Noble Synthesis of the [1,4]-Oxazine Derivatives and its Mechanistic Study

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Song, Sang-Yong

DEPARTMENT OF CHEMISTRY
GRADUATE SCHOOL
CHANGWON NATIONAL UNIVERSITY

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Under the Direction of
Professor Dong-Soo Shin

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Thesis Committee : **Chuljin Ahn** _____

Tea-Jin Won _____

Dong-Soo Shin _____

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1. Introduction

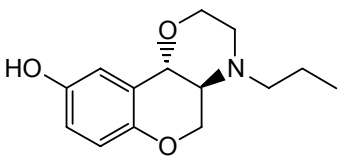
1.1. Background

The synthesis of bioactive compound, natural products and drugs are one of most important field in organic chemistry. Now days, many reports are concerned about bioactivity of [1,4]-oxazine ring structure contained natural products and candidate drugs. This subject is currently expending such as derivatives synthesis and bio-assay research.[1-5] The biological activity of [1,4]-oxazine made important target material for synthetic chemists. Therefore, synthetic method of [1,4]-oxazine ring structure and its derivatives are very important.

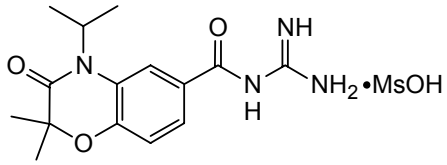
For example of the [1,4]-oxazine ring structure contained bioactive molecular, PD 128,907 (**1**) is role of inhibitor of dopamine D3 that is among the widely studied neuro-transmitters of the mammalian central nervous system (CNS) receptor. The most important thing of this molecular is it will be suitable for the development of drugs that the treatment of parkinsons disease.[2] The KB-R9032 (**2**) is potent Na/H exchange inhibitor in the cell with high water solubility and it can be candidate drug of the ischemia-reperfusion induced injury.[3] The *N*-acyl-1,2,3,4a,5,10b-hexa-hydro-[1]-benzoprano-[3,4-*b*][1,4]-oxazine-9-car -bonitrile (**3**) is candidate drug for ATP-sensitive potassium channel openers (KCOs). This molecular could be useable for the control of the urinary incontinence (UI) or urinary urge incontinence (UUI) that is widespread and distressing condition with the elderly population. The urinary urge incontinence is the largest category among the four types of incontinence, has been demonstrated to be caused by bladder detrusor muscle instability. Current treatments for UUI include

anti-muscarinic, anti-spasmodics and mixed both agents, which have met with limited success due to their low efficacy and/or high incidence of side effects.[4] The 4-{3-[4-(4-fluoro-phenyl)-piperazin-1-yl]-propyl}-4*H*-pyrido-[3,2-*b*][1,4]-oxazin-3-one (**4**) is new analgesic agents that are devoid of side effects such as tolerance, respiratory depression, constipation, physical dependency, fear of addiction and morphine-like opioid agonists, as well as of the gastro-intestinal problems associated with NSAIDs[5] (Figure 1).

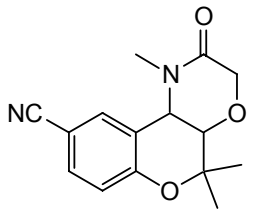
Figure 1. [1,4]-oxazine contained bioactive compounds



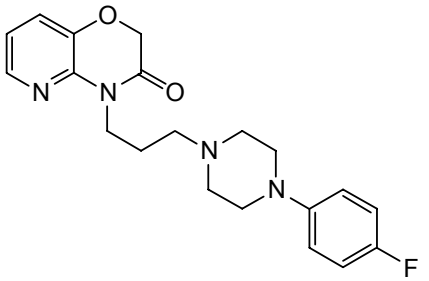
PD 128,907 (1)



KB-R9032 (2)



***N*-methyl-1,2,3,4a,5,10b-hexahydro-[1]benzoprano-[3,4-b] [1,4]oxazine-9-carbonitrile (3)**



4-{3-[4-(4-Fluoro-phenyl)-piperazin-1-yl] -propyl}-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (4)

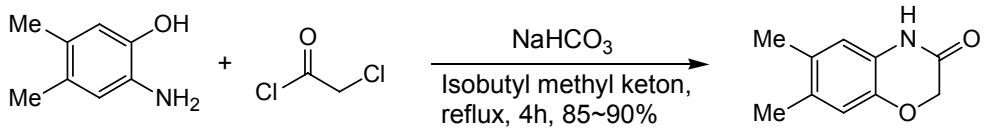
In these importances, different types of synthetic methods for [1,4]-oxazine ring structures are reported.[6-21] These reactions are classified into four major groups and their characters are as follow.

1.2. Known methods for [1,4]-oxazine synthesis

Amino alcohol and dihalo compound group

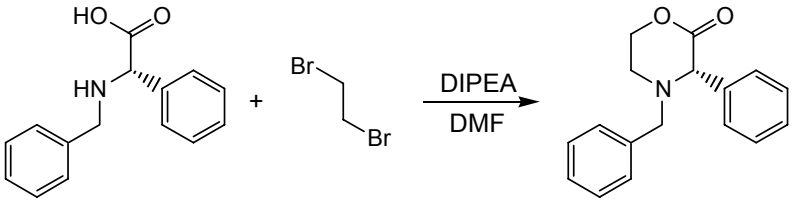
The first group of [1,4]-oxazine synthesis is simple and widely using method for basic [1,4]-oxazine structure. The cyclization is formed between amino alcohols **5a, 5b** and halo acetyl halide **6** or dihalo ethyl **8**.[6-14] In this cyclization, amine part in amino alcohol **5a, 5b** is react with acyl halide in halo acetyl halide **6**. Then, oxygen in alcohol part is SN2-type attack to the halide-attached carbon (Scheme 1). The reaction of dihalo ethyl **8** is almost same manner as a first descried reaction and product **9** is key synthetic intermediate for carboxylic polyoxin C that is NK1 receptor active molecule.[12] (Scheme 2). This reaction is simple and easily adaptable to construct of [1,4]-oxazine compounds. However, there is limitation such as if using asymmetric amino alcohol as a starting material, product obtained two cyclic compounds and cannot control its ratio.

Scheme 1



5a **6** **7**

Scheme 2



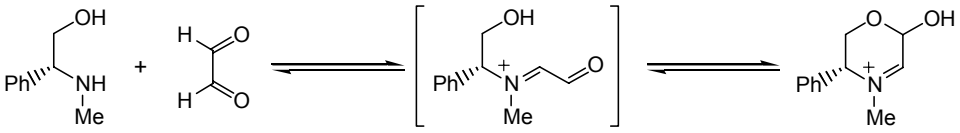
5b **8** **9**

Amino alcohol and glyoxal derivatives compound group

The second group is using *N*-protected amino alcohol **10a, 10b** and glyoxal derivatives **11a, 11b**.[15,16] This reaction is similar with the first group reaction, only difference is using glyoxal derivatives **11a, 11b** rater than using halo acetyl halide **6** or dihalo ethyl **8** derivatives as a starting materials. In addition, another difference is reaction intermediate has ammonium ion **12** and nitron **15**. The first reaction in this group, *N*-protected amino alcohol **10a** react with one of aldehyde part in glyoxal **11a** and this reaction makes ammonium ion **12**. Then, cyclized product of [1,4]-oxazine compound **13** is obtained from reaction of aldehyde with hydroxy in *N*-protected amino alcohol **10a** (scheme 3). The second reaction in this group, hydroxy amino compound **10b** is synthesized from oxaziridine and its react with glyoxylate derivatives **11b** to make nitron intermediate **14**. Finally, [1,4]-oxazine compound **15** is synthesized from cyclization of intermediate compound **14** (scheme 4). In this reaction group, the position of carbonyl group at [1,4]-oxazine compounds **13, 15** are different of other [1,4]-oxazine derivatives. Most carbonyl group in [1,4]-oxazine derivatives is located at 3-position, but this [1,4]-oxazine

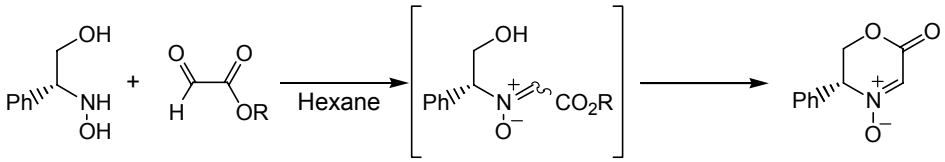
located in 2-position **15**. This makes unique point of this reaction group and geometrical specific product is allowed to synthesis of α -amino acid that is useful moiety of bioactivity compounds. Also, C=N in final products **13, 15** allowed to further reactions such as aza Diels-Alder reaction or stereo selective hydrogenation.

Scheme 3



10a **11a** **12** **13**

Scheme 4



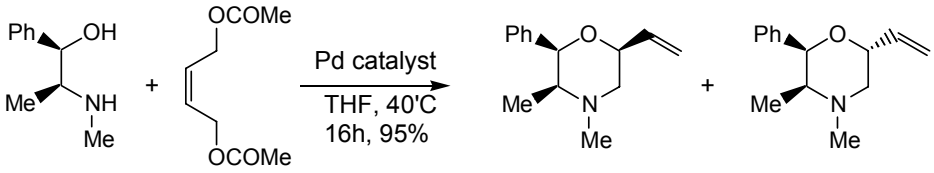
10b **11b** **14** **15**

Catalysts induced cyclization group

The third reaction group is using catalyst to the cyclization. In this reaction, only two types of reactions are reported.[17,18] The first one is palladium-catalyzed tandem allyic substitution using *N*-protected amino alcohol **16** and acetic acid 4-acetoxy-2-but-2-enyl ester (**17**) (Scheme 5). The second one is selenium oxide promoted oxidative

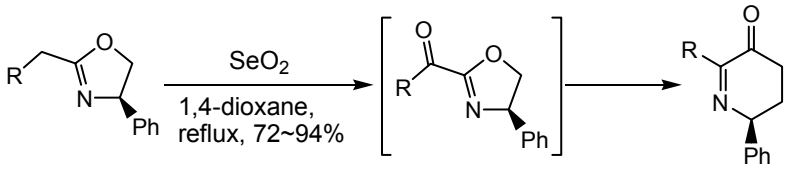
rearrangement reaction (Scheme 6).[19,20] In the first reaction, palladium catalyst is inserted to allyl and oxygen at ester **17** then, lone pair electrons at amine **16** is attacked to allyl position. When connected amine and allyl, allyl attached palladium move to opposite site of the same molecular. Further reaction is occurred by same manner, allyl position is attacked by lone pair electrons of the alcohol. This reaction makes two diastreomeric compounds **18a, 18b** and the ratio of **18a** : **18b** is 3 : 1. This ratio is controlled by the attached functional group at the *N*-protected amino alcohol **16**. The second catalyst, selenium oxide is role of oxidant and Lewis acid during the reaction. In this reaction, product **21** is formed by *via* Lewis acid catalyzed ring opening of oxazole **20**. Then, rearrangement proceed by fission and migration of the C=N bond with H_2O nucleophilic catalysis.

Scheme 5



16 **17** **18a** **18b**

Scheme 6

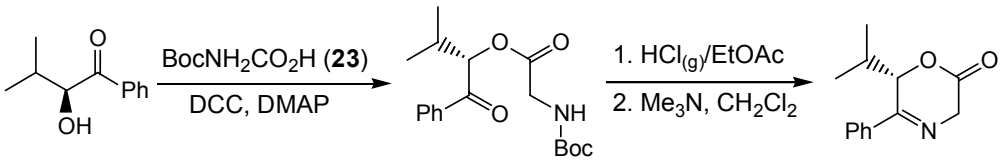


19 **20** **21**

Amino acid group

Finally, the last [1,4]-oxazine synthetic method is repeted using amino acid.[21] This reaction is progressed after condensation of *N*-Boc glycine **23** with chiral hydroxy ethanone derivatives **22**. Further deprotection of the Boc group at chiral ester **24** and subsequent treatment afforded [1,4]-oxazine **25** structure (Scheme 7). In addition, this reactions final product **25** is almost same as glyoxal derivatives final product **13, 15** and allows the further reaction at [1,4]-oxazine structure for chiral α,β-didehydro-α-amino acids.

Scheme 7

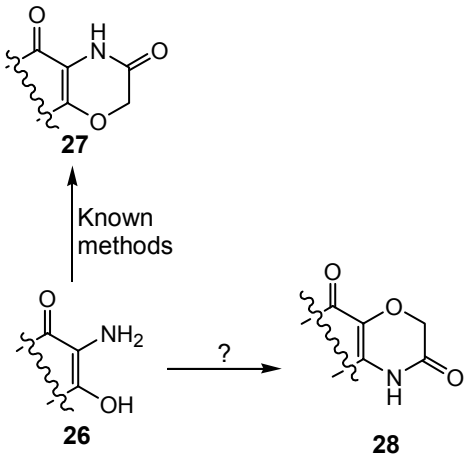


22 **24** **25**

1.3. Our idea

Despite of the much interest in [1,4]-oxazine structure, remained simple and effective method for the construct of [1,4]-oxazine ring structure. As we are noted at previous chapter, most starting material of [1,4]-oxazine was amino alcohol derivatives and this point makes limitation of synthesis of new-type [1,4]-oxazine structure such as heterocyclic compound fused [1,4]-oxazine. Because of these compounds are synthesized from heterocyclic amino alcohols and its derivatives that commercially rare amino alcohol derivatives **26**. Especially, most [1,4]-oxazine compounds that synthesized form these heterocyclic compounds are shows good biological activity for potential drugs development. From the scientific and commercial point of view, there need more various heterocyclic compound fused [1,4]-oxazine analogue and new type, such as [1,4]-oxazine part is switched compounds **28** for the development of [1,4]-oxazine (Scheme 8).

Scheme 8



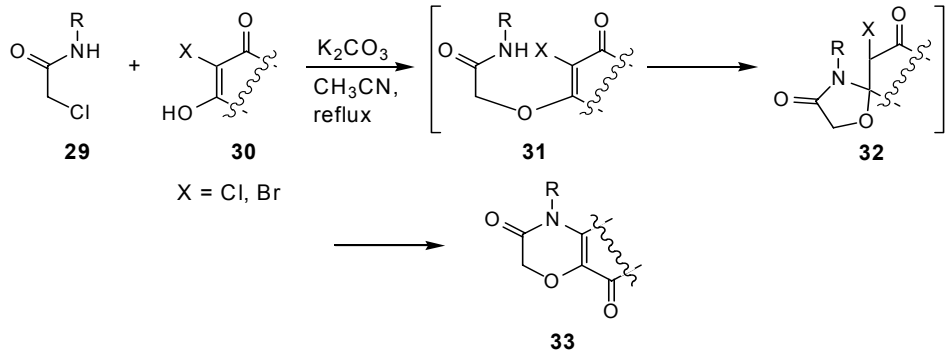
If we synthesize of compound **28**, this compound will be unique [1,4]-oxazine and adaptable for new bioactive compound or material research. Moreover, development of this reaction method will be discovering new reaction mechanism for other compounds. In this thesis, we will report of novel synthetic methods and synthesis of [1,4]-oxazine and their derivatives. In addition, we will explain its mechanism by study of intermediates and derivatives.

2. Results and discussion

2.1. Novel synthetic method of [1,4]-oxazine-and its derivatives and its mechanistic study

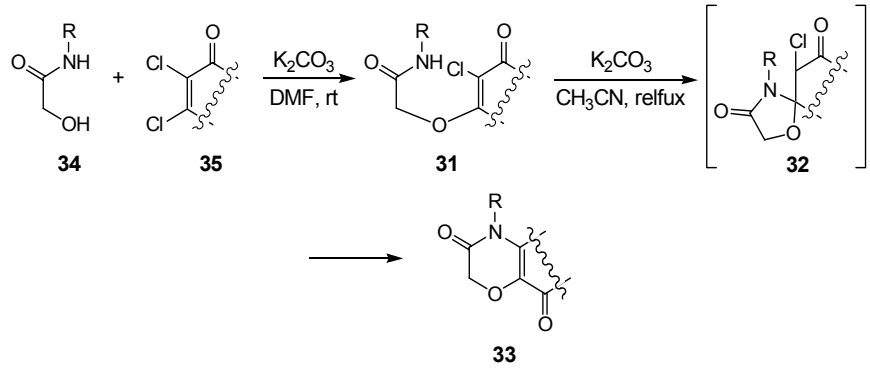
During the course of our studies related to the synthesis of bioactive compounds that containing an [1,4]-oxazines. We found novel and useful synthetic method for [1,4]-oxazine ring systems. Actually, we found unexpected final product and tried to explain its mechanism. In this reaction, we are using *N*-substituted-chloro acetamide **29** and heterocyclic compounds **30** as starting materials. In the study of reaction mechanism, we are expected *O*-alkylation **31** between two compounds by 1,4-addition. Then, this intermediate is making spiro type intermediate **32**. The formation of spiro intermediate occurred by breaking of aromatic or conjugation systems. Then, driving force to migration is oriented from re-aromaticity or re-conjugation system. By this driving force, we have expected the final product of [1,4]-oxazine ring **33** is synthesized (Scheme 9).

Scheme 9



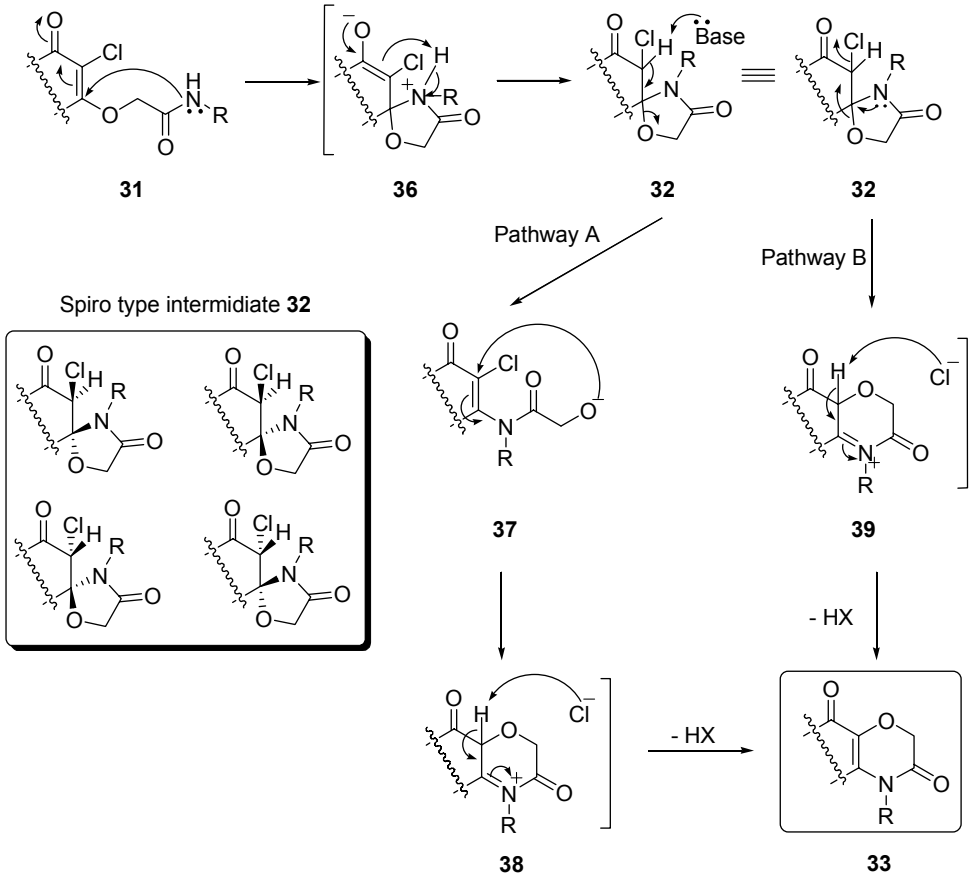
To provide this reaction mechanism, we synthesized [1,4]-oxazine derivatives **33**, using variety *N*-substituted-chloro acetamide **29** and heterocyclic compounds **30**. In addition, we tried to isolation of *O*-alkylated **31** and spiro type intermediates **32**. Nevertheless, isolation and detect of both *O*-alkylated **31** and spiro type intermediates **32** was impossible during the reaction. Therefore, we tried to synthesize of *O*-alkylated intermediate **31** using *N*-substituted-2-hydroxy acetamide **34** and dihalo heterocyclic compound **35**. Then, further cyclization of *O*-alkylated intermediate **31** to [1,4]-oxazine structure **33** is under same condition as a first one and compares both final products (Scheme 10).

Scheme 10



In addition, we have studied the expected its mechanism as shown Scheme 10. The proposed mechanism of this reaction has two possible reaction pathways. Both reaction mechanisms are showed same final product that cyclized [1,4]-oxazine **33**. However, the difference is migration step the spiro intermediate **32**. In the pathway A, the electronegativity of oxygen is 3.5 and nitrogen is 3.0. If open the spiro intermediate by the base and electronegativity, it will be make intermediate **37** then, reaction will go on. If not followed electronegativity, electron pair donation by nitrogen makes migration as pathway B (Scheme 11).

Scheme 11



31 **36** **32** **32** **37** **39** **38** **33**

To confirm the reaction mechanism, we synthesized pathway A intermediate **37** then, keep toward to synthesis of [1,4]-oxazine **33** and compare with pathway B result. Actually, we could not isolate or synthesize all intermediates in proposed reaction mechanism. However, we could think there are only two possible ways to synthesis of [1,4]-oxazine. If one of test reaction is react properly, we could think this reaction followed test reaction. If not, we could assume that this reaction followed other pathway. Therefore, we selected pathway A to model of its mechanism study. Because of synthesis of pathway A intermediates **37** are easier than pathway B intermediates **39**.

In addition, we are investigated various *N*-substituted-chloro acetamide **29** with heterocyclic compounds **30** and *N*-substituted

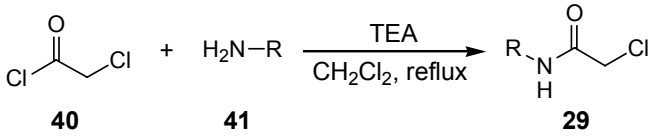
-2-hydroxy acetamide **34** with dihalo heterocyclic compounds **35** to synthesis of various [1,4]-oxazine derivatives **33**. Because, more than half of the compounds produced by nature have heterocyclic rings are incorporated in their structures. Nearly all the alkaloids are derived form heterocyclic molecules and considerable number of the substances used as drugs. Therefore, our final goal is synthesis of heterocyclic ring fused [1,4]-oxazine derivatives that has biological activate. Within these concepts, we are starting these series of investigation.

Synthesis of starting material for [1,4]-oxazine structure

Synthesis of *N*-substituted-chloro acetamide 29 derivatives

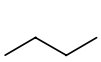
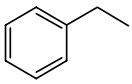
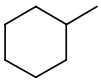
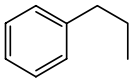
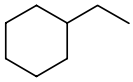
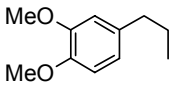
For the synthesis of starting material *N*-substituted-chloro acetamide **29**, we are using chloro acetyl chloride (**40**) and various first order amines **41** in present of triethylamine base and CH_2Cl_2 solvent at reflux condition (Scheme 12). By this reaction condition, we are obtained *N*-substituted-chloro acetamide **29** in a good yield (Table 1).

Scheme 12



40 **41** **29**

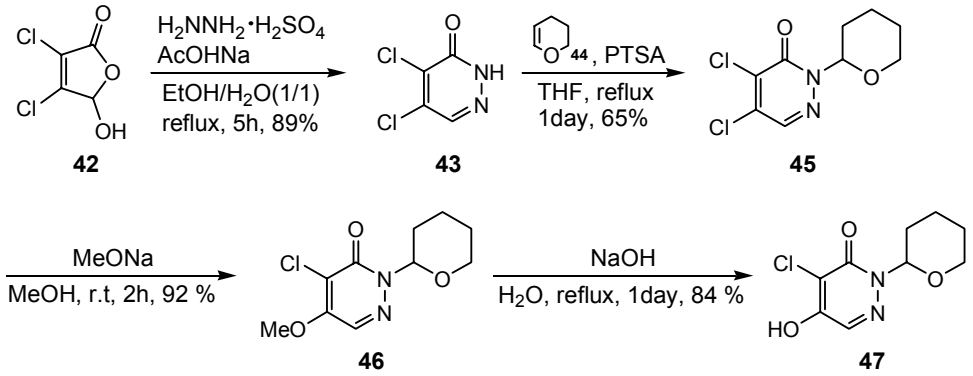
Table 1. Yield of *N*-substituted-chloro acetamide 29 derivatives

Entry No.	R	Yield (29)	Entry No.	R	Yield (29)
a		65%	d		55%
b		53%	e		66%
c		62%	f		65%

Synthesis of 4-chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (47)

Another starting material 4-chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**47**) is synthesized by the known methods.[22,23] Treatment of 3,4-dichloro-5-hydroxy-5*H*-furan-2-one (**42**) with sodium acetate and hydro-zinium sulfate are afford 4,5-dichloro-2*H*-pyridazin -3-one (**43**). Then amide-protected product of 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) is synthesized form 3,4-dihydro-2*H* -pyran (**44**) in acidic condition. For the synthesis of final product the 4-chloro-5- hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**47**) was accomplished by convert the chloride at 5-position of 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) into hydroxyl group is using sodium methoxide and sodium hydroxide in order (Scheme 13).

Scheme 13

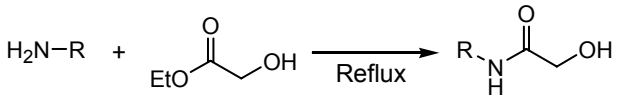


42 **43** **45** **46** **47**

Synthesis of *N*-substituted-2-hydroxy acetamide 34

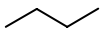
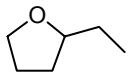
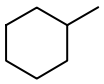
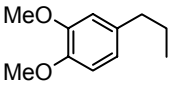
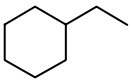
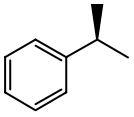
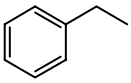
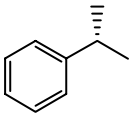
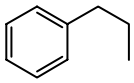
Most of methods in the literatures for the esters convert to amides are using strong base or acid.[24] Nevertheless, we are easily prepared by neat condition of the treatment of a various first order amines **41** with ethyl glycolate (**48**) in excellent yields (Scheme 14). However, in case of entry **34a**, we could not synthesized by neat condition. Because of the boiling point of propyl amine that is one of starting material was too low and could not remain in the reactor at neat reflux condition. Therefore, we are using basic condition and THF solvent for synthesis of entry **34a** (Table 2).

Scheme 14



41 **48** **34**

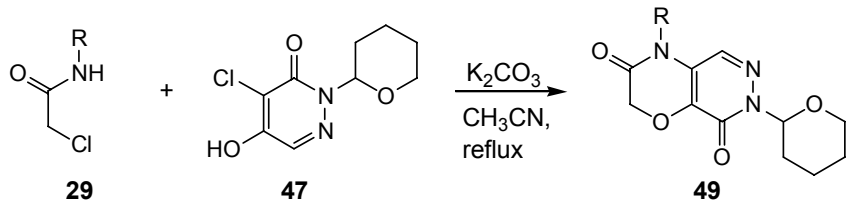
Table 2. Yield of *N*-substituted-2-hydroxy acetamide 34

Entry No.	R	Yield (34)	Entry No.	R	Yield (34)
a		**82%**	**f**		**92%**
b		**93%**	**g**		**96%**
c		**97%**	**h**		**96%**
d		**92%**	**i**		**95%**
e		**95%**			

One-pot synthesis of [1,4]-oxazine

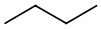
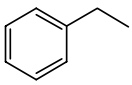
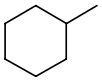
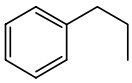
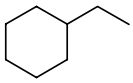
As we are described at previous chapter, one-pot synthesis was first developed reaction between *N*-substituted-chloro acetamide **29** and 4-chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**47**) in present of K_2CO_3 base and acetonitrile solvent at reflux condition. In this reaction, we synthesized unique and novel products of *N*-substituted-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine-3,8-dione **49** with good yield (Table 3). Compare with normal reaction products such as amino alcohol and dihalo compounds, this products showed that position of oxygen and nitrogen atoms in [1,4]-oxazine are switched (Scheme 15).

Scheme 15.



29 **47** **49**

Table 3. Yield of *N*-substituted-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyri -dazino-[4,5-*b*][1,4]oxazine-3,8-dione 49

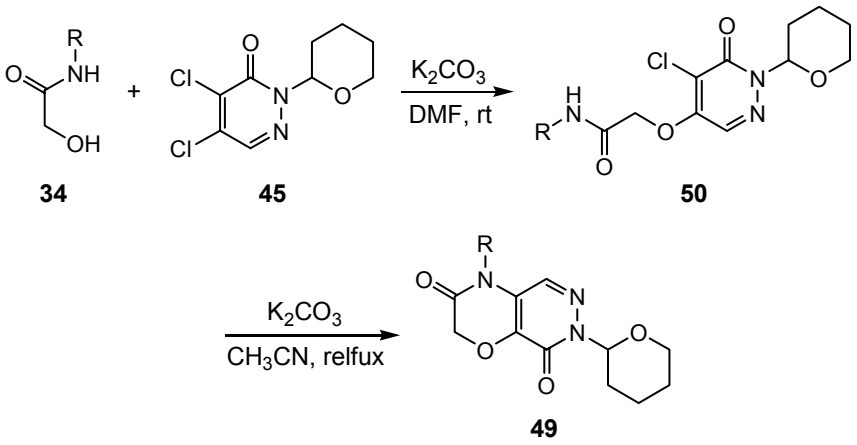
Entry No.	R	Yield (49)	Entry No.	R	Yield (49)
a		89%	d		97%
b		82%	e		90%
c		91%			

Systematic synthesis of [1,4]-oxazine

In a part of our investigation of this series of reactions, systematic synthetic method is applied to confirming of *O*-alkylated intermediate **50** that created during the one-pot synthesis method (Chapter 2.1). In this reaction, we are using *N*-substituted-2-hydroxy acetamide **34** and 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin -3-one (**45**) as starting materials in a basic condition at DMF solvent (Scheme 16). By this reaction, we could isolated *O*-alkylated product, *N*-substituted-2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyrida

zin-4-yloxy]-acetamide **50**. Then, obtained cyclized product **49** is using same condition as one-pot synthesizing condition in a good yields (Table 4). The confirming of both products one-pot synthesis product and systematic synthesis products are measured by IR, ^{1}H, ^{13}C-NMR and GC-Mass spectroscopy instruments. By the spectroscopic study, we are confirmed that both final products are identically same. As a result, we are assumed that one-pot synthetic methods are making *O*-alkylated intermediate **31** during one-pot synthesis (Scheme 9, 11).

Scheme 16



34 **45** **50** **49**

Table 4. Yield of *N*-substituted-2-[5-chloro-6-oxo-1-(tetrahydro-pyran -2-yl)-1,6-dihydro-pyridazin-4-yloxy]-acetamide (50) and *N*-substituted-7-(tetra-hydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]oxazine-3,8-dione 49

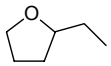
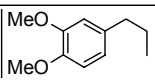
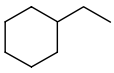
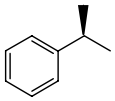
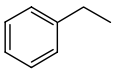
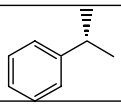
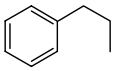
Entry No.	R	Yield (50)	Yield (49)	Entry No.	R	Yield (50)	Yield (49)
a		84%	80%	f		90%	89%
b		89%	87%	g		94%	91%
c		88%	94%	h		89%	91%
d		87%	92%	i		90%	89%
e		86%	82%				

Figure 2. X-ray structure of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl] -acetamideand (50g)

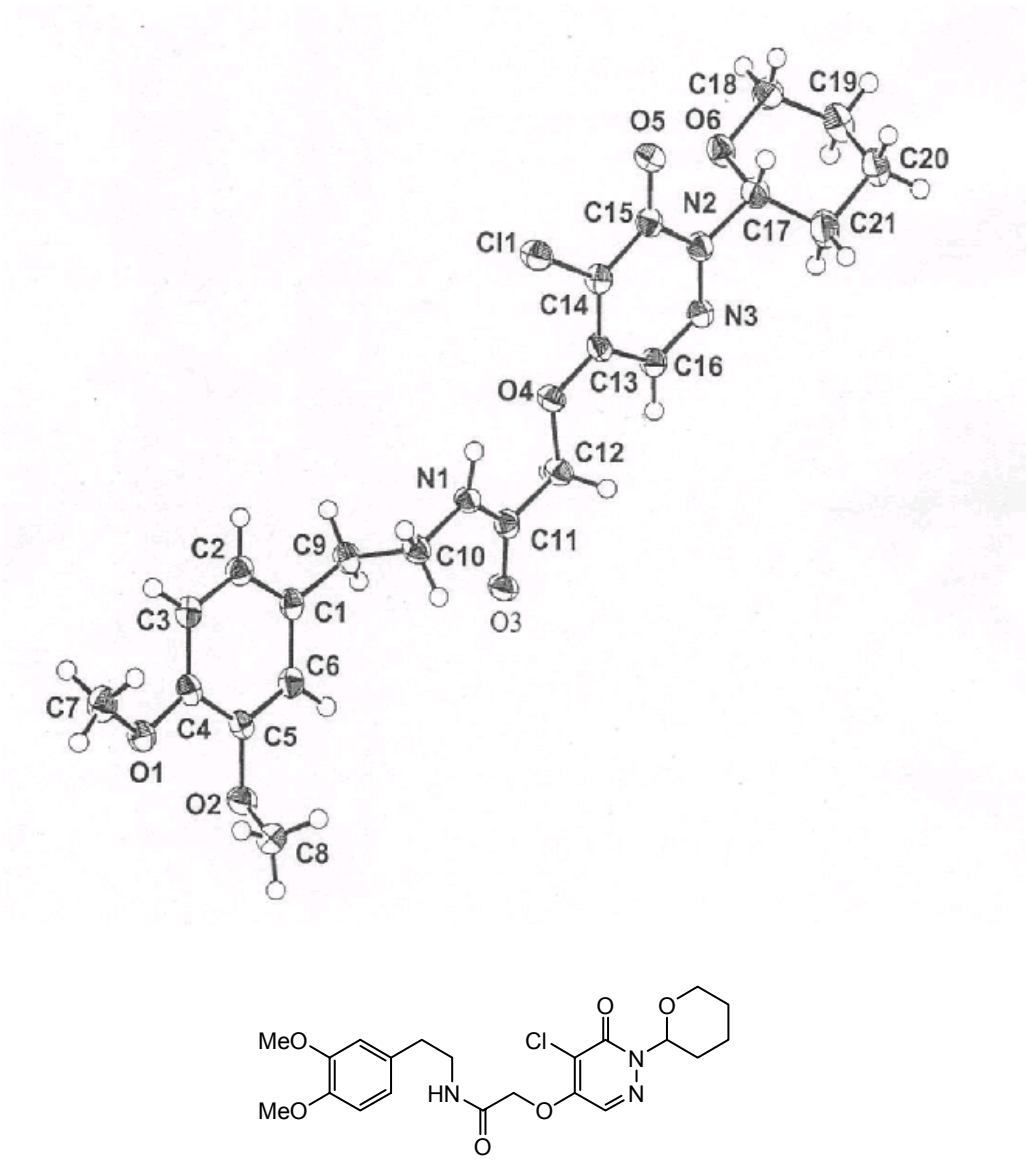
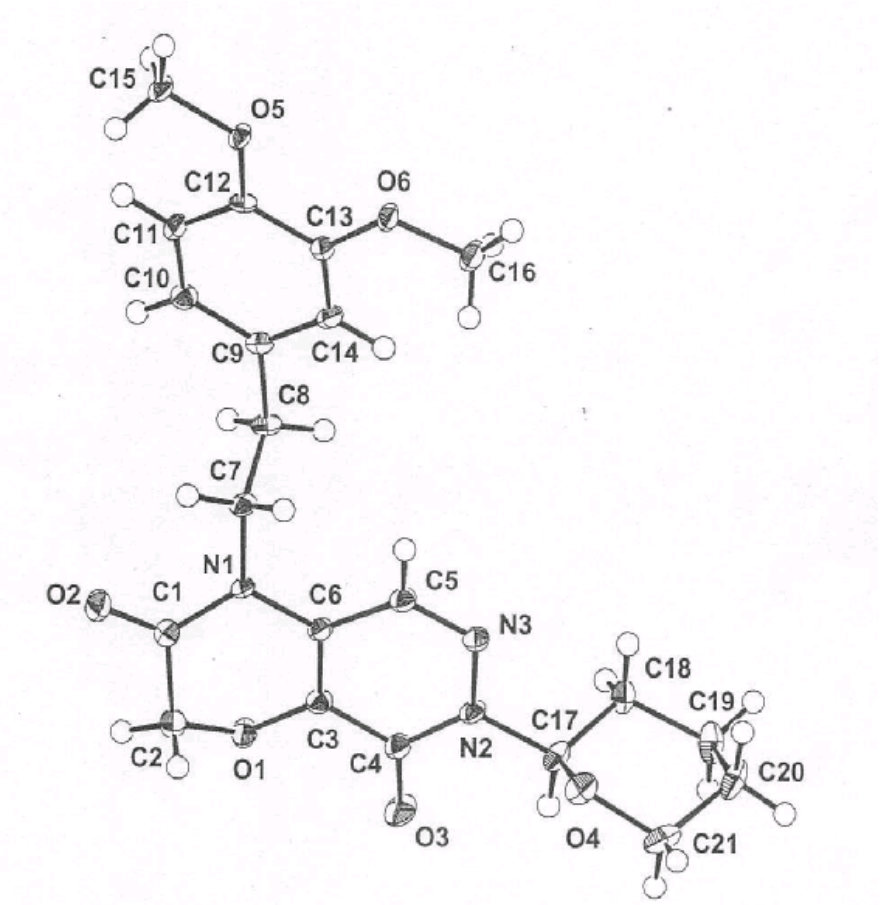
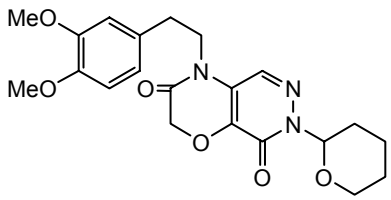


Figure 3. X-ray structure of 4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (49g)





2.2. Mechanism study of [1,4]-oxazine structures

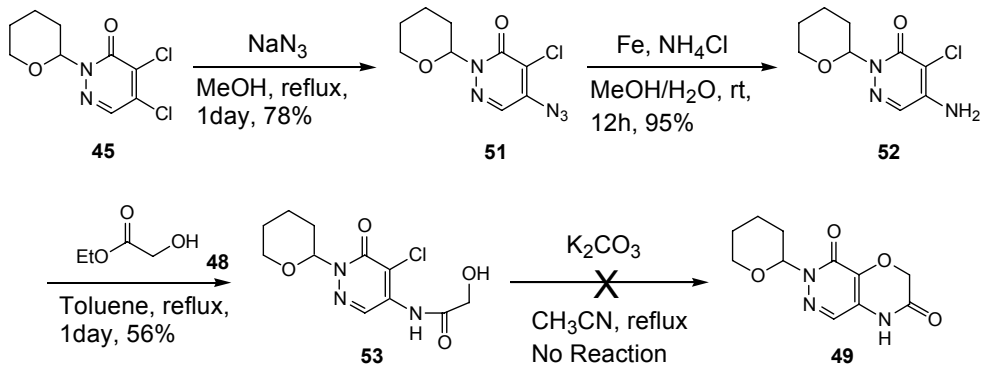
As we are noted at previous chapter, we could not isolate of

spiro type intermediate **32** nor detect by TLC and GC-Mass spectroscopic methods (Scheme 11). In our proposed mechanism, that has two reaction pathways. In the pathway A, amide type intermediate **37** is synthesized during the reaction. If this reaction under going to pathway A, amide type intermediate **33** is key compound and mechanism test will be carrying out by this intermediate **37** convert to [1,4]-oxazine structure **33** (Scheme 11).

Therefore, we tried to synthesize amide type intermediate, *N*-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yl]-2-hydroxy -acetamide (**53**). Then, synthesis of [1,4]-oxazine structure **49** is using this intermediate in the same as a general [1,4]-oxazine structure syntheses condition. To the synthesis of amide type intermediate, *N*-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yl]-2-hydroxy-acetamide (**53**), we are using 4,5-dichloro-2-tetra-hydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) as a starting material.

Followed syntheses of 5-azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**51**) and 5-amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**52**) was easily accomplished by the known method.[25] Synthesis of *N*-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yl]-2-hydroxy-acetamide (**53**) was obtained from 5-amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**52**) with ethyl glycolate (**48**) in the toluene solvent and reflux condition. Finally, we tried to synthesis [1,4]-oxazine structure **49** from *N*-[5-chloro-6-oxo -1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yl]-2-hydroxy-acetamide (**53**). However, this reaction was not react and could not obtain cyclized [1,4]-oxazine compound that 7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyri-dazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49**) (Scheme 17).

Scheme 17



This test reaction was not much clearly proved the whole mechanism. However, we are understood that this reaction was not opened the oxygen at the spiro intermediate **32** by the base and electronegativity. In addition, we are assumed this reaction would be followed pathway B (Scheme 11).

2.3. Synthesis of heterocyclic compound fused [1,4] -oxazine derivatives

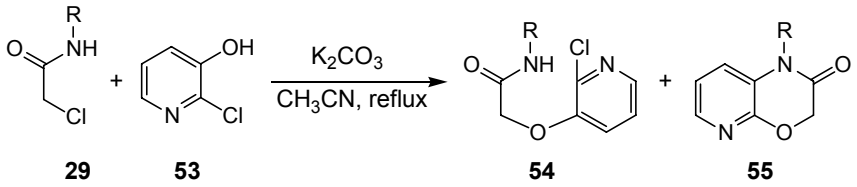
Introduction

In these currently work for synthesis of [1,4]-oxazine and its derivatives, we are investigated of verity heterocyclic ring compound fused [1.4]-oxazines. Especially, heterocyclic ring fused [1.4]-oxazines are important key materials of potentially bioactive compounds or drugs, as we are concerned at previous chapters. In addition, by the study of these series of reactions, we are fully understood that this novel [1,4]-oxazine mechanism is followed nitrogen oriented rearrangement pathway.

Synthesis of pyridine fused [1,4]-oxazine derivatives

In this investigation, we are obtained *N*-substituted-1*H*-pyrido-[2,3-*b*][1,4]-oxazin-2-one **55** using *N*-substituted-chloro acetamide (**29**) with 2-chloro-3-pyridinol (**53**) as a starting materials in the present of K_2CO_3 and acetonitrile solvent (Scheme 18).

Scheme 18



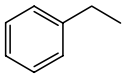
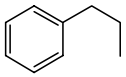
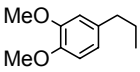
The most important thing in this reaction, we synthesized pyridine fused [1,4]-oxazine, especially that each nitrogen atoms are located at opposite side by new method. Although many scientists have tried to synthesize of this [1,4]-oxazine, no one could succeed.[26] In addition, this reaction makes *O*-alkylated compounds **54** which we could think to the reaction intermediate. The ratio of **54** and **55** are defending on reaction time and its ratio was changed by reaction time. By the flowing hours, cyclized product **55** was overwhelmed and this changing was monitored by GC-Mass spectroscopy. Final product *N*-substituted-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one **55** was confirmed by ^{1}H-NMR, ^{13}C-NMR, GC-Mass and COSY spectrum study (Table 5).

To verify [1,4]-oxazine **55** structure, we synthesized general type pyridine fused [1,4]-oxazine **59** that nitrogen atoms are located same side to compare of our product (Scheme 19).

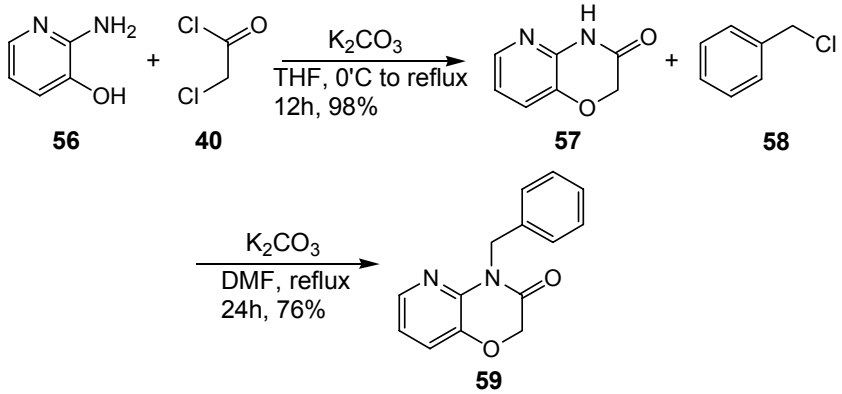
In this reaction, we are obtained 4-benzyl-4*H*-pyrido[3,2-*b*][1,4]oxazin

-3-one (**59**) in reasonable yield and examined ^{1}H-NMR, ^{13}C-NMR, GC-Mass and COSY spectrum. By the ^{1}H-NMR, ^{13}C-NMR, GC-Mass data, both *syn* and *anti* type pyridine fused [1,4]-oxazine showed differences.

Table 5. Yield of *N*-substituted-2-(2-Chloro-pyridin-3-yloxy)acetamide 54 and *N*-substituted-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one 55

Entry No.	R	Time (hours)	Yield	Ratio(54, 55)
a		48, 96	92%	28 : 72, 4 : 96
b		48, 96	94%	29 : 71, 9 : 91
c		48, 96	93%	26 : 74, 11 : 89

Scheme 19

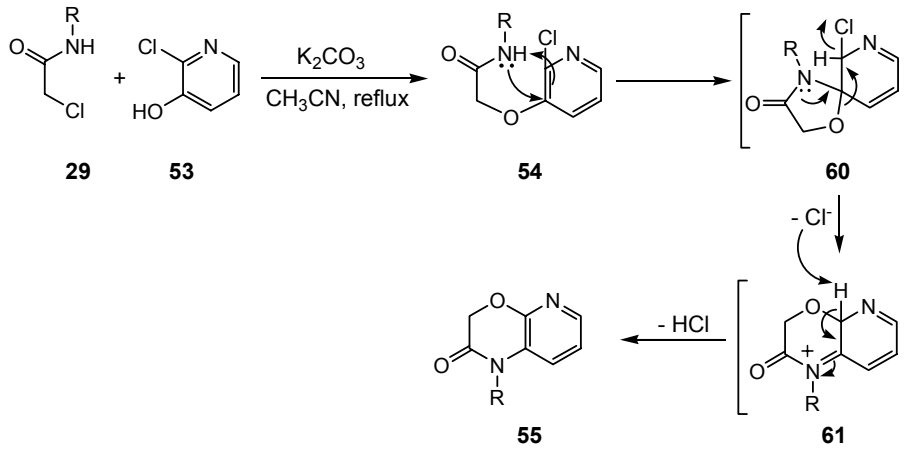


In the COSY spectrum data of **55a**, we are found long-range coupled protons that located at *alpha* position of benzyl and para position of

pyridine. However, compound **59** could not found any long-range coupling between proton at *alpha* position of benzyl and any proton of pyridine.

Compare with pyridazine fused [1,4]-oxazine derivatives **49** pyridine fused [1,4]-oxazine **54** was taking more reaction time to cyclization. We considered these results are caused by electronegativity and electron capability of nitrogen at pyridine moiety. Compare with carbonyl group at pyridazine, this results are showed that nitrogen at pyridine has weak ability of both electron effects (Scheme 11, 20).

Scheme 20

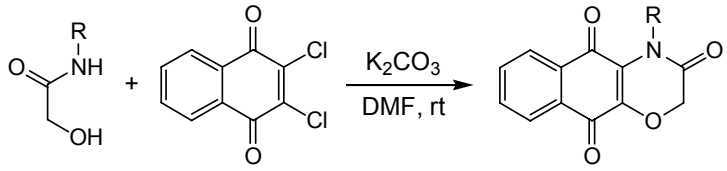


Recently developed new analgesic agents 4-{3-[4-(4-fluoro-phenyl)-piperazin-1-yl]-propyl}-4*H*-pyrido-[3,2-*b*][1,4]-oxazin-3-one (**4**) (Figure 1) has both nitrogen atoms are located at same side. However, when using our method, the results of both nitrogen atoms are located at opposite side. This is unique point of this product and potentially adaptable to mimic or new drugs development.

Synthesis of naphthoquinone fused [1,4]-oxazine derivatives

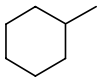
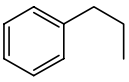
This test reaction was direct toward to synthesis of *N*-substituted-4*H*-naphtho[2,3-*b*][1,4]-oxazine-3,5,10-trione **63** derivatives and mechanism test. *N*-substituted-2-hydroxy acetamide **34** and 2,3-dichloro-[1,4]naphthoquinone (**62**) are using as a start materials in the present of K_2CO_3, acetonitrile solvent as same as former cyclization methods (Scheme 21)(Table 6).

Scheme 21



34 **62** **63**

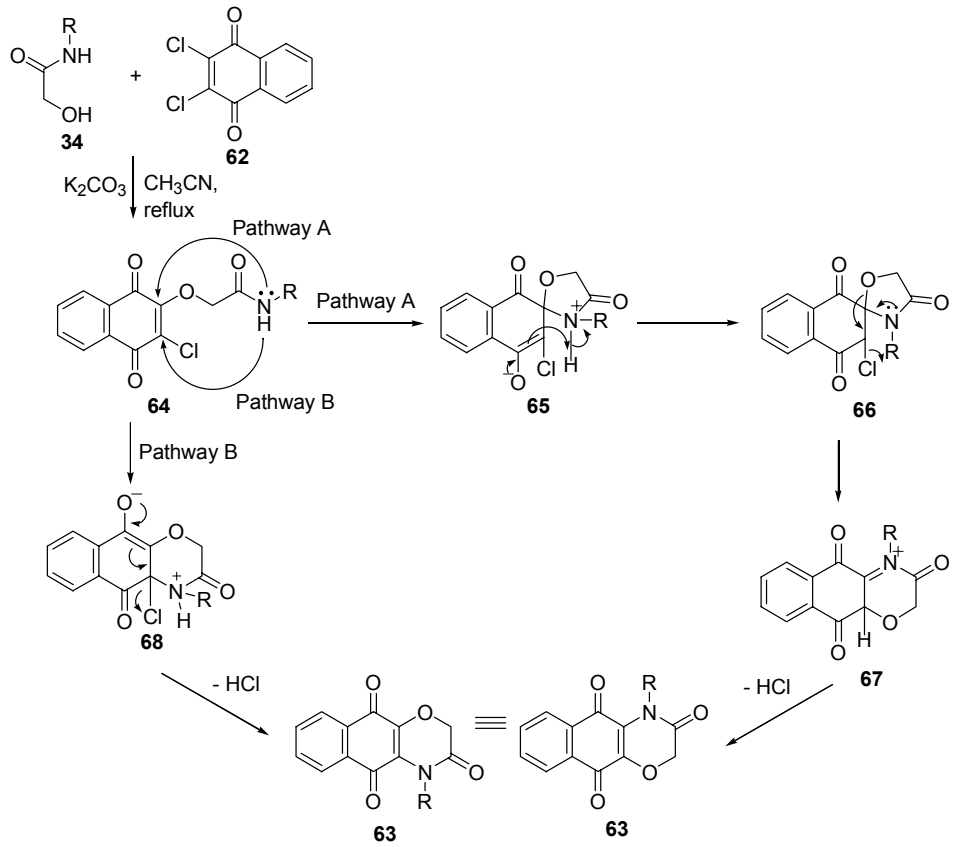
Table 6. Yield of *N*-substituted-4*H*-naphtho[2,3-*b*][1,4]-oxazine-3,5,10-trione 63

Entry No.	R	Yield (63)	Entry No.	R	Yield (63)
a		52%	b		58%

During reaction, we could not obtain *O*-alkylated compound **64** as usually obtained form other reactions and reaction time was particularly short. By the mechanistic study, we are suggesting this intermediate has unique points at the carbons. The one of unique point is *O*-alkylated carbon at naphthoquinone, this carbons electron density was very low caused by surrounding environment. By this

points, pathway A was accelerated to making spiro type intermediate **66** as other reaction in this thesis and farther reaction to cyclization compound **63** by rearrangement. Another point is halogen-attached carbon at naphthoquinone, this carbon also has low electron density and follow pathway B to 1,4-addition type Michael reaction **68**. In addition, this reactions final product is cyclization compound **63** and it is as same as pathway A final product (Scheme 22). By these reasons, this cyclization reaction is faster than other previous cyclizatied reactions.

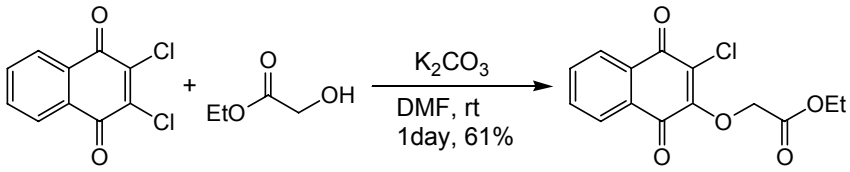
Scheme 22



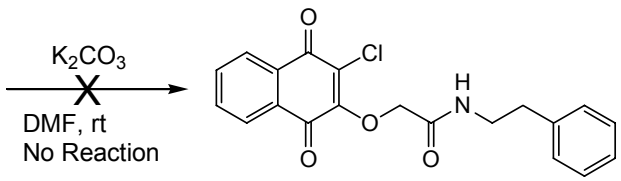
For the mechanistic study of *N*-substituted-4*H*-naphtho[2,3-*b*][1,4] -oxazine-3,5,10-trione **63**. We tried to synthesizing one of key

intermediate that is *O*-alkylated type, 2-(3-chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-yloxy)-*N*-methyl-acetamide (**64**) (Scheme 22). To prevent of cyclization during this reaction, we are choose ethyl glycolate (**48**) for starting material instead of *N*-substituted-2-hydroxy acetamide **34** then convert ester part to amide, using phenethyl amine that is *O*-alkylated intermediate **70** (Scheme 23).

Scheme 23



62 **48** **69**



70

Nevertheless, we could not obtained *O*-alkylated product and other side products by this method. Therefore, in this time, we could not suggest this reaction mechanism. If using oxygen isotope at one of carbonyl oxygen in 2,3-dichloro-[1,4]naphtha-quinone (**62**) or asymmetrical hydroquinone, we are sure that whole mechanism will be explain by NMR study.

2.4. Synthesis of 7-memberd ring system

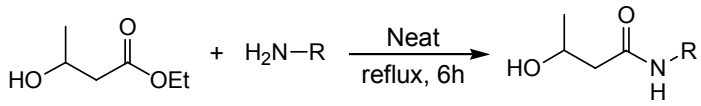
Introduction

To the expending of this series of experiment, we tried to 7-membered ring system. Recently, some of reports are mentioned about benzene fused 7-memberd ring system that has some bioactivities.[27-30] In addition, there few synthetic methods of 7-memberd ring system are reported. If we using one carbon number extended amide for starting material, we can easily obtain 7-membered ring by our method.

Synthesis of 7-memberd ring fused [1,4]-oxazine derivatives

For the test of our idea, first, we synthesized on of starting material *N*-substituted-3-hydroxy butyramide **72** using ethyl 3-hydroxy butylate (**71**) and various first order amines **41** (Scheme 24) (Table 7).

Scheme 24



71 **41** **72**

Then, *O*-alkylated compound *N*-substituted-3-[5-chloro-6-oxo-1-(tetra-hydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-methyl-butyramide **73** was synthesized from 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) and *N*-substituted-3-hydroxy butyramide **72** (Table 7). Finally, cyclization to our desired compound that *N*-substituted-

9-methyl-3-(tetrahydropyran-2-yl)-6,7-dihydro-3*H*,9*H*-5-oxa-2,3,9-triaza-benzo-cycloheptene-4,8-dione **74** are using same method as we are described in the previous chapter (Scheme 25) (Table 7).

Scheme 25

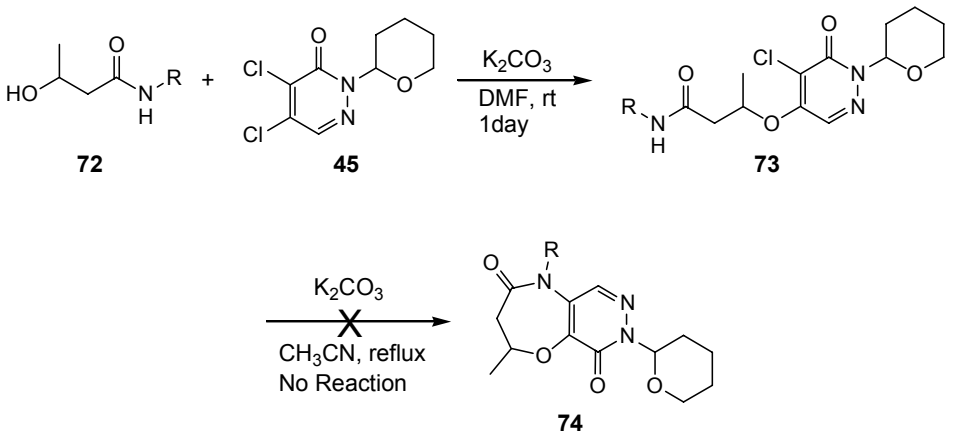
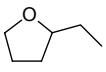
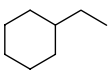
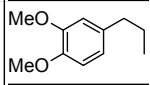
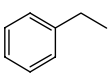
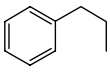


Table 7. Yield of *N*-substituted-3-hydroxy butyramide 72 and *N*-substituted-3-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-methyl-butyramide 73

Entry No.	R	Yield (72)	Yield (73)	Entry No.	R	Yield (72)	Yield (73)
a		55%	32%	e		55%	
b		62%	31%	f		63%	43%
c		60%	31%	g		62%	45%
d		61%	29%				

During the course of 7-membered ring system investigation, we could not obtained any final product that *N*-substituted-9-methyl-3-

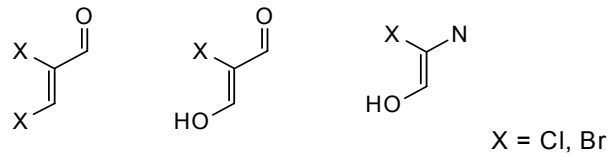
(tetrahydropyran-2-yl)-6,7-dihydro-3*H*,9*H*-5-oxa-2,3,9-triaza-benzo-cyclohe ptene-4,8-dione **74**. By the analysis of these results, it is not clear to explain but we are thinking of alkyl chain of *N*-substituted-3-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-butyramide **73** has some problem to this reaction. To explaining of this result, we thought the *O*-alkylated product has much longer and flexible carbon chain, so there is no chance to Michael type addition attacks of 3-position carbon at pyridazine moiety that is one of critical reaction in this reaction.

2.5. Synthesis of non-aromatic compound fused [1,4]-oxazine derivatives

Introduction

In this chapter, we are study non-aromatic material adapting to our system that construct of [1,4]-oxazine compound. In the pervious experiments and reaction mechanisms are seems that the conjugation of 3-halo-4-hydroxy-prop-3-en-2-one **74** or dihalo-hydroxy-but-3-en-2-one **76** and 2-nitrogen-2-halo-ethenol **77** are very important roles in our reaction (Scheme 26).

Scheme 26



75 **76** **77**

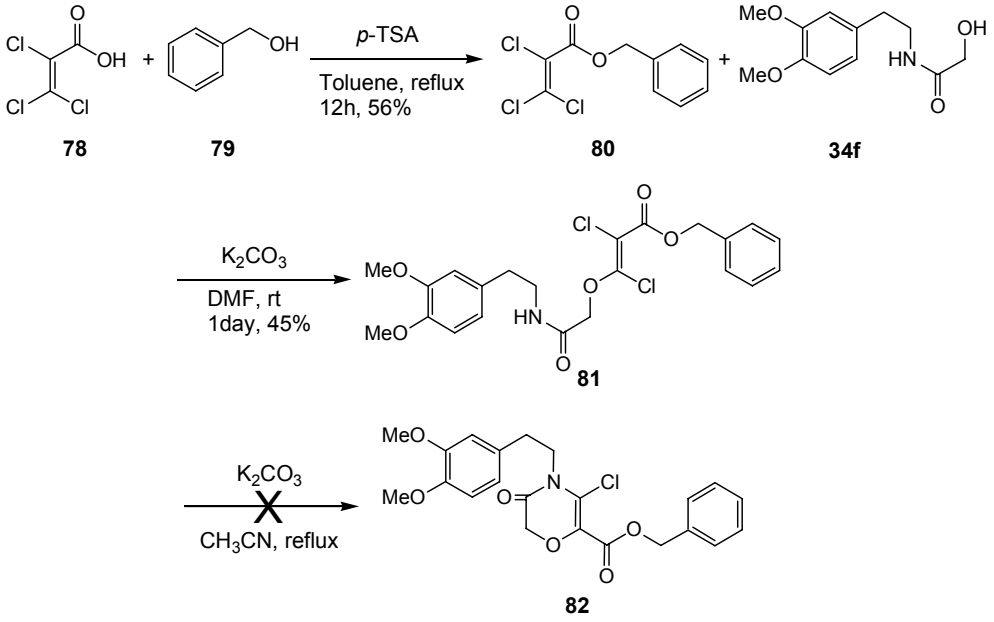
Therefore, we are easily extending our investigation area to non-aromatic system using one of these moiety-containing compounds.

For the non-aromatic system investigation, we are used simple compounds such as 2,3,3-trihalo-acrylic acid ethyl ester and 2,3-dihalo-5,5-dimethyl-cyclohex-2-enone for this series of study.

Synthesis of non-cyclic and non-aromatic compound fused [1,4]-oxazine derivative

For the synthesis of non-aromatic and non-cyclic compound fused [1,4]-oxazine, we are choose 2,3,3-trichloro-acrylic acid (**78**) as starting material and protection of acid part to ester part, using benzyl alcohol (**79**) in acidic condition. In this reaction, we are choose acidic condition, because prevent of 1,4-addition of benzyl alcohol. The *O*-alkylation with *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-2-hydroxy-acetamide (**34f**) used general method in this thesis. Finally, the cyclization of *O*-alkylated compound 2,3-dichloro-3-{[2-(3,4-dimethoxy-phenyl)-ethyl-carbamoyl]-methoxy}-acrylic acid benzyl ester (**81**), also used general method. However, we could not obtain cyclizatied compound (Scheme 27).

Scheme 27



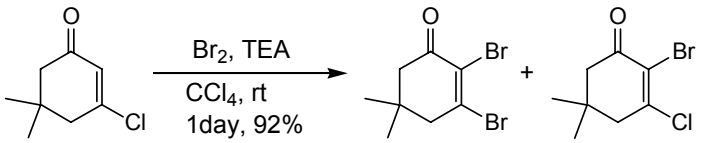
For explain of this result, we could not get any well-founded reasons. Only we are conjecture that the cyclization to [1,4]-oxazine needs geometrically fixed form such as cyclic or aromatic system and other fact that we are not discovered yet.

Synthesis of non-aromatic compound fused [1,4]-oxazine derivative

For the attestation of our genuine idea in this chapter, we are chosen cyclohex-2-enone for geometrically fixed non-aromatic compound for the test reaction. For the synthesis of starting material 2-bromo-3-chloro-5,5-dimethyl- cyclohex-2-enone (**85**), we are using 3-chloro-5,5-dimethyl-cyclohex-2-enone (**83**) as a starting material and took general brominating procedure that followed known lecture using bromine in present of triethyl amine at tetrachloro methane (Scheme

28).[31]

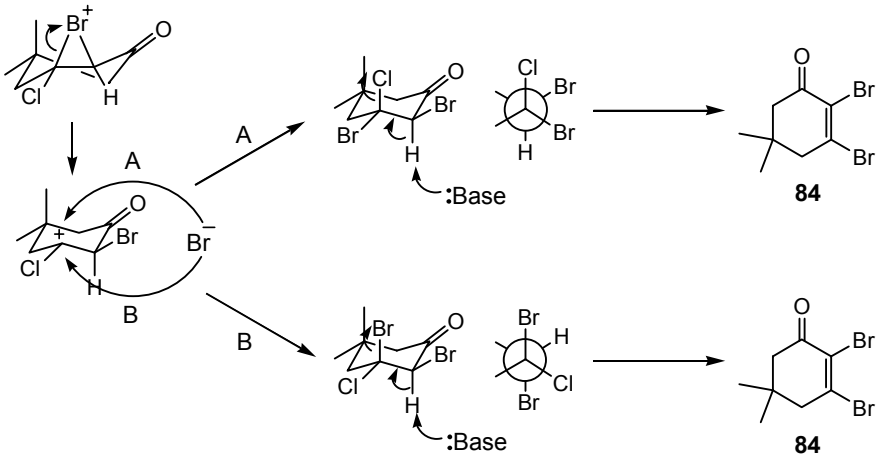
Scheme 28



83 **84** **85**

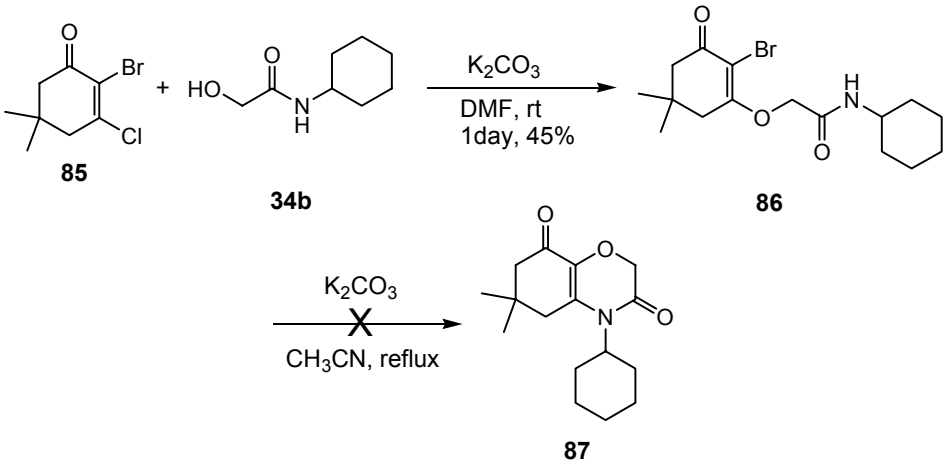
The reaction result of GC-Mass spectroscopic study showed unexpected two brome-attached products. One is 2,3-dibromo-5,5-dimethyl-cyclohex-2-enone (**84**) and the other is 2-bromo-3-chloro-5,5-dimethyl-cyclohex-2-enone (**85**). The ratio of products **84** and **85** is 45 : 55, this result confirmed by the GC-Mass study. To explaining this result, compare the leaving group abilities of brome and chloride are could be one of solution. During the eliminate step to final product of this reaction, brome and chloride are completive react to leaving for construct of double bond. However, brome has more good leaving ability and easily removed from cyclohexenone. In addition, anti-periplanner geometry could be explaining this result. After the addition of brome to cyclohexenone, there has two attaching site are exist. Compare both reaction sites, pathway B is easier than pathway A. Because, pathway A has 1,3-diaxial interactions between one of methyl group that is axial position. To avoid this interaction, pathway B is more favor than A. However, in the next step of elimination, pathway A intermediate is accelerate of elimination step by overcome of 1,3-diaxial interactions (Scheme 29, 30).

Scheme 29



However, both products are same dihalo compounds and could be using to next step synthesis of 2-(2-bromo-5,5-dimethyl-3-oxo-cyclohex-1-enyloxy)-*N*-cyclohexyl acetamide (**86**). The *O*-alkylated compound **86** was taking general procedure of cyclization for the construct of [1,4]-oxazine structure **87**. However, we could not obtain any cyclized product by this reaction (Scheme 29).

Scheme 30



As a previous results, we could not found any reasons of this failure. Nevertheless, we are presumption that from all results of this thesis,

the cyclization of [1,4]-oxazine needs conjugated 3-halo-4-hydroxy-prop-3-en-2-one (**75**) or dihalo-hydroxy-but-3-en-2-one (**76**) compound and geometrically fixed 2-nitrogen-2-halo-ethenol (**77**) form contained compound and that must be planner.

3. Conclusions

During the course of our investigation, we synthesized new-type [1,4]-oxazines such as *N*-substituted-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]oxazine-3,8-dione **49**, *N*-substituted-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one **55**, *N*-substituted-4*H*-naphtho[2,3-*b*][1,4]-oxazine-3,5,10-trione **63** and their derivatives. In addition, we are found two noble methods of [1,4]-oxazine synthesis. By the experiment of mechanism test, we are suggesting of this synthetic pathway that is follow the *O*-alkylation by SN2 type reaction / Michael type 1,4-addition between *N*-substituted-2-hydroxy **29** or halo acetamide **34** and dihalo **45** or halo hydroxy heterocyclic compound **47**. Then, *O*-alkylated product **31** making spiro type intermediate **32** by the Michael type addition. Finally, spiro intermediate **32** is making final product that [1,4]-oxazine by the nitrogen-oriented migration.

In addition, we tried to synthesize various aromatic compounds and non-aromatic compounds fused [1,4]-oxazine. In these studies, we synthesized aromatic compound fused [1,4]-oxazine but, anyhow, we could not synthesized non-aromatic compounds fused [1,4]-oxazine.

By these results, we are found that essential of this reaction. The most important thing is that the starting material has conjugated 3-halo-4-hydroxy-prop-3-en-2-one (**75**), dihalo-hydroxy-but-3-en-2-one (**76**) and 2-nitrogen-2-halo-ethenol (**77**) moieties and these materials must be geometrically fixed plane figure such as aromatic compounds.

Synthesis of bioactivity compound using these synthetic methods are will be followed and we are keeping study of heterocyclic compound such as thiophene, furan moieties fused [1,4]-oxazine.

4. Experimental

General

Unless otherwise indicated, all commercially available starting materials was used as received without purification. The solvents used purified by standard procedures and fractionally distilled. Tetrahydrofuran (THF) and diethyl ether (ether) was distilled from sodium metal and benzophenone immediately prior to use. Acetonitrile (CH_3CN) and *N,N*-dimethyl formamide (DMF) used commercially available HPLC grade and using with out farther purification. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen in glassware that had been oven dried. All glassware was dried in drying oven for 12 hours then cooled at desiccate in present of drying agent. All reactions were carried out under nitrogen atmosphere.

Analytical thin layer chromatography (TLC) was performed on Merck 60F254 silica gel plate with visualization using UV light or phosphomolybdic acid (PMA) and potassium manganese ($KMnO_4$) solution. Flash chromatography was performed using Merck D-6100 silica gel 60 (70-230 mash ASTM).

Infrared (IR) spectra were measured on a 410DSP FT-IR and reported in wavenumber (cm^{-1}). The samples were measured by neat on sodium chloride plates or pallet from using potassium bromide.

NMR spectra were obtained on JNM-LA300 instrument. Unless otherwise indicated, all spectra were obtained in deuteron chloroform ($CDCl_3$). Spectra are reported as follows; peak position (δ) downfield form TMS (multiplicity, coupling constant[s], number of protons). The peak position (δ) is in parts per million (ppm). The coupling constant (*J*) is in hertz (Hz).

Mass spectra were measured by GC-Mass that combined HP 5973MSD (Mass) and HP6890 series (GC).

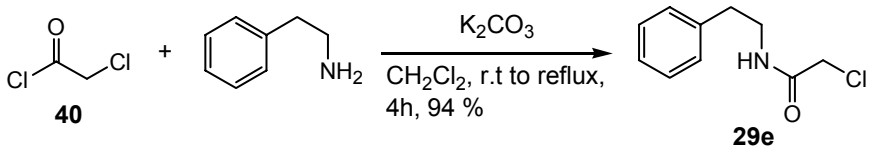
Optical rotations were measured at the sodium D line (589 nm) using

Rudolph Autopol III polarimeter calibrated using a standard quartz control cell.

The melting points of products were measured MEL-TEMP capillary melting point instrument and naming of synthesized compound was used ACD/Name IUPAC program.

***N*-Substituted-2-chloro acetamide 29**

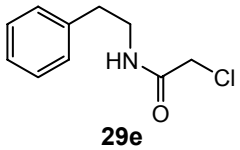
General procedure;



At the 250 ml round bottomed flask, 2-chloroacetyl chloride (6.26 g, 55.5 mmol) was added over 30 min to a room temperature mixture of phenethylamine (6.11 g, 50.4 mmol) and powdered K_2CO_3 (8.0 g, 58.0 mmol) in dichloromethane (100 ml). After 30 min, the mixture was refluxed for 4 hours, monitored by TLC and then stirred for an additional 30 min at room temperature. The reaction mixture was poured into cold water (200 ml) and extracted with dichloromethane (2 x 100 ml). The combined extracts were washed with water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (1/1, v/v) as eluent affording 2-chloro-*N*-phenethylacetamide (**29e**) (9.37 g, 94 % yield) as a white solid.

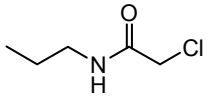
mp 64~65 ℃; IR (KBr, cm^{-1}) 3284, 3074, 2956, 1659; ^{1}H-NMR(300 MHz, $CDCl_3$) δ6.72~6.84(m, 5H), 6.62(bs, *N*H), 4.03(s, 2H), 3.54~3.56(t, *J*=6.2 Hz, 2H), 2.79~2.82(t, *J*=6.1 Hz, 2H); ^{13}C-NMR(75 MHz,

$CDCl_3$) δ165.9, 128.4, 125.7, 128.4, 127.9, 140.2, 127.9, 37.2, 44.4, 49.0; MS (m/z) 197.66.



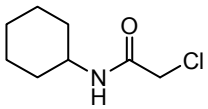
29e

29a: IR(KBr, cm-1) 3295, 3080, 2950, 2865, 1682, 1560, 1230; ^{1}H-NMR(300 MHz, $CDCl_3$) δ6.62(s, *N*H), 4.05(s, 2H), 3.28(q, *J*=6.6 Hz, 2H), 1.52~1.64(m, 2H), 0.95(t, *J*=6.2 Hz, 3H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ165.8, 55.8, 42.1, 22.5, 11.2.



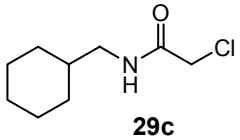
29a

29b: mp 97~99 ℃; IR(KBr, cm^{-1}): 3413, 3080, 2935, 2865, 1670, 1552, 1275; ^{1}H-NMR(300 MHz, $CDCl_3$): 6.42(s, *N*H), 4.03(s, 2H), 3.78~3.81(m, 1H), 1.18~1.94(m, 10H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ 191.30, 54.63, 48.63, 42.72, 32.78, 25.33.



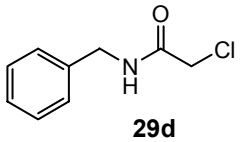
29b

29c: IR(KBr, cm^{-1}): 3426, 3062, 2919, 2842, 1680, 1545, 1280; ^{1}H-NMR(300 MHz, $CDCl_3$) δ6.62(s, *N*H), 4.06(s, 2H), 3.16(t, *J*=6.3 Hz, 2H), 0.90~1.75(m, 11H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ182.1, 77.0, 58.8, 45.9, 42.8, 37.7, 30.7.



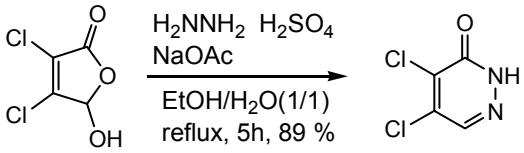
29c

29d: IR(KBr, cm^{-1}): 3421, 3058, 2991, 1675, 1568, 1280; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.26~7.35(m, 5H), 6.86(s, *N*H), 4.49(d, *J*=5.7 Hz, 2H), 4.11(s, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ137.2, 128.8, 127.8, 117.2, 105.2, 43.9, 42.6.



29d

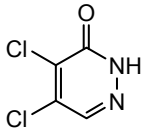
4,5-Dichloro-2*H*-pyridazin-3-one (43);



42 **43**

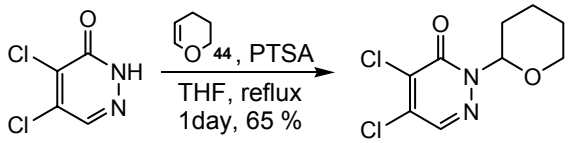
At the 1000 ml round bottomed flask, 3,4-dichloro-5-hydroxy-5*H*-furan-2-one (**42**) (30 g, 0.2 mol) was added over room temperature mixture of sodium acetate (17.7 g, 0.2 mol) water solution and hydrozinium sulfate (27.7 g, 0.2 mol) in ethyl alcohol (120 ml). The mixture was refluxed for 4 hours, monitored by TLC. The reaction mixture was concentrated under reduced pressure then poured into cold-water (500 ml X 3) washing the solid product and dried at air to give 4,5-dichloro- 2*H*-pyridazin-3-one (**43**) (29.53 g, 89 % yield) as a white solid.

mp: 206~209 ℃; IR(KBr, cm^{-1}) 3250, 3200, 3031, 2861, 1653; ^{1}H-NMR(300 MHz, DMSO-d_6) δ7.60 (s, 1H), 8.07 (bs, *N*H).



43

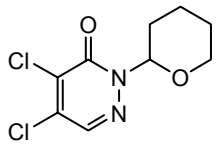
4,5-Dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (45);



43 **45**

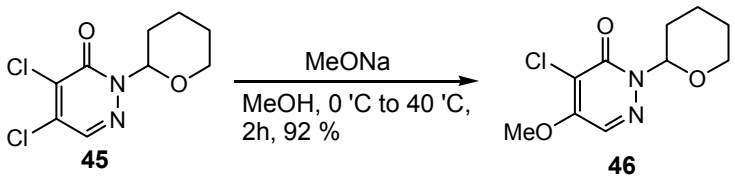
At the 250 ml round bottomed flask, 4,5-dichloro-2*H*-pyridazin-3-one (**43**) (20 g, 121.2 mmol), 3,4-dihydro-2*H*-pyran (**44**) (3 g, 36.4 mmol), *p*-toluenesulfonic acid monohydrate (2.3g , 12.1 mmol) and 100 ml of tetrahydrofuran were added. The mixture was stirred at reflux for 29 hours. Additional 3,4-dihydro-2*H*-pyran (**44**) was added at 6 hours (1.5 g, 18.15 mmol) and at 21 hours (0.8 g, 9.1 mmol), monitored by TLC. The reaction mixture was concentrated in reduced pressure to an oily residue. The residue was taken up in 200 ml of ethyl acetate, washed with 2 N sodium hydroxide (2 X 100 ml), and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (5/1, v/v) as eluent affording 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) (16.5 g, 65 % yield) as a white solid.

mp 77~80 ℃; IR(KBr, cm^{-1}) 2940, 2859, 1700, 1578; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.85(s, 1H), 6.02(d, *J*=8.14 Hz, 1H), 4.10~4.18(m, 1H), 3.68~3.81(m, 1H), 2.03~2.17(m, 2H), 1.60~1.72(m, 4H).



45

4-Chloro-5-methoxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (46);

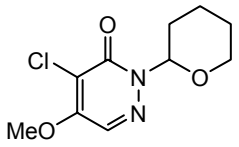


45 **46**

At the 250 ml round bottomed flask, add the 4,5-dichloro-2 -(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) over the 100 ml of methanol. The resulting solution was cooled to 0 ℃ and potassium hydroxide (19.5 g, 30.3 mmol) was added in divided small portions over approximately 10 min. The mixture was heated to 40 ℃ during 4 hours and monitored by TLC. The reaction mixture was partitioned with 200 ml of ethyl acetate and water (200 ml). The aqueous layer was extracted with ethyl acetate (200 ml X 2). The combined organic layers were washed with brine (100 ml X 2) and dried over $MgSO_4$. The organic solution was clarified by filtration and concentrated to give a dark semi solid. The residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (3/1, v/v) as eluent affording 4-Chloro-5-methoxy-2-(tetrahydro-pyran-2-yl)-2*H*-

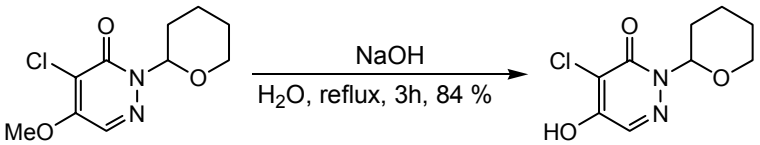
pyridazin-3-one (**46**) (6.8 g, 92 % yield) as a white solid.

mp 118~120 ℃; IR(KBr, cm^{-1}): 3100, 3030, 2950, 1638, 1100; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.85(s, 1H), 6.02(d, *J*=8.14 Hz, 1H), 4.10~4.18(m, 1H), 3.93(s, 3H), 3.68~3.81(m, 1H), 2.03~2.17(m, 2H), 1.60~1.72(m, 4H).



46

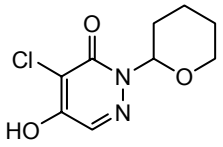
4-Chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (47);



46 **47**

At the 100 ml round bottomed flask, 4-chloro-5-methoxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**46**) (5 g, 20 mmol), potassium hydroxide (1.4 g, 42 mmol) and water (50 ml) was refluxed for 3 hours, monitored by TLC. After cooling to room temperature, concentrated hydrochloric acid (5 ml) was slowly added to the reaction mixture with stirring. The product was filtered, washed with water (100 ml) and dried in air to give 4-chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**47**) (3.8 g, 84 % yield) as a white solid.

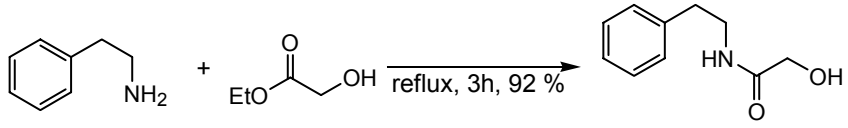
IR(KBr, cm^{-1}): 3180, 2988, 2654, 1638, 1594; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.85(s, 1H), 6.02(d, *J*=8.14 Hz, 1H), 4.10~4.18(m, 1H), 4.61 (s, 1H), 3.68~3.81(m, 1H), 2.03~2.17(m, 2H), 1.60~1.72(m, 4H).



47

***N*-Substituted-2-hydroxy acetamide 34**

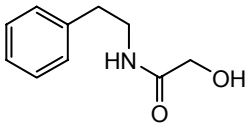
General procedure;



48 **34e**

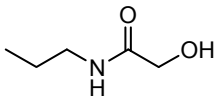
At the 100 ml round bottomed flask, ethyl glycolate (**48**) (2 g, 19.2 mmol) was added over phenethylamine (2.6 ml, 19.2 mmol). The mixture was refluxed for 3 hours, monitored by TLC then reaction mixture was concentrated under reduced pressure and washing the solid product using hexane (50 ml). The solid product and dried at air to give 2-hydroxy-*N*-phenethyl-acetamide (**34e**) (2.9 g, 86 % yield) as a white solid.

mp 66~69 ℃; IR(KBr, cm^{-1}) 3344, 3144, 2879, 1639, 1087; ^{1}H-NMR (300 MHz, $CDCl_3$) δ7.18~7.33(m, 5H), 6.78(bs, *N*H), 4.01(s, 2H), 3.50~3.57(q, *J*=7.2 Hz, 2H), 2.80~2.84(t, *J*=7.2 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ171.98, 138.47, 128.65, 128.63, 126.57, 61.97, 40.09, 35.59.



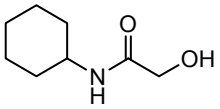
34e

34a; IR(KBr, cm^{-1}) 3313, 2965, 1675, 1120; ^{1}H-NMR(300MHz, $CDCl_3$) δ7.01(bs, *N*H), 4.91(s, OH), 4.04(s, 2H), 3.23(t, *J*=6.5 Hz), 1.54(m, 2H), 0.94(t, *J*=7.5 Hz, 3H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ171.98, 61.83, 40.56, 22.60, 11.22; MS(m/z) 117.



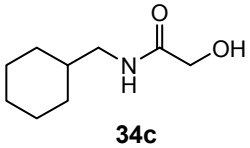
34a

34b; mp 97~99 ℃; IR(KBr, cm^{-1}) 3365, 3242, 2939, 1649, 1081; ^{1}H-NMR(300 MHz, $CDCl_3$) δ6.71(bs, *N*H), 4.33~4.37(t, *J*=5.1 Hz, OH), 4.01(d, *J*=4.2 Hz, 2H), 3.75~3.78(m, 1H), 1.17~2.04(m, 11H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ171.31, 61.56, 47.83, 32.92, 25.37, 24.73; MS(m/z) 157.



34b

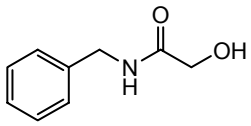
34c; IR(KBr, cm^{-1}) 3365, 3242, 2939, 1649, 1080; ^{1}H-NMR(300MHz, $CDCl_3$) δ6.77(bs, *N*H), 4.07(d, *J*=4.2 Hz, 2H), 3.82(s, OH), 3.14(t, *J*=6.6 Hz, 2H), 0.92~2.18(m, 11H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ171.98, 62.03, 45.15, 37.83, 30.72, 26.27, 25.72; MS(m/z) 171.



34c

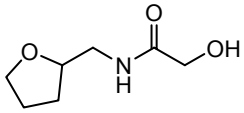
34d; IR(KBr, cm^{-1}) 3319, 3217, 3078, 2868, 1629, 1557, 1085;

^{1}H-NMR(300 MHz, $CDCl_3$) δ7.26~7.34(m, 5H), 4.46(d, *J*=5.5 Hz, 2H), 4.08(s, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ171.72, 138.47, 128.65, 128.63, 126.57, 55.57, 36.30; MS(m/z) 165.



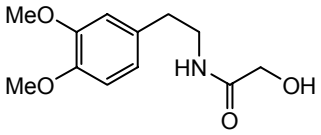
34d

34f; IR(neat, cm^{-1}) 3454, 3313, 2960, 1616, 1257, 1094; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.27(bs, *N*H), 4.92(bs, *O*H), 4.07(s, 2H), 3.88~4.00(m, 1H), 3.75~3.88(m, 2H), 3.54(m, 1H), 3.15~3.24(m, 1H), 1.89~2.01(m, 3H), 1.53~1.59(m, 1H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ172.69, 67.99, 61.83, 42.55, 28.50, 25.59, 14.00; MS(m/z) 159.



34f

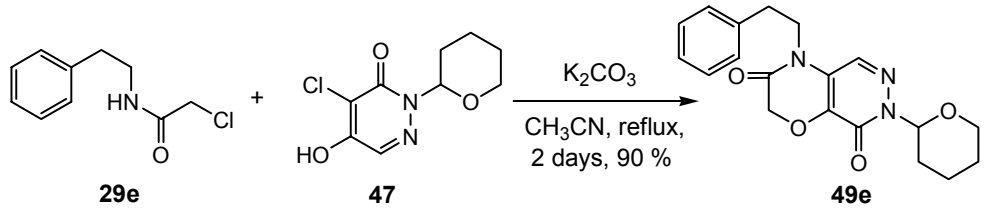
34g; IR(KBr, cm^{-1}) 3365, 3242, 3065, 2939, 1649, 1080; ^{1}H-NMR(300 MHz, $CDCl_3$) δ6.73~6.82(m, 3H), 6.71(bs, *N*H), 4.02(d, *J*=5.7 Hz, 2H), 3.85(d, *J*=3.6 Hz, 6H), 4.67(t, *J*=5.6 Hz, OH), 3.50-3.53(q, *J*=6.6 Hz, 2H), 2.75~2.80(t, *J*=6.9 Hz, 2H); ^{13}C-NMR(300 MHz, $CDCl_3$) δ171.89, 148.87, 147.58, 131.02, 120.57, 111.79, 111.29, 62.00, 55.81, 55.84, 40.14, 35.14; MS(m/z) 239.



34g

***N*-Substituted-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4] oxazine-3,8-dione 49 using one-pot method**

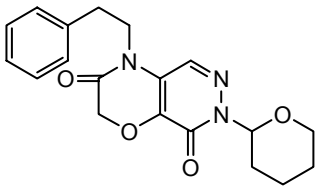
General procedure;



29e **47** **49e**

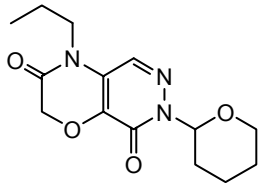
At the 100 ml round bottomed flask, 2-chloro-*N*-phenethylacetamide (**29e**) (1 g, 5.07 mmol) was added over mixture of 4-chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**47**) (1.29 g, 5.58 mmol) and K_2CO_3 (1.5 g, 10.67 mmol) in acetonitrile (50 ml). The mixture was refluxed for 2 days, monitored by TLC and then reaction mixture was concentrated under reduced pressure. The mixture was poured into dichloromethane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (5/1, v/v) as eluent affording 4-phenethyl-6-(tetrahydro-pyran-2-yl)-4,6-dihydro-pyridazino[4,5-*b*][1,4]oxazine-3,5-dione (**49e**) (1.6 g, 90 % yield) as a white solid.

IR(KBr, cm^{-1}) 2950, 1696, 1649, 1019; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 7.77(s, 1H), 7.19~7.39(m, 5H), 6.08(dd, *J*=2.44, 10.82 Hz, 1H), 4.75(s, 2H), 4.05~4.15(m, 3H), 3.73~3.80(m. 1H), 2.94(t, *J*=7.2 Hz, 2H), 1.61~2.17(m, 6H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ161.59, 158.23, 136.66, 128.62, 127.68, 126.58, 82.60, 68.67, 67.24, 42.47, 40.17, 39.89, 39.61, 33.84, 28.76, 27.67, 22.53; MS(m/z) 355.



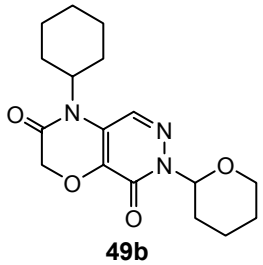
49e

49a; IR(KBr, cm^{-1}) 2965, 1705, 1659, 1022; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.81(s, 1H), 6.10(dd, *J*=2.44, 10.82Hz, 1H), 4.78(s, 2H), 4.11~4.15 (m, 1H), 3.73~3.95(m, 3H), 2.01~2.22(m, 8H), 0.98(t, *J*=7.4 Hz, 3H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ161.90, 155.21, 127.39, 124.25, 82.77, 68.92, 67.42, 42.57, 41.39, 28.95, 24.86, 22.74, 21.16, 10.97; MS(m/z) 293.



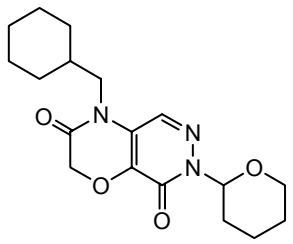
49a

49b; mp. 183~184 ℃; IR(KBr, cm^{-1}) 2945, 2978, 1702, 1659, 1274; ^{1}H-NMR(300 MHz, $CDCl_3$) δ8.04(s, 1H), 6.07(dd, *J*=2.44, 10.82Hz, 1H), 4.68(s, 2H), 4.30~4.39(m, 1H), 4.11(m. 1H), 3.73~3.80(m, 1H), 1.18~2.17(m, 16H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ163.32, 155.39, 128.58, 126.01, 82.70, 68.84, 66.26, 55.60, 30.00, 39.87, 28.91, 26.12, 25.06, 24.88, 22.73; MS(m/z) 333.



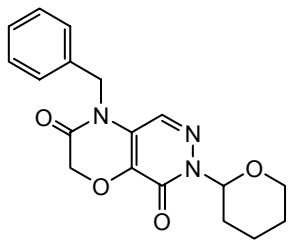
49b

49c; IR(KBr, cm^{-1}) 2945, 1702, 1635, 1020; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.82(s, 1H), 6.10(dd, *J*=2.44, 10.82Hz, 1H), 4.79(s, 2H), 4.13(m, 1H), 4.11(m. 1H), 3.78-3.89(m, 2H), 3.60~3.67(m, 1H), 4.04(m, 2H), 1.21~2.18(m, 17H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ162.11, 155.42, 127. 68, 125.02, 82.72, 68.90, 67.36, 46.75, 36.51, 30.39, 28.92, 26.24, 25.53, 25.45, 24.86, 22.72; MS(m/z) 347.



49c

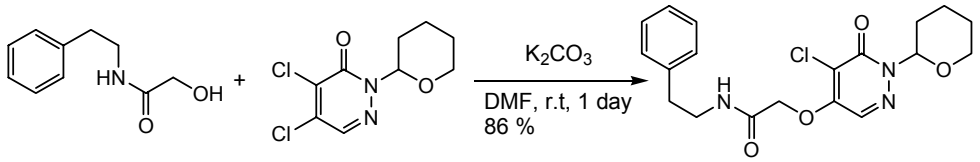
49d; IR(KBr, cm^{-1}) 3012, 2939, 1695, 1644, 1358; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.73(s, 1H), 7.20~7.38(m, 5H), 6.05~6.08(dd, *J*=2.41, 10.2 Hz, 1H), 5.02~5.27(d, *J*=15.9 Hz, 1H), 4.96~5.01(d, *J*=15.9 Hz, 1H), 4.91(s, 2H), 4.11~4.06(d, *J*=13.8 Hz, 1H), 3.70~3.77(t, *J*=11.4 Hz, 1H), 1.56~2.07(m, 6H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ162,30, 155.21, 137. 01, 134.37, 129.28, 128.27, 127.79, 126.57, 124.80, 82.70, 68.84, 67.43, 44.57, 28.89, 24.77, 22.66 ; MS(m/z) 341.



49d

***N*-Substituted-2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-acetamide 50**

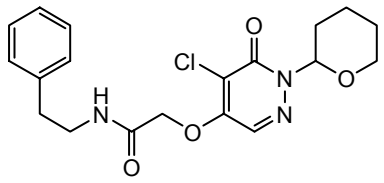
General procedure;



34e **45** **50e**

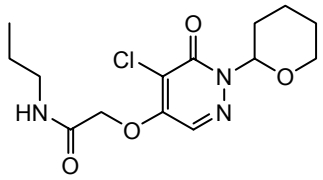
At the 100 ml round bottomed flask, 2-hydroxy-*N*-phenethyl-acetamide (**34e**) (1 g, 5.58 mmol) was added over mixture of 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) (1.2 g, 5.58 mmol) and K_2CO_3 (0.8 g, 6.14 mmol) in DMF (50 ml). The mixture was stirred 1 day, monitored by TLC and then reaction mixture was concentrated under reduced pressure. The mixture was poured into dichloromethane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (5/1, v/v) as eluent affording 2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro -pyridazin-4-yl-oxy]-*N*-phenethyl-acetamide (**50e**) (1.9 g, 86 % yield) as a white solid.

IR(KBr, cm^{-1}) 3349, 2939, 1664, 1608, 1091; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.77(s, 1H), 7.19~7.34(m, 5H), 6.59(bs, *N*H), 6.08(dd, *J*=1.72, 10.26 Hz, 1H), 4.65(s, 2H), 4.09~4.15(m, 1H), 3.64~3.79(q, *J*=6.3 Hz, 3H), 2.86~2.91(t, *J*=6.9 Hz, 2H), 1.60~2.18(m, 6H), 1.57(m, 2H), 0.97 (t, 3H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ165.24, 157.78, 152.46, 137.85, 128.82, 126.81, 118.02, 102.13, 83.56, 68.87, 68.56, 40.02, 36.21, 35.21, 28.88, 24.76, 22.65; MS(m/z) 392.



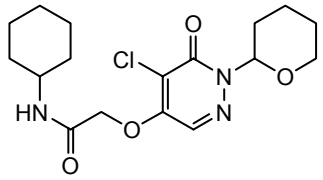
50e

50a; IR(KBr, cm^{-1}) 3293, 2966, 1675, 1644, 1095; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.84(s, 1H), 6.64(bs, *N*H), 6.06(dd, *J*=1.72, 10.26 Hz, 1H), 4.70(s, 2H), 4.12(m, 1H), 3.75(m, 1H), 3.20(t, *J*=6.5 Hz, 2H), 1.73~2.20(m, 6H), 1.57(m, 2H), 0.97(t, *J*=7.1 Hz, 3H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ165.32, 155.21, 126.02, 123.53, 83.93, 68.91, 68.47, 40.93, 40,81, 28.90, 24.78, 22.68, 22.63, 11.24; MS(m/z) 329.



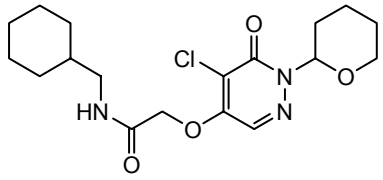
50a

50b; mp. 181~182 ℃; IR(KBr, cm^{-1}) 3334, 2945, 1675, 1649, 1260; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.82(s, 1H), 6.49(bs, *N*H), 6.09(dd, *J*=1.7, 10.26 Hz, 1H), 4.66(s, 2H), 4.10(m, 1H), 3.68~3.89(m, 1H), 3.72~3.79 (m, 1H), 1.21~2.17(m, 16H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ164.36, 157. 82, 152.75, 127.13, 83.95, 68.87, 68.54, 48.06, 32.75, 28.89, 25.29, 24.80, 24.52, 22.68; MS(m/z) 370.



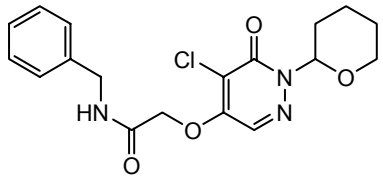
50b

50c; IR(KBr, cm^{-1}) 3372, 2942, 1655, 1612, 1516, 1081; ^{1}H-NMR (300 MHz, $CDCl_3$) δ7.91(s, 1H), 6.93(t, *N*H), 6.04(dd, *J*=1.72, 10.26 Hz, 1H), 4.1(m, 1H), 3.75(m, 1H), 3.20(t, *J*=6.2 Hz, 2H), 1.21~2.18(m, 17H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ165.33, 157.64, 152.78, 127.15, 117.33, 83.59, 68.35, 60.04, 45.04, 37.43, 30.35, 28.50, 25.94, 25.37, 24.50, 22.37; MS(m/z) 384.



50c

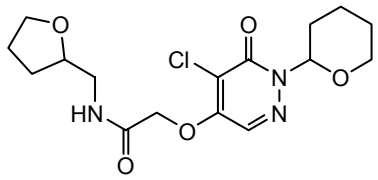
50d; IR(KBr, cm^{-1}) 3416, 3058, 2939, 1669, 1613, 1347; ^{1}H-NMR (300 MHz, $CDCl_3$) δ7.83(s, 1H), 7.27~7.35(m, 5H), 6.99(bs, *N*H), 6.03~6.07(dd, *J*=2.41, 10.2 Hz, 1H), 4.74(s, 2H), 4.55~4.57(d, *J*=5.7 Hz, 2H), 4.10~4.13(d, *J*=9.9 Hz, 1H), 3.74(t, *J*=11.4 Hz, 1H), 1.49~2.17 (m, 6H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ171.72, 155.12, 152.57, 137.11, 128.82, 127.79, 127.61, 127.13, 117.27, 83.91, 68.86, 68.51, 43.19, 28.85, 24.77, 22.75 ; MS(m/z) 378.



50d

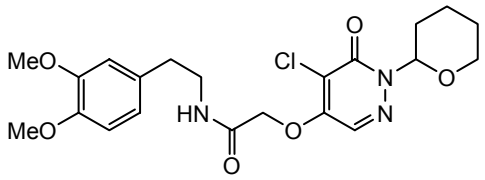
50f; IR(KBr, cm^{-1}) 3313, 2961, 1665, 1614, 1214; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.84(s, 1H), 7.29(bs, *N*H), 6.05-6.09(dd, *J* =2.4, 10.8 Hz, 1H), 4.72(s, 2H), 4.11~4.13(m, 1H), 4.01(m, 1H), 3.87~3.92(m, 1H), 3.60~3.84(m, 1H), 3.30-3.36(m, 1H), 1.52~2.11(m, 12H); ^{13}C-NMR (75

MHz, $CDCl_3$) δ165.58, 157.85, 152.72, 127.11, 83.87, 68.85, 68.45, 68.24, 68.22, 42.72, 30.88, 28.87, 28.52, 25.82, 24.76, 22.65; MS(m/z) 372.



50d

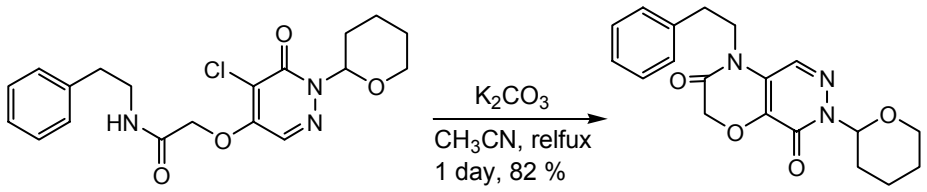
50g; IR(KBr, cm^{-1}) 3375, 3068, 2940, 1665, 1609, 1516, 1091; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.79(s, 1H), 6.73~6.82(m, 3H), 6.63(bs, *N*H), 6.06(dd, *J*=1.72, 10.26 Hz, 1H), 4.66(s, 2H), 4.11(d, *J*=6.4 Hz, 1H), 3.87(s, 6H), 3.75(m, 1H), 3.62~3.64(q, *J*=6.5 Hz, 2H), 2.81~2.85(t, *J*=6.7 Hz, 2H), 1.21~2.18(m, 6H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ165.78, 157.82, 152.53, 149.12, 130.29, 126.82, 120.63, 111.48, 111.22, 83.90, 68.88, 68.31, 55.87, 55.80, 40.23, 34.89, 28.85, 27.77, 22.66; MS(m/z) 452.



50g

_N_-Substituted-7-(tetrahydro-pyran-2-yl)-4_H_,7_H_-pyridazino-[4,5-_b_][1,4] oxazine-3,8-dione 49 using systematic method

General procedure;



50e **49e**

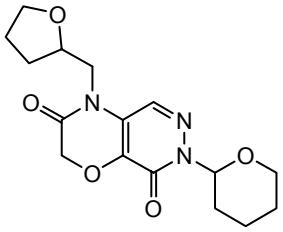
At the 100 ml round bottomed flask, 2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yl-oxy]-*N*-phenethyl-acetamide (**50e**) (1 g, 2.65 mmol) was added over K_2CO_3 (0.4 g, 2.91 mmol) in acetonitrile (20 ml). The mixture was refluxed for 1 day, monitored by TLC and then reaction mixture was concentrated under reduced pressure. The mixture was poured into dichloromethane (50 ml) and washed with water (100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (5/1, v/v) as eluent affording 4-phenethyl-6-(tetrahydro-pyran-2-yl)-4,6-dihydro-pyridazino[4,5-*b*][1,4]oxazine-3,5-dione (**49e**) (0.8 g, 82 % yield) as a white solid.

IR(KBr, cm^{-1}) 2950, 1696, 1649, 1019; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 7.77(s, 1H), 7.19~7.39(m, 5H), 6.08(dd, *J*=2.44, 10.82 Hz, 1H), 4.75(s, 2H), 4.05~4.15(m, 3H), 3.73~3.80(m. 1H), 2.94(t, *J*=7.2 Hz, 2H), 1.61~2.17(m, 6H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ161.59, 158.23, 136.66, 128.62, 127.68, 126.58, 82.60, 68.67, 67.24, 42.47, 40.17, 39.89, 39.61, 33.84, 28.76, 27.67, 22.53; MS(m/z) 355.

Data of **49a** to **49d** are identically same as previous data.

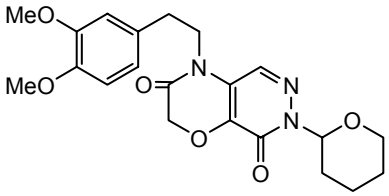
49f; IR(KBr, cm^{-1}) 2945, 1706, 1659, 1021; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.84(s, 1H), 7.29(bs, *N*H), 6.05~6.09(dd, *J*=2.4, 10.8Hz, 1H), 4.72(s, 2H), 4.11~4.13(m, 1H), 4.01(m, 1H), 3.87~3.92(m, 1H), 3.60~3.84(m, 1H), 3.30~3.36(m, 1H), 1.52~2.11(m, 12H); ^{13}C-NMR(75 MHz, $CDCl_3$)

δ165.58, 157.85, 152.72, 127.11, 83.87, 68.85, 68.45, 68.24, 68.22, 42.72, 30.88, 28.87, 28.52, 25.82, 24.76, 22.65; MS(m/z) 372.



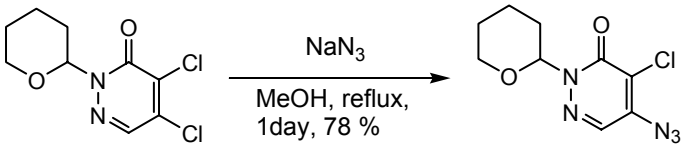
49f

49g; IR(KBr, cm^{-1}) 3015, 2935, 2978, 1700, 1639, 1019; ^{1}H-NMR (300 MHz, $CDCl_3$) δ7.75(s, 1H), 6.70~6.81(m, 3H), 6.09(dd, *J*=2.44, 10.82 Hz, 1H), 4.76(s, 2H), 4.30~4.39(m, 1H), 4.11(m. 1H), 4.04(m, 2H), 3.86(s, 6H), 3.77(m, 1H), 2.88(t, *J*=6.5 Hz, 2H), 1.18~2.17(m, 6H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ161.76, 154.95, 149.06, 148.05, 136.83, 129.09, 127.2, 124.74, 120.70, 111.63, 82.74, 68.87, 67.40, 55.84, 55.79, 42.73, 33.64, 28.95, 24.80, 22.67; MS(m/z) 415.



49g

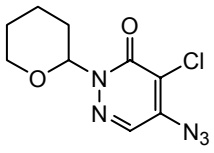
5-Azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (51);



45 **51**

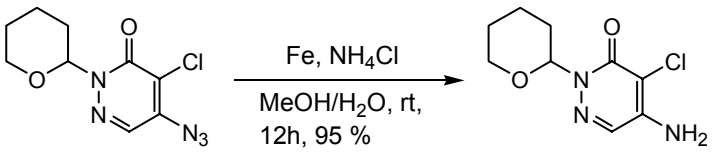
At the 100 ml round bottomed flask, 4,5-dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**) (5 g, 17.9 mmol) was added over sodium azaide (1.4 g, 21.5 mmol) in methanol (50 ml). The mixture was refluxed for 1 day, monitored by TLC and then reaction mixture was concentrated under reduced pressure. The mixture was poured into dichloromethane (10 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (3/1, v/v) as eluent affording 5-azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**51**) (3.5 g, 78 % yield) as a white solid.

IR(KBr, cm^{-1}) 2940, 2140, 2120, 1650; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 7.68(s, 1H), 6.02(d, *J*=8.14 Hz, 1H), 4.10~4.15(d, *J*=11.6 Hz, 1H), 3.68~ 3.81(t, *J*=11.6 Hz, 1H), 2.03~2.17(m, 2H), 1.60~1.72(m, 4H).



51

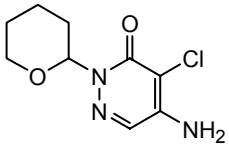
5-Amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (52);



51 **52**

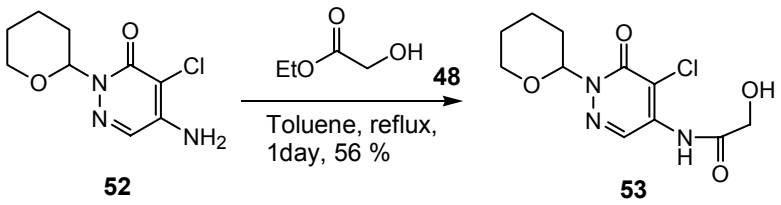
At the 100 ml round bottomed flask, 5-azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**51**) (2 g, 7.8 mmol) was added over to mixture of ion (3g, catalytic amount) and ammonium chloride (0.6 g, 11.7 mmol) in methanol (50 ml). The mixture was refluxed for 12 hours, monitored by TLC and then reaction mixture was filtrated. The organic solution was concentrated under reduced pressure. The mixture was poured into dichloromethane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (2/1, v/v) as eluent affording 5-amino -4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**52**) (1.6 g, 95 % yield) as a white solid.

IR(KBr, cm^{-1}) 3395, 3196, 2940, 1639; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 7.71(s, 1H), 5.99(d, *J*=8.12 Hz, 1H), 4.07~4.11(d, *J*=12.3 Hz, 1H), 3.67~3.75(t, *J*=12.3 Hz, 1H), 2.95(s, *N*H2), 2.00~2.17(m, 2H), 1.57~ 1.69(m, 4H).



52

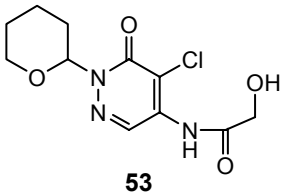
***N*-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yl] -2-hydroxy-acetamide (53)**;



52 **53**

At the 100 ml round bottomed flask, 5-amino-4-chloro-2-(tetrahydro -pyran-2-yl)-2*H*-pyridazin-3-one (**52**) (2 g, 7.8 mmol) was added to ethyl glycolate (**48**) (0.86 g, 8.58 mmol) toluene (50 ml). The mixture was refluxed for 1 day, monitored by TLC then reaction mixture was concentrated under reduced pressure and washing the solid product using hexane (50 ml). The solid product and dried at air to affording 5-amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**53**) (1.3 g, 56 % yield) as a white solid.

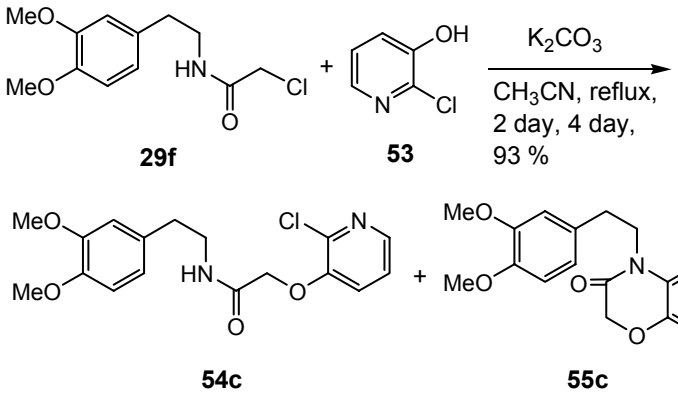
IR(KBr, cm^{-1}) 3395, 3374, 3196, 2940, 1639; ^{1}H-NMR(300 MHz, $CDCl_3$) δ8.75(bs, *N*H), 7.72(s, 1H), 5.79(d, *J*=8.12 Hz, 1H), 4.72(s, 2H), 4.05~4.13(d, *J*=12.3 Hz, 1H), 3.67~3.75(t, *J*=12.3 Hz, 1H), 2.00~2.17(m, 2H), 1.57~1.69(m, 4H).



53

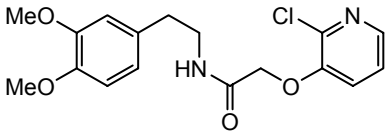
_N_-Substituted-2-(2-Chloro-pyridin-3-yloxy)acetamide 54 and _N_- substituted-1_H_-pyrido[2,3-_b_][1,4]oxazin-2-one 55

General procedure;



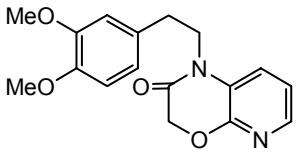
At the 250 ml round bottomed flask, 2-chloro-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (**29f**) (2.96 g, 11.5 mmol) was added to mixture of 2-chloro-3-pyridinol (**53**) (1.49 g, 11.5 mmol), K_2CO_3 (3.98 g, 28.8 mmol) and acetonitrile (50 ml). The mixture was heated to reflux with vigorous stirring for 48~96hrs, monitored by TLC. The mixture was concentrated under reduced pressure. The mixture was poured into dichloromethane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (6/1, v/v) as eluent affording 2-(2-chloro-pyridin-3-yloxy)-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (**54c**) and 1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one (**55c**) (93 % total yield) as a white solid.

54c: mp 112~113 ℃; IR(KBr, cm^{-1}) 3402, 3075, 2977, 2935, 2837, 1669; ^{1}H-NMR(300 MHz, $CDCl_3$) δ8.12(d, 1H), 7.23(t, 1H), 7.07(d, 1H), 6.80(s, 1H), 6.70~6.77(m, 3H), 4.52(s, 2H), 3.87(s, 3H), 3.85(s, 3H), 3.63~3.70(t, 2H), 2.83(t, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ34.6, 40.1, 53.3, 56.3, 67.8, 76.6, 76.8, 111.8, 112.2, 119.1, 121.1, 123.0, 130.2, 142.6, 148.0, 151.5, 167.2; MS (m/z): 395.



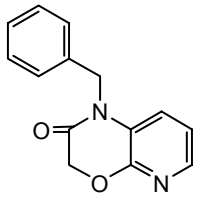
54c

55c: mp. 139~140 ℃, IR (KBr, cm^{-1}) 3053, 2983, 2929, 2827, 1691, 1578; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.93(d, *J*=3.3 Hz, 1H), 7.19(d, *J*=7.2, 1H), 7.01(q, *J*=7.5 Hz, 1H), 6.65~6.81(m, 3H), 4.81(s, 2H), 4.05~4.13(t, *J*=6.4 Hz, 2H), 3.88(s, 3H), 3.85(s, 3H), 2.86(t, *J*=6.5 Hz, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ33.1, 42.8, 53.2, 56.5, 67.6, 76.8, 77.0, 111.9, 112.3, 118.8, 121.2, 122.5, 129.3, 141.8, 147.6, 163.0, 176.8; MS(m/z) 314.



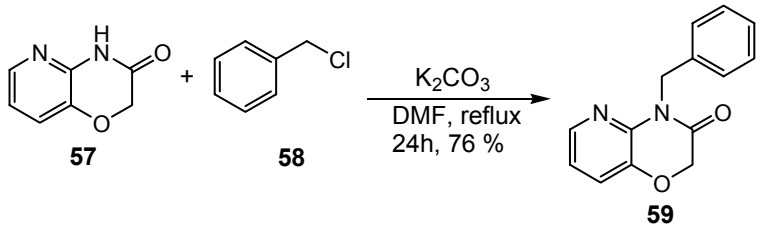
55c

55a: mp. 53~55 ℃, IR (KBr, cm^{-1}) 3042, 2991, 2910, 1685, 1557; ^{1}H-NMR(500 MHz, $CDCl_3$) δ7.86(d, *J*=3.5 Hz, 1H), 7.30~7.33(t, *J*=7.5 Hz, 2H), 7.24~7.27(t, *J*=7, 1H), 7.22~7.24(d, *J*=7.5 Hz, 2H), 7.14~7.16(d, *J*=8 Hz, 1H), 6.86~6.89(m, 1H), 5.12(s, 2H), 4.73(s, 2H); ^{13}C-NMR(125 MHz, $CDCl_3$) δ163.8, 151.98, 141.98, 135.17, 129.31, 128.08, 126.86, 123.38, 123.58, 119.10, 67.62, 45.08; MS(m/z) 240.



55a

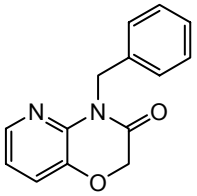
4-Benzyl-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one 59;



57 **58** **59**

At the 250 ml round bottomed flask, add the 4*H*-pyrido[3,2-*b*] [1,4]oxazin-3-one (3 g, 20.0 mmol) to the mixture of benzyl chloride (2.8 g, 22.0 mmol) to the mixture or, K_2CO_3 (2.8 g, 22.0 mmol) and DMF (100 ml). The mixture was stirred for 1 day under reflux condition, monitored by TLC. The mixture was concentrated under reduced pressure, then poured into dichloromethane (200 ml) and washed with water (2 X 200 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (10/1, v/v) as eluent affording 4-benzyl-4*H* -pyrido[3,2-*b*][1,4]oxazin-3-one (**59**) (3.9 g, 76 % yield) as a white solid.

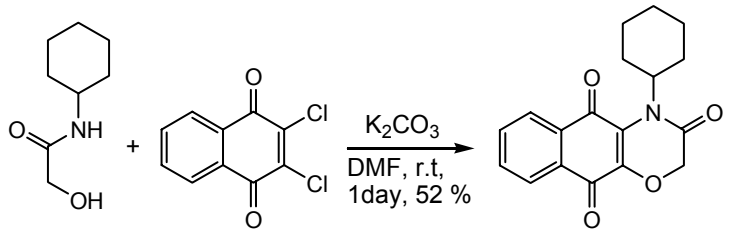
mp. 53~55 ℃; IR(KBr, cm^{-1}) 3402, 3075, 2977, 2935, 2837, 1669; ^{1}H-NMR(500 MHz, $CDCl_3$) δ7.98 (dd, *J*=1.0, 4,5 Hz, 1H), 7.40 (dd, *J*=1.5, 8.0 Hz, 1H), 7.27~7.31(m, 4H), 7.21~7.23 (m, 1H), 7.04 (dd, *J*=5.0, 8.0 Hz, 3H), 5.25 (s, 2H), 4.86 (s, 2H); ^{13}C-NMR(125 MHz, $CDCl_3$) δ166.1, 142.7, 142.0, 141.8, 138.6, 129.6, 128.6, 128.3, 124.8, 120.8, 68.3, 43.3; MS (m/z) 240.



59

***N*-Substituted-4*H*-naphtho[2,3-*b*][1,4]-oxazine-3,5,10-trione 63**

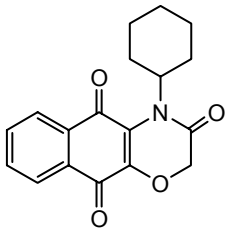
General procedure;



34b **62** **63a**

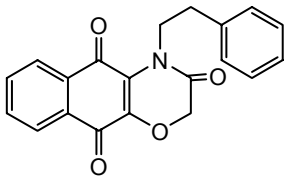
At the round bottomed flask, add the cyclohexyl-2-hydroxy acetamide (**29b**) (2 g, 12.7 mmol) to the mixture of 2,3-dichloro-[1,4] naphthoquinone (**62**) (2.8 g, 12.7 mmol), K_2CO_3 (3.4 g, 26.67 mmol) and DMF (50 ml). The mixture was stirred for 1 day, monitored by TLC. The mixture was concentrated under reduced pressure then poured into dichloromethane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (10/1, v/v) as eluent affording 4-cyclohexyl-4*H*-naphtho[2,3-*b*][1,4]oxazine-3,5,10-trione (**63a**) (2 g, 52 % yield) as a yellow solid.

^{1}H-NMR(300 MHz, $CDCl_3$) δ8.00~7.73(m, 4H), 4.83(s, 2H), 3.54(m, 1H), 1.18~2.17(m, 10H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ187.0, 165.2, 144.3, 137.2, 134.8, 130.2, 110.4, 44.5, 31.1, 22.4, 27.1; MS(m/z) 311, 229, 201, 215, 173, 132, 104, 76, 67, 55, 41.



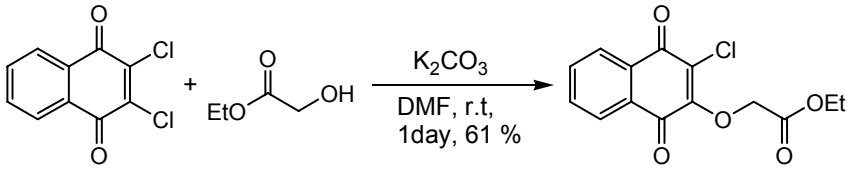
63a

63b; ^{1}H-NMR(300 MHz, $CDCl_3$) δ8.12~7.73(m, 4H), 7.14~7.06(m, 5H), 4.85(s, 2H), 4.46(s, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ187.0, 165.8, 144.9, 142.4, 134.8, 137.9, 130.2, 127.1, 128.3, 126.5, 110.4, 71.2, 50.2; MS(m/z) 333, 291, 242, 229, 214, 173, 154, 104, 91, 77, 65, 61, 42.



63b

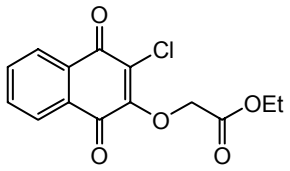
(3-Chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-yloxy)-acetic acid ethyl ester (69);



62 **48** **69**

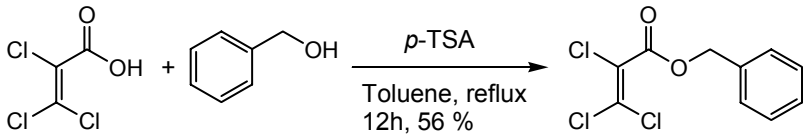
At the round bottomed flask, add the 2,3-dichloro-[1,4]naphthoquinone (**62**) (3 g, 13.3 mmol) to the mixture of ethyl glycolate (1.5 g, 14.6 mmol) to the mixture or, K_2CO_3 (2 g, 14.6 mmol) and DMF (50 ml). The mixture was stirred for 1 day, monitored by TLC. The mixture was concentrated under reduced pressure, then poured into dichloro-methane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (5/1, v/v) as eluent affording (3-Chloro-1,4-dioxo-1,4-dihydro-naphthalen -2-yloxy)-acetic acid ethyl ester (**69**) (2.3 g, 61 % yield) as a yellow solid.

^{1}H-NMR(300 MHz, $CDCl_3$) δ8.10~7.53(m, 4H), 4.92(s, 3H), 4.12(q, *J*=5.4 Hz, 2H), 1.30(t, *J*=5.5 Hz, 3H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ 187.0, 171.0, 164.6, 137.9, 134.8, 130.2, 109.2, 70.0, 59.5, 13.6.



69

2,3,3-Trichloro-acrylic acid benzyl ester (80);

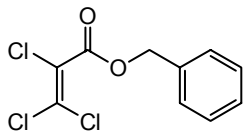


78 **79** **80**

At the 100 ml round bottomed flask, add the 2,3,3-trichloro-acrylic

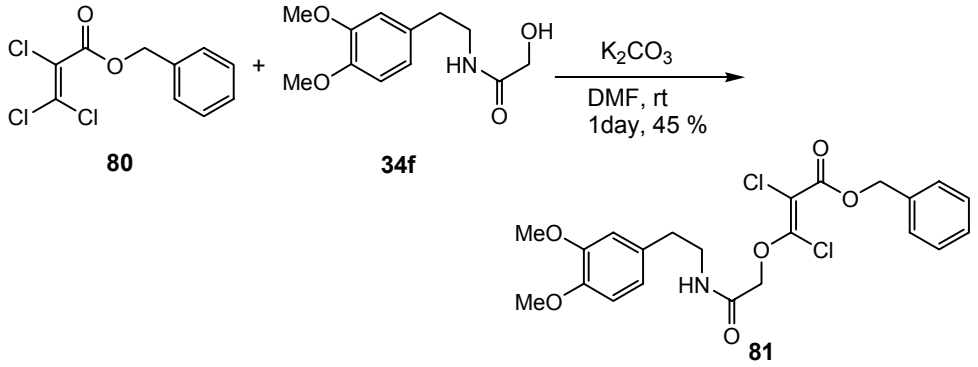
acid (**78**) (2 g, 11.5 mmol) to the mixture of benzyl alcohol (**79**) (1.2 g, 11.5 mmol), *p*-toluene sulfonic acid (0.1 g, 1.1 mmol) and toluene (50 ml). The mixture was refluxed for 12 hours, monitored by TLC. The mixture was concentrated under reduced pressure, then poured into ethyl acetate (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (2/1, v/v) as eluent affording 2,3,3-trichloro-acrylic acid benzyl ester (**80**) (1.7 g, 56 % yield) as a yellow oil.

IR(neat, cm^{-1}) 3027, 2919, 1731, 1530, 1245; ^{1}H-NMR(300 MHz, $CDCl_3$) δ7.39~7.07(d, 5H), 5.27(s, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ 160.26, 134.38, 128.74, 128.63, 128.32, 125.90, 68.49, 41.42.



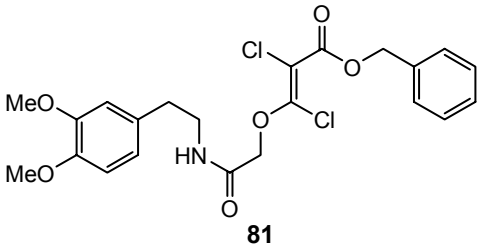
80

2,3-Dichloro-3-{[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-methoxy}-acrylic acid benzyl ester (81);



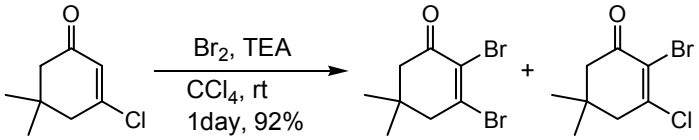
At the 100 ml round bottomed flask, add 2,3,3-trichloro-acrylic acid benzyl ester (**80**) (1 g, 3.78 mmol) to the mixture of *N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-2-hydroxy-acetamide (**34f**) (0.9 g, 4.1 mmol), K_2CO_3 (0.5 g, 4.1 mmol) and DMF (50 ml). The mixture was refluxed for 1 day, monitored by TLC. The mixture was concentrated under reduced pressure, then poured into dichloromethane (100 ml) and washed with water (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (4/1, v/v) as eluent affording 2,3-dichloro-3-{[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-methoxy}-acrylic acid benzyl ester (**81**) (0.7 g, 45% yield) as a yellow oil.

IR(neat, cm^{-1}) 3528, 2945, 1813, 1731; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 6.74~6.82(m, 8H), 4.63(s, 2H), 3.87(d, *J*=6 Hz, 6H), 3.76~3.79(t, *J*=6.3 Hz, 2H), 2.90~2.96(t, *J*=8.1 Hz, 2H), 2.18(s, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ170.16, 165.0, 148.93, 147.89, 129.16, 128.54, 127.57, 127.32, 121.12, 120.80, 111.69, 111.18, 67.71, 55.84, 45.27, 41.12, 32.81, 30.92.



81

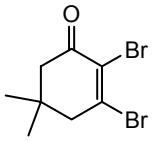
2,3-Dibromo-5,5-dimethyl-cyclohex-2-enone (85) and 2-bromo-3-chloro-5,5-dimethyl-cyclohex-2-enone (84);



83 **84** **85**

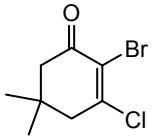
At the 100 ml round bottomed flask, add brome (1.1 g, 6.93 mmol) to the mixture of 2-chloro-5,5-dimethyl hexanone (**83**) (1 g, 6.3 mmol), triethyl amine (0.7 g, 6.93 mmol) and tetrachloro methane (50ml). The mixture was stirred for 1 day, monitored by TLC. The mixture was poured into water (100 ml) and extracts with ethyl acetate (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane: ethyl acetate (8/1, v/v) as eluent affording 2,3-dibromo-5,5-dimethyl-cyclohex-2-enone (**85**) and 2-bromo-3-chloro-5,5-dimethyl-cyclohex-2-enone (**84**) (1.6 g, 92 % yield) as yellow oil.

84; MS(m/z) 282, 201, 146, 122, 107, 94, 77, 67, 55, 39



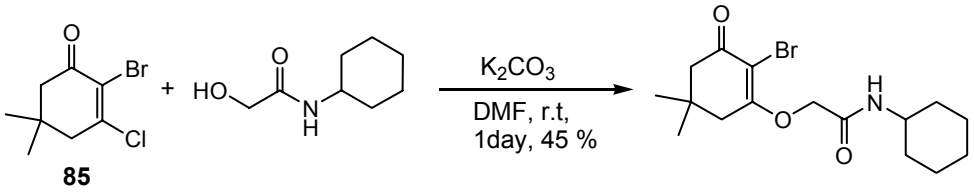
84

85; MS(m/z) 238, 157, 122, 102, 91, 77, 67, 55, 39.



85

2-(2-Bromo-5,5-dimethyl-3-oxo-cyclohex-1-enyloxy)-*N*-cyclohexyl-acetamide (86);

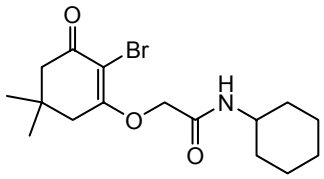


85 **34b** **86**

At the 100 ml round bottomed flask, add 2-bromo-3-chloro-5,5-dimethyl-cyclohex-2-enone (**84**) (1 g, 8.05 mmol) to the mixture of *N*-cyclohexyl-2-hydroxy-acetamide (**34b**) (1.2 g, 8.85 mmol), K_2CO_3 (1.1 g, 8.85 mmol) and DMF (20 ml). The mixture was stirred for 1 day, monitored by TLC. The mixture was poured into water (100 ml) and extracts with ethyl acetate (2 X 100 ml). Extracts the combined organic layer and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column

chromatography on silica gel using *n*-hexane: ethyl acetate (2/1, v/v) as eluent affording 2-(2-bromo-5,5-dimethyl-3-oxo-cyclohex-1-enyloxy) -*N*-cyclohexyl-acetamide (**86**) (1.3 g, 45 % yield) as yellow oil.

^{1}H-NMR(300 MHz, $CDCl_3$) δ7.85(bs, *N*H), 4.85(s, 2H), 3.54(m, 1H), 2.86(s, 2H), 2.76(s, 2H), 2.12(s, 6H), 1.18~1.94(m, 10H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ197.6, 171.2, 170.6, 80.3, 71.5, 52.3, 51.0, 45.1, 44.7, 33.2, 27.5, 27.1, 22.0.



86

5. Bibliography

1. a) Boswell, G. E.; Musso, D. L.; Kelley, L. J. *J Heterocyclic Chem.* **1996**, *33*, 33.
   b) Kuroita, T.; Marubayashi, N.; *et. al*., *Chem. Pharm. Bull.* **1996**, *44*, 2051.
   c) Hale, J. J.;Mills, S. G.; *et. al.*, *J. Med. Chem*. **2000**, *43*, 1234.
   d) Kundu, N. G.; Chaudhuri, G. *J. Org. Chem.* **2001**, *66*, 20.
2. a) Matzanke N.; Lowe W.; Stark H. *Eur. J. Med*. *Chem*. **1999**, *34*, 791.
   b) Rodenhuis N.; Dihkstra D.; Wikstrom H. *J. Med. Chem*. **2000**, *43*, 2871.
3. Yamamoto T.; Hor M.; Watanabe I.; Tsutsui H. *Chem. Pharm. Bull*. **1999**, *47*, 22.
4. Chiu H.; Lin Y.; Cheng C.; Tasi M. *Bioorg. Med. Chem*. **2001**, *9*, 383.
5. Savelon L.; Bizot-Espiard J.; Caignard D.; Pfeiffer B.; Renard P. *Bioorg. Med. Chem*. **1998**, *6*, 133.
6. Shrudhar D. R.; Jogbhukuta M.; Krishnan V. S. H. *Org. Prep. Proced. Int.* **1982**, *14*, 195.
7. Dartsch H.; Schwarz O. *J. Heterocyclic Chem*. **1982**, *19*, 1189.
8. Chioccara F.; Novellino E. *J. Heterocyclic Chem*. **1985**, *22*, 1021.
9. Baker W.; Condon S.; Spanton S. *Tetrahedron Lett*. **1992**, *33*, 1573.
10. Kuroita T.; Marubayashi N.; Sano M.; Kanzaki K. *Chem. Pharm. Bull.* **1996**, *44*, 2051.
11. Dastlik K. Files R.; Roos G. *Tetrahedron Asymmetry*. **1996**, *7*, 2525.
12. Norman B.; Jroin J. *J. Org. Chem*. **1996**, *61*, 4990.
13. Ashwood M.; Cottrell I.; Davies A. *Tetrahedron Asymmetry*. **1997**, *8*, 957.

14. Bouron E.; Goussard G.; Marchand C.; Bonin M. *Tetrahedron Lett*. **1999**, *40*, 7227.
15. Agami C.; Couty F.; Prince B.; Venier O. *Tetrahedron Lett.* **1993**, *34*, 7061.
16. Tamura O.; Gotanda K.; Yoshino J.; Morita Y.; Tershima R. *J. Org. Chem*. **2000**, *65*, 8544.
17. Thorey C.; Wilken J.; Henin F. *Tetrahedron Lett.* **1995**, *36*, 5527.
18. Sun G.; Savle S. P.; Gandour R. D.; Fronczek F. R. *J. Org. Chem.* **1995**, *60*, 6688.
19. Shafer C.; Molinski T. *J. Org. Chem.* **1996**, *61*, 2044.
20. Shafer C.; Morse D.; Molinski T. *Tetrahedron Lett*. **1996**, *52*, 4475.
21. Chinchilla R.; Falvello K.; Galindo N.; Najera C. *J. Org. Chem*. **2000**, *65*, 3034.
22. Bryant R.; Kunng F.; South M. *J. Heterocyclic Chem.* **1995**, *32*, 1473.
23. Cho S-D.; Kweon D-H.; Kang Y-J.; Yoon Y-J. *J. Heterocyclic Chem*. **1998**, *35*, 1.
24. Cho, S-D.; Choi, W-Y.; Yoon, Y-J. *J. Heterocyclic Chem.* **1996**, *33*, 1579.
25. Maiti S.; Spevak P.; Reddy N. *Synthetic Comm*. **1998**, *18*, 1201.
26. Axelle Arrault; Frederique Touzeau; Jean-Yves Merour *Tetrahedron*, **2002**, *58*, 8145.
27. Khatana S.; Boschelli D.; Karmer J.; Conner D. *J. Org. Chem*., **1996**, *61*, 6060.
28. Matyus P.; Varga I.; Zara E.; Mezei A. *Bioorg. Med. Chem. Lett*. **1997**, *22*, 2857.
29. Ouyang X.; Tamayo N.; Kiselyov A. *Tetrahedron* **1999**, *55*, 2827.
30. Elisa O.; Karolyhazy L.; *et. al., J. Molecular Structure* **2001**, *545*, 75.
31. Abrous L.; Hynes J.; Friedrich S.; *Org. Lett*. **2001**, *3*, 1089.

6. Appendixes :

IR, ^{1}H-NMR, ^{13}C-NMR, GC-Mass Data

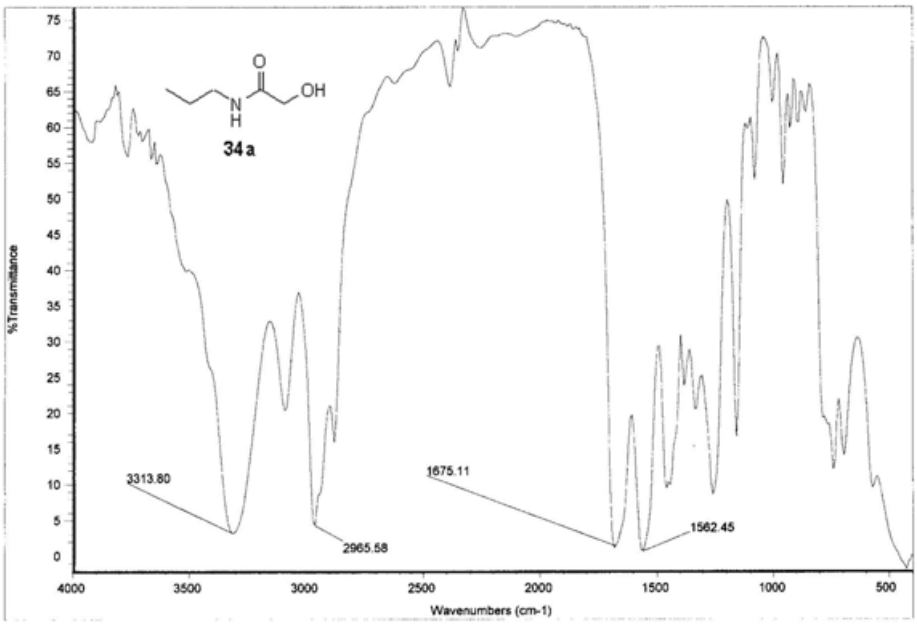


Figure A.1a IR spectrum of 2-Hydroxy-*N*-propyl-acetamide (**34a**)

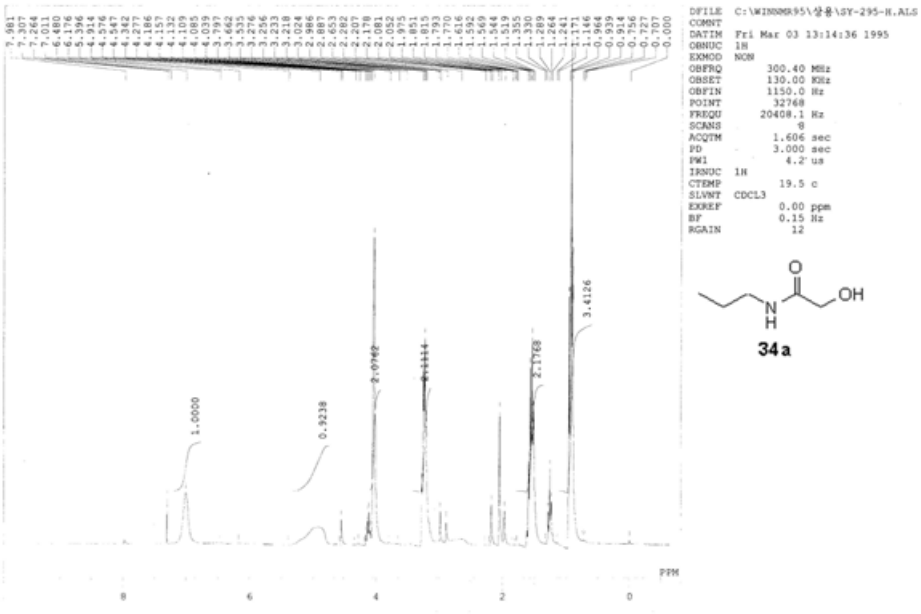


Figure A.1b ^{1}H-NMR spectrum of 2-Hydroxy-*N*-propyl-acetamide (**34a**)

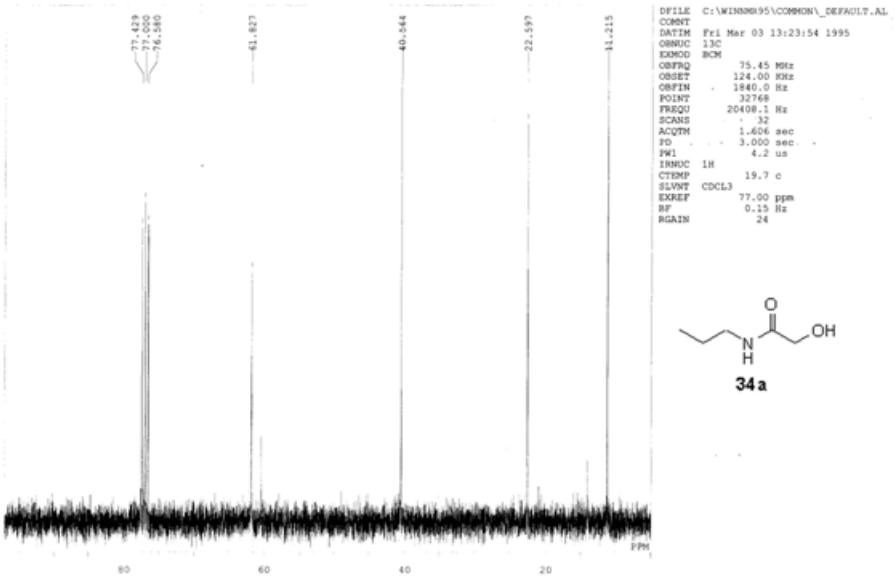


Figure A.1c ^{13}C-NMR spectrum of 2-Hydroxy-*N*-propyl-acetamide (**34a**)

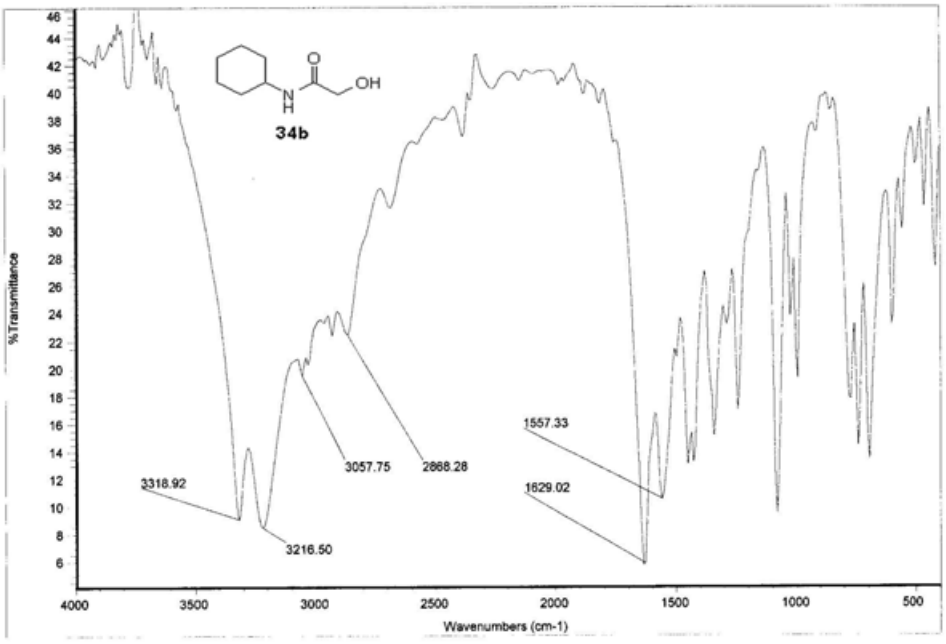


Figure A.2a IR spectrum of *N*-Cyclohexyl-2-hydroxy-acetamide (**34b**)

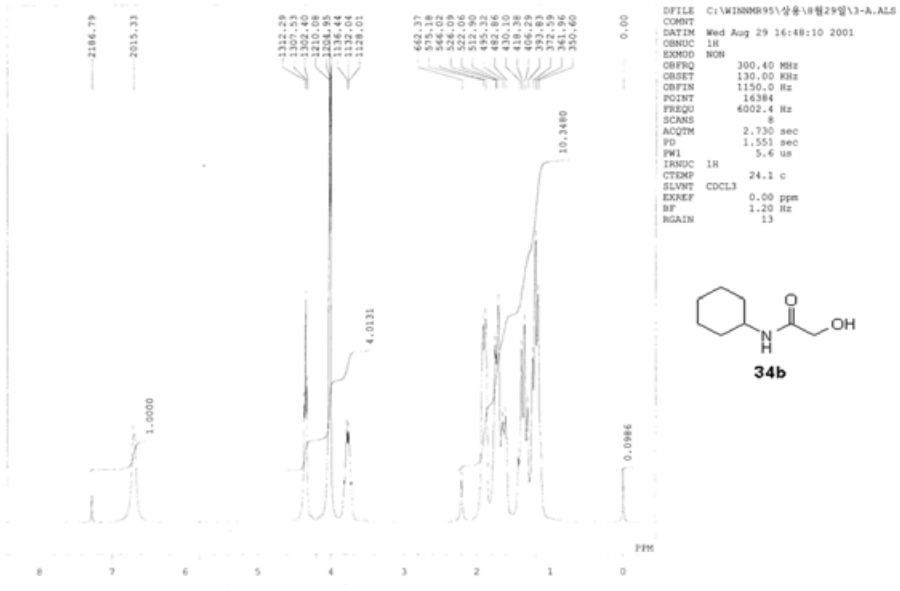


Figure A.2b ^{1}H-NMR spectrum of *N*-Cyclohexyl-2-hydroxy-acetamide (**34b**)

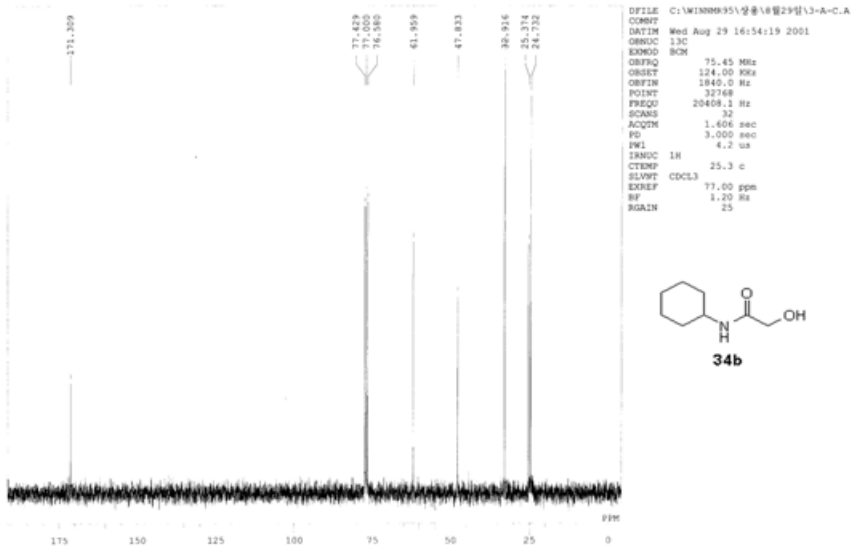


Figure A.2c ^{13}C-NMR spectrum of *N*-Cyclohexyl-2-hydroxy-acetamide (**34b**)

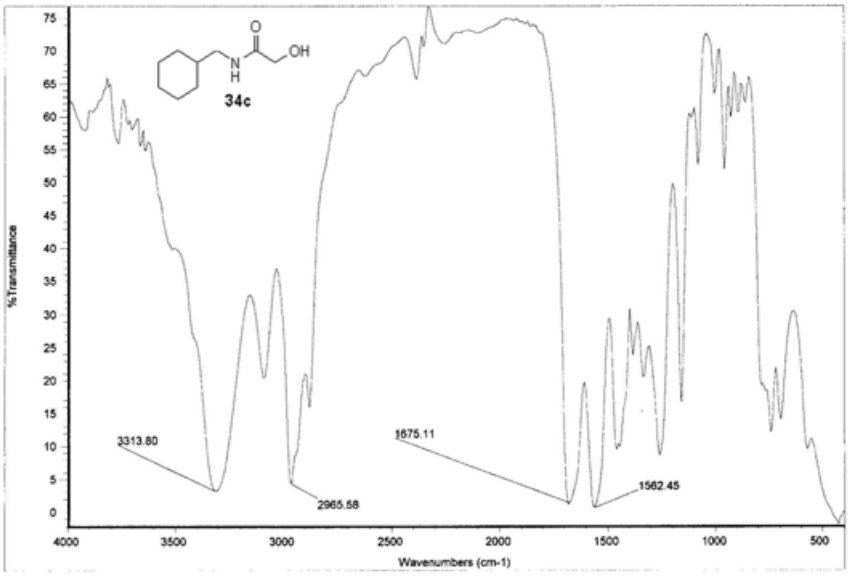


Figure A.3a IR spectrum of *N*-Cyclohexylmethyl-2-hydroxy-acetamide (**34c**)

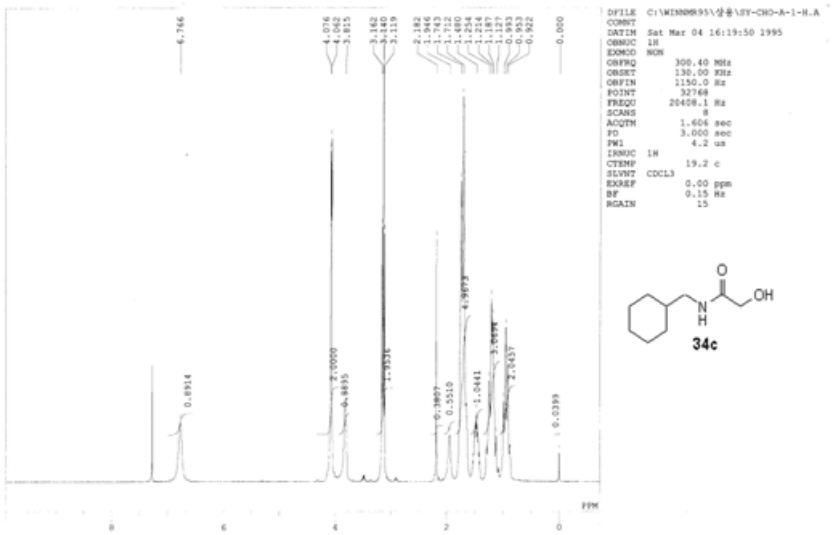


Figure A.3b ^{1}H-NMR spectrum of *N*-Cyclohexylmethyl-2-hydroxy-acetamide (**34c**)

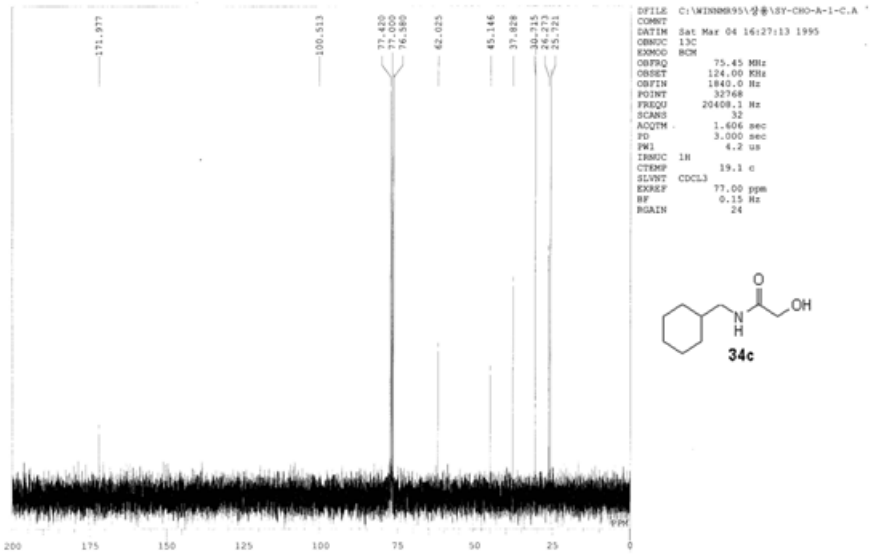


Figure A.3c ^{13}C-MNR spectrum of *N*-Cyclohexylmethyl-2-hydroxy-acetamide (**34c**)

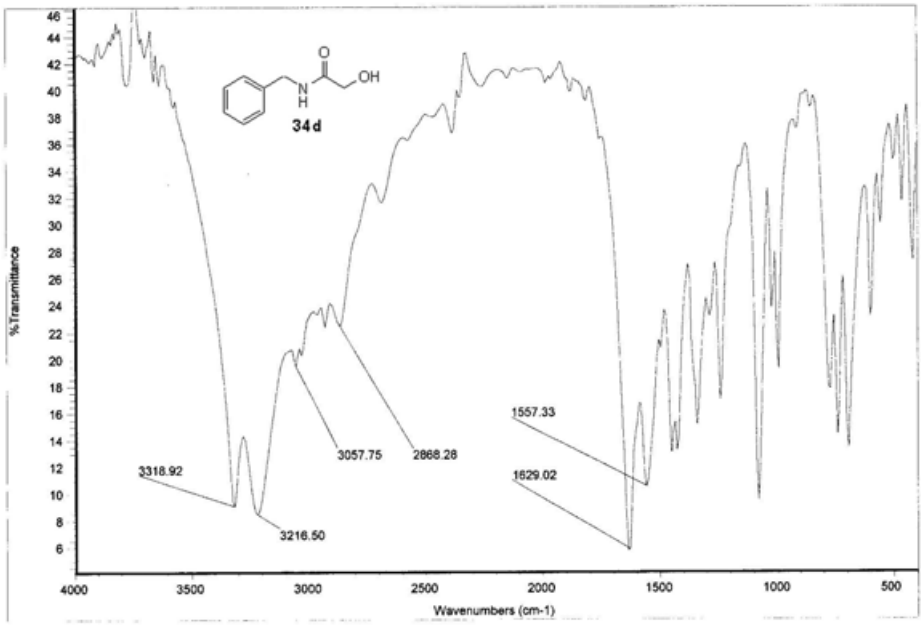


Figure A.4a IR spectrum of *N*-Benzyl-2-hydroxy-acetamide (**34d**)

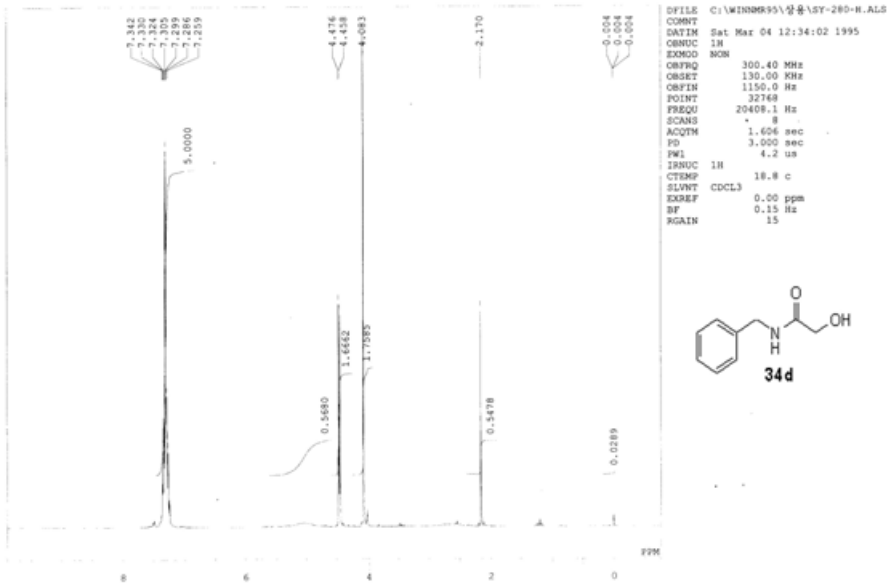


Figure A.4b ^{1}H-NMR spectrum of *N*-Benzyl-2-hydroxy-acetamide (**34d**)

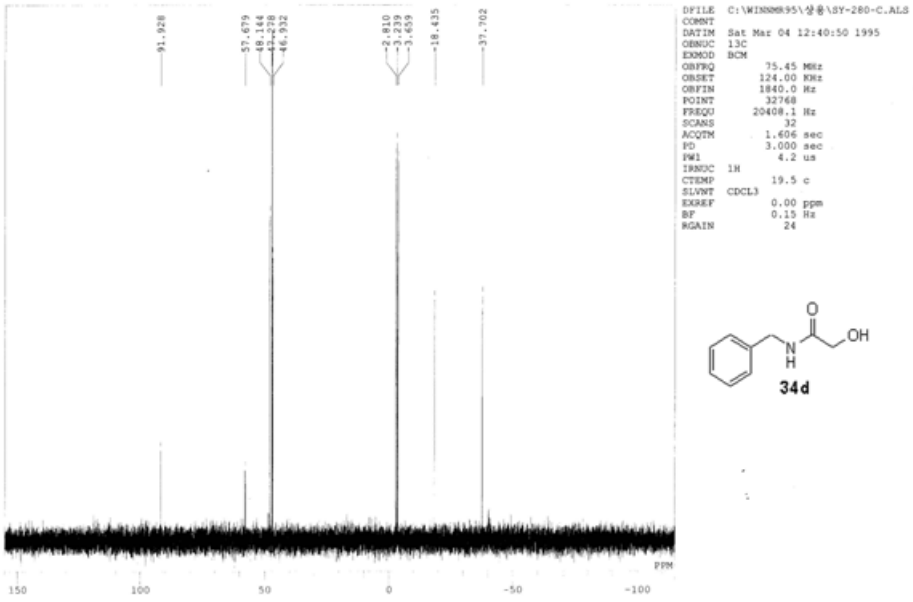


Figure A.4c ^{13}C-NMR spectrum of *N*-Benzyl-2-hydroxy-acetamide (**34d**)

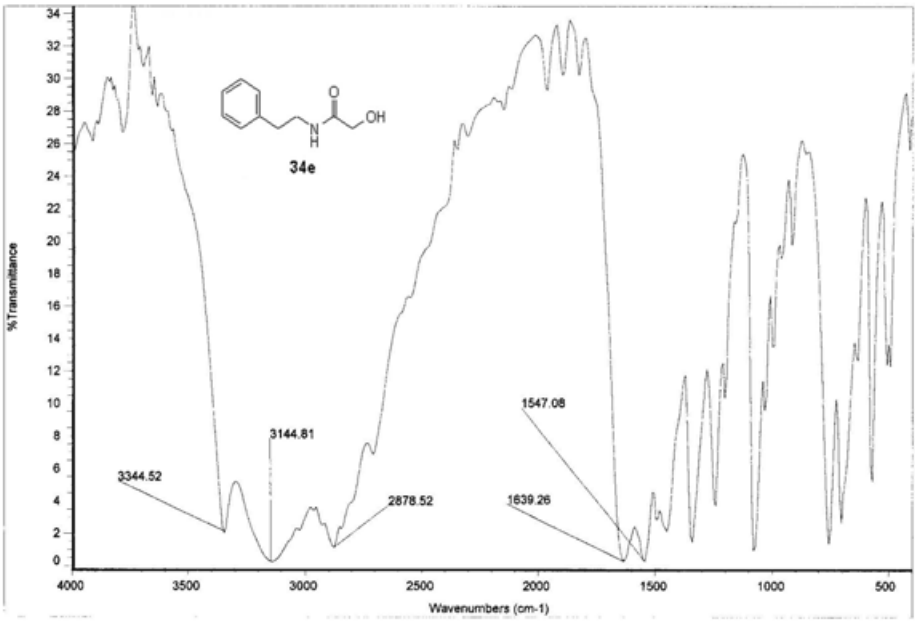


Figure A.5a IR spectrum of 2-Hydroxy-*N*-phenyl-acetamide (**34e**)

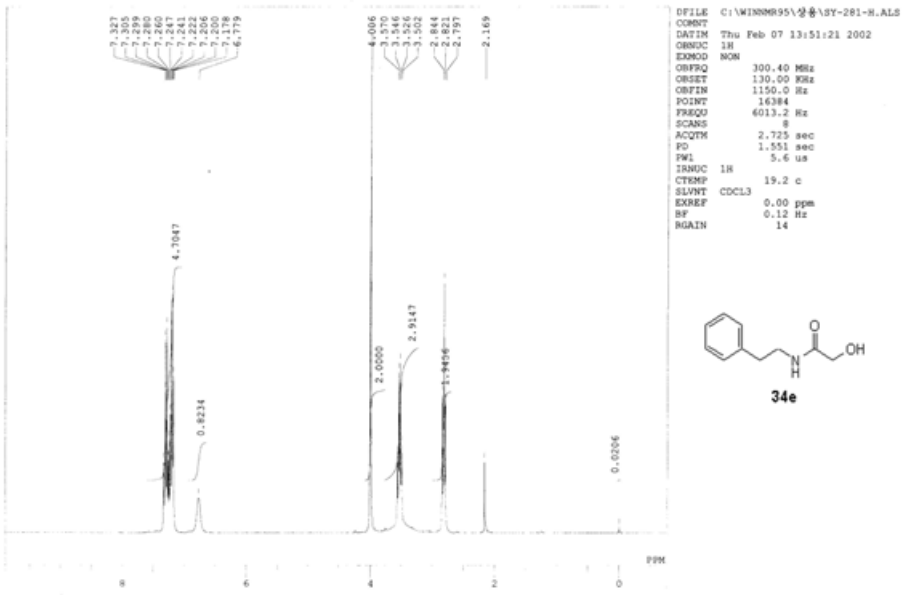


Figure A.5b ^{1}H-NMR spectrum of 2-Hydroxy-*N*-phenyl-acetamide (**34e**)

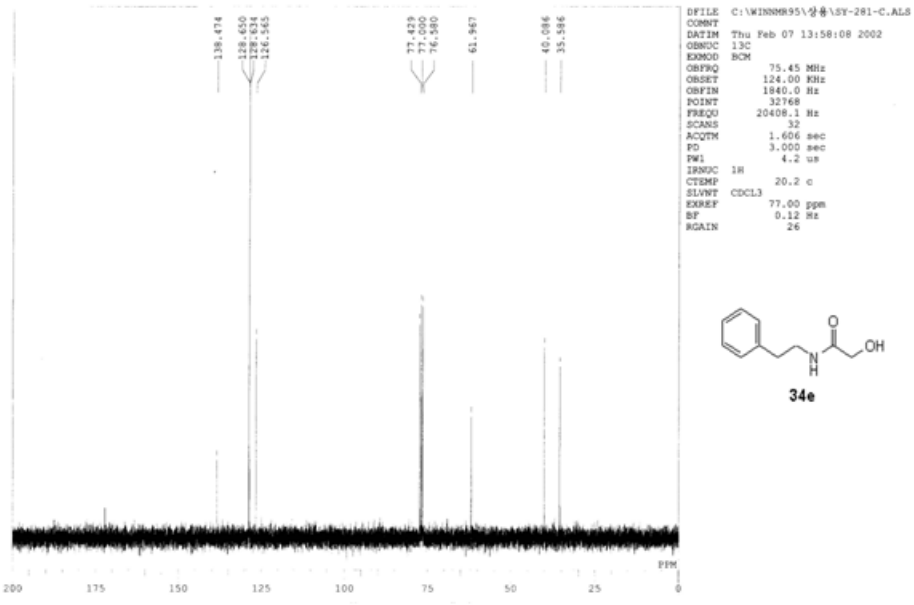


Figure A.5c ^{13}C-NMR spectrum of 2-Hydroxy-*N*-phenyl-acetamide (**34e**)

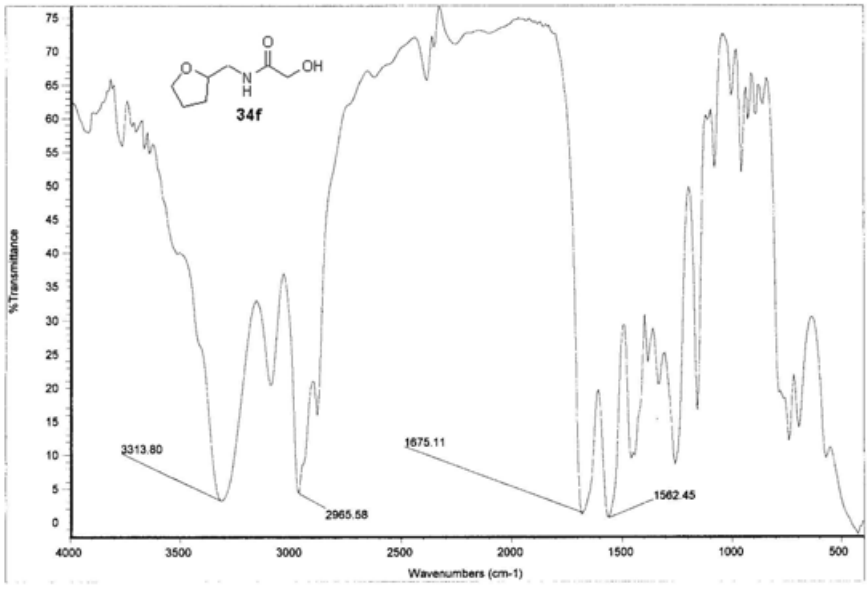


Figure A.6a IR spectrum of
2-Hydroxy-*N*-(tetrahydro-furan-2-yl)-acetamide (**34f**)

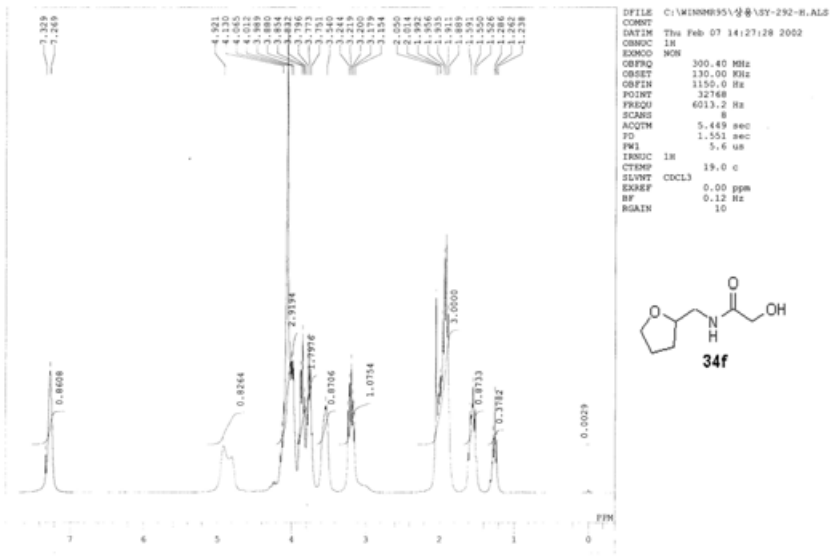


Figure A.6b ^{1}H-NMR spectrum of
2-Hydroxy-*N*-(tetrahydro-furan-2-yl)-acetamide (**34f**)

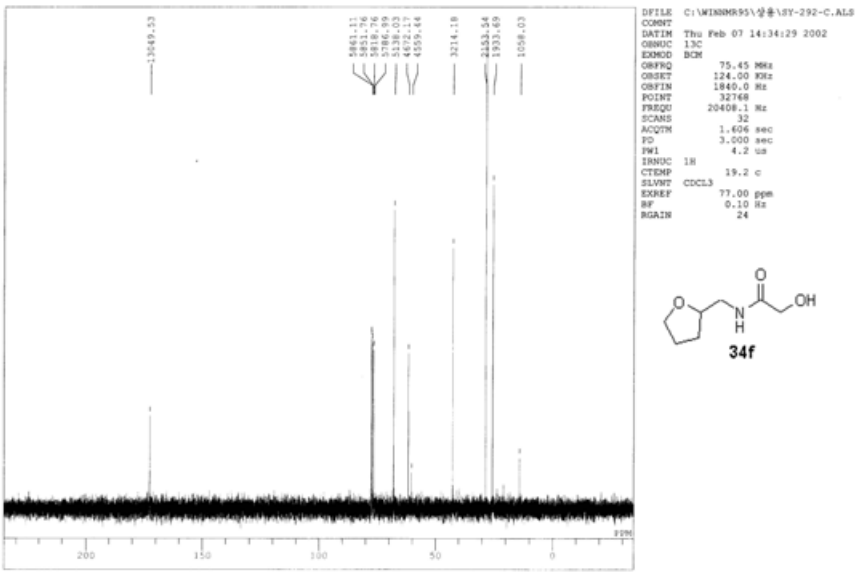


Figure A.6c ^{13}C-NMR spectrum of
2-Hydroxy-*N*-(tetrahydro-furan-2-yl)-acetamide (**34f**)

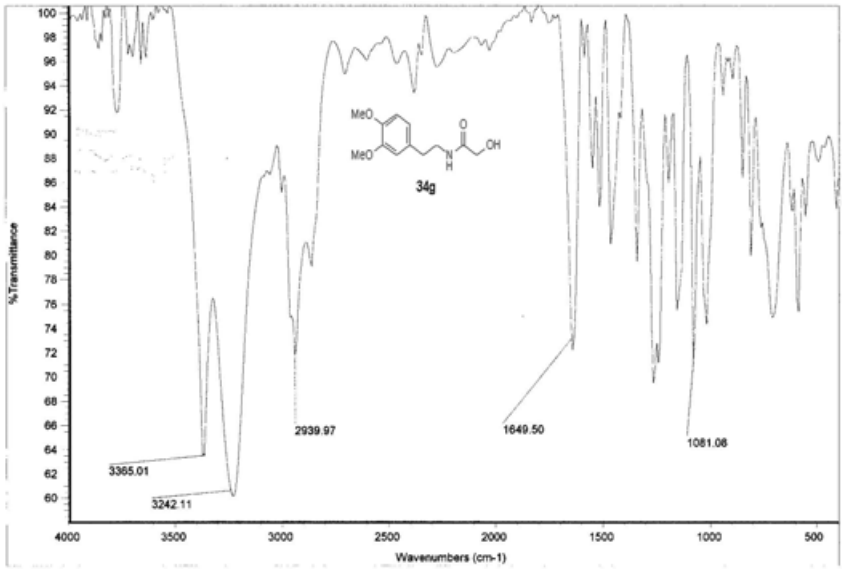


Figure A.7a IR spectrum of
N-(3,4-Dimethoxy-benzyl)-2-hydroxy-acetamide (**34g**)

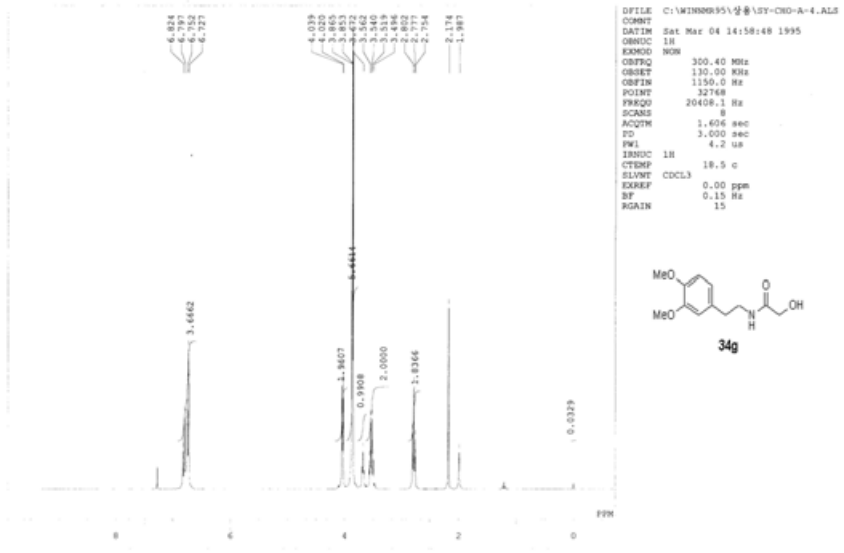


Figure A.7a ^{1}H-NMR spectrum of
N-(3,4-Dimethoxy-benzyl)-2-hydroxy-acetamide (**34g**)

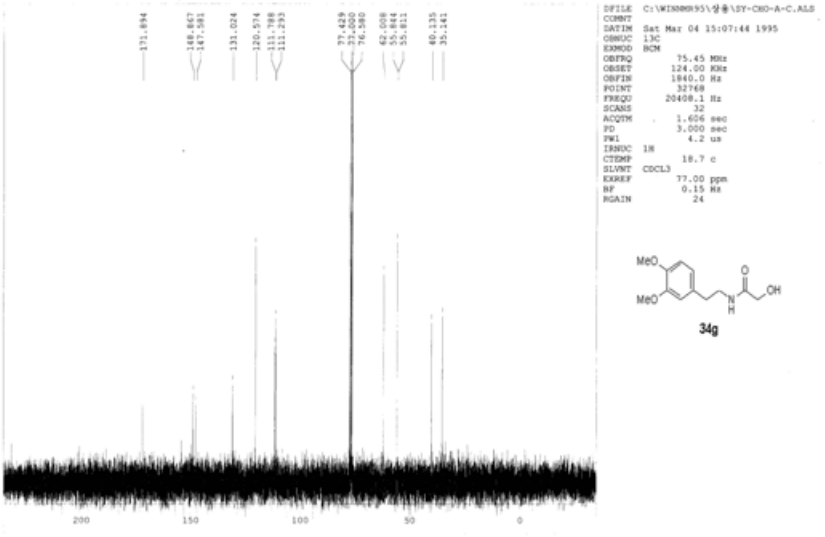


Figure A.7c ^{13}C-NMR spectrum of
N-(3,4-Dimethoxy-benzyl)-2-hydroxy-acetamide (**34g**)

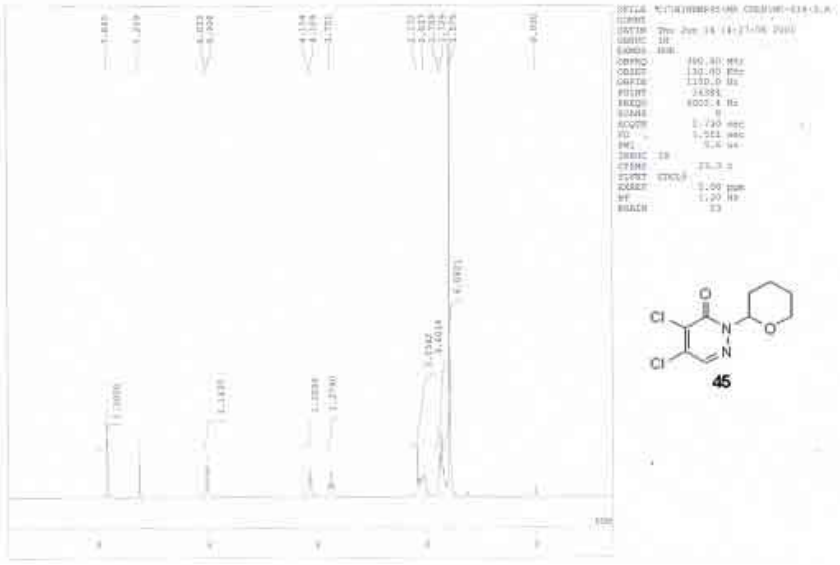


Figure A.8 ^{1}H-NMR spectrum of
4,5-Dichloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**45**)

Figure A.9 ^{1}H-NMR spectrum of
4-Chloro-5-methoxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**46**)

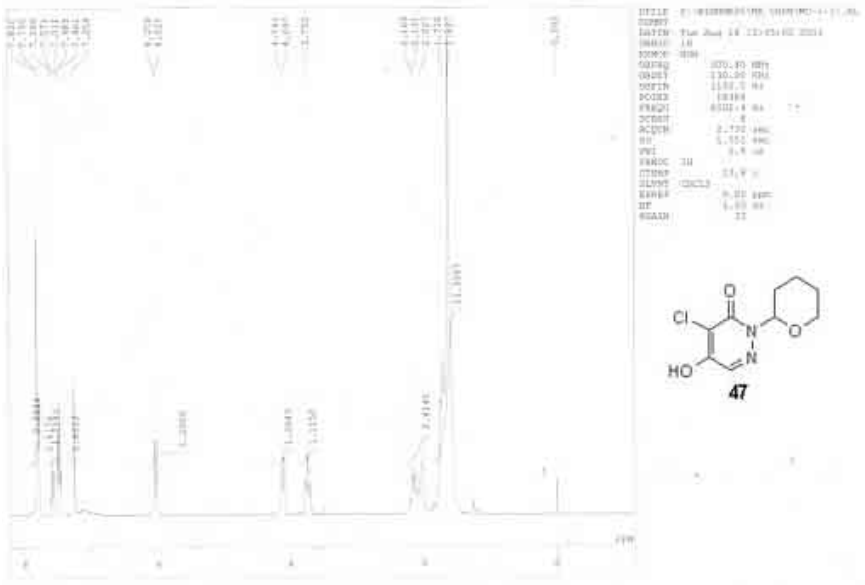


Figure A.11 ^{13}C-NMR spectrum of
4-Chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**47**)

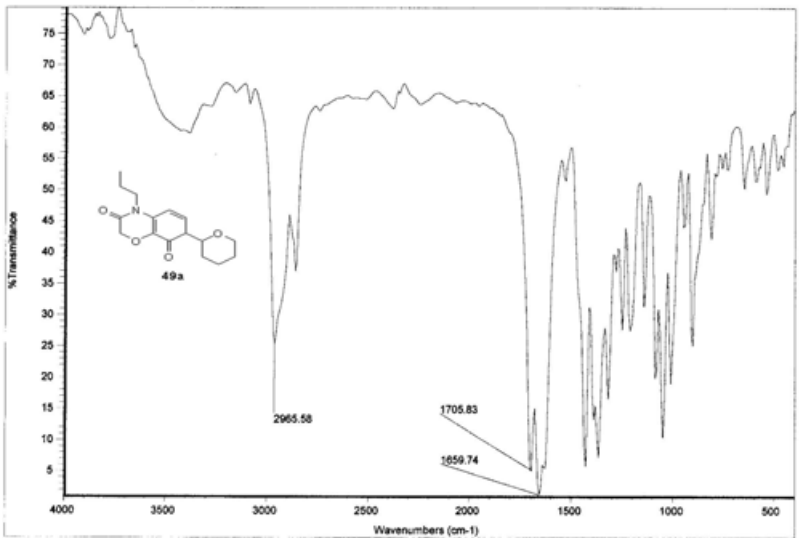


Figure A.12a IR spectrum of 4-Propyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49a**)

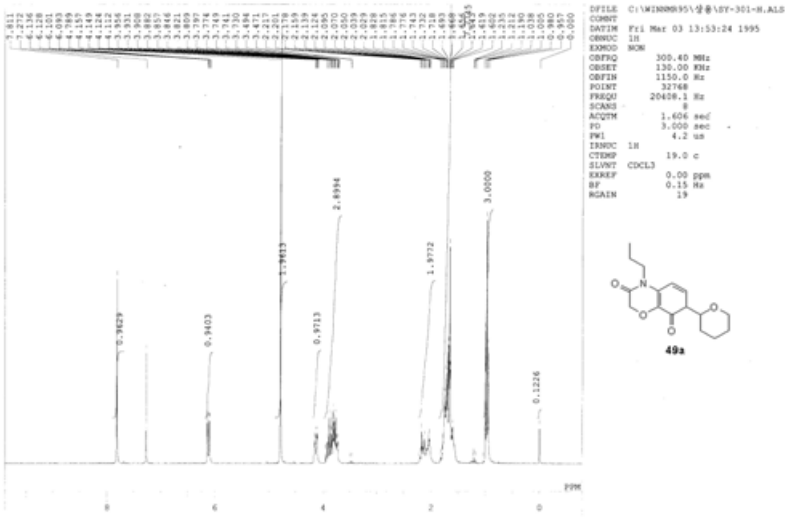


Figure A.12b ^{1}H-NMR spectrum of 4-Propyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49a**)

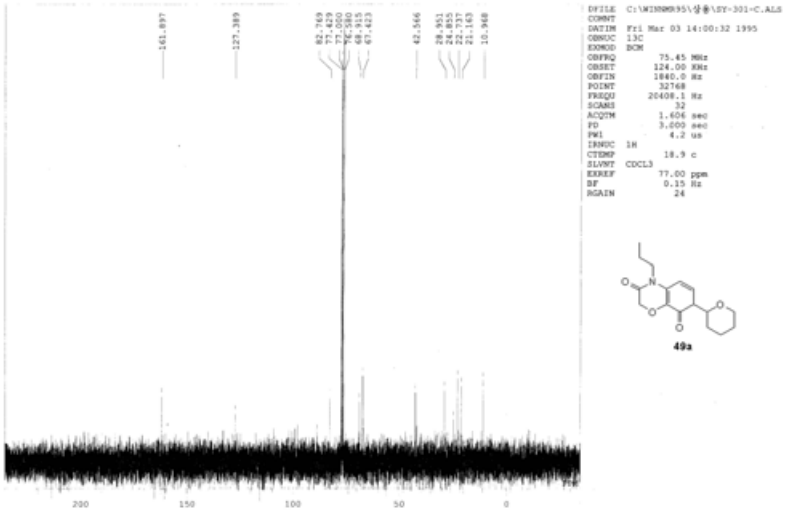


Figure A.12c ^{1}H-NMR spectrum of 4-Propyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49a**)

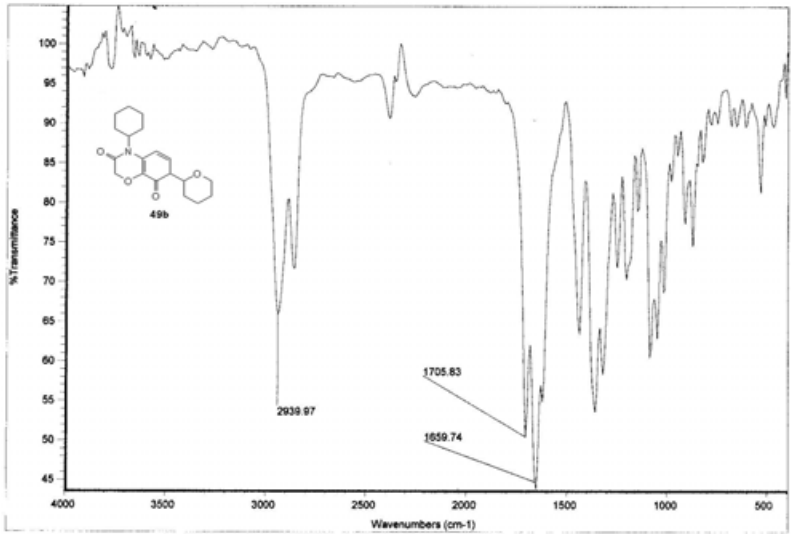


Figure A.13a IR spectrum of 4-Cyclohexyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49b**)

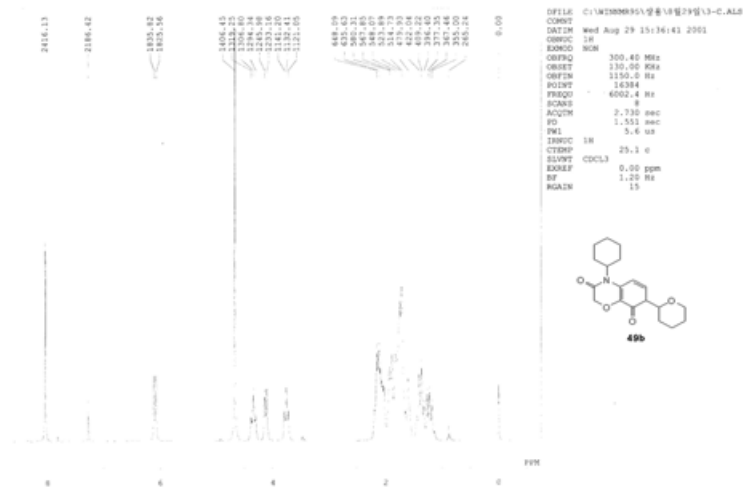


Figure A.13b ^{1}H-NMR spectrum of 4-Cyclohexyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49b**)

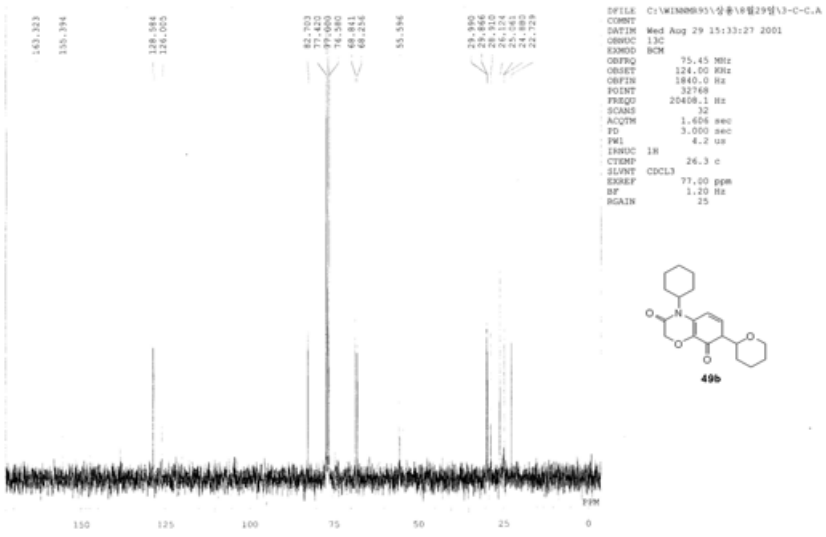


Figure A.13c ^{13}C-NMR spectrum of 4-Cyclohexyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]-oxazine-3,8-dione (**49b**)

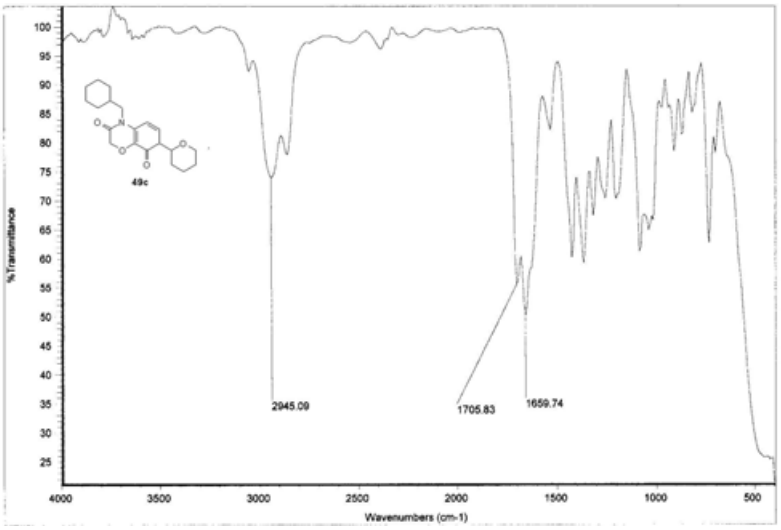


Figure A.14a IR spectrum of 4-Cyclohexylmethyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4] oxazine-3,8-dione (**49c**)

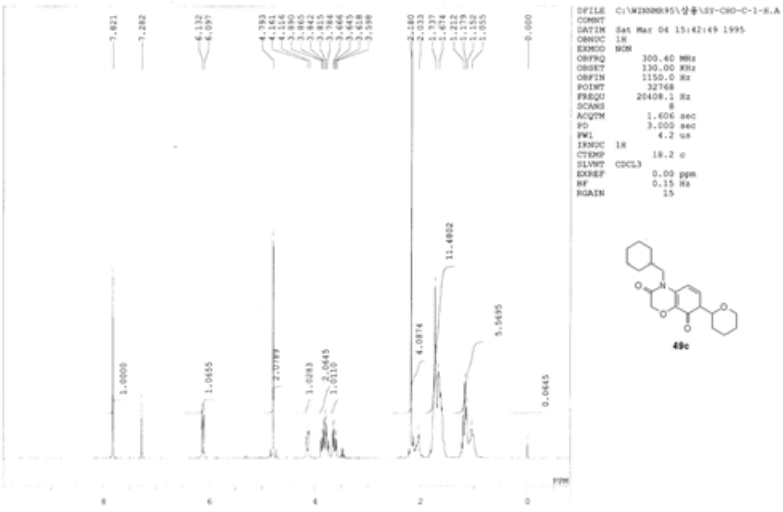


Figure A.14b ^{1}H-NMR spectrum of 4-Cyclohexylmethyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4] oxazine-3,8-dione (**49c**)

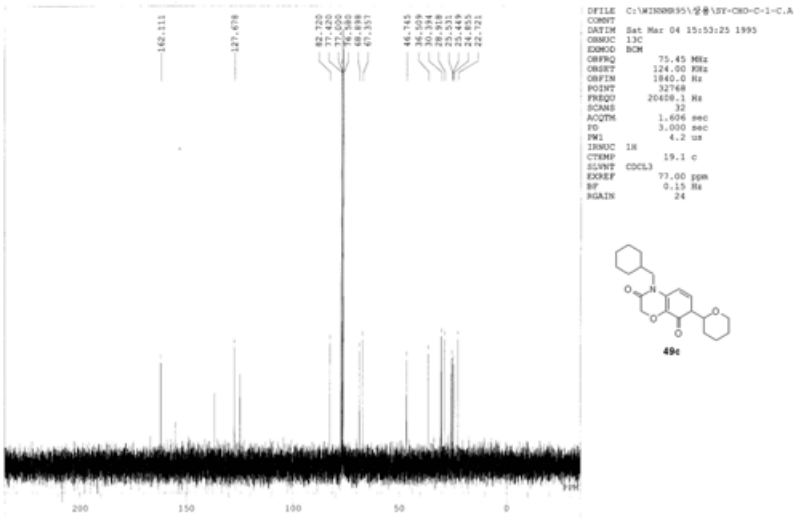


Figure A.14c ^{13}C-NMR spectrum of 4-Cyclohexylmethyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4] oxazine-3,8-dione (**49c**)

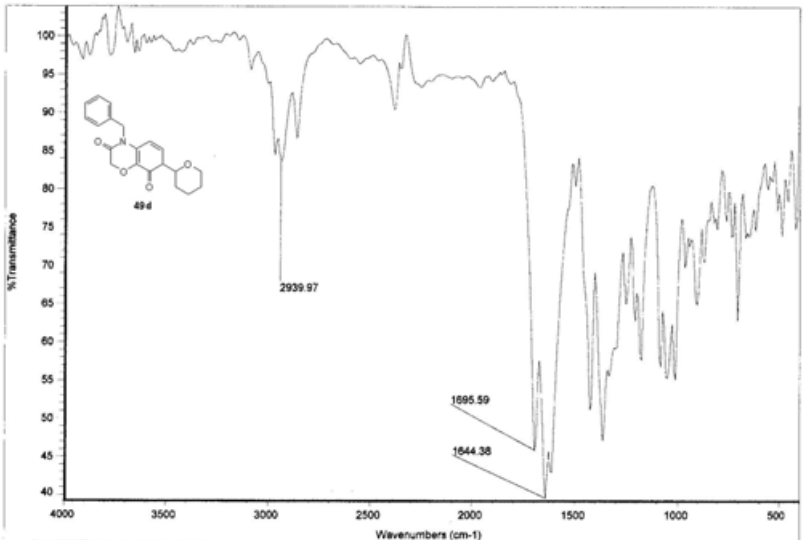


Figure A.15a IR spectrum of 4-Benzyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine-3,8-dione (**49d**)

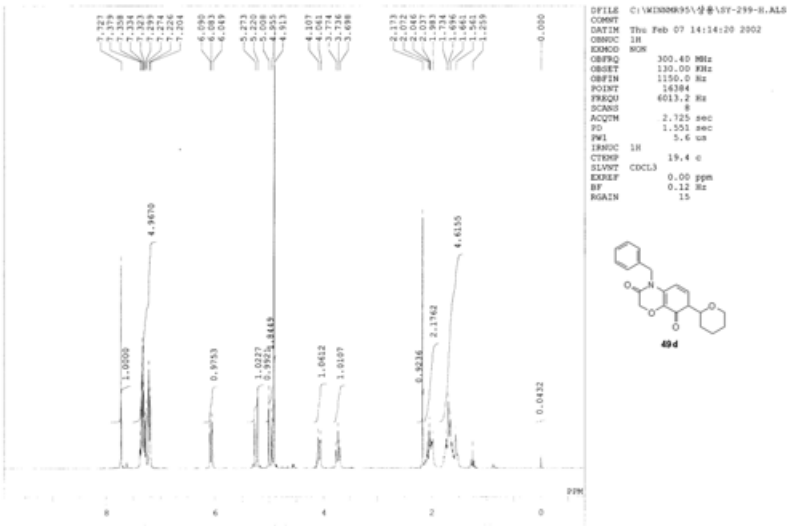


Figure A.15b ^{1}H-NMR spectrum of 4-Benzyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine-3,8-dione (**49d**)

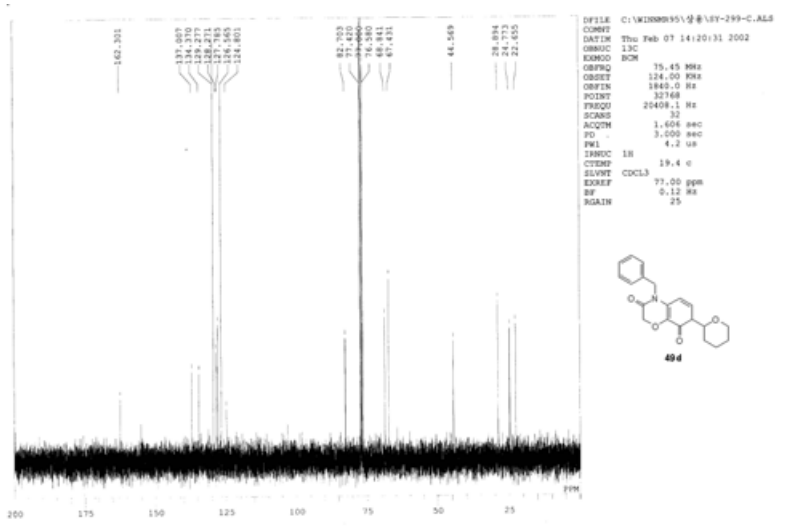


Figure A.15c ^{13}C-NMR spectrum of 4-Benzyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine-3,8-dione (**49d**)

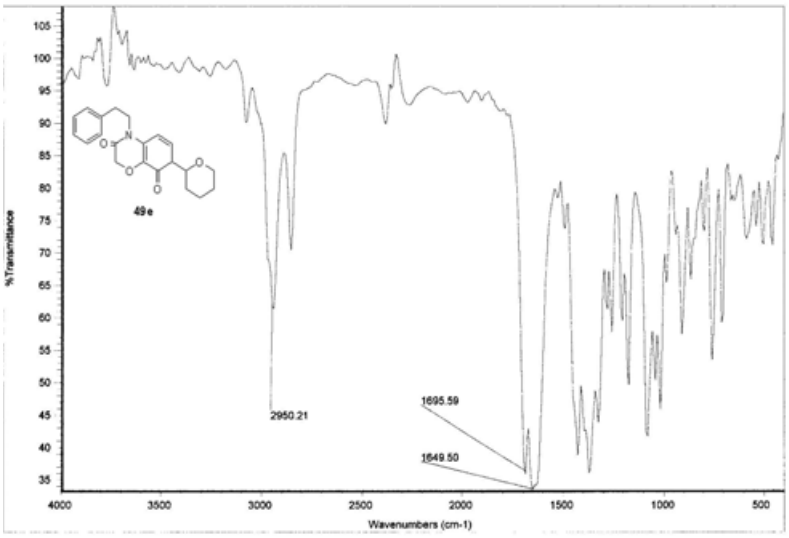


Figure A.16a IR spectrum of 4-Phenethyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine -3,8-dione (**49e**)

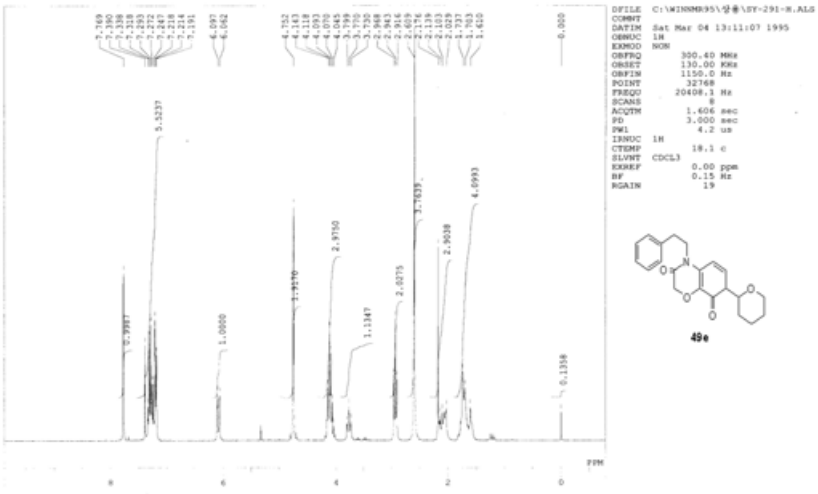


Figure A.16b ^{1}H-NMR spectrum of 4-Phenethyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine -3,8-dione (**49e**)

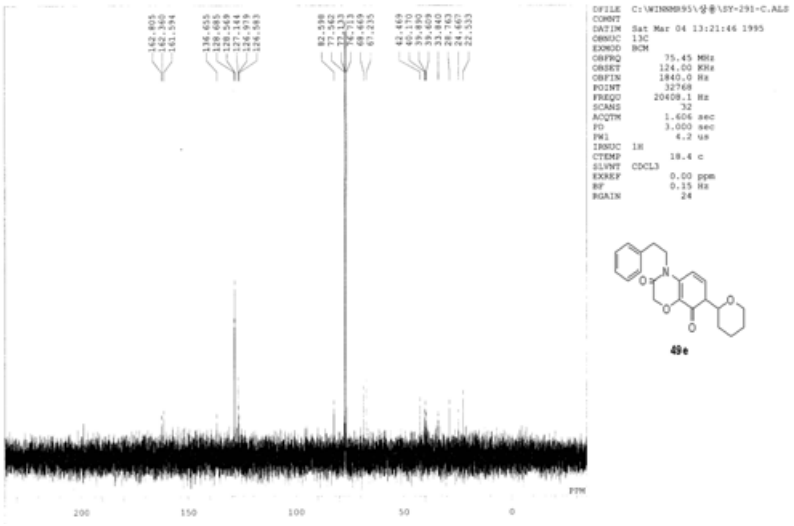


Figure A.16c ^{13}C-NMR spectrum of 4-Phenethyl-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino-[4,5-*b*][1,4]-oxazine -3,8-dione (**49e**)

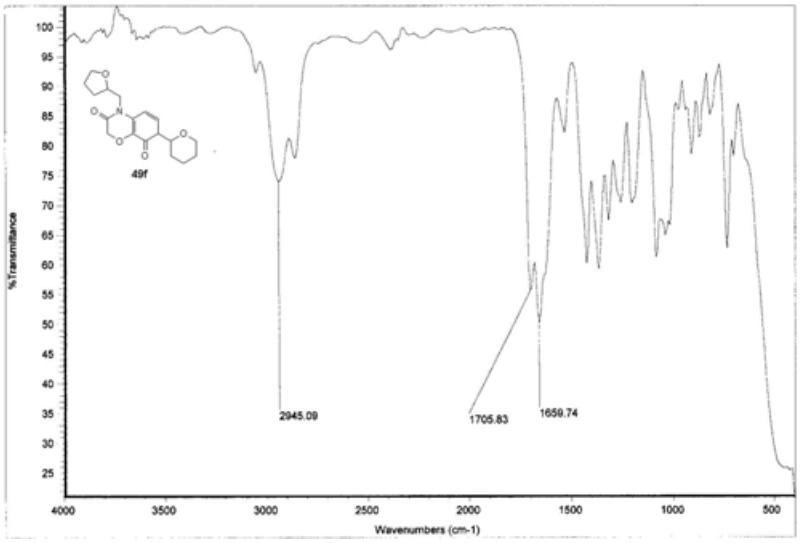


Figure A.17a IR spectrum of 4-(Tetrahydro-furan-2-ylmethyl)-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino [4,5-*b*][1,4]oxazine-3,8-dione (**49f**)

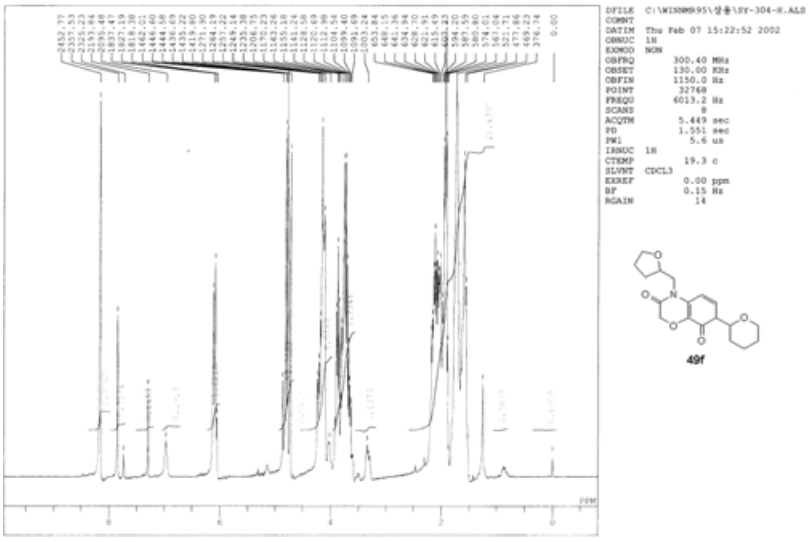


Figure A.17b ^{1}H-NMR spectrum of 4-(Tetrahydro-furan-2-ylmethyl)-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino [4,5-*b*][1,4]oxazine-3,8-dione (**49f**)

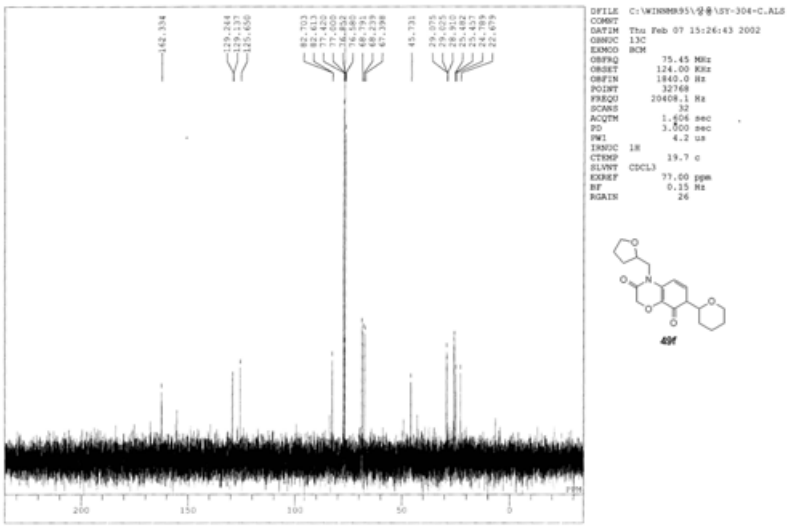


Figure A.17c ^{13}C-NMR spectrum of 4-(Tetrahydro-furan-2-ylmethyl)-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino [4,5-*b*][1,4]oxazine-3,8-dione (**49f**)

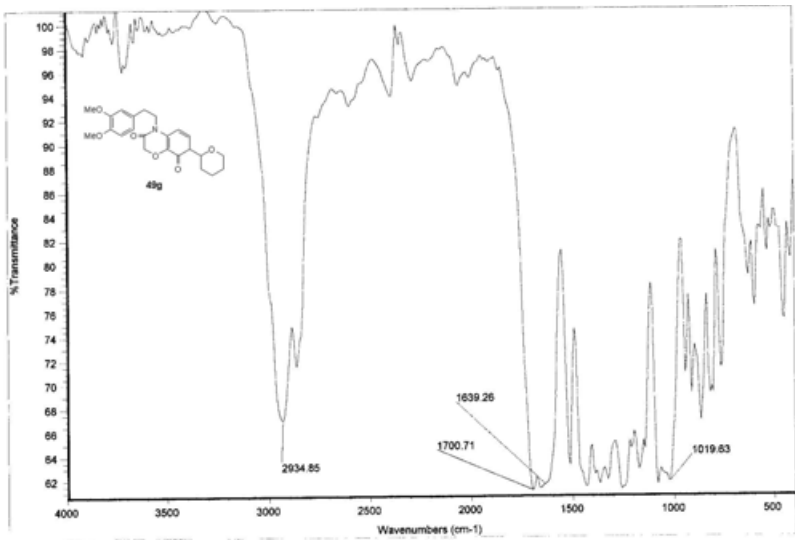


Figure A.18a IR spectrum of 4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (**49g**)

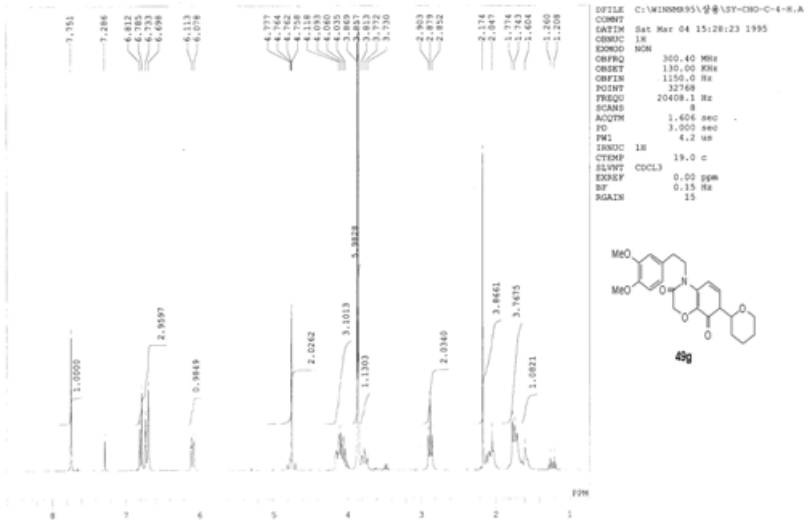


Figure A.18b ^{1}H-NMR spectrum of 4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (**49g**)

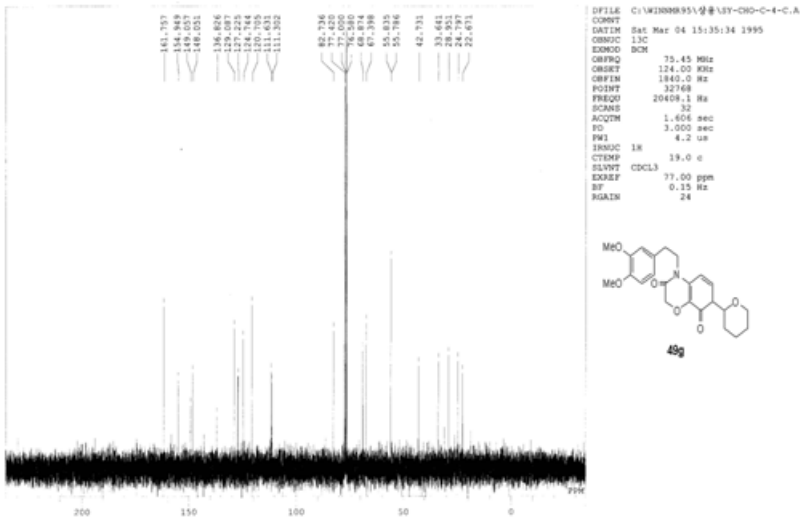


Figure A.18c ^{13}C-NMR spectrum of 4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-7-(tetrahydro-pyran-2-yl)-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (**49g**)

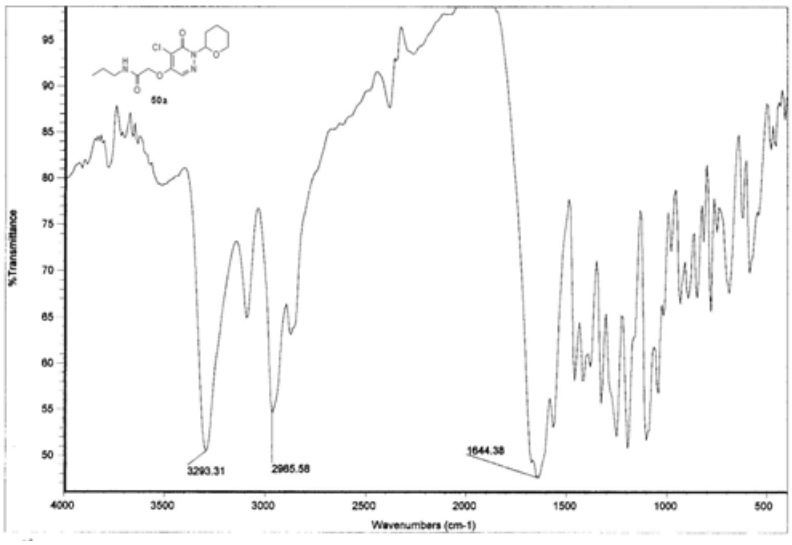


Figure A.19a IR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-propyl-acetamide (**50a**)

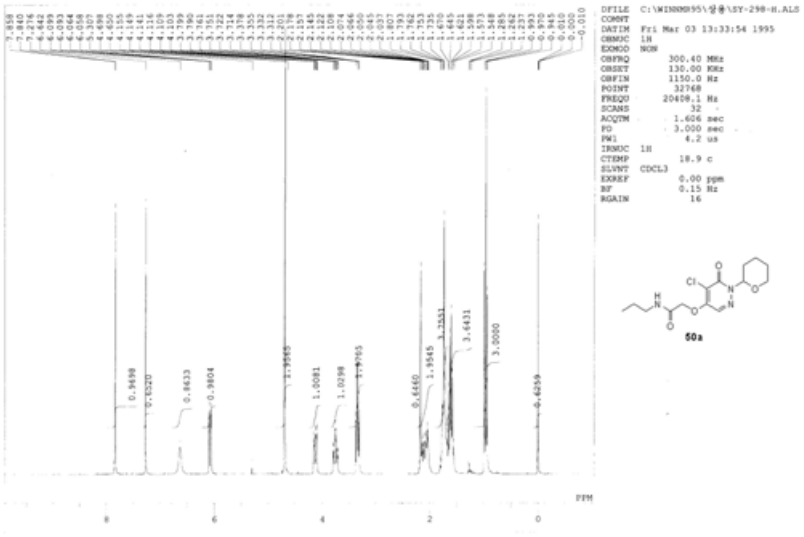


Figure A.19b ^{1}H-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-propyl-acetamide (**50a**)

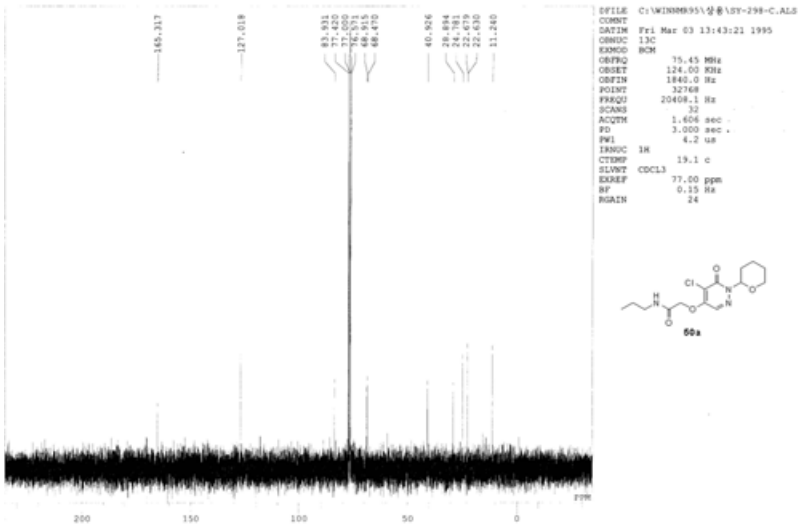


Figure A.19c ^{13}C-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-propyl-acetamide (**50a**)

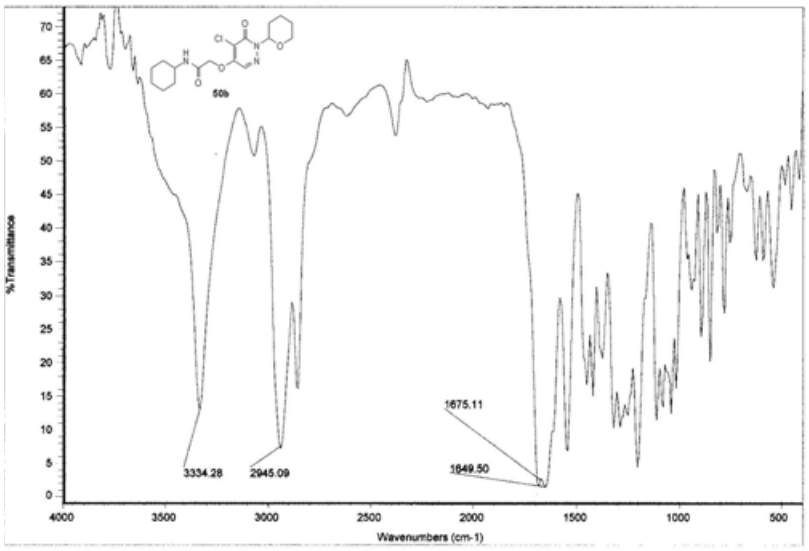


Figure A.20a IR spectrum of
2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-cyclohexyl-acetamide (**50b**)

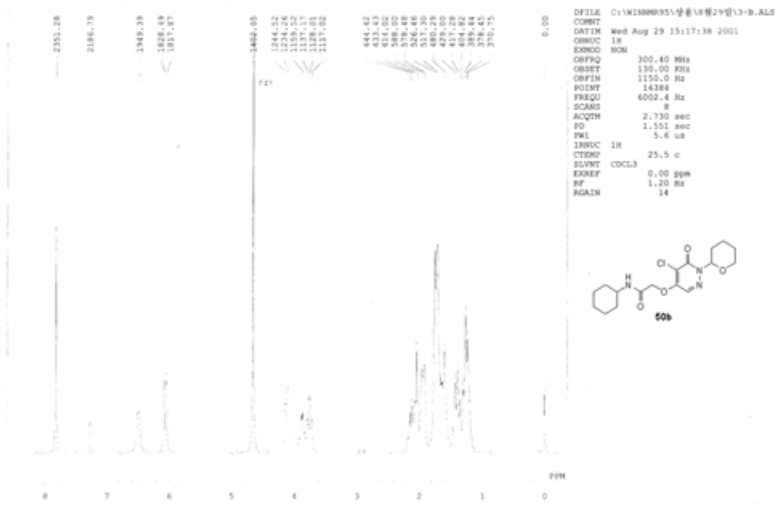


Figure A.20b ^{1}H-NMR spectrum of
2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-cyclohexyl-acetamide (**50b**)

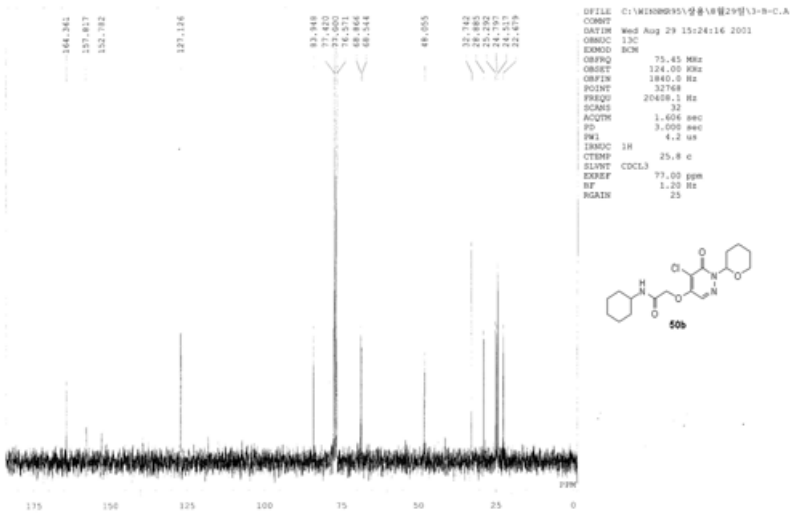


Figure A.20c ^{13}C-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-cyclohexyl-acetamide (**50b**)

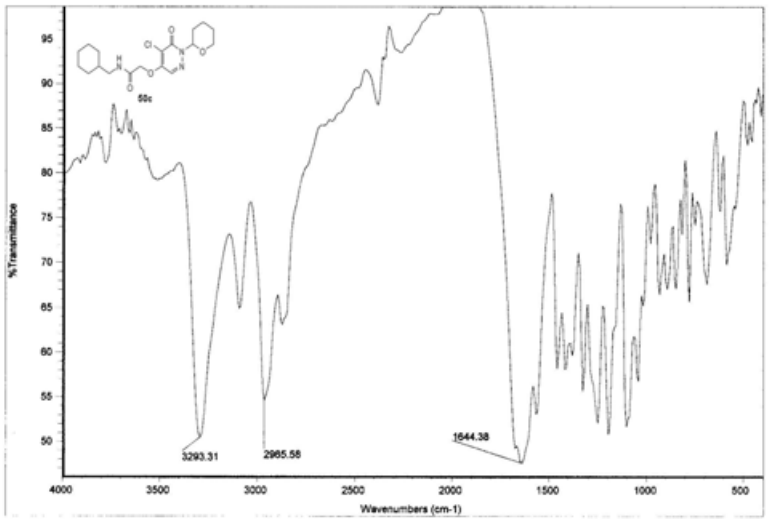


Figure A.21a IR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-cyclohexylmethyl-acetamide (**50c**)

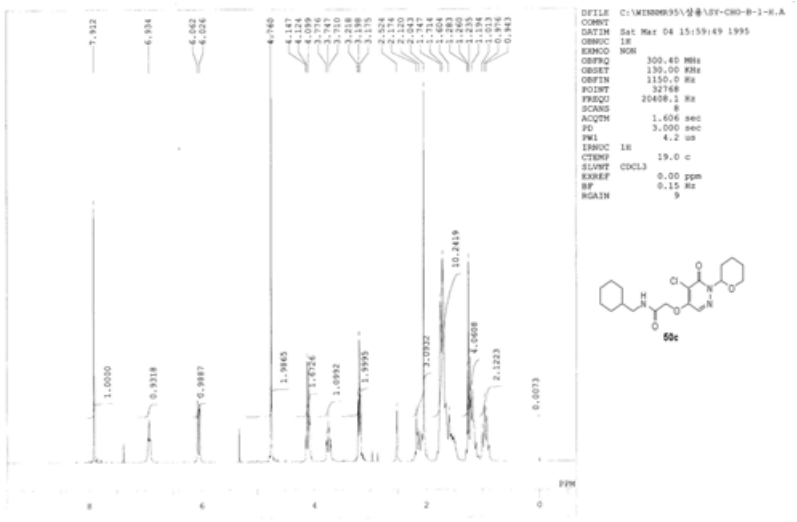


Figure A.21b ^{1}H-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-cyclohexylmethyl-acetamide (**50c**)

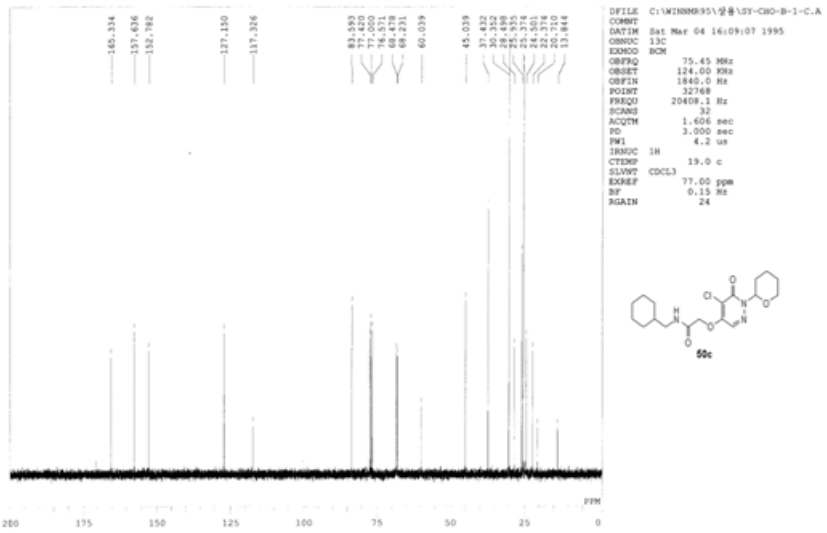


Figure A.21c ^{13}C-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-cyclohexylmethyl-acetamide (**50c**)

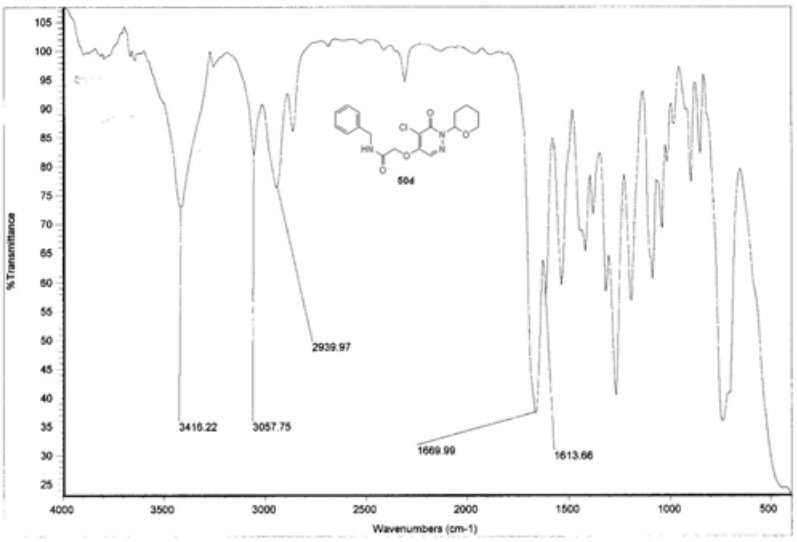


Figure A.22a IR spectrum of *N*-Benzyl-2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-acetamide (**50d**)

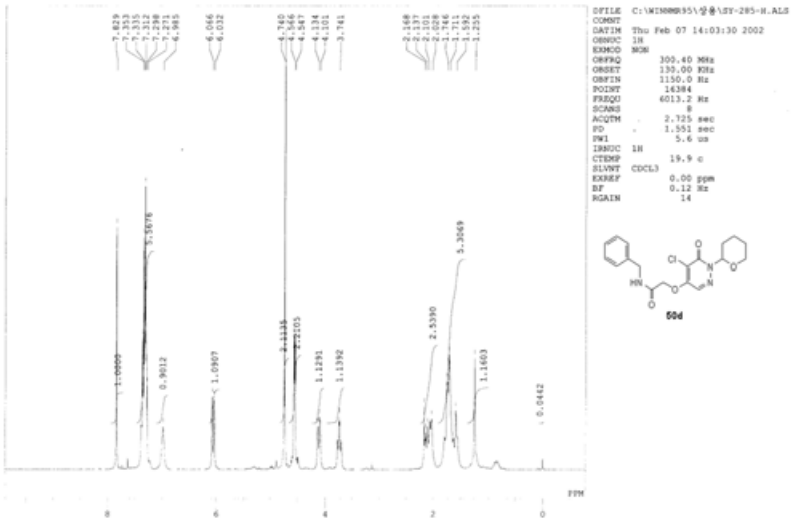


Figure A.22b ^{1}H-NMR spectrum of *N*-Benzyl-2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-acetamide (**50d**)

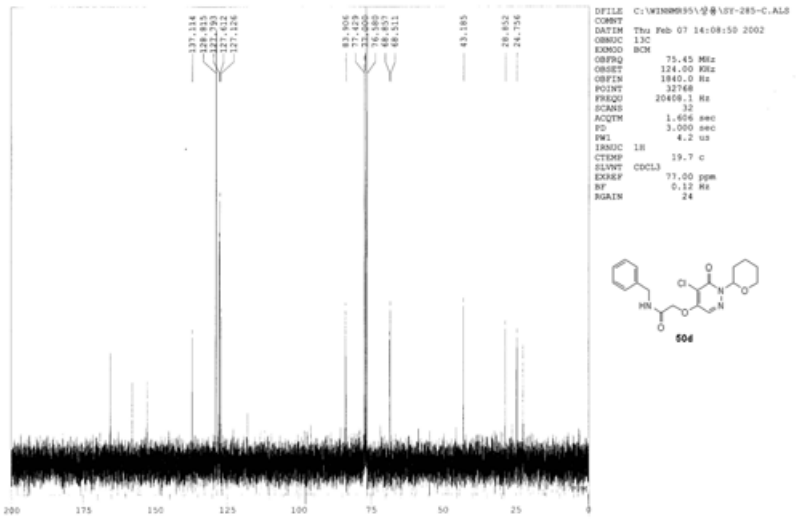


Figure A.22c ^{13}C-NMR spectrum of *N*-Benzyl-2-[5-chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-acetamide (**50d**)

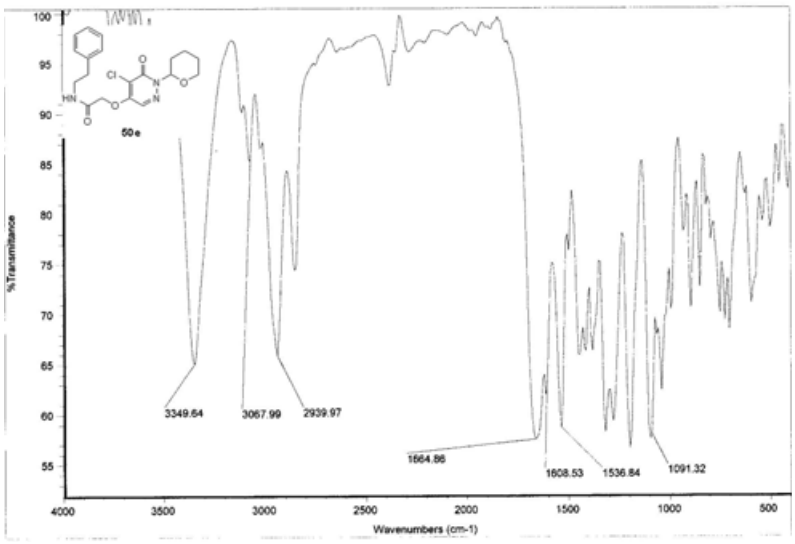


Figure A.23a IR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-phenethyl-acetamide (**50e**)

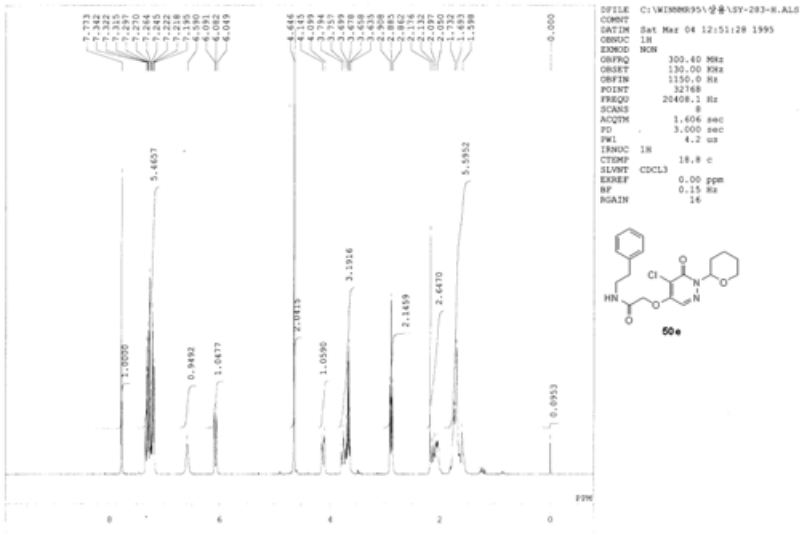


Figure A.23b ^{1}H-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-phenethyl-acetamide (**50e**)

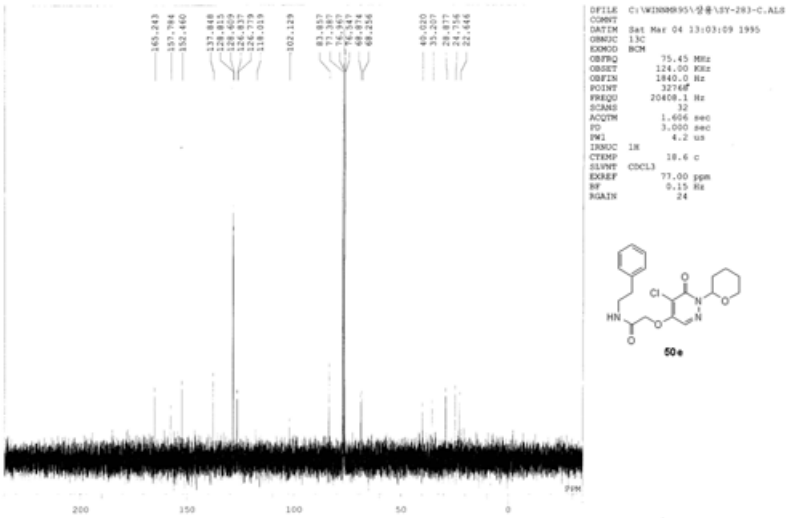


Figure A.23c ^{13}C-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-phenethyl-acetamide (**50e**)

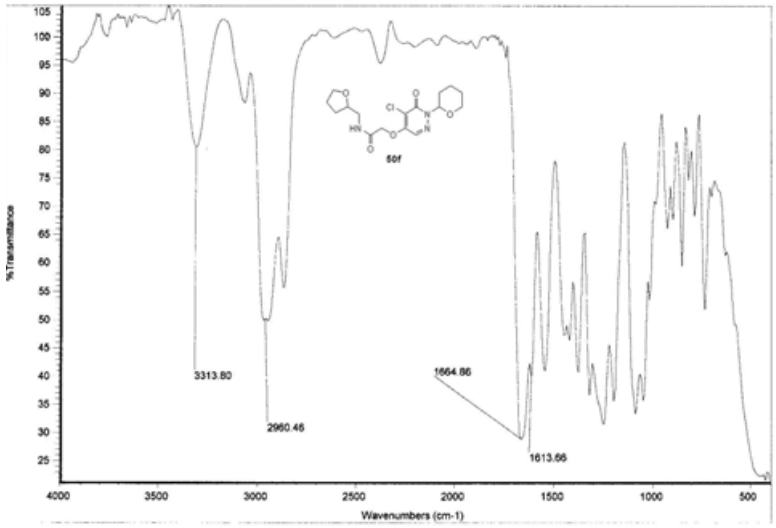


Figure A.24a IR spectrum of
2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-
N-(tetrahydro-furan-2-ylmethyl)-acetamide (**50f**)

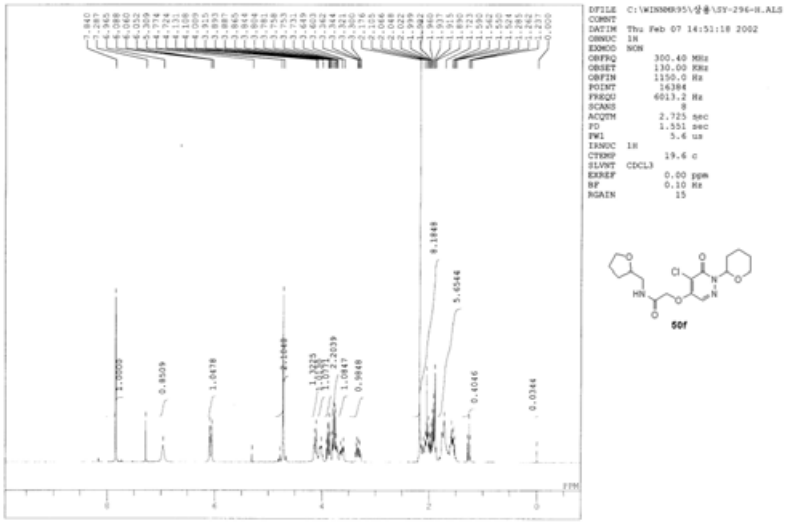


Figure A.24b ^{1}H-NMR spectrum of
2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-
N-(tetrahydro-furan-2-ylmethyl)-acetamide (**50f**)

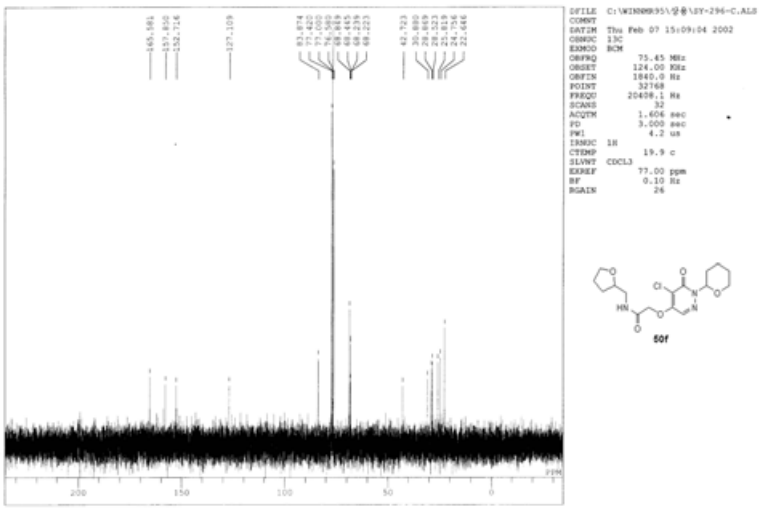


Figure A.24c ^{13}C-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-(tetrahydro-furan-2-ylmethyl)-acetamide (**50f**)

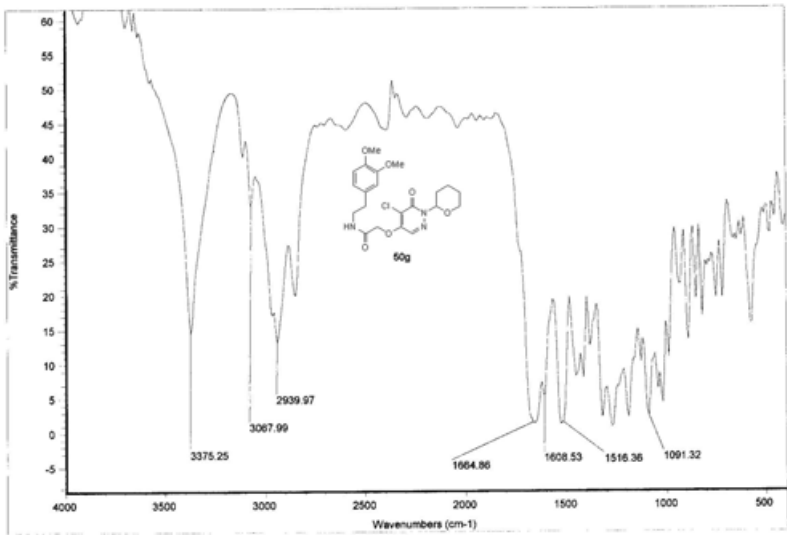


Figure A.25a IR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (**50g**)

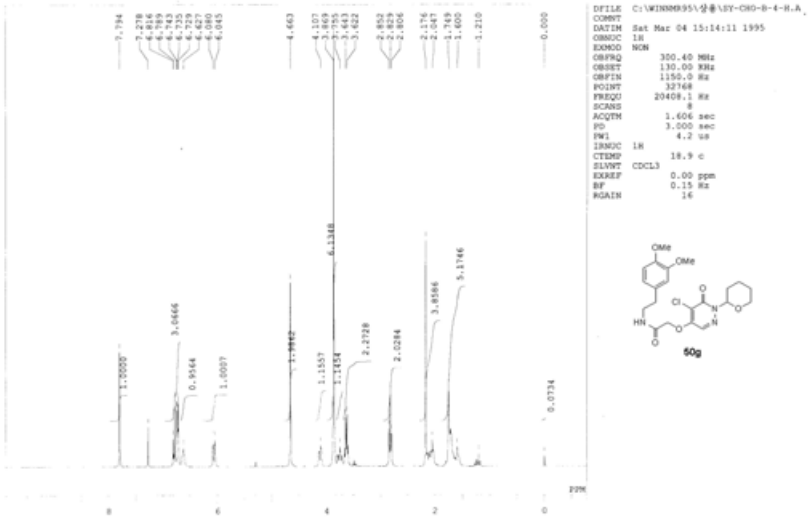


Figure A.25b ^{1}H-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (**50g**)

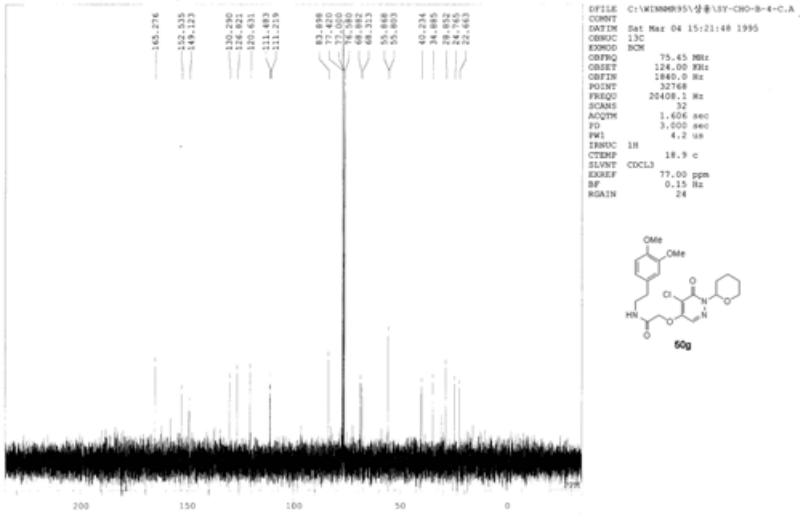


Figure A.25c ^{13}C-NMR spectrum of 2-[5-Chloro-6-oxo-1-(tetrahydro-pyran-2-yl)-1,6-dihydro-pyridazin-4-yloxy]-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (**50g**)

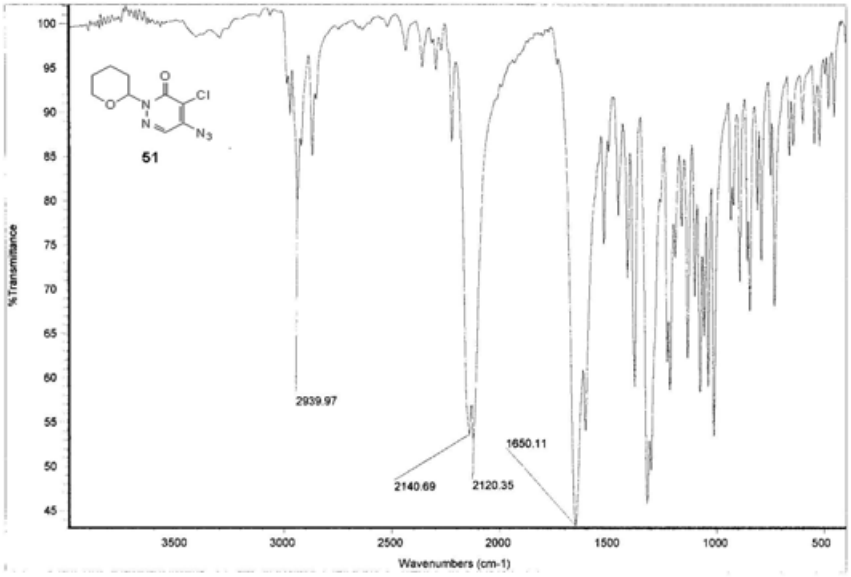


Figure A.26a IR spectrum of
5-Azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**51**)

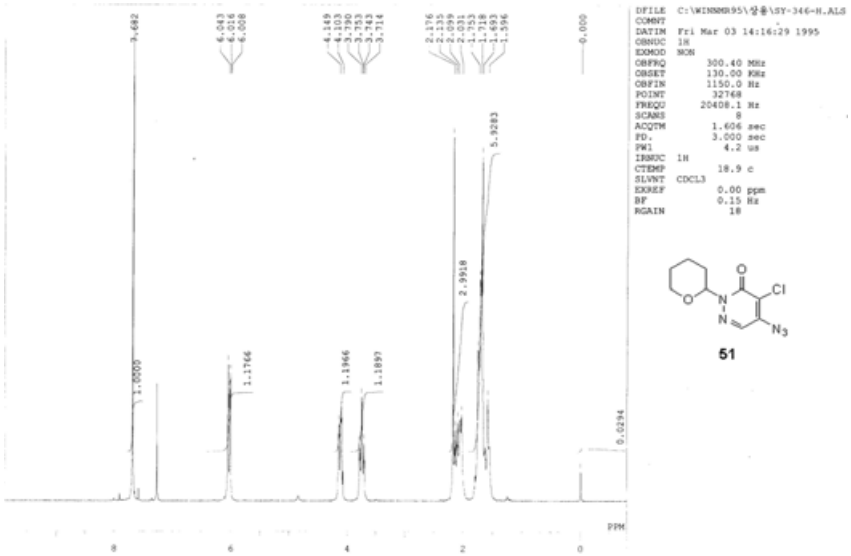


Figure A.26b ^{1}H-NMR spectrum of
5-Azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**51**)

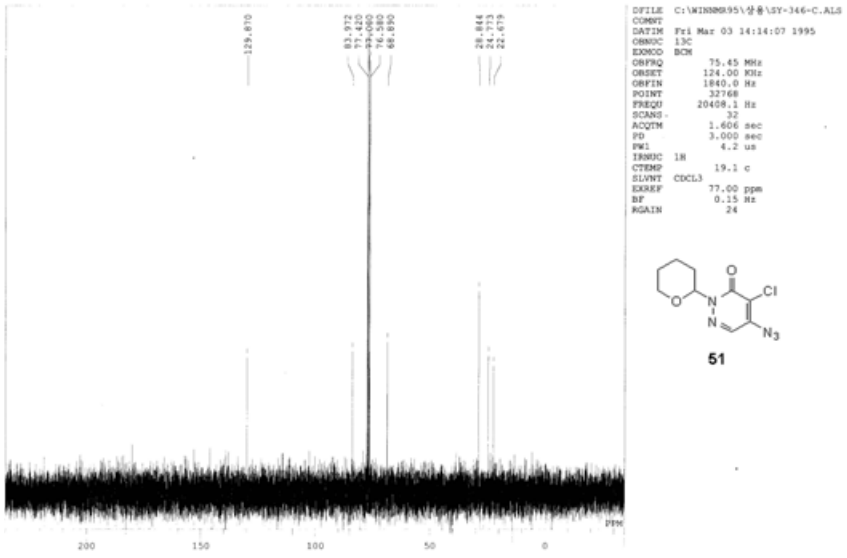


Figure A.26c ^{13}C-NMR spectrum of
5-Azido-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**51**)

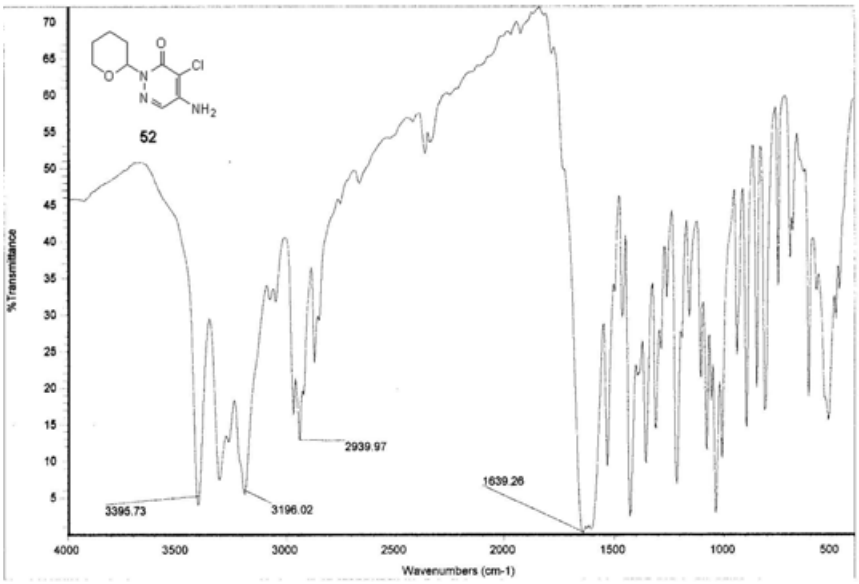


Figure A.27a IR spectrum of
5-Amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**52**)

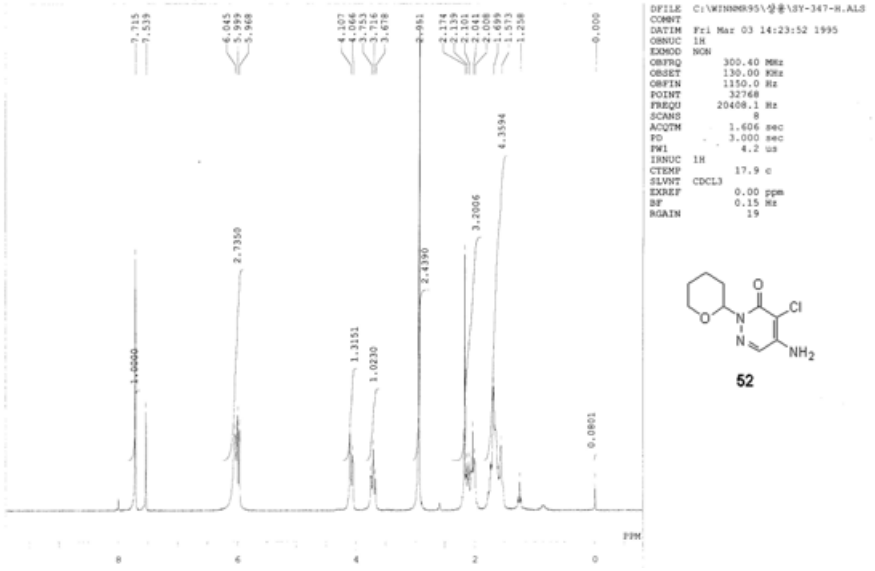


Figure A.27b ^{1}H-NMR spectrum of
5-Amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**52**)

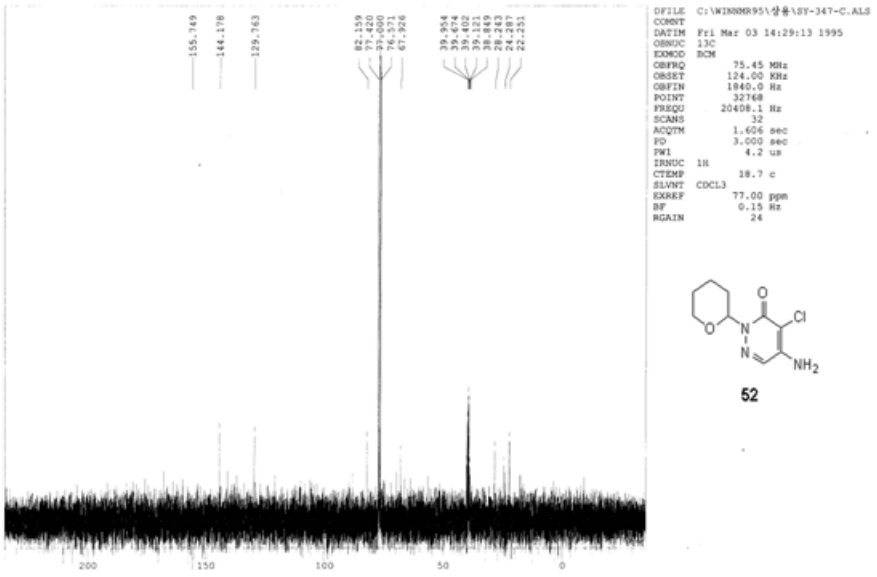


Figure A.27c ^{13}C-NMR spectrum of
5-Amino-4-chloro-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (**52**)

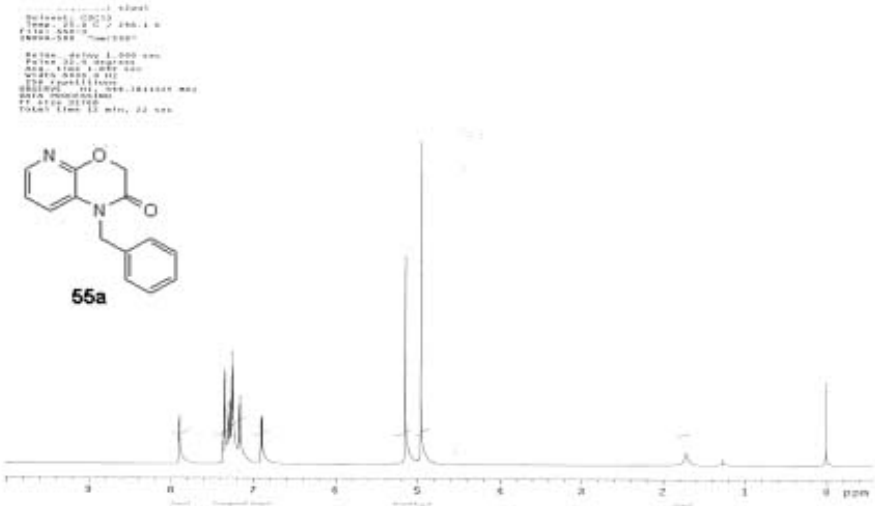


Figure A.28a ^{1}H-NMR spectrum of
1-Benzyl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one (**55a**)

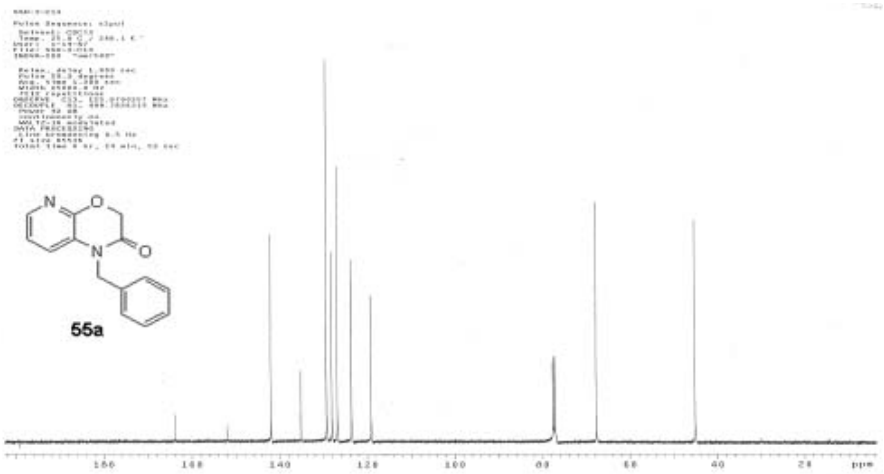


Figure A.28b ^{13}C-NMR spectrum of
1-Benzyl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one (**55a**)

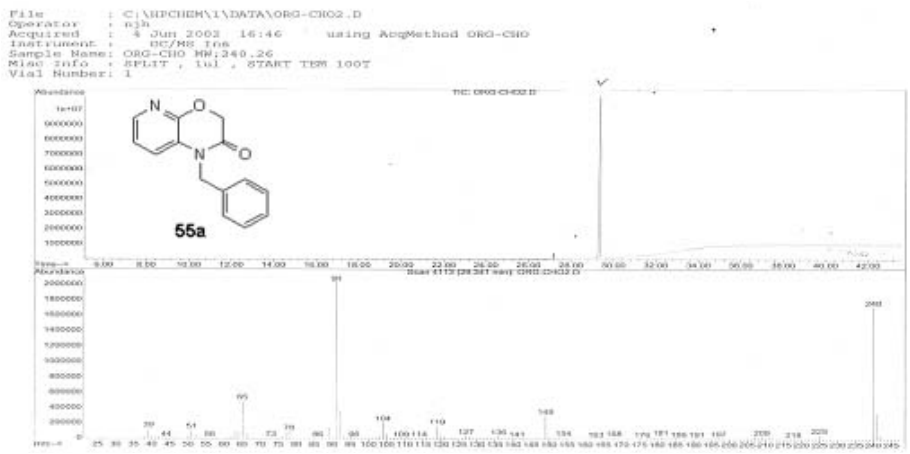


Figure A.28c GC-Mass spectrum of
1-Benzyl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one (**55a**)

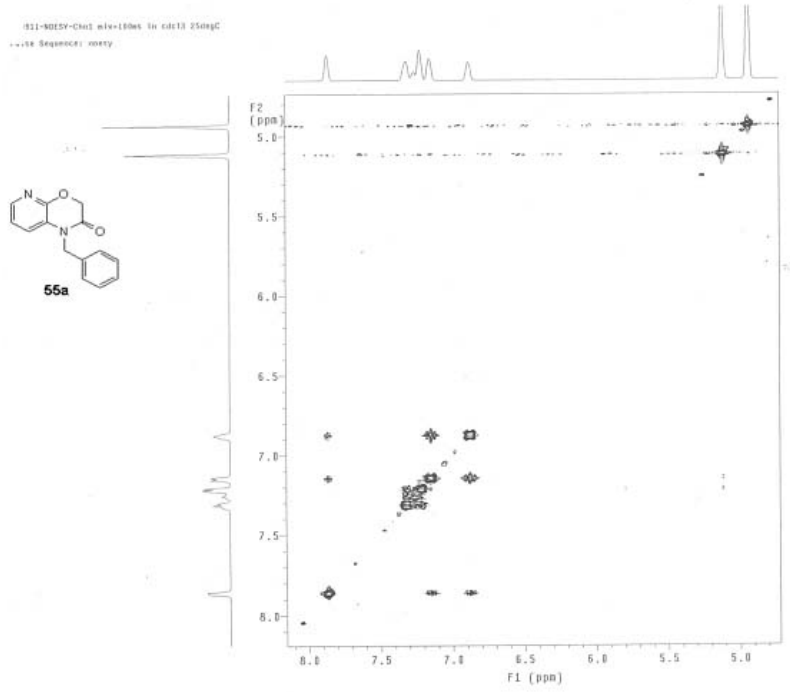


Figure A.28d COSY spectrum of
1-Benzyl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one (**55a**)

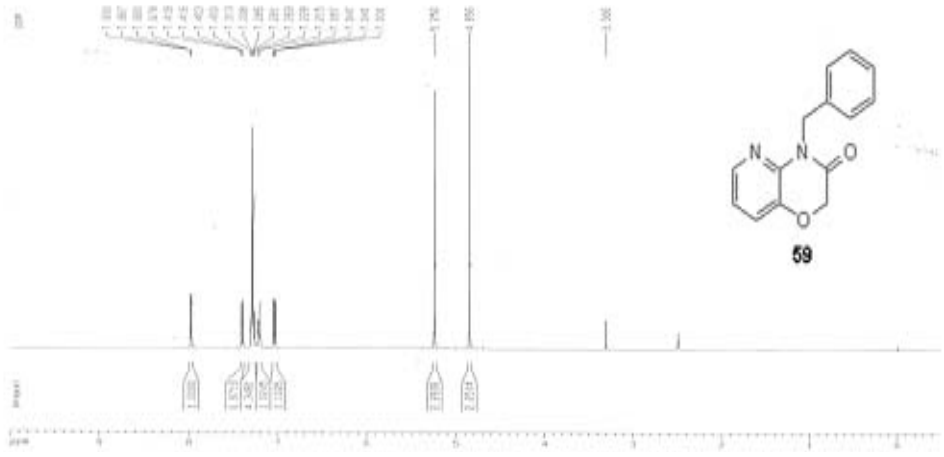


Figure A.29a ^{1}H-NMR spectrum of
4-Benzyl-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (**59**)

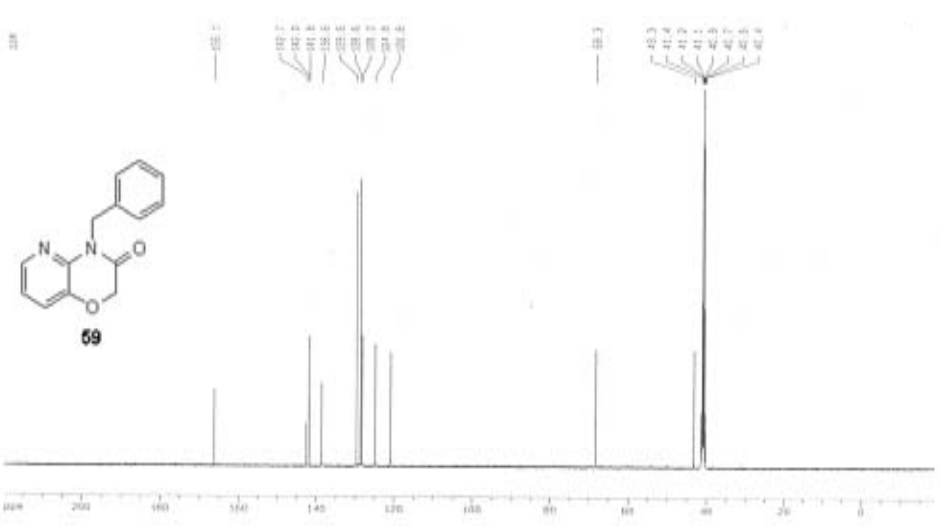


Figure A.29b ^{13}C-NMR spectrum of
4-Benzyl-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (**59**)

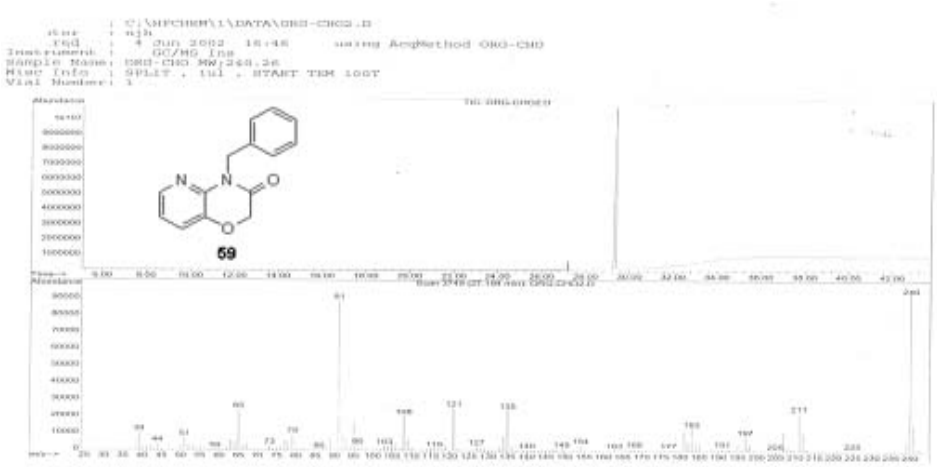


Figure A.29c GC-Mass spectrum of
4-Benzyl-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (**59**)

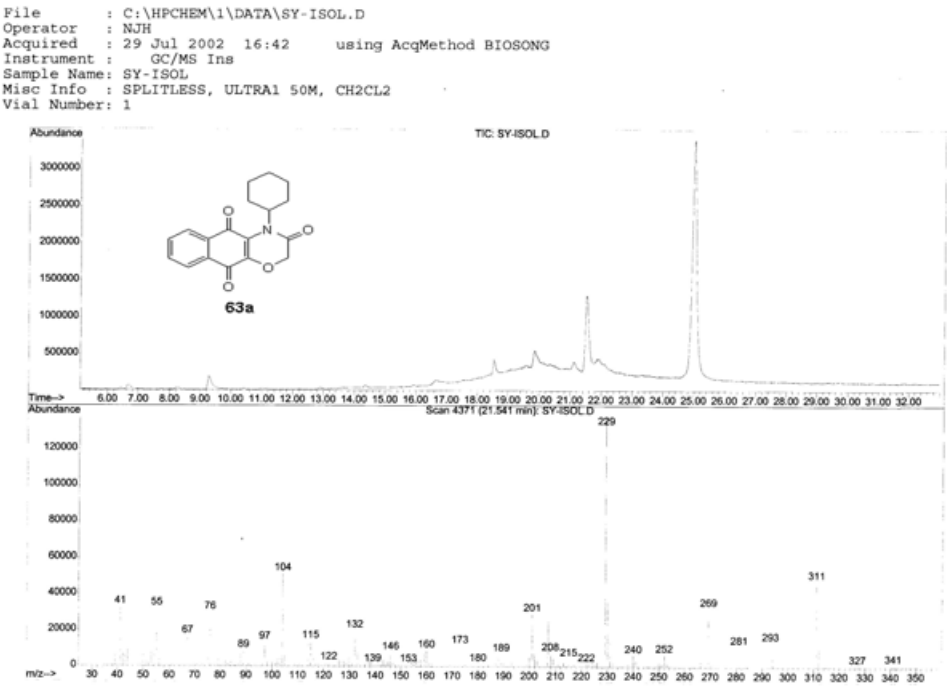


Figure A.30a GC-Mass spectrum of
4-Cyclohexyl-4*H*-naphtho[2,3-*b*][1,4]oxazine-3,5,10-trione (**63a**)

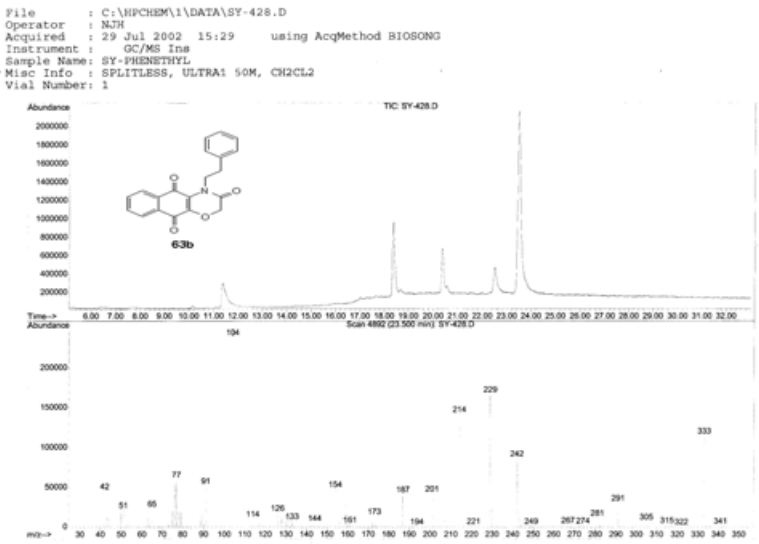


Figure A.31 GC-Mass spectrum of 4-Phenethyl-4*H*-naphtho[2,3-*b*][1,4]oxazine-3,5,10-trione (**63b**)

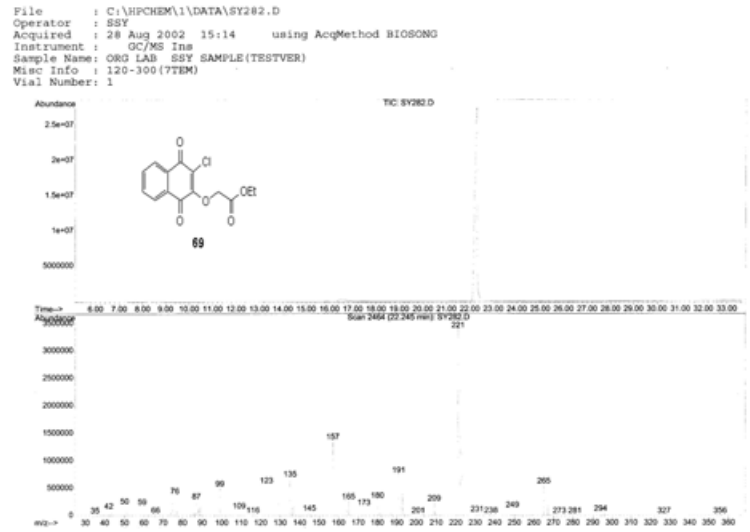


Figure A.32 GC-Mass spectrum of (3-Chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-yloxy)-acetic acid ethyl ester (**69**)

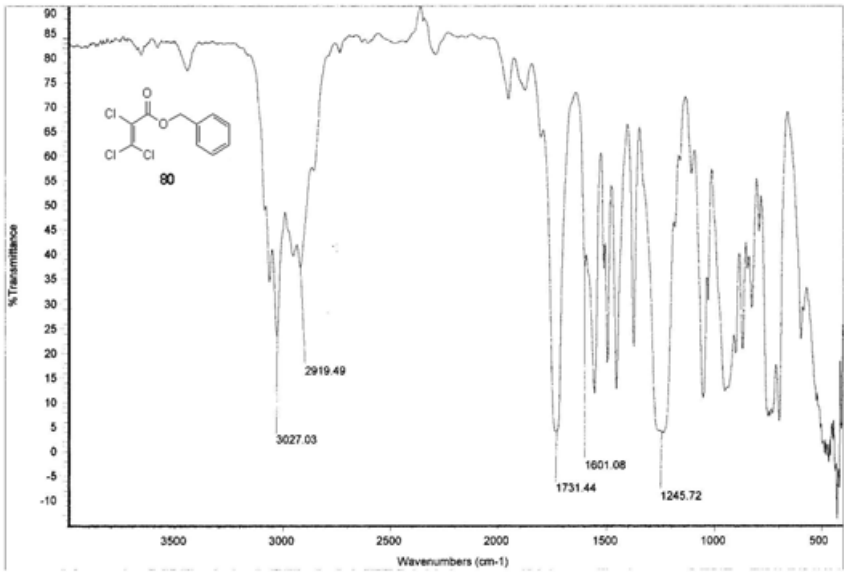


Figure A.33a IR spectrum of 2,3,3-Trichloro-acrylic acid benzyl ester (**80**)

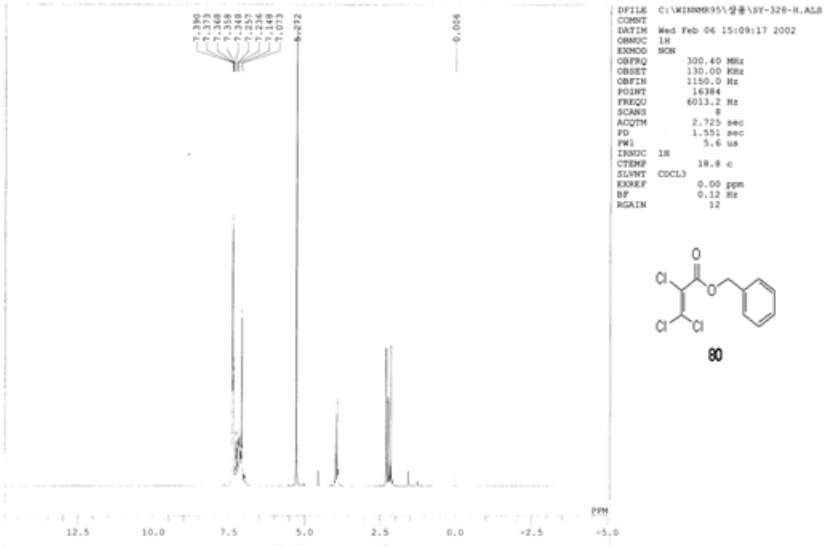


Figure A.33b ^{1}H-NMR spectrum of 2,3,3-Trichloro-acrylic acid benzyl ester (**80**)

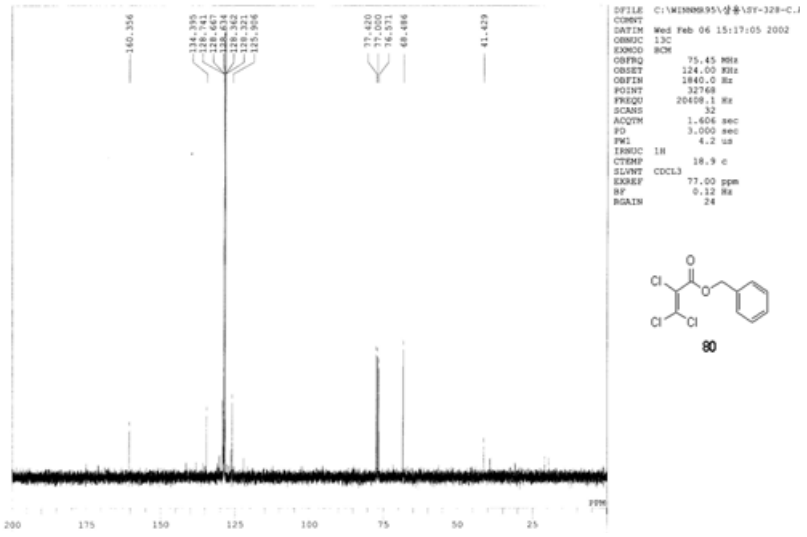


Figure A.33c ^{13}C-NMR spectrum of 2,3,3-Trichloro-acrylic acid benzyl ester (**80**)

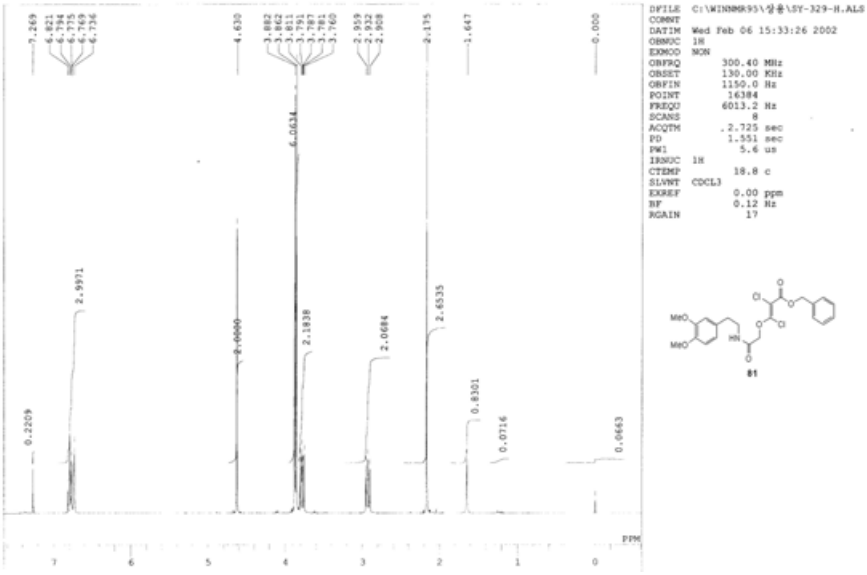


Figure A.34a ^{1}H-NMR spectrum of 2,3-Dichloro-3-{[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-methoxy}-acrylic acid benzyl ester (**81**)

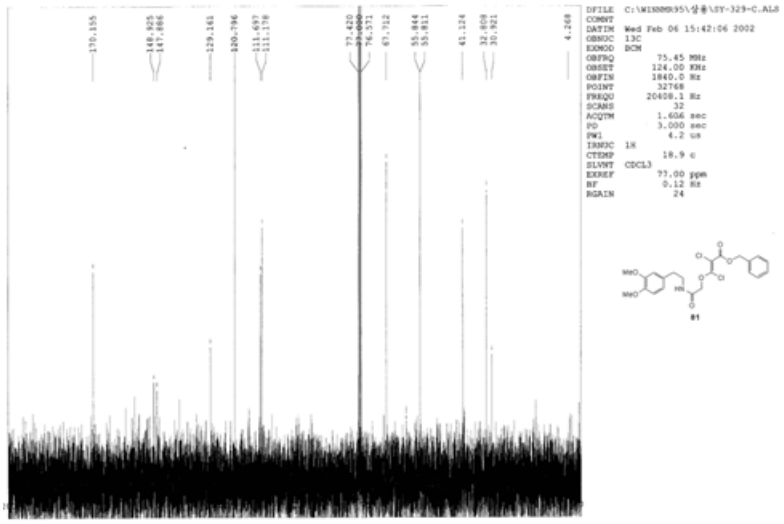


Figure A.34b ^{13}C-NMR spectrum of 2,3-Dichloro-3-{[2-(3,4-dimethoxy-phenyl)-ethylcarbamoyl]-methoxy}-acrylic acid benzyl ester (**81**)

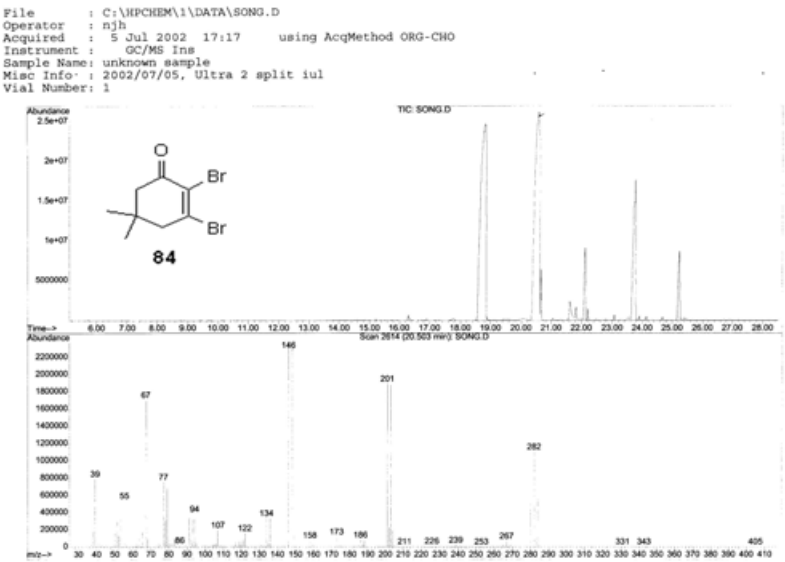


Figure A.35a GC-Mass spectrum of 2,3-Dibromo-5,5-dimethyl-cyclohex-2-enone (**84**)

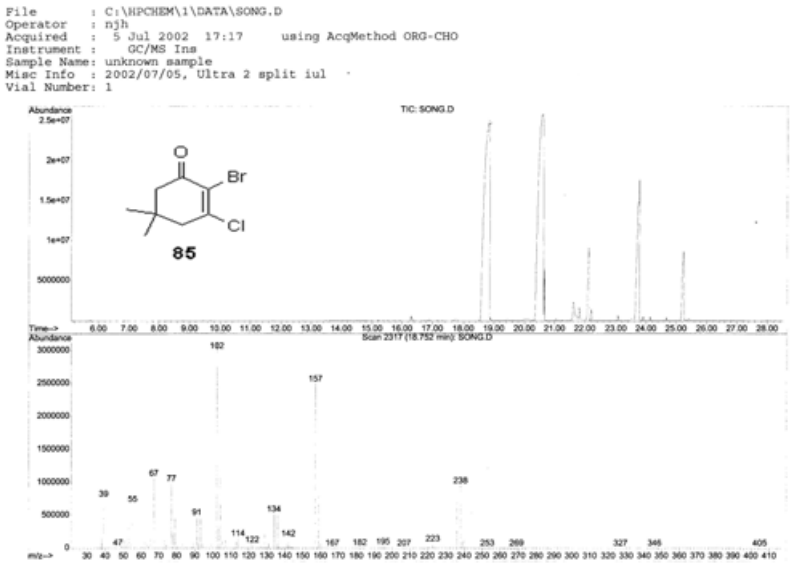


Figure A.36a GC-Mass spectrum of 3-Bromo-2-chloro-5,5-dimethyl-cyclohex-2-enone (**85**)

Abstract

Noble Synthesis of the [1,4]-Oxazine Derivatives and its Mechanistic Study

by
Song, Sang-Yong

DEPARTMENT OF CHEMISTRY
GRADUATE SCHOOL
CHANGWON NATIONAL UNIVERSITY

The [1,4]-oxazine structure is one of important backbone in natural products and biological activity compounds. However, there are fewer synthetic methods are reported. Herein, we are introducing of noble and convenient synthetic method of [1,4]-oxazine and their derivatives using 3-halo-4-hydroxy-prop-3-en-2-one / dihalo-hydroxy-but-3-en-2-one and *N*-substituted-2-hydroxy / halo acetamide compound as starting materials. In addition, this method can be adaptable to synthesis of pyridazine, pyridine and naphthoquinone fused [1,4]-oxazines. Also, we are suggested that this reaction mechanism is followed *via* Michael type addition or SN2 type reaction between 3-halo-4-hydroxy-prop-3-en-2-one/dihalo-hydroxy-but-3-en-2-one and *N*-substituted-2-hydroxy / halo acetamide compound and then inter-molecular nitrogen oriented migration.