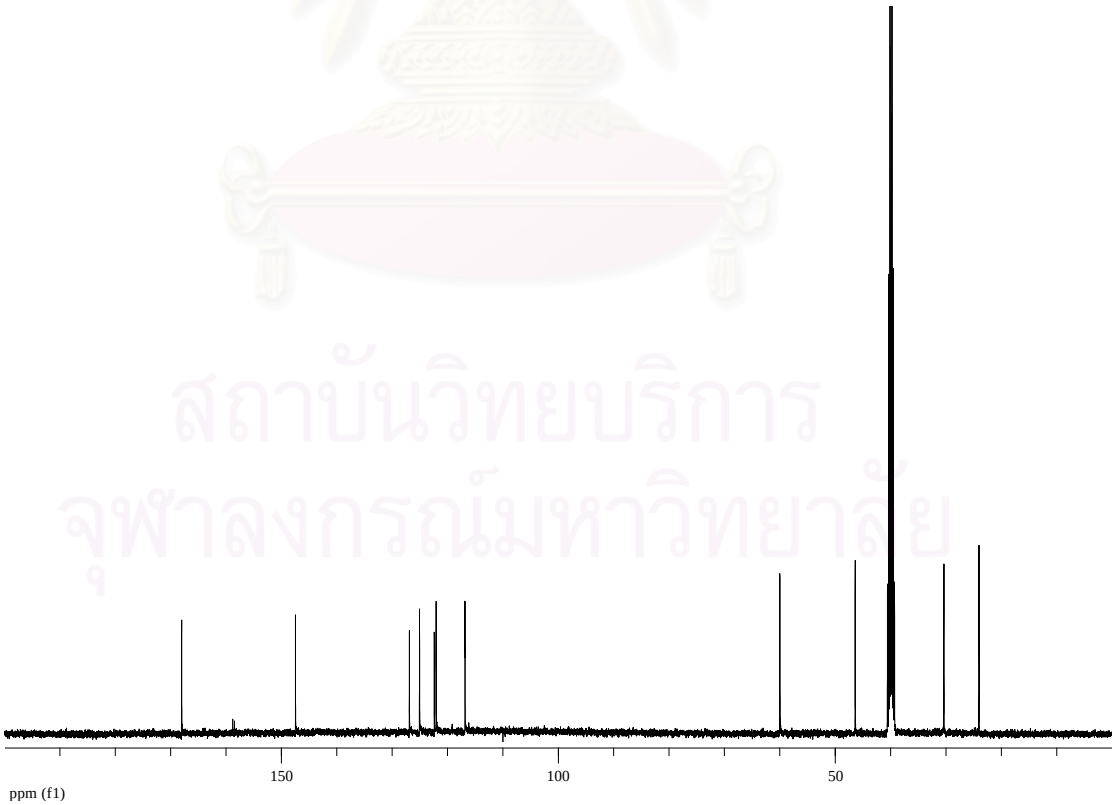


Figure 4 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28a·TFA)**

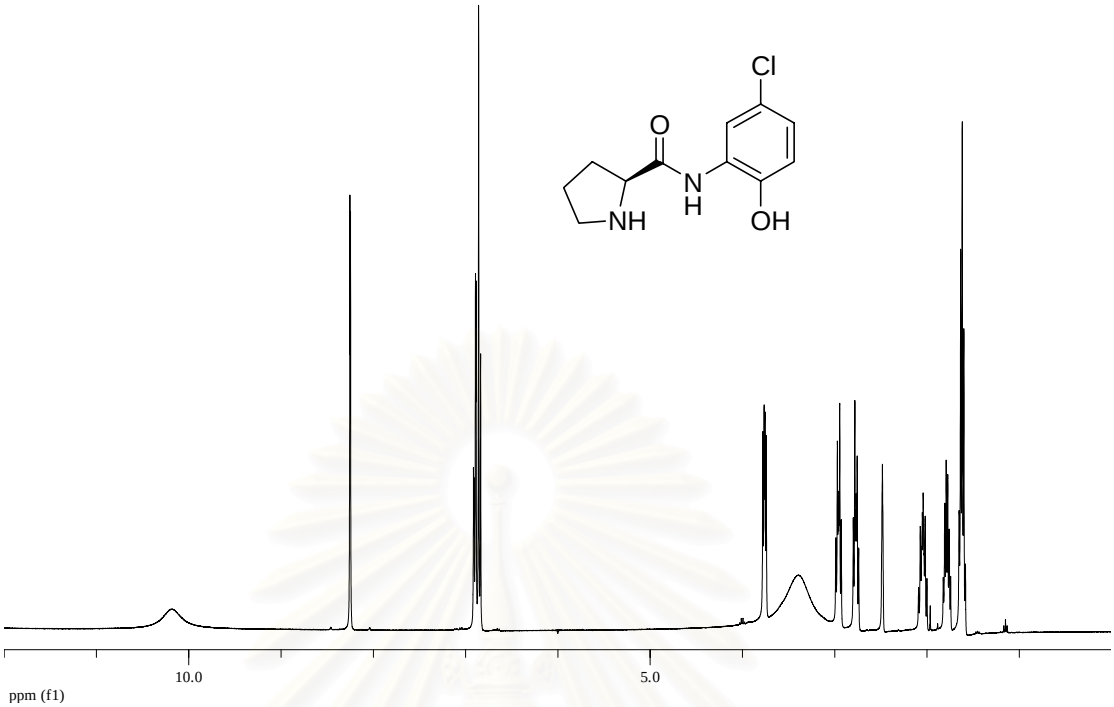


Figure 5 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide **(28a)**

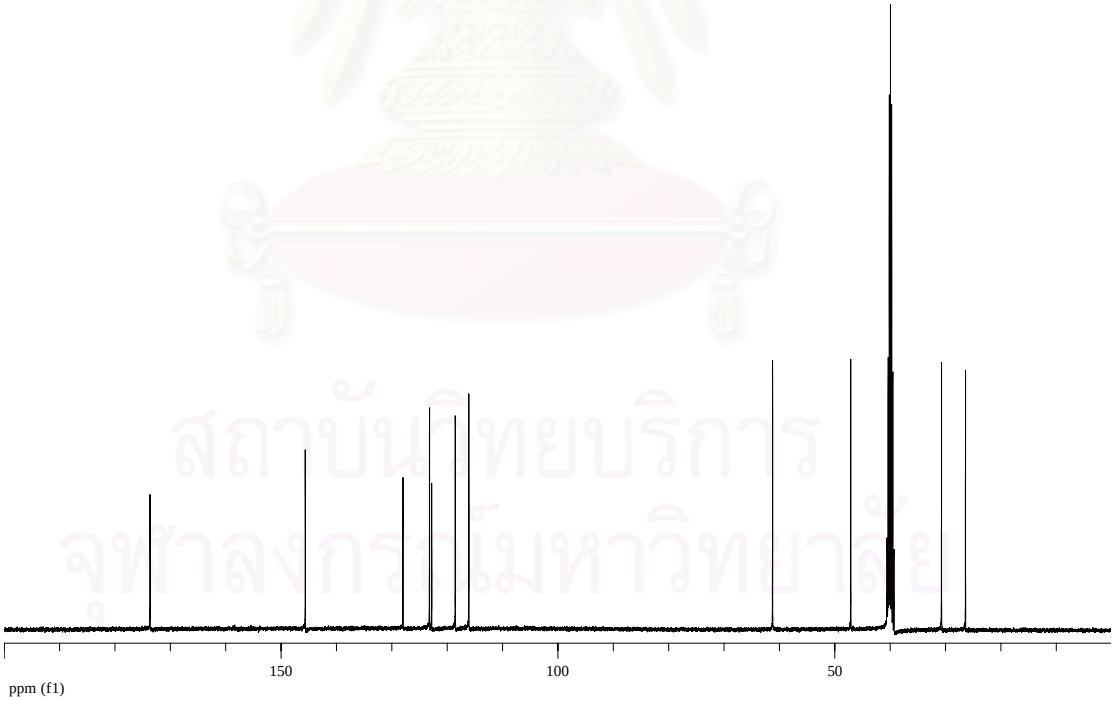


Figure 6 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-phenyl)-amide **(28a)**

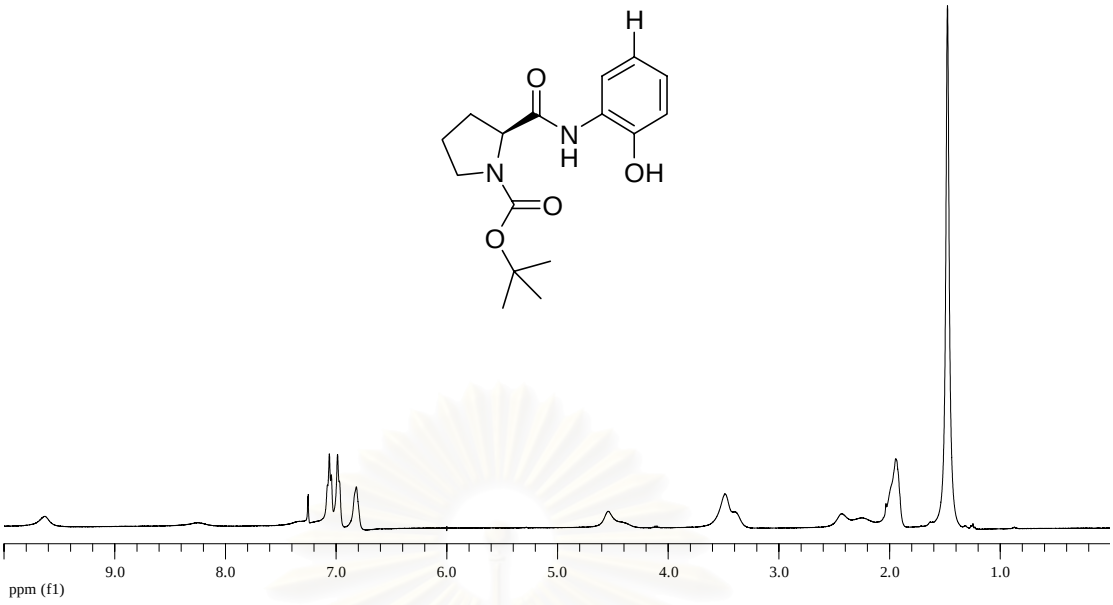


Figure 7 ^{1}H-NMR of 2-(2´-Hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(29)**

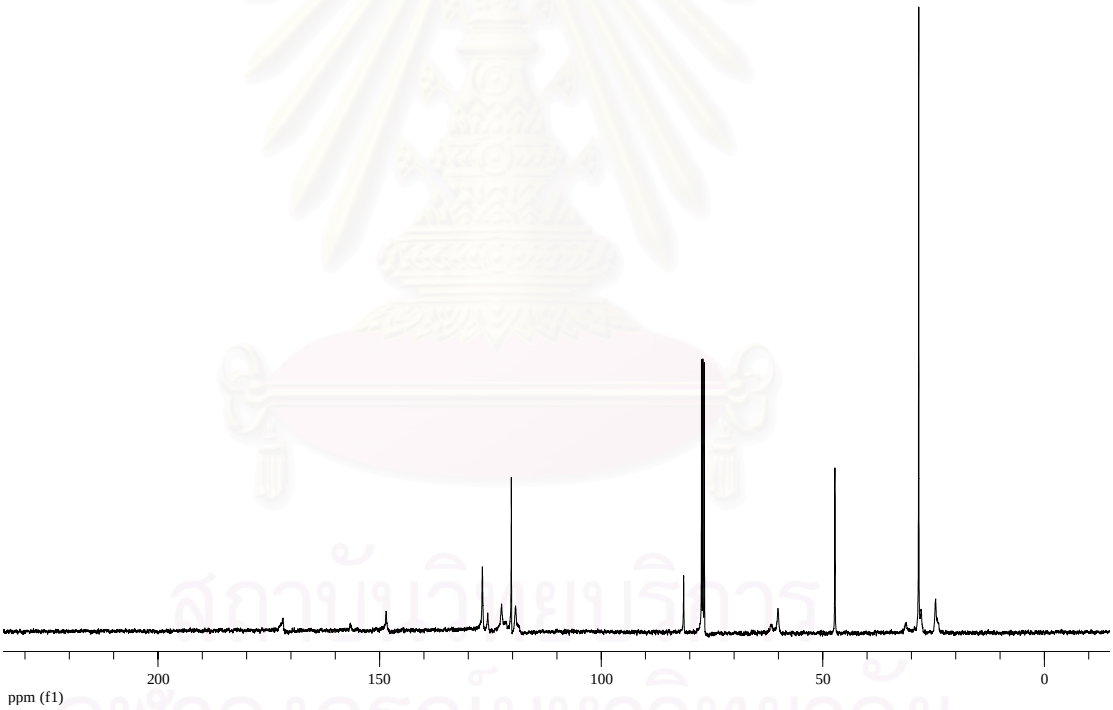


Figure 8 ^{13}C-NMR of 2-(2´-Hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(29)**

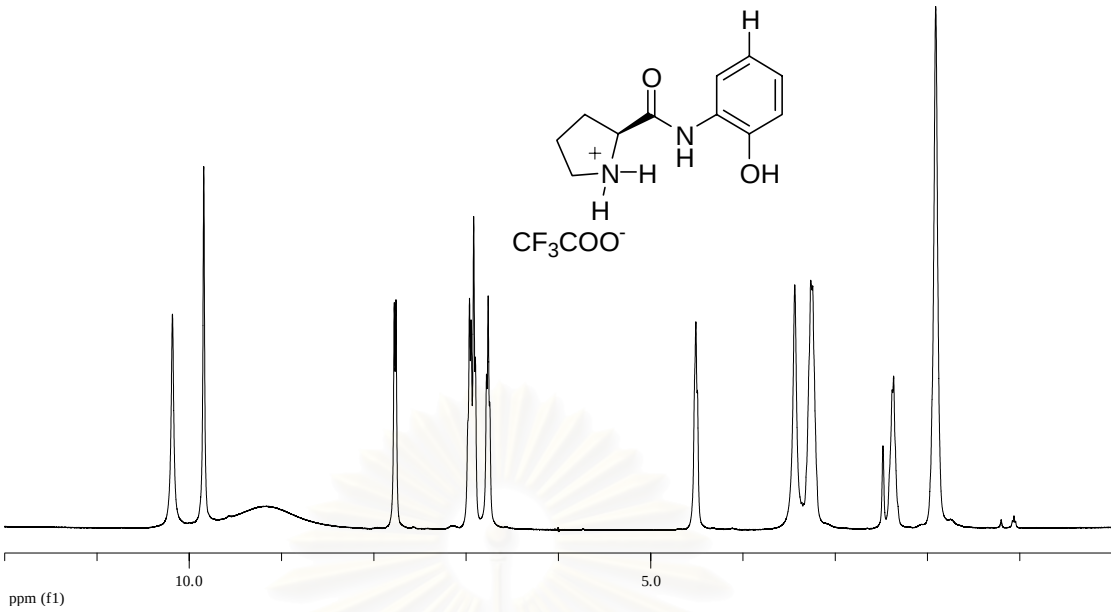


Figure 9 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide trifluoroacetate **(28b·TFA)**

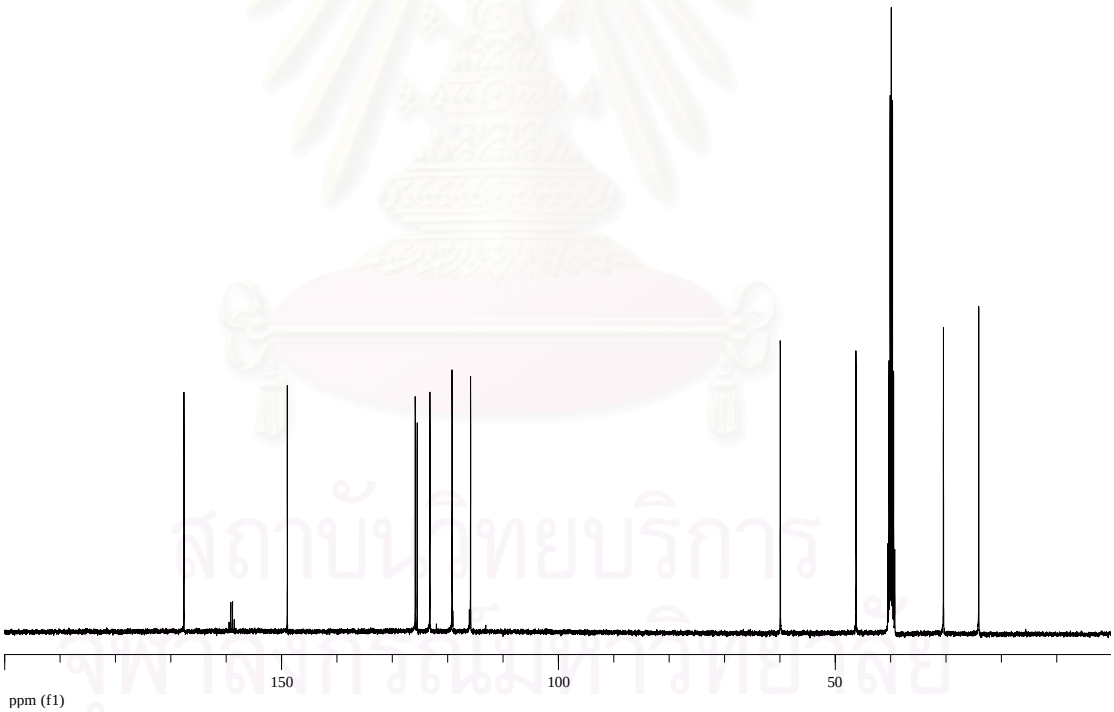


Figure 10 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide trifluoroacetate **(28b·TFA)**

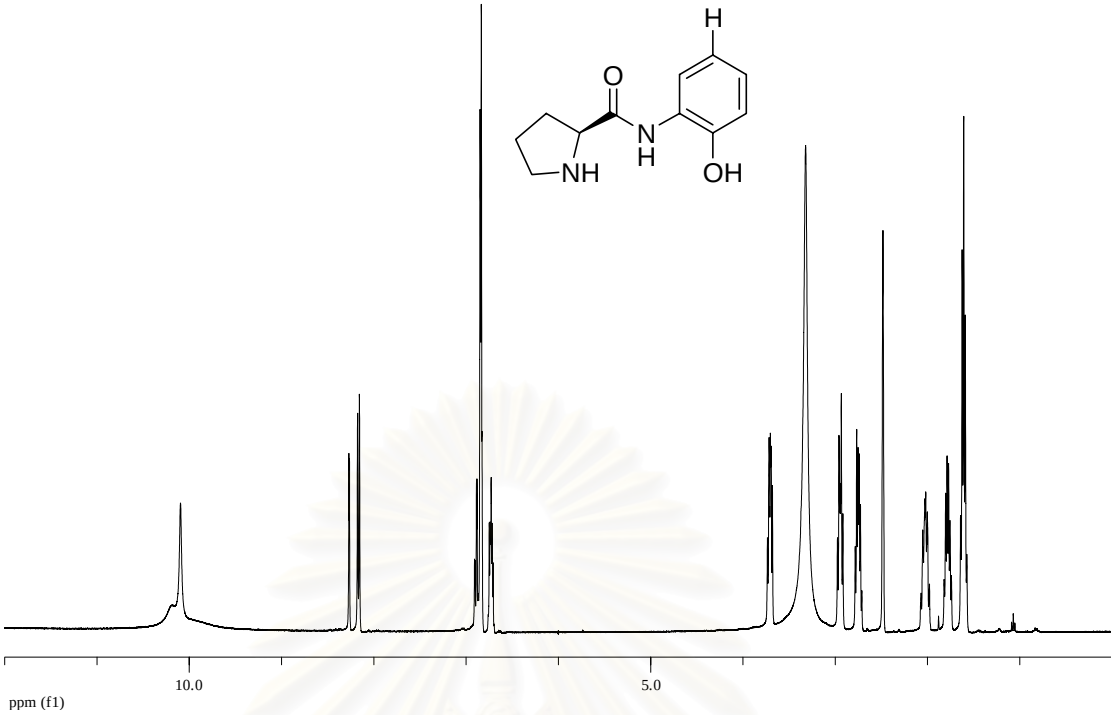


Figure 11 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide **(28b)**

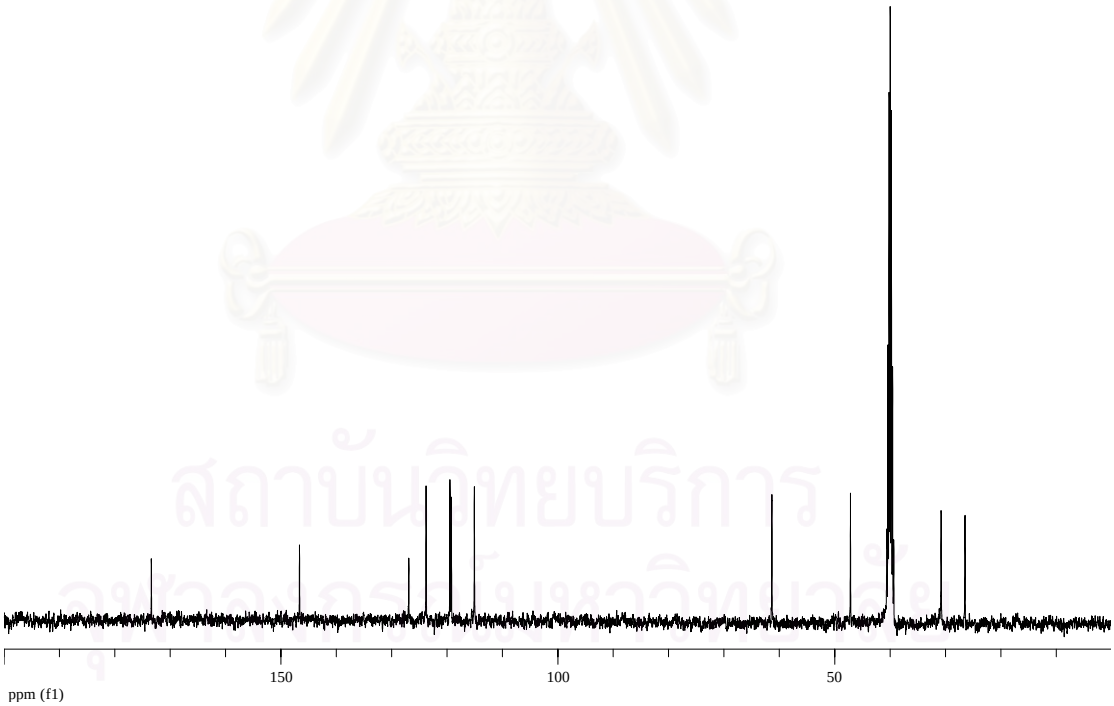


Figure 12 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-phenyl)-amide **(28b)**

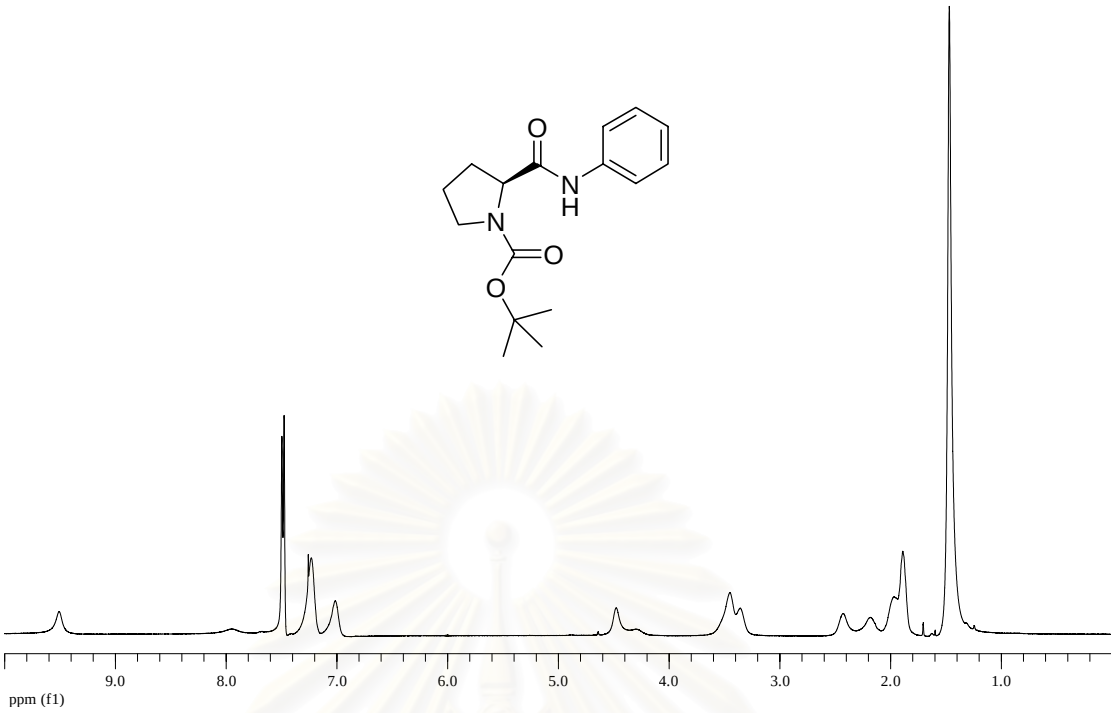


Figure 13 ^{1}H-NMR of 2-Phenylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(30)**

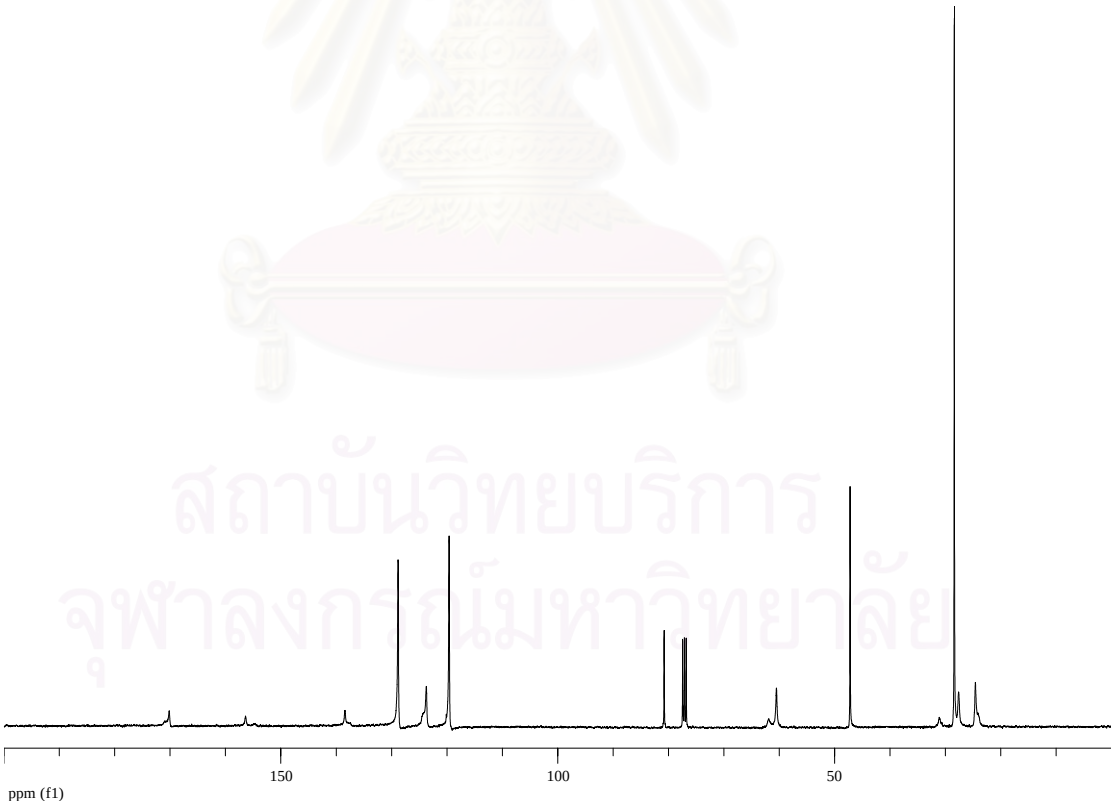


Figure 14 ^{13}C-NMR of 2-Phenylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(30)**

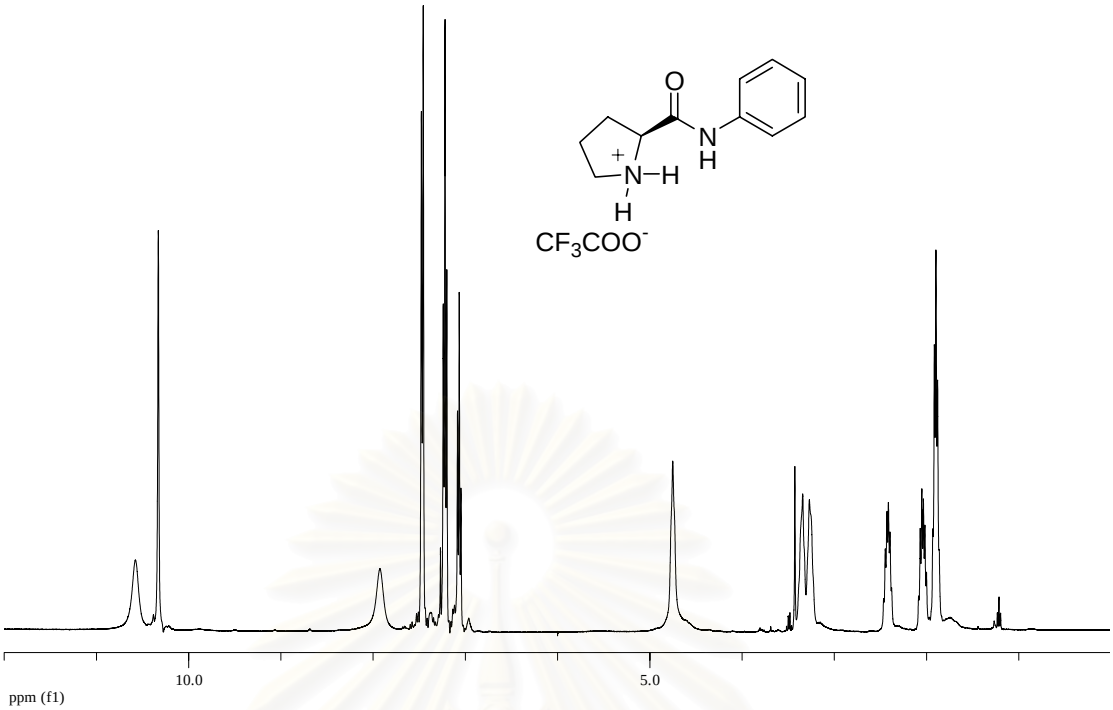


Figure 15 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid phenylamide trifluoroacetate **(31)**

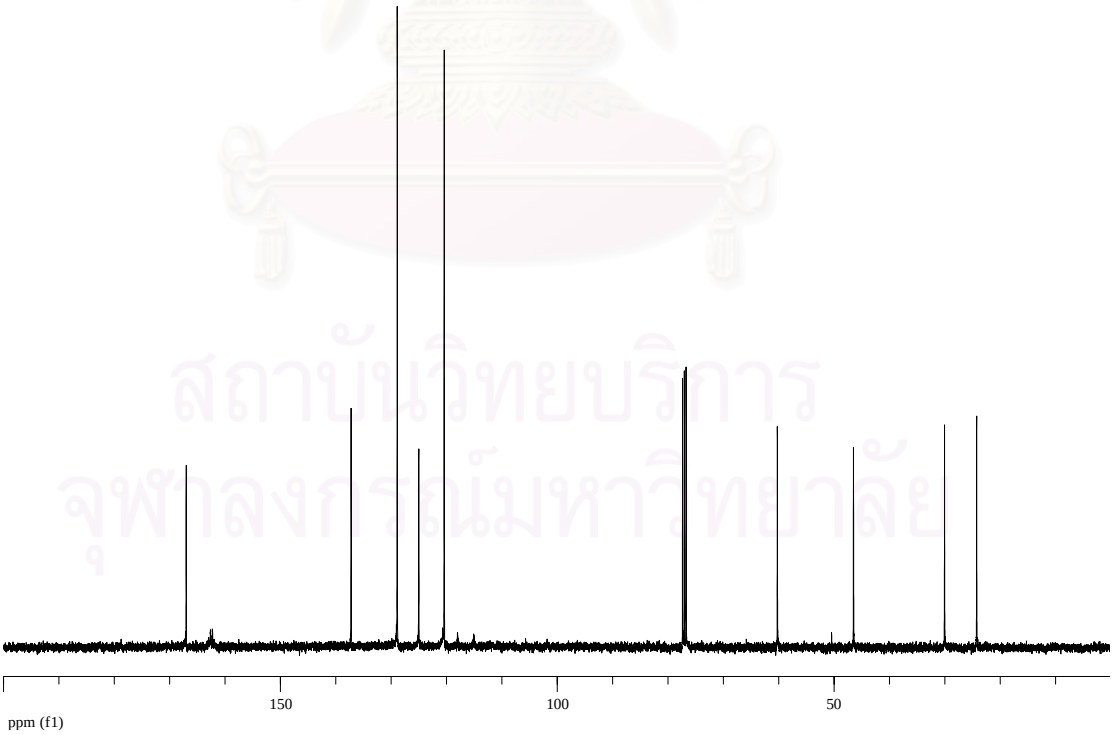


Figure 16 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid phenylamide trifluoroacetate **(31)**

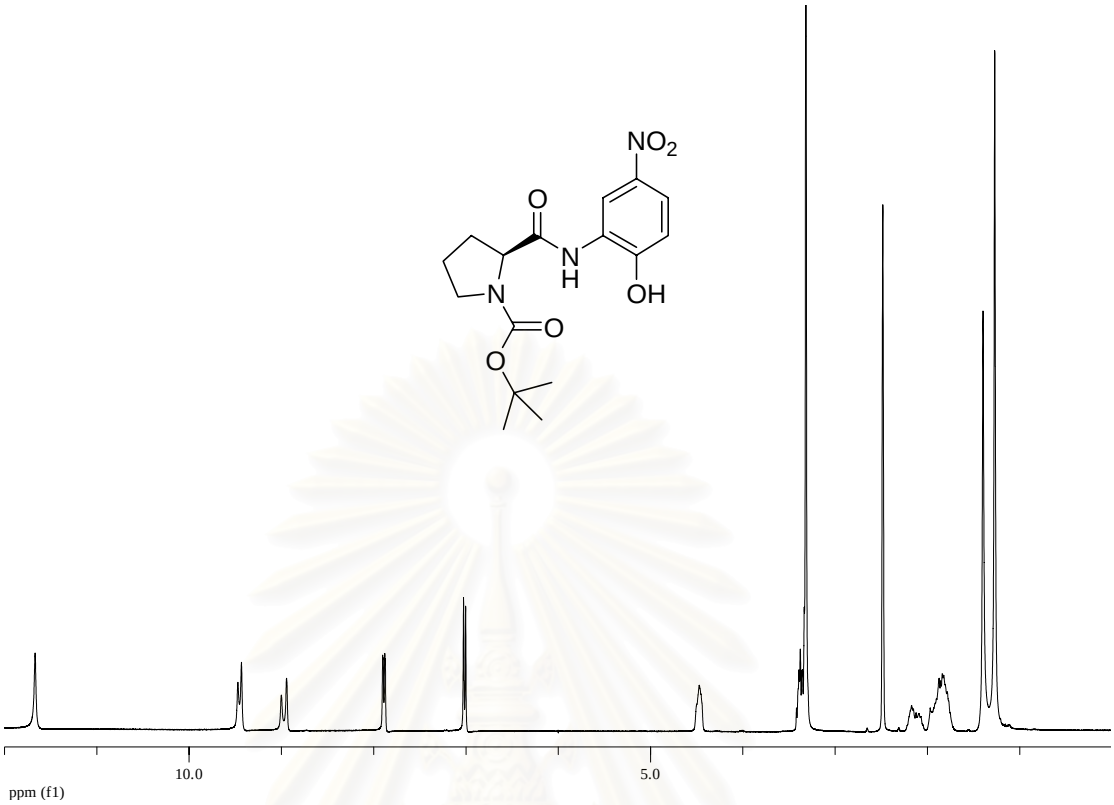


Figure 17 ^{1}H-NMR of 2-(2´-Hydroxy-5´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(32)**

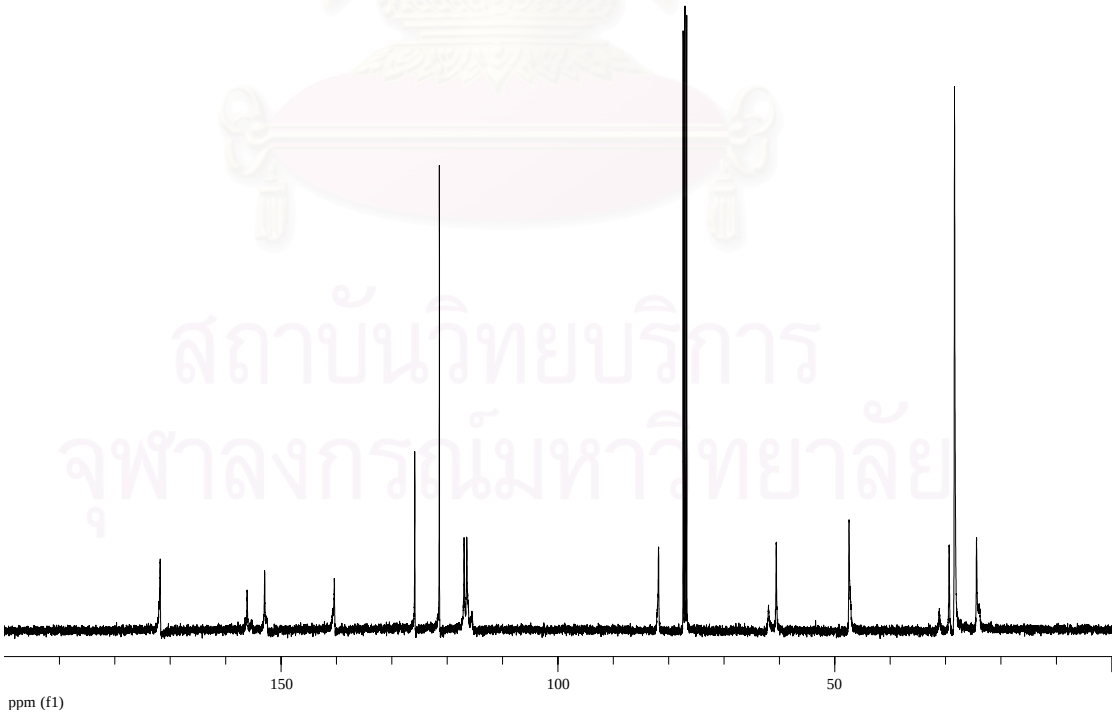


Figure 18 ^{13}C-NMR of 2-(2´-Hydroxy-5´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(32)**

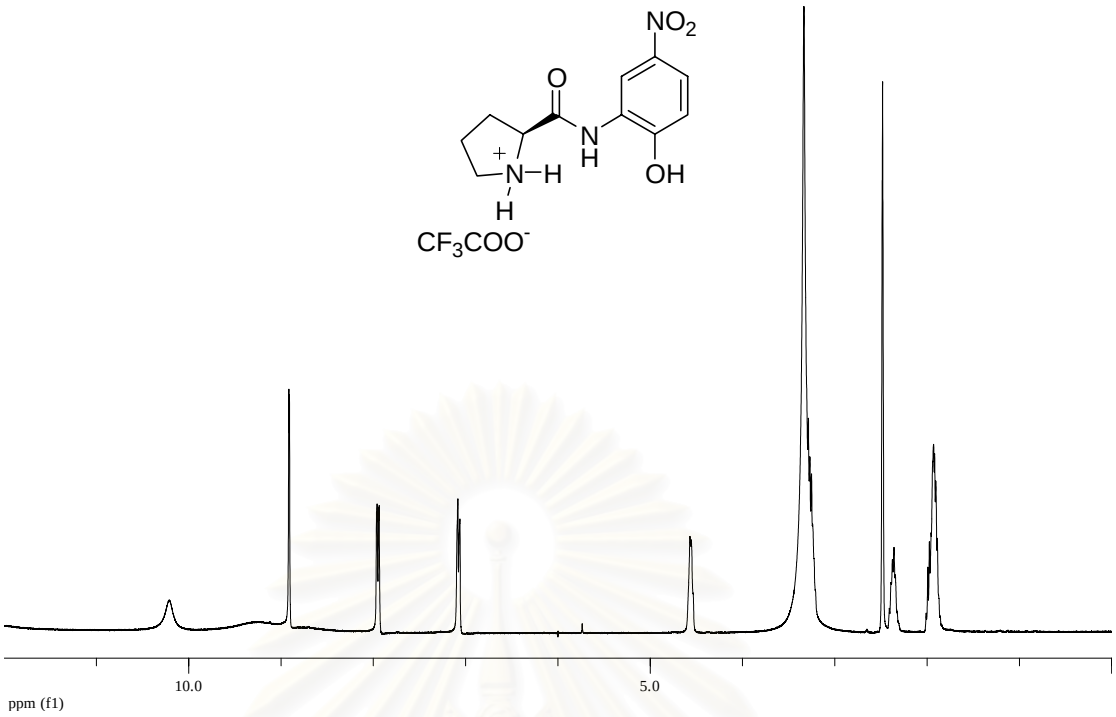


Figure 19 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-nitro-phenyl)-amide trifluoroacetate **(28g)**

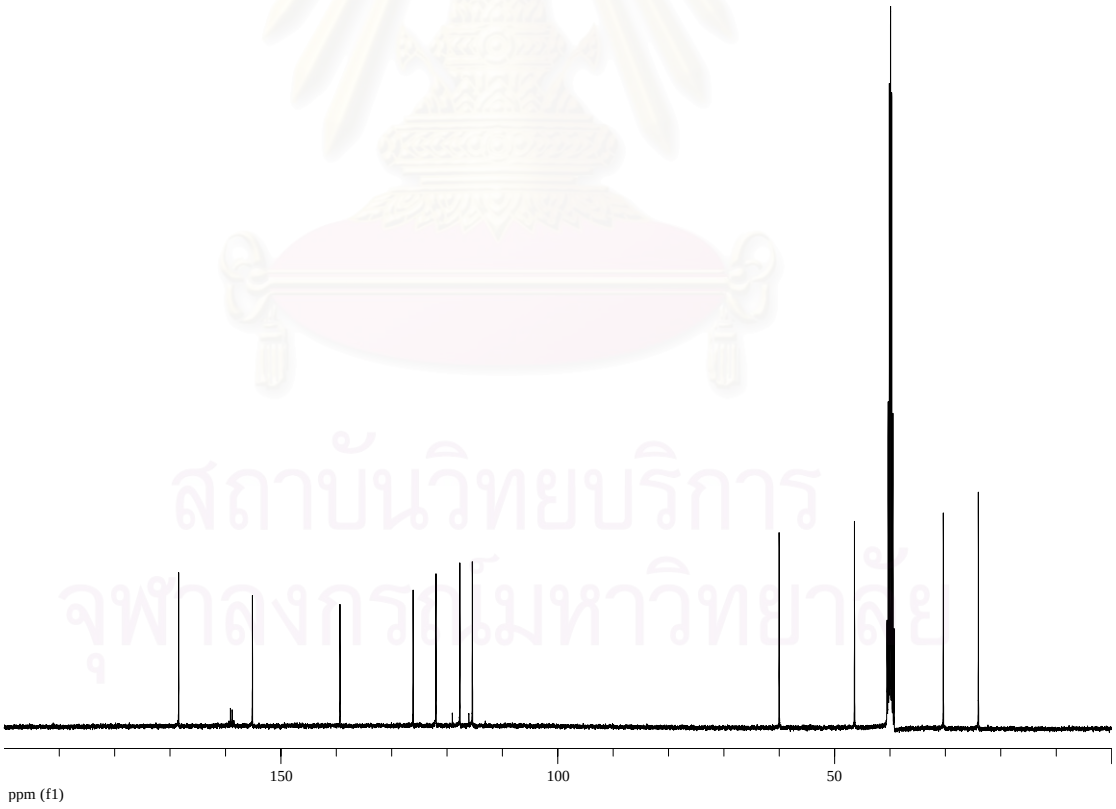


Figure 20 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-nitro-phenyl)-amide trifluoroacetate **(28g)**

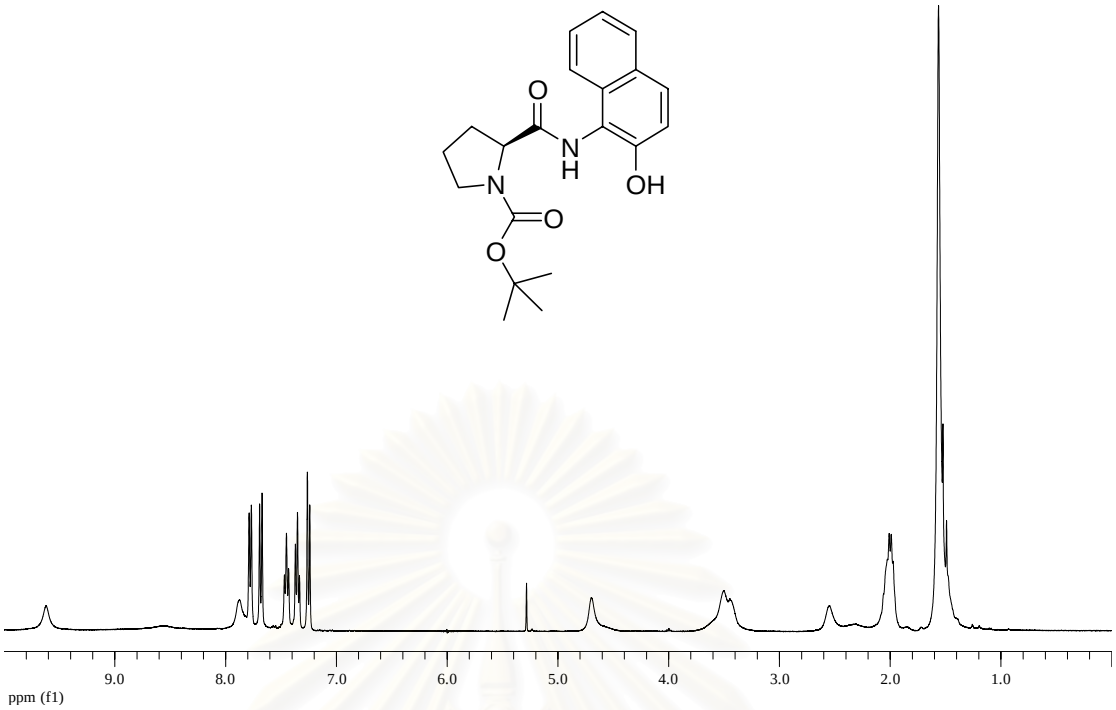


Figure 21 ^{1}H-NMR of 2-(2´-Hydroxy-naphthalen-1´-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(33)**

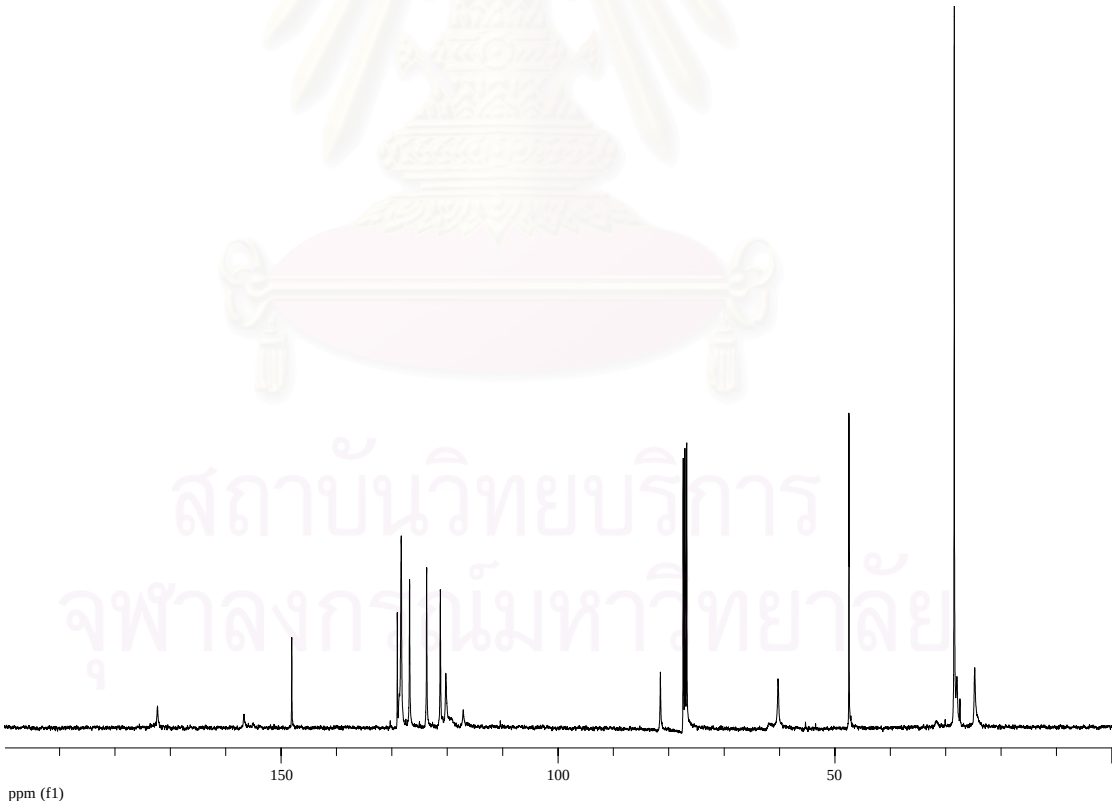


Figure 22 ^{13}C-NMR of 2-(2´-Hydroxy-naphthalen-1´-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(33)**

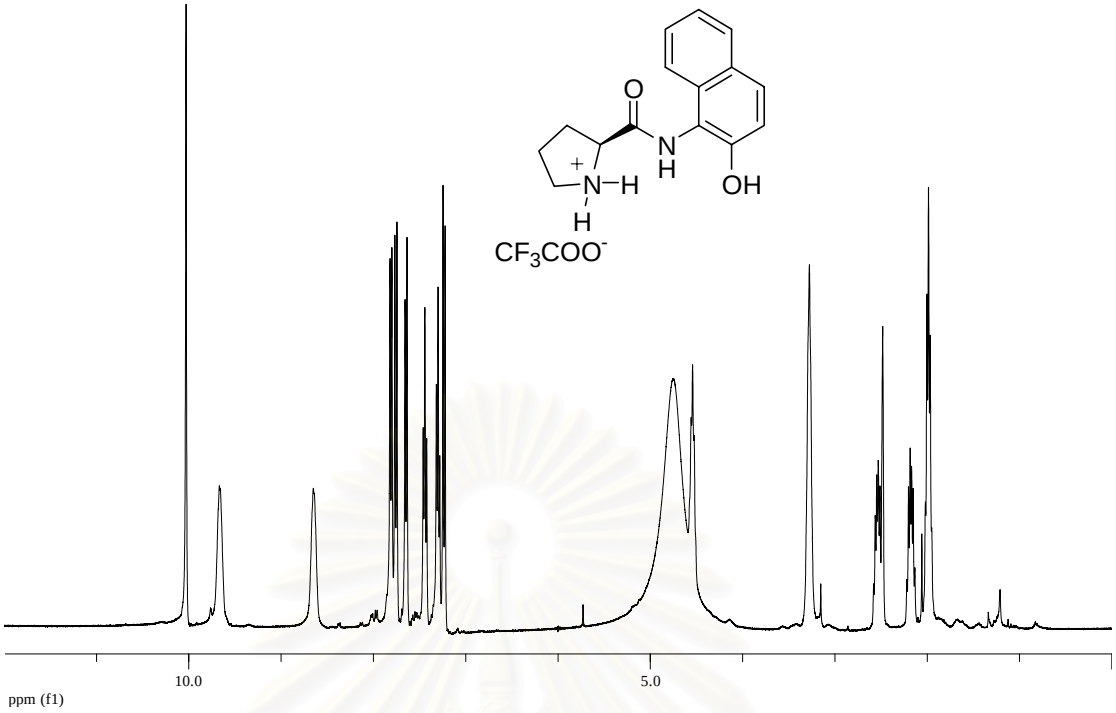


Figure 23 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide trifluoroacetate **(28e·TFA)**

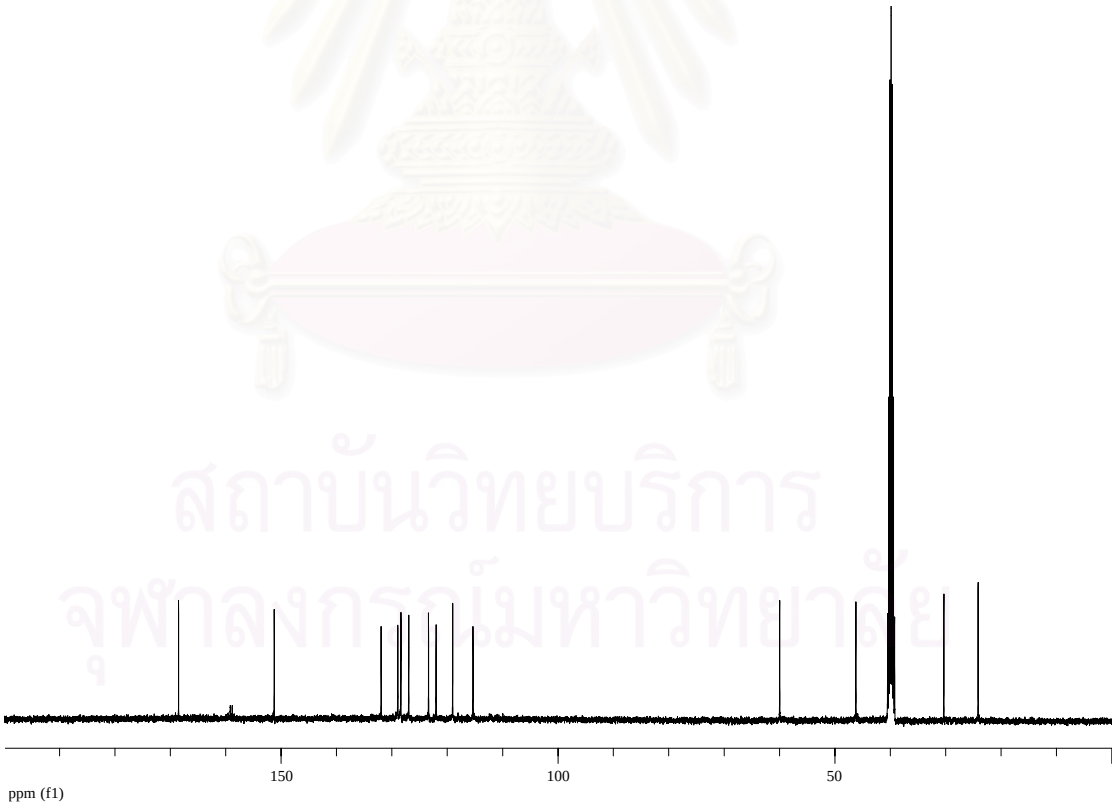


Figure 24 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide trifluoroacetate **(28e·TFA)**

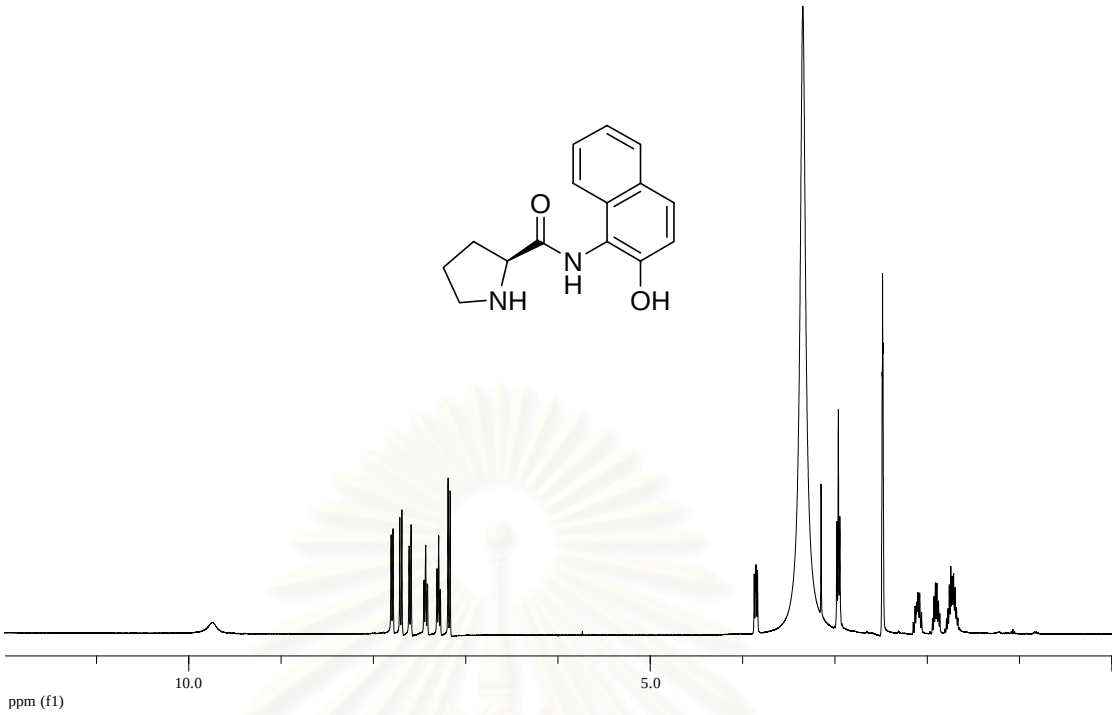


Figure 26 ^{1}H -NMR Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide **(28e)**

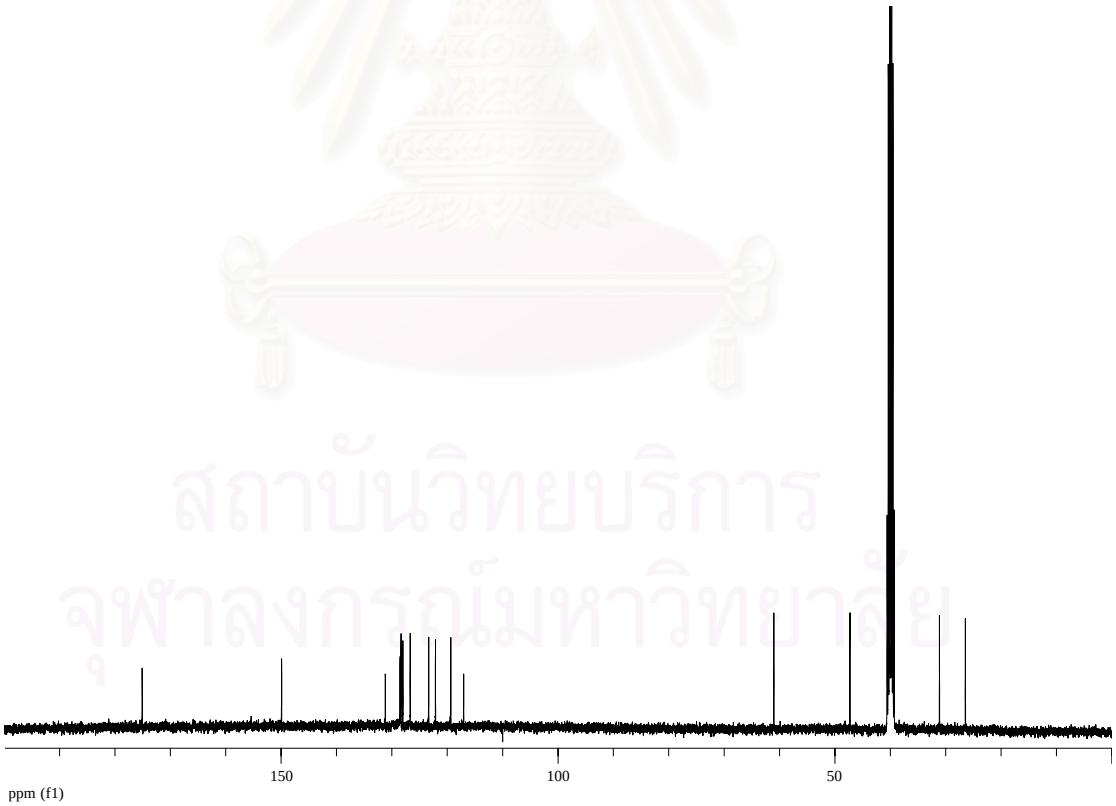


Figure 26 ^{13}C-NMR Pyrrolidine-2-carboxylic acid (2´-hydroxy-naphthalen-1´-yl)-amide **(28e)**

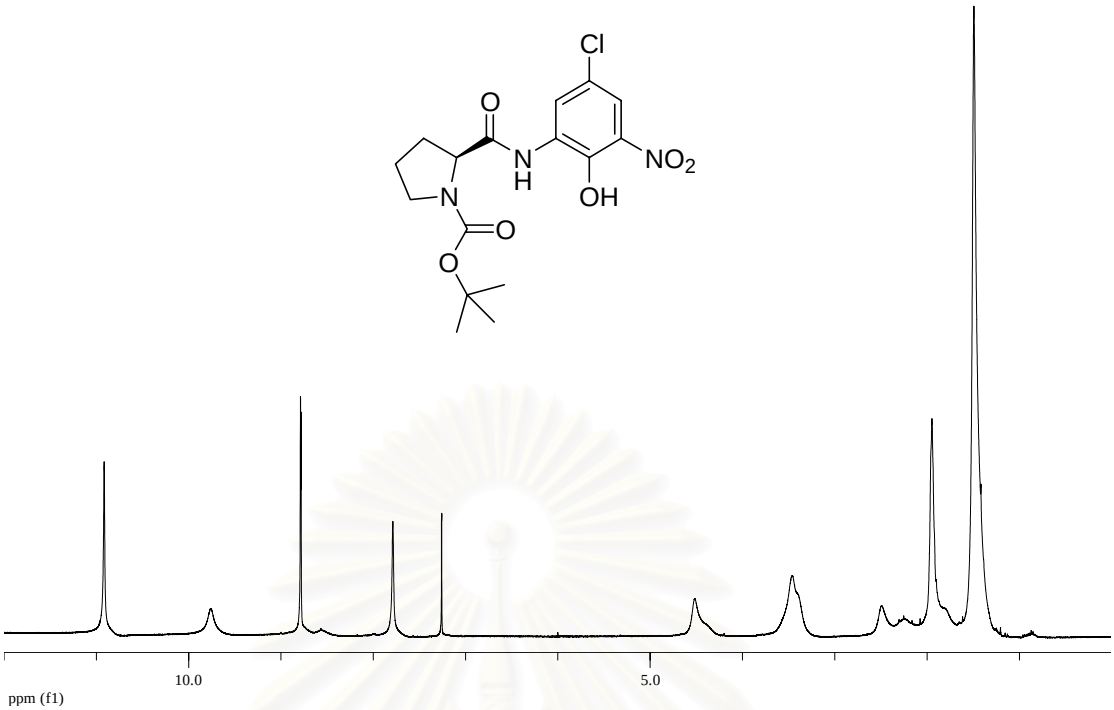


Figure 27 ^{1}H-NMR of 2-(5´-Chloro-2´-hydroxy-3´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(34)**

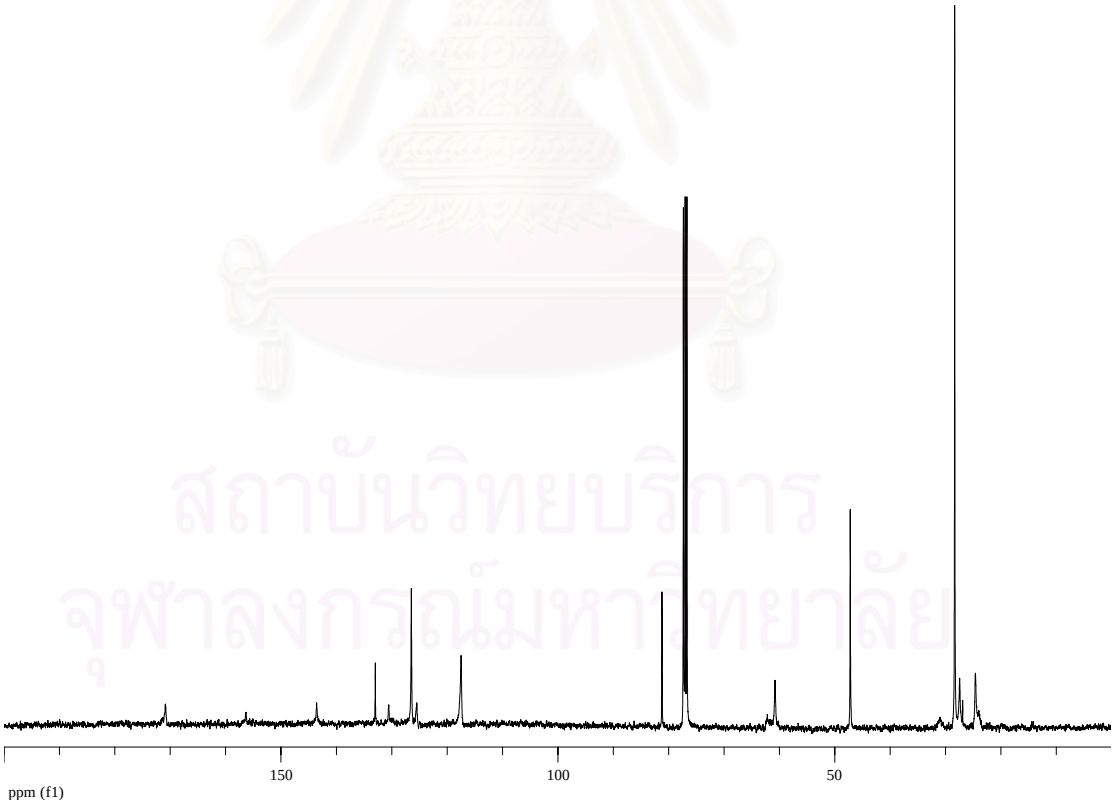


Figure 28 ^{13}C-NMR of 2-(5´-Chloro-2´-hydroxy-3´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(34)**

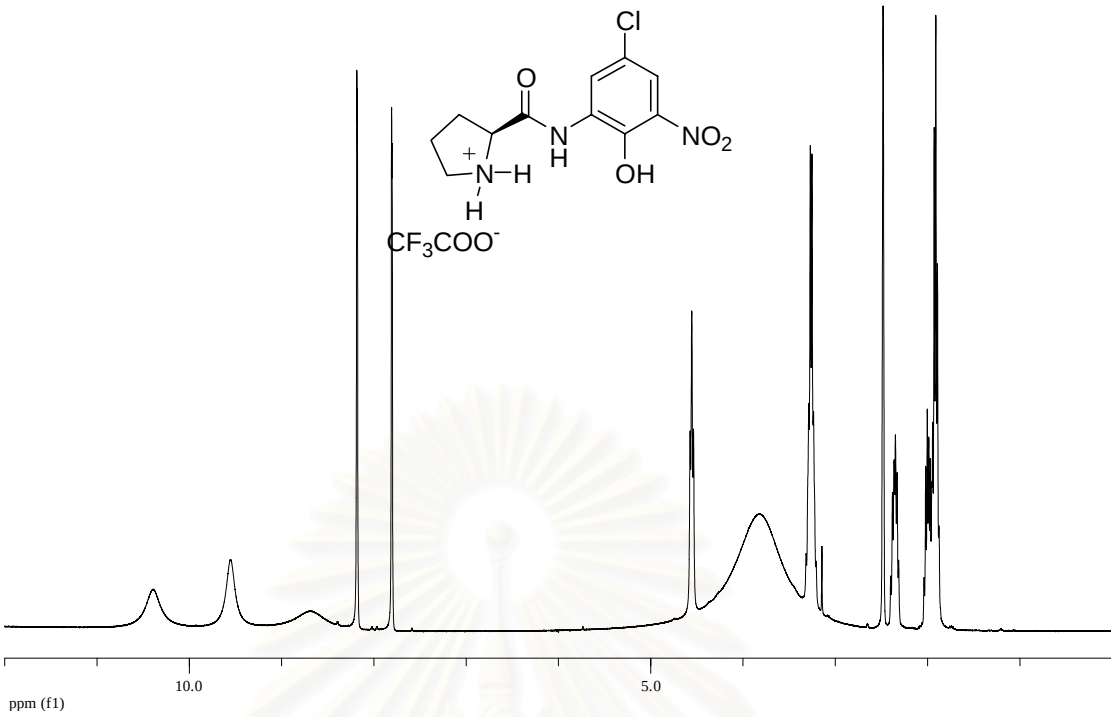


Figure 29 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-3´-nitro-phenyl)-amide trifluoroacetate **(28p)**

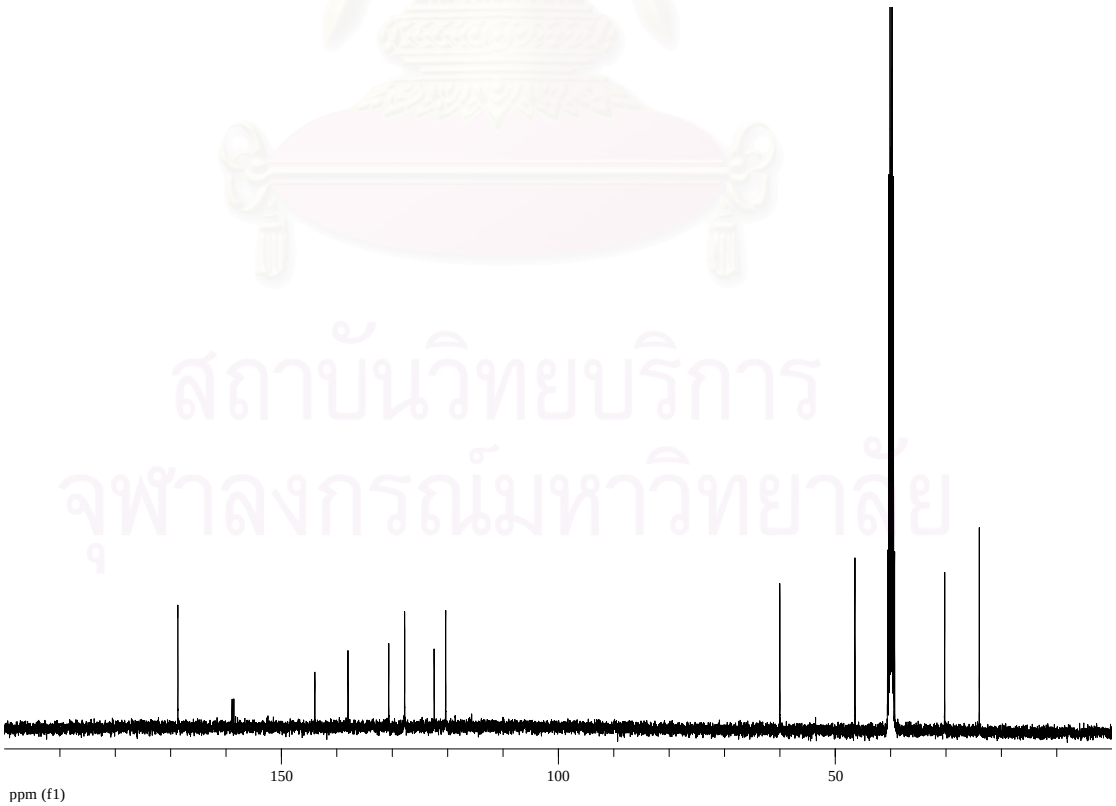


Figure 30 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-3´-nitro-phenyl)-amide trifluoroacetate **(28p)**

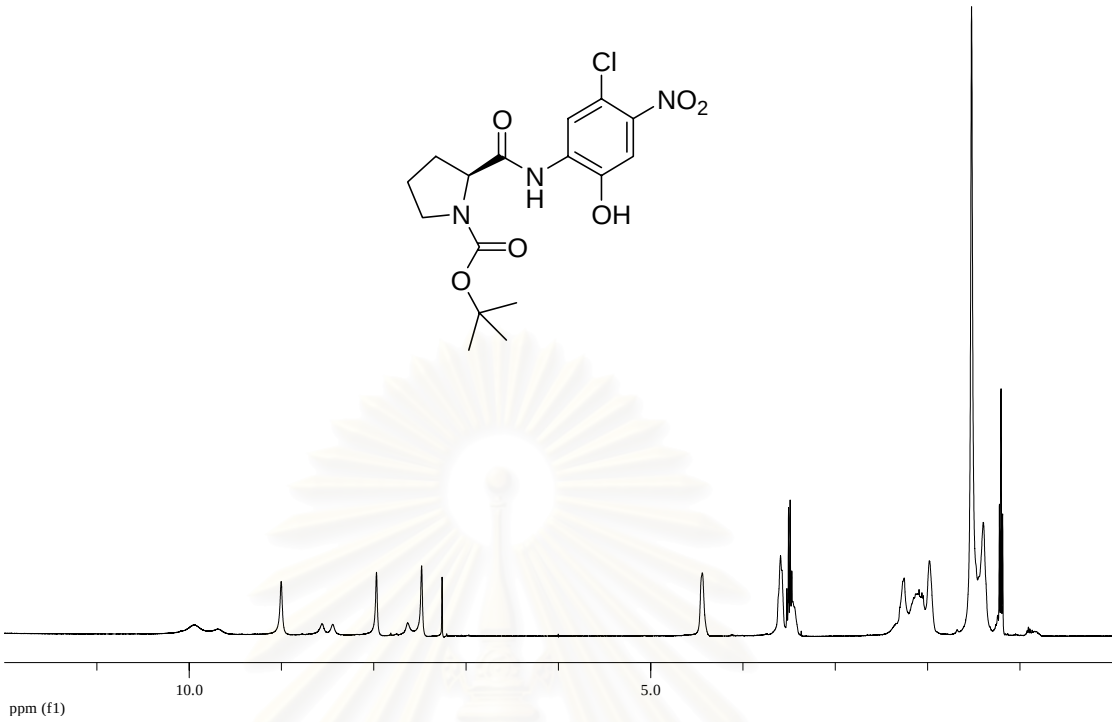


Figure 31 ^{1}H-NMR of 2-(5´-Chloro-2´-hydroxy-4´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(35)**

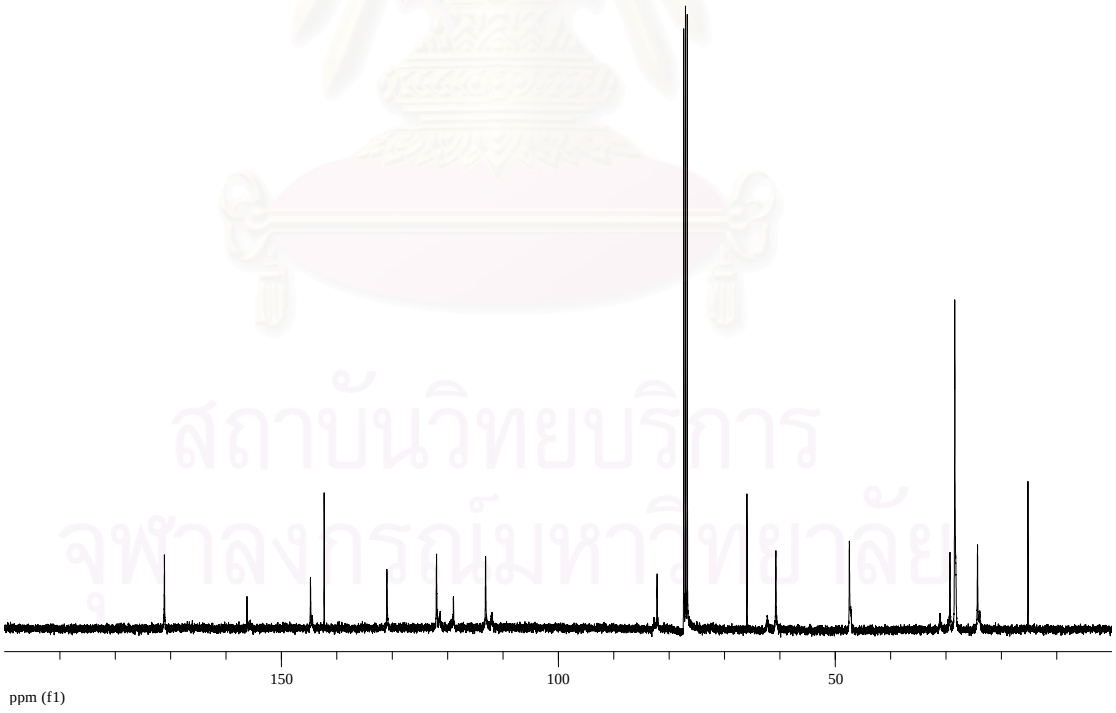


Figure 32 ^{13}C-NMR of 2-(5´-Chloro-2´-hydroxy-4´-nitro-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(35)**

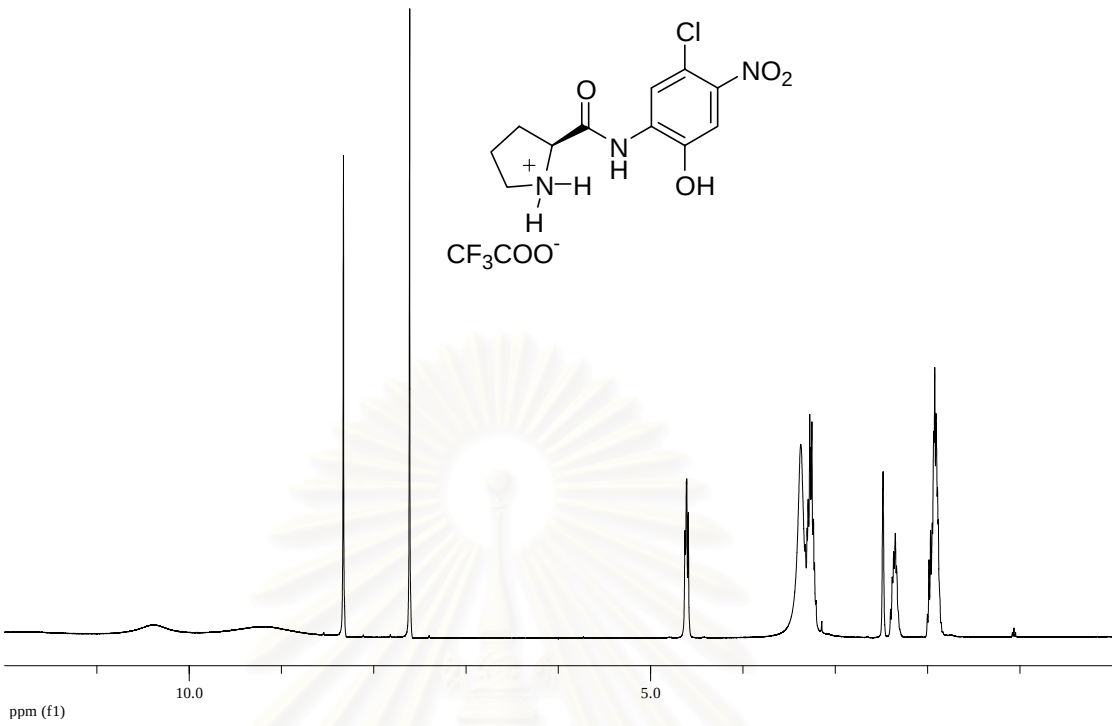


Figure 33 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-4´-nitro-phenyl)-amide trifluoroacetate **(28o)**

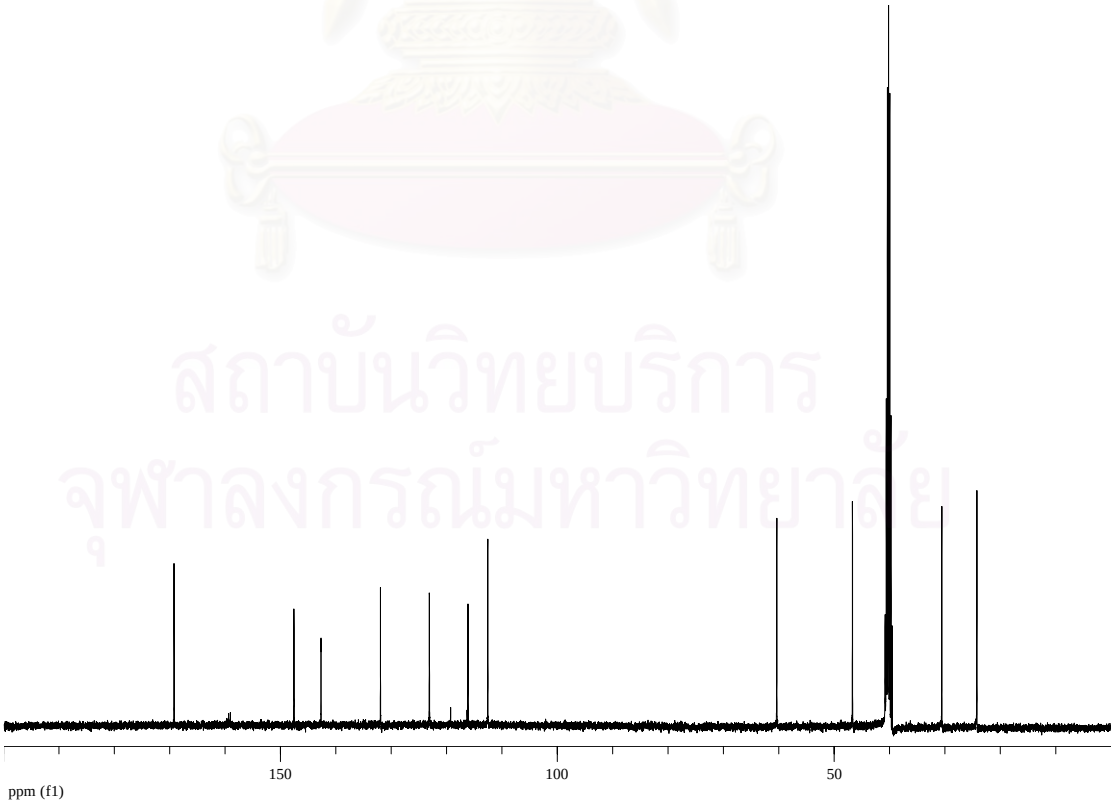


Figure 34 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-hydroxy-4´-nitro-phenyl)-amide trifluoroacetate **(28o)**

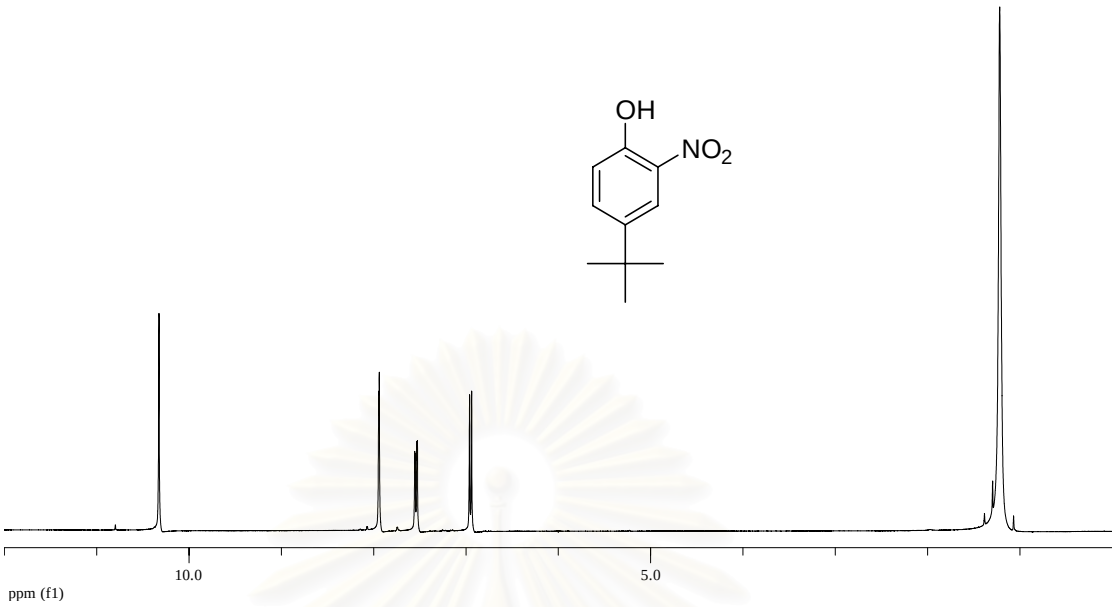


Figure 35 ^{1}H-NMR of 4-*tert*-Butyl-2-nitro-phenol **(36)**

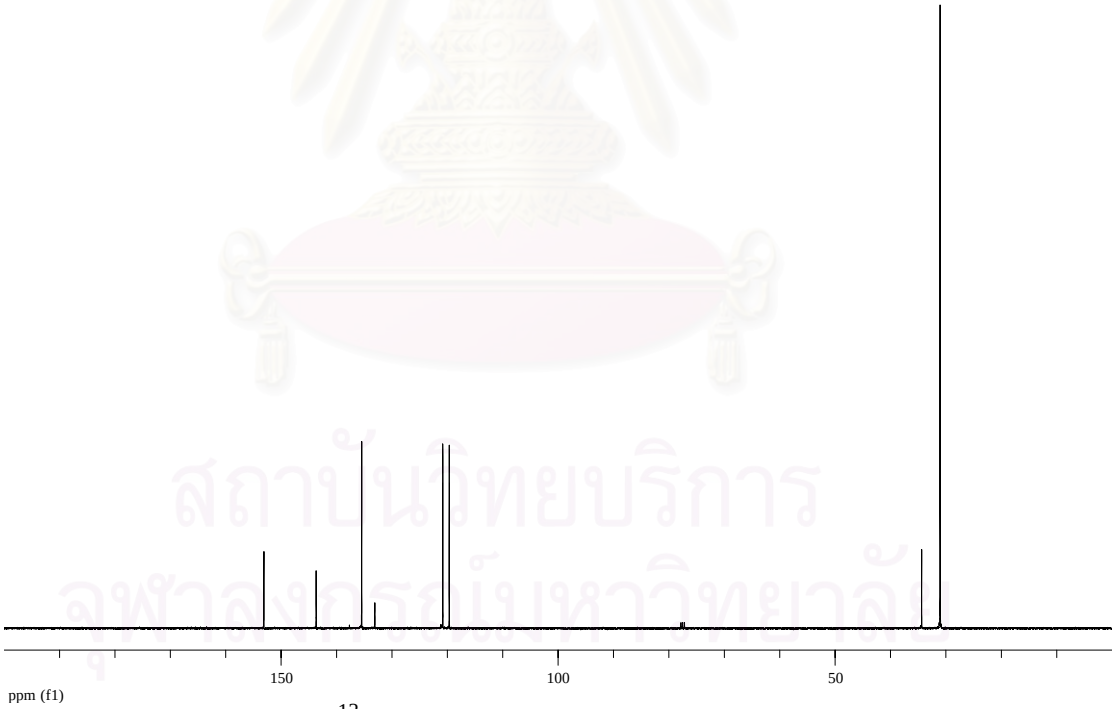


Figure 36 ^{13}C-NMR of 4-*tert*-Butyl-2-nitro-phenol **(36)**

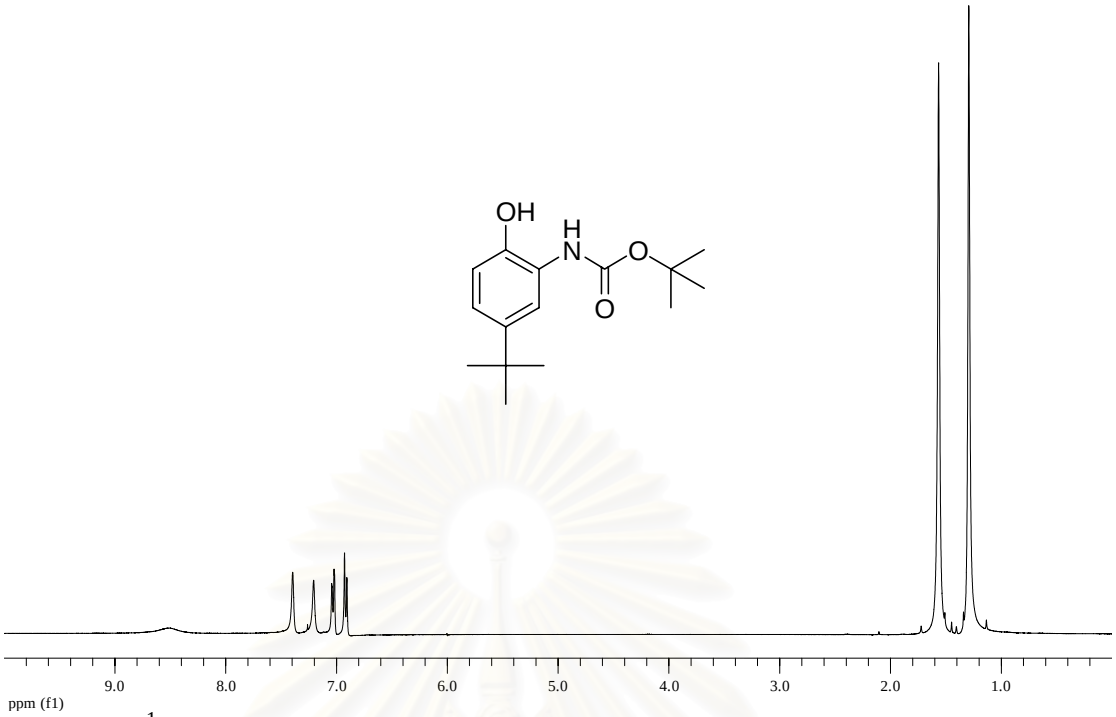


Figure 37 ^{1}H-NMR of (5-*tert*-Butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(37)**

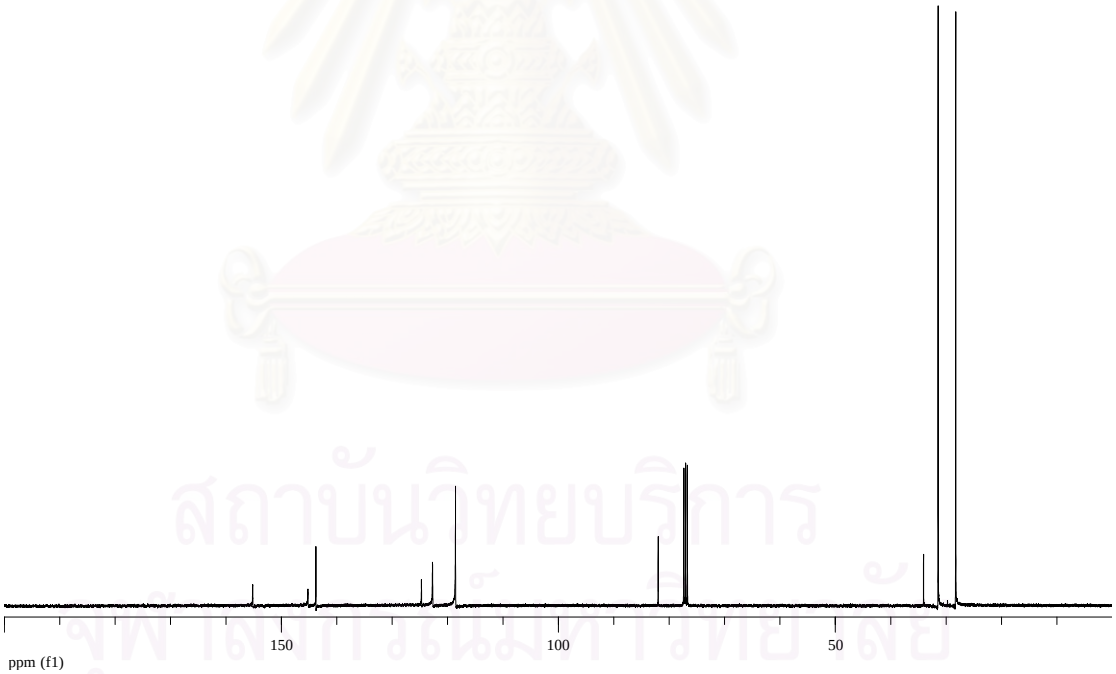


Figure 38 ^{13}C-NMR of (5-*tert*-Butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(37)**

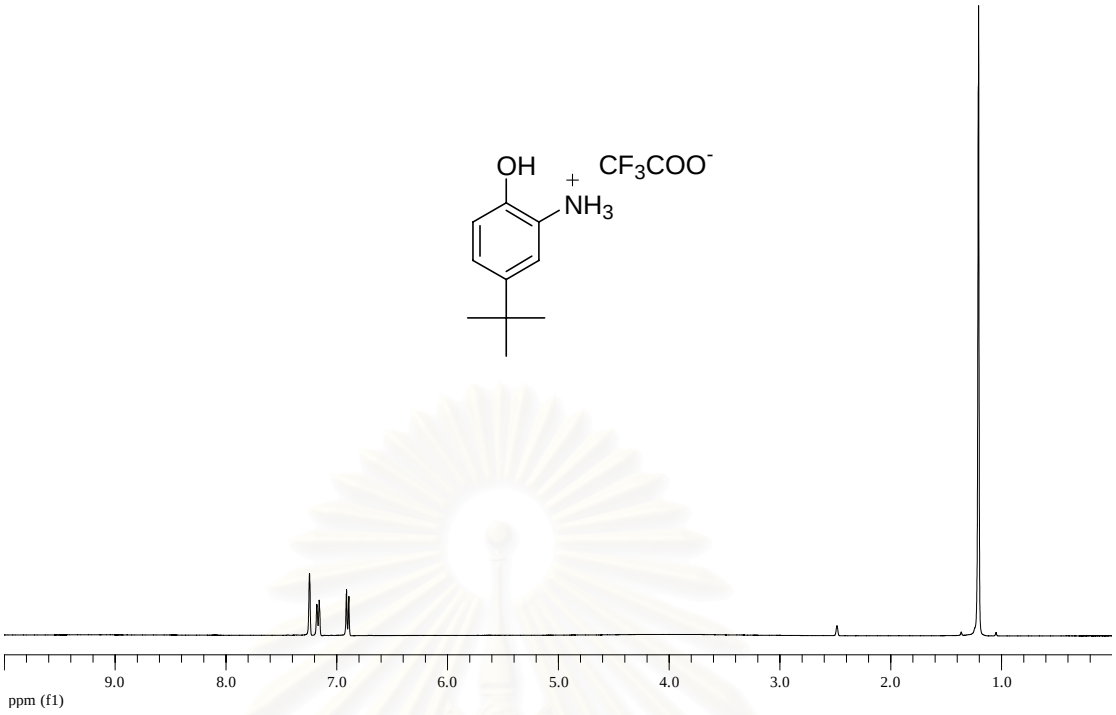


Figure 39 ^{1}H-NMR of 4-*tert*-butyl-2-aminophenol trifluoroacetate salt **(38)**

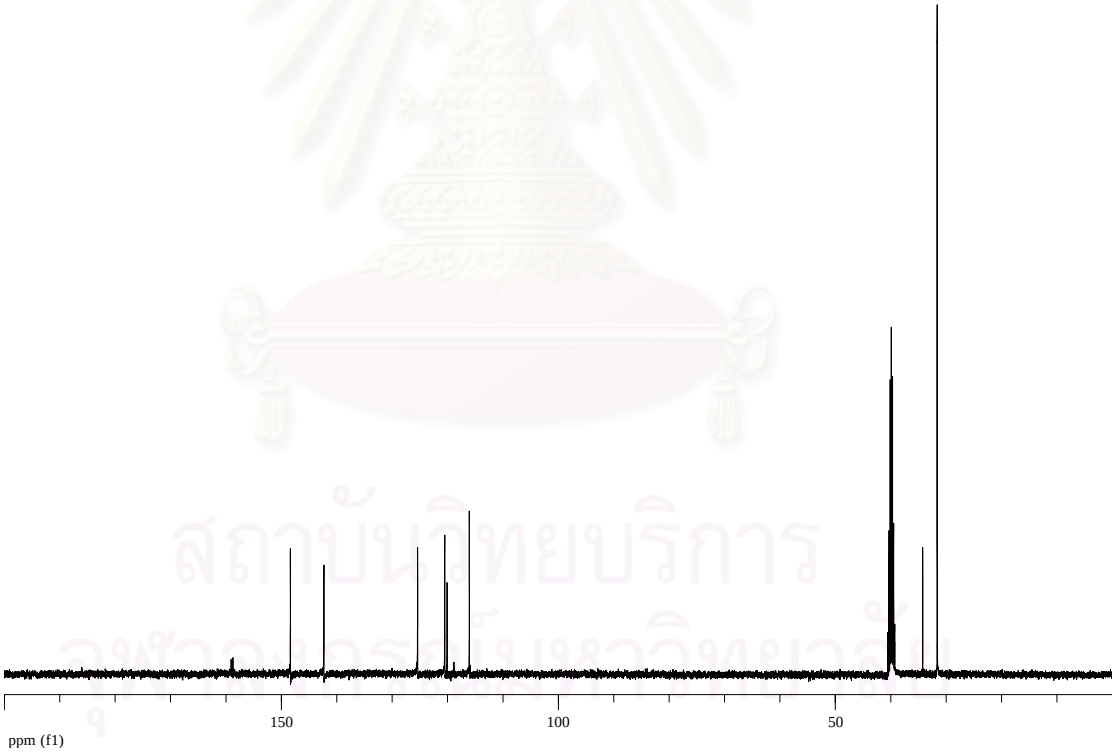


Figure 40 ^{13}C-NMR of 4-*tert*-butyl-2-aminophenol trifluoroacetate salt **(38)**

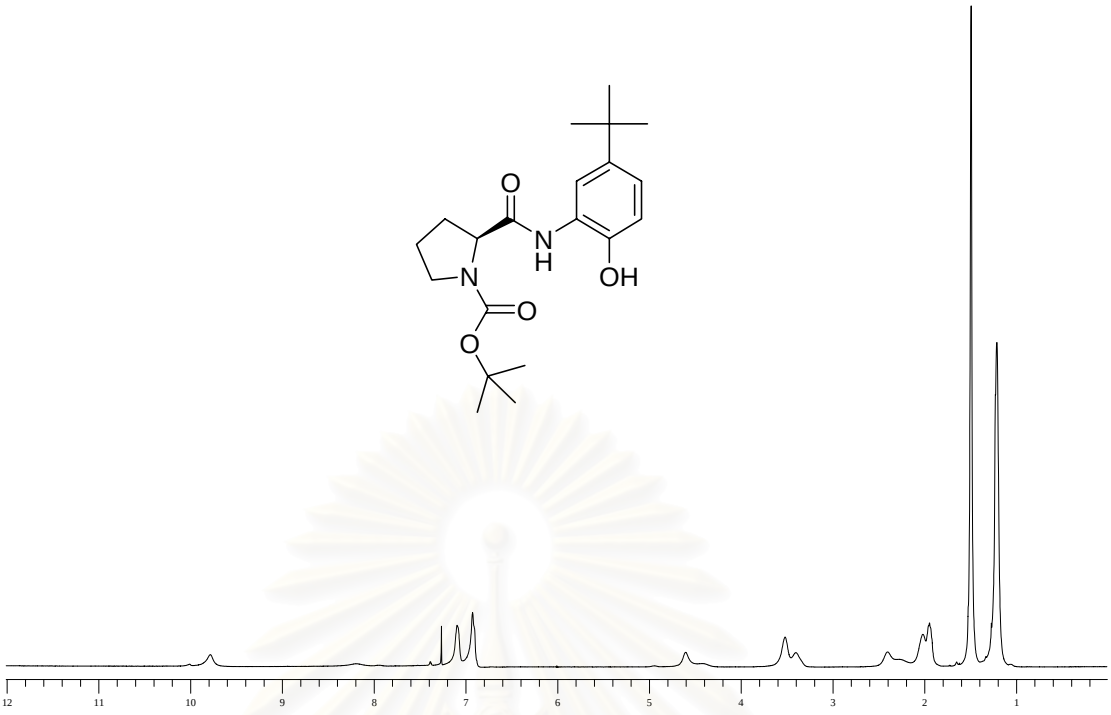


Figure 41 ^{1}H-NMR of 2-(5´-*tert*-Butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(39)**

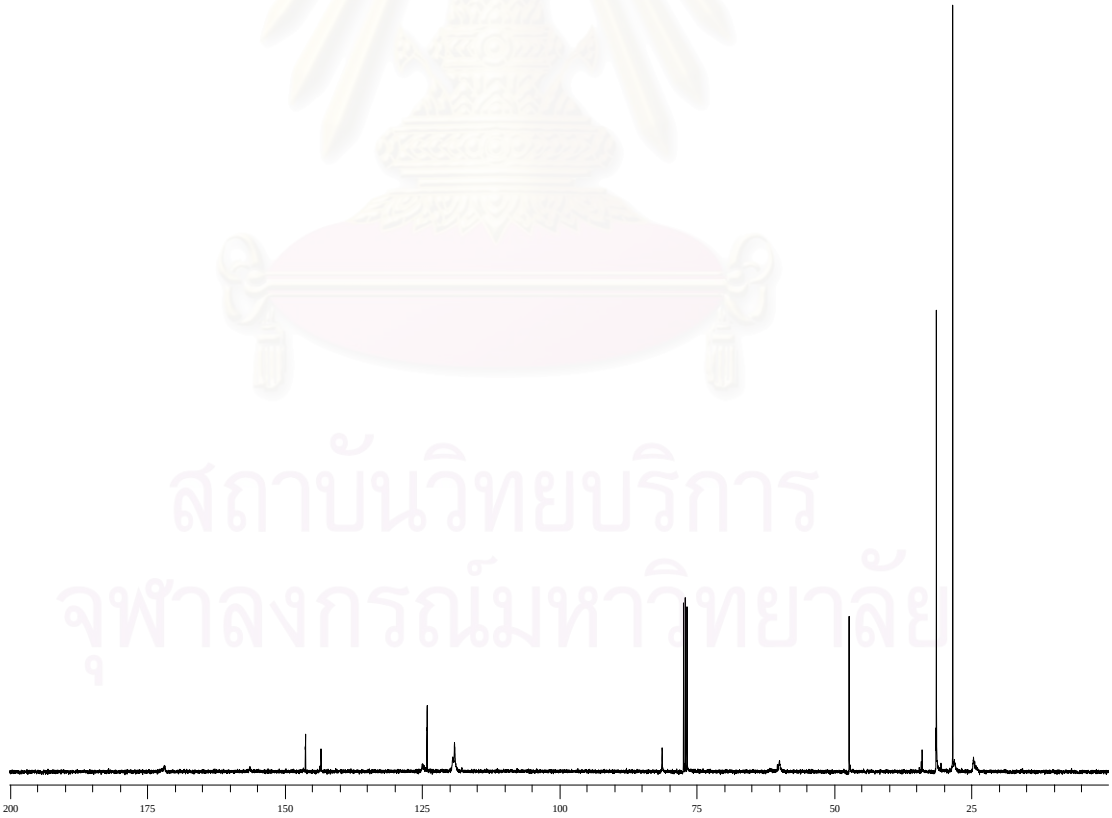


Figure 42 ^{13}C-NMR of 2-(5´-*tert*-Butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(39)**

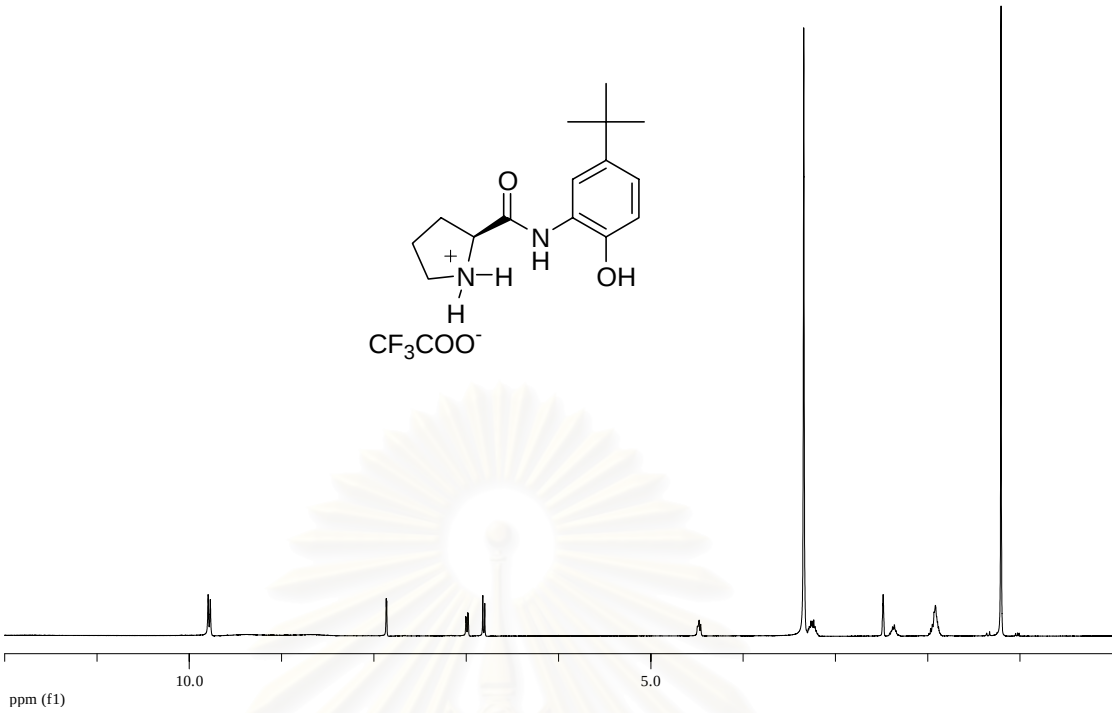


Figure 43 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate **(28c)**

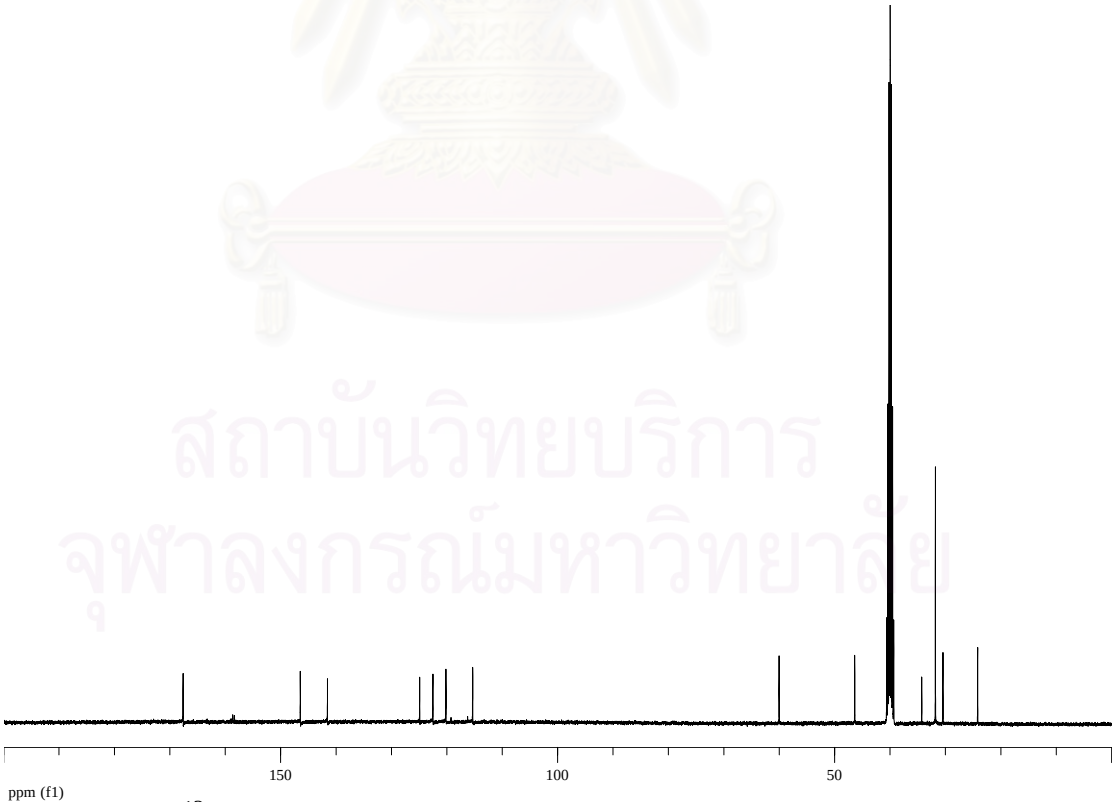


Figure 44 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate **(28c)**

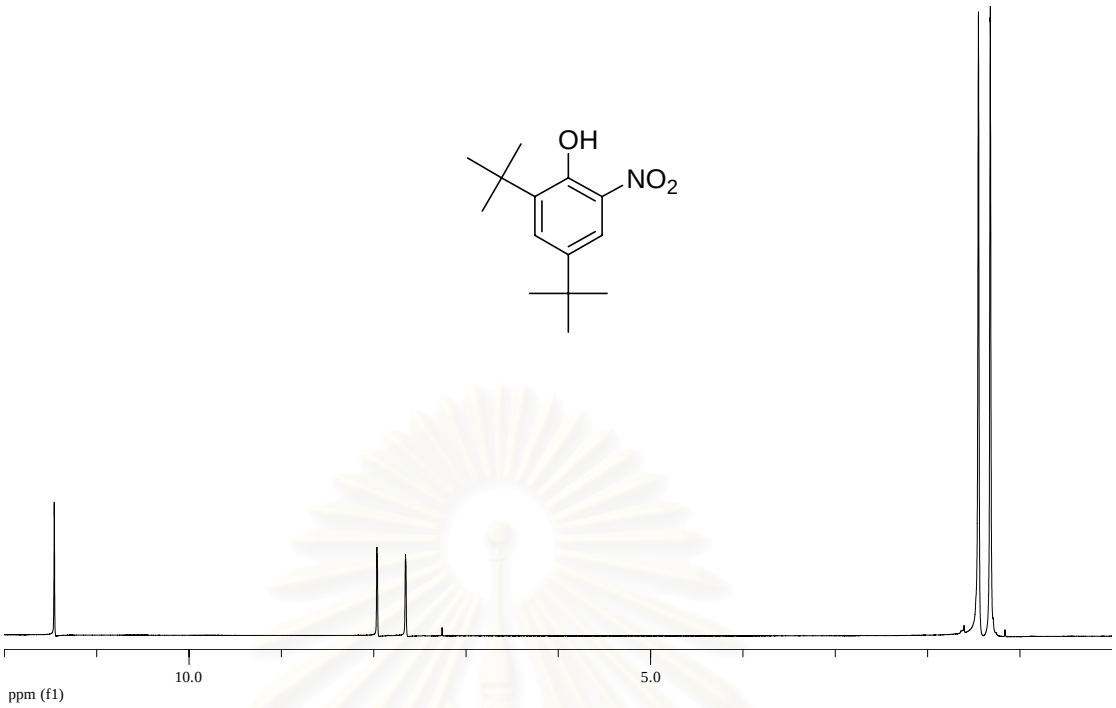


Figure 45 ^{1}H-NMR of 2,4-Di-*tert*-butyl-6-nitro-phenol **(40)**

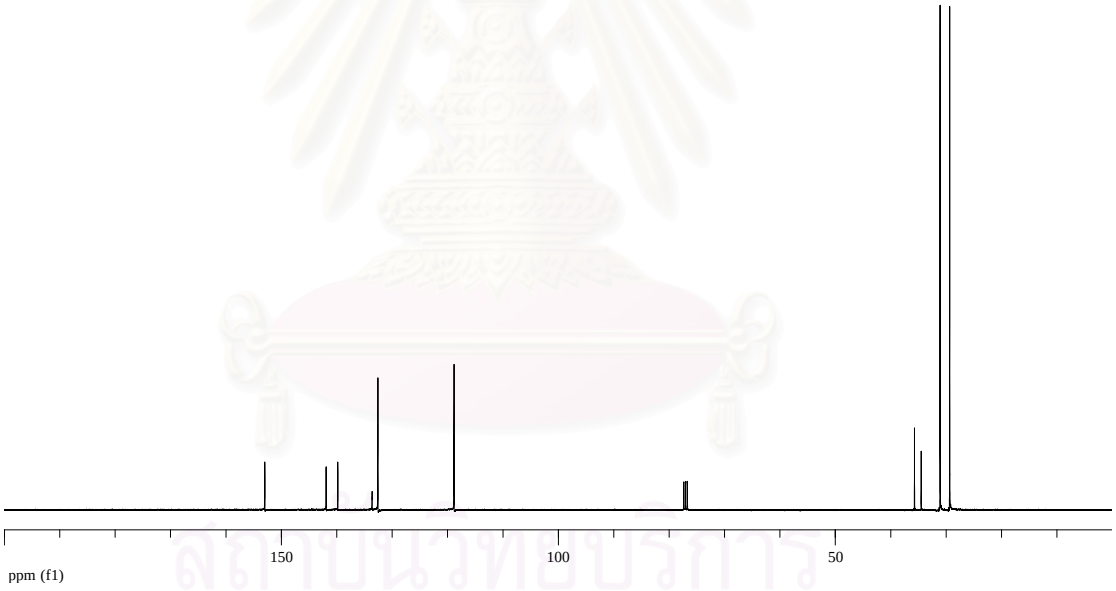


Figure 46 ^{13}C-NMR of 2,4-Di-*tert*-butyl-6-nitro-phenol **(40)**

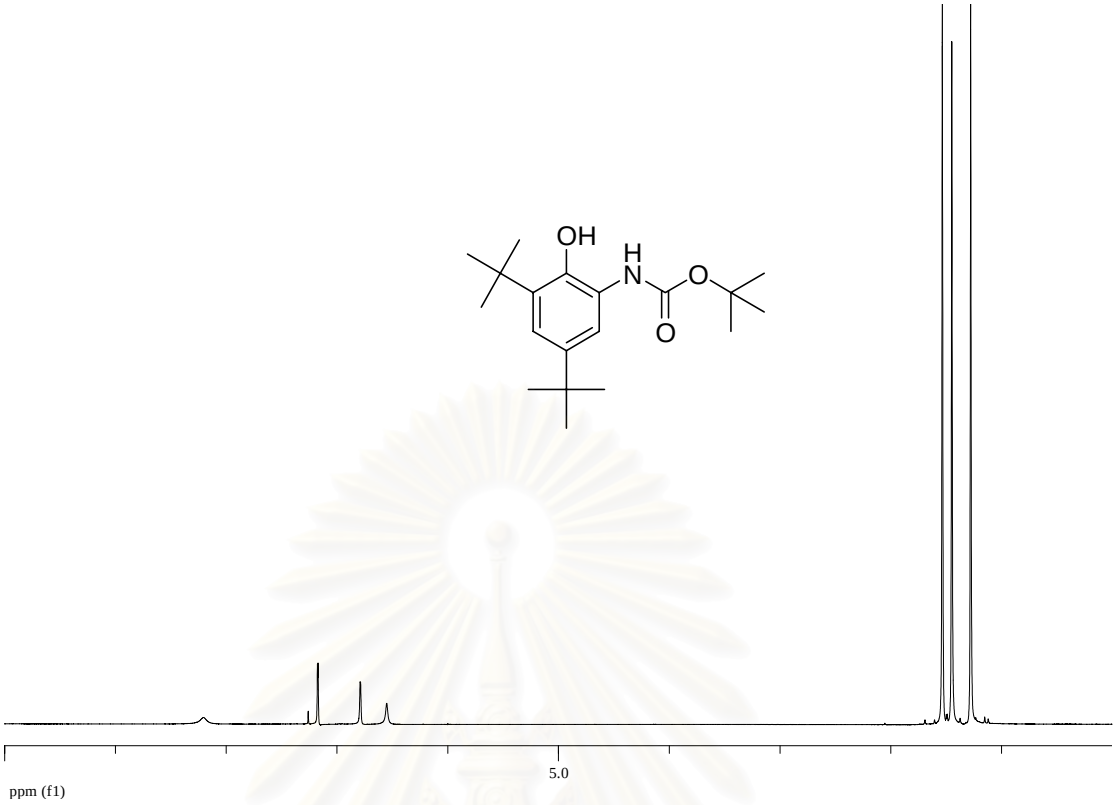


Figure 47 ^{1}H-NMR of (3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(41)**

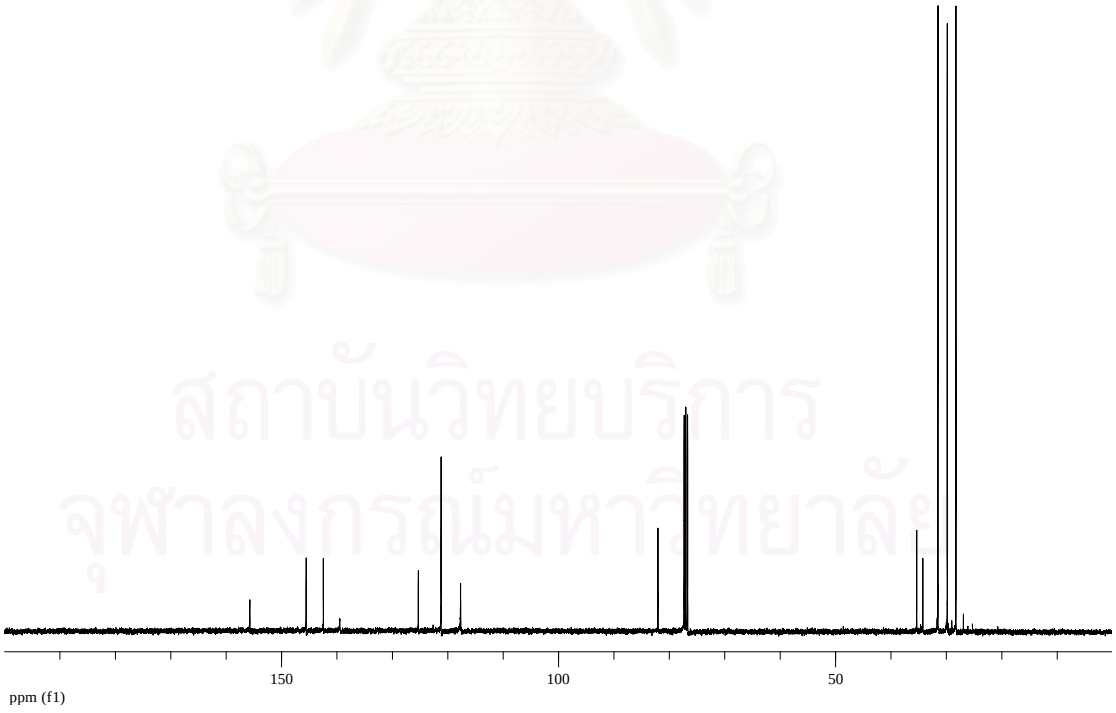


Figure 48 ^{13}C-NMR of (3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(41)**

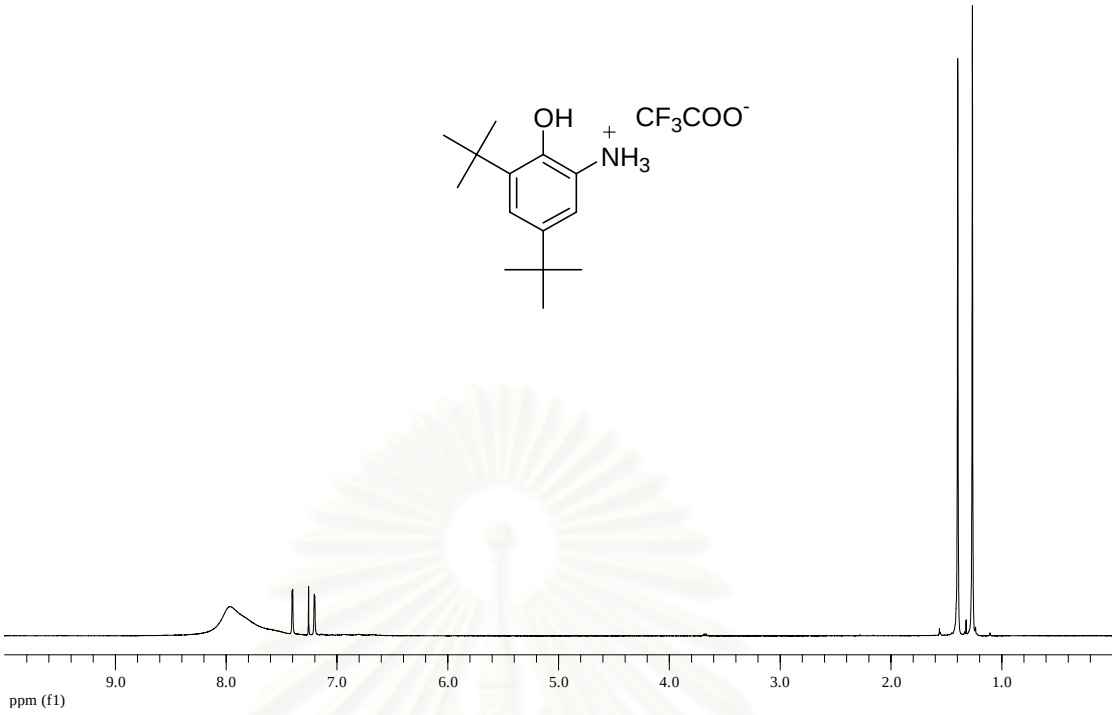


Figure 49 ^{1}H-NMR of 2,4-Di-*tert*-butyl-6-aminophenol trifluoroacetate salt **(42)**

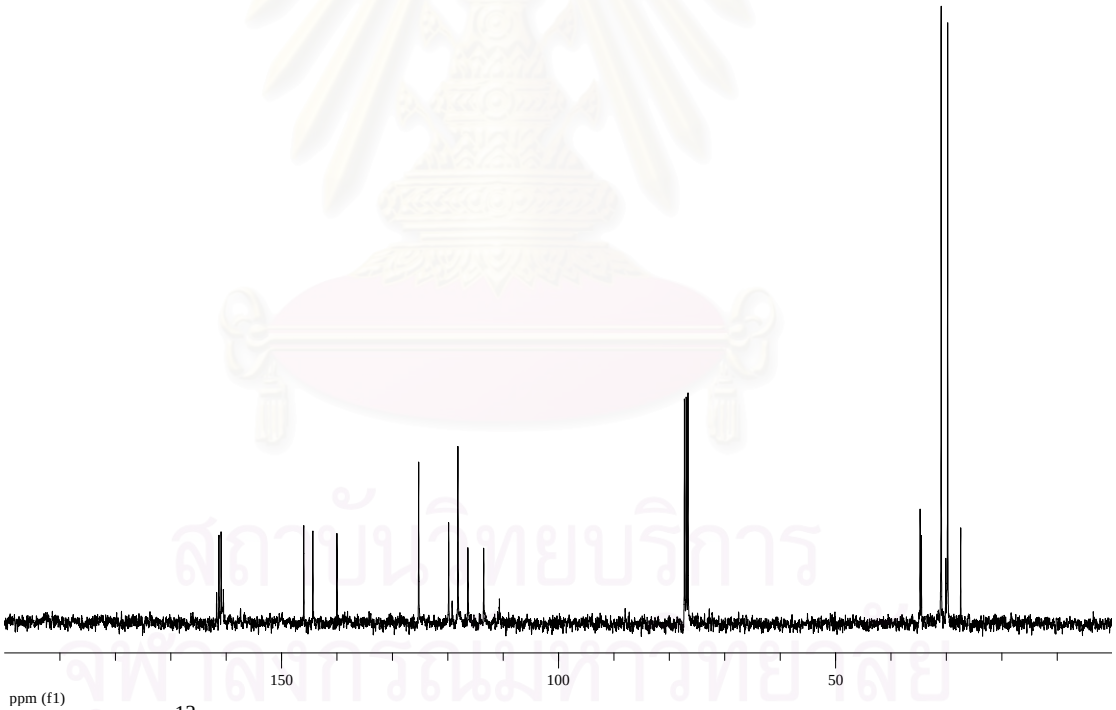


Figure 50 ^{13}C-NMR of 2,4-Di-*tert*-butyl-6-aminophenol trifluoroacetate salt **(42)**

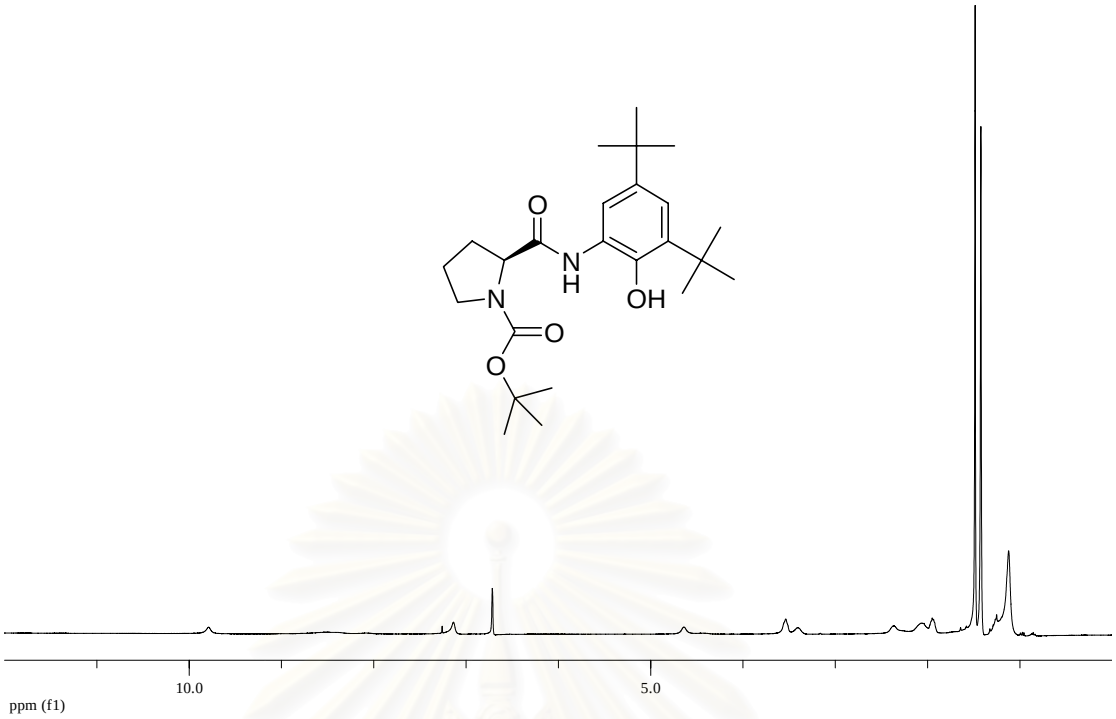


Figure 51 ^{1}H-NMR of 2-(3´,5´-Di-*tert*-butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(43)**

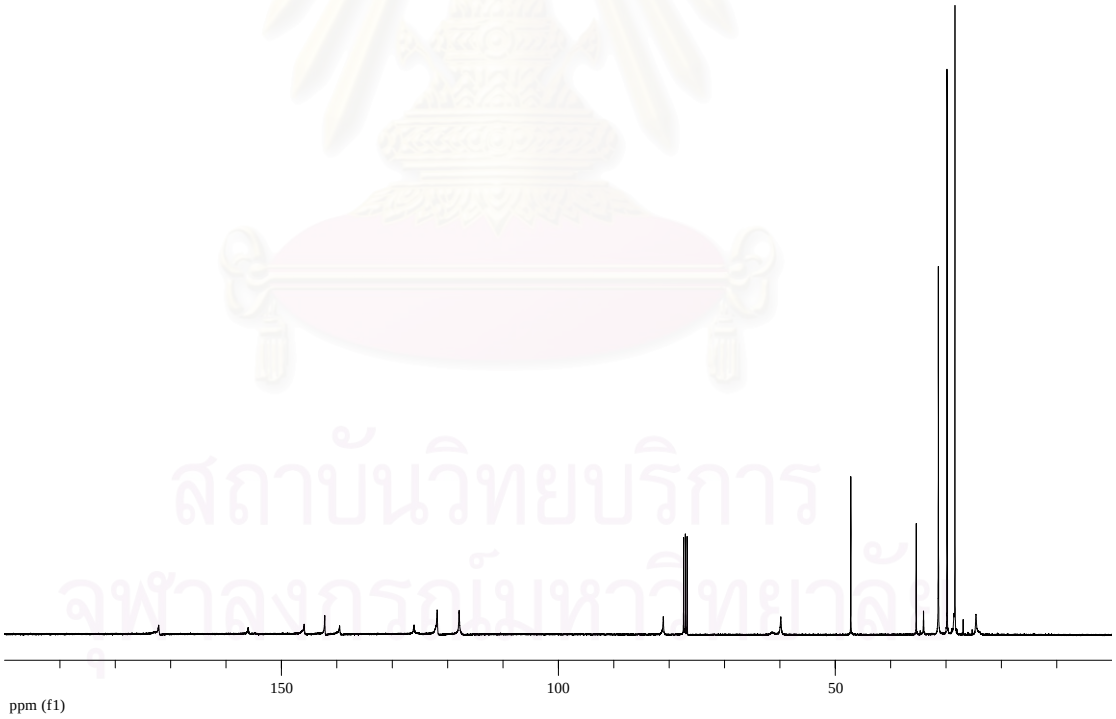


Figure 52 ^{13}C-NMR of 2-(3´,5´-Di-*tert*-butyl-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(43)**

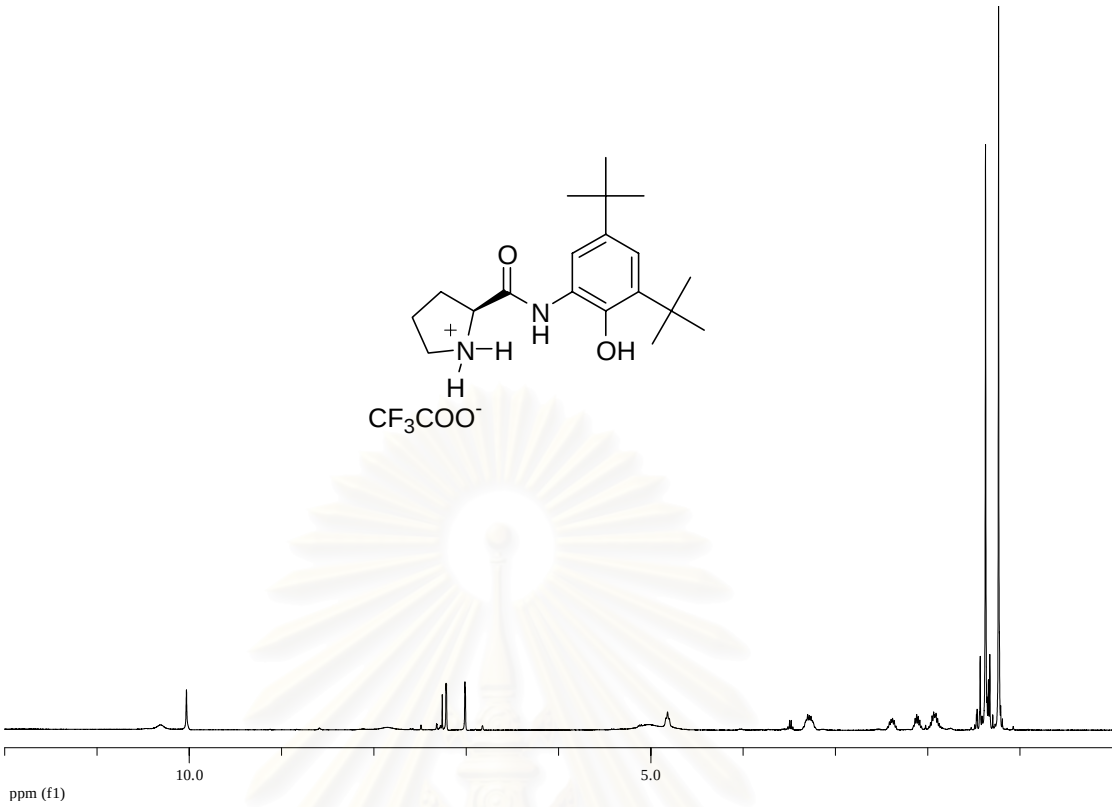


Figure 53 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (3´,5´-di-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate **(28d)**

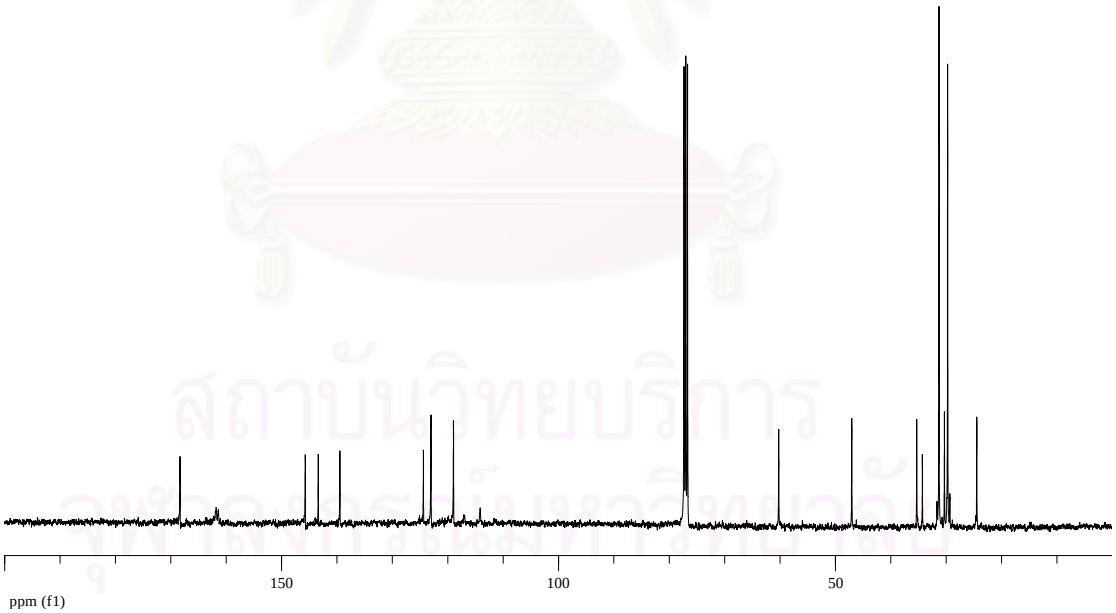


Figure 54 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (3´,5´-di-*tert*-butyl-2´-hydroxy-phenyl)-amide trifluoroacetate **(28d)**

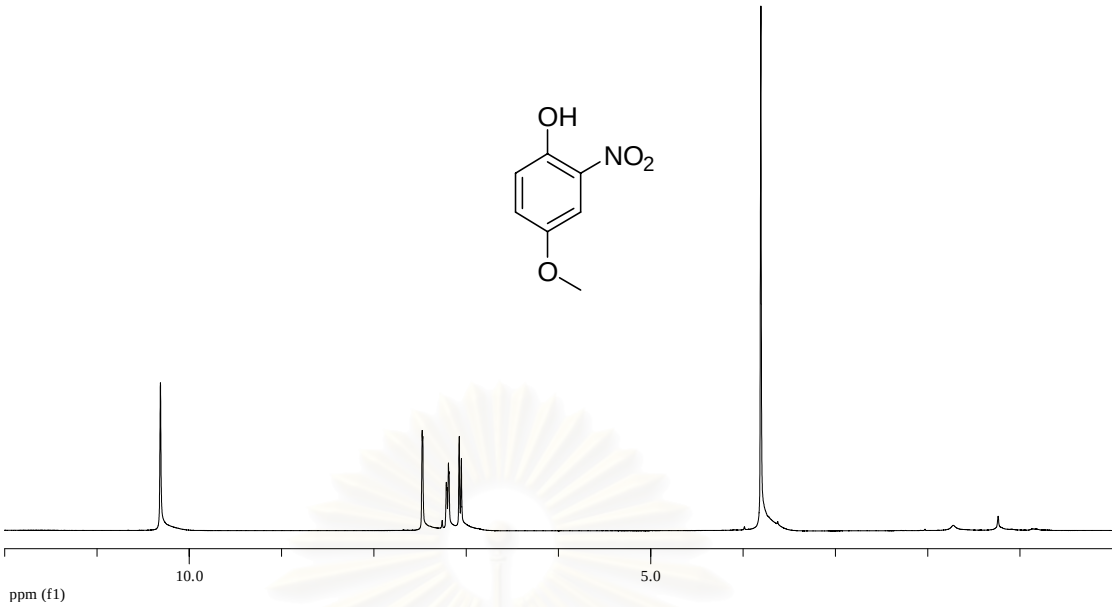


Figure 55 ^{1}H-NMR of 4-Methoxy-2-nitro-phenol **(44)**

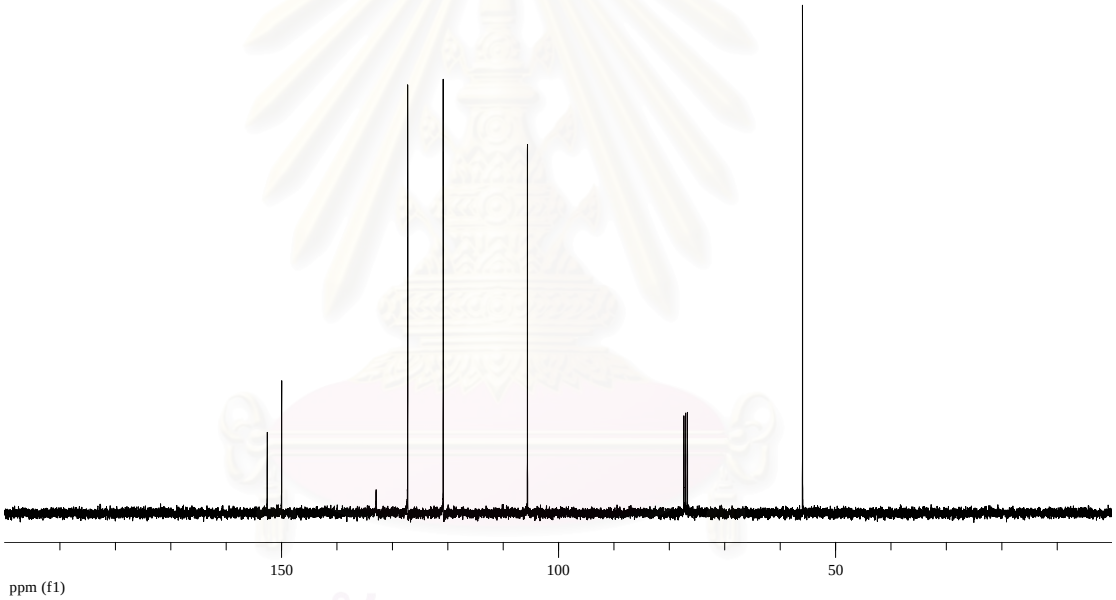


Figure 56 ^{13}C-NMR of 4-Methoxy-2-nitro-phenol **(44)**

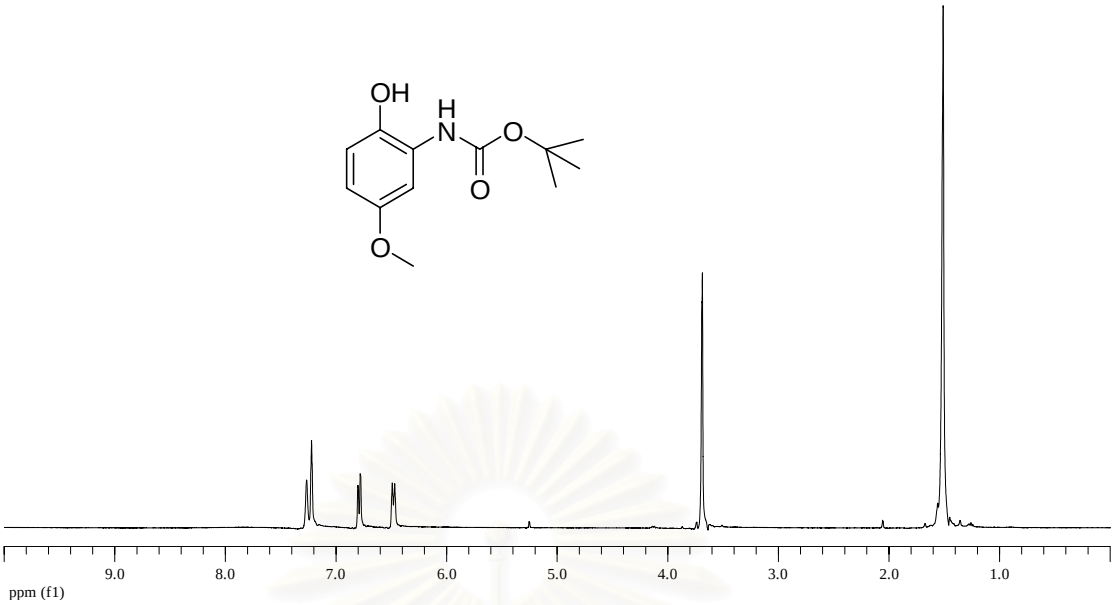


Figure 57 ^{1}H-NMR of (2-Hydroxy-5-methoxy-phenyl)-carbamic acid tert-butyl ester **(45)**

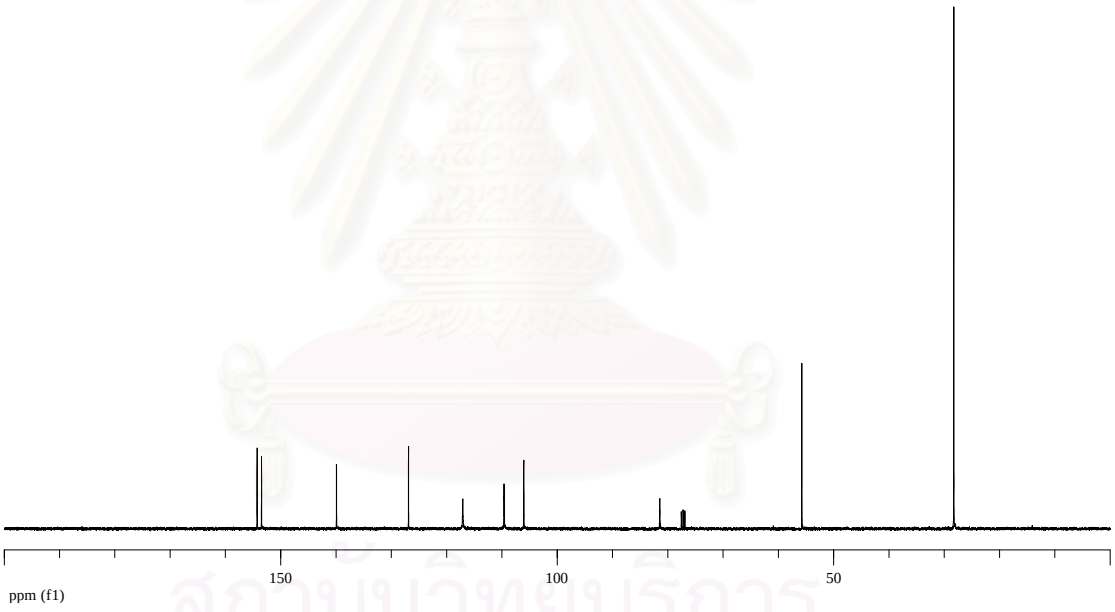


Figure 58 ^{13}C-NMR of (2-Hydroxy-5-methoxy-phenyl)-carbamic acid tert-butyl ester **(45)**

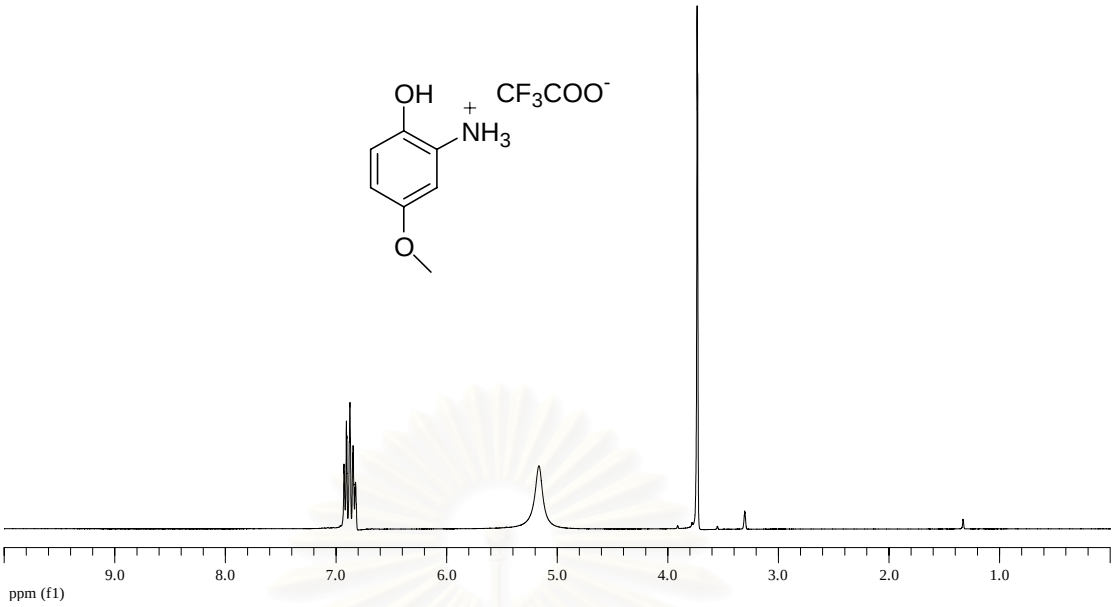


Figure 59 ^{1}H-NMR of 4-Methoxy-2-aminophenol trifluoroacetate salt **(46)**

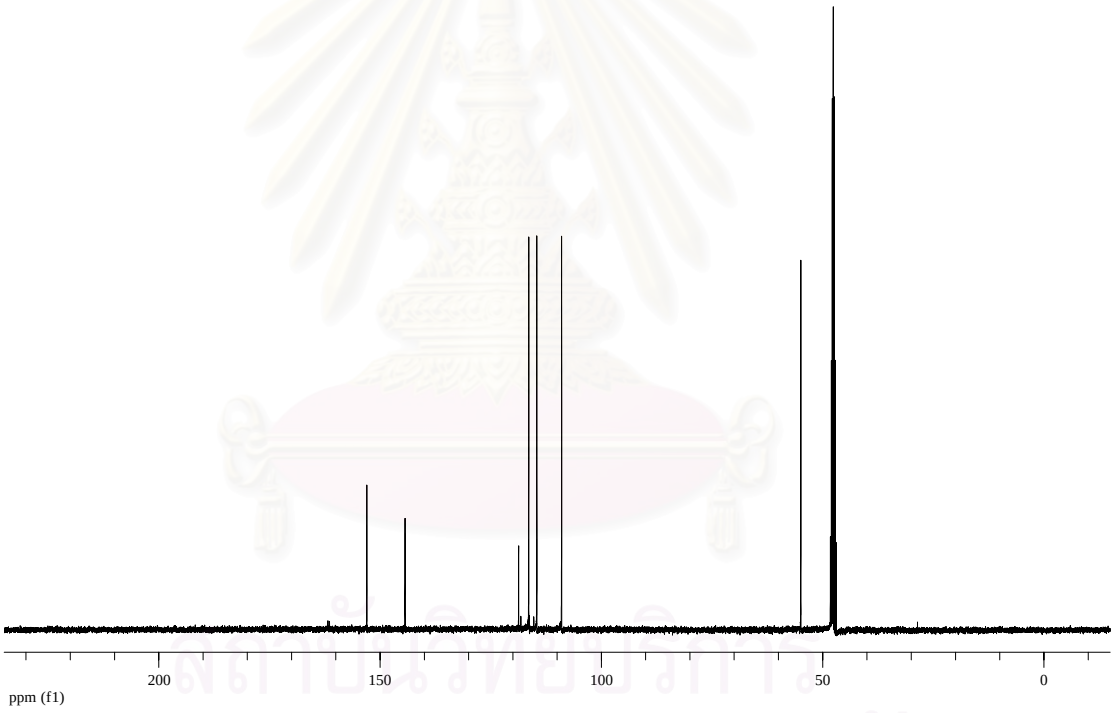


Figure 60 ^{13}C-NMR of 4-Methoxy-2-aminophenol trifluoroacetate salt **(46)**

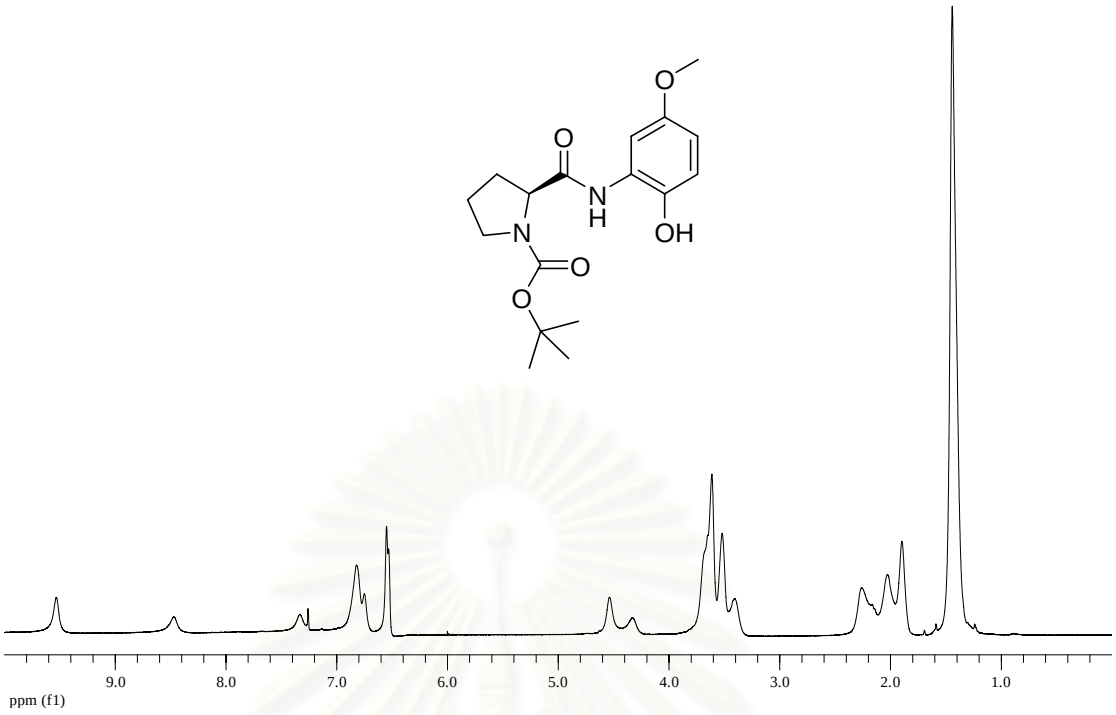


Figure 61 ^{1}H-NMR of 2-(2´-Hydroxy-5´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(47)**

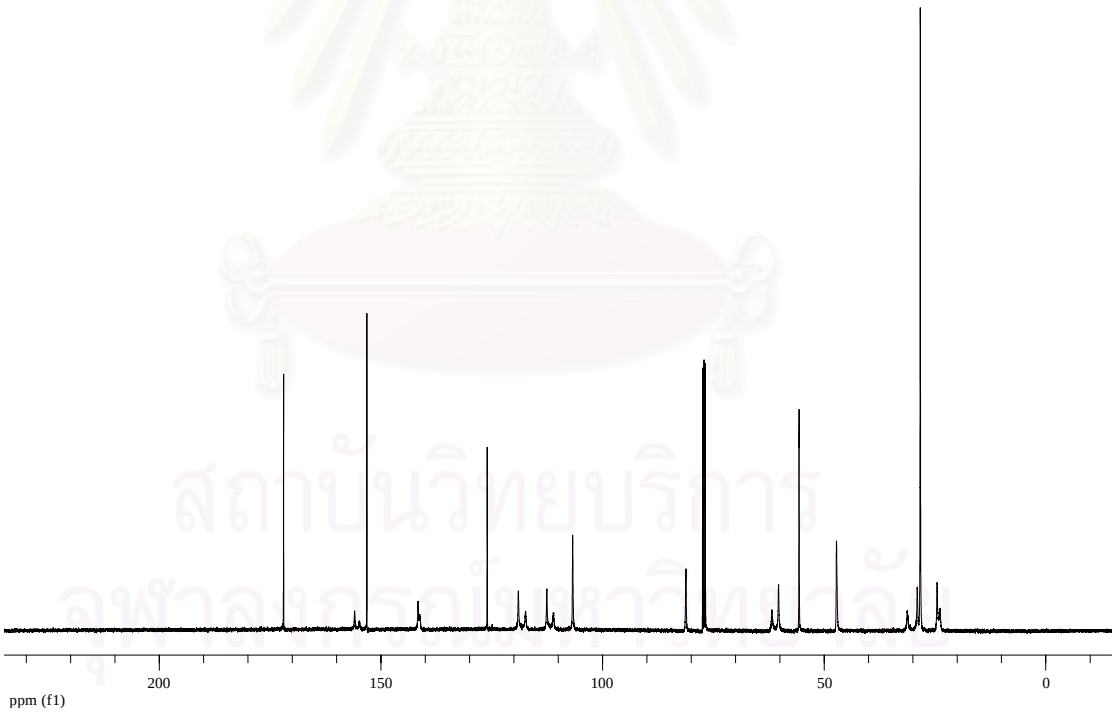


Figure 62 ^{13}C-NMR of 2-(2´-Hydroxy-5´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(47)**

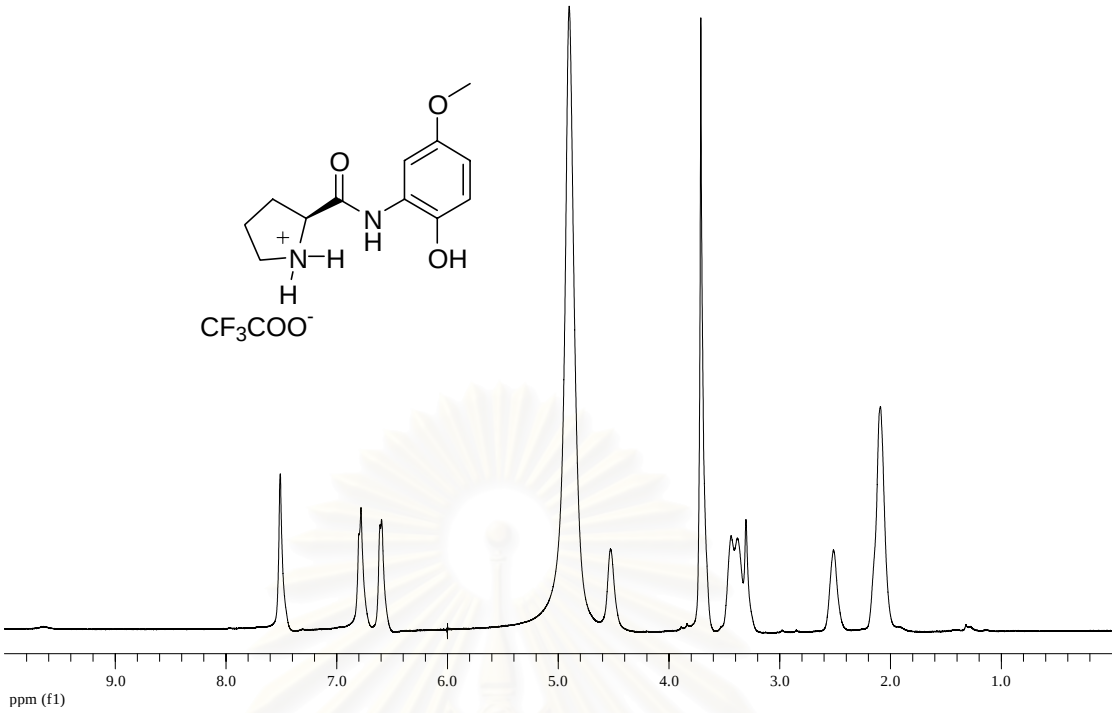


Figure 63 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-methoxy-phenyl)-amide trifluoroacetate **(28f)**

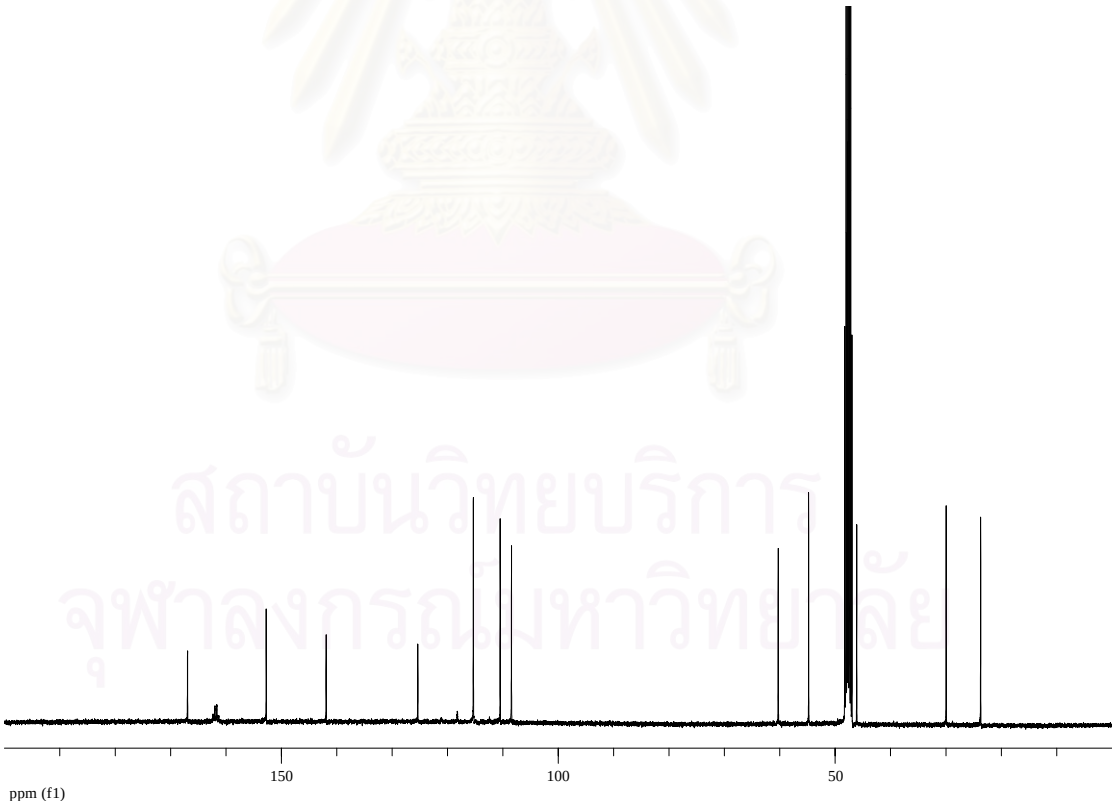


Figure 64 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-methoxy-phenyl)-amide trifluoroacetate **(28f)**

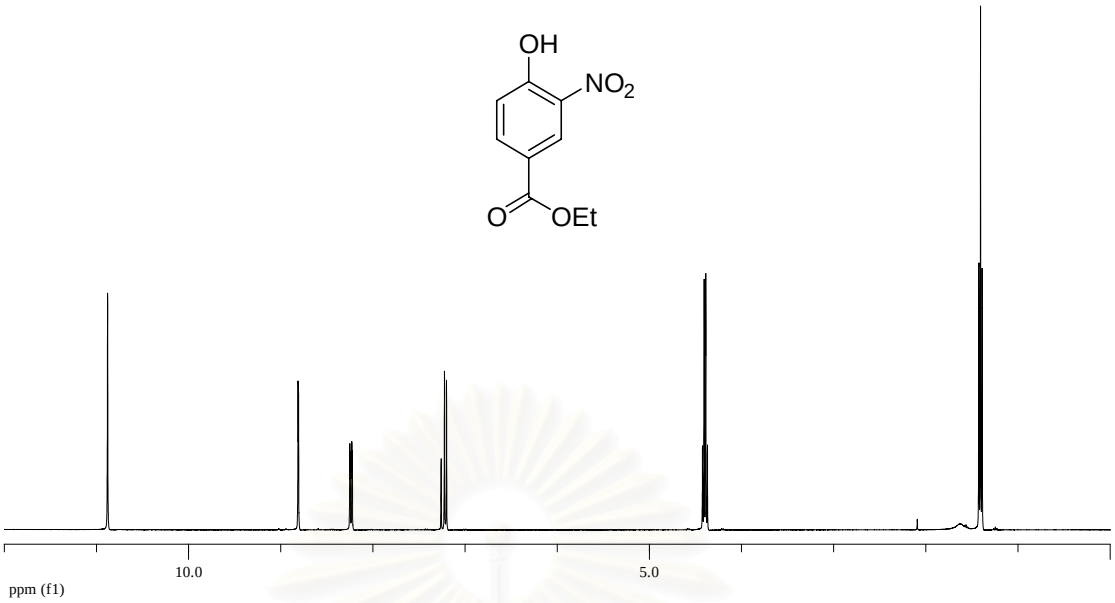


Figure 65 ^{1}H-NMR of 1-(4-Hydroxy-3-nitro-phenyl)-propan-1-one **(48)**

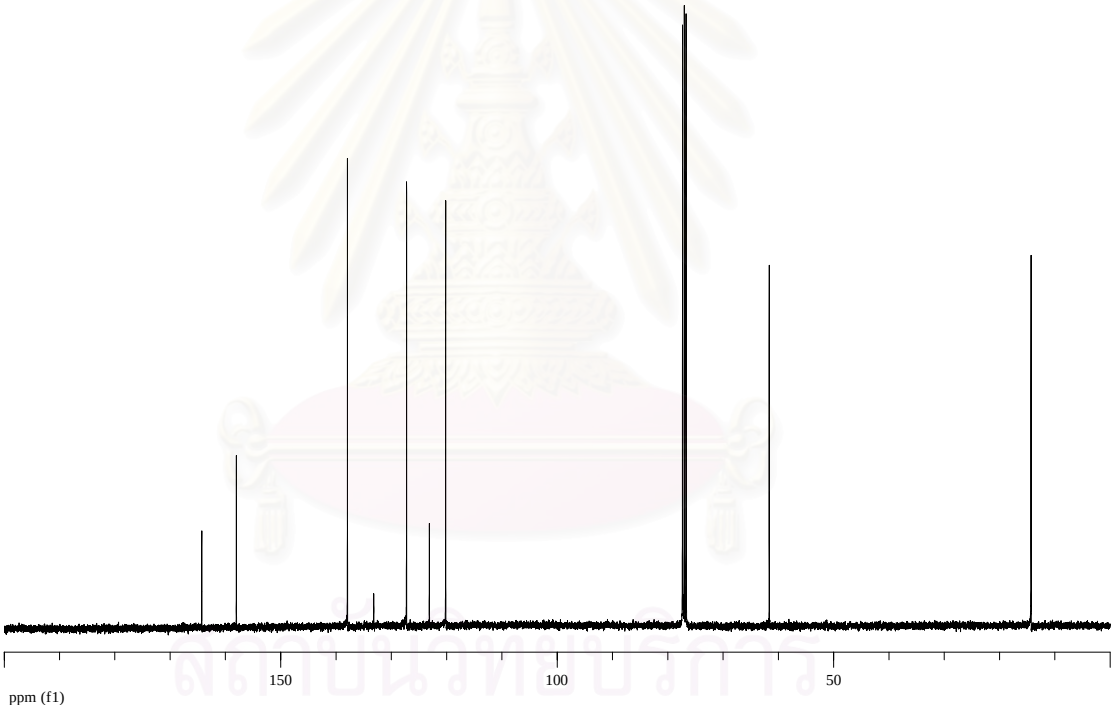


Figure 66 ^{13}C-NMR of 1-(4-Hydroxy-3-nitro-phenyl)-propan-1-one **(48)**

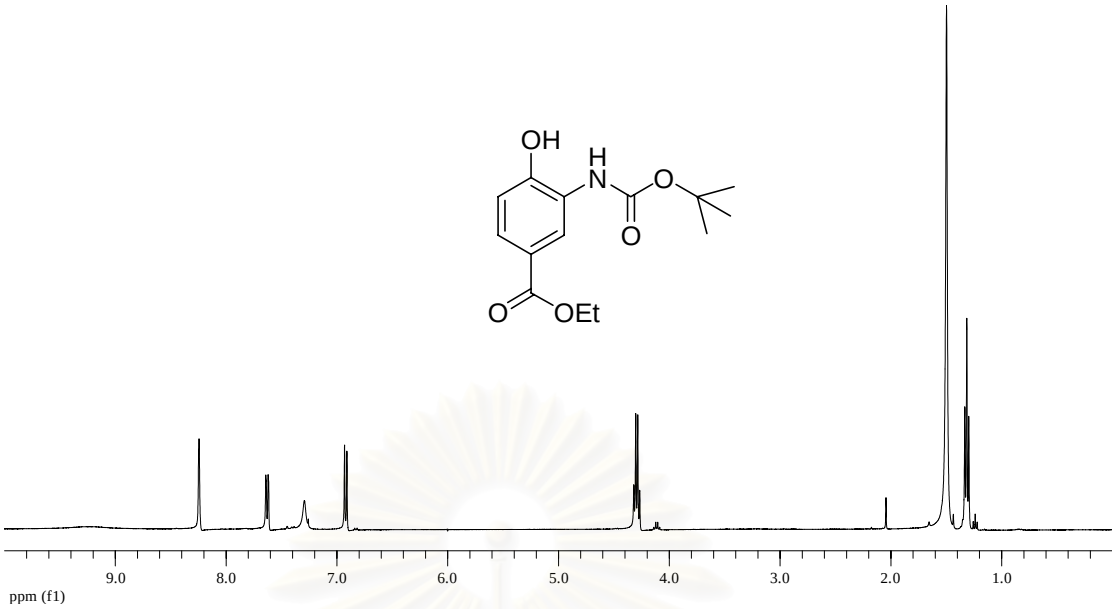


Figure 67 ^{1}H-NMR of (2-Hydroxy-5-propionyl-phenyl)-carbamic acid *tert*-butyl ester **(49)**

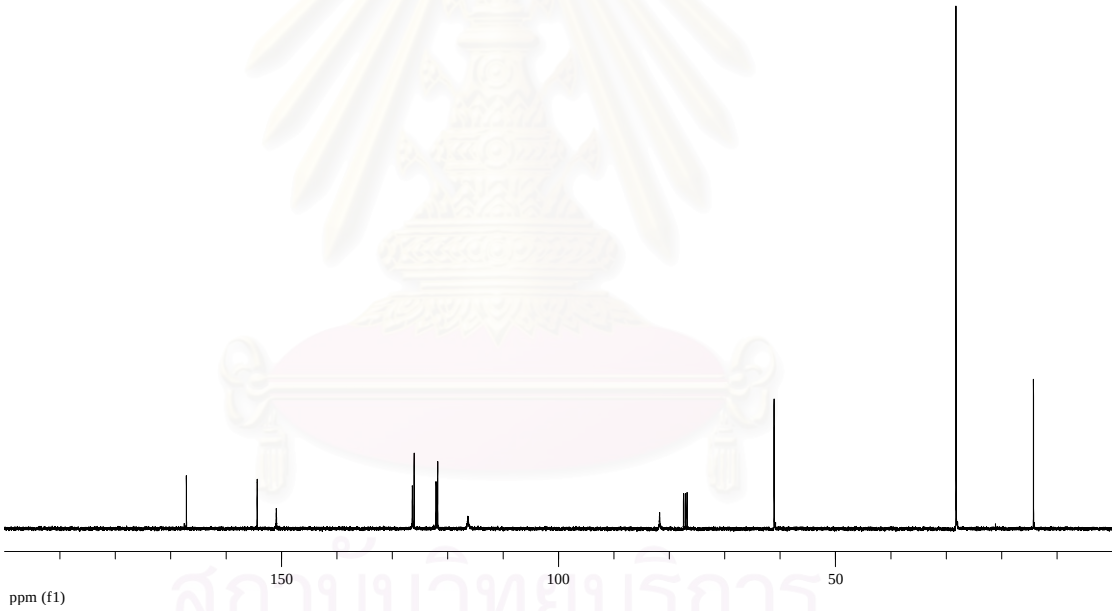


Figure 68 ^{13}C-NMR of (2-Hydroxy-5-propionyl-phenyl)-carbamic acid *tert*-butyl ester **(49)**

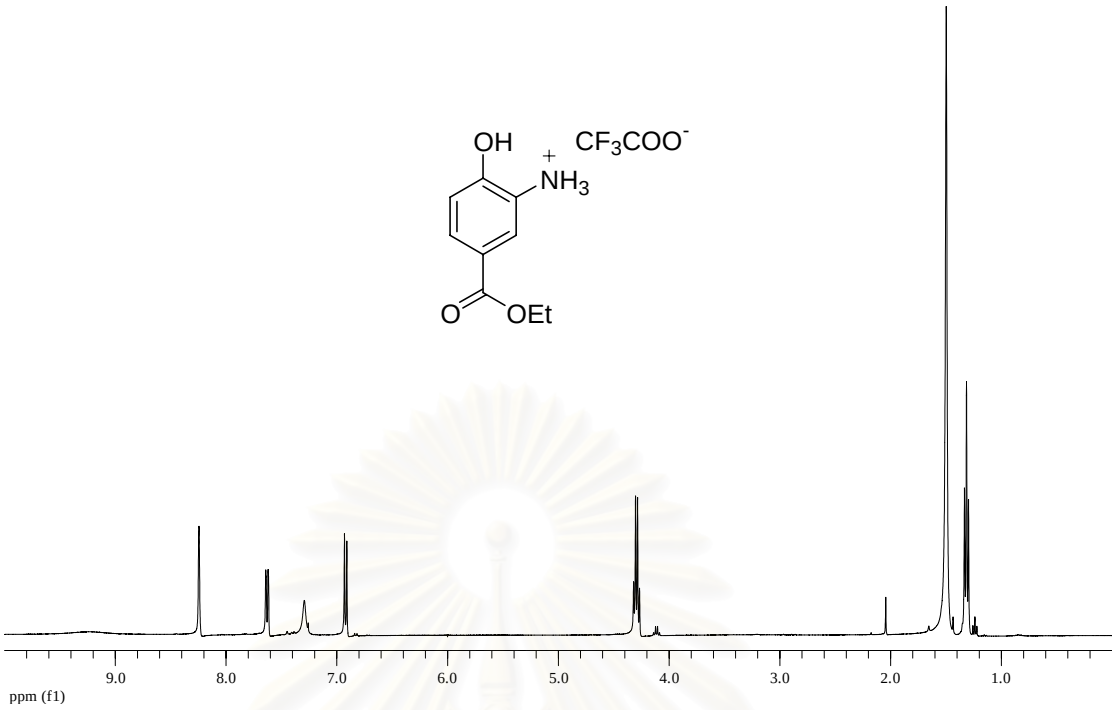


Figure 69 ^{1}H-NMR of Ethyl-4-hydroxy-3-aminobenzoate trifluoroacetate salt **(50)**

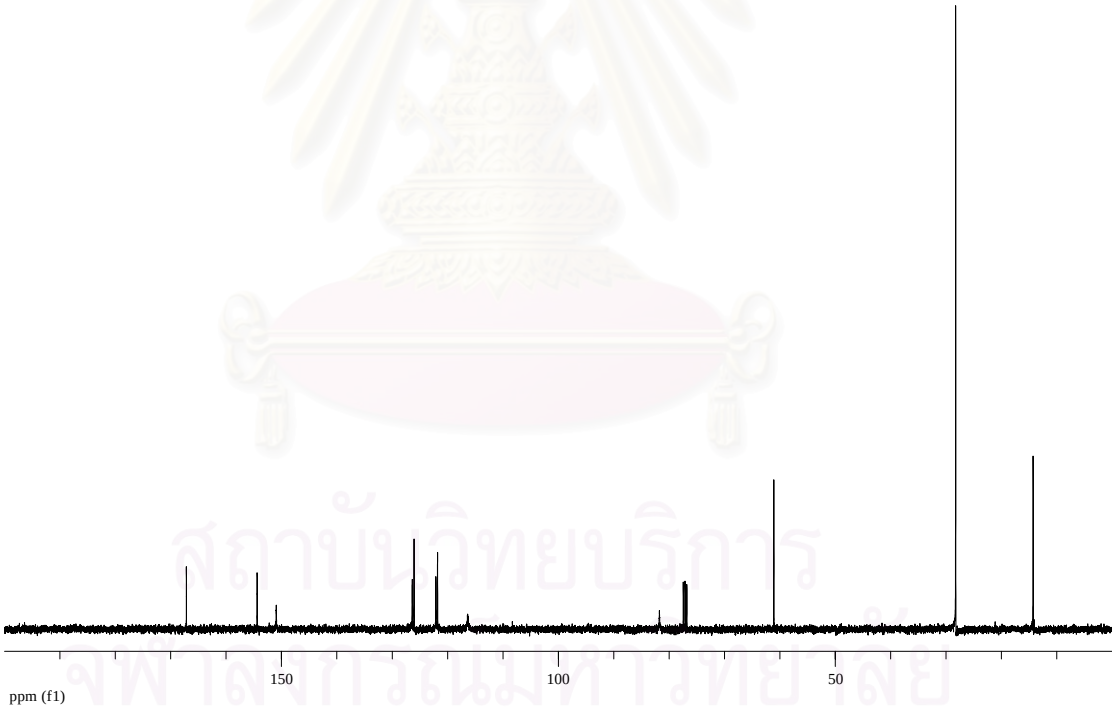


Figure 70 ^{13}C-NMR of Ethyl-4-hydroxy-3-aminobenzoate trifluoroacetate salt **(50)**

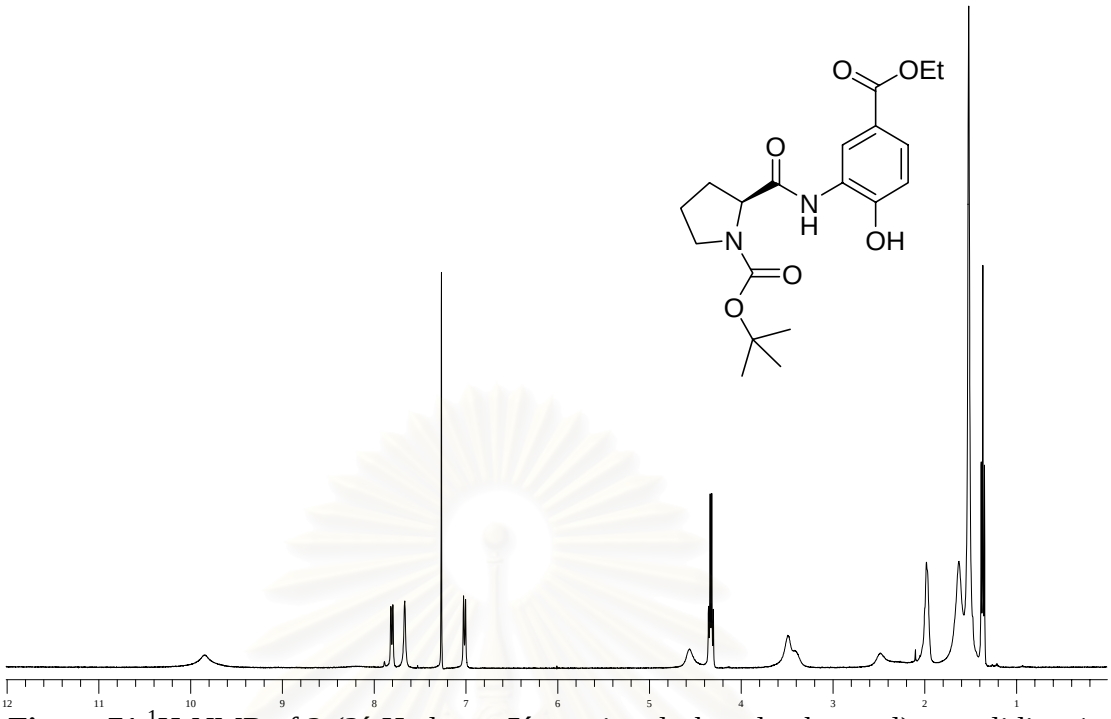


Figure 71 ^{1}H-NMR of 2-(2´-Hydroxy-5´-propionyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(51)**

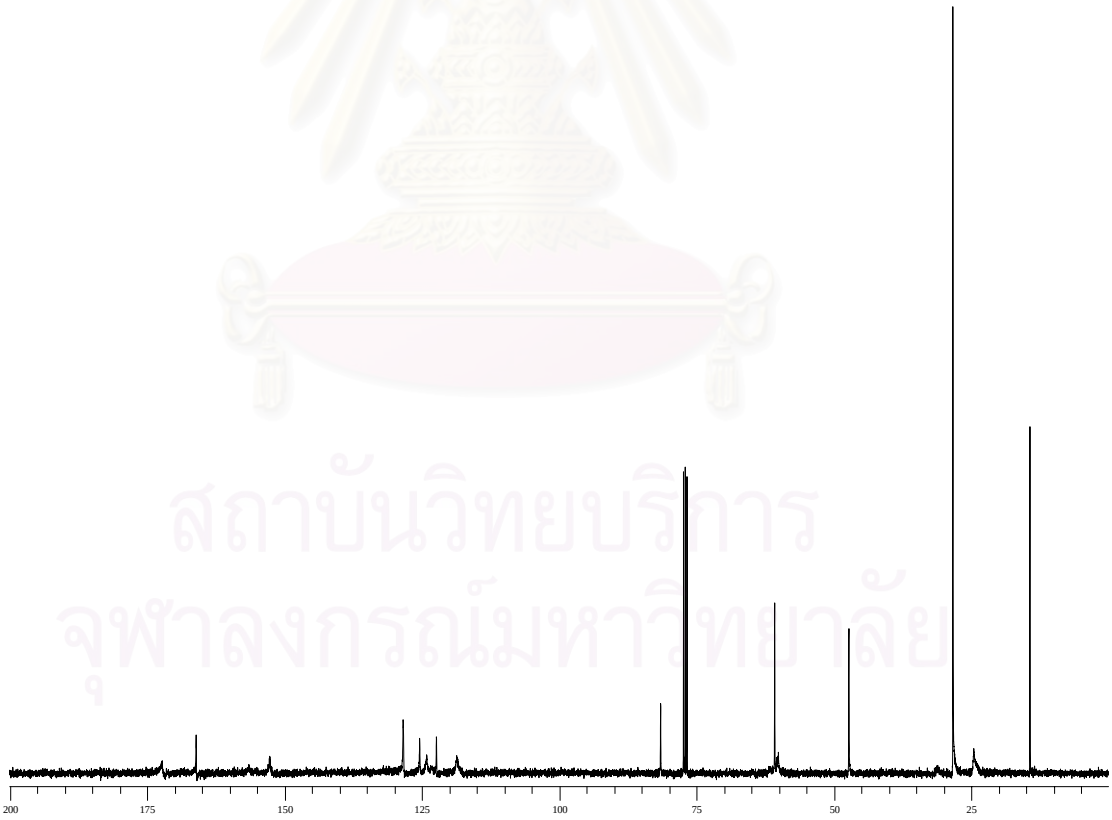


Figure 72 ^{13}C-NMR of 2-(2´-Hydroxy-5´-propionyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(51)**

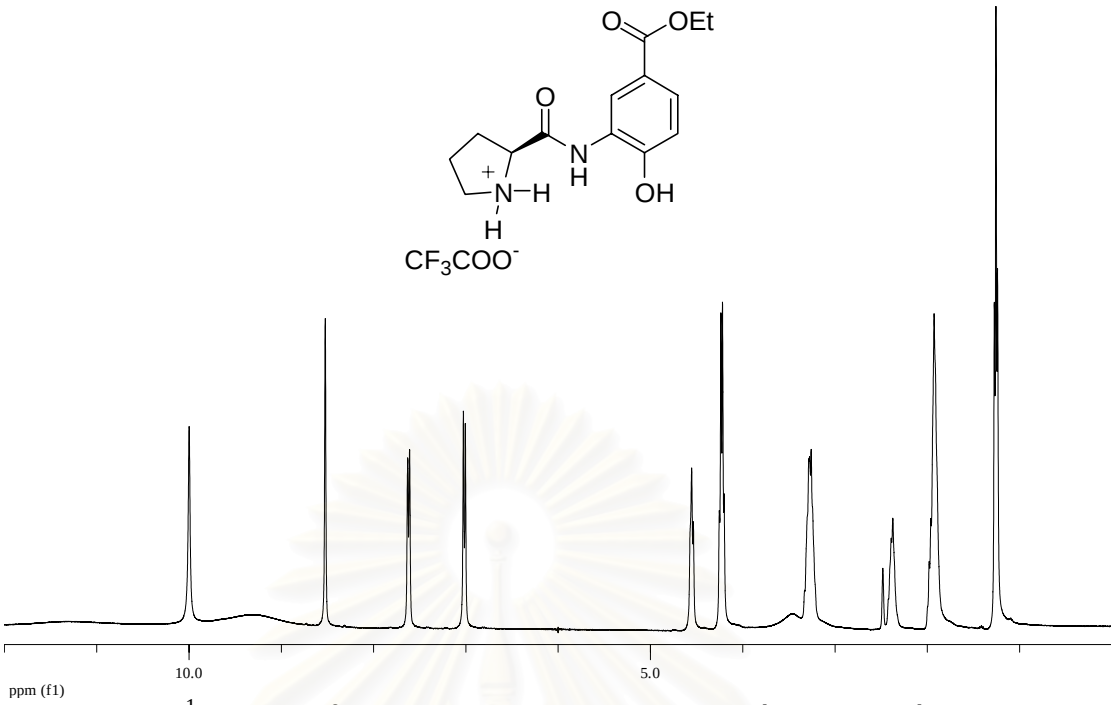


Figure 73 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-propionyl-phenyl)-amide trifluoroacetate **(28h)**

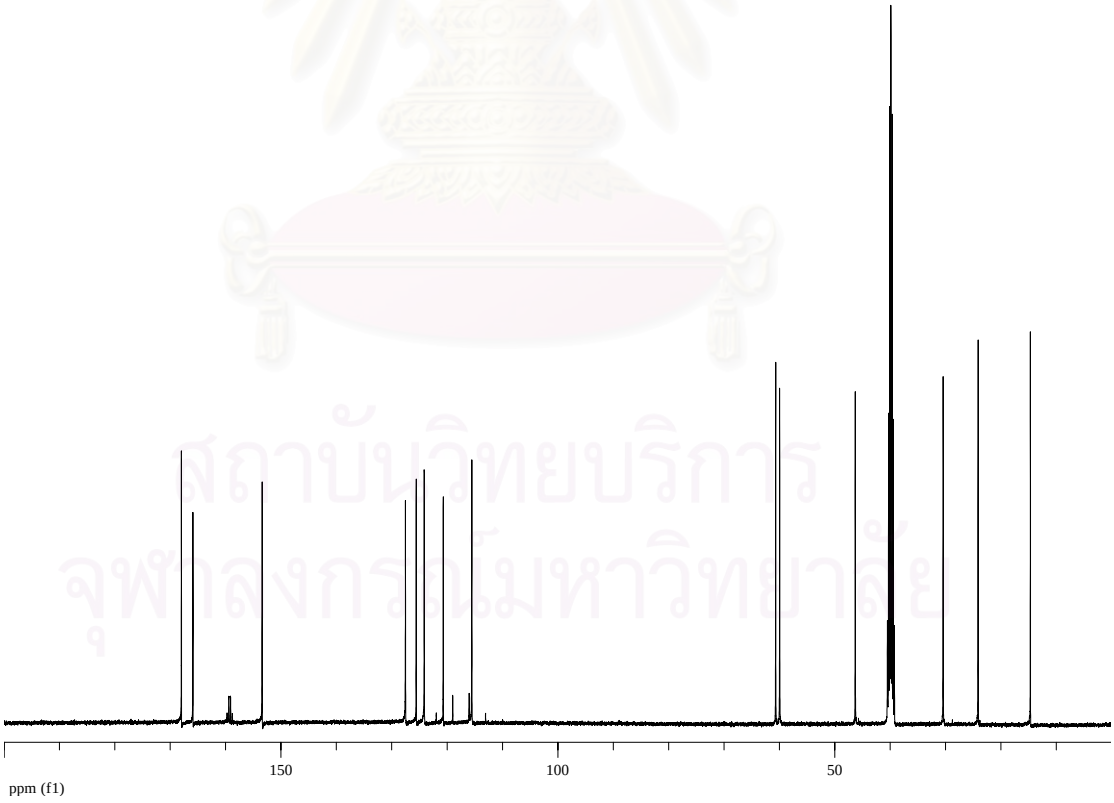


Figure 74 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-5´-propionyl-phenyl)-amide trifluoroacetate **(28h)**

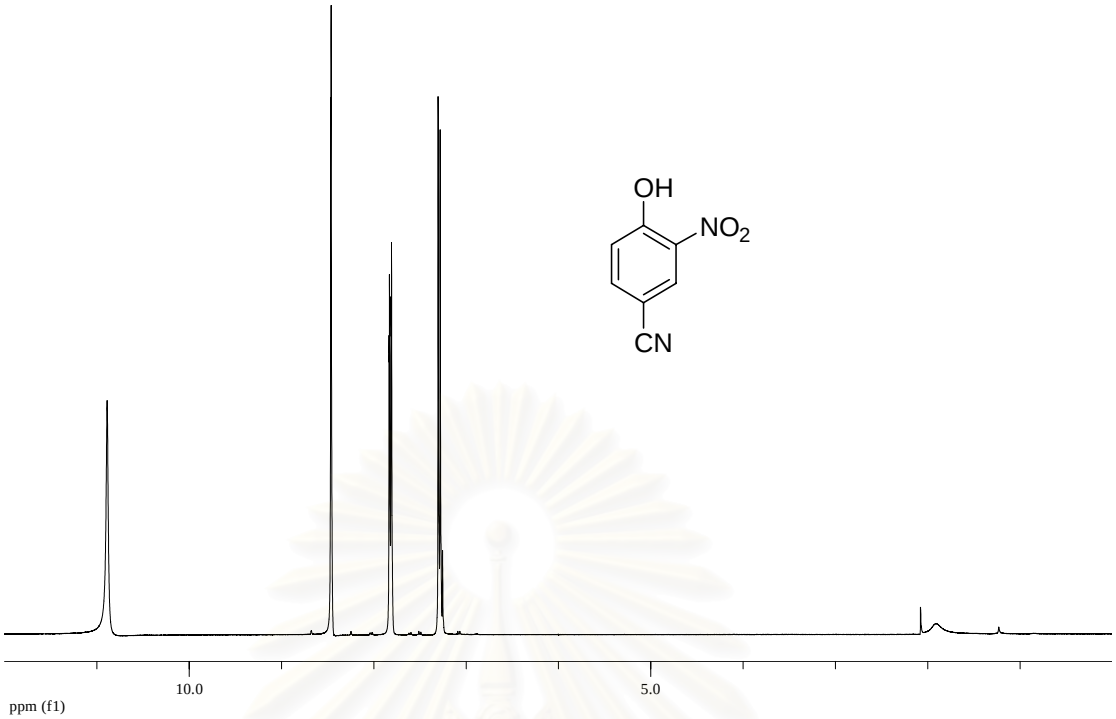


Figure 75 ^{1}H-NMR of 4-Hydroxy-3-nitro-benzonitrile **(52)**

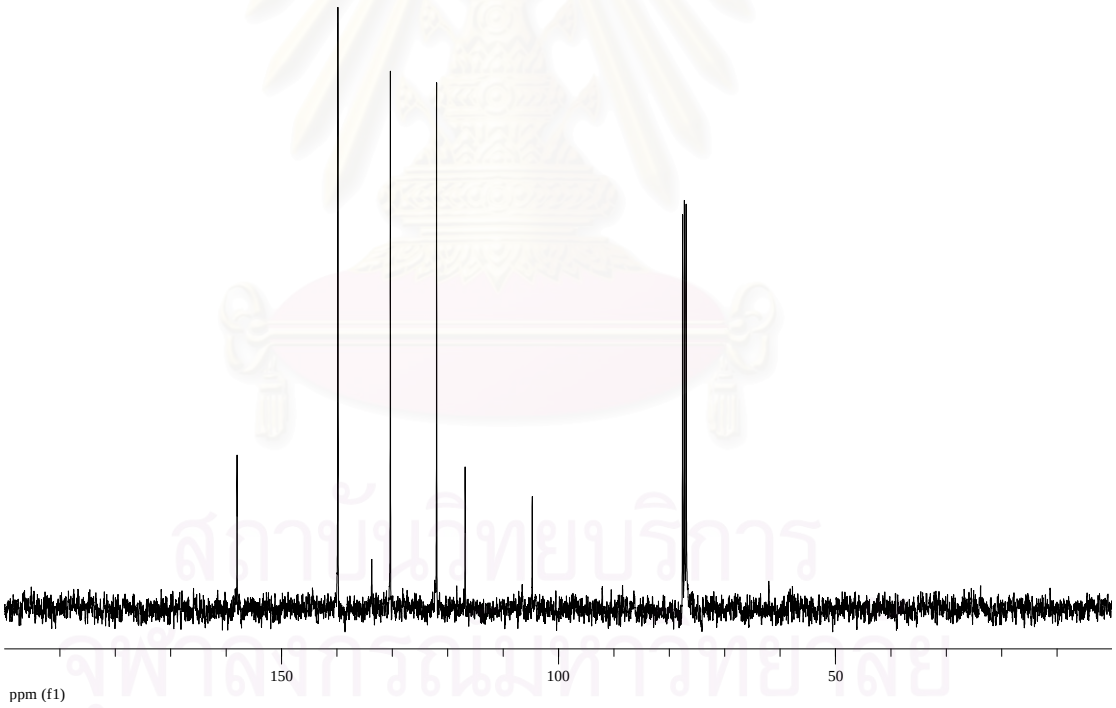


Figure 76 ^{13}C-NMR of 4-Hydroxy-3-nitro-benzonitrile **(52)**

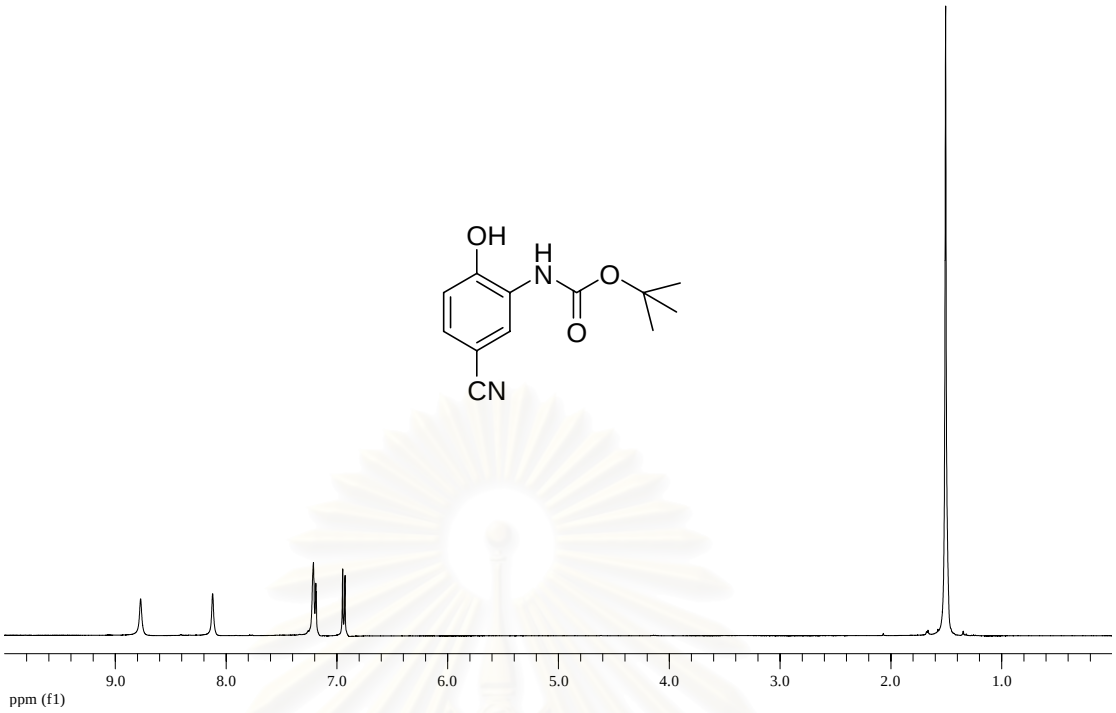


Figure 77 ^{1}H-NMR of (5-Cyano-2-hydroxy-phenyl)-carbamic acid tert-butyl ester **(53)**

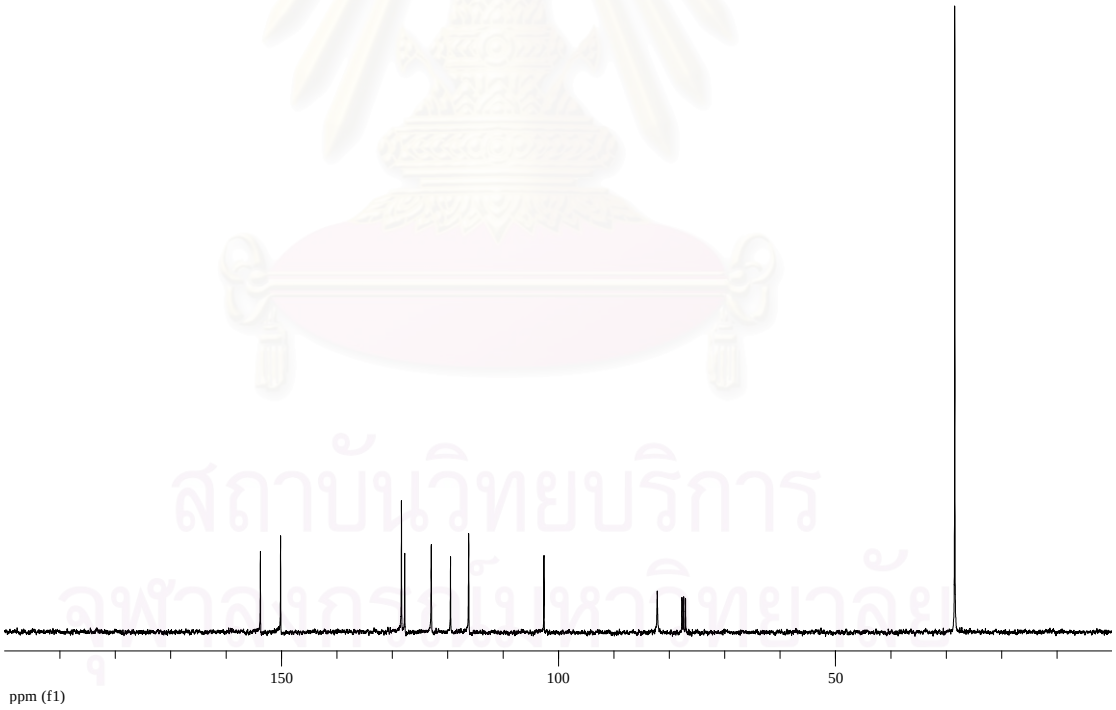


Figure 78 ^{13}C-NMR of (5-Cyano-2-hydroxy-phenyl)-carbamic acid tert-butyl ester **(53)**

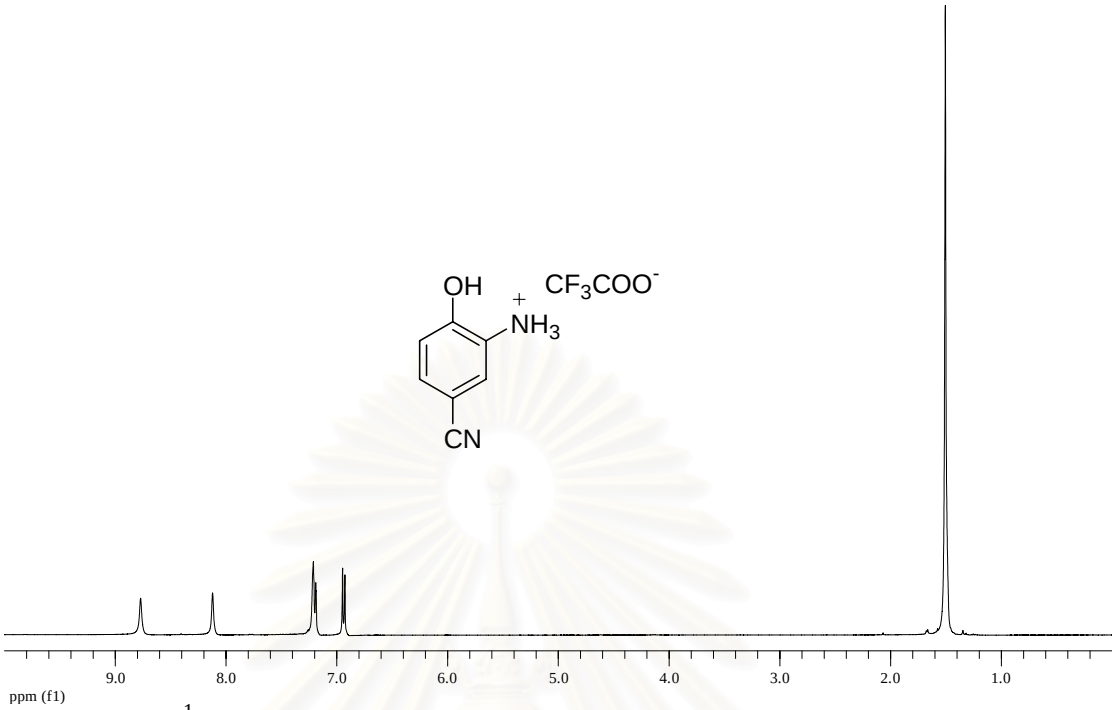


Figure 79 ^{1}H-NMR of 4-Hydroxy-3-aminobenzonitrile trifluoroacetate salt **(54)**

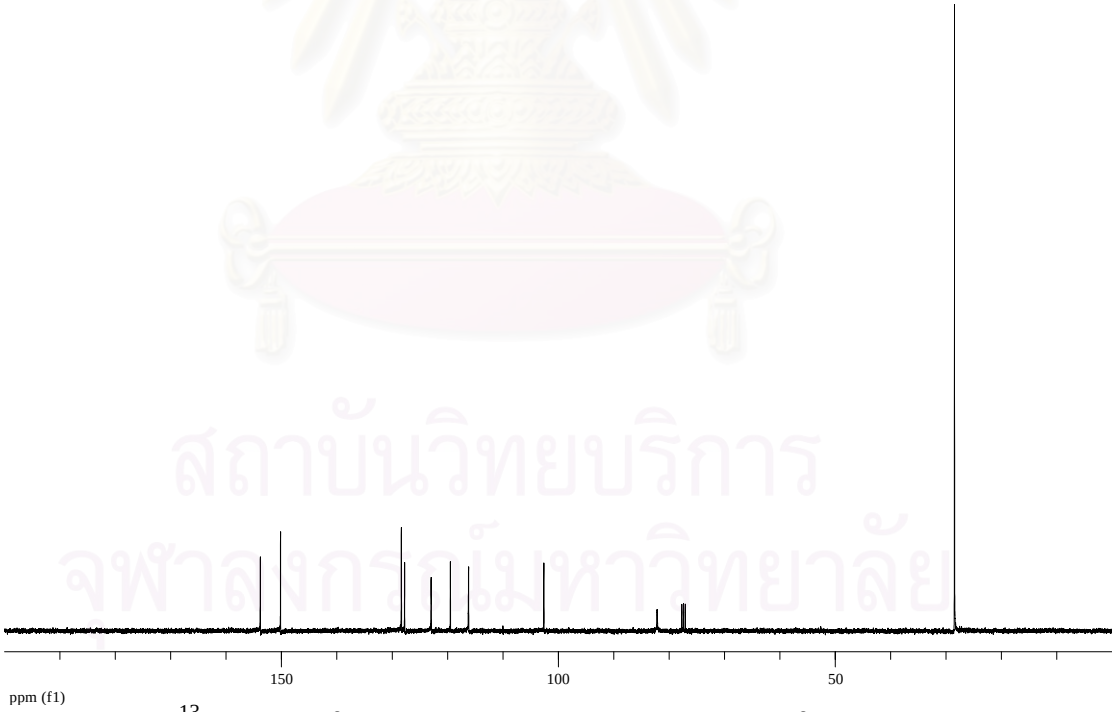


Figure 80 ^{13}C-NMR of 4-Hydroxy-3-aminobenzonitrile trifluoroacetate salt **(54)**

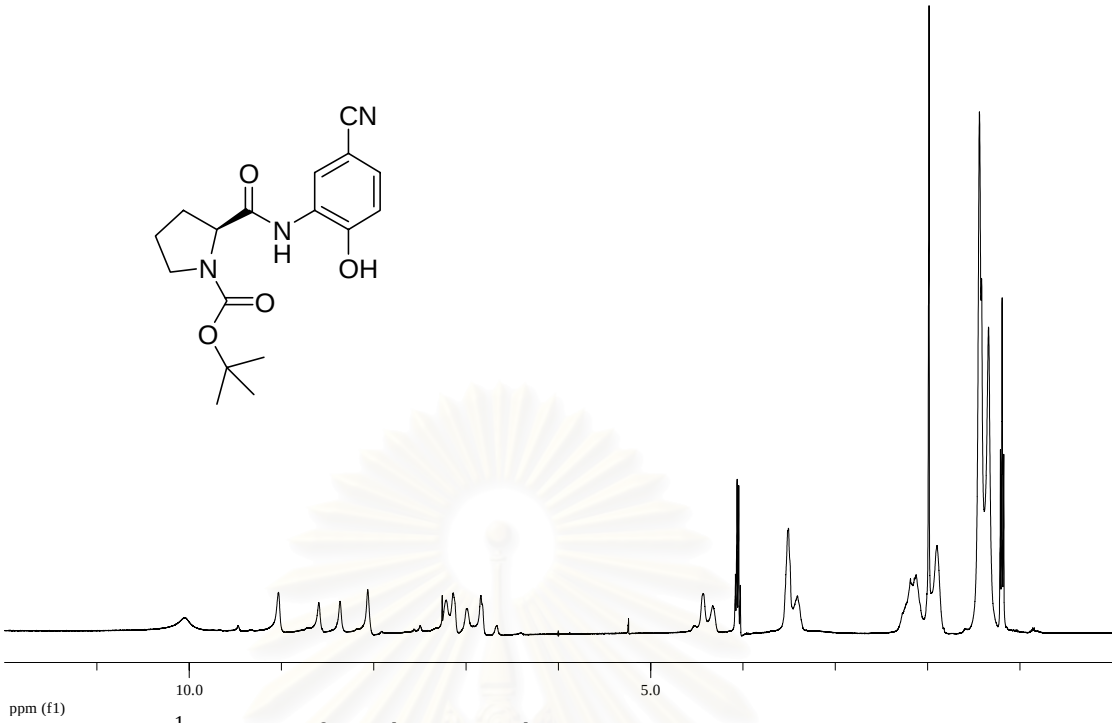


Figure 81 ^{1}H-NMR of 2-(5´-Cyano-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(55)**

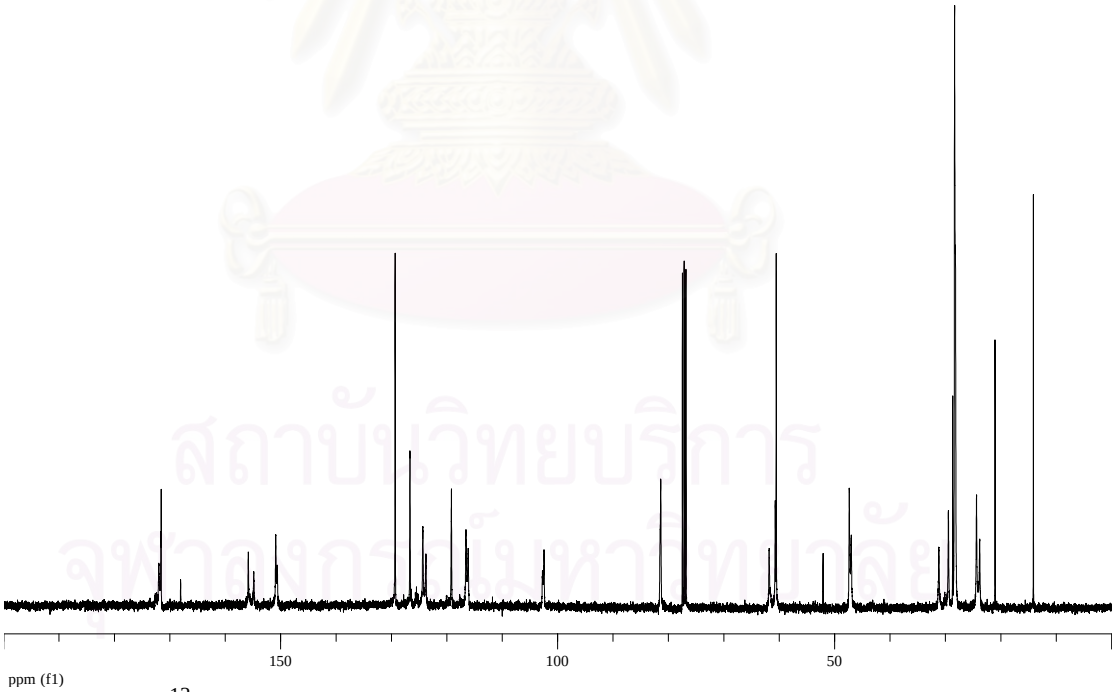


Figure 82 ^{13}C-NMR of 2-(5´-Cyano-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(55)**

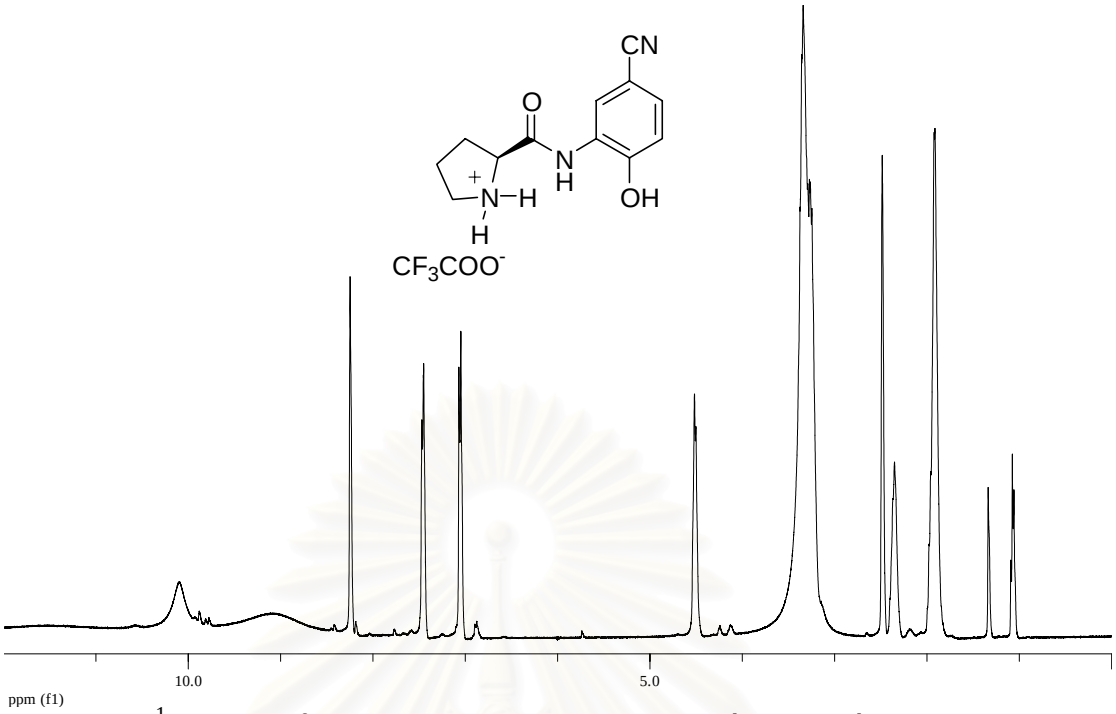


Figure 83 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-cyano-2´-hydroxy-phenyl)-amide trifluoroacetate **(28i)**

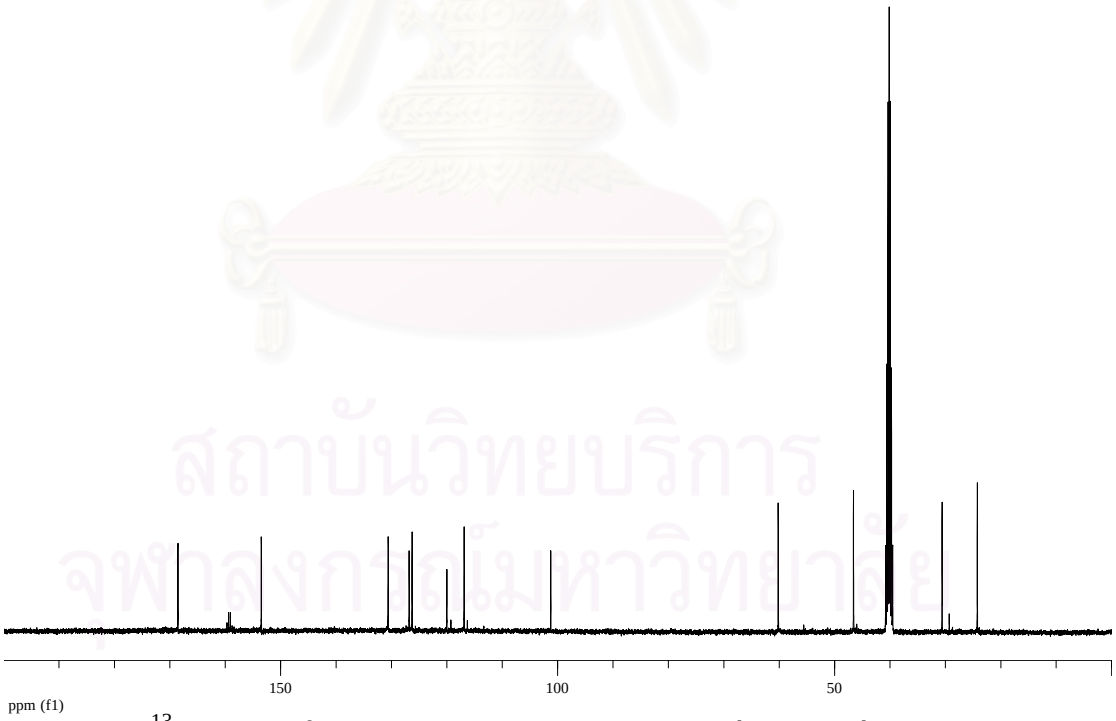


Figure 84 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-cyano-2´-hydroxy-phenyl)-amide trifluoroacetate **(28i)**

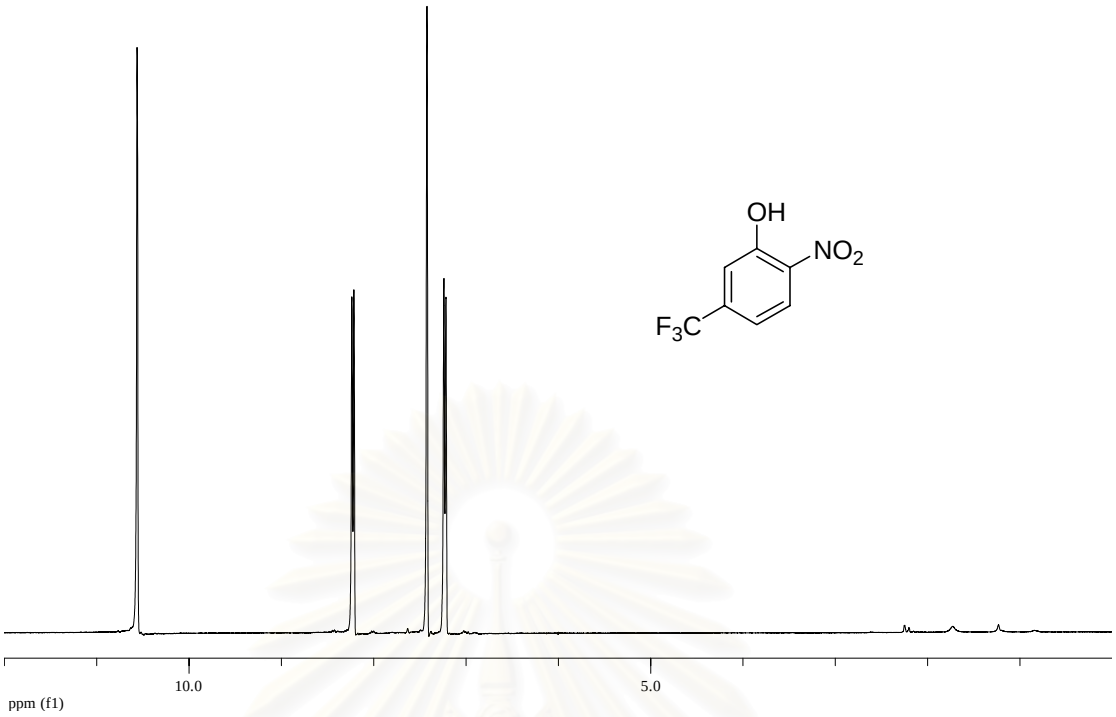


Figure 85 ^{1}H-NMR of 2-Nitro-5-trifluoromethyl-phenol **(56)**

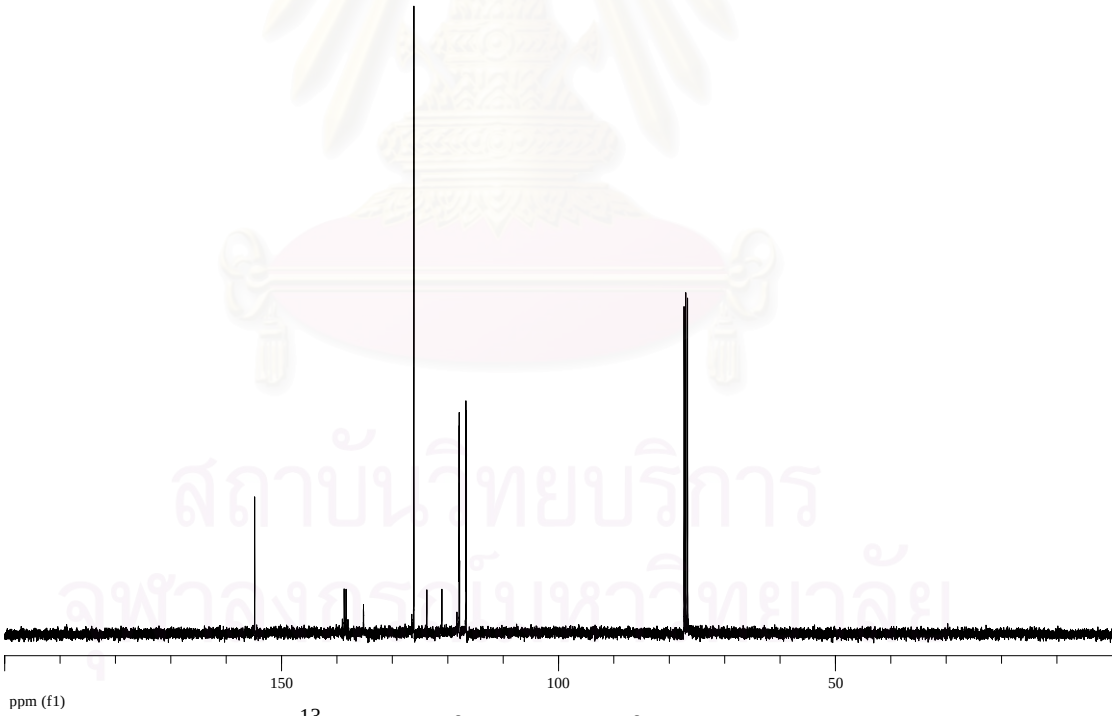


Figure 86 ^{13}C-NMR of 2-Nitro-5-trifluoromethyl-phenol **(56)**

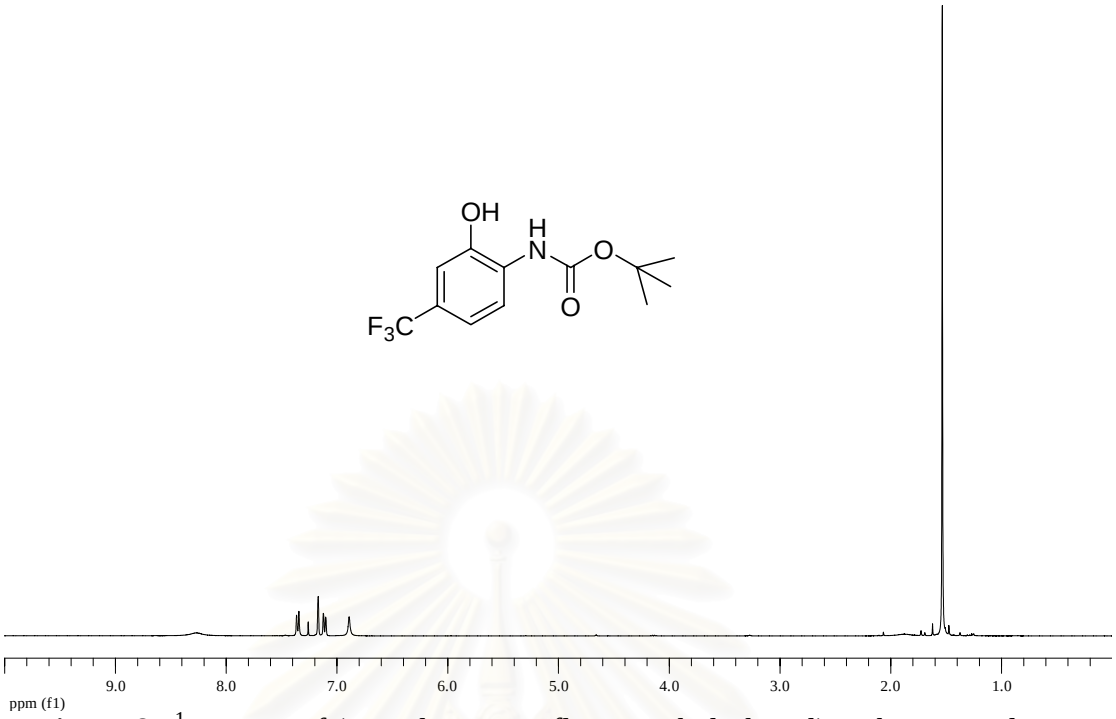


Figure 87 ^{1}H-NMR of (2-Hydroxy-4-trifluoromethyl-phenyl)-carbamic acid *tert*-butyl ester **(57)**

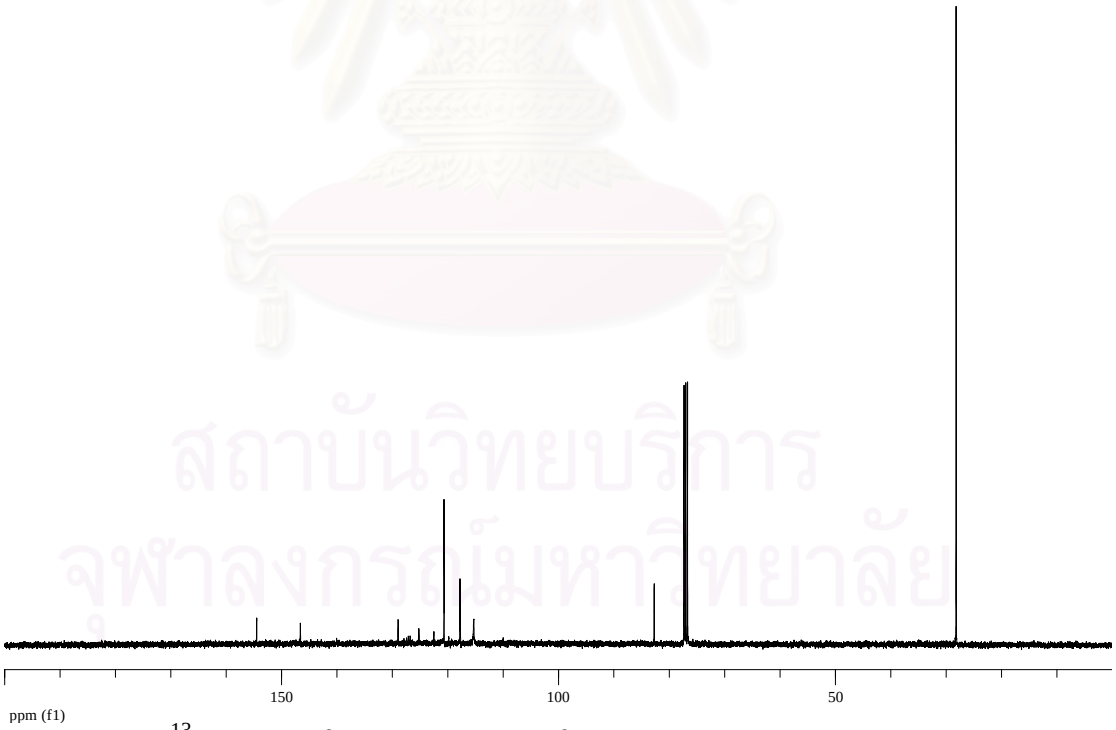


Figure 88 ^{13}C-NMR of (2-Hydroxy-4-trifluoromethyl-phenyl)-carbamic acid *tert*-butyl ester **(57)**

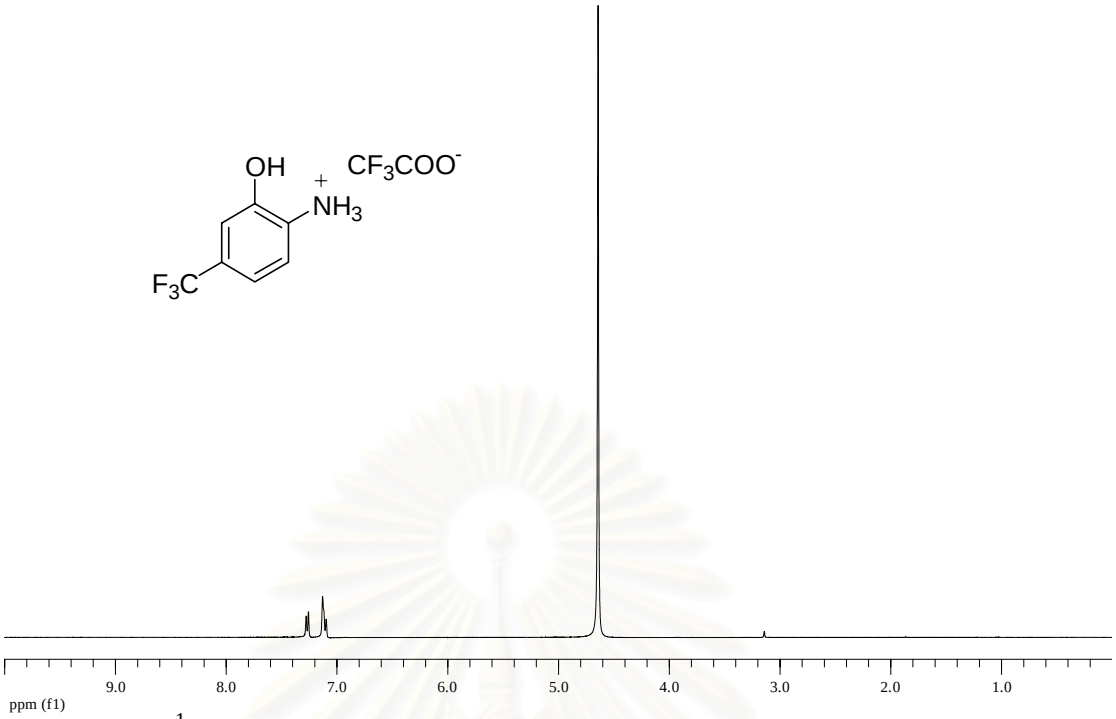


Figure 89 ^{1}H-NMR of 5-trifluoromethyl-2-aminophenol trifluoroacetate salt **(58)**

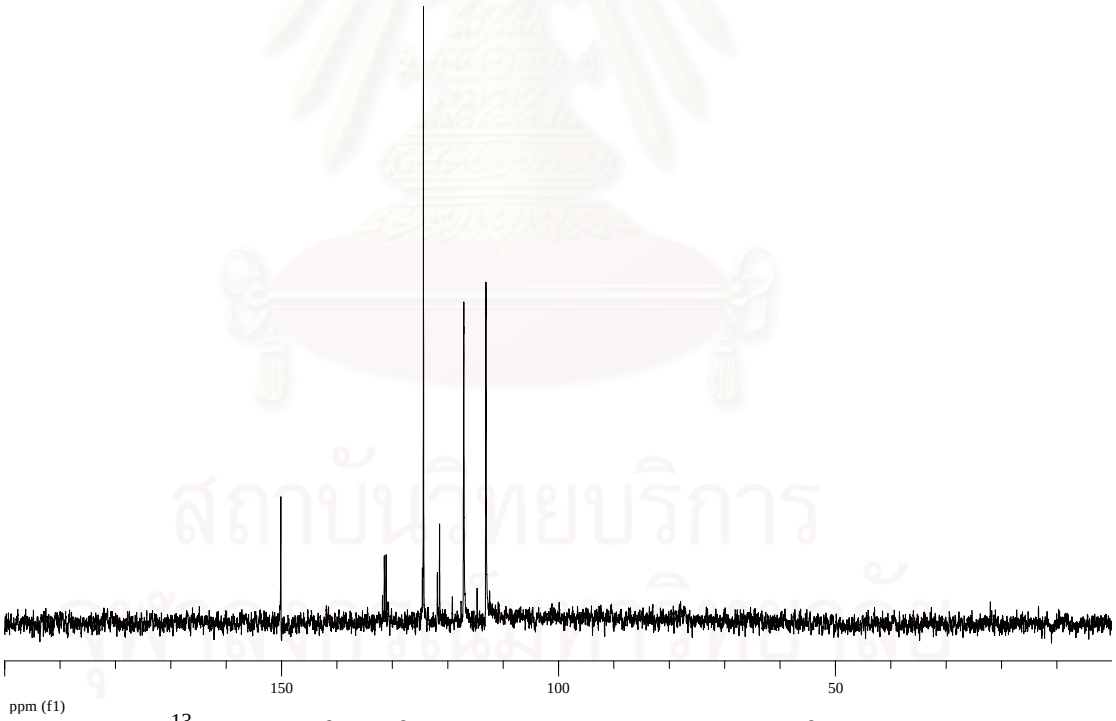


Figure 90 ^{13}C-NMR of 5-trifluoromethyl-2-aminophenol trifluoroacetate salt **(58)**

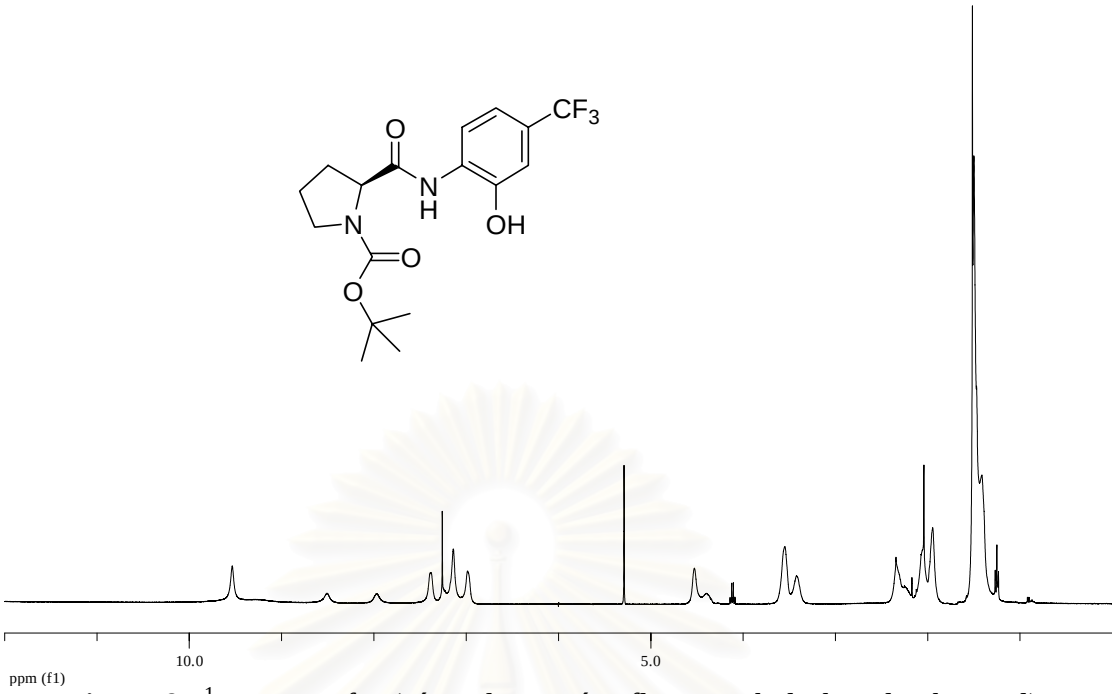


Figure 91 ^{1}H-NMR of 2-(2´-Hydroxy-4´-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(59)**

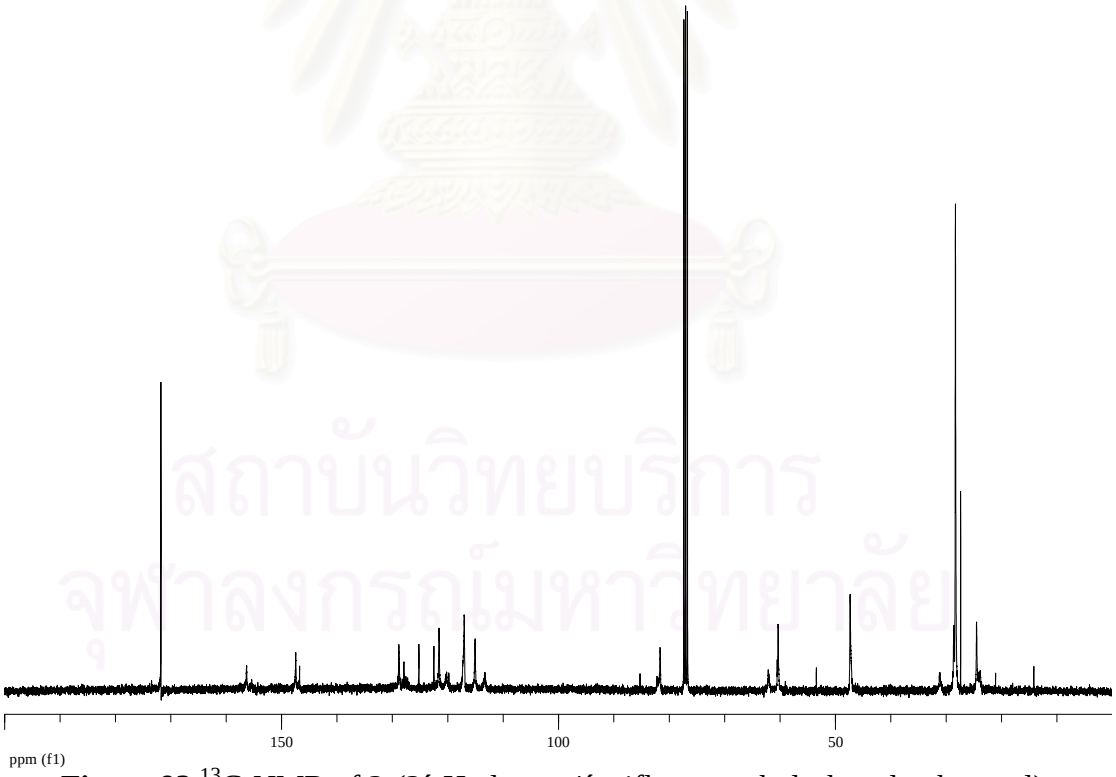


Figure 92 ^{13}C-NMR of 2-(2´-Hydroxy-4´-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(59)**

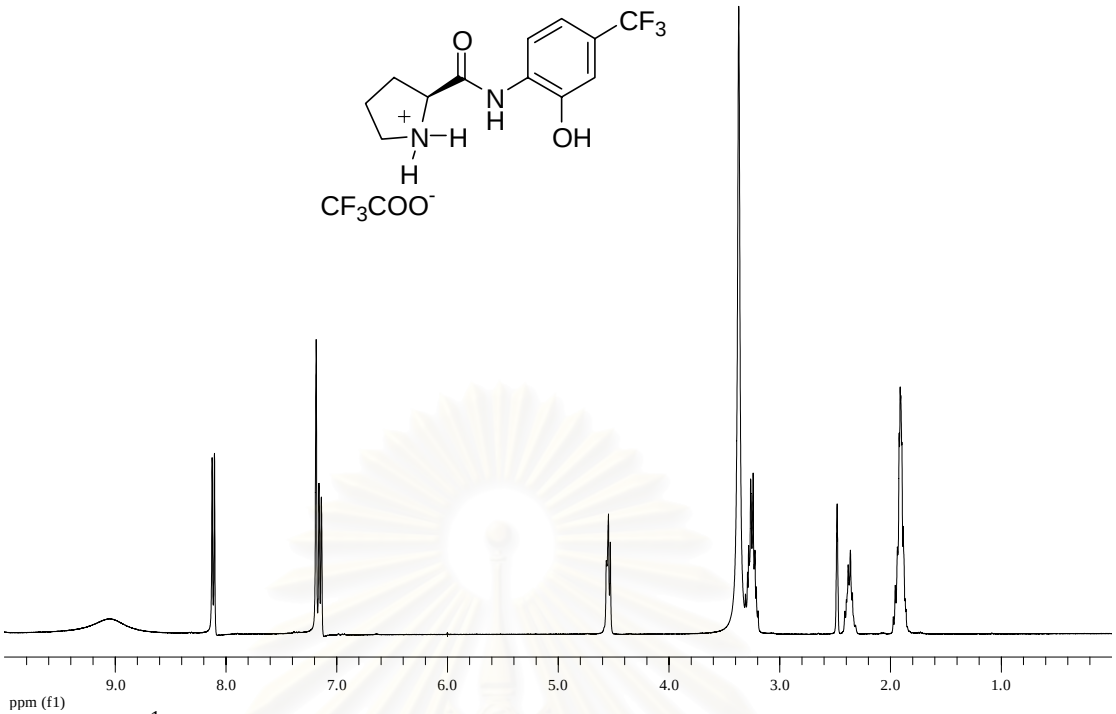


Figure 93 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-4´-trifluoromethyl-phenyl)-amide trifluoroacetate **(28j)**

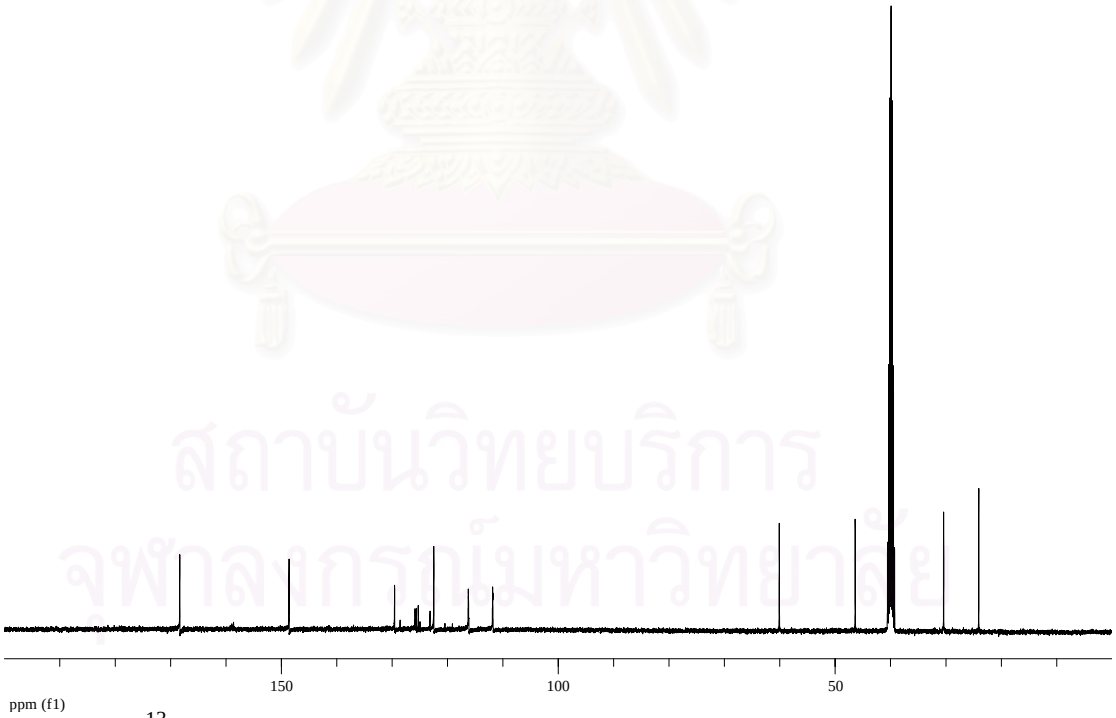


Figure 94 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (2´-hydroxy-4´-trifluoromethyl-phenyl)-amide trifluoroacetate **(28j)**

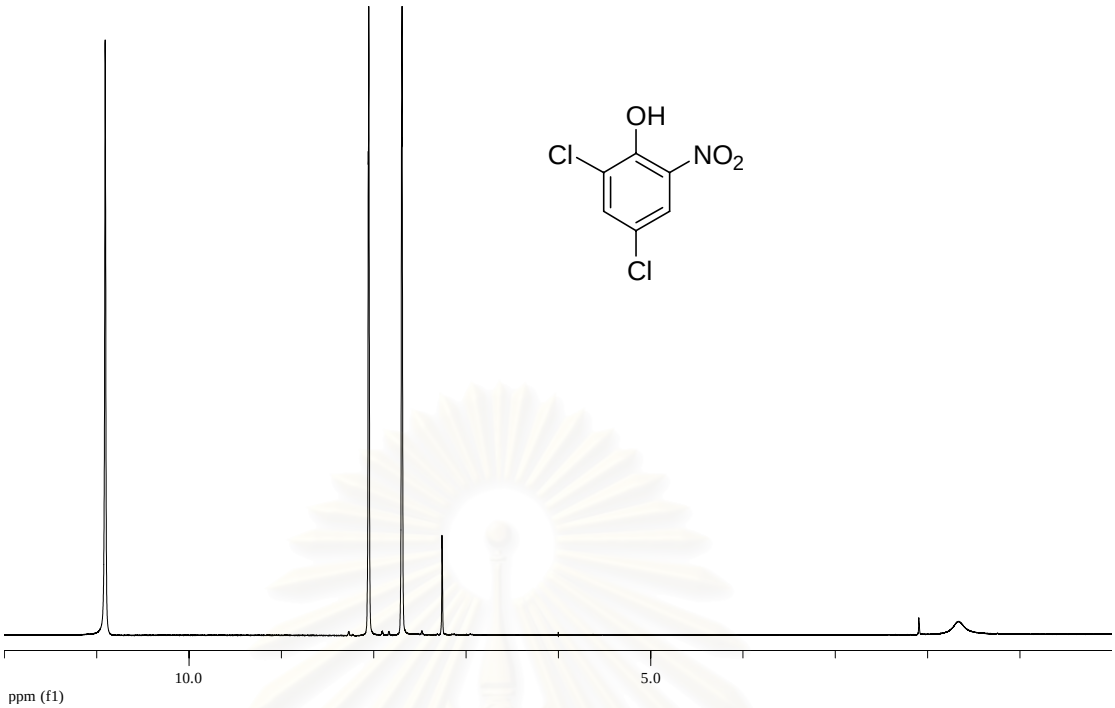


Figure 95 ^{1}H-NMR of 2,4-Dichloro-6-nitro-phenol **(60)**

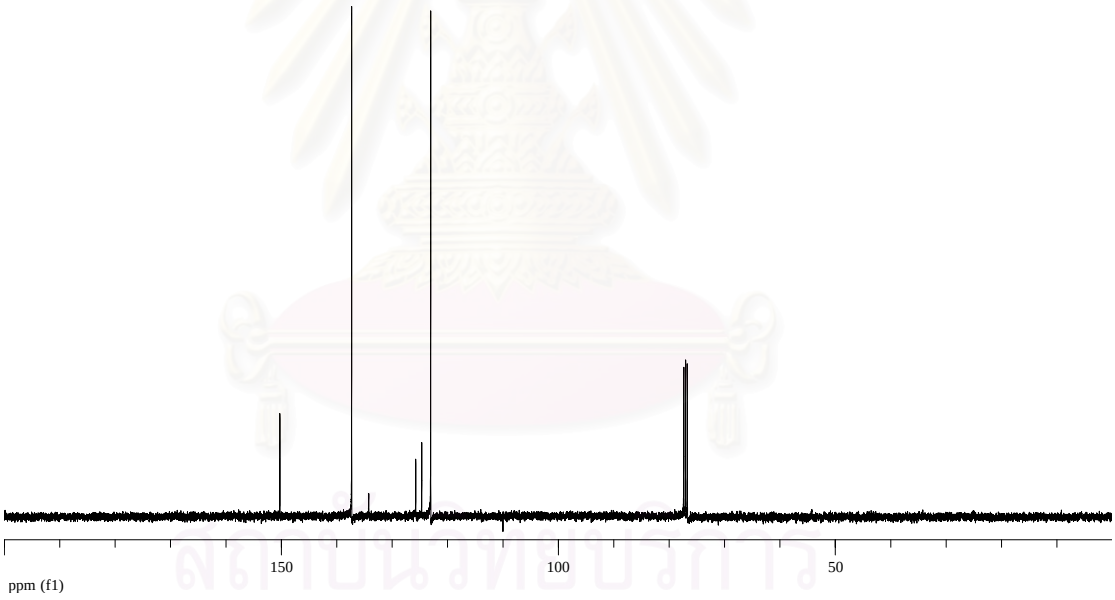


Figure 96 ^{13}C-NMR of 2,4-Dichloro-6-nitro-phenol **(60)**

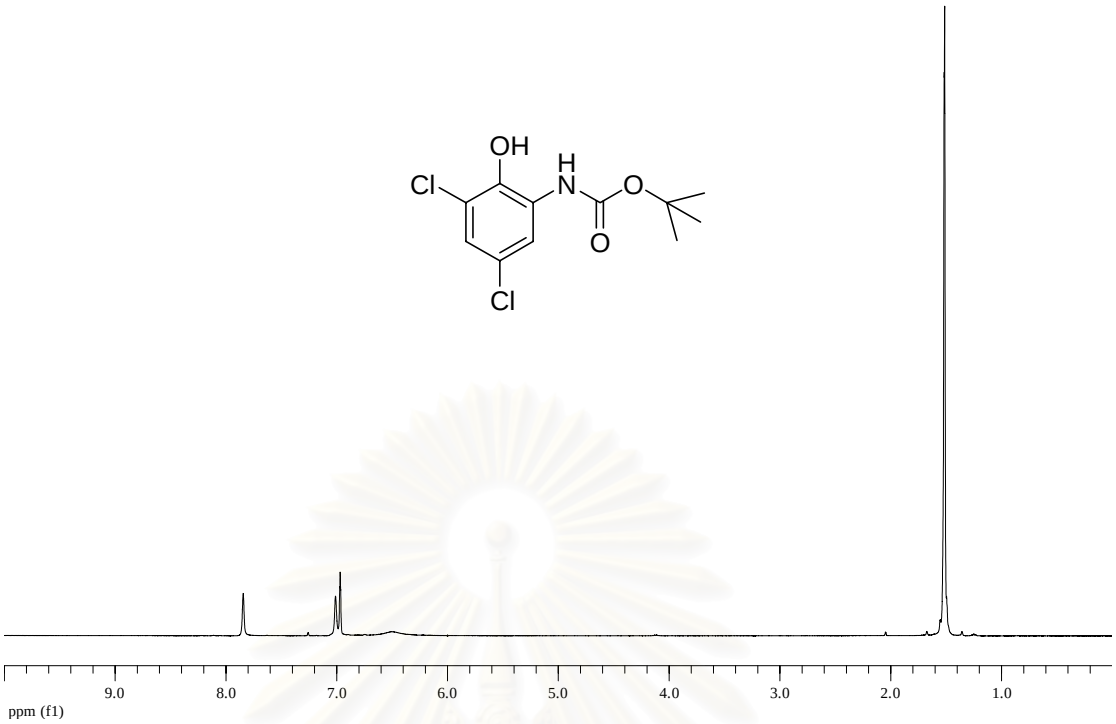


Figure 97 ^{1}H-NMR of (3,5-Dichloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(61)**

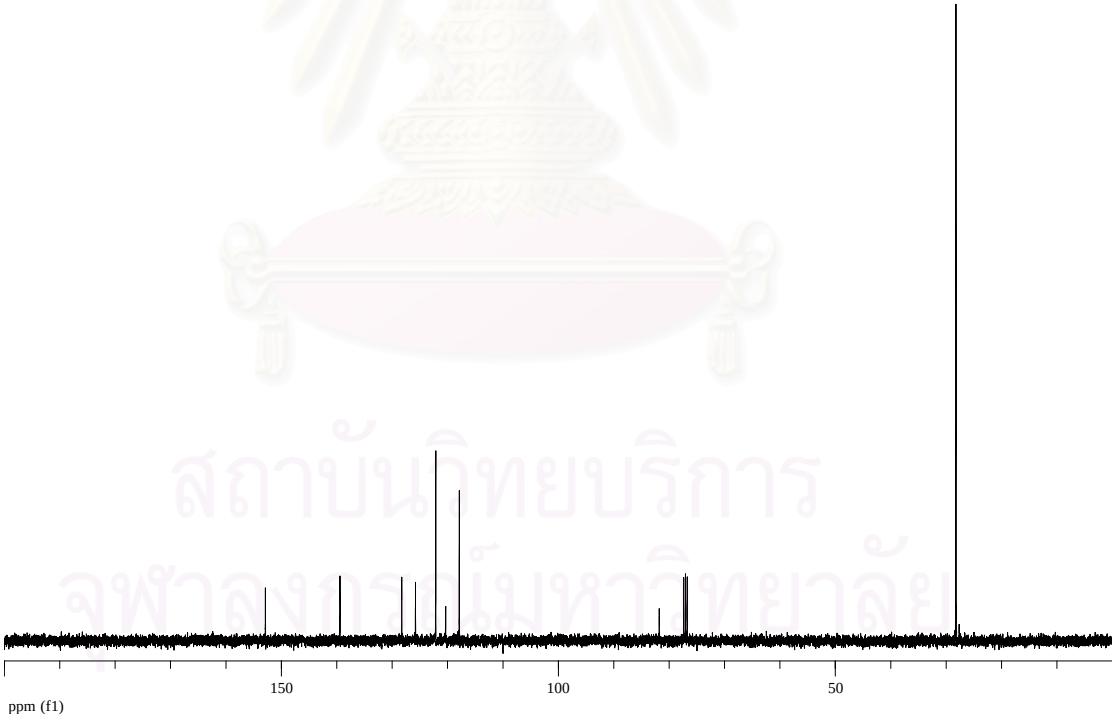


Figure 98 ^{13}C-NMR of (3,5-Dichloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(61)**

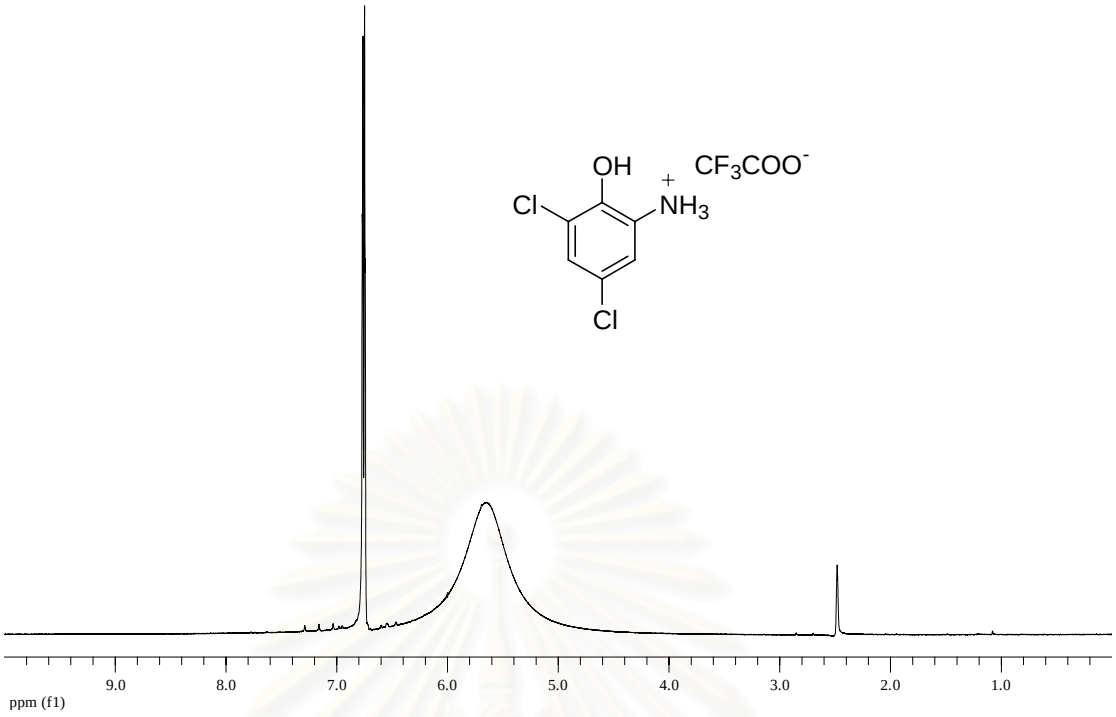


Figure 99 ^{1}H-NMR of 2,4-Dichloro-6-aminophenol trifluoroacetate salt **(62)**

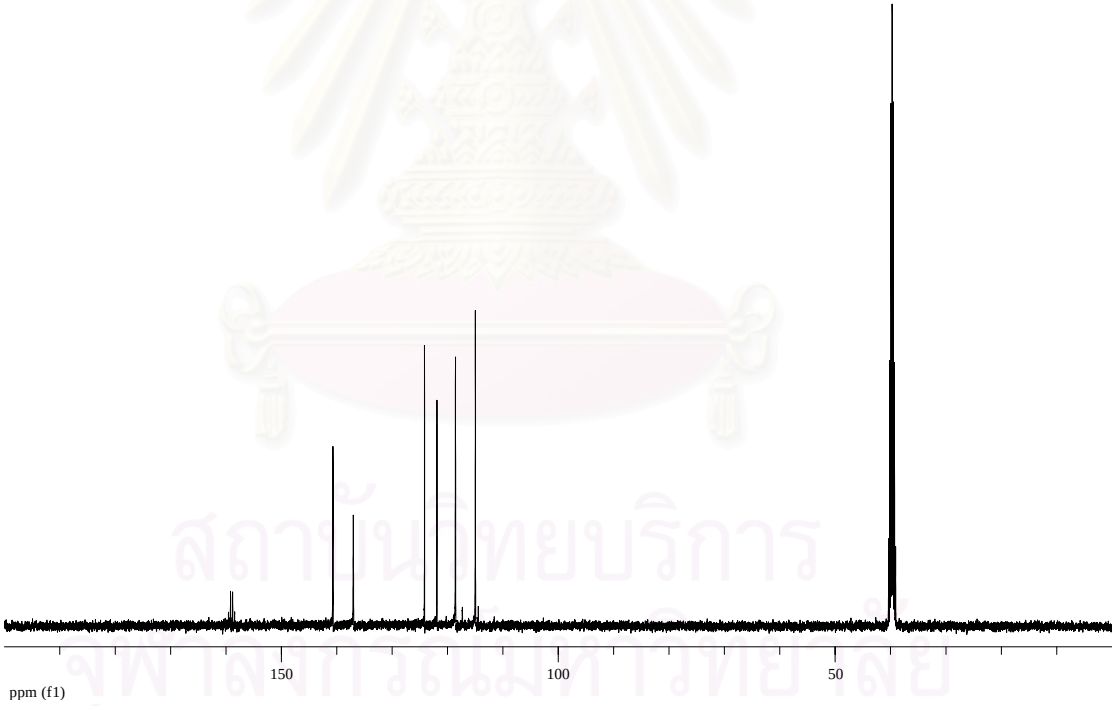


Figure 100 ^{13}C-NMR of 2,4-Dichloro-6-aminophenol trifluoroacetate salt **(62)**

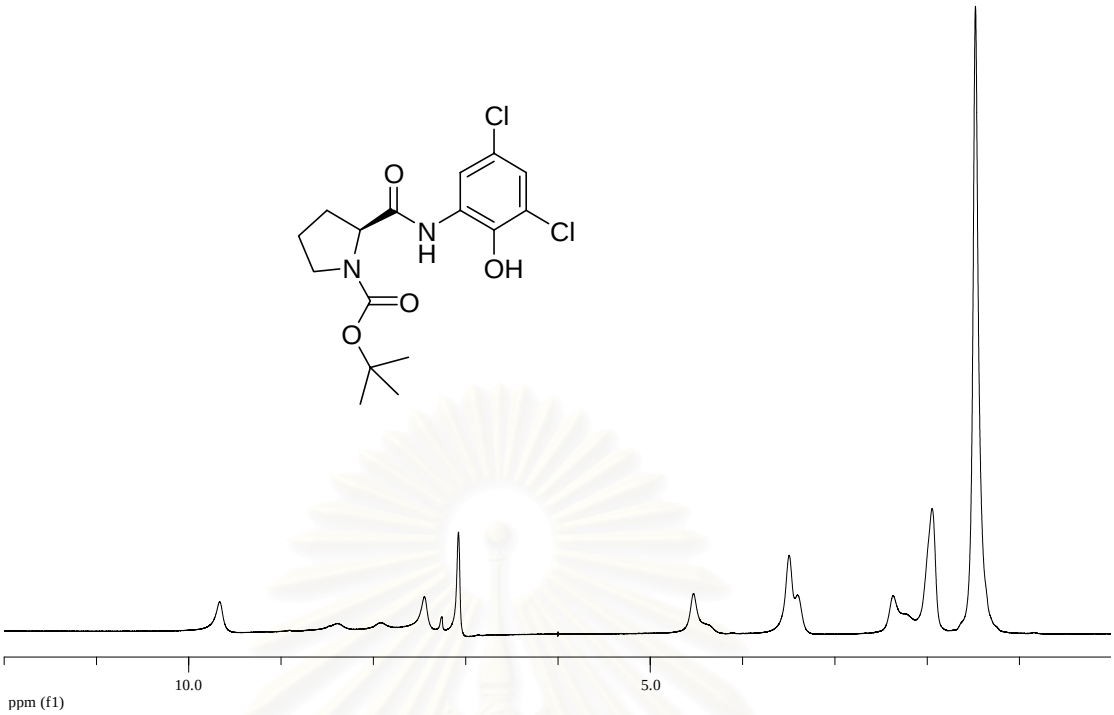


Figure 101 ^{1}H-NMR of 2-(3´,5´-Dichloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(63)**

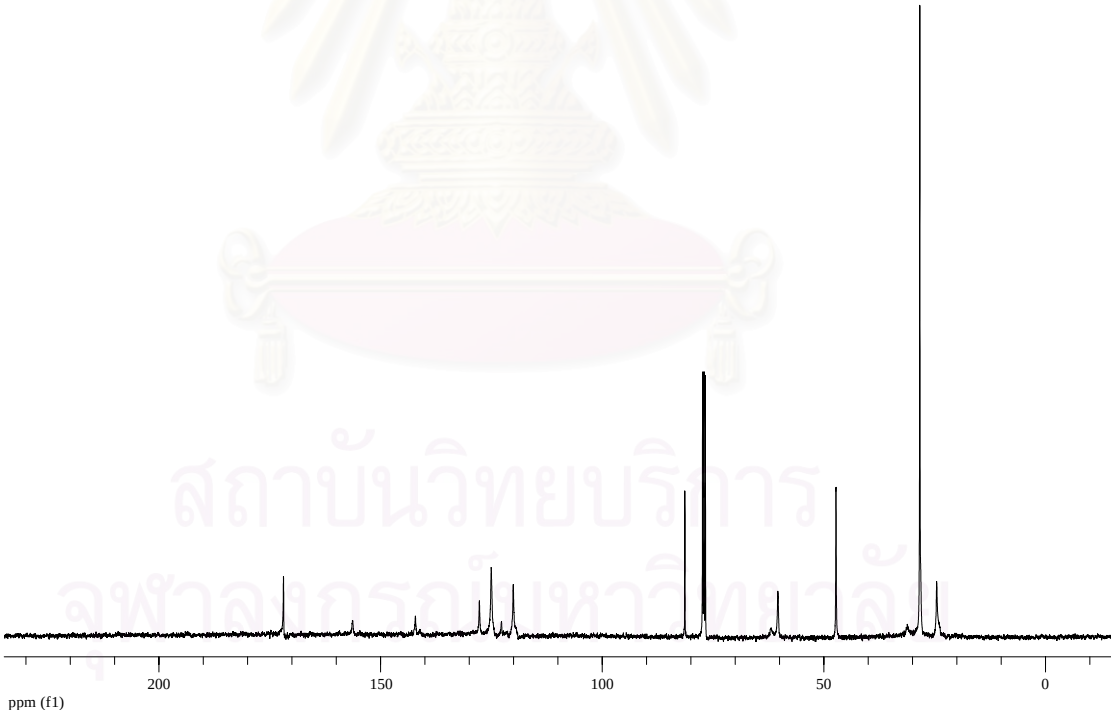


Figure 102 ^{13}C-NMR of 2-(3´,5´-Dichloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(63)**

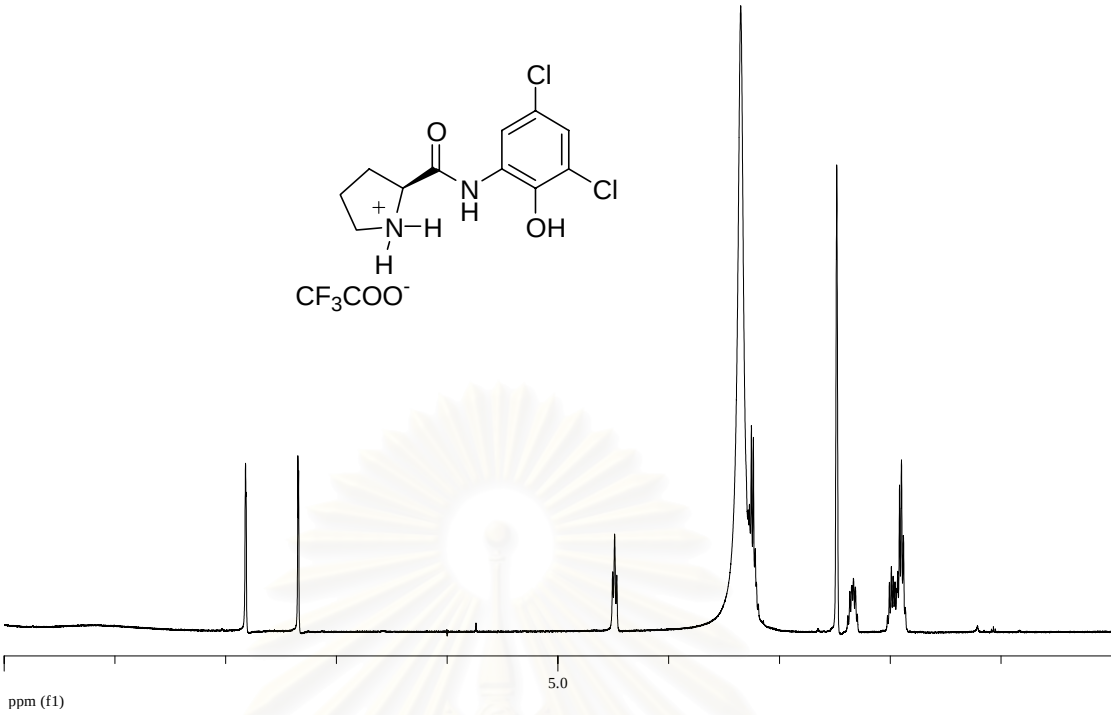


Figure 103 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (3´,5´-dichloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28k)**

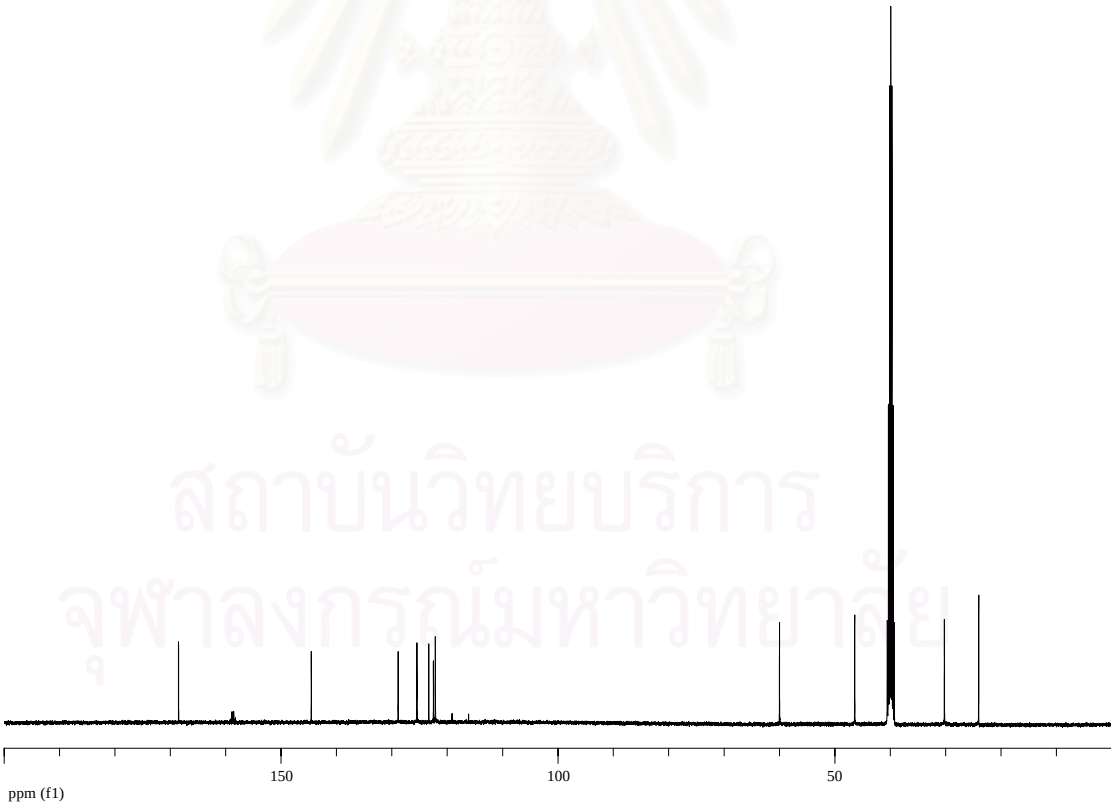


Figure 104 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (3´,5´-dichloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28k)**

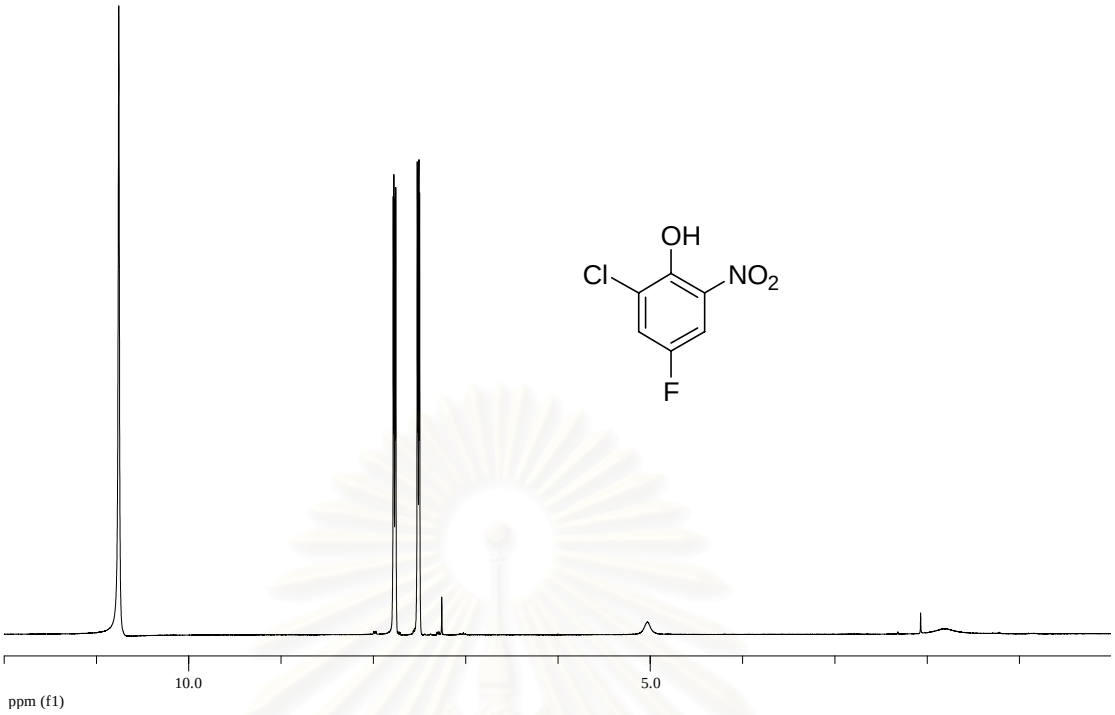


Figure 105 ^{1}H-NMR of 2-Chloro-4-fluoro-6-nitro-phenol **(64)**

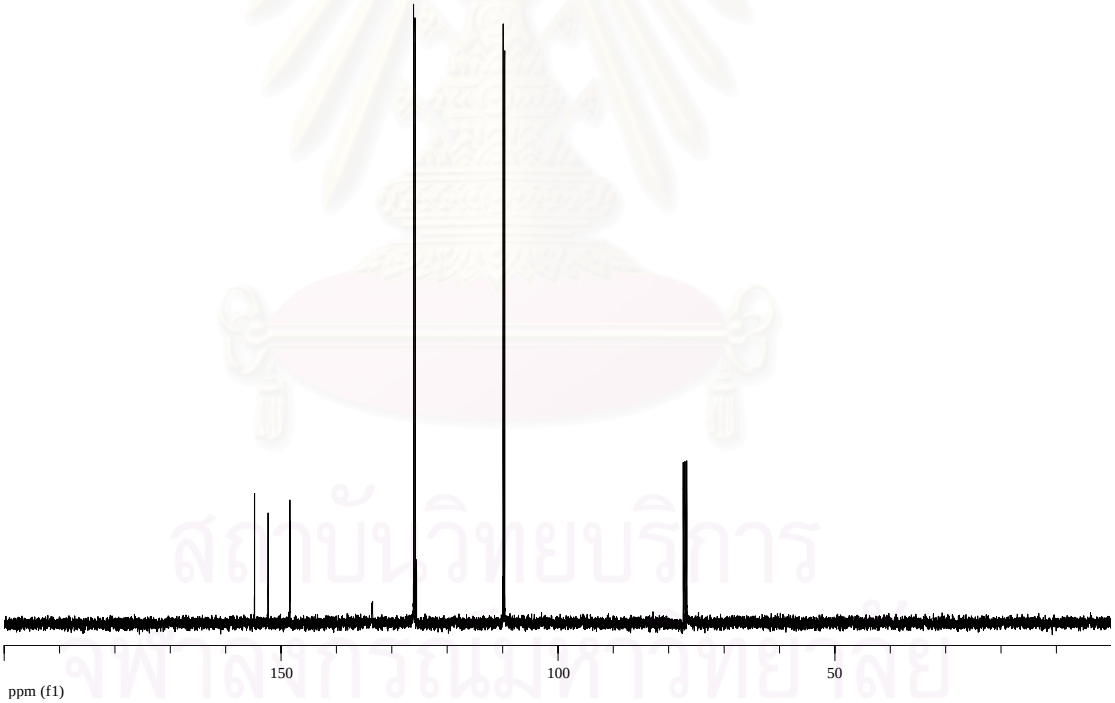


Figure 106 ^{13}C-NMR of 2-Chloro-4-fluoro-6-nitro-phenol **(64)**

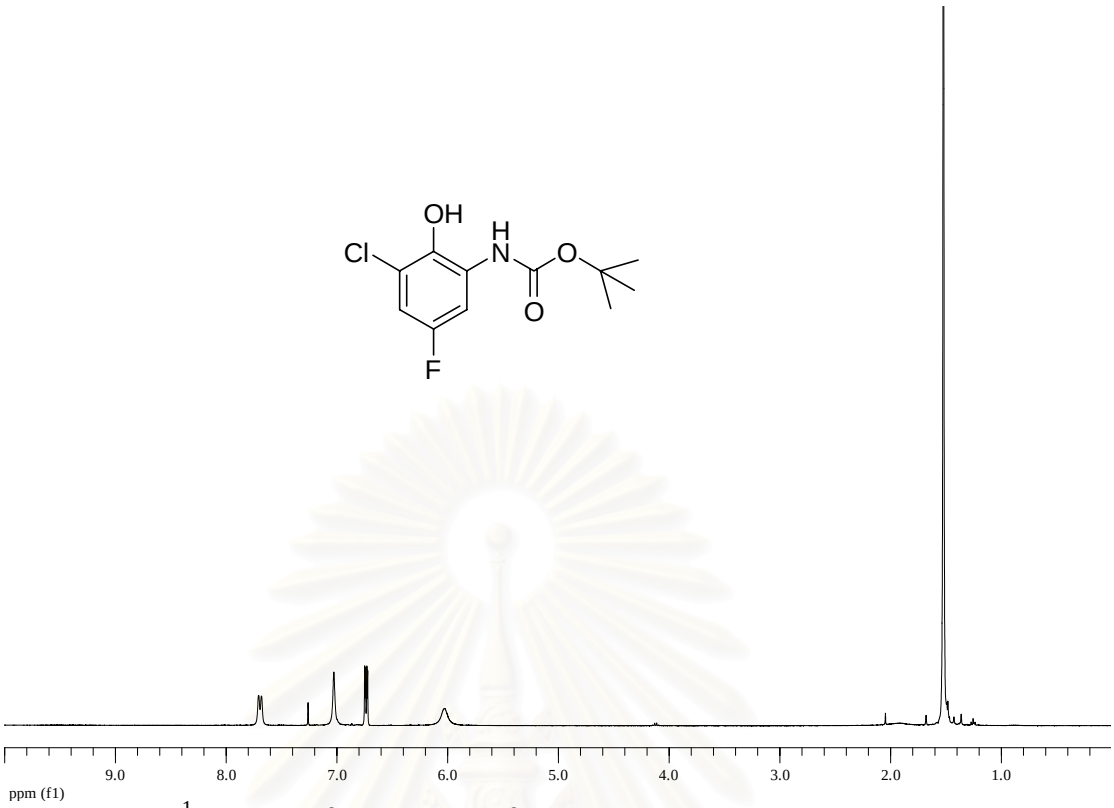


Figure 107 ^{1}H-NMR of (3-Chloro-5-fluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(65)**

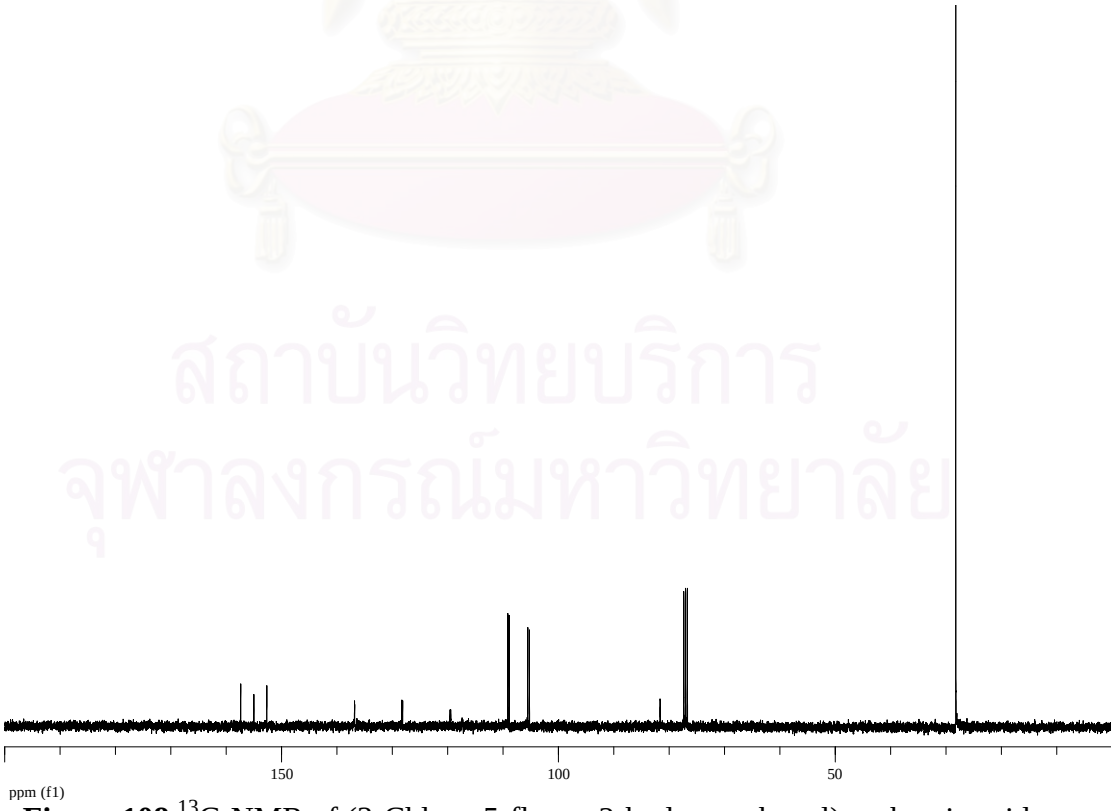


Figure 108 ^{13}C-NMR of (3-Chloro-5-fluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(65)**

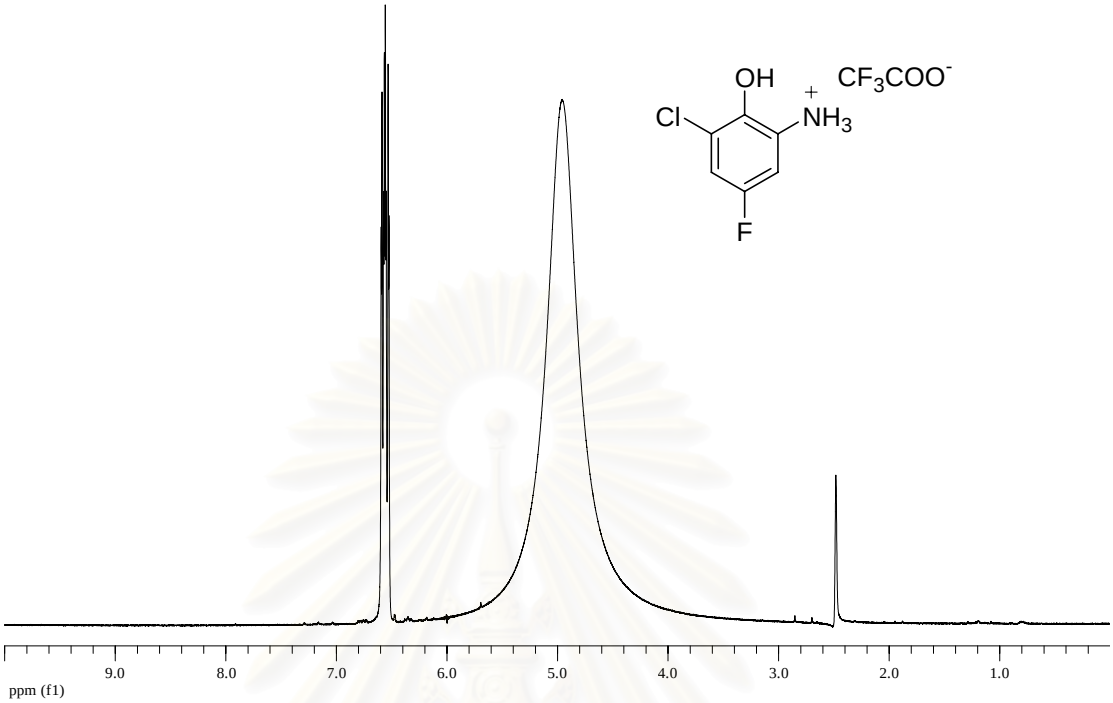


Figure 109 ^{1}H-NMR of 2-Chloro-4-fluoro-6-aminophenol trifluoroacetate salt **(66)**

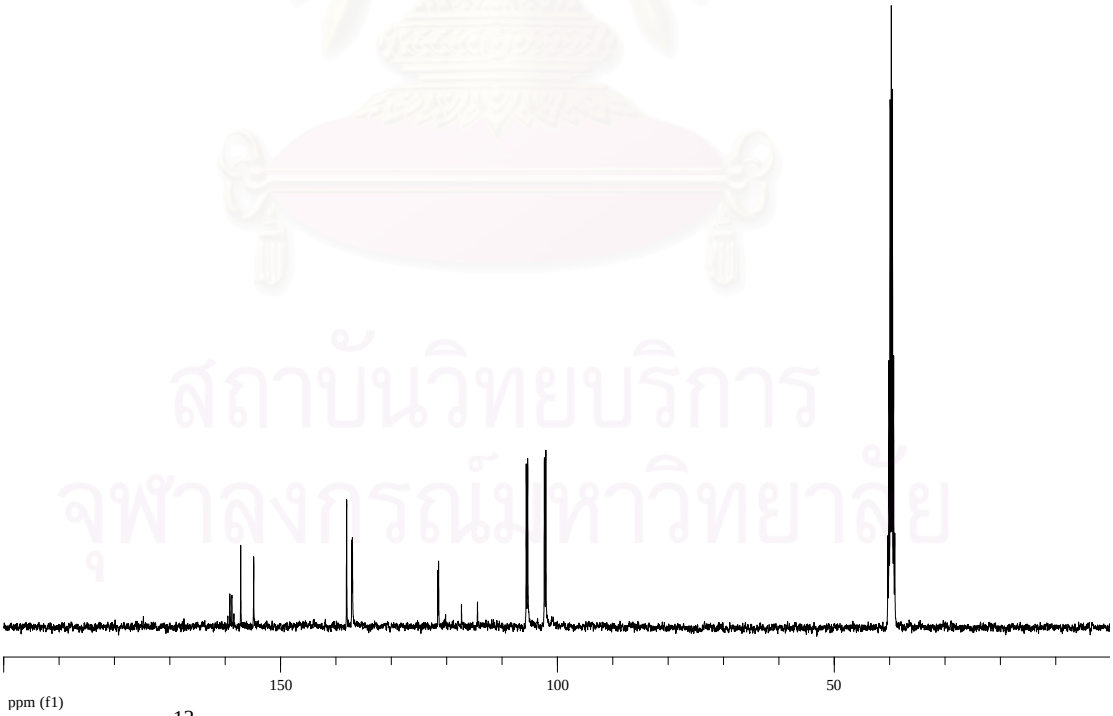


Figure 110 ^{13}C-NMR of 2-Chloro-4-fluoro-6-aminophenol trifluoroacetate salt **(66)**

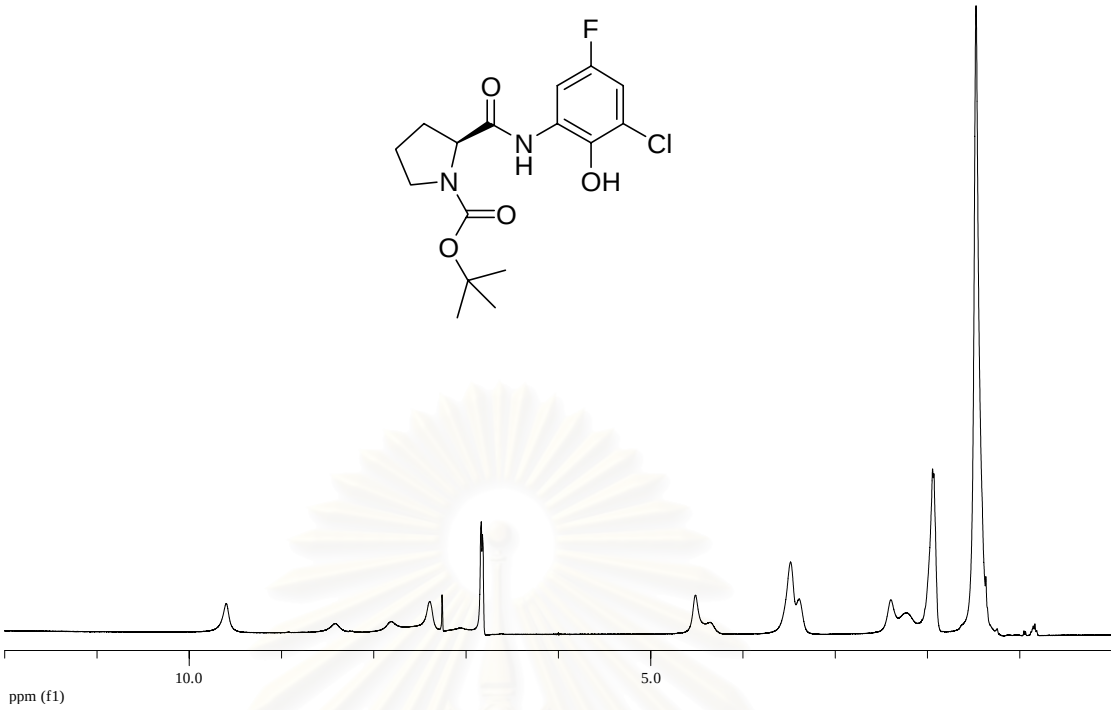


Figure 111 ^{1}H-NMR of 2-(3´-Chloro-5´-fluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(67)**

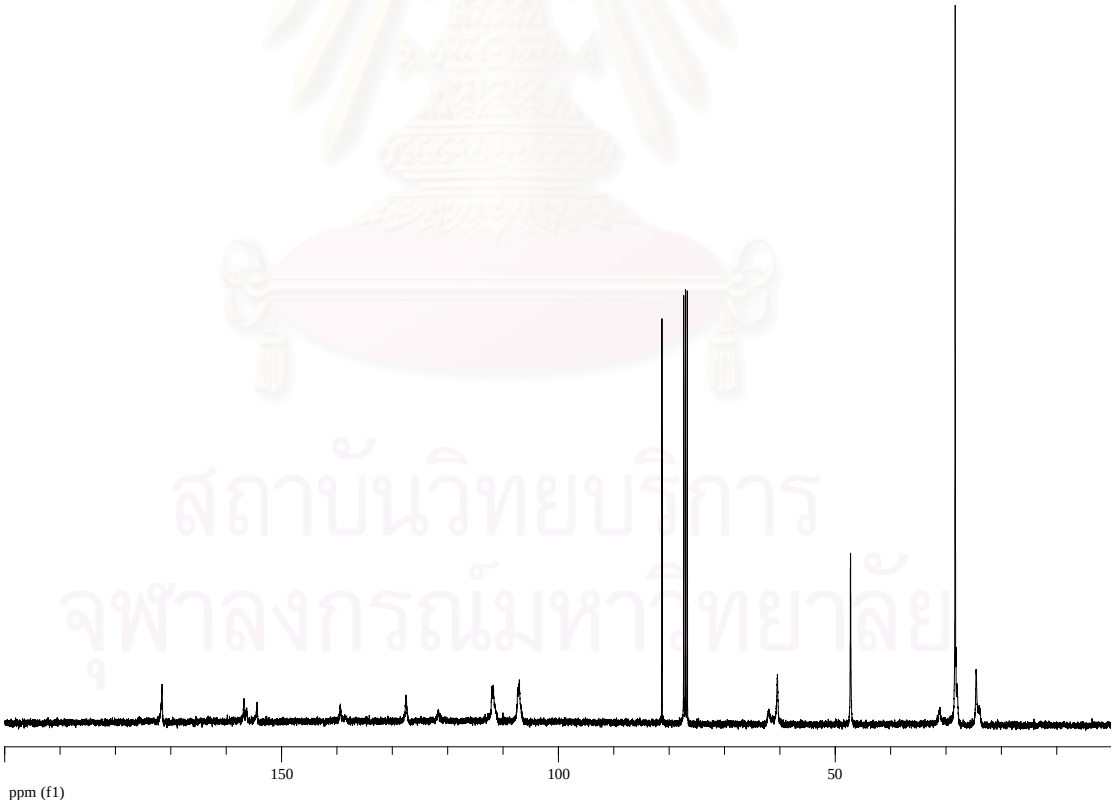


Figure 112 ^{13}C-NMR of 2-(3´-Chloro-5´-fluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(67)**

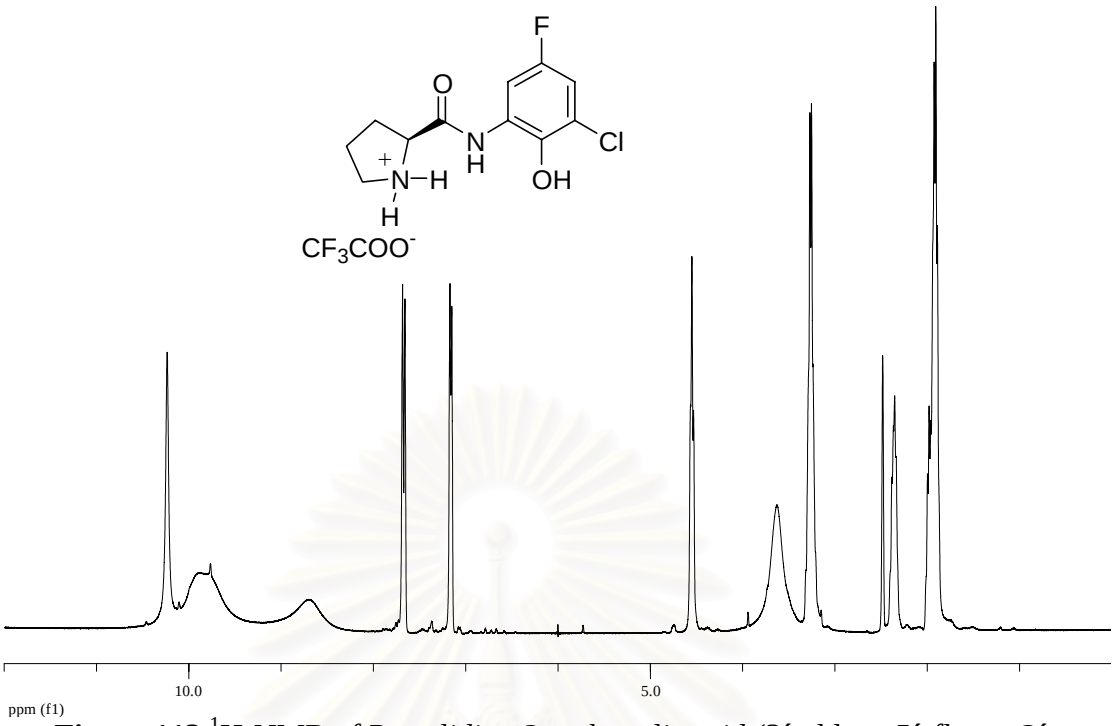


Figure 113 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (3´-chloro-5´-fluoro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28l)**

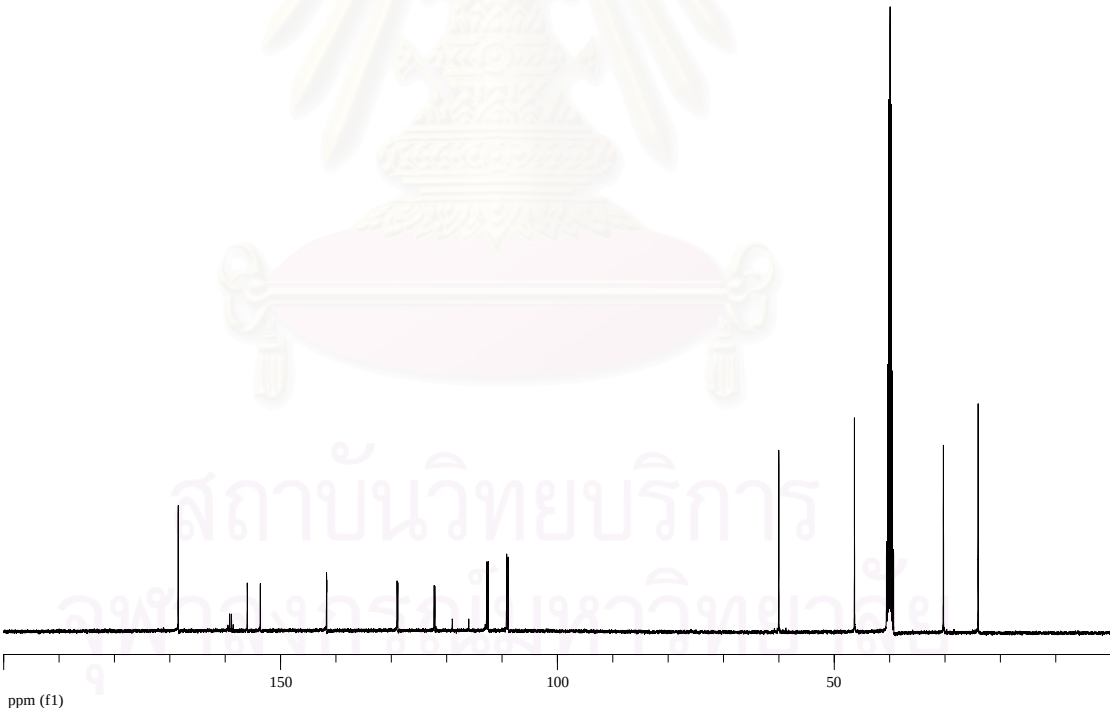


Figure 114 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (3´-chloro-5´-fluoro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28l)**

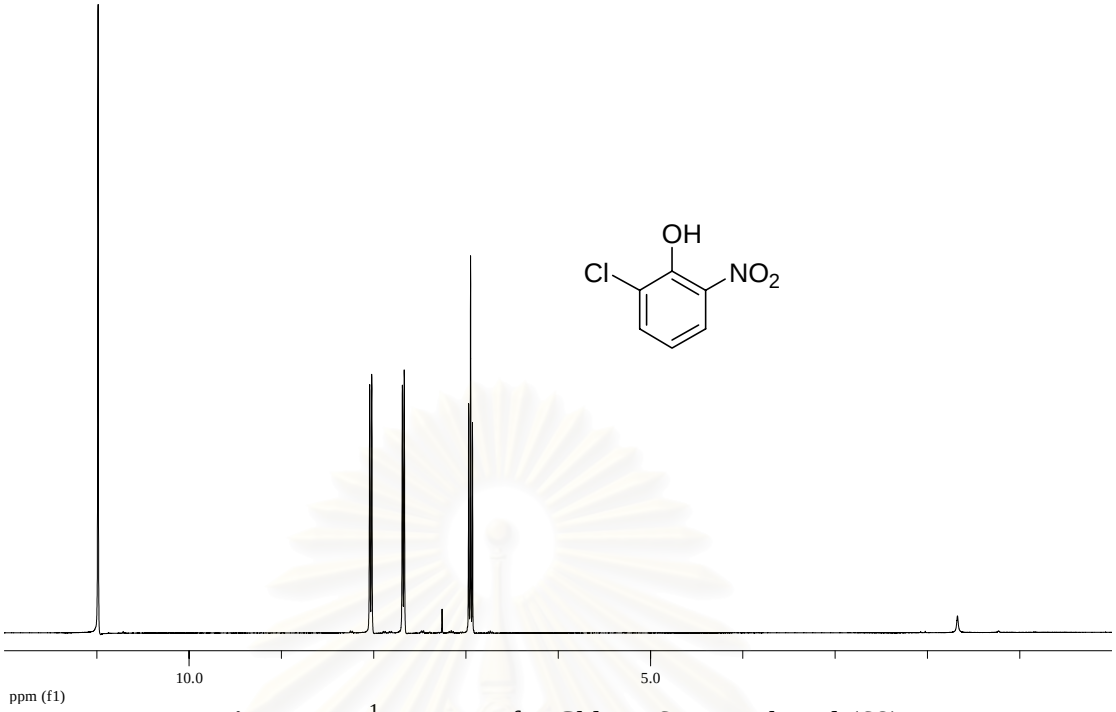


Figure 115 ^{1}H-NMR of 2-Chloro-6-nitro-phenol **(68)**

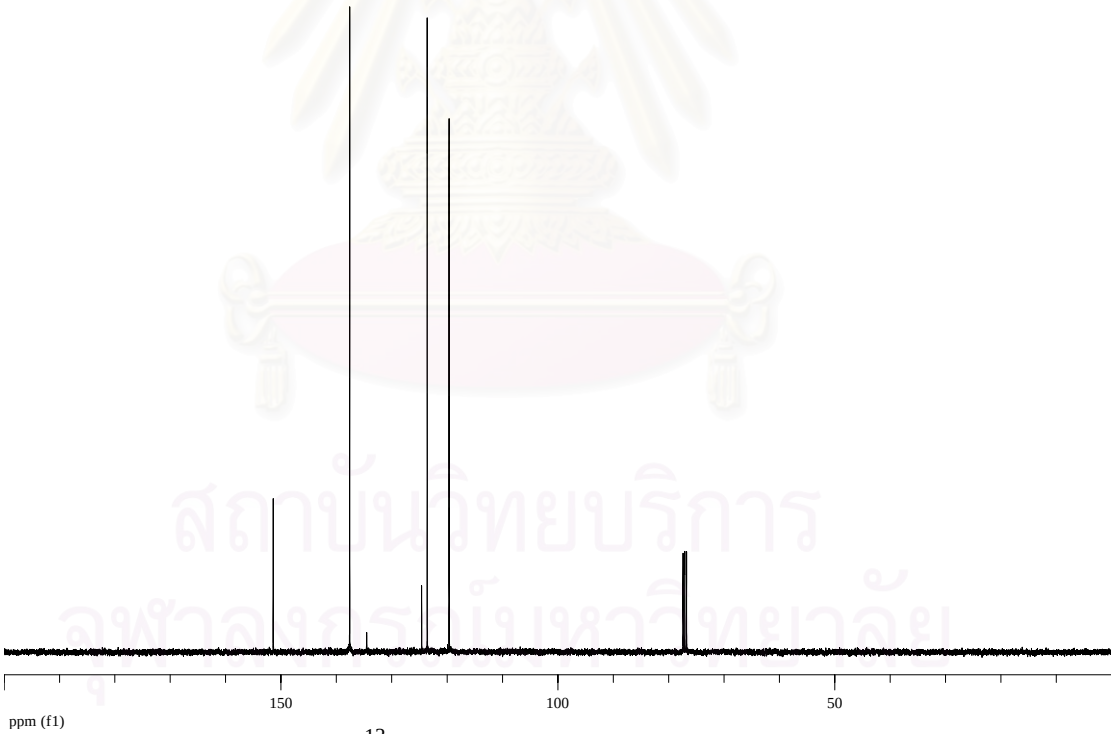


Figure 116 ^{13}C-NMR of 2-Chloro-6-nitro-phenol **(68)**

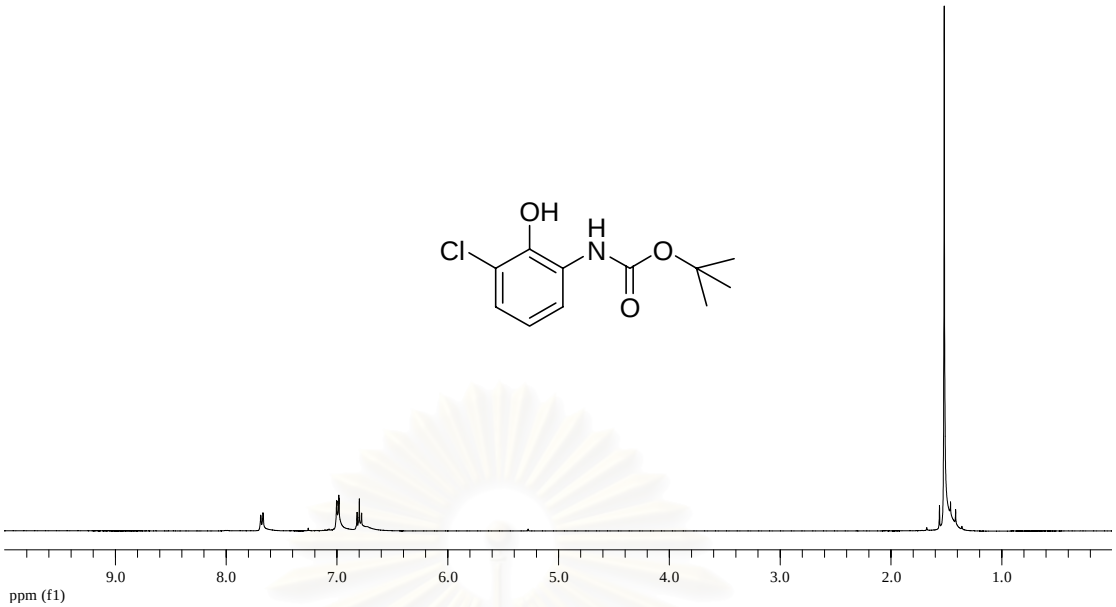


Figure 117 ^{1}H-NMR of (3-Chloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(69)**

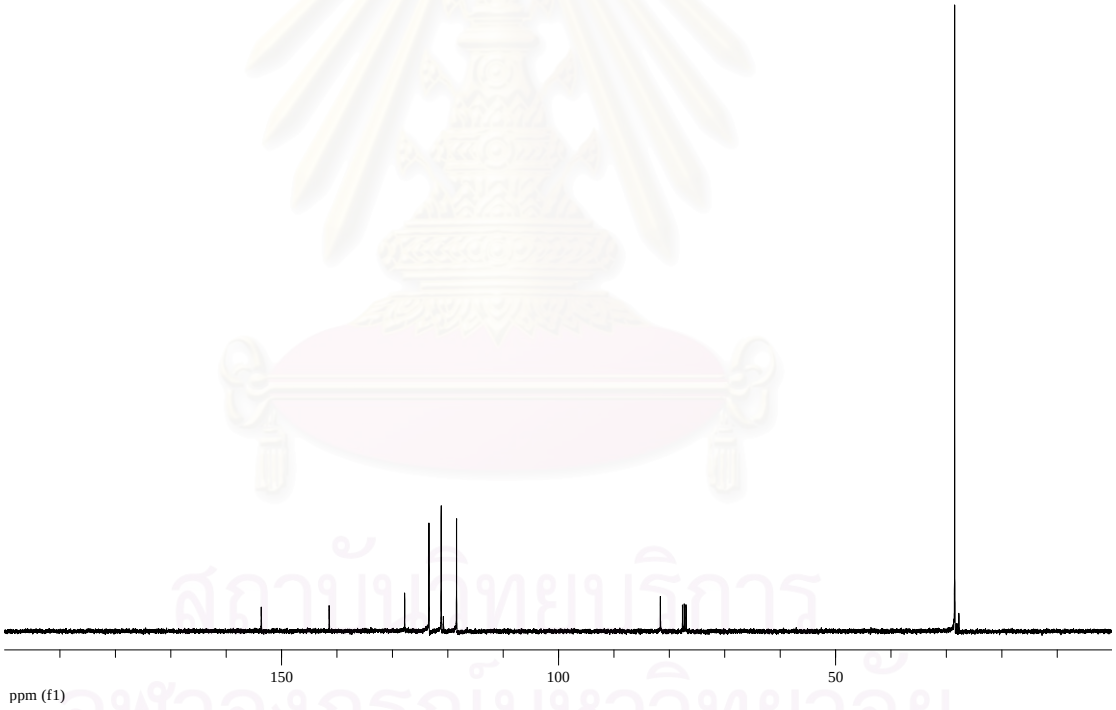


Figure 118 ^{13}C-NMR of (3-Chloro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(69)**

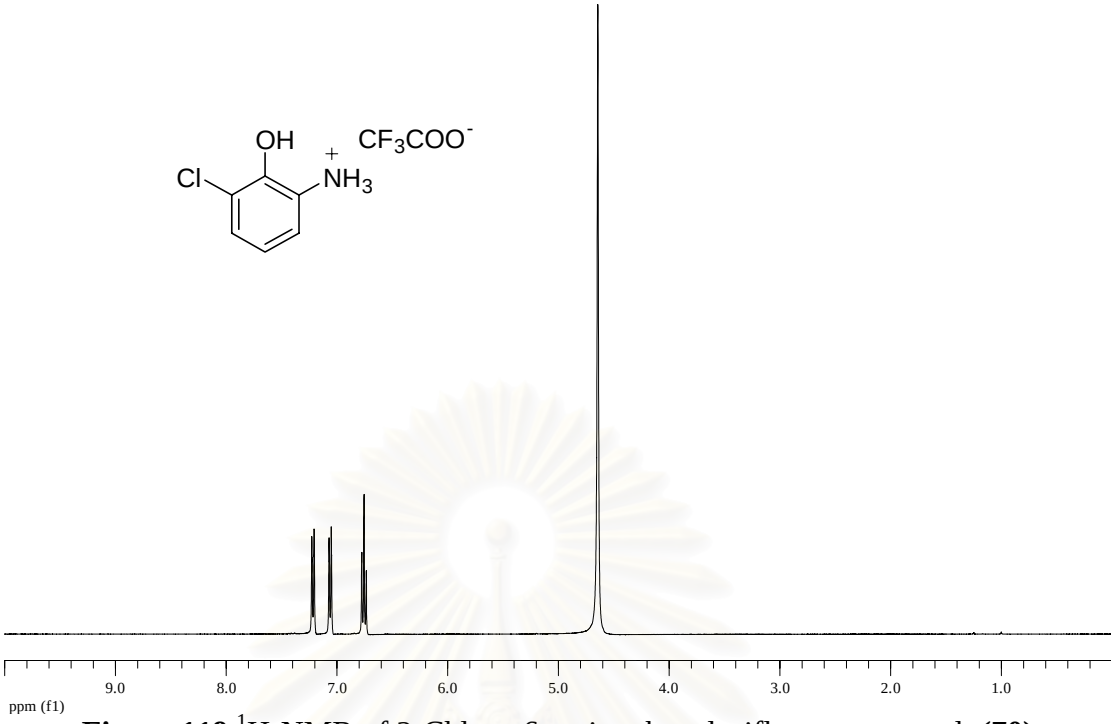


Figure 119 ^{1}H-NMR of 2-Chloro-6-aminophenol trifluoroacetate salt **(70)**

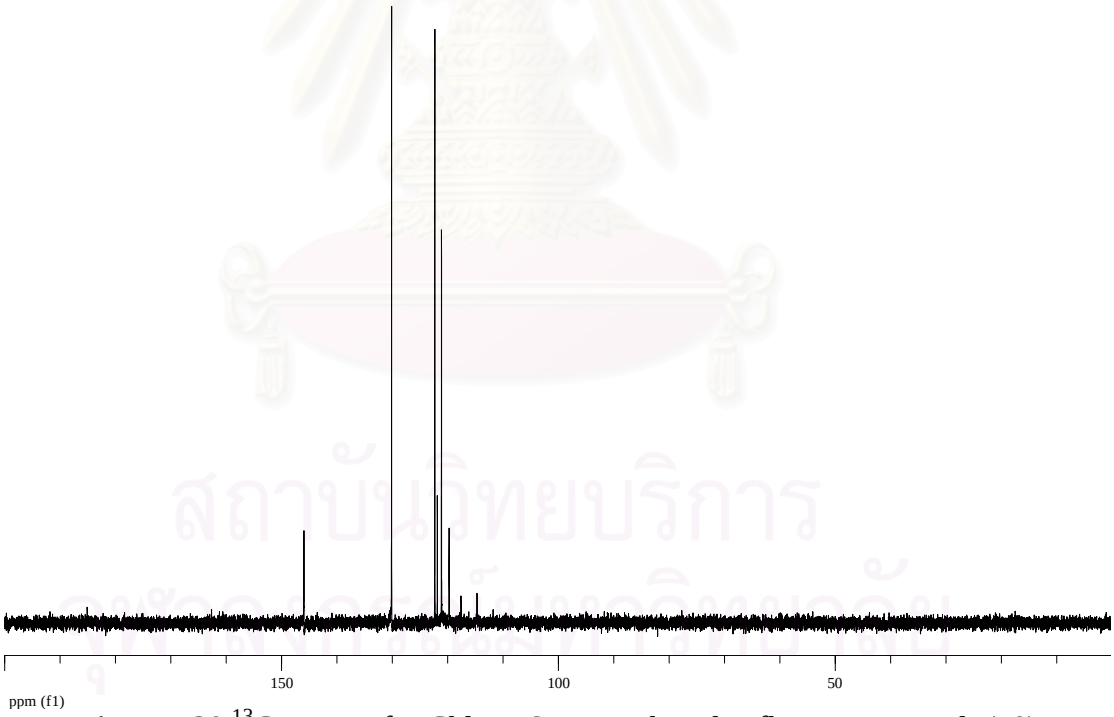


Figure 120 ^{13}C-NMR of 2-Chloro-6-aminophenol trifluoroacetate salt **(70)**

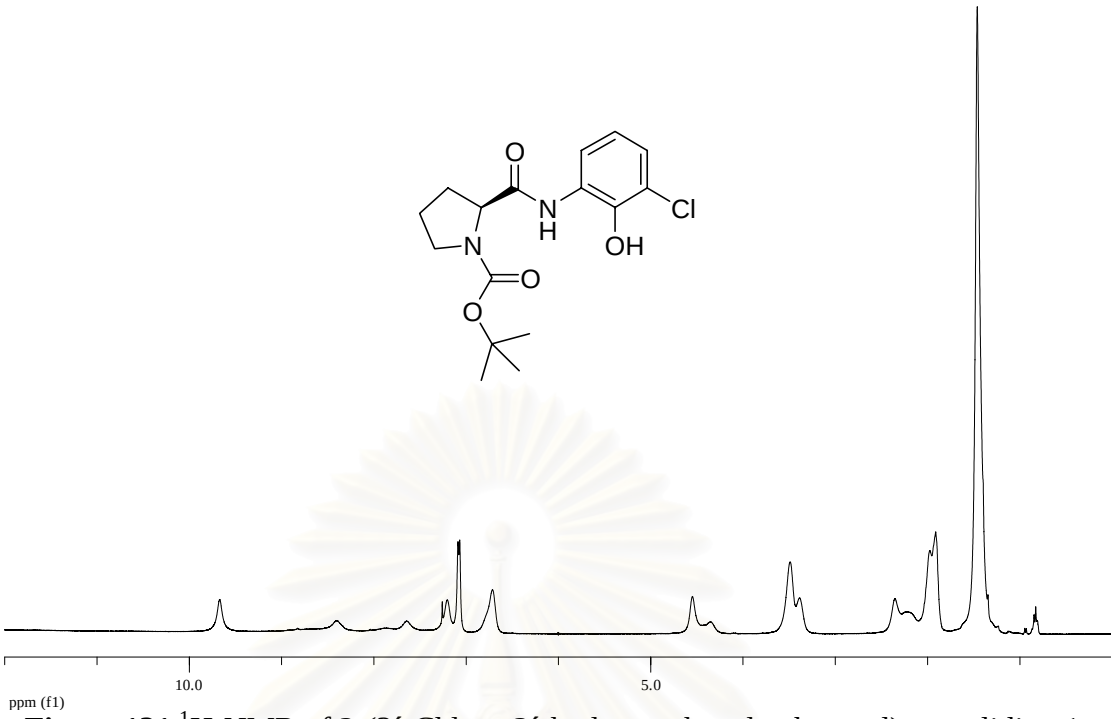


Figure 121 ^{1}H-NMR of 2-(3´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(71)**

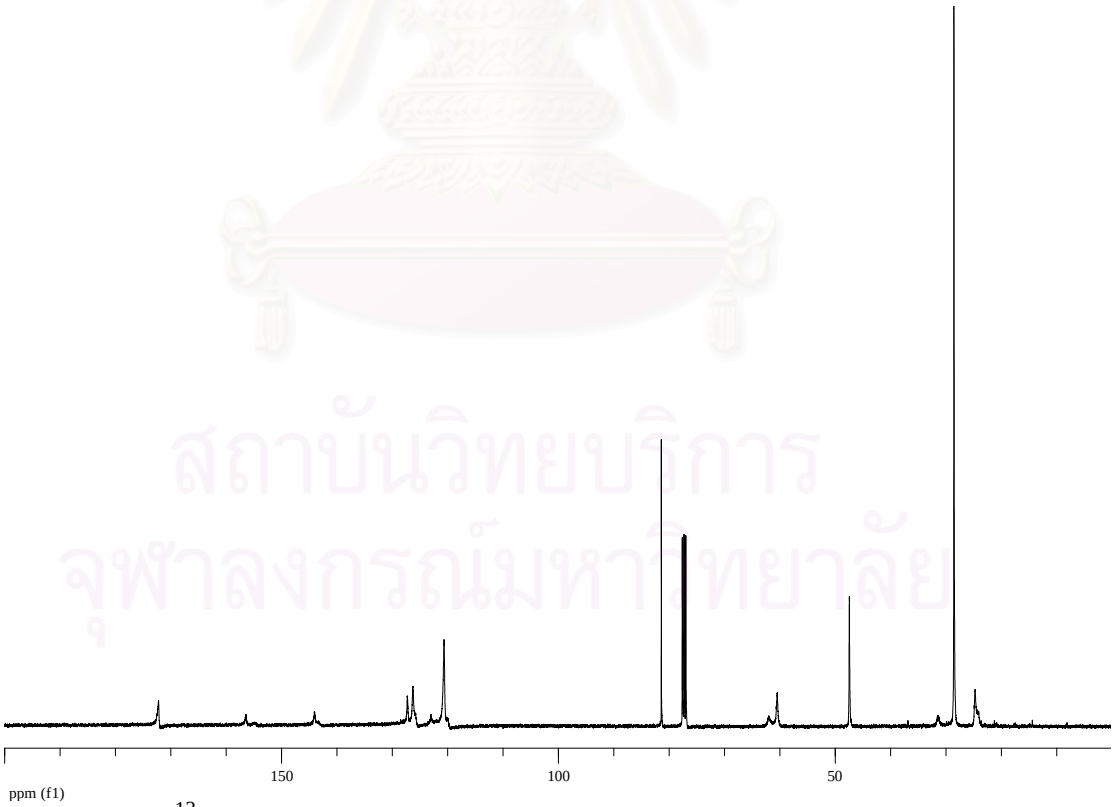


Figure 122 ^{13}C-NMR of 2-(3´-Chloro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(71)**

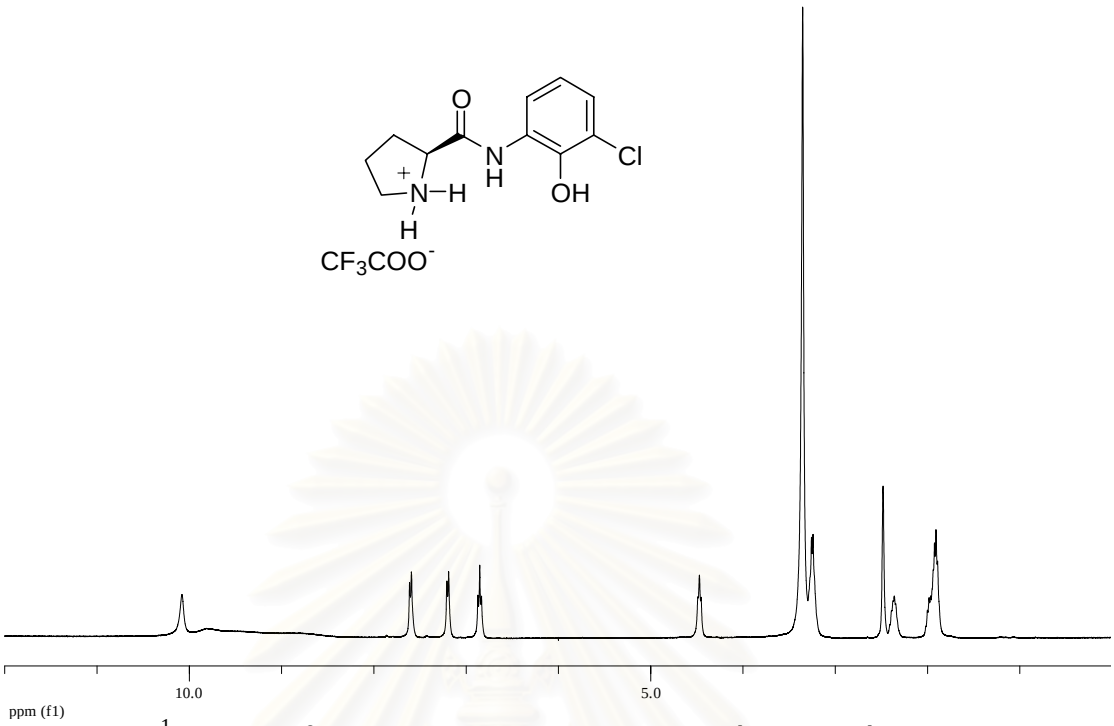


Figure 123 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (3´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28m)**

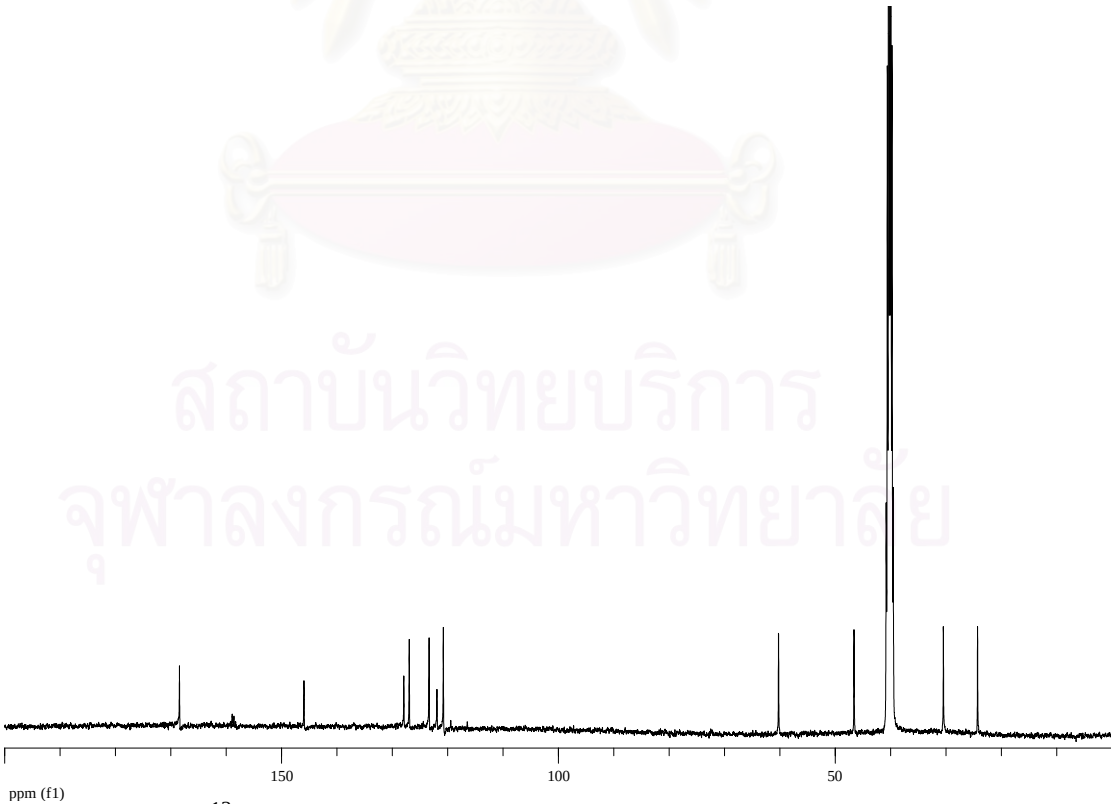


Figure 124 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (3´-chloro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28m)**

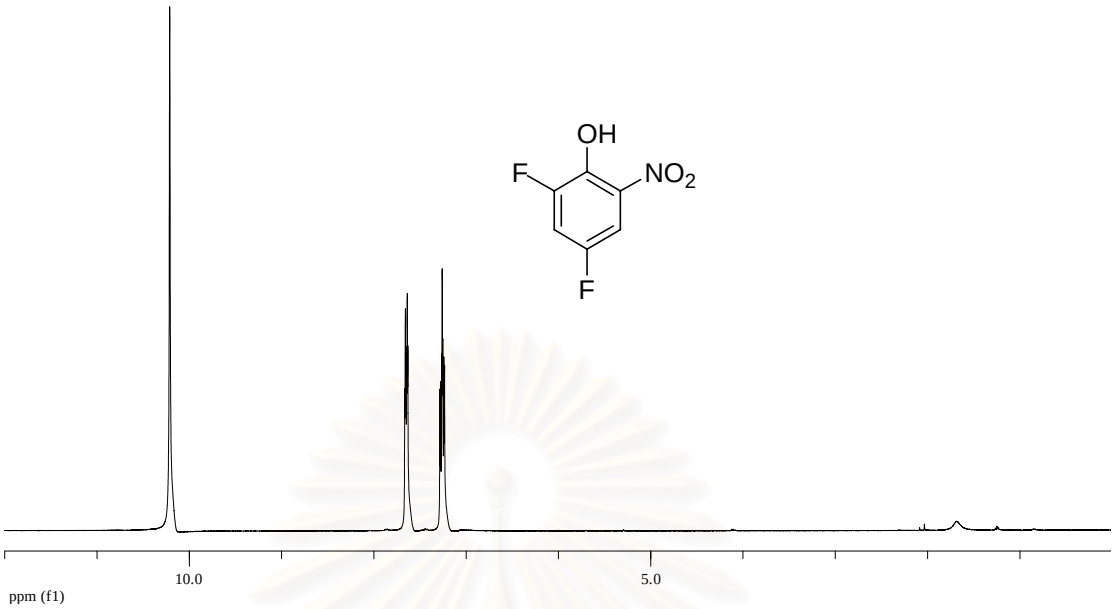


Figure 125 ^{1}H-NMR of 2,4-Difluoro-6-nitro-phenol **(72)**

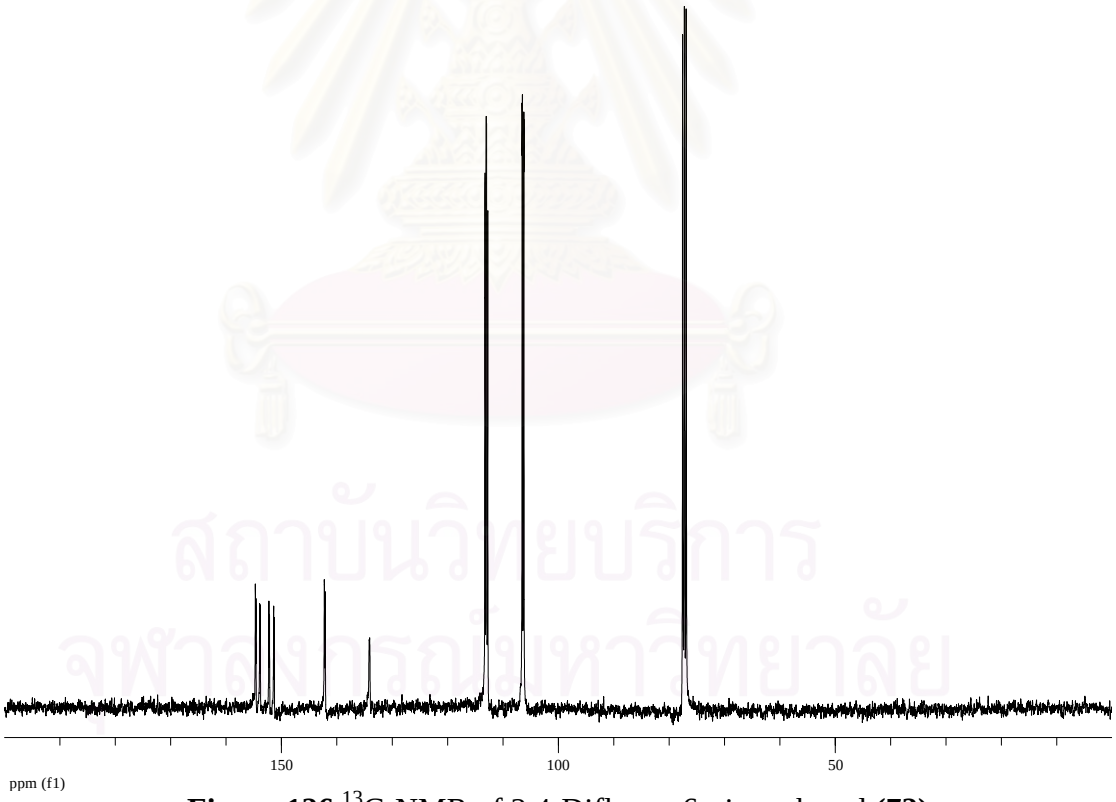


Figure 126 ^{13}C-NMR of 2,4-Difluoro-6-nitro-phenol **(72)**

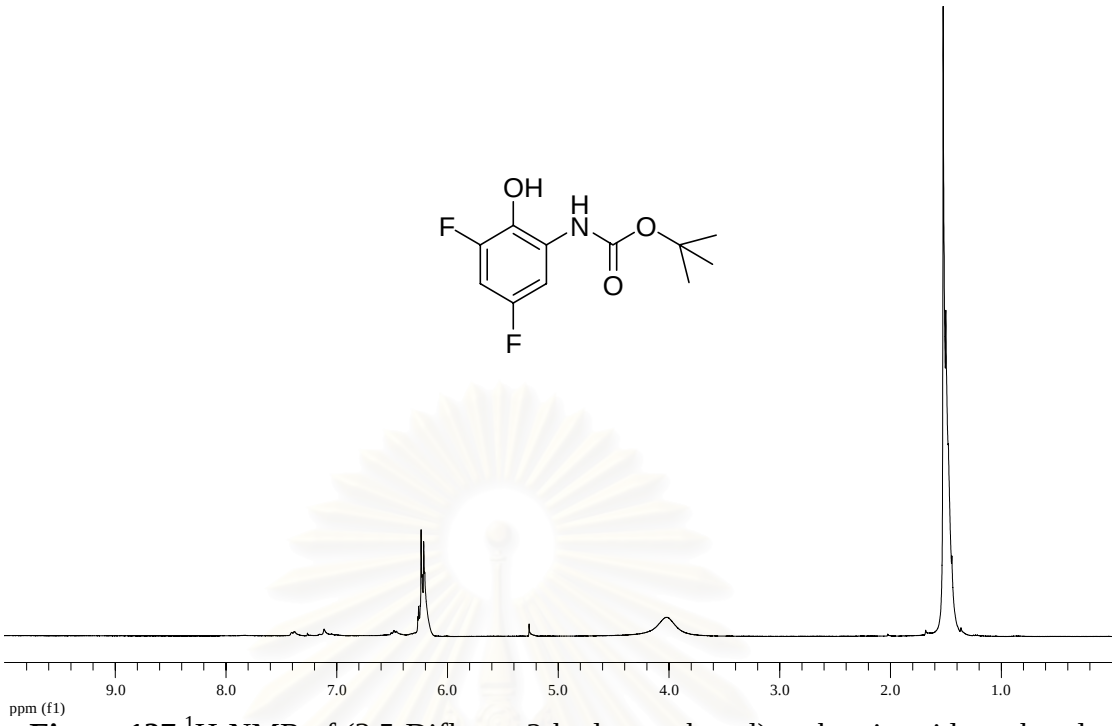


Figure 127 ^{1}H-NMR of (3,5-Difluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(73)**

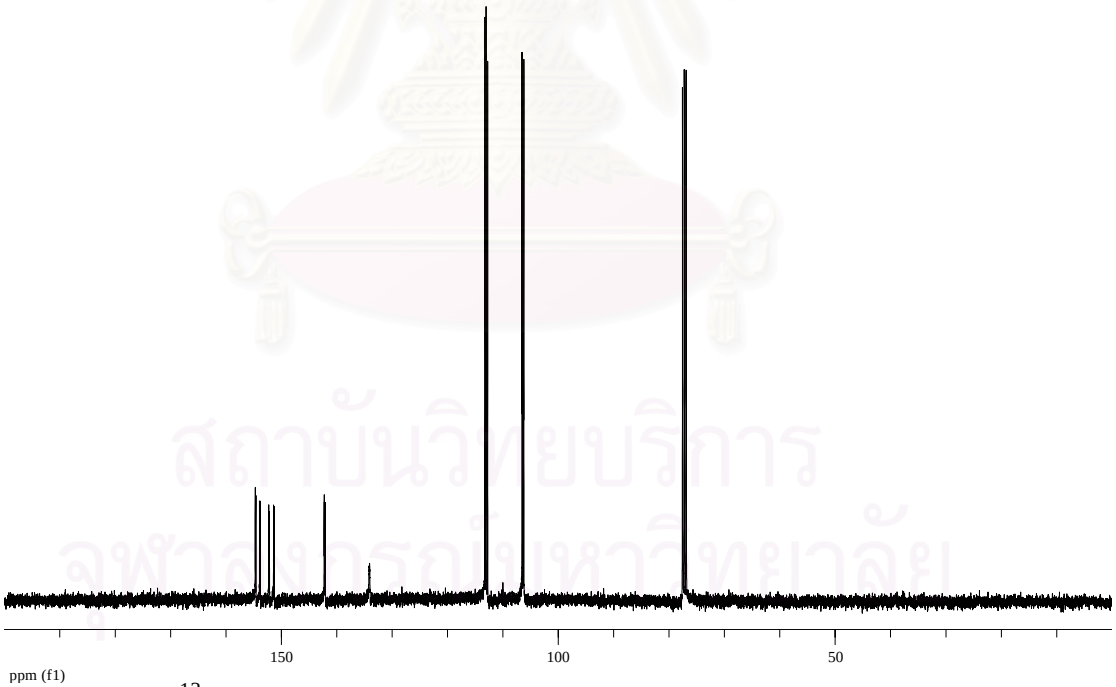


Figure 128 ^{13}C-NMR of (3,5-Difluoro-2-hydroxy-phenyl)-carbamic acid *tert*-butyl ester **(73)**

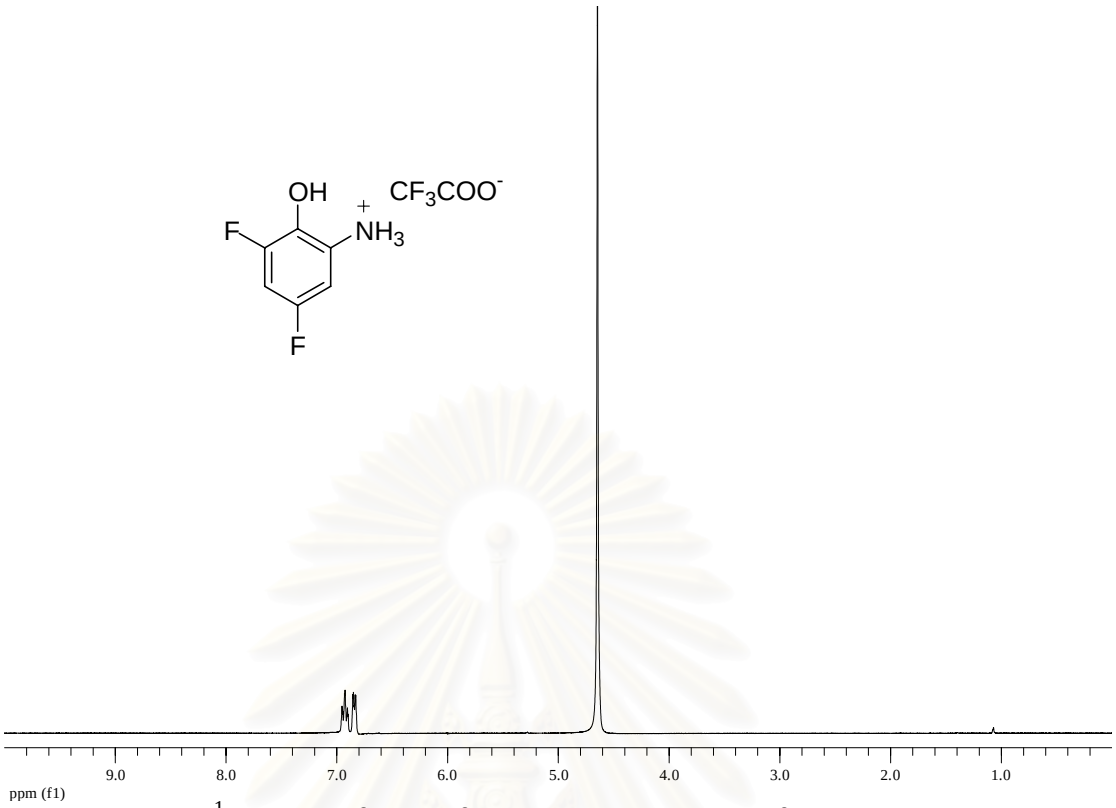


Figure 129 ^{1}H-NMR of 2,4-Difluoro-6-aminophenol trifluoroacetate salt **(74)**

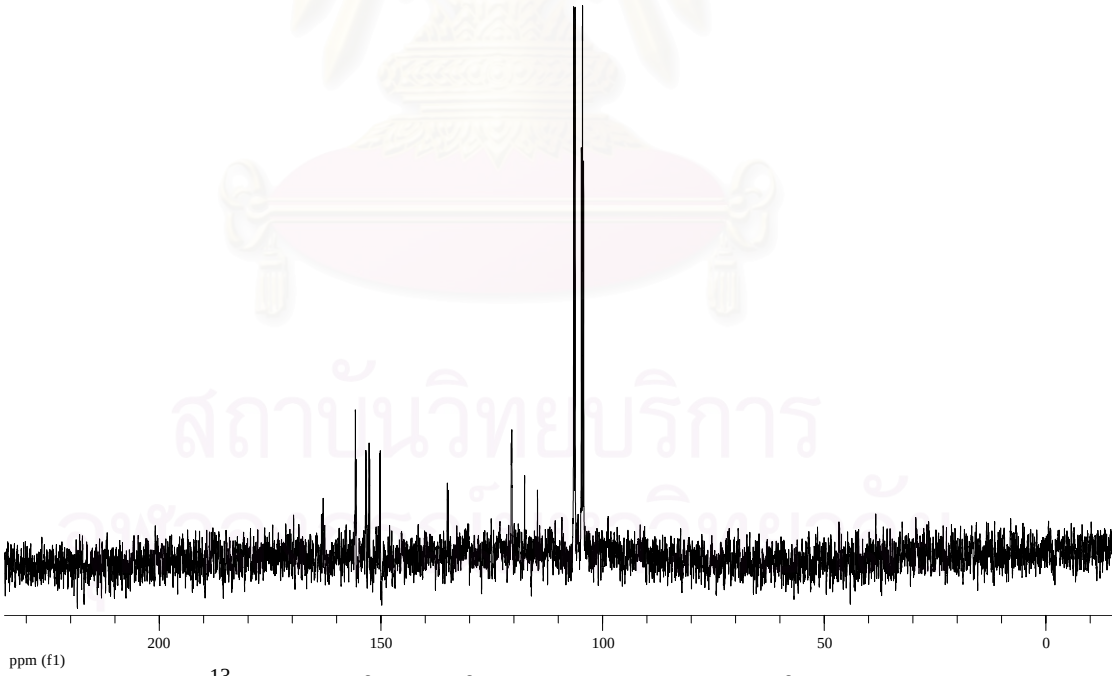


Figure 130 ^{13}C-NMR of 2,4-Difluoro-6-aminophenol trifluoroacetate salt **(74)**

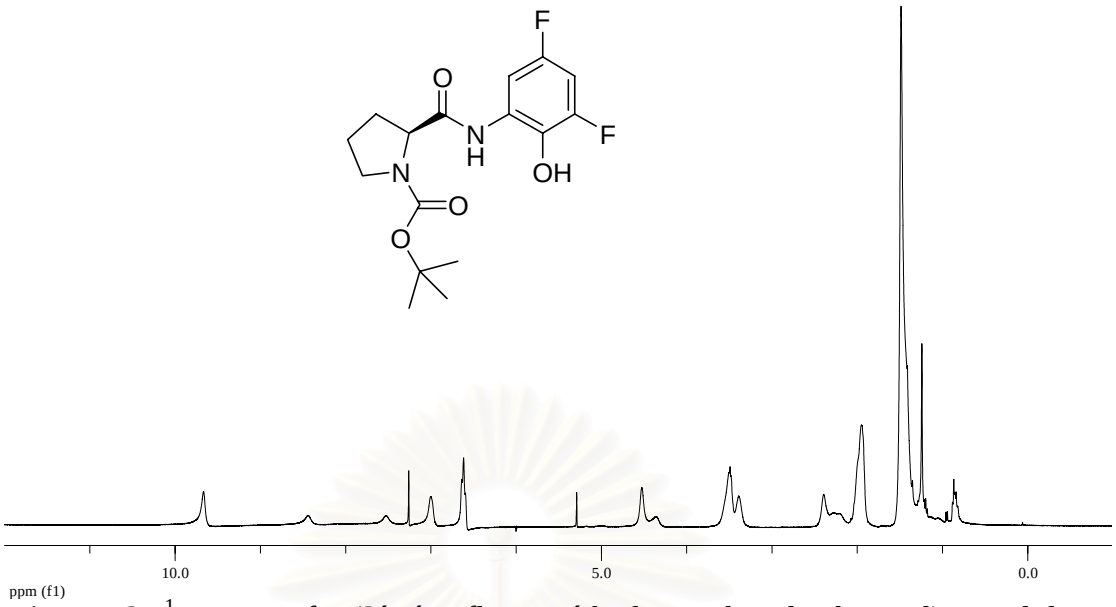


Figure 131 ^{1}H-NMR of 2-(3´,5´-Difluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(75)**

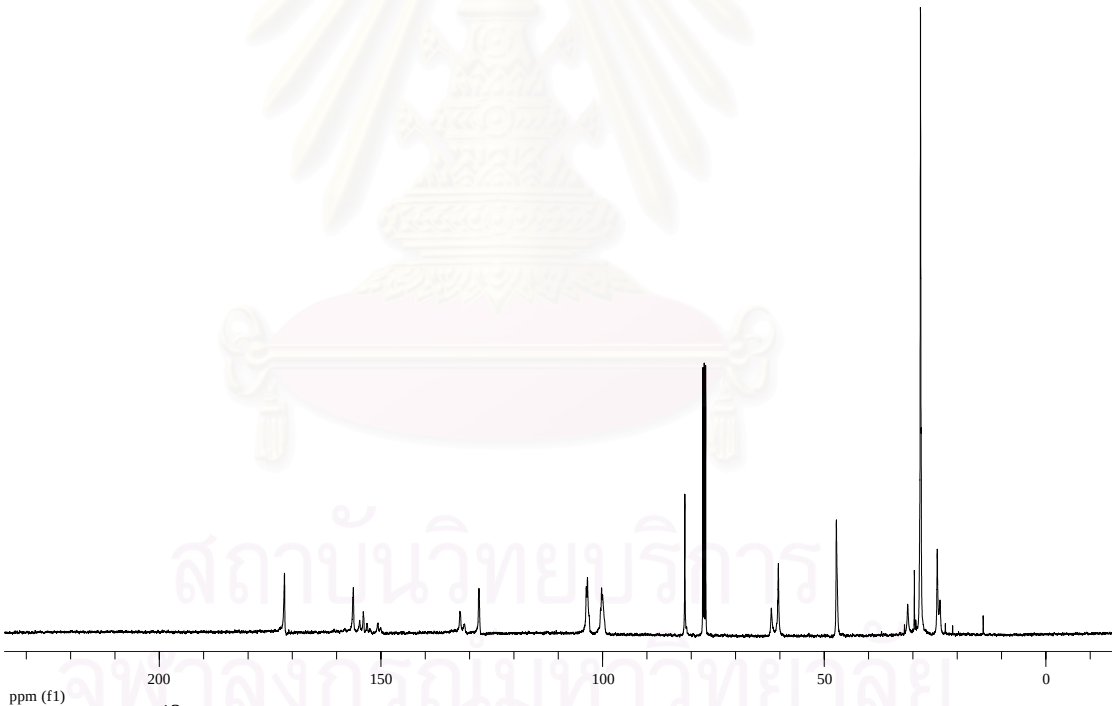


Figure 132 ^{13}C-NMR of 2-(3´,5´-Difluoro-2´-hydroxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(75)**

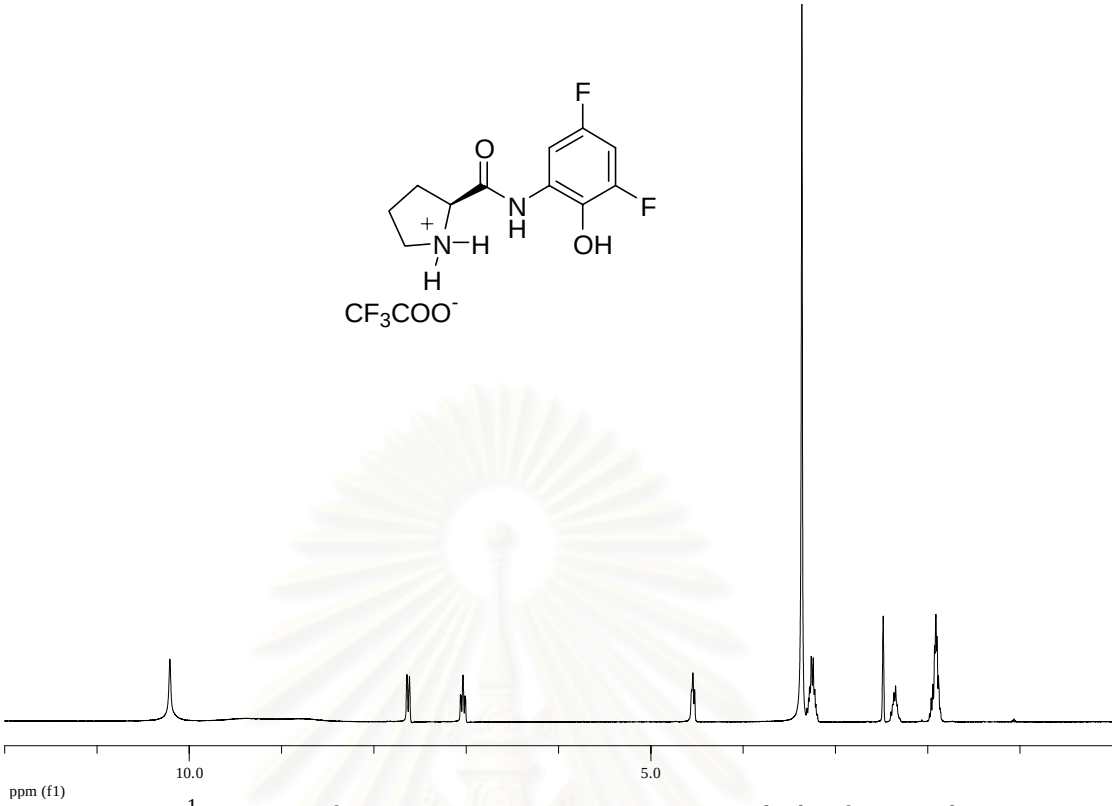


Figure 133 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (3´,5´-difluoro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28n)**

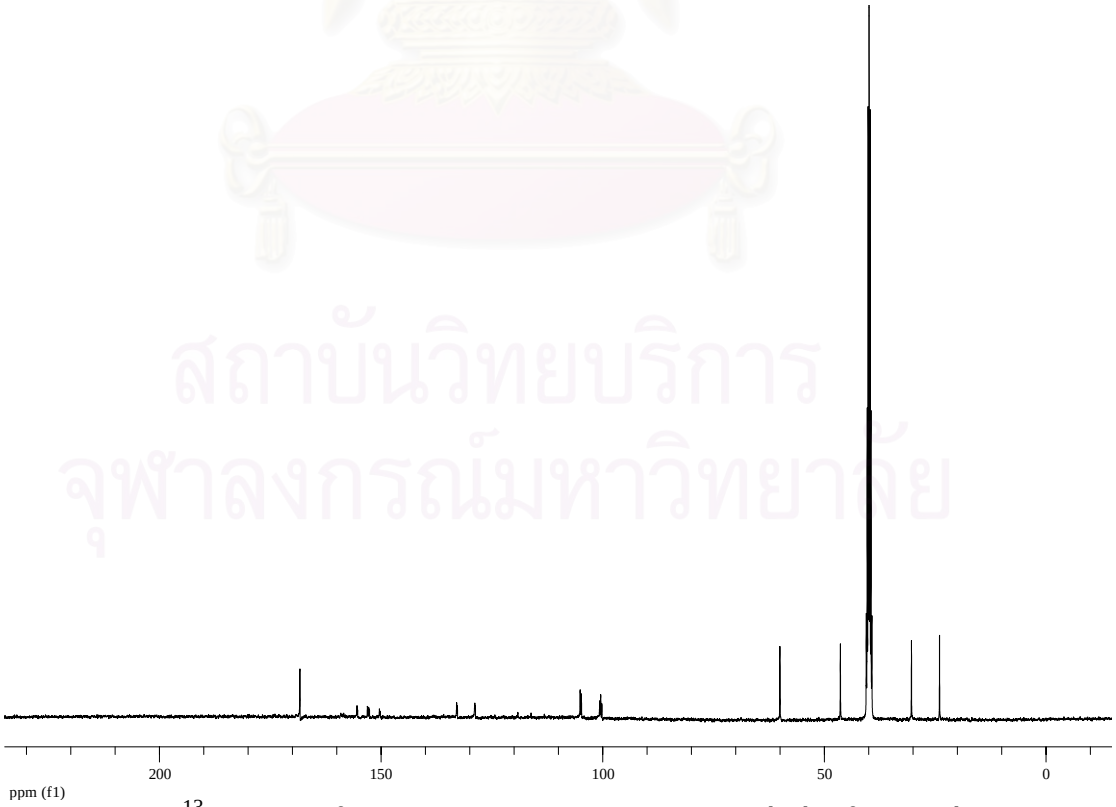


Figure 134 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (3´,5´-difluoro-2´-hydroxy-phenyl)-amide trifluoroacetate **(28n)**

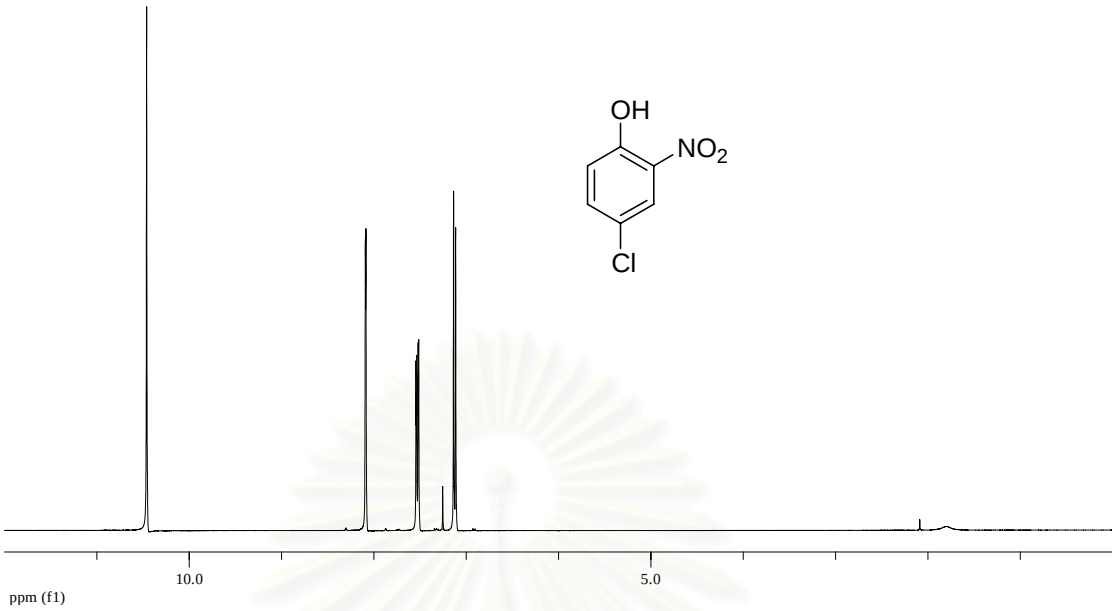


Figure 135 ^{1}H-NMR of 4-Chloro-2-nitro-phenol **(76)**

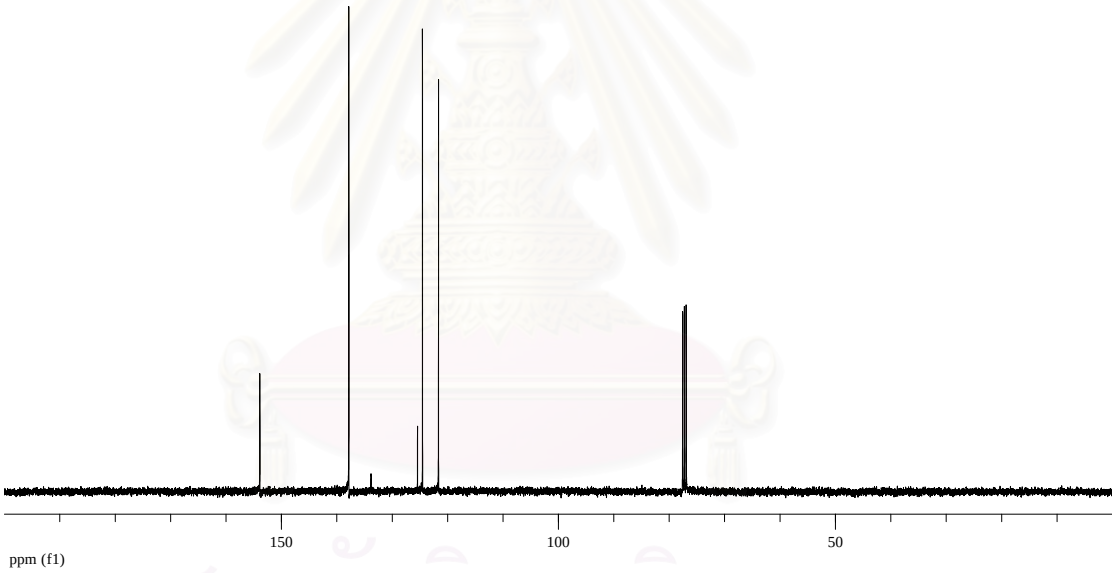


Figure 136 ^{13}C-NMR of 4-Chloro-2-nitro-phenol **(76)**

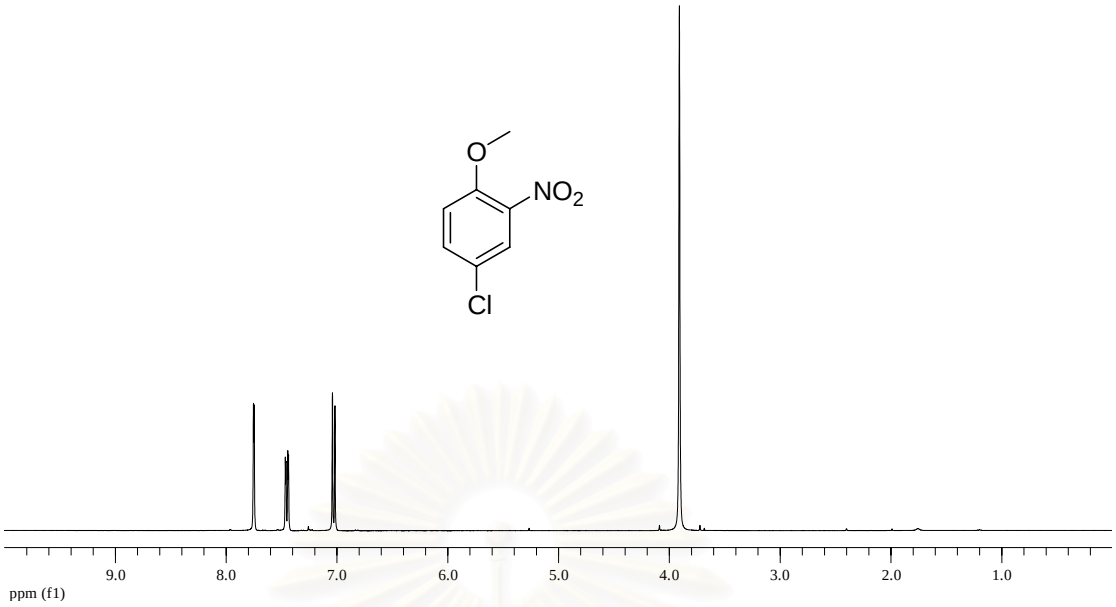


Figure 137 ^{1}H-NMR of 4-Chloro-1-methoxy-2-nitro-benzene **(77)**

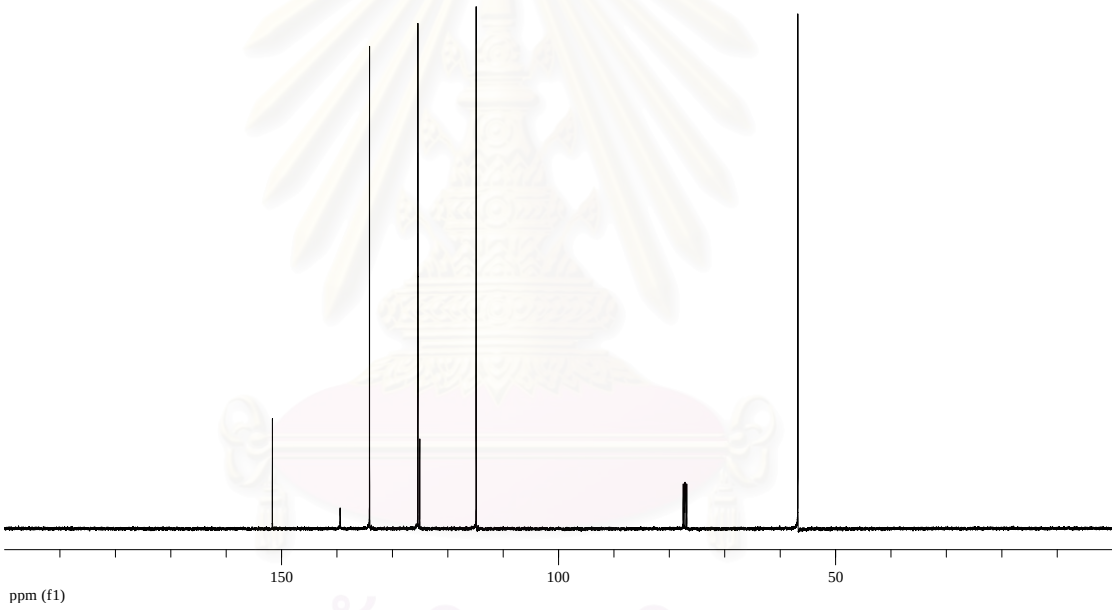


Figure 138 ^{13}C-NMR of 4-Chloro-1-methoxy-2-nitro-benzene **(77)**

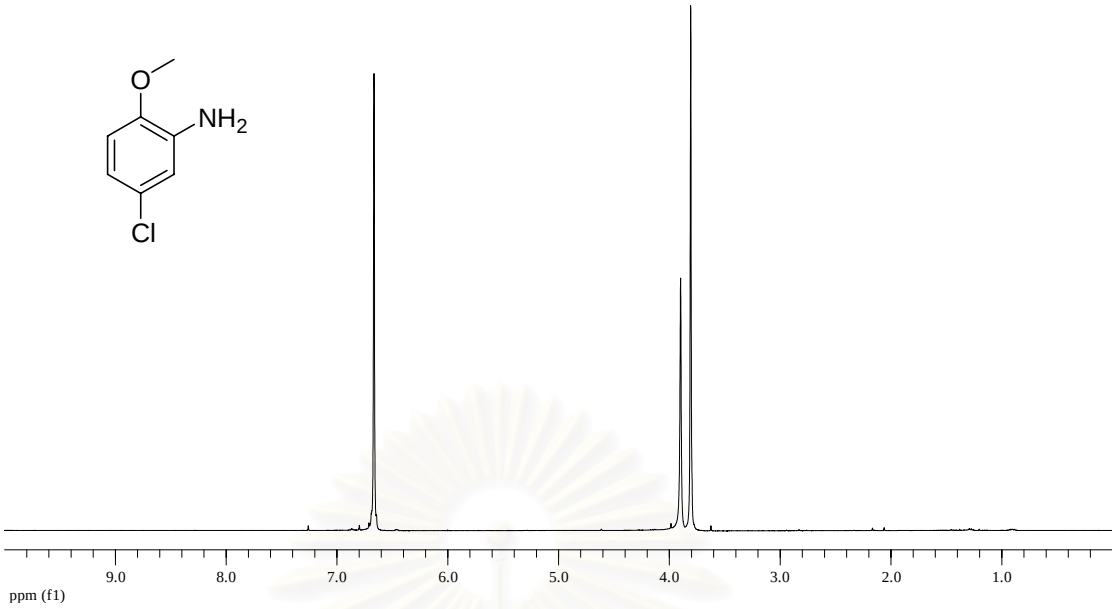


Figure 139 ^{1}H-NMR of 5-Chloro-2-methoxy-phenyl-ammonium trifluoroacetate **(78)**

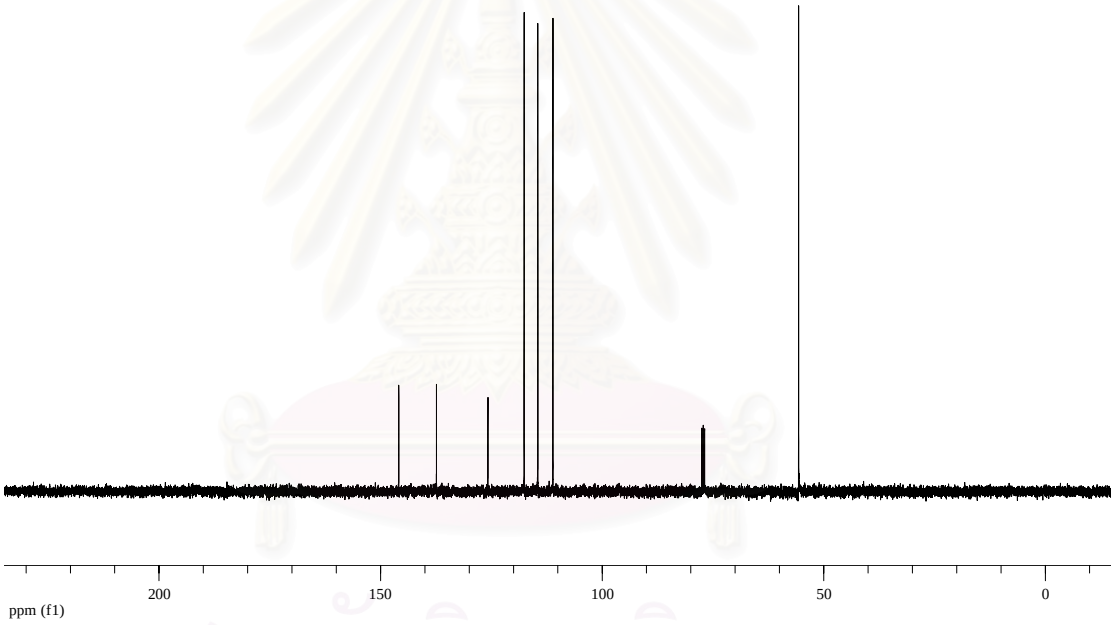


Figure 140 ^{13}C-NMR of 5-Chloro-2-methoxy-phenyl-ammonium trifluoroacetate **(78)**

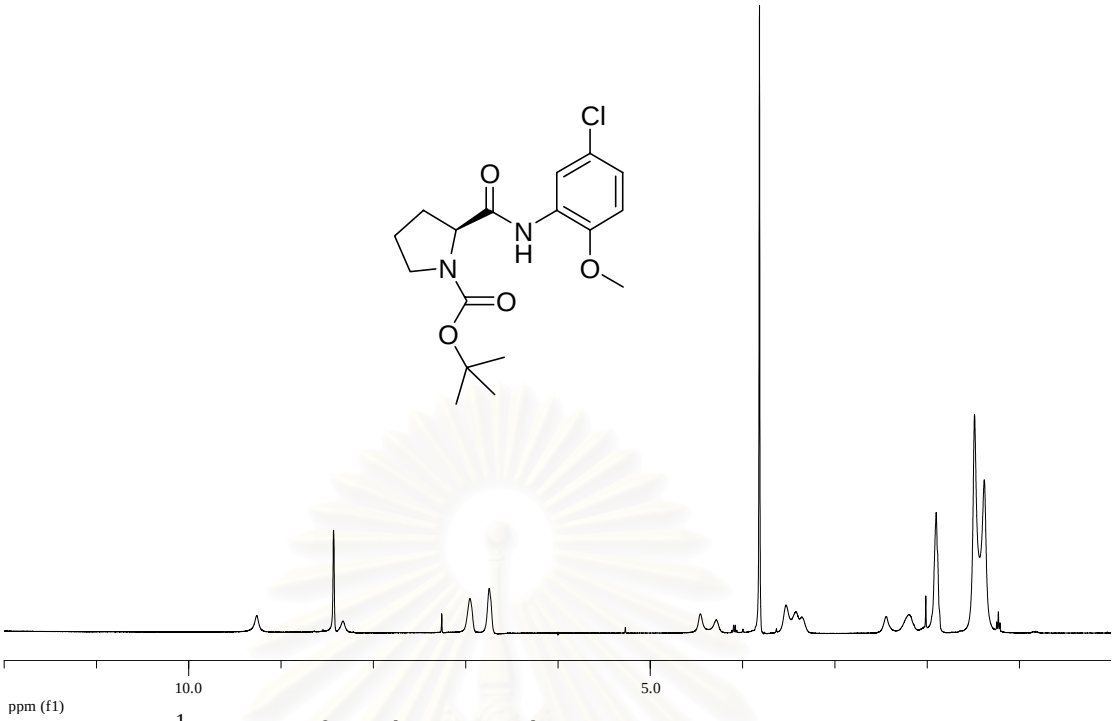


Figure 141 ^{1}H-NMR of 2-(5´-Chloro-2´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(79)**

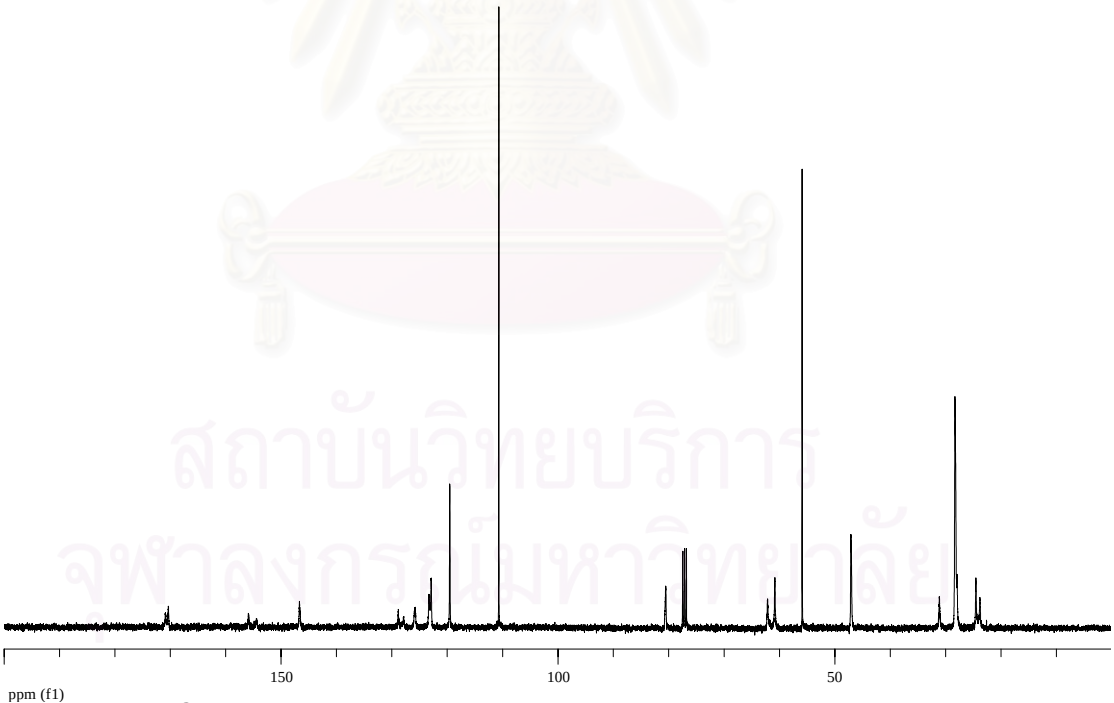


Figure 142 ^{13}C-NMR of 2-(5´-Chloro-2´-methoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **(79)**

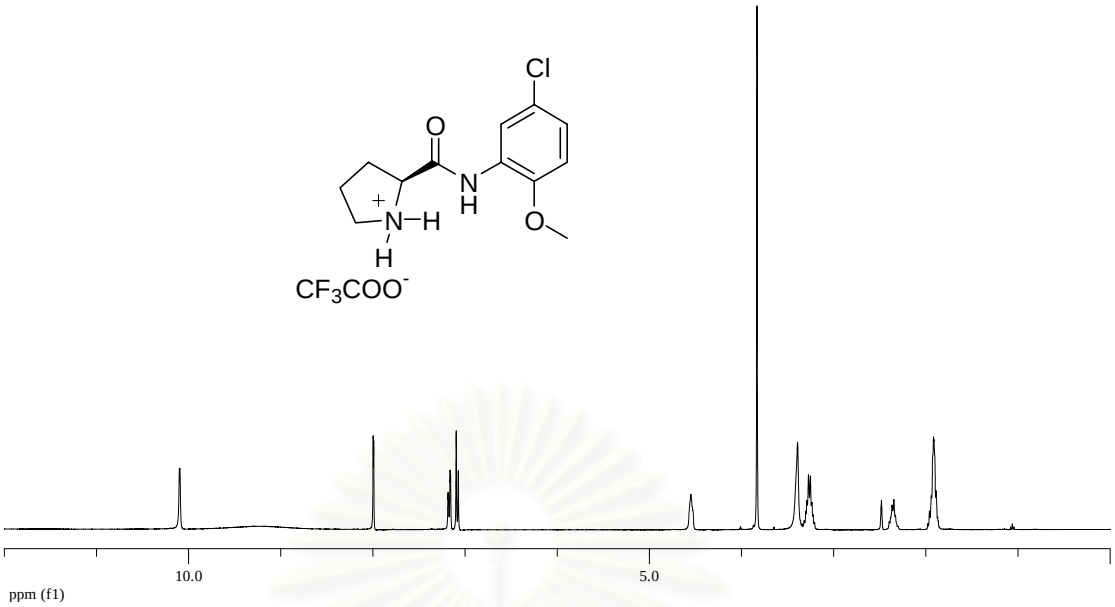


Figure 143 ^{1}H-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-methoxy-phenyl)-amide trifluoroacetate **(28q)**

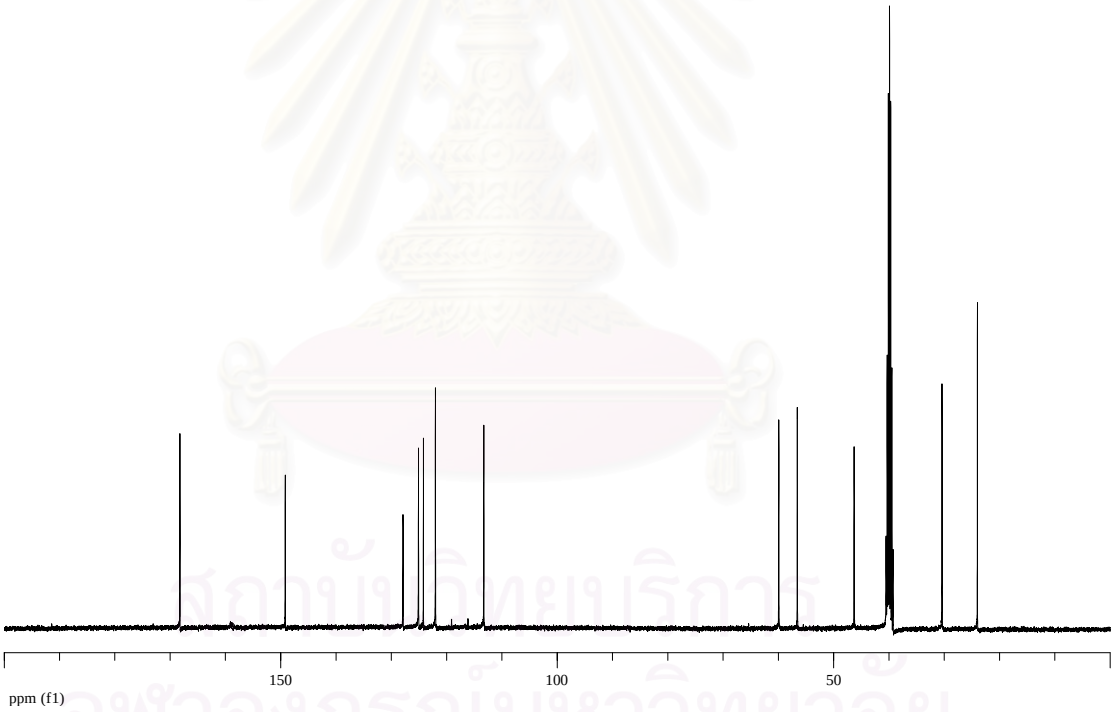


Figure 144 ^{13}C-NMR of Pyrrolidine-2-carboxylic acid (5´-chloro-2´-methoxy-phenyl)-amide trifluoroacetate **(28q)**

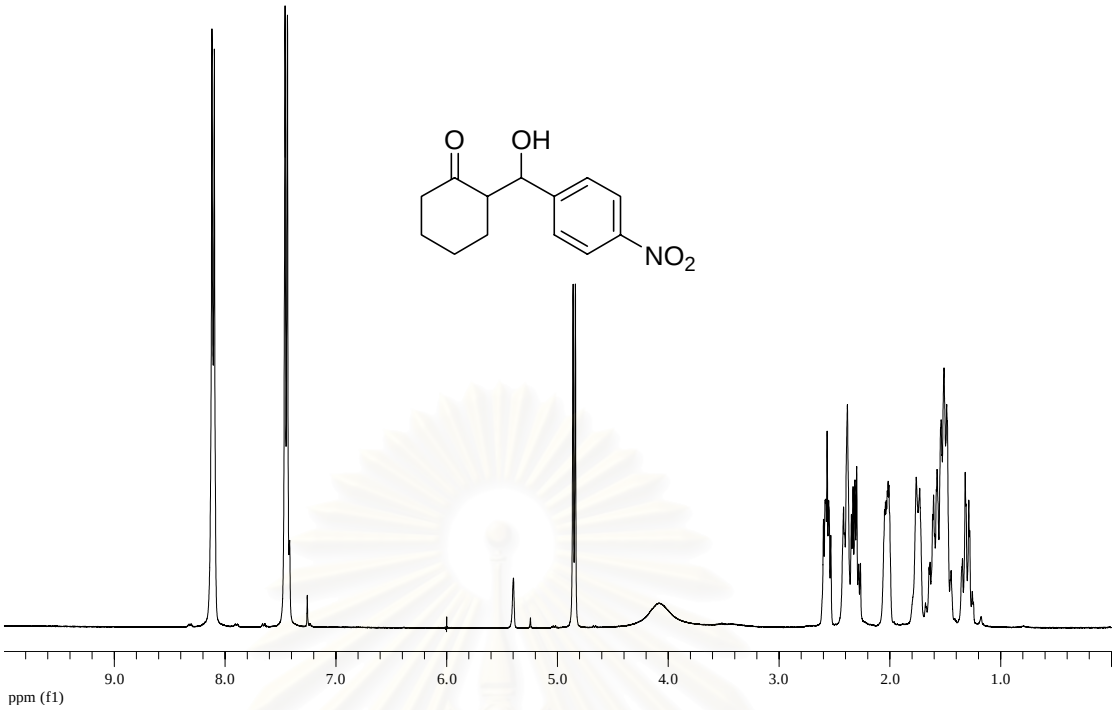


Figure 145 ^{1}H-NMR of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(81a)**

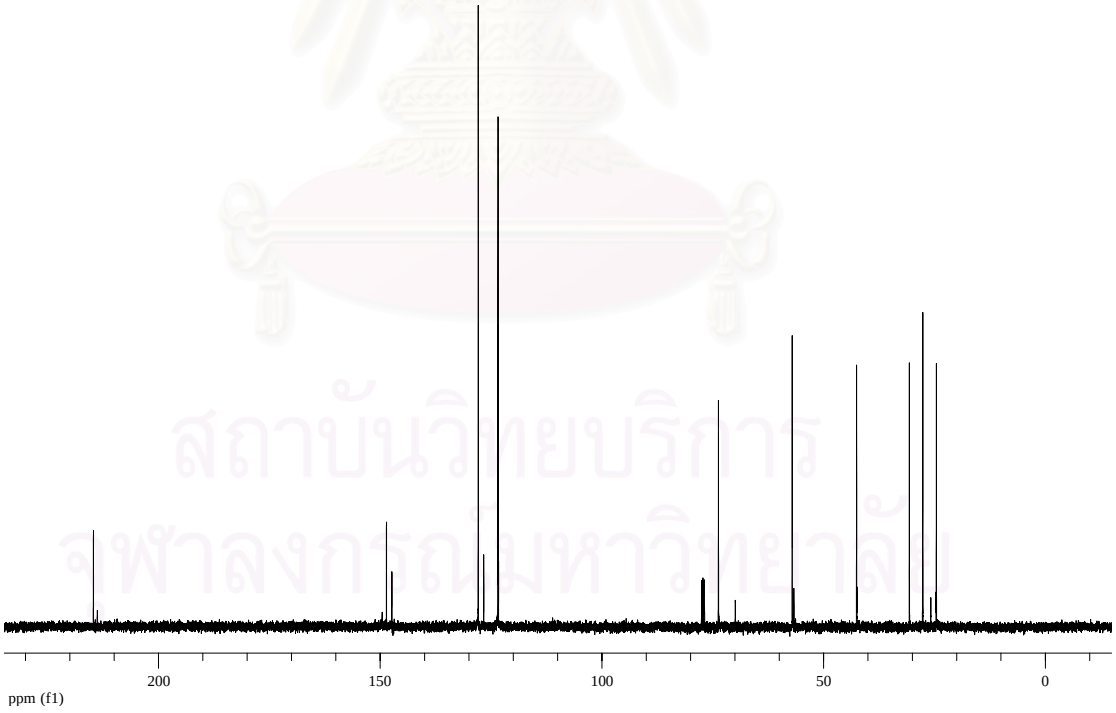


Figure 146 ^{13}C-NMR of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(81a)**

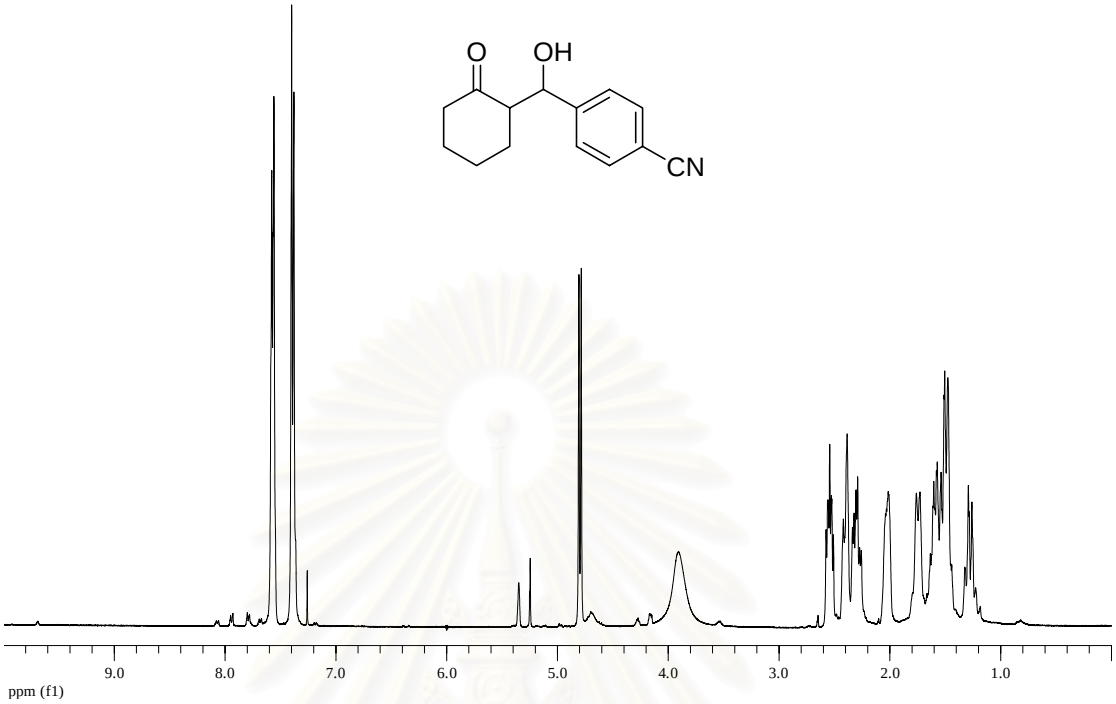


Figure 147 ^{1}H-NMR of 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(81b)**

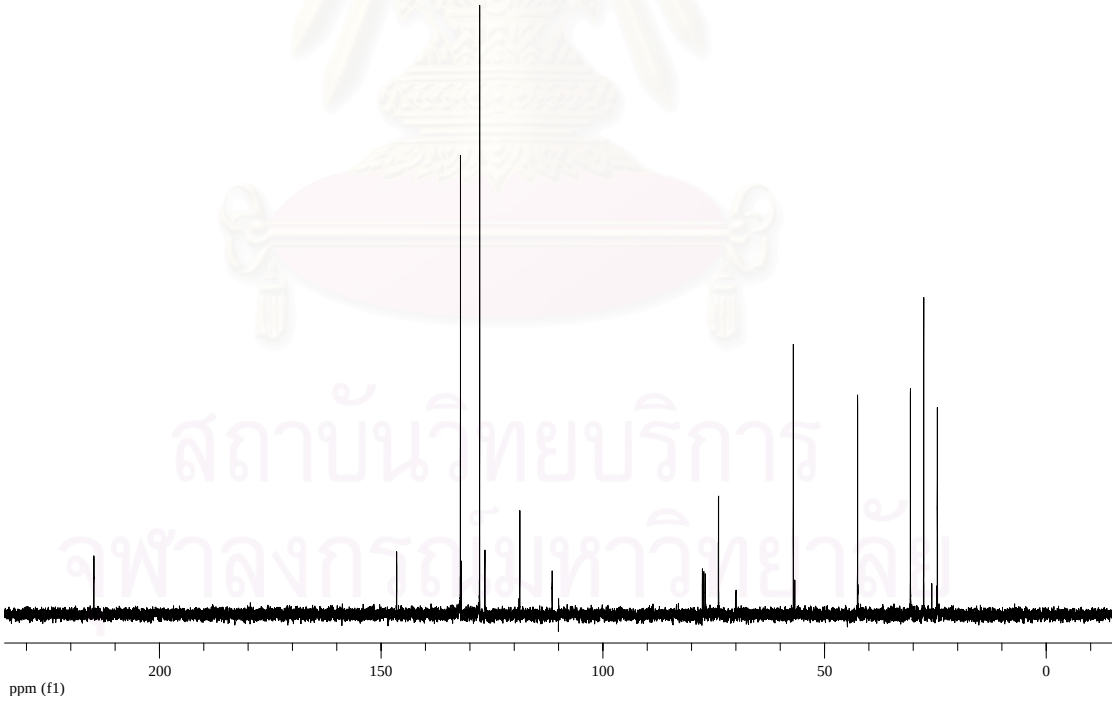


Figure 148 ^{13}C-NMR of 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(81b)**

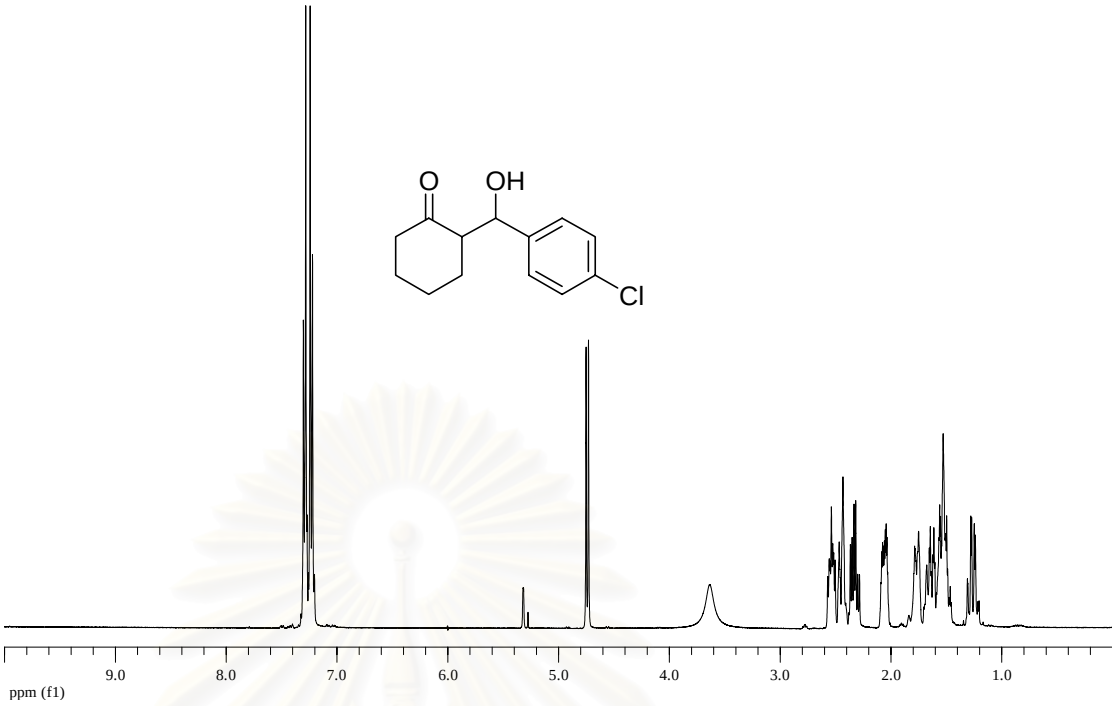


Figure 149 ^{1}H-NMR of 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(81c)**

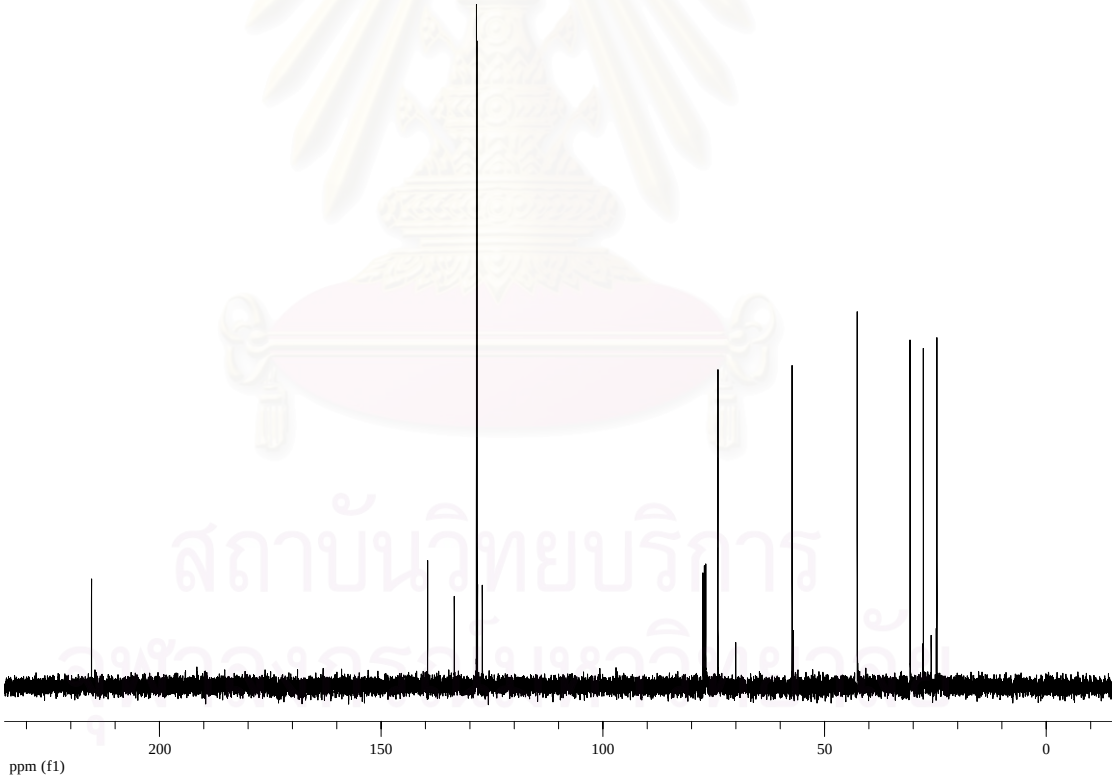


Figure 150 ^{13}C-NMR of 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(81c)**

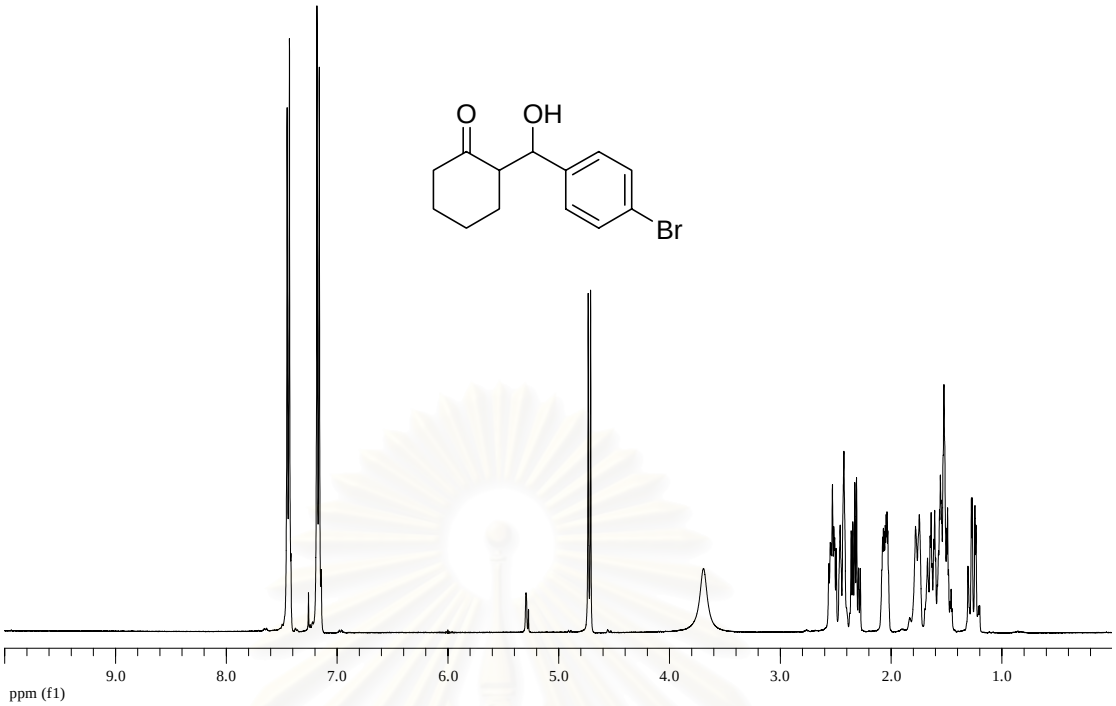


Figure 151 ^{1}H-NMR of 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(81d)**

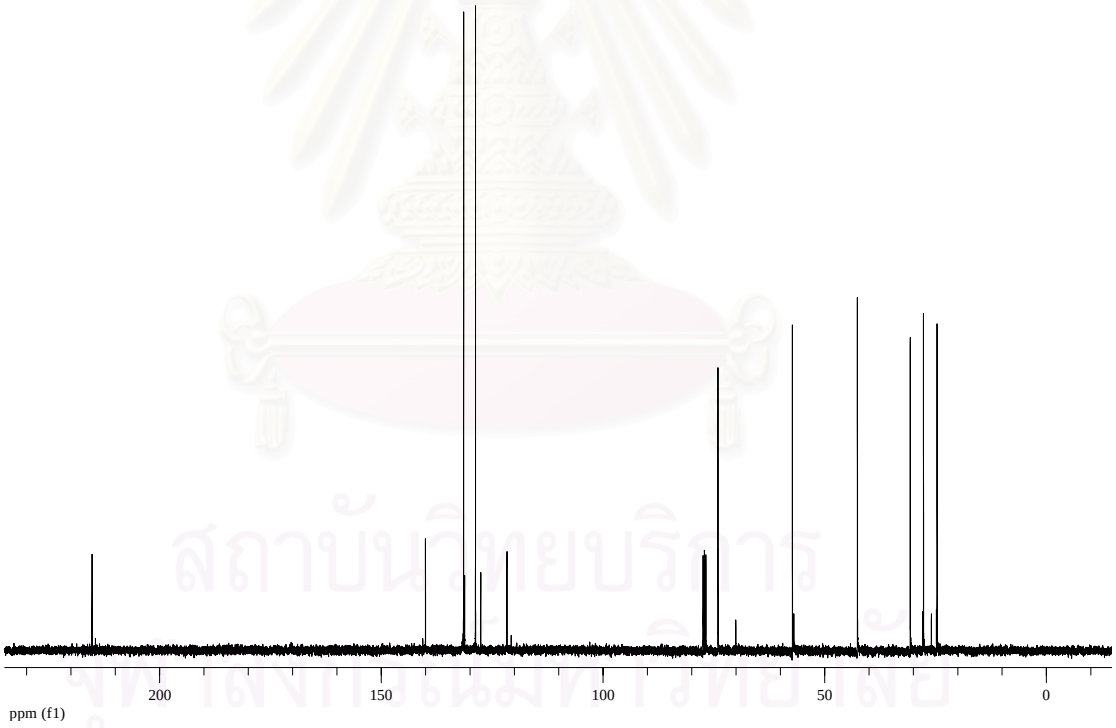


Figure 152 ^{13}C-NMR of 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(81d)**

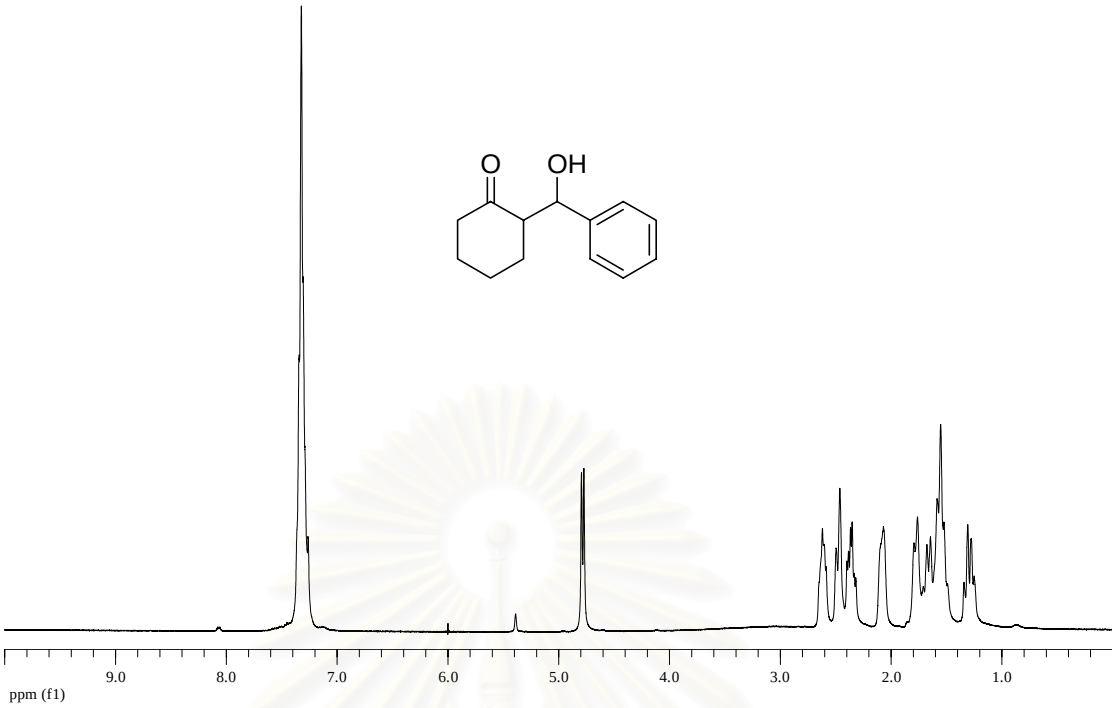


Figure 153 ^{1}H-NMR of 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(81e)**

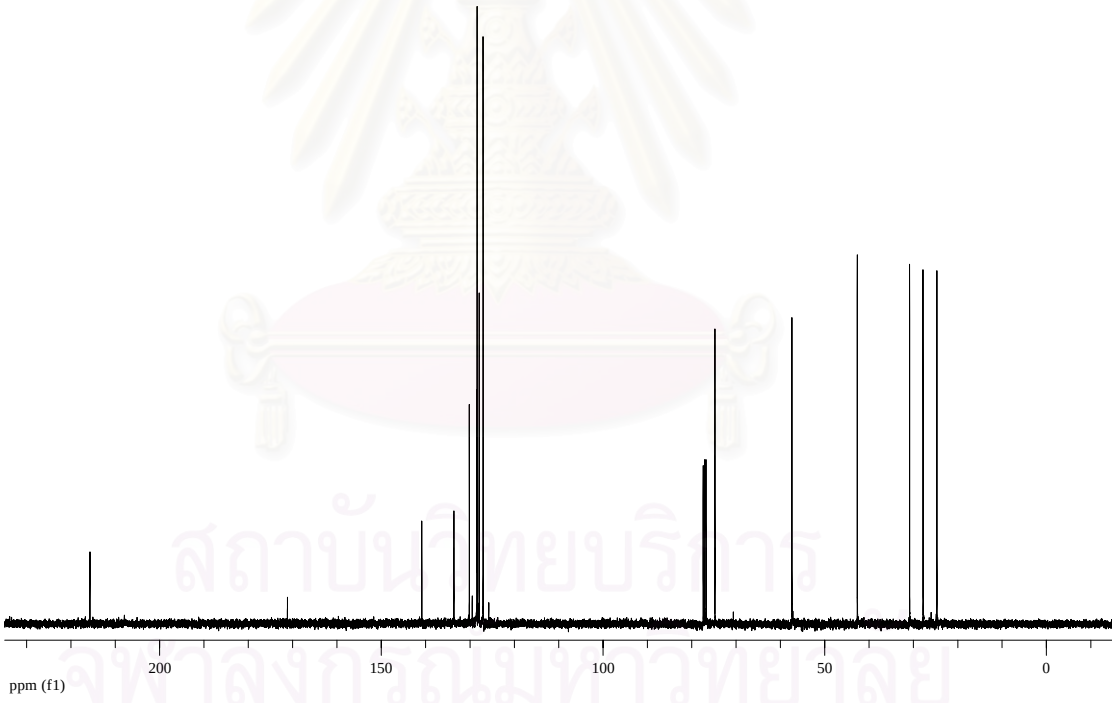


Figure 154 ^{13}C-NMR of 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(81e)**

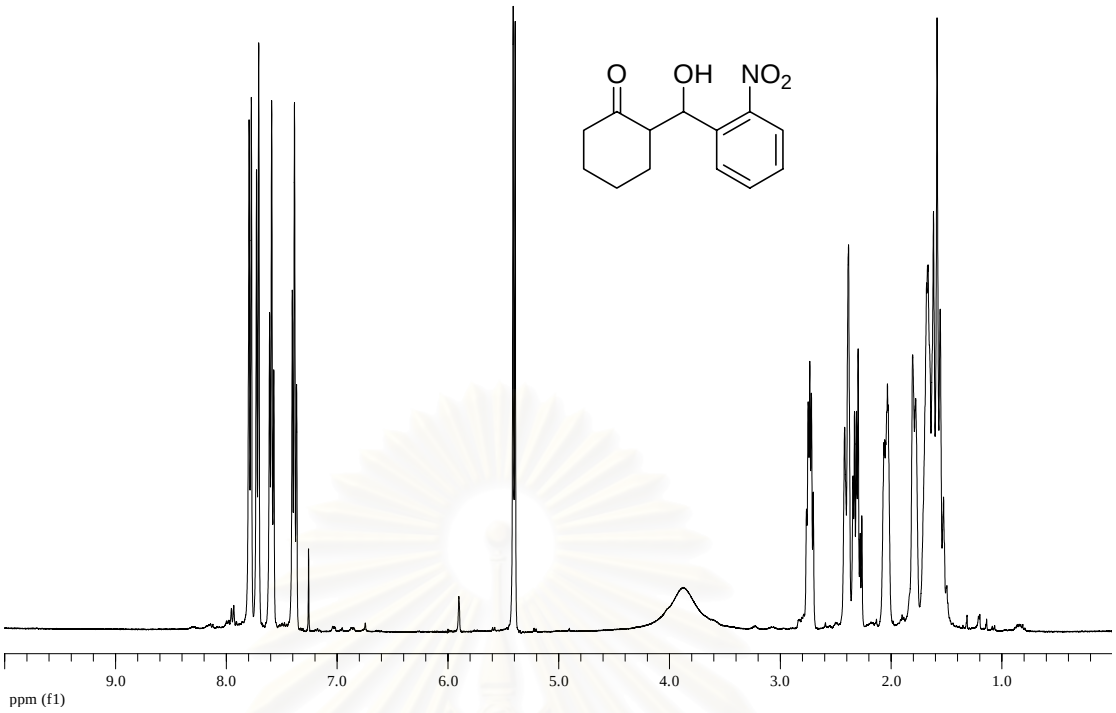


Figure 155 ^{1}H-NMR of 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(81f)**

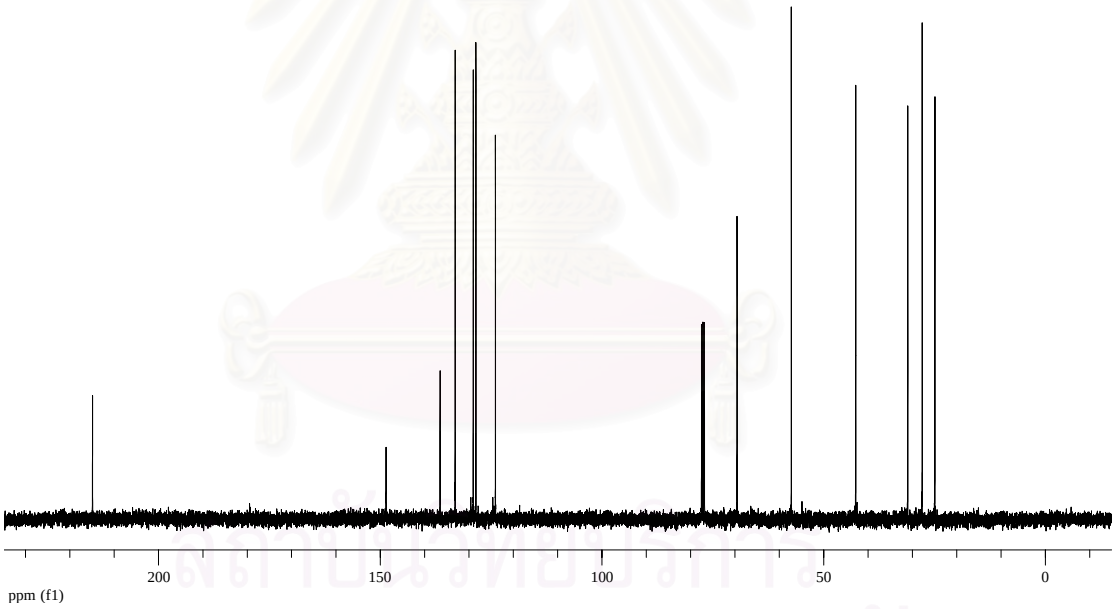


Figure 156 ^{13}C-NMR of 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(81f)**

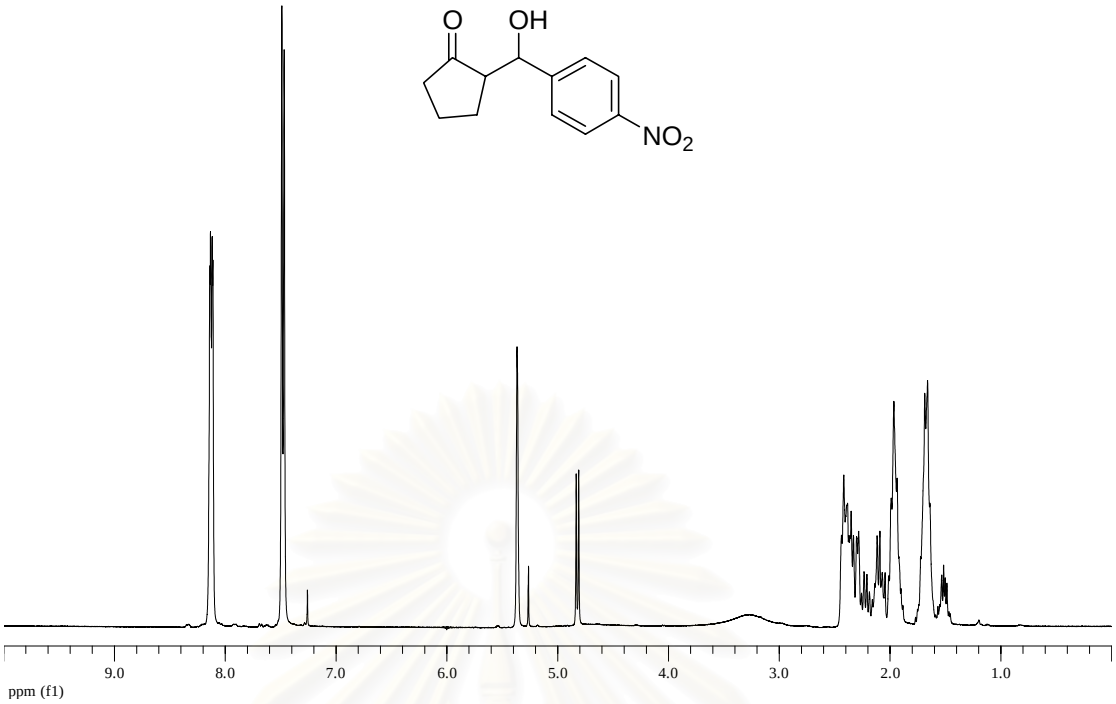


Figure 157 ^{1}H-NMR of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **(81g)**

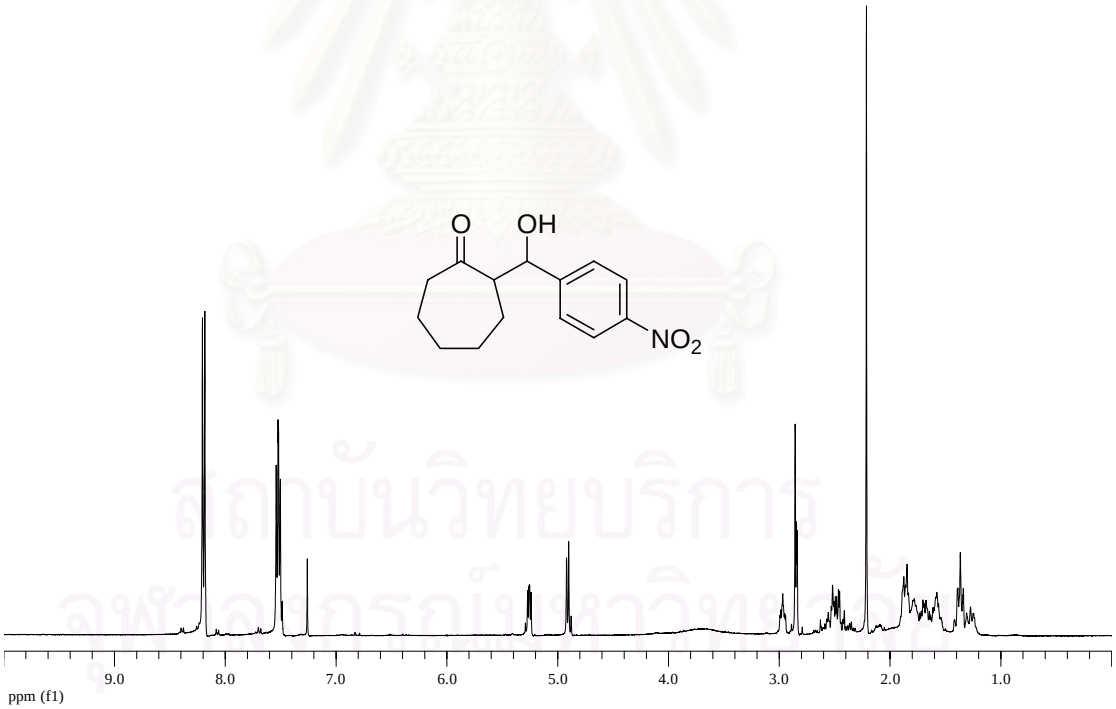


Figure 158 ^{1}H-NMR of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cycloheptanone **(81h)**

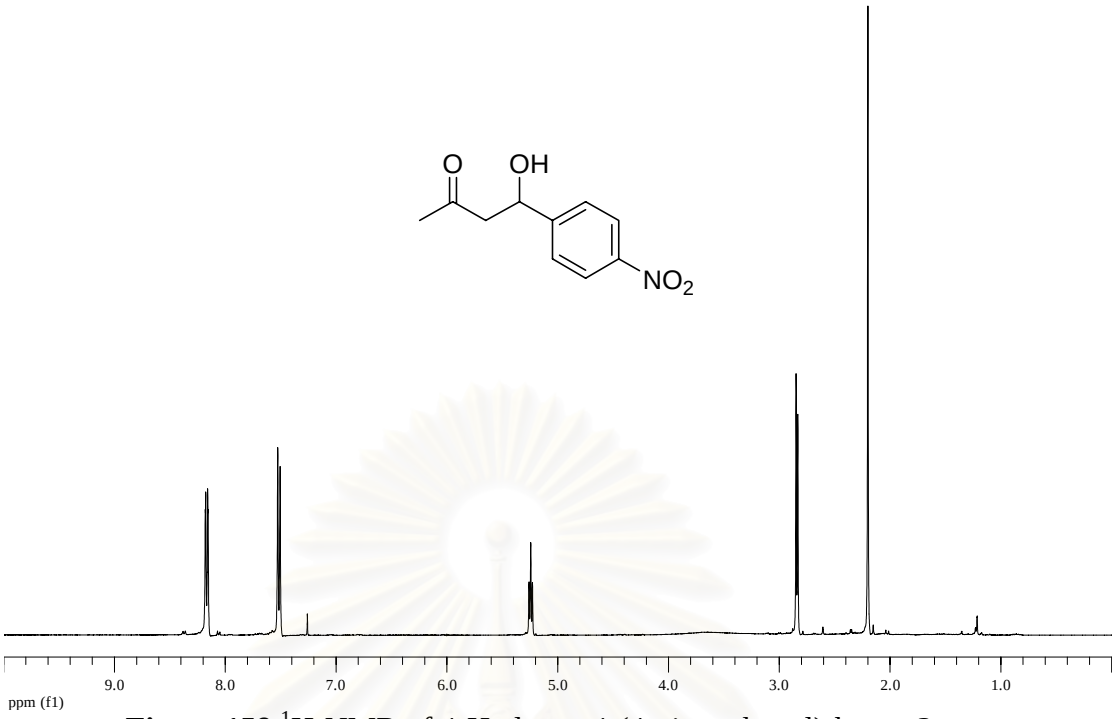


Figure 159 ^{1}H-NMR of 4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one **(81i)**

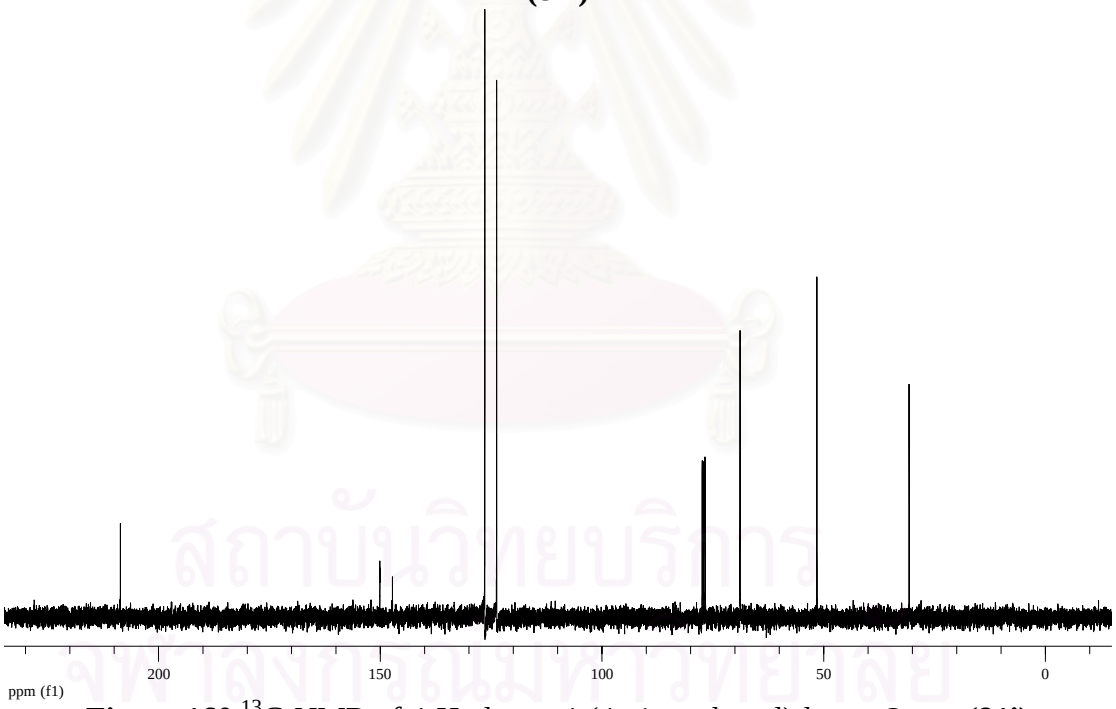


Figure 160 ^{13}C-NMR of 4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one **(81i)**

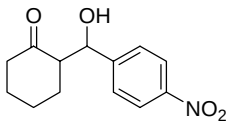
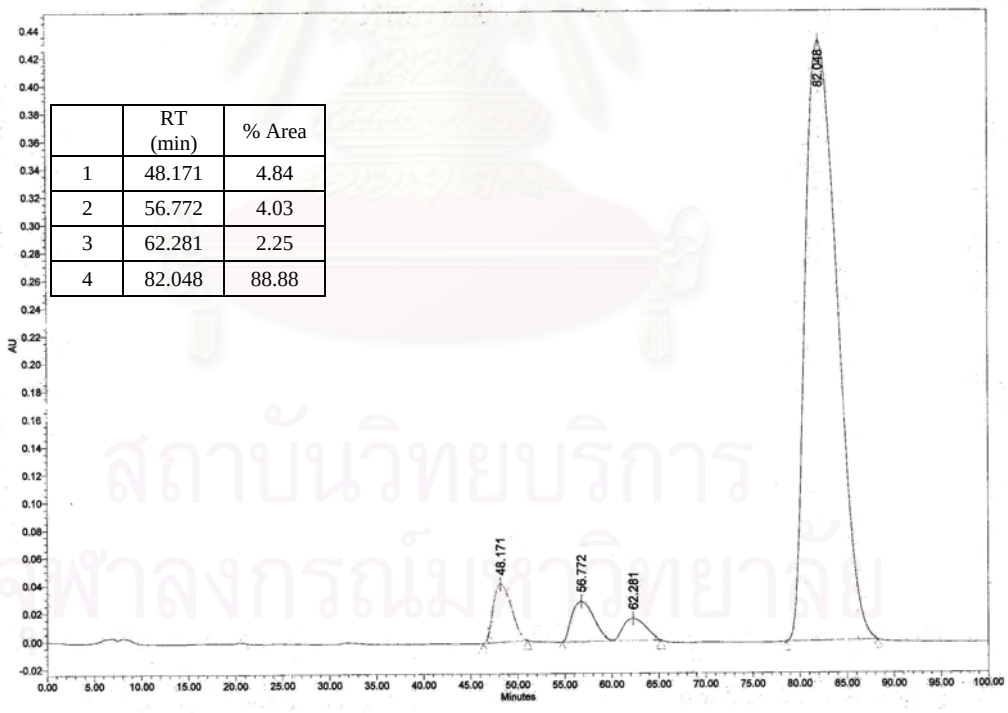
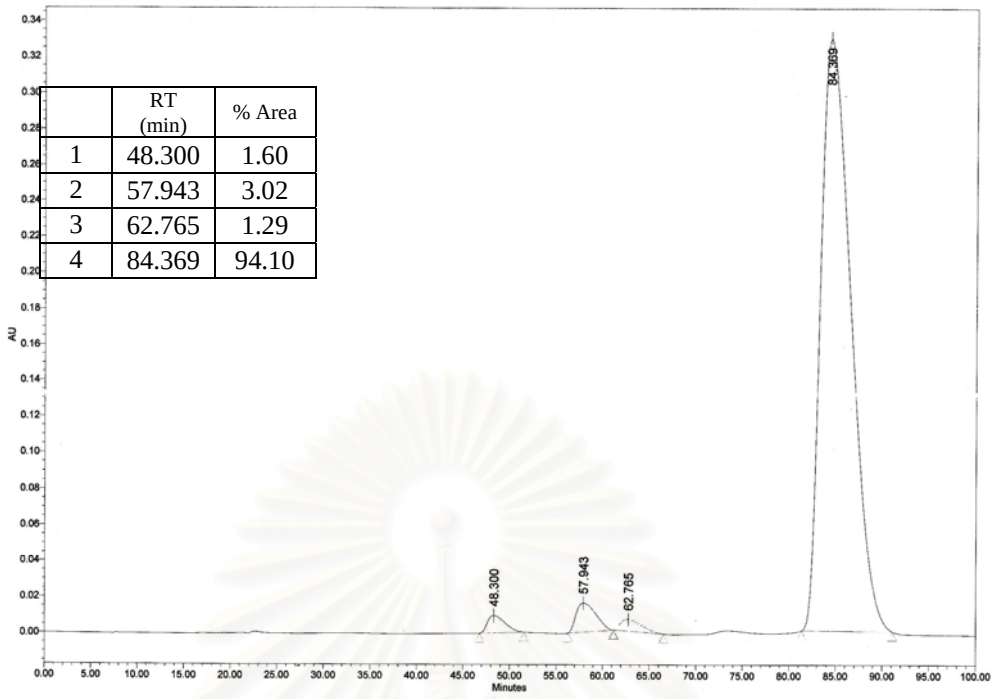


Figure 161 HPLC chromatogram of racemate 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(80a)**



	RT (min)	% Area
1	48.171	4.84
2	56.772	4.03
3	62.281	2.25
4	82.048	88.88

Figure 162 HPLC chromatogram of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(80a)** with catalyst 3l, $CHCl_3$



	RT (min)	% Area
1	48.300	1.60
2	57.943	3.02
3	62.765	1.29
4	84.369	94.10

Figure 163 HPLC chromatogram of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **(80a)** with catalyst 3l, H_2O

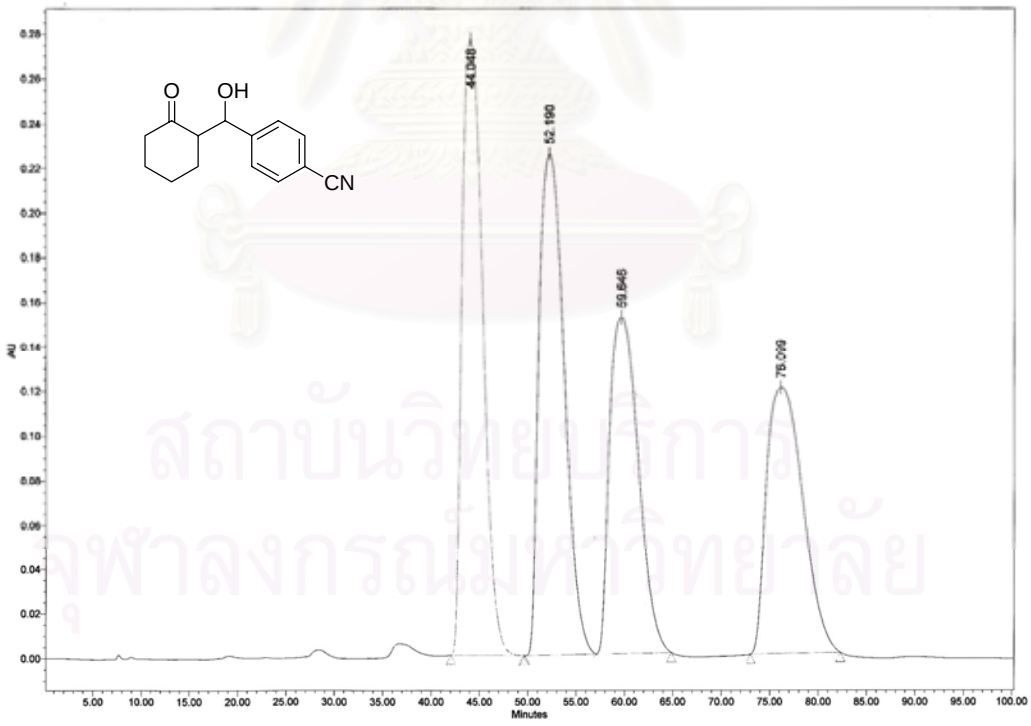


Figure 164 HPLC chromatogram of racemate 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(80b)**

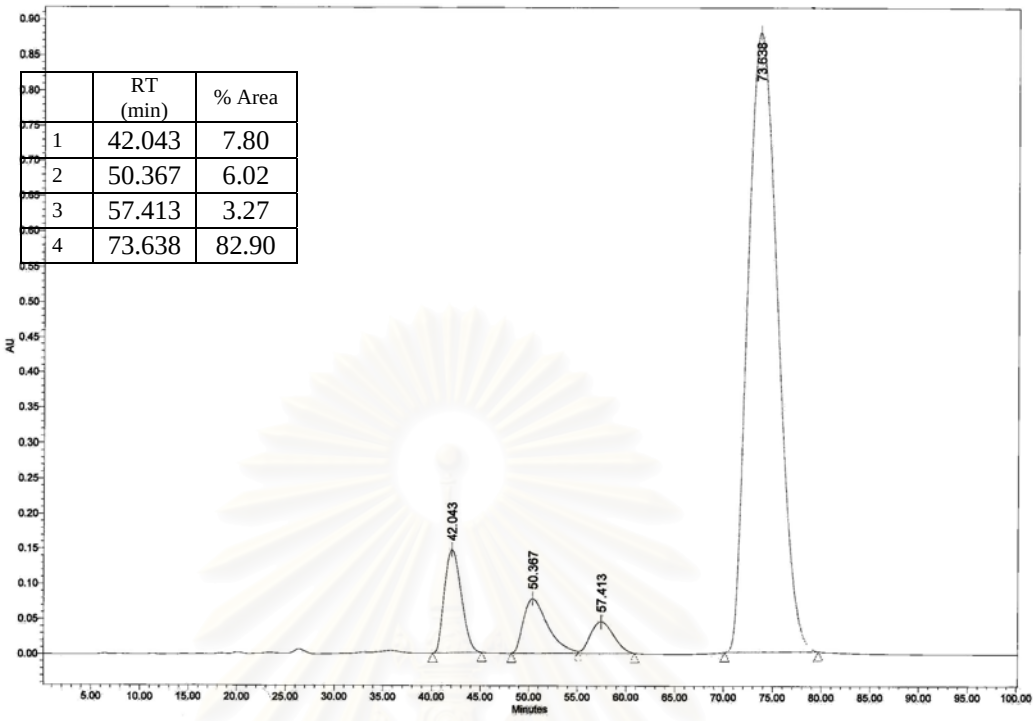


Figure 165 HPLC chromatogram of 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(80b)** with catalyst 3l, $CHCl_3$

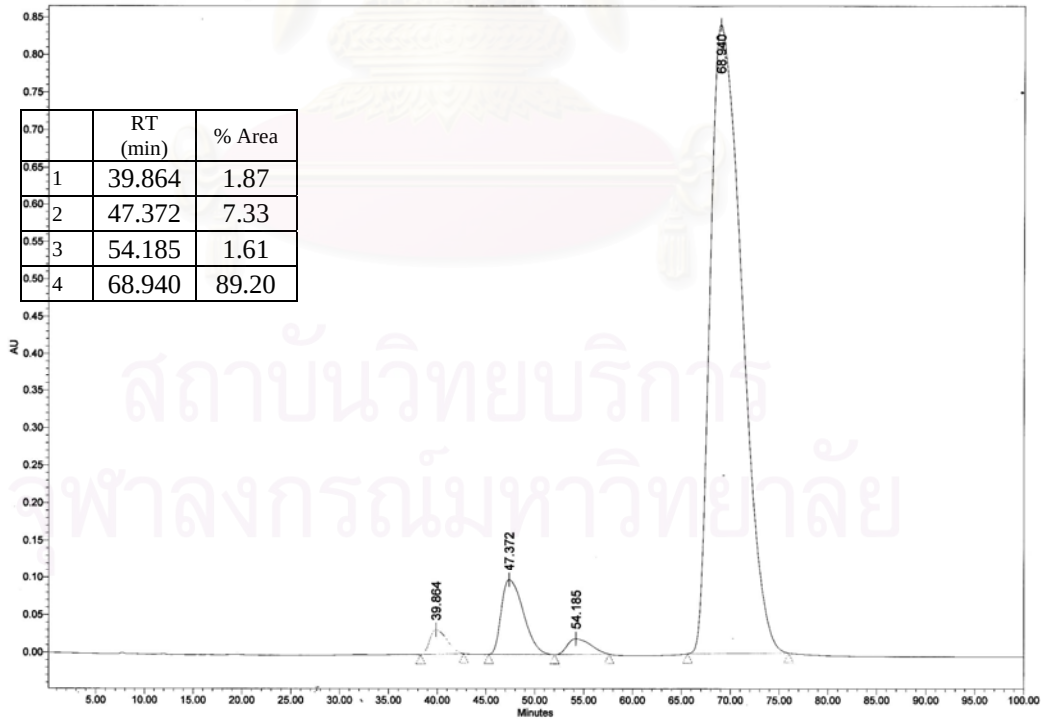


Figure 166 HPLC chromatogram of 4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **(80b)** with catalyst 3l, H_2O

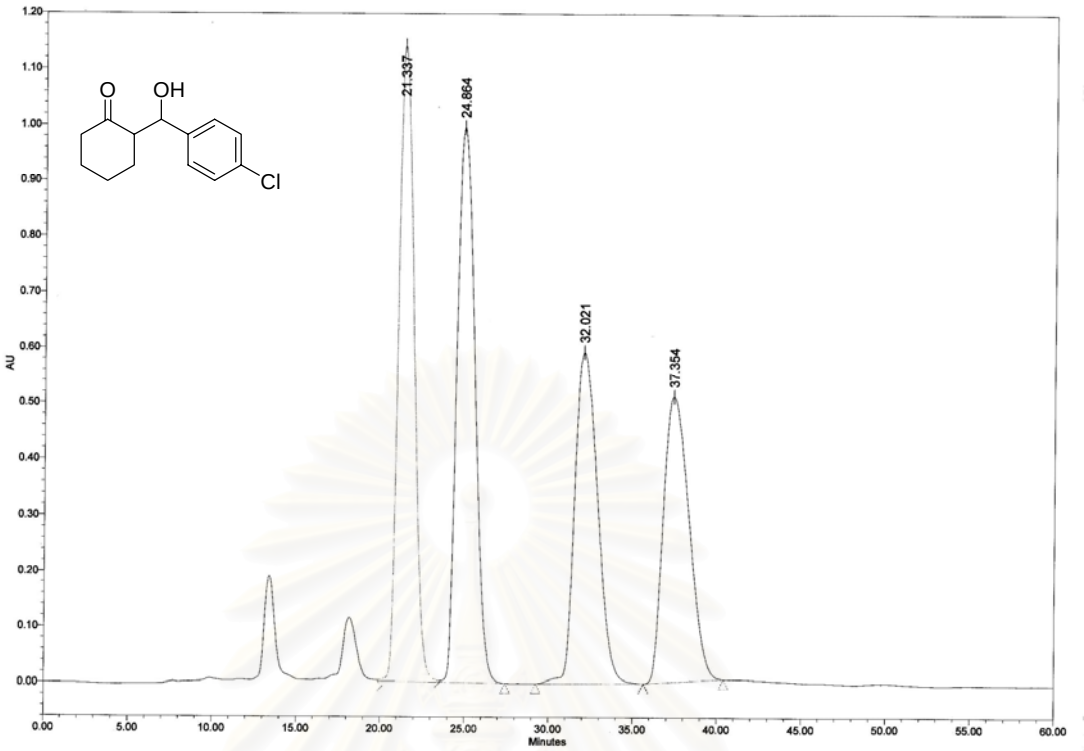
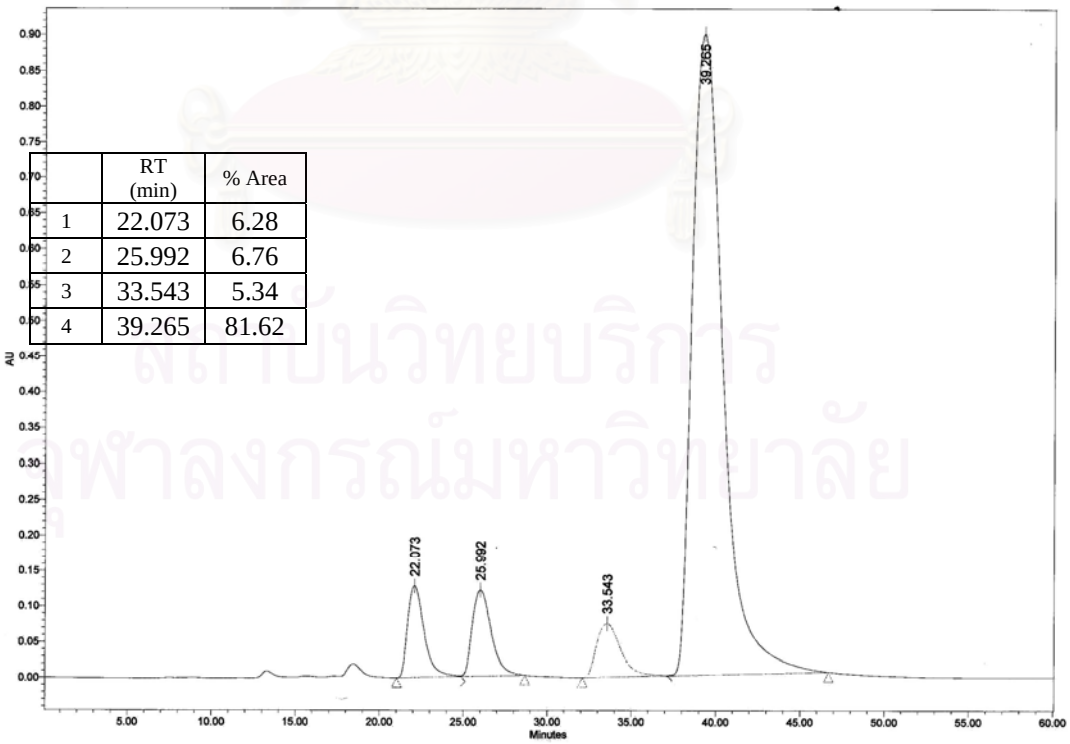
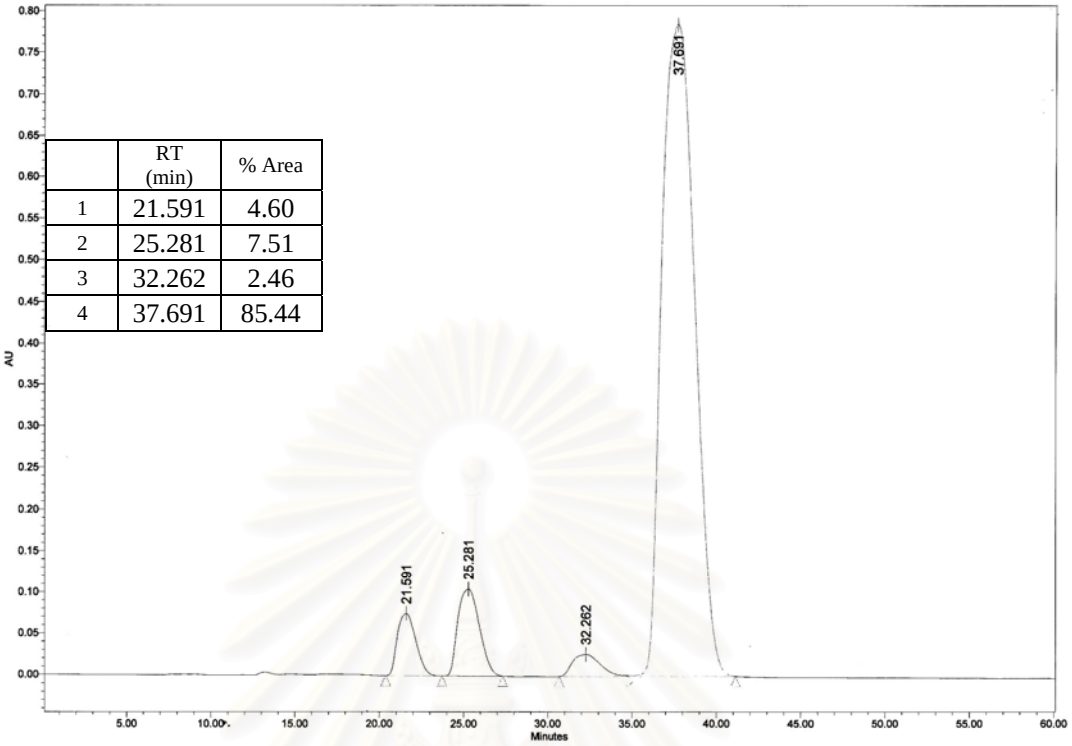


Figure 167 HPLC chromatogram of racemate 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(80c)**



	RT (min)	% Area
1	22.073	6.28
2	25.992	6.76
3	33.543	5.34
4	39.265	81.62

Figure 168 HPLC chromatogram of 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(80c)** with catalyst 3l, $CHCl_3$



	RT (min)	% Area
1	21.591	4.60
2	25.281	7.51
3	32.262	2.46
4	37.691	85.44

Figure 169 HPLC chromatogram of 2-[(4-Chloro-phenyl)-hydroxy-methyl]-cyclohexanone **(80c)** with catalyst 3l, H_2O

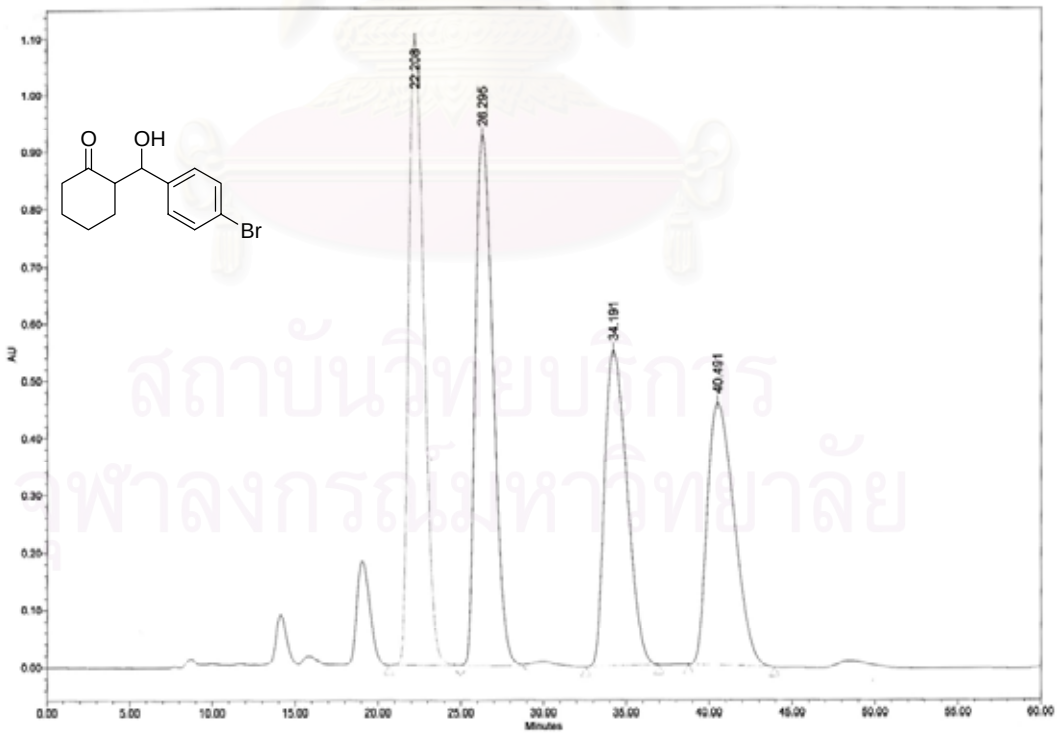
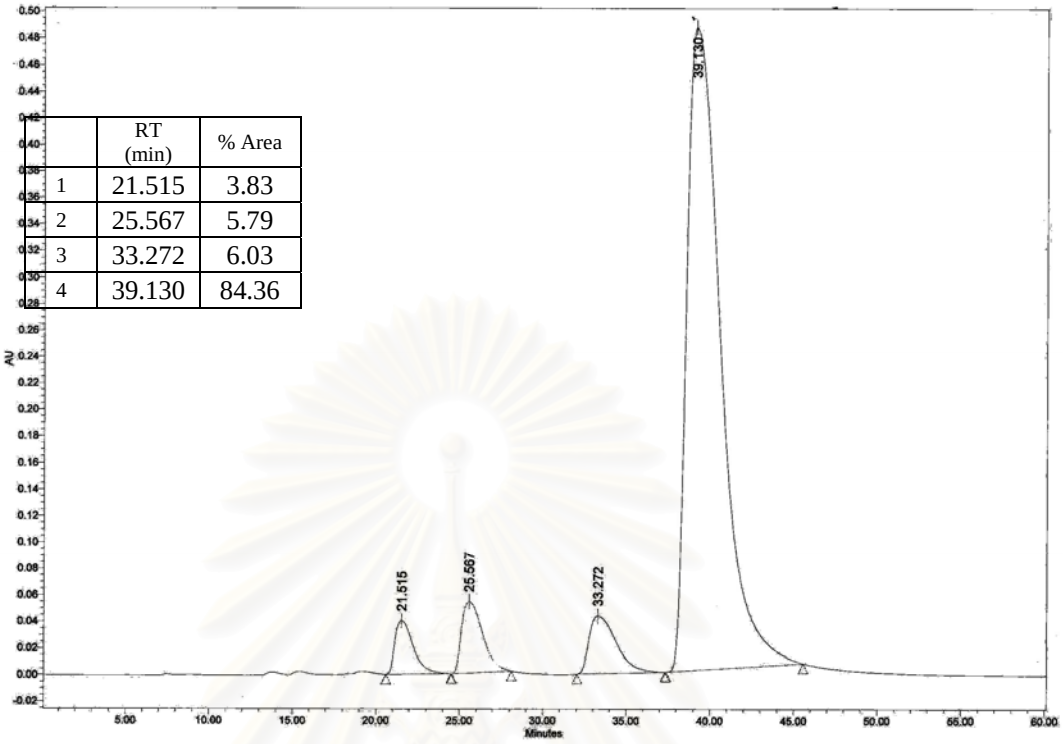
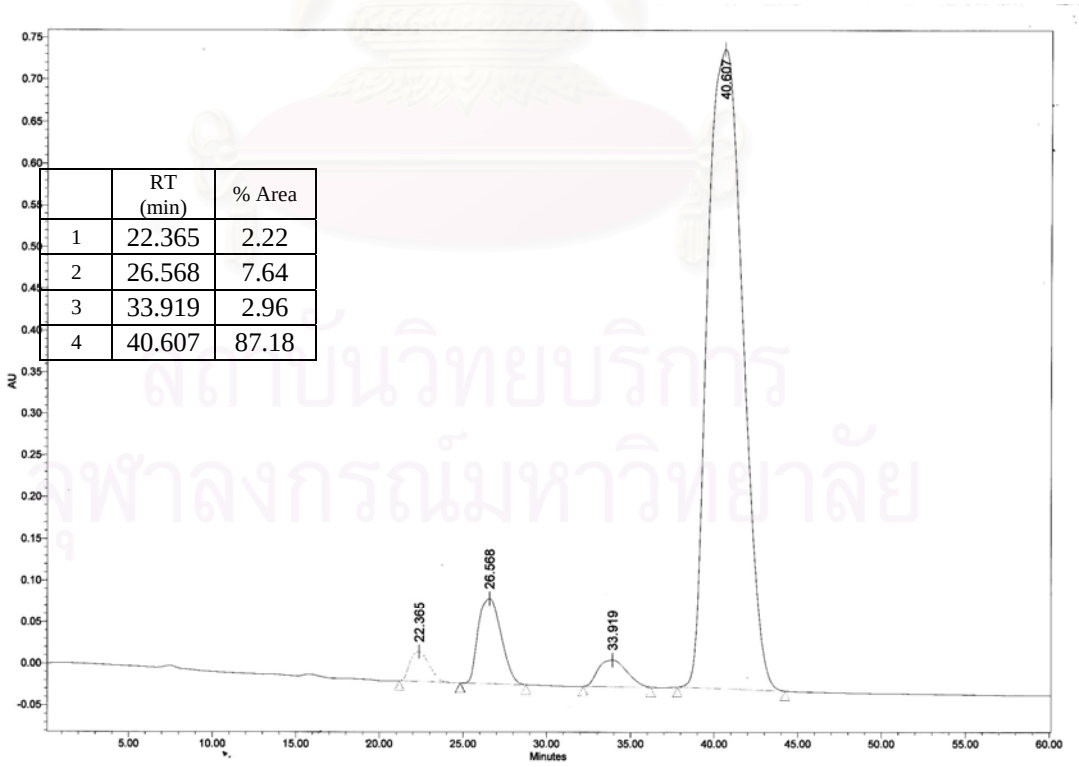


Figure 170 HPLC chromatogram of racemate 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(80d)**



	RT (min)	% Area
1	21.515	3.83
2	25.567	5.79
3	33.272	6.03
4	39.130	84.36

Figure 171 HPLC chromatogram of 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(80d)** with catalyst 3l, $CHCl_3$



	RT (min)	% Area
1	22.365	2.22
2	26.568	7.64
3	33.919	2.96
4	40.607	87.18

Figure 172 HPLC chromatogram of 2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **(80d)** with catalyst 3l, H_2O

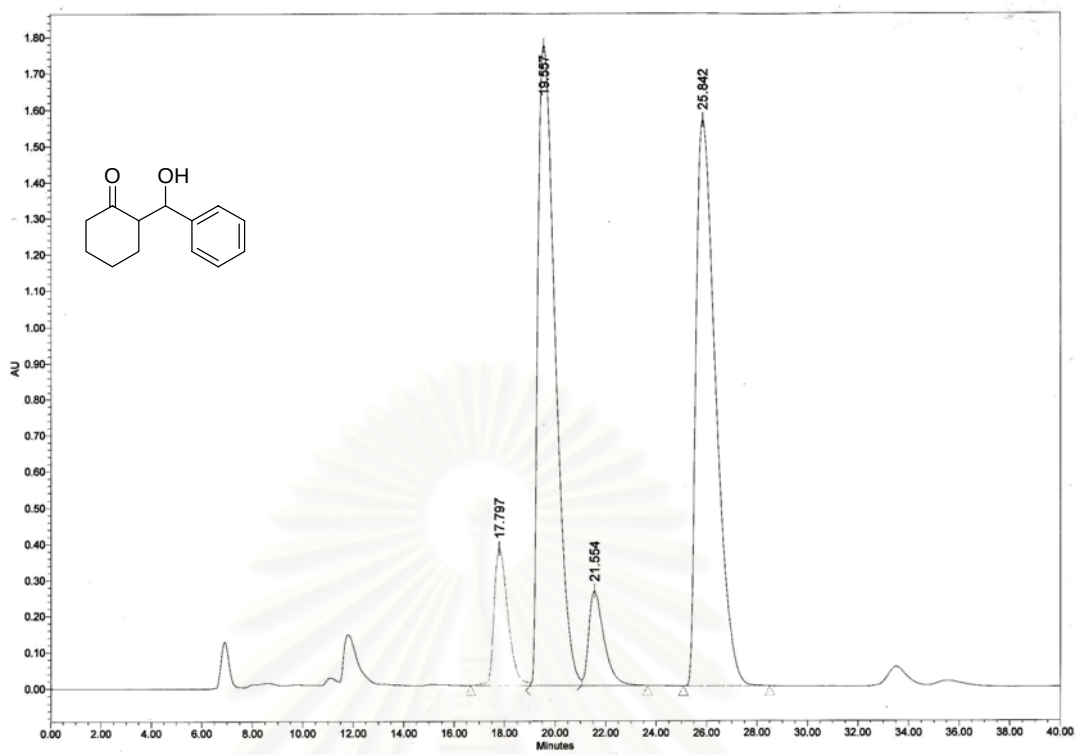
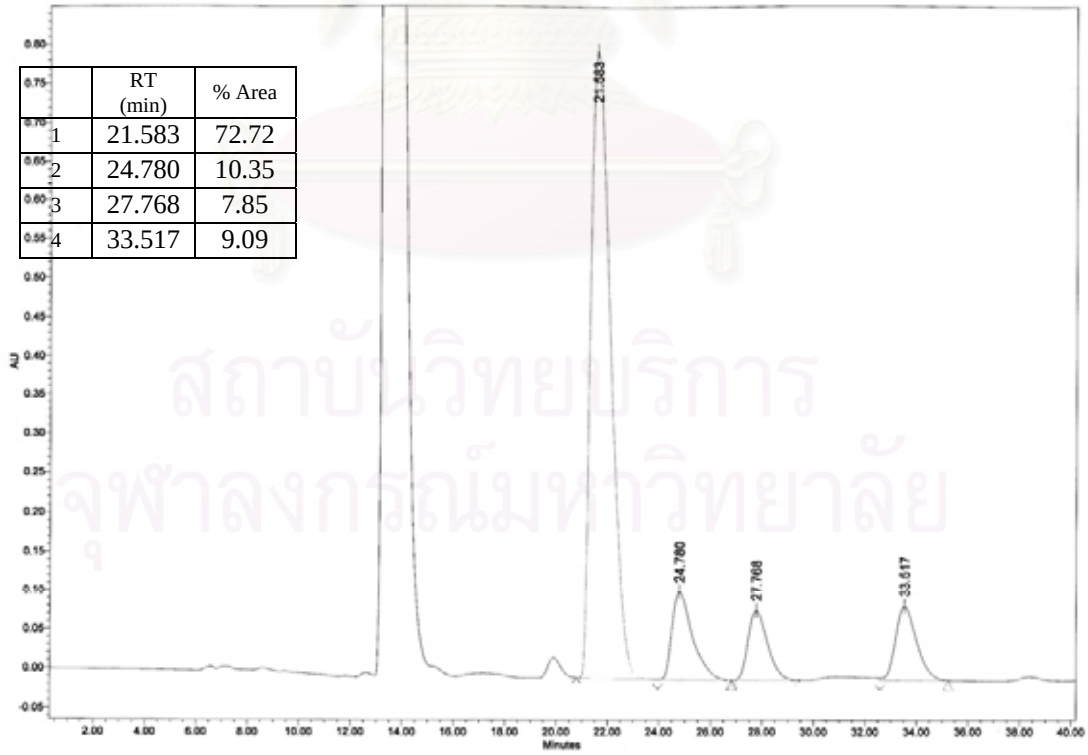


Figure 173 HPLC chromatogram of racemate 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(80e)**



	RT (min)	% Area
1	21.583	72.72
2	24.780	10.35
3	27.768	7.85
4	33.517	9.09

Figure 174 HPLC chromatogram of 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(80e)** with catalyst 3l, $CHCl_3$

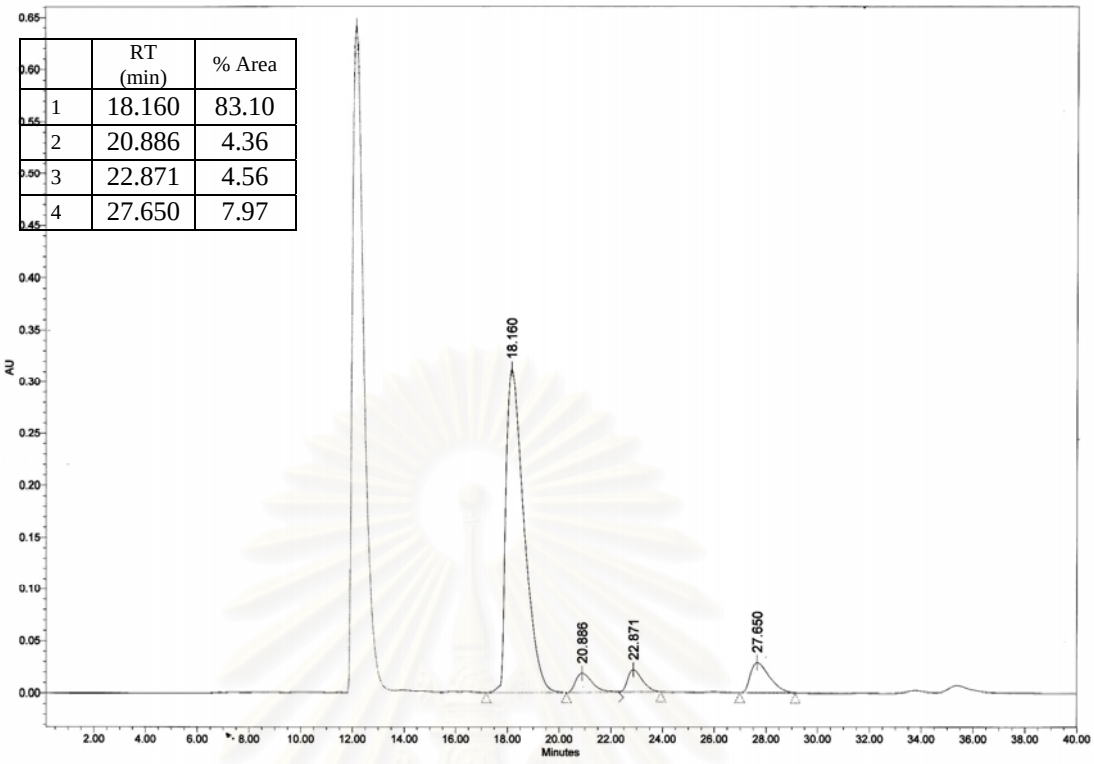


Figure 175 HPLC chromatogram of 2-(Hydroxy-phenyl-methyl)-cyclohexanone **(80e)** with catalyst 3l, H_2O

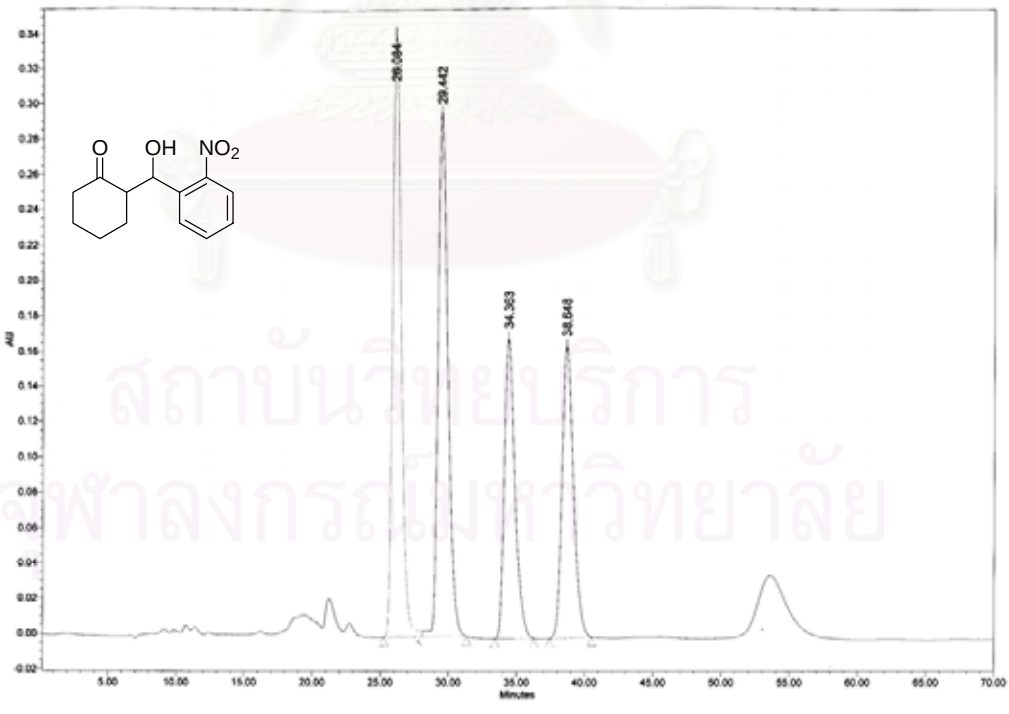
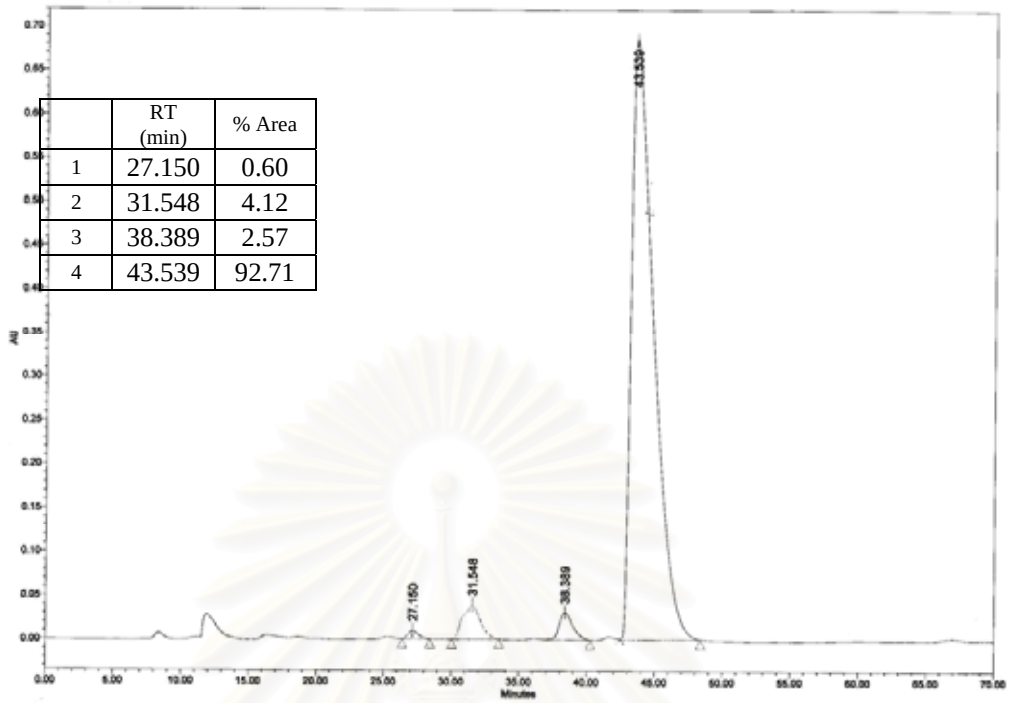
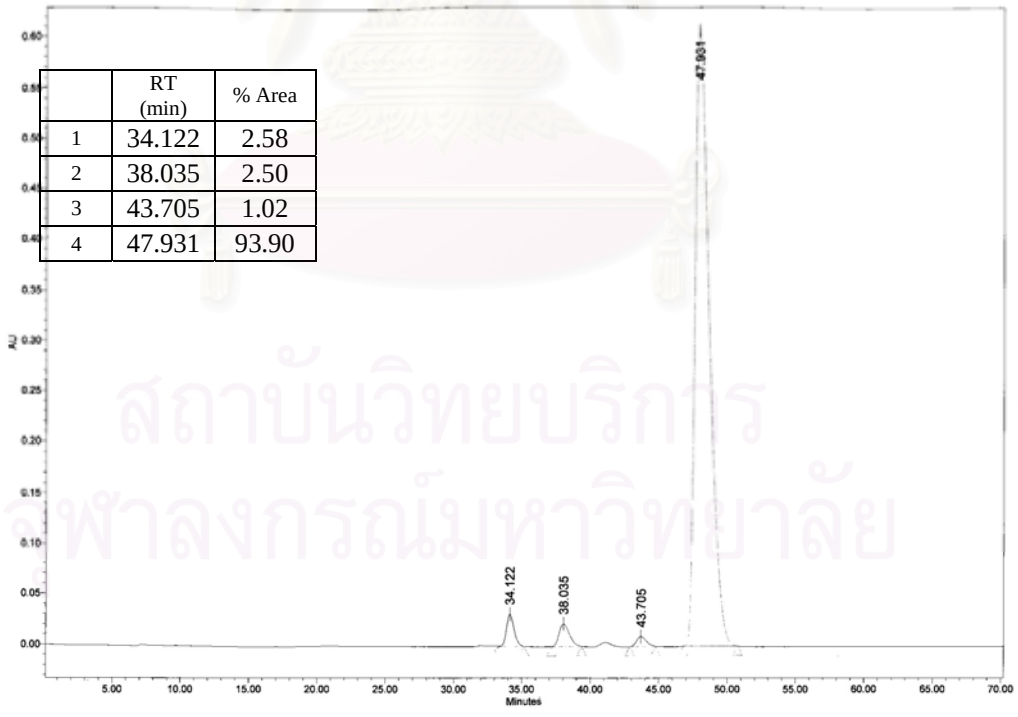


Figure 176 HPLC chromatogram of racemate 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(80f)**



	RT (min)	% Area
1	27.150	0.60
2	31.548	4.12
3	38.389	2.57
4	43.539	92.71

Figure 177 HPLC chromatogram of 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(80f)** with catalyst 3l, $CHCl_3$



	RT (min)	% Area
1	34.122	2.58
2	38.035	2.50
3	43.705	1.02
4	47.931	93.90

Figure 178 HPLC chromatogram of 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone **(80f)** with catalyst 3l, H_2O

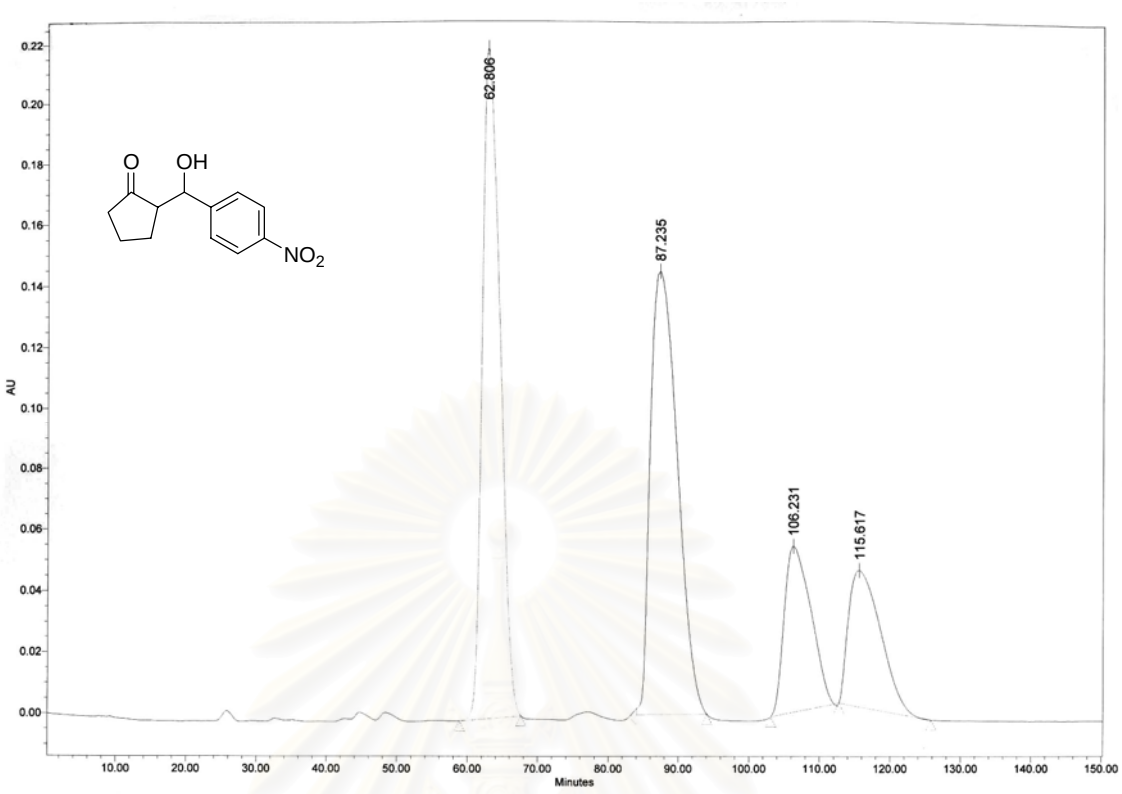
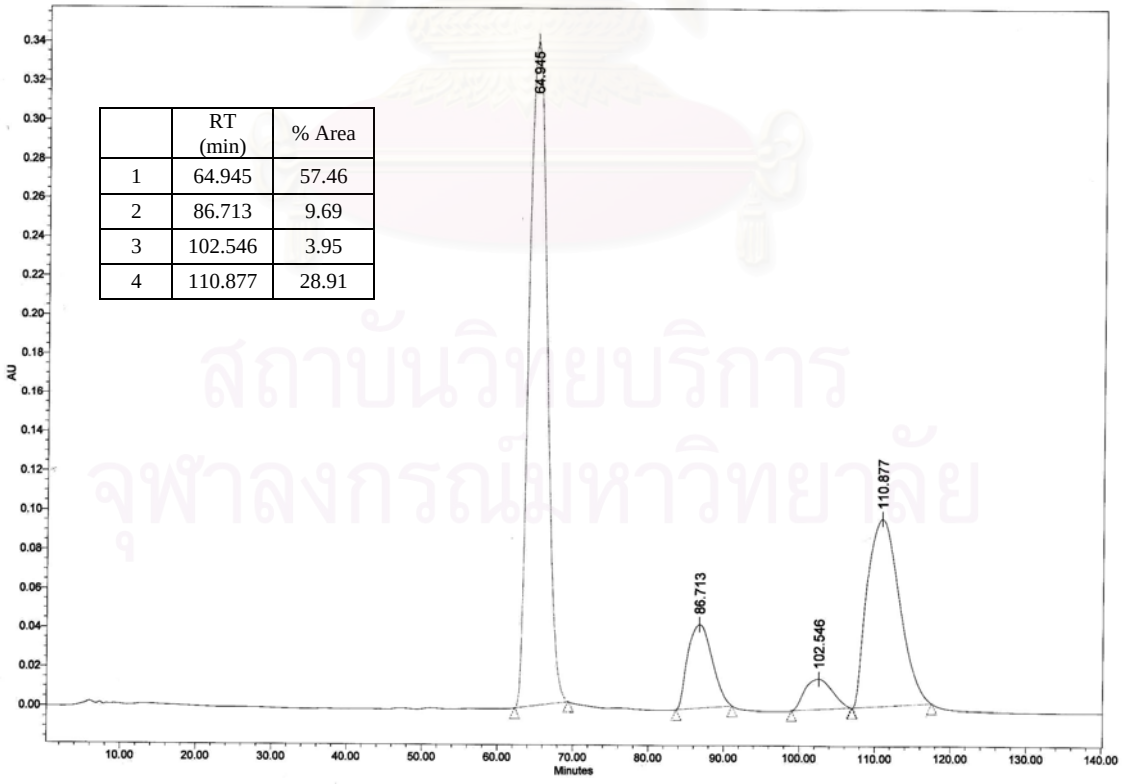
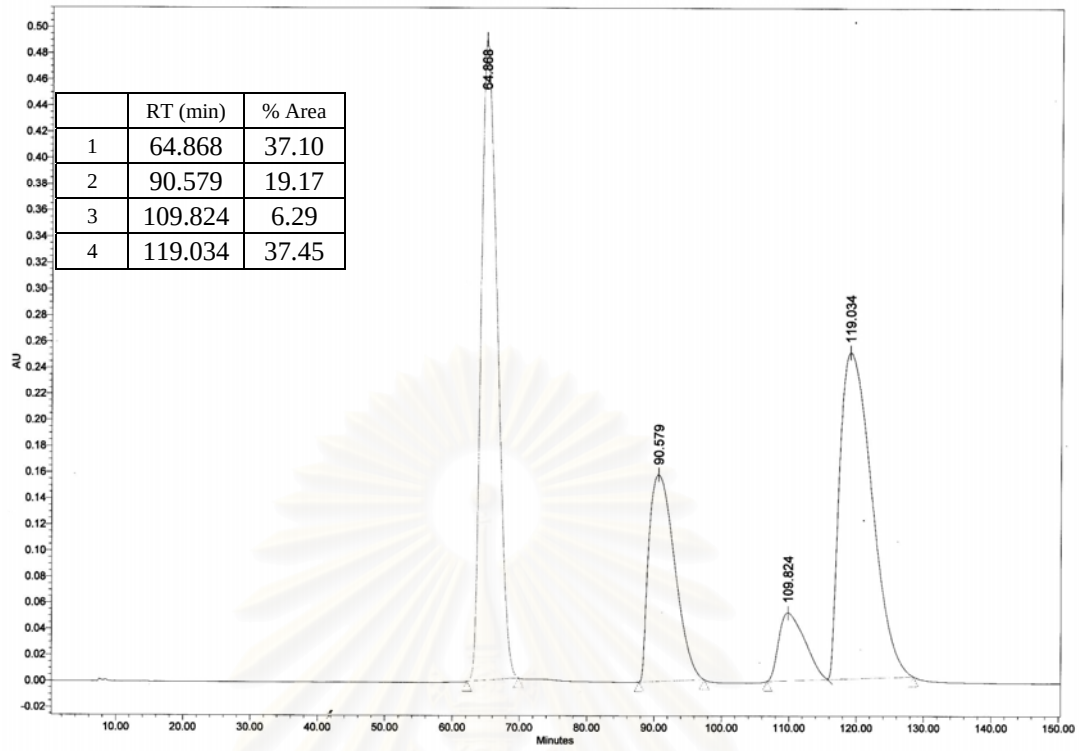


Figure 179 HPLC chromatogram of racemate 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **(80g)**



	RT (min)	% Area
1	64.945	57.46
2	86.713	9.69
3	102.546	3.95
4	110.877	28.91

Figure 180 HPLC chromatogram of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **(80g)** with catalyst 3l, $CHCl_3$



	RT (min)	% Area
1	64.868	37.10
2	90.579	19.17
3	109.824	6.29
4	119.034	37.45

Figure 181 HPLC chromatogram of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **(80g)** with catalyst 3l, H_2O

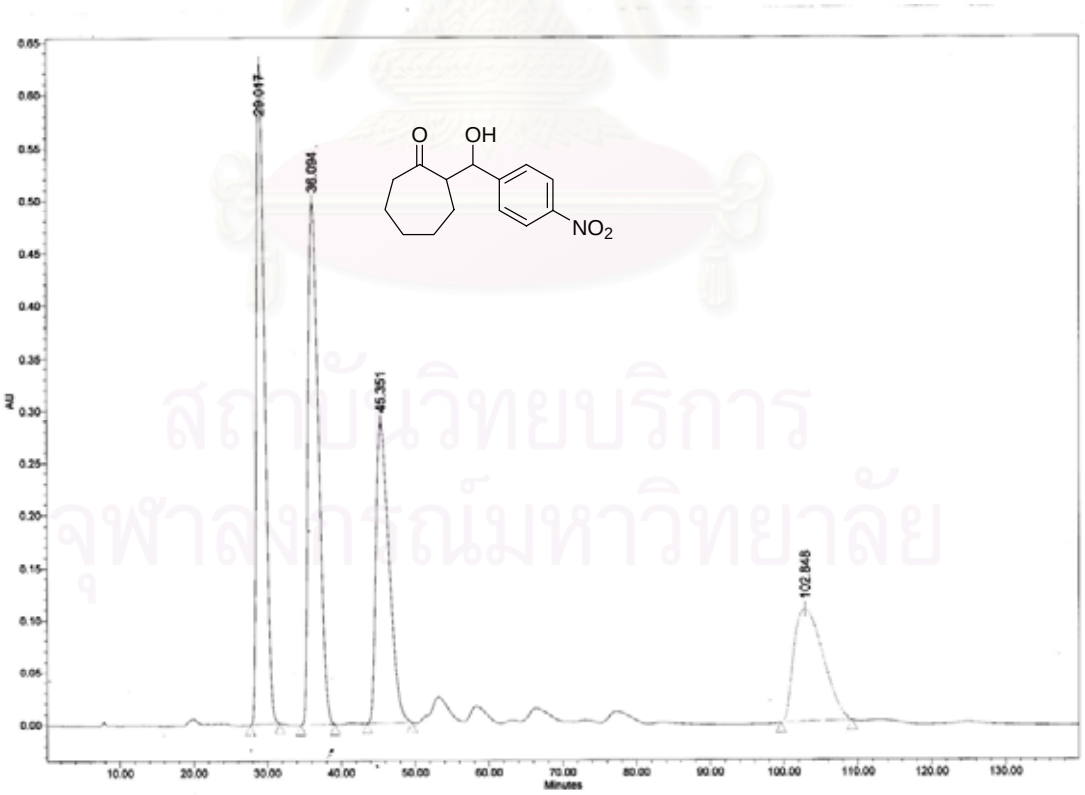
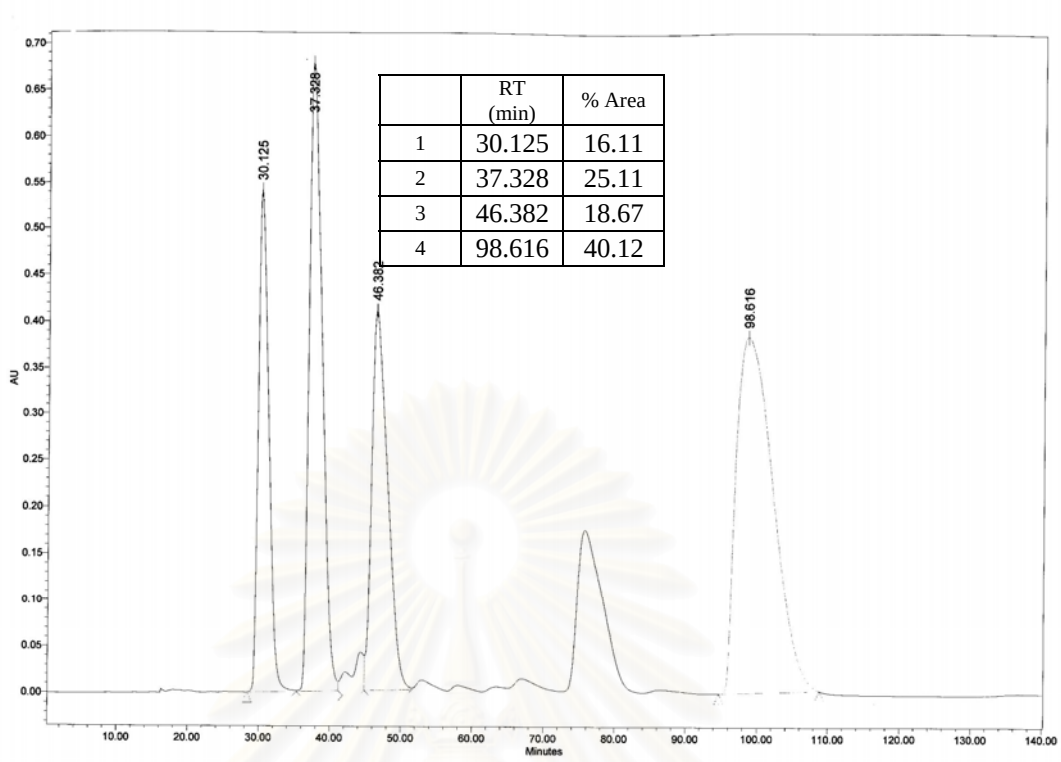


Figure 182 HPLC chromatogram of racemate 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cycloheptanone **(80h)**



	RT (min)	% Area
1	30.125	16.11
2	37.328	25.11
3	46.382	18.67
4	98.616	40.12

Figure 183 HPLC chromatogram of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cycloheptanone **(80h)** with catalyst 3l, $CHCl_3$

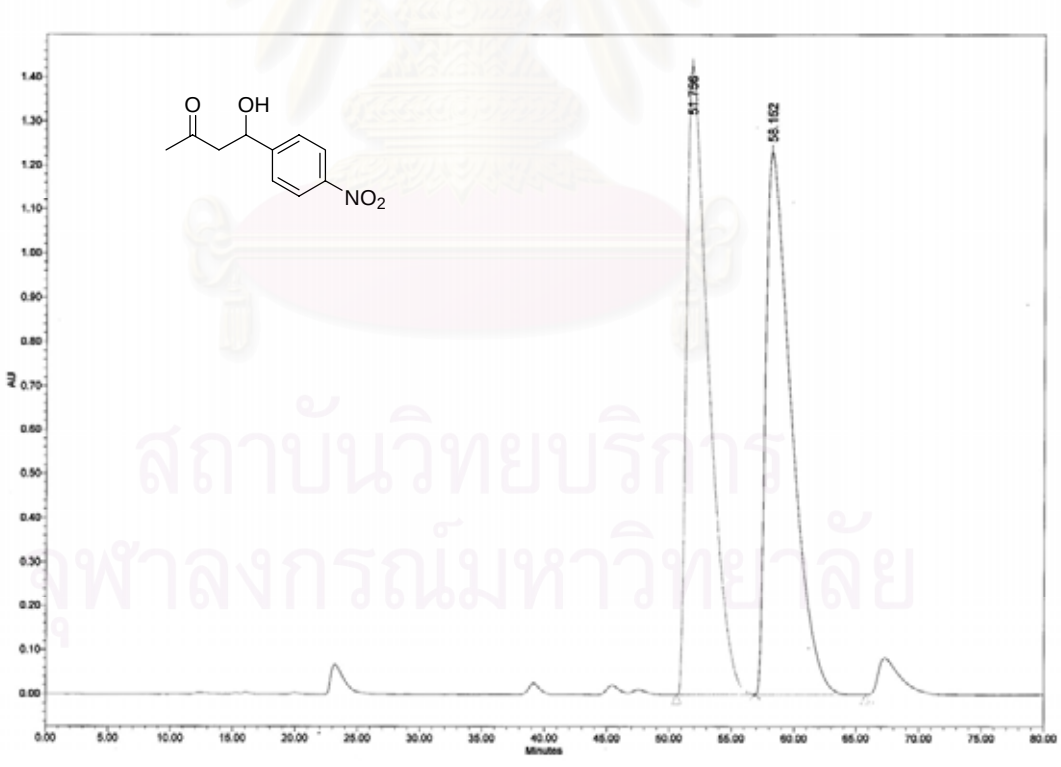
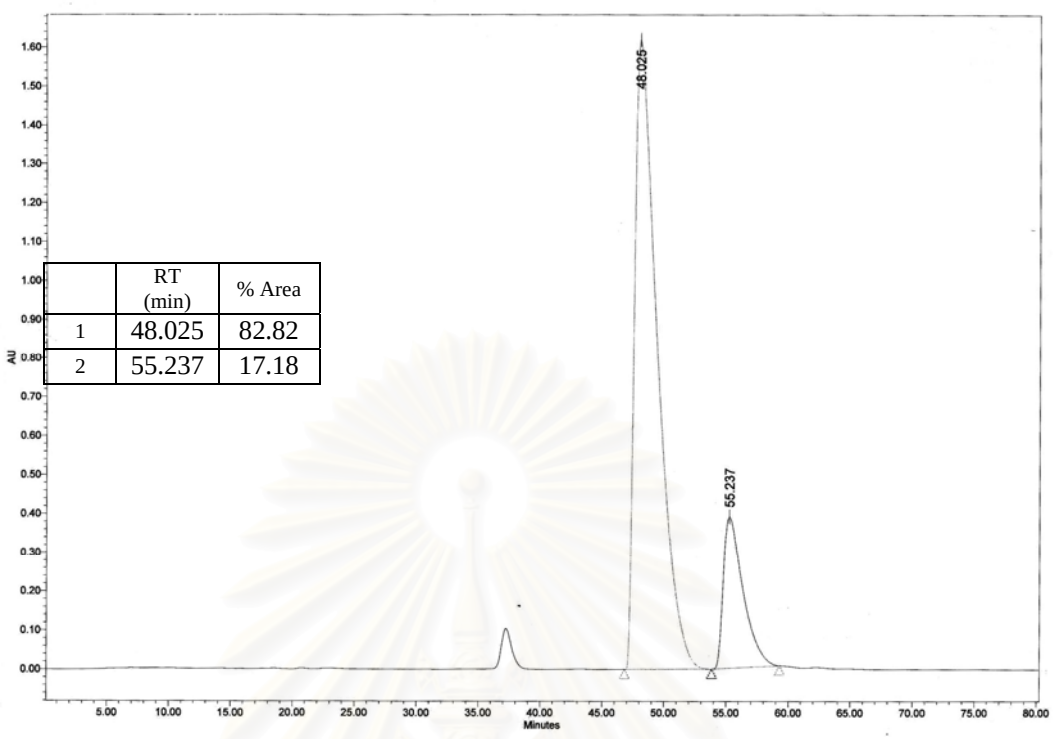


Figure 184 HPLC chromatogram of racemate 4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one **(80i)**



	RT (min)	% Area
1	48.025	82.82
2	55.237	17.18

Figure 185 HPLC chromatogram of 4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one **(80i)**with catalyst 3l, $CHCl_3$

VITA

Sornpranart Sathapornvajana was born on August 30, 1983 in Bangkok, Thailand. He received Bachelor Degree of Science in Chemistry from Chulalongkorn University in 2003. Since 2003 he has become a student in Master Degree of Science of Chulalongkorn University studying in Department of Chemistry.