Enantioselective synthesis of tetrahydrofuran-imidazole based human histamine H_3 and H_4 receptor agonists

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften
Dr. rer. nat.
an der Fakultät für Chemie und Pharmazie
der Universität Regensburg

vorgelegt von

Chinna Ashalu Kashamalla

aus

Warangal (Indien)

Regensburg 2009

Die Arbeit wurde angeleitet von:	Prof. Dr. O. Reiser
Promotionsgesuch eingereicht am:	14 September, 2009
Promotionskolloquium am:	02 Oktober, 2009
Prüfungsausschuss:	Vorsitz: Prof. Dr. Armin Buschauer
	1. Gutachter: Prof. Dr. Oliver Reiser
	2. Gutachter: Prof. Dr. Burkhard König
	3. Prüfer: Prof. Dr. Sigurd Elz

Der experimentelle Teil der vorliegenden Arbeit wurde unter der Leitung von Herrn Prof. Dr. Oliver Reiser in der Zeit von August 2005 bis Mai 2009 am Institut für Organische Chemie der Universität Regensburg, Regensburg, Germany.

Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

Dedicated to my family.

Contents

1. Introduction

Aim of the work

2. Enantioselective synthesis of histamine H_3 and H_4 receptor potential agonists based on γ-butyrolactones

2.7 Introduction to tetrahydrofuran-imidazole based histamine H_3 and H_4 receptor agonists

Summary

Aim of the work

3. Synthesis of histamine H_3 and H_4 receptor potential agonists by NBS mediated cyclopropane ring opening methodology

3.2 Enantioselective synthesis of histamine H_3 and H_4 receptor potential agonists by imidazole-furan cyclopropane ring opening methodology.

Abbreviations

AC	adenylyl cyclase
AChE	acetylcholinesterase
AD	asymmetric dihydroxylation
ADDP	1,1-(azodicarbonyl)dipiperidine
AMP	Adenosine Monophosphate
9-BBN	9-Borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
BOX	bis(oxazoline)
BuLi	*n*-butyl lithium
cAMP	cyclic 3′, 5′-adenosine monophosphate
Cbz	benzyloxycarbonyl
cDNA	Complementary Deoxyribonucleic Acid
CI	chemical ionization
CNS	central nerves system
COSY	Correlation spectroscopy
CREB	cAMP response element binding protein
DA	Donar-Acceptor
DAG	Diacylglycerol
DAO	diamine oxidase
DCM	dichloro methane
DEAD	diethyl azodicarboxylate
DHDT	4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMF	dimethyl formamide
DMS	dimethyl sulfide
EA	ethyl acetate
EC_{50}	half maximal effective concentration
ECL	extracellular loops
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylendiaminetetraacetic acid
EI	electronic impact ionization
Ent	enantiomer

GABA	γ-aminobutyric acid
GBL	γ-butyrolactone
GDP	guanosine diphosphate
GPCRs	G-protein couple receptors
GTP	guanosine triphosphate
h	hour
hH_1R	human histamine H_1 receptor
hH_2R	human histamine H_2 receptor
hH_3R	human histamine H_3 receptor
hH_4R	human histamine H_4 receptor
HMBC	heteronulcear multiple bond correlation
HNMT	histamine *N*-methyltransferase
HOBT	Hydroxybenzotriazole
HPLC	high performance (pressure) liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
ICL	intracellular loops
IC_{50}	half maximal inhibitory concentration
IgE	immunoglobuline E
IPC_2BH	diisopinocampheylborane
IP_3	inositol-1,4,5-trisphosphate
IR	infra red
LA	Lewis Acid
LDA	lithium diisopropyl amine
mAChR	muscarinic acetylcholine receptor
MAO	monoamine oxidase
MAPK	mitogen-activated protein kinase
m-CPBA	*m*-chloroperbenzoic acid
MS	molecular sieve
NA	neuraminidase
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMO	N-Methylmorpholine-N-Oxide
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
PKA	protein kinase A
PLCβ	phospholipase Cβ
PNS	peripheral nervous system
PPARs	Peroxisome proliferator-activated receptors
R	inactive state of a GPCR
R*	active state of a GPCR
rac	racemic
ROM	ring opening metathesis
rpm	revolutions per minute
RT	room temperature
S.E.M.	standard error of the mean
SEMCl	2-(Trimethylsilyl)ethoxymethyl chloride
Sf9	*Spodoptera frugiperda* insect cell line
SM	starting material
Sp	Sparteine
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl
TEAD	N, N, N', N'-tetraethyl azodicarboxylate
TFA	trifluoroacetic acid
TIPA	N,N,N',N'-tetraisopropylazodicarboxamide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAD	N, N, N', N'-tetramethylazodicarboxamide
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide or iodo(trimethyl)silane
Tris	tris(hydroxymethyl)aminomethane
Ts	tosyl

Chapter 1

1. Introduction

1.1 Medicinal Chemistry

Medicinal chemistry is a scientific discipline at the intersection of chemistry and pharmacology, involved with designing, synthesizing and developing pharmaceutical drugs.[1] It is a highly interdisciplinary science combining organic chemistry with biochemistry, pharmacology, molecular biology and molecular modeling.[2] The medicinal chemist attempts to design and synthesize a medicine or a pharmaceutically active compound, which has to satisfy the following criteria. It has to exert the intended effect without side effects and interactions with other drugs.[3]

How many medicines fit these criteria?

The short answer is none and there is no pharmaceutical compound on the market today which can completely satisfy all these conditions. Admittedly, some drugs come quite close to the ideal. For example, penicillin has been one of the most effective antibacterial agents ever discovered and has also been one of the safest. However, it still has some drawbacks, neither it has been able to kill all known bacteria nor it totally avoid allergic reactions. There are many patients who show an allergic reaction to penicillin and are required to take alternative antibacterial agents.[3]

Why should drugs work?

Indeed we take it for granted that they work, but why should chemicals some of which having remarkably simple structures, have such an important effect on a complicated and large structure such as a human body? The answer lies in the way, the human body operates. If we go to the molecular level of our body we would see a magnificent array of chemical reactions taking place, keeping the body healthy and functioning. Drugs which may be mere chemicals entering this world of chemical reactions with which they are interacting, can have an effect. However, the surprise might be their specific effects, which is the result of where they react in the body.[3]

Where do drugs work?

Since life is made up of cells, then quite clearly drugs must act on cells. The structure of a typical cell is shown in figure 1. The cell membrane, is a semipermeable lipid bilayer, which is separating the interior of a cell from the external environment.[4] It contains a wide variety of biological molecules, primarily proteins and lipids, which are involved in a vast array of cellular processes such as cell adhesion, ion channel conductance and cell signaling. The two

layers of phospholipids, in the cell membrane are arranged in such a way that the hydrophobic tails point to each other and form a fatty hydrophobic centre, while the ionic (hydrophilic) head-groups are placed at the inner and outer surfaces of the cell membrane.[3]

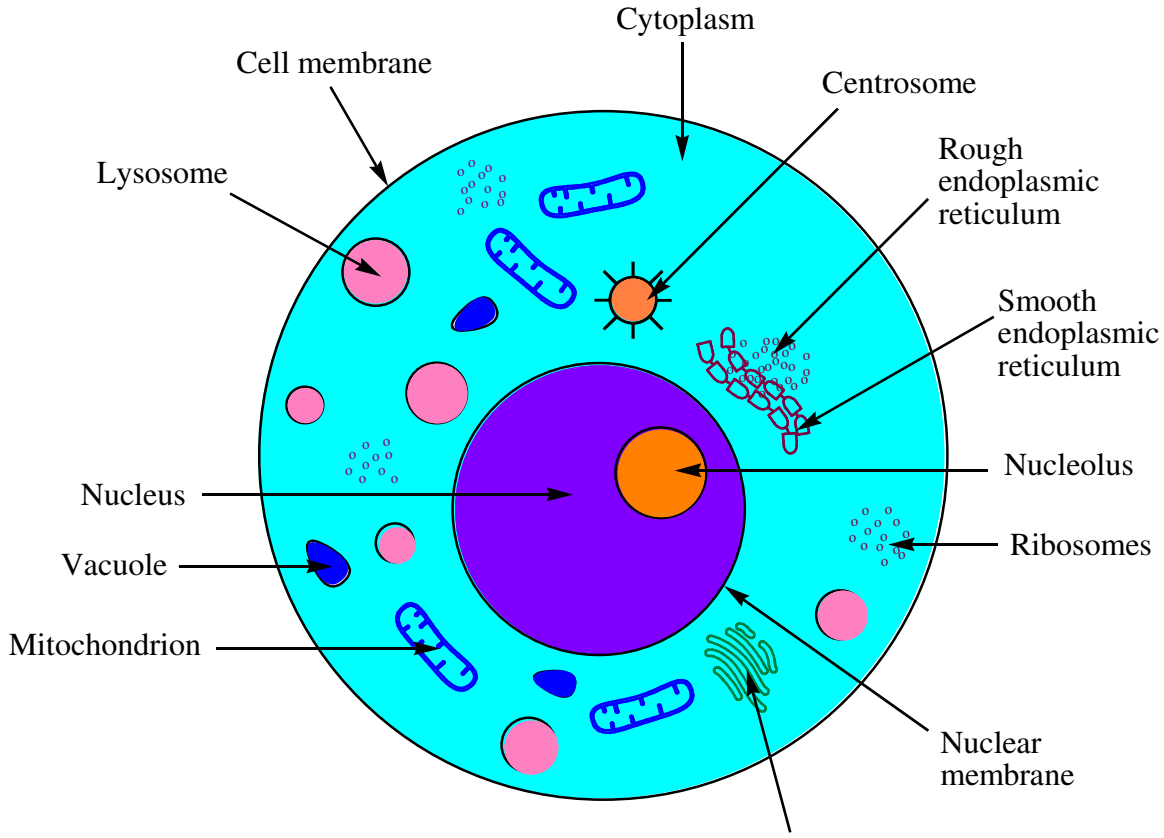


Figure 1. A typical cell

Modified from www.enchantedlearning.com/subjects/animals/cell/anatomy.GIF

The cell membrane does not only consist of phospholipids, but there are a large variety of proteins situated in the cell membrane (Figure 2). Some proteins lie on the surface of the membrane and other proteins are embedded in it with part of their structure exposed to outer or inner surface of the membrane. The structure of protein domains depends on the location where it is present. Portions of proteins embedded in the cell membrane have a large number of hydrophobic amino acids, whereas those portions, which stick out on the surface have a large number of hydrophilic amino acids. Different drugs act at different locations in the cell and there is no particular target site which can be pinpointed as the spot where drugs can act. Now it would be closer to understand how drugs work by classifying them with regard to the particular cell component they interact.[3]

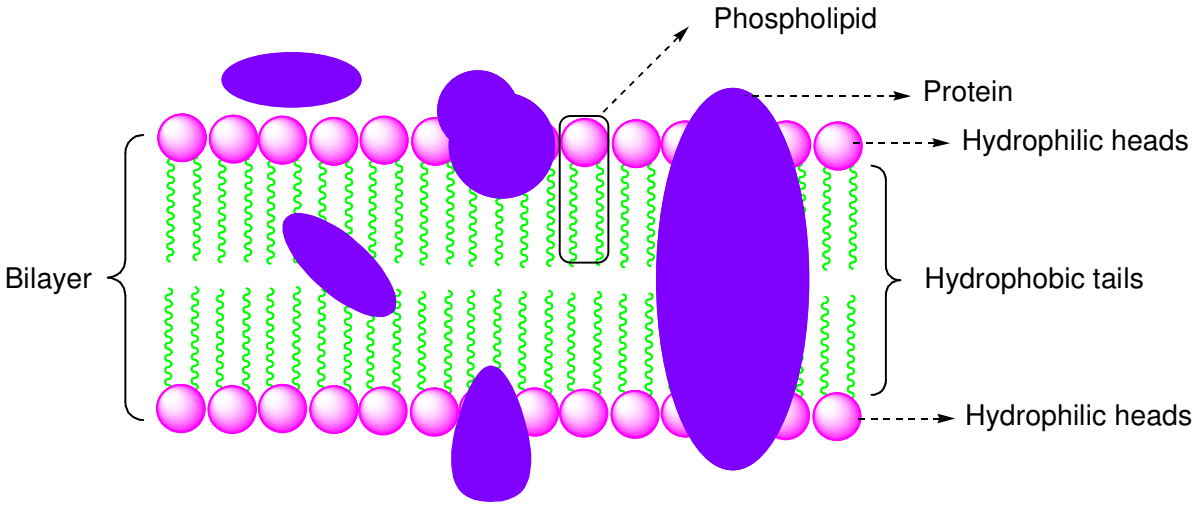


Figure. 2 The position of proteins associated with the cell membrane

Adapted from An introduction to medicinal chemistry, Graham L.. Patric, 1995, 1st edition

To understand this, we have to look at the molecular level and find out, which type of molecules in the cell are affected by drugs. There are three important molecular targets, namely lipids, proteins and nucleic acids.

The number of drugs which interact with lipids are relatively small in general, they all act in the same way by disrupting the lipid structure of cell membranes. In order to understand how drugs interact with proteins, it is necessary to understand their structure. Proteins have four levels of structure which are primary, secondary, tertiary and quaternary. The primary structure is quite simple, in which the individual amino acids are linked through peptide bonds. The secondary structure consists of protein chain regions, ordered as α-helices and β-sheets. The tertiary structure is the overall 3D shape of a protein. The tertiary structure of enzymes and receptors is crucial to their function and also to their interaction with drugs. Enzymes and receptors fold up on themselves to form more complex tertiary structures by van der Waals interaction, hydrogen bonding, ionic, covalent bonds and hydrophobic interactions. Quaternary structure is confined to those proteins which are made up of a number of protein subunits.[3]

1.2 Drug action at receptors

1.2.1 The receptor role

Receptors are one of the major targets for drugs. Drugs which interact with receptors are amongst the most important in medicine and provide treatment for ailments such as pain, depression, Parkinson's disease, psychosis, heart failure, asthma, and many other problems.[3]

What are these receptors and what do they do?

Cells are all individual, yet in a complex organism such as human body, they have to get along with their neighbors. There has to be some sort of communication system.

Communication is essential to make sure that all the body's organs to function in a coordinated and controlled fashion. Control and communication comes primarily from the central nervous system (CNS) which receives and sends messages via a vast network of nerves. The nerves do not connect directly to their target cells and they stop just a short distance away from the cell surface. The distance is about 100 Å, but it is a space which the electrical impulse is unable to jump. Therefore, there should be a way of carrying the message across the gap between the nerve ending and the cell. This is done by the release of a chemical messenger (neurotransmitter) from the nerve cell. Once released, this neurotransmitter can diffuse across the gap to the target cell, where it can bind and interact with a specific protein (receptor) embedded in the cell membrane. It is noteworthy to remember that the communication system depends crucially on a chemical messenger. Since a chemical process is involved, it should be possible for other chemicals (drugs) to interfere or to take part in the process.[3]

1.2.2 Neurotransmitters

Neurotransmitters are chemicals which relay, amplify and modulate signals between a neuron and another cell.[3] There are a large variety of neurotransmitters and many of them are quite simple molecules. Neurotransmitters include compounds such as acetylcholine, noradrenaline, dopamine, γ-aminobutyric acid (GABA), serotonin, histamine and even glycine.[3]

In general, a nerve releases only one type of neurotransmitter and the receptor, which awaits it on the target cell, will be specific for that messenger. However, this does not mean that the target cell has only one type of receptor protein. Each target cell has a large number of nerves communicating with it and they do not all use the same neurotransmitter. (From one and the same nerve cell, also more than one neurotransmitter can be released). Therefore, the target cell will also have other types of receptors specific for those neurotransmitters. When the neurotransmitter is released it will interact with a receptor and a message is received. The cell responds to that message, changes its internal chemistry and a biological response results accordingly.[3]

Communication is clearly essential for the normal working of the human body and if it becomes faulty then it leads to diseases such as depression, heart problems, schizophrenia, muscle fatigue and many other problems.

What sort of things could go wrong?

One problem would be if too many messengers were released, the target cell could become over stimulated. Alternatively, if too few messengers were sent out the activation level of the target cell could become too low. At this point drugs can play a role by either substituting

messengers (if there is a lack of the body's own messengers) or by blocking the receptors for the physiological (natural) messengers (if there are too many host messengers). Drugs of the former type are known as *agonists* and those of the latter type are known as *antagonists*.[3]

What determines whether a drug is an agonist or an antagonist and is it possible to predict whether a new drug will act as one or the other?

In order to answer that, we have to understand what happens at the molecular level when a small molecule such as a drug or a neurotransmitter interacts with a receptor protein. Let us look at receptors, when one of the body's own neurotransmitters interacts with it.[3]

1.3 Receptors

A receptor is a protein molecule, embedded in either the plasma membrane or cytoplasm of a cell, to which a mobile signaling molecule may attach. A molecule which binds to a receptor is called a "ligand," and it may be a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin. It is embedded within the cell membrane with part of its structure facing outside of the cell. The protein surface has a complicated 3D shape with a specific area, which has the correct shape to accept the incoming messenger. This area is known as the binding site and it is analogous to the active site of an enzyme. When the chemical messenger fits into this site, it 'switches on' the receptor molecule and a message is received (Figure 3).[3]

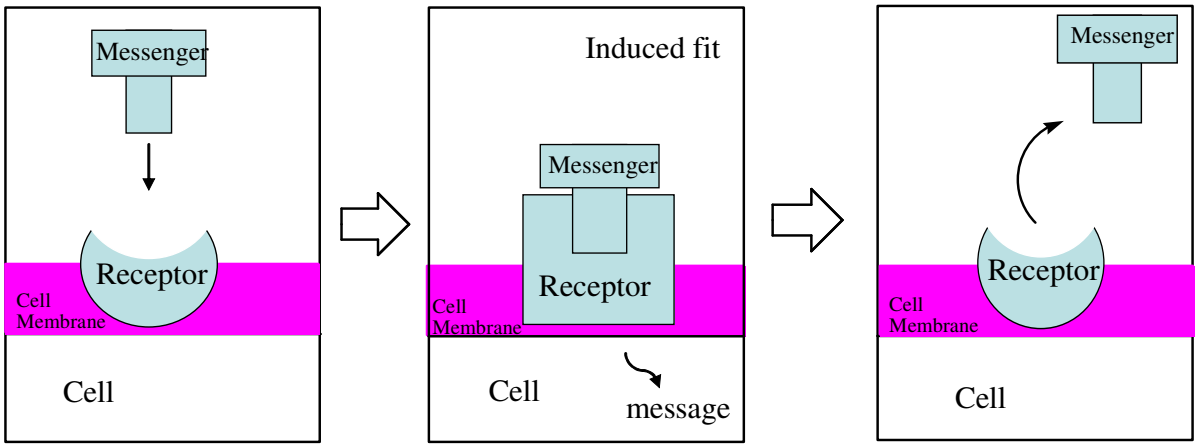


Figure 3. Binding of a messenger to a receptor

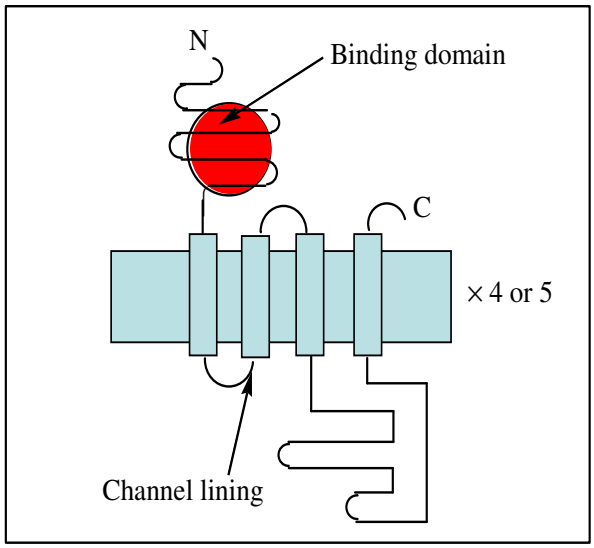
Adapted from An introduction to medicinal chemistry, Graham L. Patric 1995 1st edition

Receptors can be regarded as the sensing elements in the system of chemical communication that coordinate the function of all the different cells in the body, the chemical messengers being hormones or transmitter substances. Many therapeutically useful synthetic drugs act, either as agonists or antagonists, on receptors for endogenous mediators.[3]

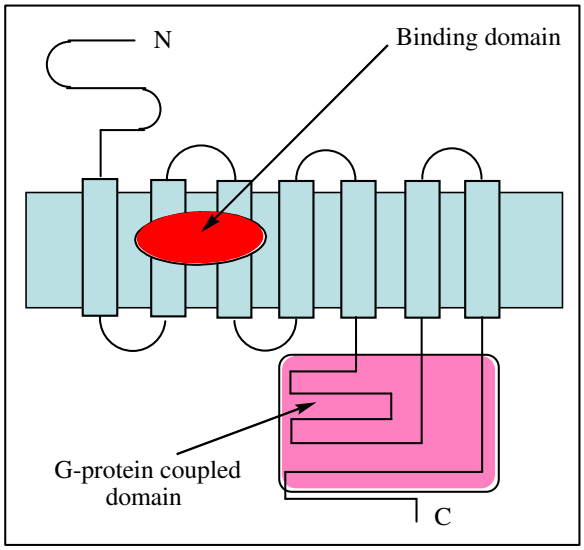
1.3.1 Receptor families

In terms of both molecular structure and nature of the transduction mechanism, we can distinguish four receptor types (Figure 4).[4]

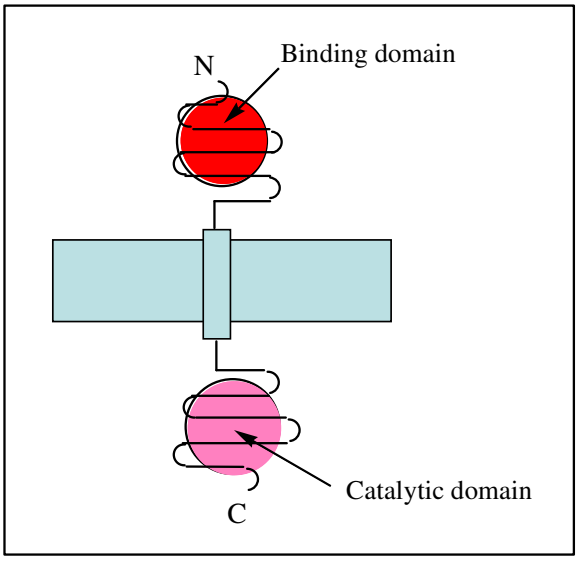
(A) Direct ligand gated channel type (type 1)



(B) G-protein coupled type (type 2)



(C) Tyrosine kinase type (type 3)



(D) Intracellular steriod type (type 4)

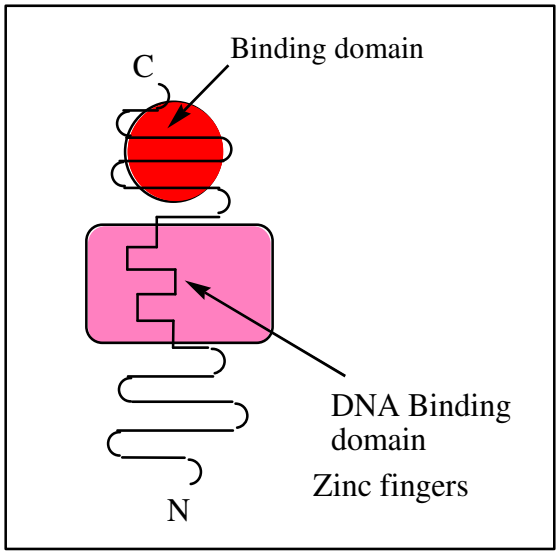


Figure 4. General structure of four receptor super families

Adapted from Pharmacology, fourth edition, Churchill, livingstone Inc. 1995

Type 1: receptors for fast neurotransmitters, coupled directly to an ion channel, example the nicotinic acetylcholine receptor, the $GABA_A$ receptor, the glutamate receptor.

Type 2: receptors for many hormones and slow transmitters, coupled to effector system via a G-protein, example, the muscarinic acetylcholine receptor (mAChR), noradrenergic receptors and histamine receptors.

Type 3: receptors for insulin and various growth factors, which are directly linked to tyrosine kinase.

Type 4: receptors for steroid hormones, thyroid hormone and other agents such as retinoic acid and vitamin D.

Receptors of the first three categories are membrane proteins, whereas the steroid receptors are intracellular proteins. The molecular organization of these four types of receptors is shown in fig 4. With in the same family of GPCRs, the sequence varies in particular regions and lengths of intracellular and extracellular loops, but the overall structural patterns of the receptors are consistent. The identification of these superfamilies represents a major step forward in understanding how drugs act.[4]

1.4 G-protein coupled receptors

G-protein coupled receptors (GPCRs) comprise one of the largest superfamilies of human genome.[5] The recent achievement of human genome project has revealed that there are approximately 900 GPCR genes in the human genome.[6] Most of these genes are identified on the basis of sequence homology to known GPCR genes. For most of these receptors natural ligands have been identified. However the ligands for some receptors have not yet been identified and they are, therefore reffered to as orphan GPCRs. Orphan GPCR research is therefore important from the perspctives of both basic and applied science. The identification of ligands for orphan GPCRs should yield important clues as to their physiological functions and will help determine weather they are suitable as drug targets. The identification of ligands for orphan GPCRs is expected to lead to the discovery of new regulatory mechanism of human body. Further more, GPCRs have been historically proven to be the most successful targets in the field of drug discovery.[5]

G-protein coupled receptors (GPCRs), also known as seven-transmembrane domain receptors, 7TM receptors or hepta helical receptors, consist of a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and ultimately cellular responces. G-protein coupled receptors are found only in eukaryotes including yeast, plants, chaonoflagellates and animals.[7] G protein-coupled receptors are involved in many diseases, and are also the target of around half of all modern medicinal drugs. The ligands that bind and activate these receptors include phermones,

hormones and neurotransmitters. They vary in size from small molecules to peptides to large proteins.[7]

There are two principal signal transduction pathways involving the G-protein coupled receptors, the cAMP signal pathway and the phosphatidylinositol pathway.[8] GPCRs can be grouped into 6 classes based on sequence homology and functional similarity.[9,10]

- Class A (Rhodopsin-like)
- Class B (Secretin receptor family)
- Class C (Metabotropic glutamate/phermone)
- Class D (Fungal mating pheromone receptors)
- Class E (Cyclic AMP receptors)
- Class F (Frizzled/Smoothened)

The very large rhodopsin A group has been further subdivided into 19 subgroups (A1-A19).[9]

1.4.1 Molecular structure of GPCRs

Dixon and coworkers characterized and cloned β-adreno receptor as a first receptor of GPCRs family.[4] Most GPCRs consists of a single poly peptide chain of 400-500 residues and about 40-60 kDa of molecular mass, whose general anatomy is shown in fig 4B.[4] They all poses seven trans membrane α-helices, and the helices are connected via three intracellular and extracellular loops, ICL 1-3 and ECL 1-3, respectively. Both the extra cellular *N*-terminus and the intracellular *C*-terminus vary greatly in length and sequence. The other highly variable region is the long third cytoplasmic loop. Site directed mutagenesis experiments show that the cytoplasmic loop is the region of the molecule that couples to the G-protein. Therefore deletion or modification of this section results in receptors that still bind ligands but cannot associate with G-proteins or produce response. Usually, a particular receptor subtype couples selectively with a particular G-protein and it has been proven, by genetic engineering, that the third cytoplasmic loop is one of the structural elements conferring G-protein selectivity.[4]

1.4.2 G-Proteins and their role

The guanine nucleotide-binding proteins (G proteins), are a family of proteins involved in second messenger cascades. G-proteins are so called because they function as "molecular switches", alternating between an inactive GDP and active GTP bound state, ultimately going on to regulate downstream cell processes. G-proteins belong to the larger group of enzymes

called GTPases[5] and are important signal transducing molecules in cells. In fact, diseases such as diabetes, allergies, depression, cardiovascular defects and certain forms of cancer, among other pathologies, are thought to arise due to disorder of G-protein signaling.[5] They are the go between proteins, the so called G-proteins because of their interaction with the guanine nucleotides, GTP and GDP. G-proteins are currently the object of much interest. Alfred G. Gilman and Martin Rodbell got nobel prize in physiology in the year 1994 for their discovery of G-proteins and their role in signal transduction.[6]

1.4.3 G-Protein cycle and Classification of G-Proteins

1.4.4 Types of G proteins

G-proteins can be roughly classified into two distinct families of proteins.[7] The first category 'heterotrimeric' or the "large" G-proteins that are activated by G-protein-coupled receptors are made up of an α subunit, and a βγ dimer. The second category, *"small" G-proteins* (20-25 kDa), belong to the Ras superfamily of small GTPases. These proteins are homologous to the α- subunit which is found in heterotrimers and are in fact monomeric. However, they also bind to GTP, GDP and are involved in signal transduction. Heterotrimeric G-proteins share a common mode of action, that is activation in response to a conformation change in the G-protein-coupled receptor, followed by exchange of GTP for GDP and finally dissociation in order to activate further proteins in the signal transduction pathway. However, the specific mechanism differs between different types of G-proteins.[8]

1.4.5 G-protein cycle

Receptor activated G-proteins are bound to the inner surface of the cell membrane. They consist of Gα and the tightly associated Gβγ subunits. There are four main families of Gα subunits, $G\alpha_{s,}$ $G\alpha_{i/o}$, $G\alpha_{q/11}$ and $G\alpha_{12/13}$.[8] These groups differ primarily in effector recognition, but share a similar mechanism of activation.

When agonist (ligand) binds to GPCR, it induces a conformational change and promotes GDP dissociation. This allows an interaction between the activated protein and the nucleotide-free G-protein, forming a ternary complex (step 1). These G-proteins consist of a Gα-subunit and a Gβγ-dimer. The next step is GDP exchanges with GTP on the Gα subunit, that allows the receptor to function as guanine nucleotide exchange factor (step 2). This exchange reduces the affinity of Gα subunit to the Gβγ dimer leading to a disruption of the ternary complex as a result the G-protein dissociates to Gα-GTP and the Gβγ dimmer (step 3). The dissociated Gα-GTP and the Gβγ dimer activates or inhibits several effector proteins causing a variety of intracellular effects (step 4). After a certain period, the Gα-GTP subunit undergoes hydrolysis

into Gα-GDP and P_i and the intrinsic activity of Gα subunit deactivates (step 5). Finally reassociation of Gα-GDP and βγ heterodimer closing the G-protein cycle (step 6).[9]

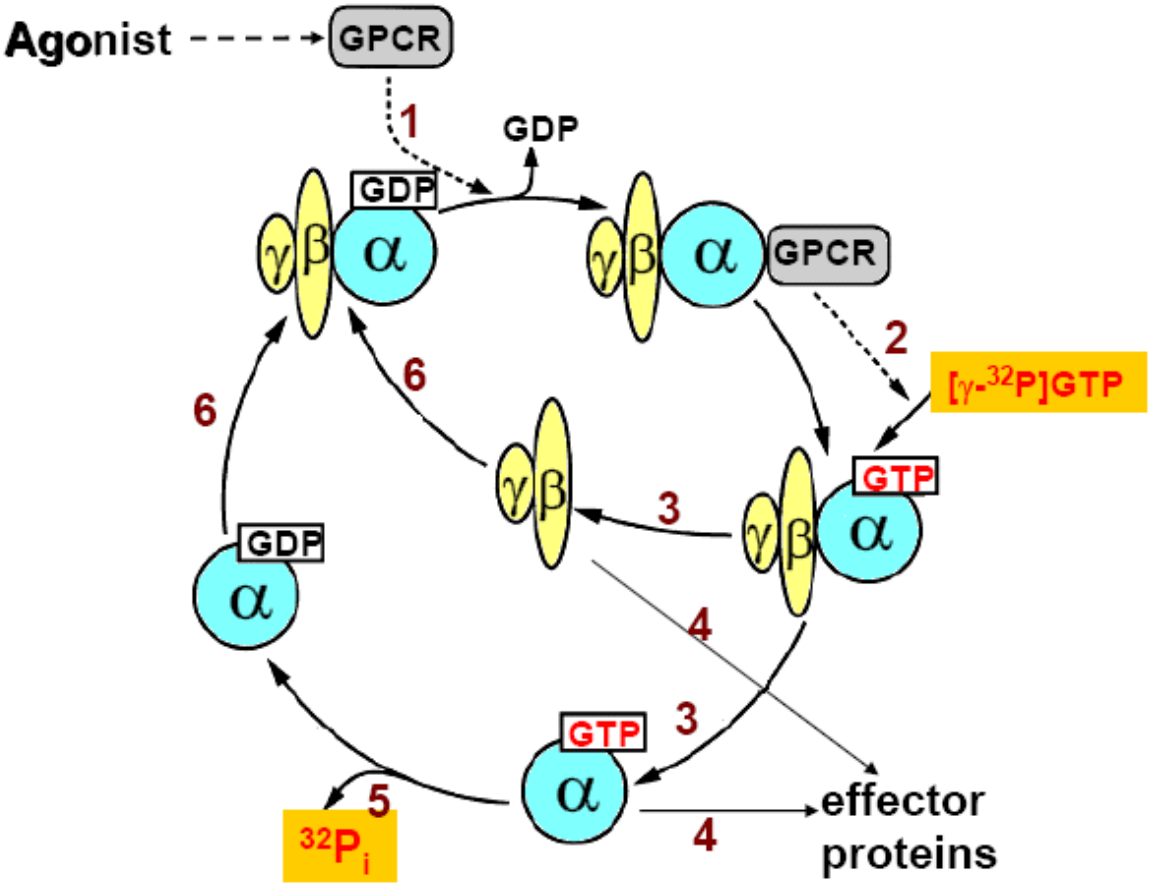


Figure 5. Activation of G-protein cycle
Adapted from Seifert *et al,* Life Sciences, **2003,** *73,* 2263

1.5 Two state activation model of GPCRs and ligand classification

The two-state model of GPCR activation is an elegant way to explain and describe the actions of GPCR ligands.[10] According to this model, a GPCR can be in an active state R* and an inactive state R, which are in equilibrium. Agonists are substances which can bind to the receptor and stabilize the active conformation. Neutral antagonists do not alter the equilibrium, but only block the binding site of the natural ligand. The active state is able to bind to a G-protein and cause GDP/GTP exchange, whereas the inactive state hardly interacts with G-proteins. However, since both receptor states are in equilibrium, there always exist some active receptors with no agonist bound. This phenomenon is known as "constitutive activity" and it is supposed to be (to a variable extent) a common feature of all wild type GPCRs and in some cases the cause of diseases.[10] The concept of constitutive activity leads to a totally new class of receptor ligands called "inverse agonists" which are able to stabilize the inactive form of the receptor, and thus reduces the constitutive activity.[9] The formylpeptide receptor is a known example for a constitutively active receptor.[9]

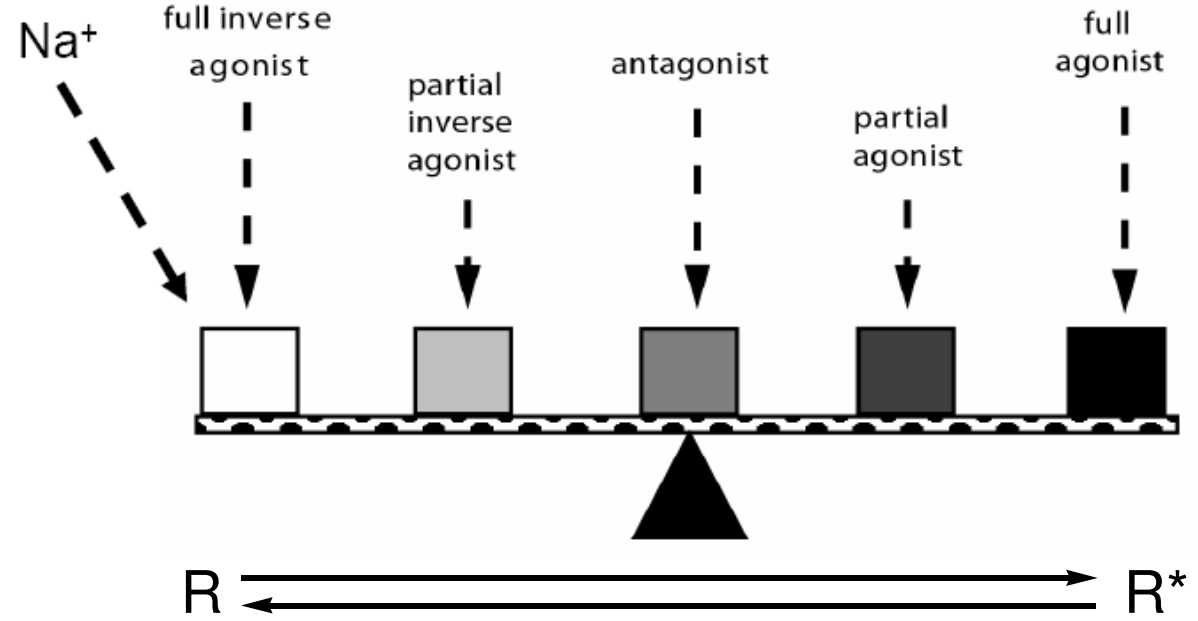


Figure 6. Two state model of GPCR activation I

Adapted from Seifert *et al, Life Sci* **2003**, *73,* 2263

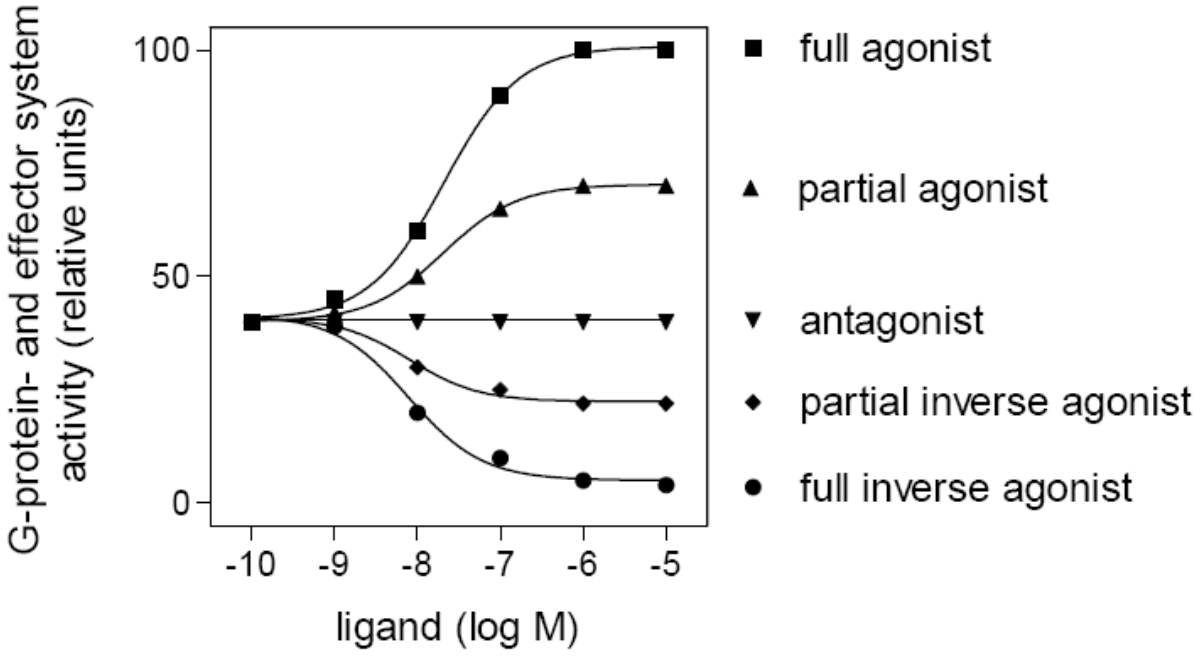


Figure 7. Two state model of GPCR activation II

Adapted from Seifert et al Life Sci **2003**, *73,* 2263

Ligands can be classified as full agonists, partial agonists, antagonists, partial inverse agonists and full inverse agonists based on the biological response they provoke.[13]

Full agonists: An agonist is a substance that binds to a receptor and triggers 100% response in the cell.

Partial agonists: Partial agonists are compounds that induce a submaximal response even if they fully occupy the receptor.

Antagonists: Antagonist is a ligand that binds to a receptor without causing activation but impairs agonist binding.

Inverse agonists: Inverse agonists are ligands that reduce the constitutive activity.

1.6 Histamine

Histamine was first discovered in 1910 by the British physiologist Sir Henry Hallett Dale as a contaminant of ergot, generated by bacterial action.[11] It was first synthesized before its physiological significance was known and due to its wide range of biological activity, it has become one of the most important biogenic amines in medicine and biology. The word 'histamine' comes from Greek, *histos*, which means tissue. Most of the early studies on the biological actions of histamine were carried out by Sir Henry Dale and his colleagues. Dale had shown that a local anaphylactic reaction was result of an antigen-antibody reaction in sensitized tissue. He subsequently demonstrated that histamine could largely mimic both *in vitro* and *in vivo* anaphylactic responses.[11]

Histamine is an important chemical mediator and neurotransmitter on a broad range of physiological and pathophysiological conditions. Its specific effects are mediated by four different aminergic G-protein coupled receptor (GPCR) subtypes (H_1-H_4) in central and peripheral tissues.[15] The biogenic amine is known to participate in allergic, inflammatory, gastric acid secretion, immunomodulation, and neurotransmission conditions.[15]

Histamine is used to maintain homeostasis (the body's natural balance of chemicals, temperature, metabolic rates). It is also a neurotransmitter and plays a role in our immune system by acting as a chemoattractant. Histamine imbalances in our body cause a variety of effects. Histamine shortage (*Histapenia*) causes effects ranging from heavy body hair growth and headaches to anaphylactic shock and paranoia. Histamine abundance (*Histadelia*) in the body also causes a variety of effects ranging from the mundane (such as phobias, symptoms of seasonal allergies - such as runny nose, inflammation, soreness, etc - and an increased metabolism) to the serious (like chronic depression).[11]

1.6.1 Metabolism of histamine

The histamine *N*-methyltransferase (*HNMT*) plays an important role in metabolism of histamine within the human airways and gut. It is the only enzyme responsible for the termination of neurotransmitter actions.[12] The *HNMT* inactivates histamine by transferring a methyl group from S-adenosyl-L-methionine to the imidazole ring. Inactive N^{π}-methylhistamine is excreted in urine or can be further oxidized by diamine oxidase (*DAO*) or

monoamine oxidase (*MAO*) into N^{τ}-methyl-imidazole-aldehyde, which can be further oxidized into its corresponding acid (Fig. 8). The histamine metabolism pathway starting with *DAO* is only relevant in Peripheral Nervous System (PNS).[13]

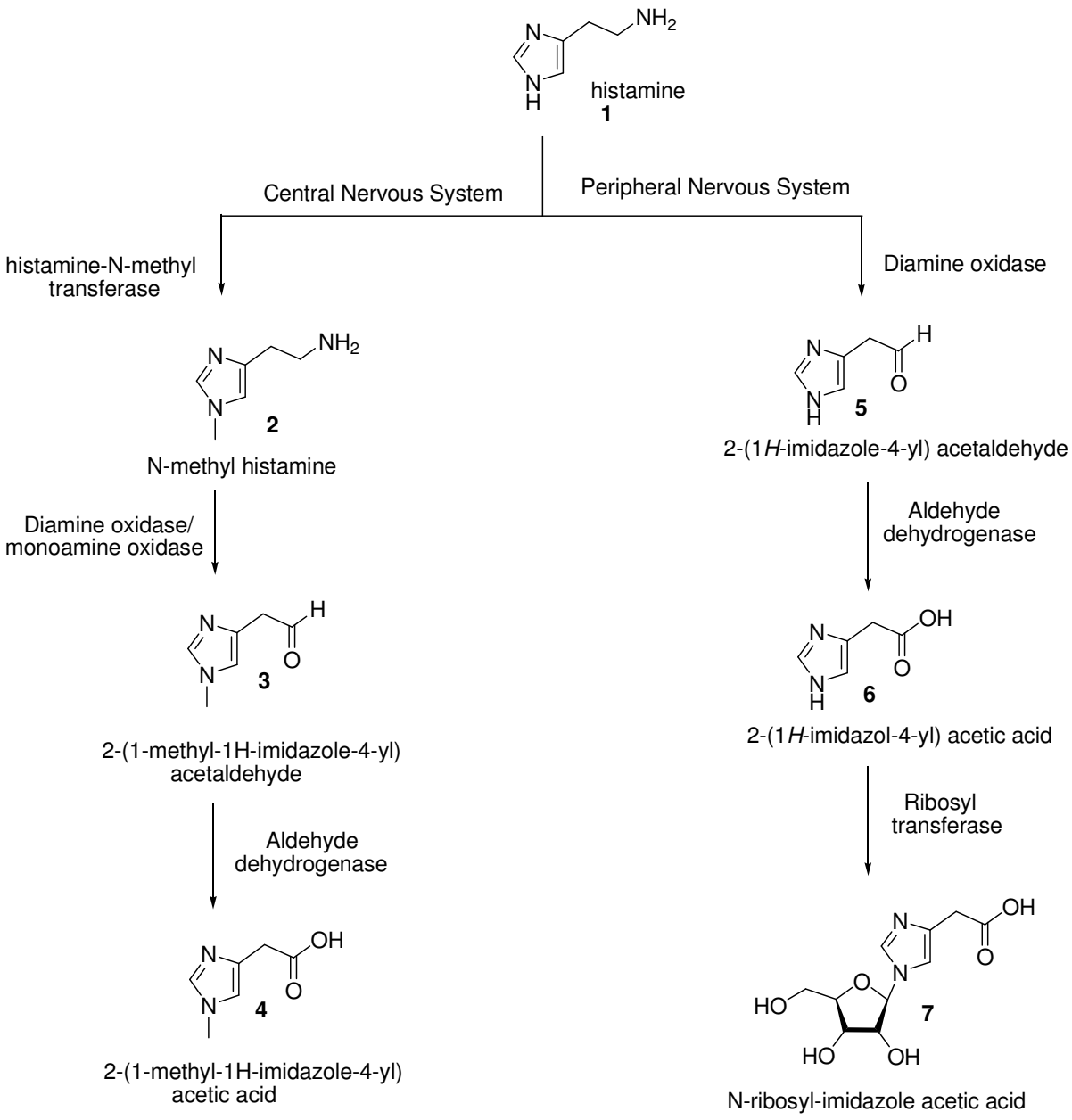
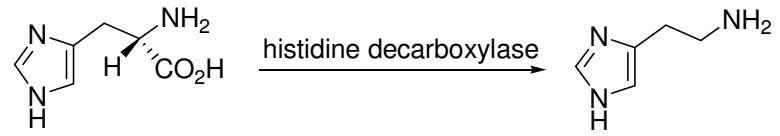


Figure. 8 Metabolism of histamine

1.6.2 Synthesis and storage

Histamine is a basic amine, 2-(4-imidazolyl)-ethyl-amine and is synthesized in the body from histidine by the enzyme histidine decarboxylase (Figure 9). It is found in most tissues of the body and skin. On the other hand histamine is present in high concentrations in the lungs and in the gastrointestetinal tract. At the cellular level, it is found largely in mast cells and basophils.[13] Its synthesis in Golgi apparatus can be blocked by α–fluoromethylhistidine.[14]



L-histidine
8

histamine
1

Figure. 9

1.6.3 Release

Histamine is released from mast cells by a secretory process during inflammatory or allergic reactions. The mast cell membrane has receptors both for a special class of antibody (IgE) and for complement components C3a and C5a. The cell can be activated to secrete mediators through these receptors and also by direct physical damage. The secretory process is intiated by a rise in intra-cellular calcium. This follows cross linking of receptors which intiates an increase in calcium permeability and a release of calcium from intracellular stores. Some neuropeptides release histamine, though the concentrations required are fairly high.[4]

Agents which increase cAMP formation (example β-adrenoreceptor agonists) inhibit histamine secretion, so it seems that, in these cells, cAMP dependent protein kinase is an intracellular ‘‘braking’’ mechanism. Replenishment of the histamine content of mast cell or basophil, after secretion, is a slow process which may take days or weeks, where as turnover of histamine in the gastric ‘histaminocyte’ is very rapid.[4]

Histamine is metabolized by diamine oxidase and by the methylating enzyme imidazole *N*-methyl-transferase. Sensitivity to the effects of histamine varies between tissues and species. The guinea pig is very sensitive and mouse is very insensitive to this agent. Human sensitivity lies between these two extremes.[4]

1.6.4 Actions

1.6.5 Gastric secretion

Histamine stimulates the secretion of gastric acid via H_2-receptor. In clinical terms this is the most important action of histamine, since it is implicated in the pathogenesis of peptic ulcer.[4]

1.6.6 Smooth muscle effects

Histamine acting on H_1-receptors causes contractions of the smooth muscle of the ileum, the bronchi, bronchioles and the uterus. The effects on the ileum is not as marked in man as it is in the guinea pig.[4] The response of guinea pig ileum to histamine is the basis of the standard bioassay for histamine. Bronchial construction by histamine is also more marked in guinea pigs than in man, though the histamine may be one of the many factors causing reduction of

air-flow in the first phase of bronchial asthma. Uterine muscle in most species is contracted and in human this is only significant if a massive release of histamine is produced by anaphylaxis during pregnancy, which may lead to abortion.[4]

1.6.7 Cardiovascular effects

Histamine expands blood vessels by an action on H_1-receptors in man and by a combined action on H_1 and H_2-receptors in some experimental animals. The effect may be partly endothelium-dependent. It increases the rate and output of the heart by action on cardiac H_2-receptor. This is a direct effect which may be coupled to an indirect, reflex response if there is a fall in blood pressure.[4]

When injected intradermally, histamine causes a reddening of the skin and a wheal with a surrounding flare. This combination of effects was described by Sir Thamos Lewis over 60 years ago and was termed the 'triple response'.[4] The reddening is due to vasodilation of the small arterioles, precapillary sphincters and the wheal is due to increased permeability of postcapillary venules. These effects are mainly due to activation of H_1-receptor.[4]

1.7 Histamine Receptors

Histamine produces its action by an effect on specific receptors, which comprise four main types, H_1, H_2, H_3 and H_4 that can be distinguished by means of selective agonist or antagonist drugs. Even though all histamine receptor subtypes belong to one family of rhodopsin-like class A GPCRs, they strongly differ in receptor distribution, ligand binding, signaling pathways and functions (Table 1).[15]

Table 1.Molecular pharmacology profile of histamine receptor subtypes[15]

	hH_1R	hH_2R	hH_3R	hH_4R
Chromosomal gene location	3p25	5q35.2	20q13.33	18q11.2
Amino acids	487	359	445	390
Isoforms			+	+
G-protein coupling	$G_{q/11}$	G_s	G_i/G_o	G_i/G_o
Signal transduction	PLC↑ Ca^{2+} ↑	cAMP↑	cAMP↓ Ca^{2+} ↑ MAPK↑	cAMP↓ Ca^{2+} ↑ MAPK↑
Tissues	Lung, brain, vessels	Heart, stomach, brain	Neurons (CNS, PNS)	Mast cells, eosinophils
Physiological relevance	Contraction of smooth muscles, food intake, sleep-wake regulation	Gastric acid secretion	Sleep, food intake	Chemotaxis
Pathophysiological relevance	Allergic reaction	Gastric ulcer	Cognitive impairment, seizure, metabolic syndrome	Inflammation, immune reaction

1.7.1 The histamine H_1 receptor

The histamine H_1 receptor was cloned from cattle in 1991[16] and then from human in 1993.[17] The human histamine H_1 receptor, (hH_1R) is a 56 k Da protein with 487 amino acids.[18] The histamine H_1 receptor is expressed in smooth muscle, endothelial cells, the adrenal medulla, gastrointestinal tract, the heart and the central nervous system (CNS).[18]

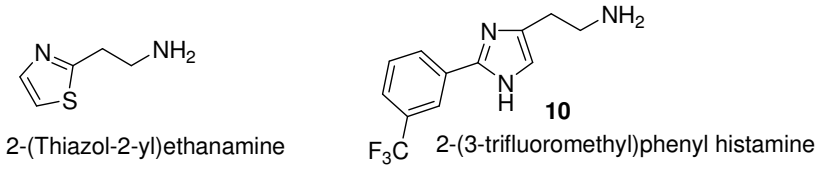
Histamine H_1 receptor preferentially couples to a pertussis-toxin insensitive $G\alpha_{q/11}$-protein.[19] Signal transduction of the histamine H_1 receptor involves calcium mobilization via the

activation of phospholipase C. H_1 receptor activation inhibits immediate responses of type I allergic reaction like redness, itching and swelling (‘‘triple response’’). On the other hand the H_1 receptor-mediated effects are food and water intake, convulsion, attention and sleep regulation taken as a central ones. Rhinitis, asthma, anaphylaxis and urticaria can be taken as peripherially.[15]

The histamine H_1-receptor is an important therapeutic target for allergic conditions.[18] Histamine H_1 receptor agonists are mainly used as pharmacological tools instead of therapeutic drugs.[19] The moderate potent H_1 receptor agonist betahistine (Aequamen®) is used in therapy for Meniere’s disease.[24] Replacement of imidazole ring with thiozole or aromatic rings lead to H_1 receptor agonist compounds.[15] The 2-substituted histamine derivates (e.g. histaprodifen series) led to compounds with higher affinity and efficacy.[15]

Therapeutically H_1 receptor antagonists are more important than the agonists. Sedation was one of the drawback with the application of first generation H_1 antihistamines such as bamipine, dimetindene, diphenylhydramine, and mepyramine (Figure 10). Newer second generation H_1-antihistamines do not penetrate the blood-brain barrier or poorly penetrates and prevent the sedation. Some of the newer non-sedative antagonists are hydroxyzine--cetrizine, terfenadine---fexofenadine, ebastine---carebastine, loratidine---desloratidine.[15] Many histamine –mediated effects cannot be blocked by H_1 antihistamines.[25] H_1R antagonists such as cetirizine (**14**, Zyrtec®) and fexofenadine (**16**, Telfast®) are top selling blockbuster drugs.[14] The high affinity H_1R antagonist [^{3}H] mepyramine is the most commonly used radioligand.[26] The ligands (agonists and antagonists) for H_1 receptor was shown in figure 10.

H_1R agonists



H_1R antagonists

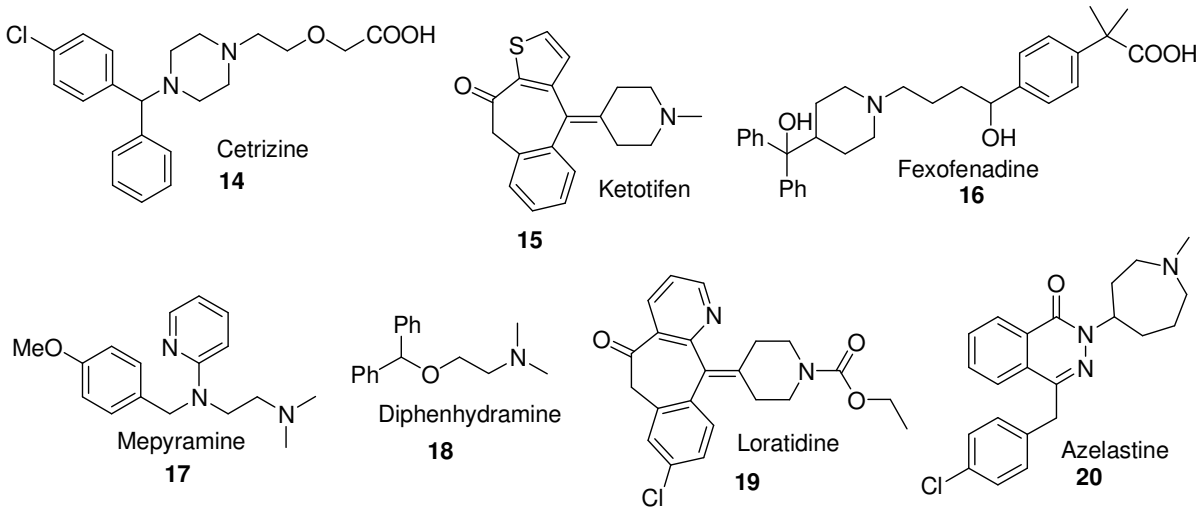


Figure.10 Structures of H_1R ligands

The histamine H_1R is characterized by a large third intracellular loop and a relatively short C terminal tail.[14] Molecular modeling and site-directed mutagenesis suggest that, histamine can bind to the hH_1R by forming an ionic interaction between its protonated amino group and the conserved Asp-107 of TM3. Lys-191 in TM5 is possibly interact with N^{π} of the imidazole ring, whereas the Asn-198 is believed to form a hydrogen bond with N^{τ}-H. In place of Asn-198, (Figure 11)[27-29] N^{τ}-H may interact with Thr-194.

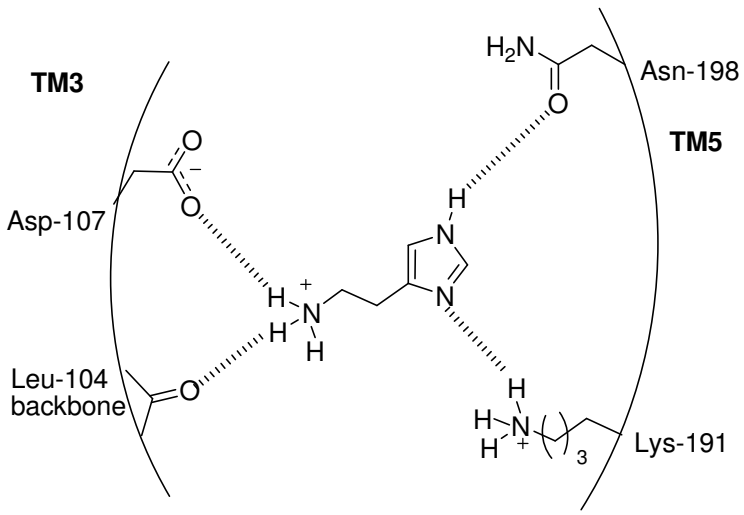


Figure. 11 Proposed binding mode of histamine at the human H_1R[47]

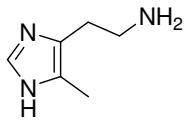
1.7.2 The histamine H_2 receptor

The human histamine H_2-receptor, (hH_2R) is a 40 kDa protein with 359 amino acids.[18] The histamine H_2 receptor is found in gastric parietal cells, vascular smooth muscle, suppressor T cells, neutrophils, brain and cardiac tissues. It is mainly involved in stimulation of gastric acid secretion. It couples to a Gs-protein, resulting in an increase in cAMP turnover.[30-33] Signal transduction of the histamine H_2 receptor involves increased cAMP accumulation via activation of adenylate cyclase.

Furthermore histamine mediates smooth muscle relaxation in airway, uterine and blood vessels *via* the H_2R.[34,35] H_2R has numerous functions in the immune system, for example, it has been shown to inhibit T-cell proliferation[36,37] to block the histamine release from mast cells and to modulate cytokine production.[38-40]

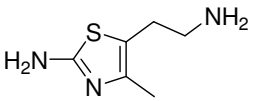
H_2 receptor activates positive inotropic and chronotropic effects on atrial and ventricular tissues. On the other hand H_2 receptor activation in the CNS, can inhibit nerve cells and block the long-lasting after hyperpolarization and thus increase working memory. Because of their positive inotropic effect, H_2R agonists are of potential therapeutical interest for the treatment of congestive heart failure. The histamine H_2 receptor is an important therapeutic target in the treatment of gastric ulcers.[18]

Amine type H_2R agonists



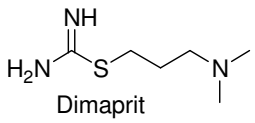
5-Methyl histamine

21



Amthamine

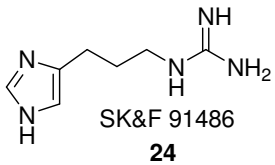
22



Dimaprit

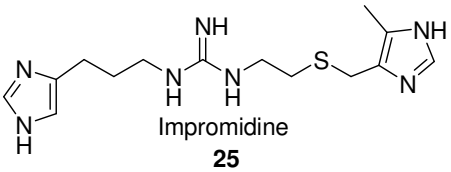
23

Guanidine type H_2R agonists



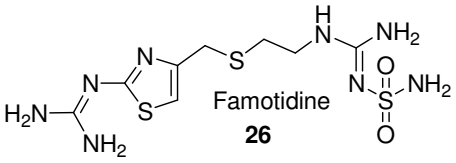
SK&F 91486

24



Impromidine

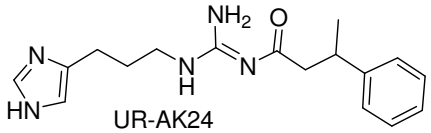
25



Famotidine

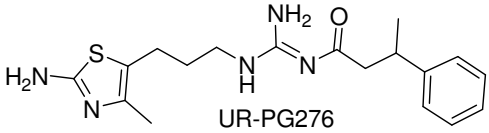
26

Acylguanidine type H_2R agonists



UR-AK24

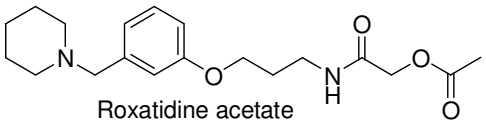
27



UR-PG276

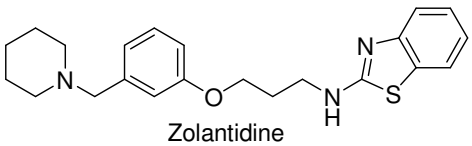
28

H_2R antagonists



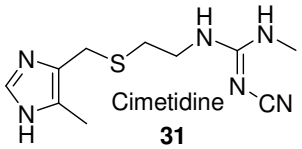
Roxatidine acetate

29



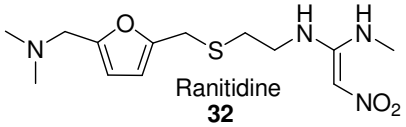
Zolantidine

30



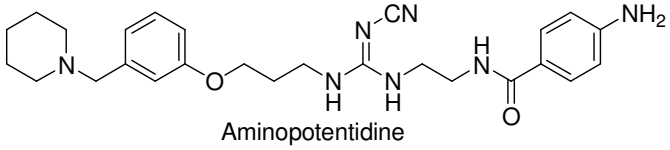
Cimetidine

31



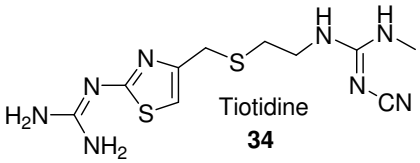
Ranitidine

32



Aminopotentidine

33



Tiotidine

34

Figure. 12 Structures of H_2R ligands

The H_2 receptor agonists dimaprit and its rigid aromatic analogue amthamine have been developed, of which the latter shows improved selectivity and potency as compare to that of histamine.[15] The guanidin derivatives like impromidine or arpromidine have much higher affinities and poses positive inotropic and vasodilatory effects. Further developments led to

metiamide and then to cimetidine as the first compound for the therapy of gastric ulcer.[15] Ranitidine, nizatidine, famotidine and roxatidine were compounds with much higher affinities and larger interaction potential.[15] H_2R antagonists are mainly used for the treatment of heartburn and peptic ulcer for example cimetidine **31**.[41]

Unlike the H_1R, the H_2R possesses a substantially shorter third intracellular loop and a longer palmitoylated C-terminus.[14] The endogenous ligand histamine is assumptive to bind in its N^{π}-tautomeric form to amino acids located in TM3 and TM5 of the hH_2R. The protonated amino group interacts with Asp-98 of TM3 and the imidazole N^{π}-H forms a hydrogen bond with Asp-186 of TM5. Imidazole N^{τ} interacts with Tyr-182 likewise located in TM5 (Figure 13).[42,43] In contrast to Tyr-182, Thr-190 may participate in histamine binding.[44]

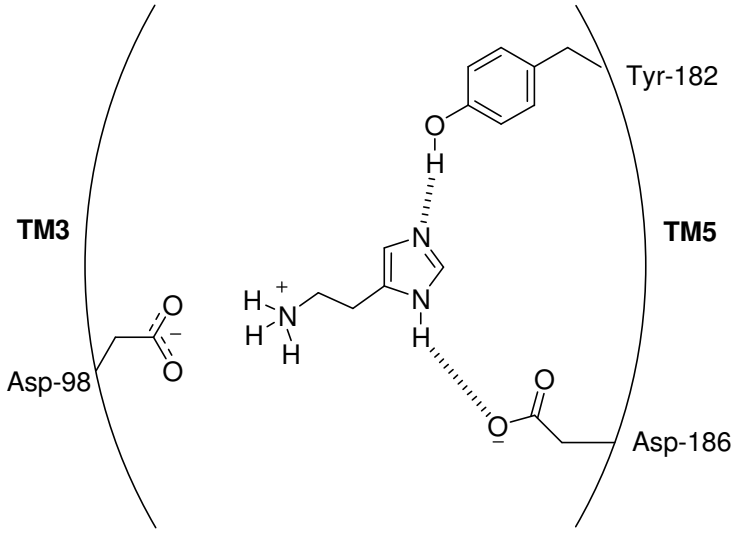


Figure. 13 Proposed binding mode of histamine at the human H_2R[47]

1.7.3 The histamine H_3 receptor

The human histamine H_3-receptor, (hH_3R), was cloned by Lovenberg *et al.* in 1999.[20] It is a 49-kDa protein with 445 amino acids.[18] The histamine H_3 receptor anatomically localized primarily to the CNS with prominent expression in basal ganglia, hippocampus, cortex and straital area.[15] In the periphery H_3 receptors can be found with low density in gastrointestinal, bronchial and cardiovascular system.[15] Several therapeutic indications for the histamine H_3 receptor have been suggested, for example, sleep, wakefulness, cognition, memory processes, attention-deficit hyperactivity disorder, obesity.[15]

It is a presynaptic autoreceptor on histaminergic neurons for controlling the synthesis and release of histamine. As a heteroreceptor it modulates the release of several other neurotransmitters.[45,46]

The H_3R receptor couples to $G\alpha_{i/o}$-proteins and has been demonstrated to influence several signal transduction pathways.[47] For example forskolin-induced cAMP production, inhibition of adenylyl cyclase (AC), stimulation of mitogen-activated protein kinase (MAPK), phospholipase A2 (PLA2), inhibition of Na^+/H^+ antiporter and K^+ induced Ca^{+2} mobilization take place (Table 1). In contrast to the H_1R and H_2R, gene encoding the H_3R contains two[48] or possibly three[49] introns resulting in at least 20 hH_3R isoforms.[50] This leads to the assumption that signaling fine tuning may be controlled by formation of isoforms or receptor oligomerization.

As H_3 autoreceptor activation stimulates the negative feed-back mechanism, reduced central histaminergic activity is observed.[15] Involvement in cognition, sleep-wake status, energy homeostatic regulation and inflammation has attracted pharmaceutical research for numerous therapeutic approaches in different peripheral but mainly central diseases.[15]

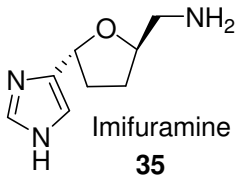
H_3R agonists perhaps therapeutic value for the treatment of insomnia,[51] pain,[52] inflammation,[53,54] or migraine.[55] Potent stimulation of H_3 receptors has been observed by histamine derivatives. The methylated histamine derivates, N^{α}-methyl histamine and the more potent and selective (*R*)-α-methyl histamine are used for receptor characterization and are also available as tritiated radioligands.[15] Although uncountable experiments with these tools have been reported, selectivity concerning H_4 receptors may be a problem with some investigations. Imetit, immepip, imifuramine and recently immethridine have been introduced as useful agonists.[15]

H_3R antagonists are of potential therapeutical interest for the treatment of obesity, epilepsy and myocardial dysfunction, as well as cognitive and sleep disorders.[56]

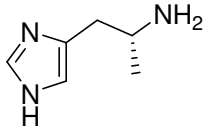
The floating change from agonist to antagonist is even more complex with histamine H_3 receptors than with any other histamine receptor subtype. Due to high constitutive activity of H_3 receptors inverse agonists can be found as well as neutral antagonists.[15]

Proxyfan was the first compound as agonist for H_3 receptors.[15] First generation of H_3 receptor antagonists were monoalkyl-substituted imidazole derivatives like ciproxifan, thioperamide or clobenpropit.[15] Numerous therapeutic indications are claimed in which cognitive impairment, attention-deficiet hyperactivity disorder, schizophrenia, narcolepsy, seizure and obesity are mostly mentioned.[15] Promising compounds like BP2.649, GSK-189254 and JNJ-17216498 have already entered clinical phase.[15] H_3R antagonists have been extensively studied by many pharmaceutical companies as drug candidates for the treatment of obesity,[57] schizophrenia,[58] attention-deficit hyperactivity disorder,[59] narcolepsy[60] or Alzheimer's disease.[61,62]

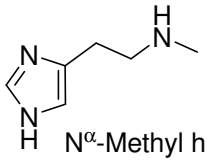
H_3R agonists



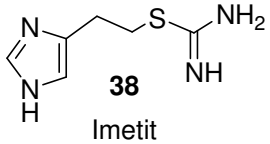
Imifuramine
35



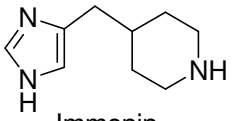
R-α-Methyl histamine
36



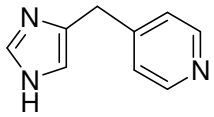
N^{α}-Methyl histamine
37



38
Imetit

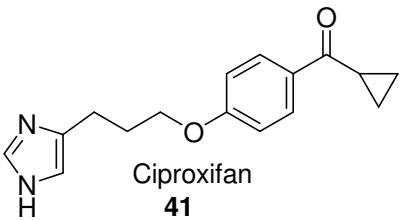


Immepip
39

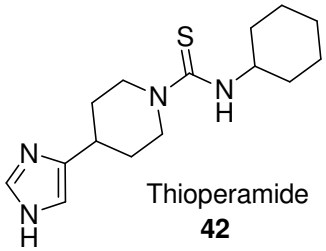


Immethridine
40

Imidazole containing H_3R antagonists

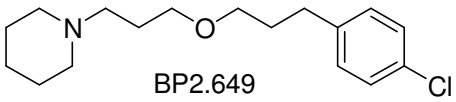


Ciproxifan
41

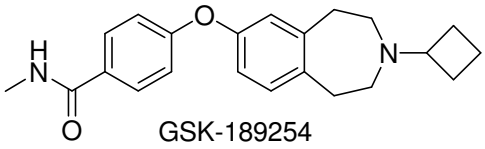


Thioperamide
42

Non-Imidazole containing H_3R antagonists



BP2.649
43



GSK-189254
44

Figure. 14 Structures of H_3R ligands

Yao and coworkers reported that, histamine is assumed to interact with the conserved Asp-114 of TM3 *via* the protonated amino group.[63] Asp-80 in TM2 apparently forms a hydrogen bridge with N^{τ}-H, which is crucial for receptor activation. The imidazole N^{π} is likely to interact with Asn-404 in TM7 (Figure 15).[63] In contrast, Uveges and colleagues suggested that the imidazole ring could interact with Glu-206 in TM5.[64]

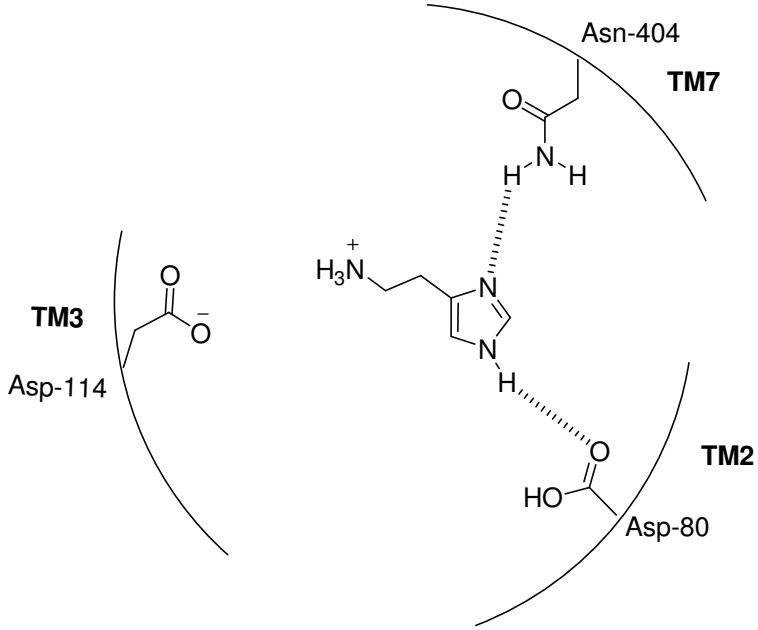


Figure. 15 Proposed binding mode of histamine at the human H_3R[47]

1.7.4 The histamine H_4 receptor

The human histamine H_4-receptor, (hH_4R), was cloned and characterized in the year 2000 through homology searching for new GPCRs in human genomic databases.[65-67] The human H_4-receptor (hH_4R) is a 44 kDa protein with 390 amino acids. The deduced amino acid sequence showed homology particularly to the human histamine H_3 receptor, with about 40% overall identity and even more (58%) within the trans-membrane domains. The genomic structure of the H_4 receptor is comparable to that the H_3 receptor with two large introns and three exons with large interspecies variations from 65-72% homology in sequences.[18]

The histamine H_4 receptor shows several hallmarks of the biogenic amine subfamily of GPCRs. An aspartate residue (Asp 61) in the second transmembrane domain (TM 2) and a DRY motif at the end of TM 3 (Asp 111-Tyr 113), which are important for receptor activation; and also another aspartate residue (Asp 94) in TM 3, which is the putative binding site for the primary amine; other hallmarks includes a disulfide bridge between the first (Cys 87) and the second (Cys164) extracellular loops; tryptophan residues (Trp 140 and Try 316) in TM 4 and TM 6; proline residues (Pro186 and Pro 318) in TM 5 and TM 6; an asparagine residue (Asn 350) and an NPXXY motif (Asn 354-Tyr358) in TM 7; and a potential palmitoylation site in the C-terminus region (Cys 374) (Figure 16).[66,75]

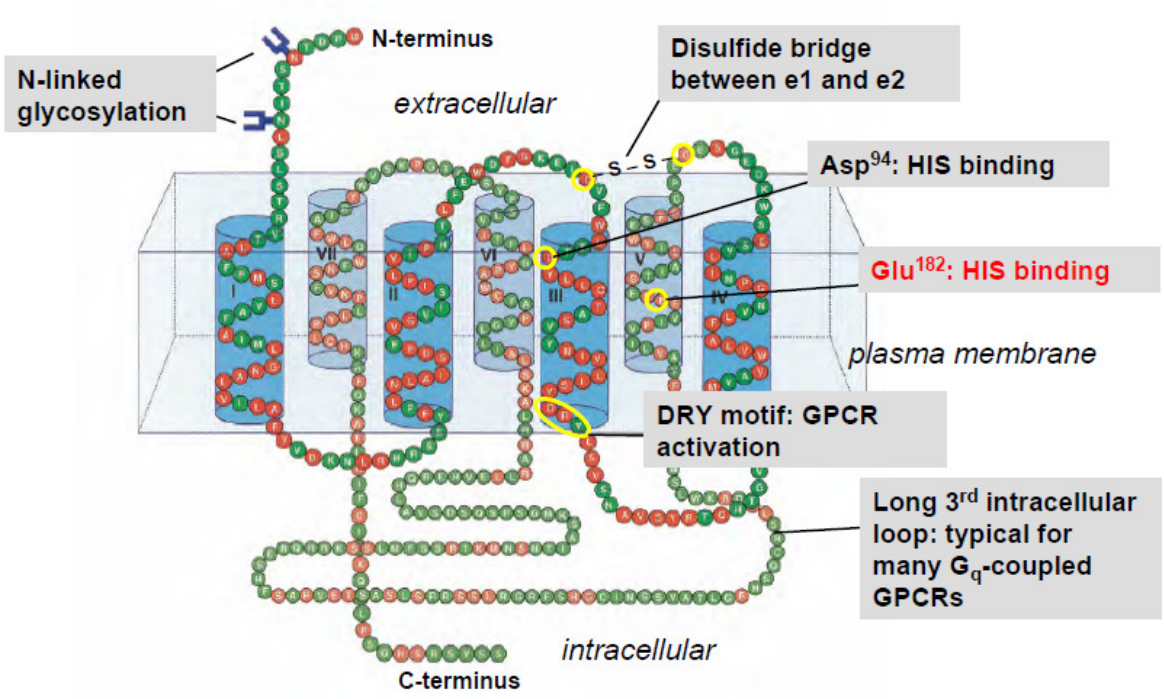


Figure 16. Human histamine H_4 receptor

Modified from *Mol. Pharmacol.* **2001**, *59*, 427

The histamine H_4-receptor has been found in bone marrow and leukocytes, particularly in immune cells such as eosinophils, mast cells, dendritic cells, basophils and T-cells.[68-71] On the other hand its expression can be found with moderate levels in spleen, small intestine and also with low level in brain.[15]

About the physiological and pathophysiological role of the H_4R is not much known. The H_4R has been shown to trigger chemotaxis and to induce Ca^{2+}-mobilization in mast cells,[79] eosinophils. In addition, stimulation of the H_4R results in actin polymerization, shape change and up regulation of adhesion proteins in eosinophils.[72,73] The H_4 receptor seems to be present in most tissues at low level and connected to cells of hematopoietic linage. Furthermore, the H_4R was found to be expressed in synovial cells of patients suffering from rheumatoid arthritis. The observed variations in the expression levels of the H_4R perhaps related to severity and duration of the rheumatoid arthritis.[74] These findings suggested that this H_4R may play a crucial role in inflammatory and immunological processes.

Like the H_3 receptor, the H_4 receptor is also coupled to $G\alpha_{i/o}$ proteins. H_4 receptor activation leads to a pertussis-toxin-sensitive decrease in the forskolin-induced cAMP production. On the other hand the H_4 receptor activation inhibits cAMP responsive element-binding protein (CREB)-dependent gene transcription.[67,68, 69,75] In addition, H_4 receptor stimulation results in the pertussis-toxin-sensitive activation of downstream mitogen-acitvated protein kinase (MAPK) pathways.[65] H_4 receptor-mediated Ca^{2+} signalling in mast cells is sensitive to both

pertussis toxin and the phospholipase C β inhibitor U73122. Furthermore phospholipase C is activated via Gβγ subunits that dissociate from Gαi/o proteins following H_4 receptor stimulation in mast cells (Figure 17).[71]

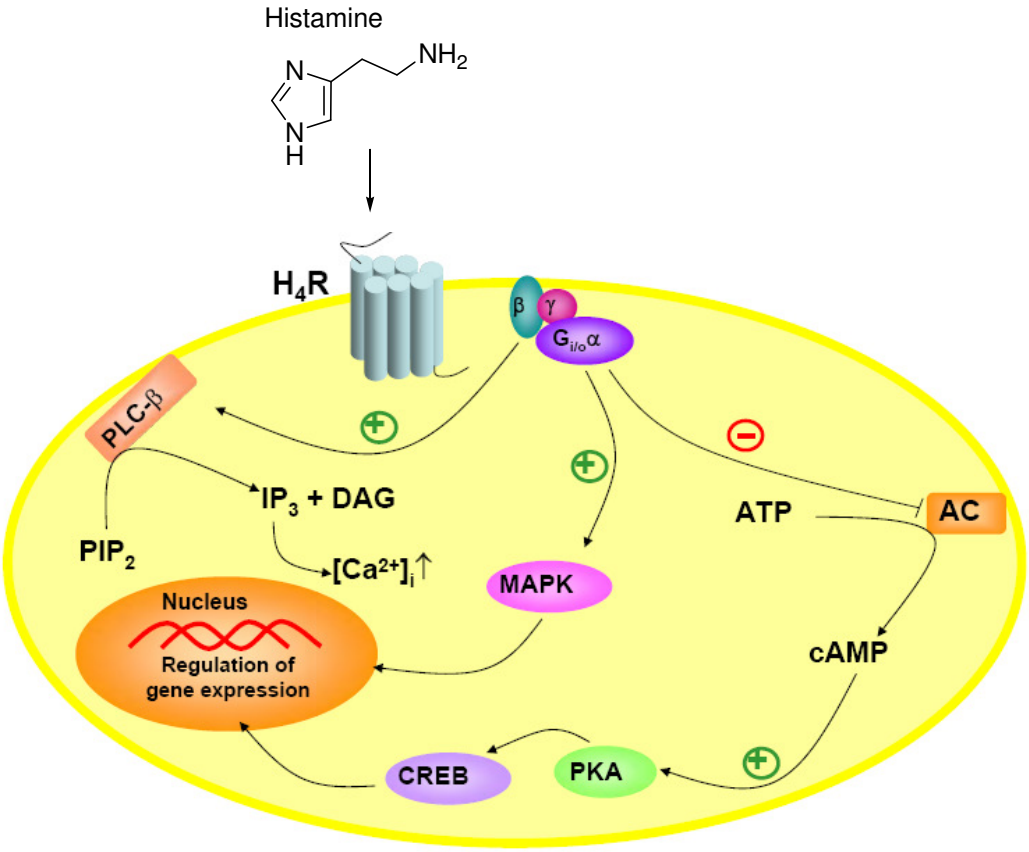


Figure 17. Signal transduction of histamine H_4-receptor
Adapted from Trends in Pharmacological Science **2005,** *26,* 462

Many compounds with reported affinity for H_3 receptor, also have affinity for H_4 receptor.[15] This is the case especially for imidazole containing compounds even though there are numerous exceptions.[15] Considering the high sequence similarity with the H_3 receptor it is not surprising that the H_4 receptor is activated by several H_3 receptor agonists, including immepip (H_4 receptor, K_i=9 nM), imetit (H_4 receptor,K_i=5 nM) and (R)-α-methylhistamine (H_4 receptor, K_i=146 nM). Furthermore, the H_4 receptor is activated by the H_2 and H_3 receptor antagonist burimamide (H_4 receptor, K_i=180 nM) and the H_3 receptor antagonist clobenpropit (H_4 receptor, K_i=13 nM). Thioperamide, an inverse agonist at H_3 receptors, is also an inverse agonist at the H_4 receptor (H_4 receptor, K_i=27 nM).[72-75]

Recently, OUP16 has been described as a full agonist with moderate affinity and selectivity for the H_4 receptor.[76] Furthermore, 4(5)-methylhistamine has been identified as a more potent and selective H_4 receptor agonist than OUP16.[76] Following high throughput screening and medicinal chemistry input, JNJ7777120 and its analogue JNJ10191584 have been identified

as H_4 receptor antagonists with high affinity and selectivity.[76] But in contrast to the nonselective H_3 and H_4 receptor inverse agonists these compounds act as neutral antagonists. The first highly selective and orally active H_4 receptor ligand described has been the antagonist JNJ 7777120. Unfortunately this compound is rapidly metabolized in liver microsomes and has a limited half-life of about 1-2 hours in vivo.[15] Numerous heterocyclic compounds such as indolylpiperazines, 2-aminopyrimidine derivatives are developed as H_4 receptor antagonists (Figure 18).[78-80]

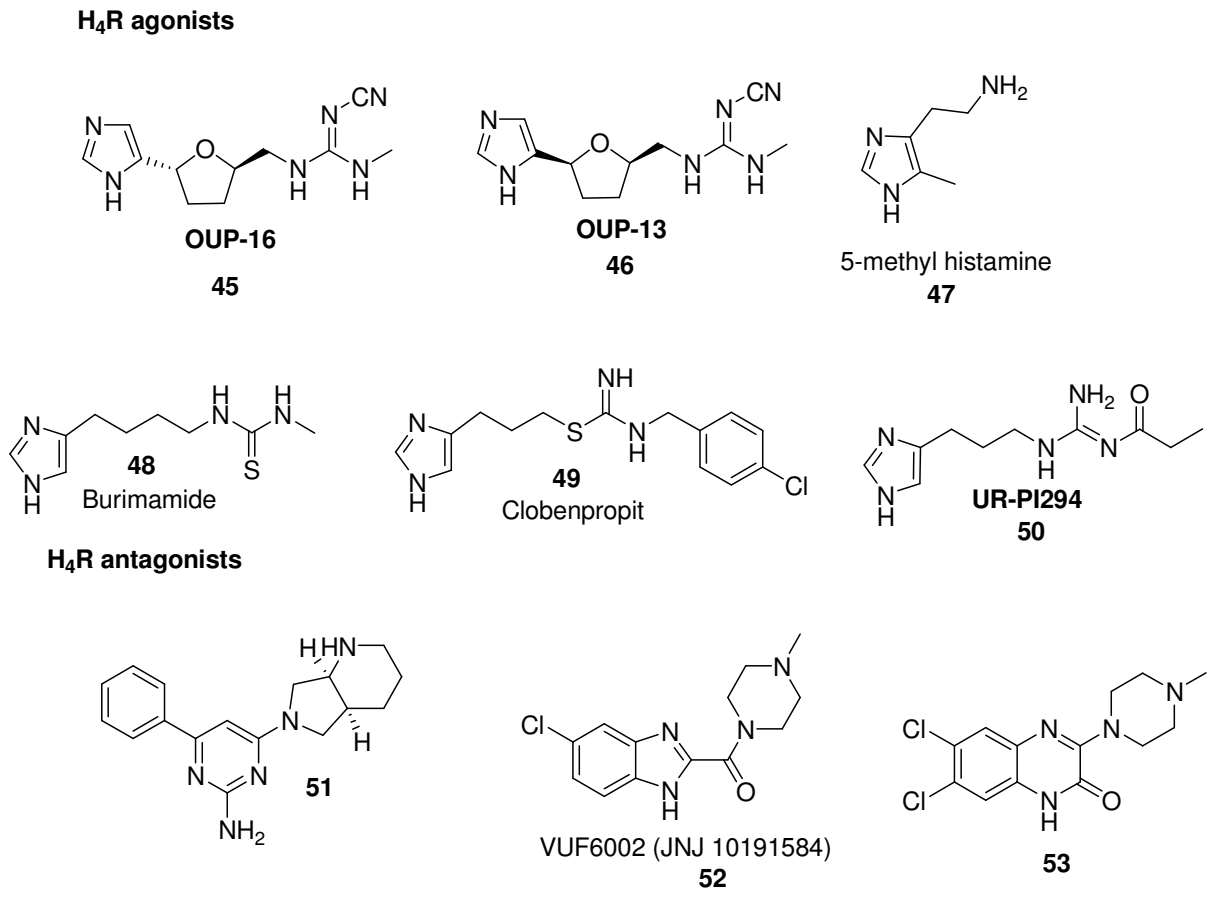


Figure. 18 Structures of H_4R ligands

Antagonists show general anti-inflammatory potency in models of asthma, arthritis, colitis and pruritus. Further results in autoimmune disorders, allergic conditions and nociceptive responses can be expected in the near future.[76] Shin *et al.*[81] and Jongejan *et al.*[82] reported the molecular modeling and site-directed mutagenesis for the binding mode of histamine H_4 receptor.

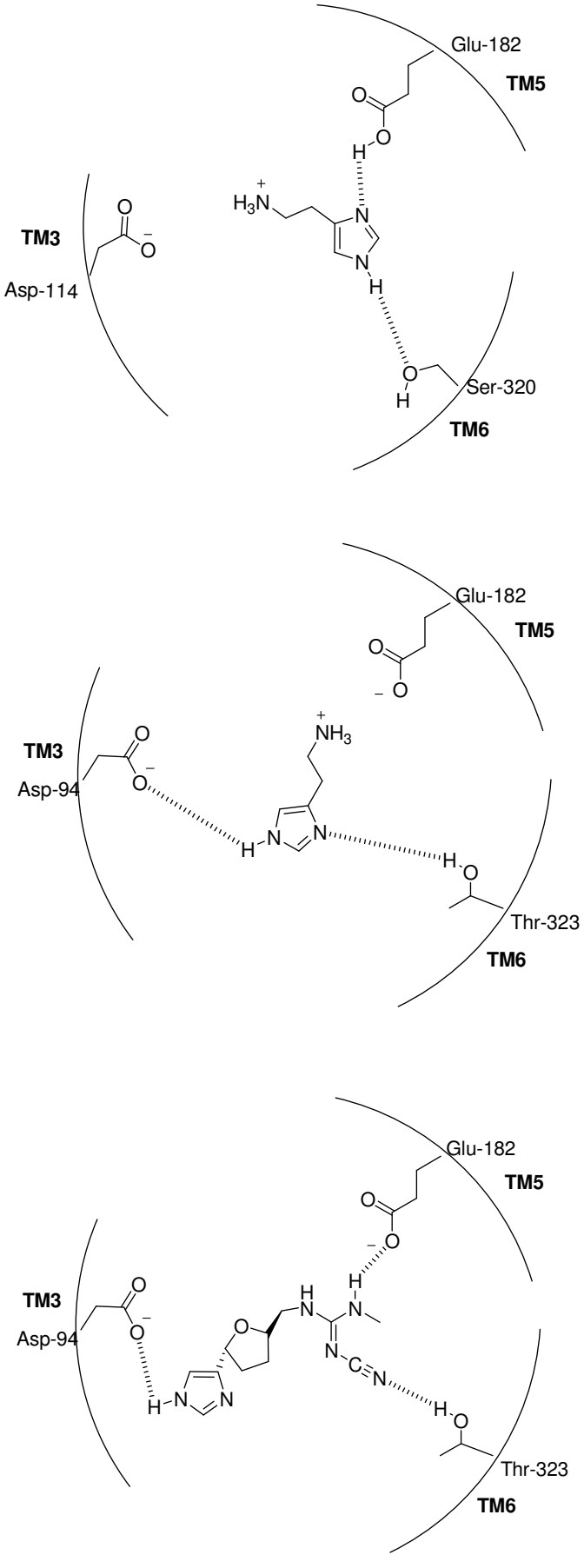


Figure. 19 Proposed binding mode of histamine (A, B) and OUP-16 (C) at the human H_4R [47,81-84]

It was assumed that the histamine can interact via its protonated amino group with Asp-94 in TM3 of the hH_4R, whereas the imidazole ring is considered to mainly interact with Glu-182 of TM5. Jongejan *et al*. proposed the imidazole N^{π} to form a hydrogen bond with the protonated Glu-182 and the imidazole N^{τ}-H to interact with Ser-320 of TM6 (Figure 19 A).[82]
In contrast, Kiss and coworkers suggested a reverse binding mode of histamine at the hH_4R to be more favorable and it was expected that the protonated amino group to interact with Glu-182. Asp-94 is presumed to form a hydrogen bond with the imidazole $N\tau$-H and Thr-323 of TM6 to interact with the imidazole N^{π} (Figure 19 B).[83] Furthermore, the authors describe a possible binding mode of the cyanoguanidine-type H_4R agonist OUP-16 at the hH_4R. The imidazole N^{τ}-H of this compound is considered to interact like histamine with Asp-94, whereas an *N*-H group of the cyanoguanidine moiety apparently forms a hydrogen bond with Glu-182. Furthermore, a hydrogen bond between the nitrile group and Thr-323 is expected (Figure 19 C).[83] In addition, very recently the importance of Phe-169 in the second extracellular loop of the hH_4R for agonist binding has been demonstrated.[84]
The histamine H_1 and H_2 receptors have been successful targets of block buster drugs for treating allergic diseases and gastric ulcer, respectively. The development of ligands (agonist, antagonists) for histamine H_3 and H_4 receptor are essential and highly interest for these new therapeutic targets. There are very few chiral compounds known as histamine receptor ligands and the development of chiral compounds is particular interest in synthetic point of view.
Different advances in histamine receptors ligands have ever attracted pharmaceutical developments. Where as ligands for histamine H_1 and H_2 receptors have been introduced long back into market, the run for the first selective H_3 and H_4 receptor ligands in the market is highly topical. Numerous pharmaceutical companies and academic institutions have programs with diverse lead structures and some even with first candidates in to clinical trails.[15]
Histamine receptor subtypes have been important drug targets for many decades. Histamine H_3 and H_4 receptors have led to a strong renewal of the interest in this biogene amine as well as to intensified research on the ligands and the potential therapeutic indications. Although at present histamine related development in pharmaceutical industry is mainly fixed on these receptor subtypes, basic research on re-uptake mechanism, isoform activation, receptor cross-talk etc, may open new fields for novel therapeutic applications of new ligands.[15]

References

1. http://en.wikipedia.org/wiki/Medicinal_chemistry
2. http://www.reference.com/browse/Medicinal+chemistry?jss=1
3. An introduction to medicinal chemistry, Graham L. Patric, 1995, 1st edition
4. Pharmacology, Rang, H. P.; Dale, M.M, Ritter, J. M.; Gardener, D. 1995, 4th edition
5. G Protein-Coupled Receptors in Drug Discovery, Wayne R. Leifert, **2009**, 552
6. http://nobelprize.org/nobel_prizes/medicine/laureates/1994/press.html
7. King, N.; Hittinger, C. T.; Carroll, S. B.; *Science,* **2003**, *301,* 361
8. Joost, P.; Methner, A. *Genome Biology,* **2002**, *3* (11):research0063.1 - 0063.16
9. Seifert, R.; Wenzel-Seifert, K. *Life Sci* **2003**, *73,* 2263.
10. Seifert, R.; Wenzel-Seifert, K. *Naunyn Schmiedebergs Arch Pharmacol* **2002**, *366,* 381.
11. http://www.chm.bris.ac.uk/motm/histamine/jm/history.htm
12. Horton, J. R.; Sawada, K.; Nishibori, M.; Zhang, X.; Cheng, X. *Structure* **2001**, *9*, 837.
13. Patil, R. *Ph.D Thesis.* **2006**, University of Regensburg.
14. Hill, S. J.; Ganellin, C. R.; Timmerman, H.; Schwartz, J. C.; Shankley, N. P.; Young, J. M.; Schunack, W.; Levi, R.; Haas, H. L. *Pharm. Rev.* **1997**, *49*, 253.
15. Stark, H. BIOTREND Reviews no 1, November **2007**
16. Yamashita, M.; Fukui, H.; Sugama, K.; Horio, Y.; Ito, S.; Mizuguchi, H.; Wada, H. *Proc. Natl. Acad. Sci. U. S. A.* **1991**, *88*, 11515.
17. De Backer, M. D.; Gommeren, W.; Moereels, H.; Nobels, G.; Van Gompel, P.; Leysen, J. E.; Luyten, W. H. M. L. *Biochem. Biophys. Res. Commun.* **1993**, *197*, 1601.
18. Nakamura, T.; Itadani, H.; Hidaka, Y.; Ohta, M.; Tanaka, K. *Biochem. Biophys. Res. Commun.* **2000**, *279,* 615
19. Pertz, H. H.; Elz, S.; Schunack, W. *Mini Rev in Med Chem* **2004**, *4*, 935.
20. Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. *Mol. Pharmacol.* **1999**, *55*, 1101.
21. Oliviera, L.; Paiva, A. C. M.; Sander, C.; Vriend, G. *Trends Pharmacol. Sci.* **1994**, *15*, 170.
22. Scheer, A.; Fanelli, F.; Costa, T.; De Benedetti, P. G.; Cotecchia, S. *EMBO J.* **1996**, *15*, 3566.
23. Leurs, R.; Hoffmann, M.; Wieland, K.; Timmerman, H. *Trends Pharmacol. Sci.* **2000**, *21*, 11.

24. Barak, N. *Expert Opin. Investig. Drugs* **2008**, *17,* 795.
25. Arunlakshna, O.; Schild, H.O. *Br. J. Pharmacol,* **1959**, *14,* 48
26. Hill, S. J.; Young, J. M.; Marrian, D. H. *Nature* **1977**, *270,* 361.
27. Ohta, K.; Hayashi, H.; Mizuguchi, H.; Kagamiyama, H.; Fujimoto, K.; Fukui, H. *Biochem. Biophys. Res. Commun.* **1994**, *203*, 1096.
28. Jongejan, A.; Leurs, R. *Arch. Pharm. (Weinheim).* **2005**, *338,* 248.
29. Elz, S.; Kramer, K.; Pertz, H. H.; Detert, H.; ter Laak, A. M.; Kuhne, R.; Schunack, W. *J. Med. Chem.* **2000**, *43,* 1071.
30. Gantz, I.; Munzert, G.; Tashiro, T.; Schaffer, M.; Wang, L.; DelValle, J.; Yamada, T. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 1386.
31. Klein, I.; Levey, G. S. *J. Clin. Invest.* **1971**, *50*, 1012.
32. Johnson, C. L.; Mizoguchi, H. *J. Pharmacol. Exp. Ther.* **1977**, *200*, 174.
33. Johnson, C. L.; Weinstein, H.; Green, J. P. *Mol. Pharmacol.* **1979**, *16,* 417.
34. Eyre, P., Chand, N. Histamine receptor mechanisms of the lung. In *Pharmacology of Histamine Receptors*, Ganellin, C. R., Parsons, M. E., Eds. Wright PSG: Bristol, London, Boston, **1982**, pp 298-322.
35. Verma, S. C.; McNeill, J. H. *Res. Commun. Chem. Pathol. Pharmacol.* **1976**, *13,* 55.
36. Jutel, M.; Watanabe, T.; Klunker, S.; Akdis, M.; Thomet, O. A.; Malolepszy, J.; Zak-Nejmark, T.; Koga, R.; Kobayashi, T.; Blaser, K.; Akdis, C. A. *Nature* **2001**, *413*, 420.
37. Rezai, A. R.; Salazar-Gonzalez, J. F.; Martinez-Maza, O.; Bramhall, J.; Afrasiabi, R.; Kermani-Arab, V. *Immunopharmacol. Immunotoxicol.* **1990**, *12*, 345.
38. Lippert, U.; Moller, A.; Welker, P.; Artuc, M.; Henz, B. M. *Exp. Dermatol.* **2000**, *9*, 118.
39. Lichtenstein, L. M., Gillespie, E. *J. Pharmacol. Exp. Ther.* **1975**, *192*, 441.
40. Bissonnette, E. Y. *Am. J. Respir. Cell Mol. Biol.* **1996**, *14*, 620.
41. Erich Schneider, Ph.D, Thesis , **2005**, University of Regensburg.
42. Nederkoorn, P. H. J.; van Lenthe, J. H.; van der Goot, H.; Donné-Op den Kelder, G. M.; Timmermann, H. *J. Comput. Aided Mol. Des.* **1996**, *10*, 461.
43. Nederkoorn, P. H. J.; van Gelder, E. M.; Donné -Op den Kelder, G. M.; Timmermann, H. *J. Comput. Aided Mol. Des.* **1996**, *10*, 479.
44. Gantz, I.; DelValle, J.; Wang, L. D.; Tashiro, T.; Munzert, G.; Guo, Y. J.; Konda, Y.; Yamada, T. *J. Biol. Chem.* **1992**, *267*, 20840.
45. Schlicker, E.; Betz, R.; Gothert, M. *Naunyn Schmiedebergs Arch Pharmacol,* **1988**, *337*, 588.

46. Schlicker, E.; Fink, K.; Detzner, M.; Gothert, M. *J Neural Transm Gen Sect,* **1993**, *93*, 1.
47. Patric Igel, *Ph.D Thesis*, **2008**, University of Regensburg.
48. Wiedemann, P.; Bonisch, H.; Oerters, F.; Bruss, M. *J. Neural Transm.* **2002**, *109*, 443.
49. Coge, F.; Guenin, S. P.; Audinot, V.; Renouard-Try, A.; Beauverger, P.; Macia, C.; Ouvry, C.; Nagel, N.; Rique, H.; Boutin, J. A.; Galizzi, J. P. *Biochem. J.* **2001**, *355*, 279.
50. Bongers, G.; Bakker, R. A.; Leurs, R. *Biochem. Pharmacol.* **2007**, *73*, 1195.
51. Lin, J. S. *Sleep Med. Rev.* **2000**, *4*, 471.
52. Cannon, K. E.; Nalwalk, J. W.; Stadel, R.; Ge, P., Lawson, D.; Silos-Santiago, I.; Hough, L. B. *Eur. J. Pharmacol.* **2003**, *470*, 139.
53. Matsubara, T.; Moskowitz, M. A.; Huang, Z. *Eur. J. Pharmacol.* **1992**, *224*, 145.
54. Ichinose, M.; Belvisi, M. G.; Barnes, P. J. *J. Appl. Physiol.* **1990**, *68*, 21.
55. Millan-Guerrero, R. O.; Pineda-Lucatero, A. G.; Hernandez-Benjamin, T.; Tene, C. E.; Pacheco, M. F. *Headache* **2003**, *43*, 389.
56. Passani M. B.; Lin J. S.; Hancock, A.; Crochet, S.;Blandina, P. *Trends Pharmacol Sci* **2004**, *25*, 618.
57. Hancock, A. A. *Curr. Opin. Investig. Drugs* **2003**, *4*, 1190.
58. Ito, C.; *Drug News Perspect.* **2004**, *17*, 383.
59. Howard, H. R. *Expert Opin. Ther. Patents* **2004**, *14*, 983.
60. Leurs, R.; Bakker, R. A.; Timmerman, H.; de Esch, I. J. P. *Nat. Rev. Drug Discov.* **2005**, *4*, 107.
61. Giovannini, M. G.; Bartolini, L.; Bacciottini, L.; Greco, L.; Blandina, P. *Behav. Brain Res.* **1999**, *104*, 147.
62. Prast, H.; Argyriou, A.; Philippu, A. *Brain Res.* **1996**, *734*, 316.
63. Yao, B. B.; Hutchins, C. W.; Carr, T. L.; Cassar, S.; Masters, J. N.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Neuropharmacology* **2003**, *44*, 773.
64. Uveges, A. J.; Kowal, D.; Zhang, Y.; Spangler, T. B.; Dunlop, J.; Semus, S.; Jones, P. G. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 451.
65. Morse, K. L.; Behan, J.; Laz, T. M.; West, R. E. Jr.; Greenfeder, S. A.; Anthes, J. C.; Umland, S.; Wan, Y.; Hipkin, R. W.; Gonsiorek, W.; Shin, N.; Gustafson, E. L.; Qiao, X.; Wang, S.; Hedrick, J. A.; Greene, J.; Bayne, M.; Monsma, F. J. Jr. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1058.

66. Nguyen, T.; Shapiro, D. A.; George, S. R.; Setola, V.; Lee, D. K.; Cheng, R.; Rauser, L.; Lee, S. P.; Lynch, K. R.; Roth, B. L.; O'Dowd, B. F. *Mol. Pharmacol.* **2001**, *59*, 427.

67. Zhu, Y.; Michalovich, D.; Wu, H.-L.; Tan, K. B.; Dytko, G. M.; Mannan, I. J.; Boyce, R.; Alston, J.; Tierney, L. A.; Li, X.; Herrity, N. C.; Vawter, L.; Sarau, H. M.; Ames, R. S.; Davenport, C. M.; Hieble, J. P.; Wilson, S.; Bergsma, D. J.; Fitzgerald, L. R. *Mol. Pharmacol.* **2001**, *59*, 434.

68. Liu, C.; Ma, X.-J.; Jiang, X.; Wilson, S. J.; Hofstra, C. L.; Blevitt, J.; Pyati, J.; Li, X.; Chai, W.; Carruthers, N.; Lovenberg, T. W. *Mol. Pharmacol.* **2001**, *59*, 420.

69. Oda, T.; Morikawa, N.; Saito, Y.; Masuho, Y.; Matsumoto, S. *J. Biol. Chem.* **2000**, *275*, 36781.

70. Morse, K. L.; Behan, J.; Laz, T. M.; West, R. E. Jr.; Greenfeder, S. A.; Anthes, J. C.; Umland, S.; Wan, Y.; Hipkin, R. W.; Gonsiorek, W.; Shin, N.; Gustafson, E. L.; Qiao, X.; Wang, S.; Hedrick, J. A.; Greene, J.; Bayne, M.; Monsma, F. J. Jr. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1058.

71. Hofstra, C. L.; Desai, P. J.; Thurmond, R. L.; Fung-Leung, W. P. *J. Pharmacol Exp Ther* **2003**, *305*, 1212

72. Ling, P.; Ngo, K.; Nguyen, S.; Thurmond, R. L.; Edwards, J. P.; Karlsson, L.; Fung-Leung, W.-P. *Br. J. Pharmacol.* **2004**, *142*, 161.

73. Buckland, K. F.; Williams, T. J.; Conroy, D. M. *Br. J. Pharmacol.* **2003**, *140*, 1117.

74. Nakaya, M.; Takeuchi, N.; Kondo, K.; *Ann. Otol. Rhinol. Laryngol.* **2004**, *113*, 552.

75. Nakamura, T. *Biochem. Biophys. Res. Commun.* **2000,** *279*, 615.

76. de Esch, I. J. P.; Thurmond, R. L.; Jongejan, A.; Leurs, R.; *Trends Pharmacol. Sci.* **2005**, *26*, 462.

77. Liu, C. *J. Pharmacol. Exp. Ther*. **2001,** *299*, 121.

78. Jablonowski, J. A. *J. Med. Chem.* **2003**, *46*, 3957.

79. Altenbach, R. J.; Adair, R. M.; Bettencourt, B. M.; Black, L. A.; Fix-Stenzel, S. R.; Gopalakrishnan, S. M.; Hsieh, G. C.; Liu, H.; Marsh, K. C.; McPherson, M. J.; Milicic, I.; Miller, T. R.; Vortherms, T. A.; Warrior, U.; Wetter, J. M.; Wishart, N.; Witte, D. G.; Honore, P.; Esbenshade, T. A.; Hancock, A. A.; Brioni, J. D.; Cowart, M. D. *J. Med. Chem.* **2008**, *51*, 6571.

80. Jablonowski, J. A.; Carruthers, N. I.; Thurmond, R. L. *Mini Rev. Med. Chem.* **2004**, *4*, 993.

81. Shin, N.; Coates, E.; Murgolo, N. J.; Morse, K. L.; Bayne, M.; Strader, C. D.; Monsma, F. J. Jr. *Mol. Pharmacol.* **2002**, *62*, 38.
82. Jongejan, A.; Lim, H. D.; Smits, R. A.; de Esch, I. J. P.; Haaksma, E.; Leurs, R. *J. Chem. Inf. Model.* **2008**, *48*, 1455.
83. Kiss, R.; Noszál, B.; Rácz, Á.; Falus, A.; Erós, D.; Keseru, G. M. *Eur. J. Med. Chem.* **2008**, *43*, 1059.
84. Lim, H. D.; Jongejan, A.; Bakker, R. A.; Haaksma, E.; de Esch, I. J. P.; Leurs, R. *J. Pharmacol. Exp. Ther.* **2008**, *327*, 88.

Aim of the work

In this part of work, a new strategy for the enantioselective synthesis of tetrahydrofuran imidazole based human histamine H_3 and H_4 receptor potential agonists was designed based on the lead structures **35** (imifuramine) and **45** (**OUP-16**) (Figure 2.1). The application of γ-butyrolactones as starting materials towards analogues of **35** and **45** was shown for the first time by enantioselective synthesis. Analogues of imifuramine and their cyanoguanidine derivatives were aimed to be synthesized with an extended side chain as well as additional functional groups to gain insight into structure-activity relationships. The development of agonists for the recently discovered histamine H_3 and H_4 receptors would be an important step towards therapeutics for the treatment of insomnia, pain, migraine, inflammation and immunological disorders.

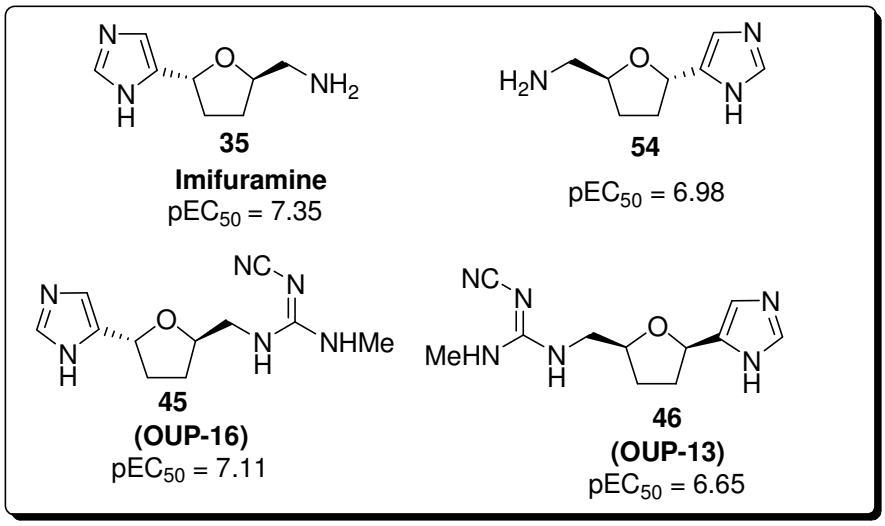


Figure 2.1 Histamine H_3 and H_4 receptor agonists developed by Kurihara *et al*

Based on the histamine H_3 and H_4-receptor agonists **35** (imifuramine) and **OUP-16** (lead structures) this part of work was designed to use the γ-butyrolactone **55** as starting material (Figure 2.2). Protection of aldehyde functional group of γ-butyrolactone **55** followed by reduction of lactone would give the corresponding lactol. Treatment of this anomeric lactol with bisprotected imidazole may afford the corresponding diols possibly as two diastereomers which can be cyclized by Mitsunobu reaction to obtain the cyclic building blocks **56** and **57.** Side chain modification of allyl group of **56** and **57** by hydroboration, phthalimidition followed by reductive cleavage of phthalimide and deprotection of protecting groups would give the amines **58** and **60** for the histamine H_3 receptor potential agonists. Introduction of cyanoguanidine moiety on **58** and **60** could afford the target molecules **59** and **61** for the histamine H_4 receptor potential agonists. Deprotection of cyclic acetal group of the building

blocks **56** and **57** followed by reductive amination may obtain the amines **62** amd **63**. γ-Butyrolactone (GBL)-**55** may provide variety of tetrahydrofuran-imidazole derivatives (**56-63**, Figure 2.2) as structurally and biologically important class of human histamine H_3 and H_4 receptor potential agonists.

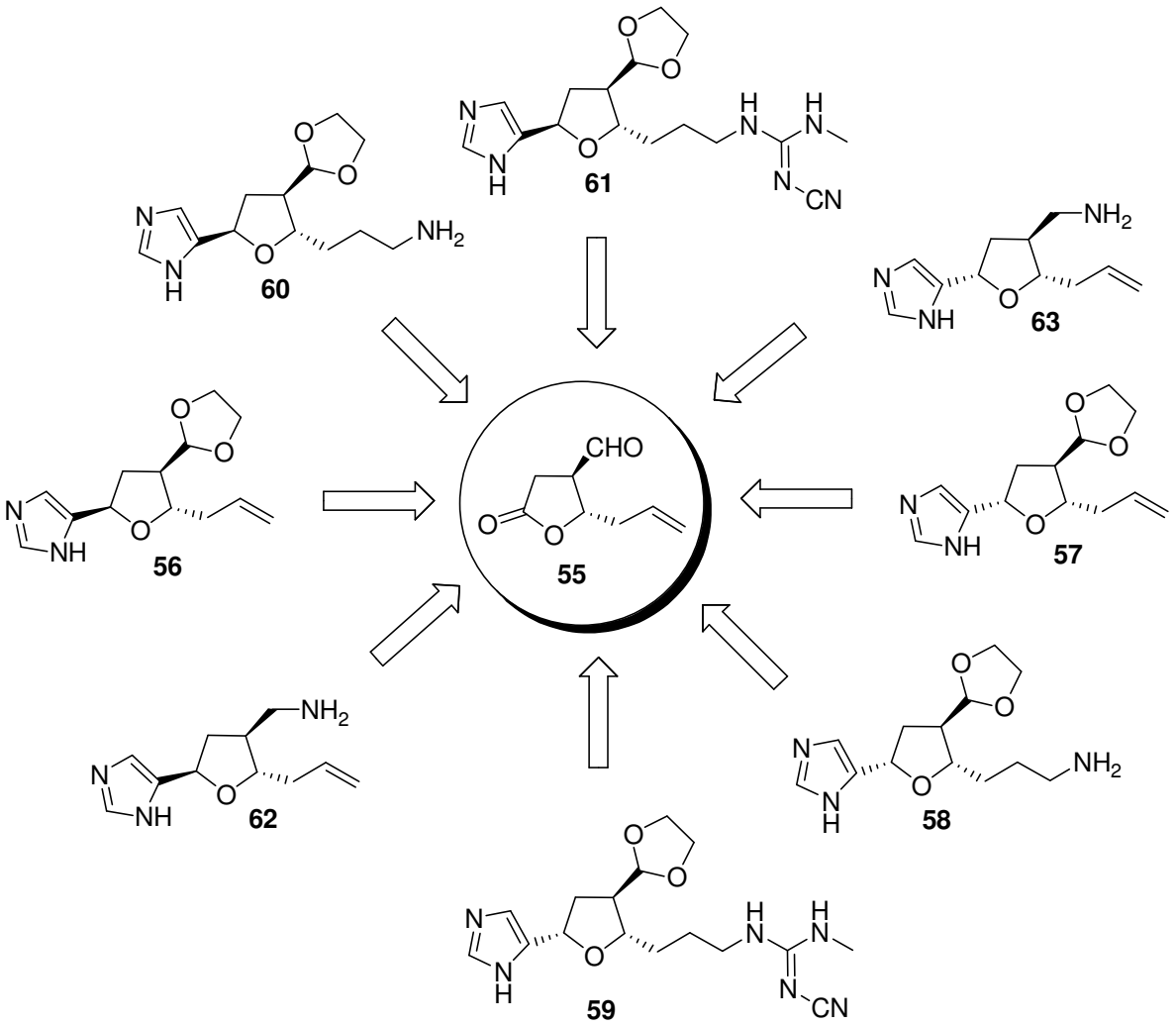


Figure 2.2 Tetrahydrofuran imidazole based potential agonists for histamine H_3 and H_4 receptors

As explained above by using the same synthetic strategy GBL **64** may afford the cyclic buiding blocks, which can be converted to variety of histamine H_3 and H_4 receptor potential agonists (Figure 2.3). Compounds **65** to **72** could be obtained from cyclic building blocks of GBL **64** by side chain modification and different functionalization. Since imidazole acylguanidine derivatives are also known as histamine H_3 and H_4 receptor agonists, it is also possible to convert the four amines **65-70** in to their corresponding acylguanidine derivatives.

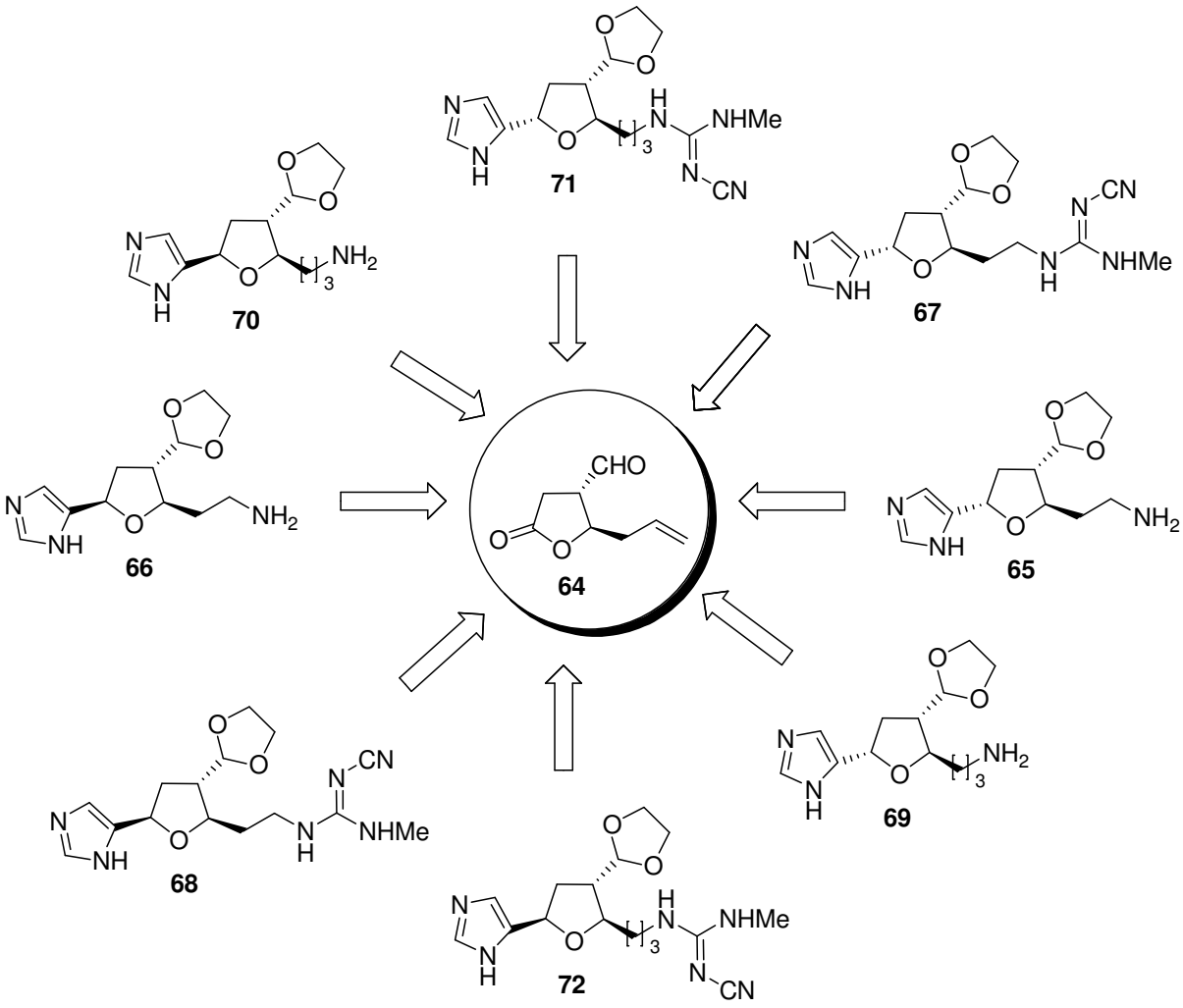


Figure 2.3 Tetrahydrofuran imidazole based potential agonists for histamine H_3 and H_4 receptors

Chapter 2

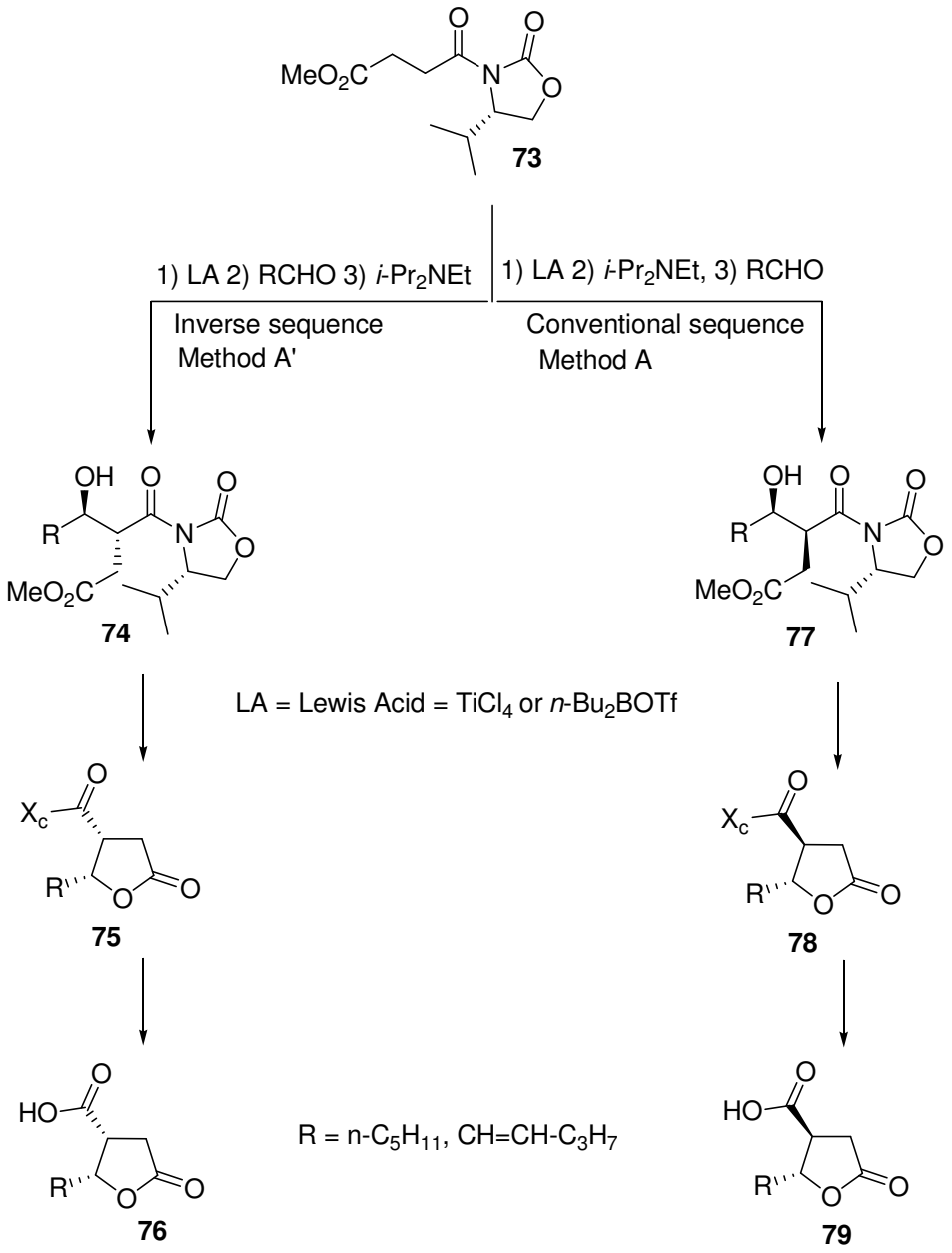
2. Enantioselective synthesis of histamine H_3 and H_4 receptor potential agonists based on γ-butyrolactones

2.1. Stereoselective Synthesis of γ-Butyrolactones (GBLs)

Functionalized γ-butyrolactones have attracted substantial attention in recent years due to their synthetic importance as building blocks in natural product synthesis[1] as well as in medicinally active synthetic compounds. The development of new methods for the synthesis of chiral γ-butyrolactones has been one of the current interests in asymmetric synthesis.[2] Recent examples include the transformation of (i) chiral natural products[3] (ii) chiral allylic alcohols[4] (iii) chiral propagyl alcohols[5] (iv) and stoichiometric or catalytic use of organometallic reagents.[6] In most of these methods, a multistep process that is more than four steps is required to reach the desired γ-butyrolactones.

Several research groups have synthesized γ-butyrolactones, a few methods are described here briefly.

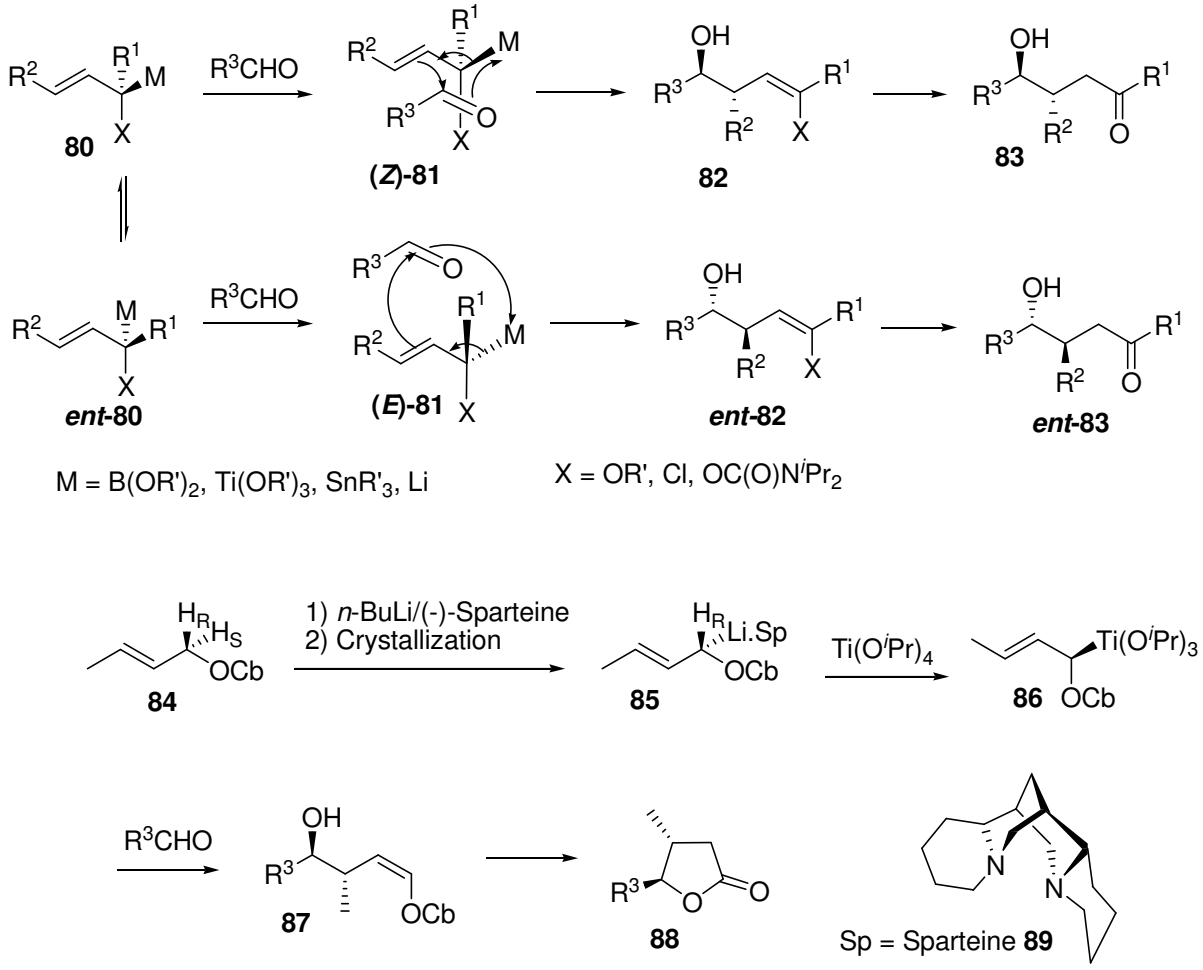
The recent synthesis of both *syn*- and *anti*-lactones by asymmetric aldol reactions was demonstrated by Hajra and coworkers.[7-9] The authors reported that the formation of both *syn*- and *anti*-aldol products from the same set of reactants is possible by simply inverting the addition sequence of the base and aldehyde using Evans type chiral auxiliary (*N*-acyl-2-oxazolidinones). Under the conventional method, addition of $TiCl_4$, base, followed by aldehyde (Method A), the aldol reaction of **73** with variety of aldehydes at low temperature and *in situ* lactonization of **77** (*syn*-aldol product) provided *trans*-4,5-disubstituted-γ-butyrolactone **79** in good yields and high diastereoselectivity via intermediate **78**.[7-9] However under the inverse method, addition of $TiCl_4$, aldehyde, followed by base (Method A′), the aldol reaction of **73** with variety of aldehydes at low temperature furnished **74** (*anti*-aldol product) with high diastereoselectivity and in good yield. *In situ* lactonization of **74** and **77** gave the corresponding lactones **75** and **78** having chiral auxilaries in there. The selective removal of the chiral auxiliaries of lactones **75** and **78** provided γ-butyrolactones **76** and **79** as a general approach for the synthesis of (+)- and (-)-4,5-*trans*- and *cis*-paraconic acids, for example (+)- and (-)- methylenolactocins (4,5-*trans*) and phaseolenic acids (4,5-*cis*) has been demonstrated (Scheme 2.4).



Scheme 2.4 Synthesis of γ-butyrolactones by Hajra *et al*

Hoppe and coworkers reported a chiral homoenolate reagents of type **80** that reliably adds to aldehydes through cyclic Zimmerman-Traxler transition states[10] **81** to form the homoaldol adducts **82** or *ent*-**82** with essentially complete γ-regio- and *anti*-diastereoselectivity. Covalently bound ‘‘cations’’ M gave rise to complete transfer of chirality from position 1 in **80** to position 3 in the addition products **82** and *ent*-**82**. Depending on whether the heterosubstituent X takes a pseudoaxial or a pseudoequatorial position [(*Z*)-**81** or (*E*)-**81**][11] an opposite sense of chirality is induced in the products **82** and *ent*-**82**, with enantiomeric γ-hydroxy carbonyl compounds **80** and *ent*-**80**, respectively, being formed after hydrolysis (Scheme 2.5).

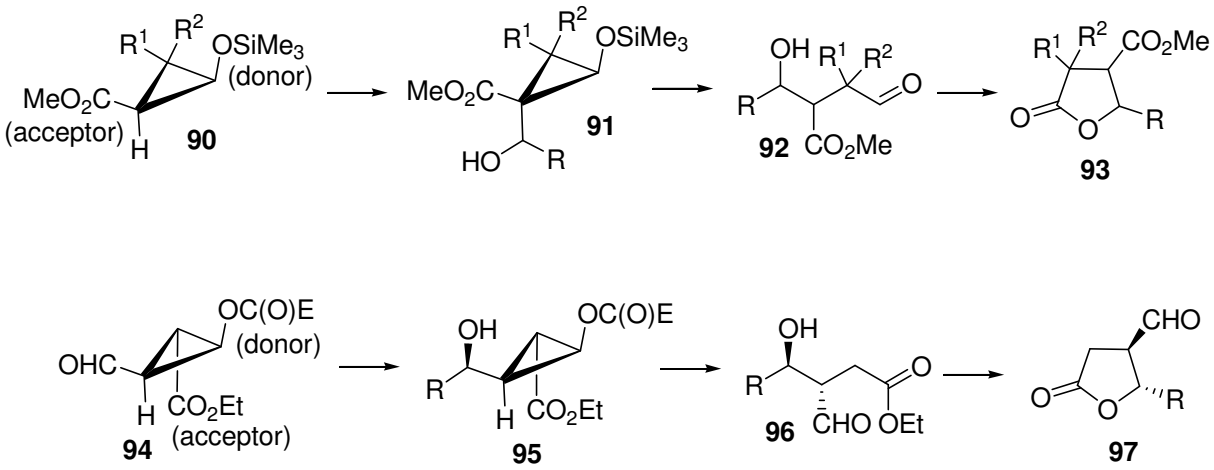
Hoppe *et al* introduced α-metallated 2-alkenyl *N*,*N*-diisopropylcarbamates as versatile homoenolate reagents. Because of the strongly activating properties of *N*,*N*-diisopropylcarbamoyloxy groups, these are easily prepared by facile deprotonation and the cation is fixed in the α-position by chelation. Exchange of lithium by tetra(isopropoxy)titanium dramatically enhances the regioselectivity and diastereoselectivity of the aldehyde addition.[12]



Scheme 2.5 Synthesis of GBLs by Hoppe *et al*

Hoppe type enantioenriched lithiated carbamates are configurationally stable at -78 °C and can be obtained by deprotonation of the optically active precursors or through kinetic resolution of the racemic carbamates by *n*-butyllithium/(−)-sparteine (**89**).[13] It is known that, the removal of the (*pro*-*S*) protons of the carbamates such as **84** by butyllithium/sparteine is kinetically favoured, as found for the *O*-alkyl derivatives,[14,15] however a rapid epimerisation takes place even at -78 °C. The sparteine complex (*S*)-**85** crystallised from the pentane/cyclohexane solution with simultaneous dynamic kinetic resolution, resulting in up to 92% *de* in the solid. The metal exchange proceeded with inversion of the configuration and gave rise to the allyltitanium intermediate (*R*)-**86**, which was stable in solution. The

homoaldol adducts of aldehydes and ketones were obtained with 90% ee. These are easily transformed into optically active γ-lactones such as **88** (Scheme 2.6).[16]



Scheme 2.6Synthesis of GBLs by Reissig *et al* and Reiser *et al* via donor-acceptor cyclopropane derivatives

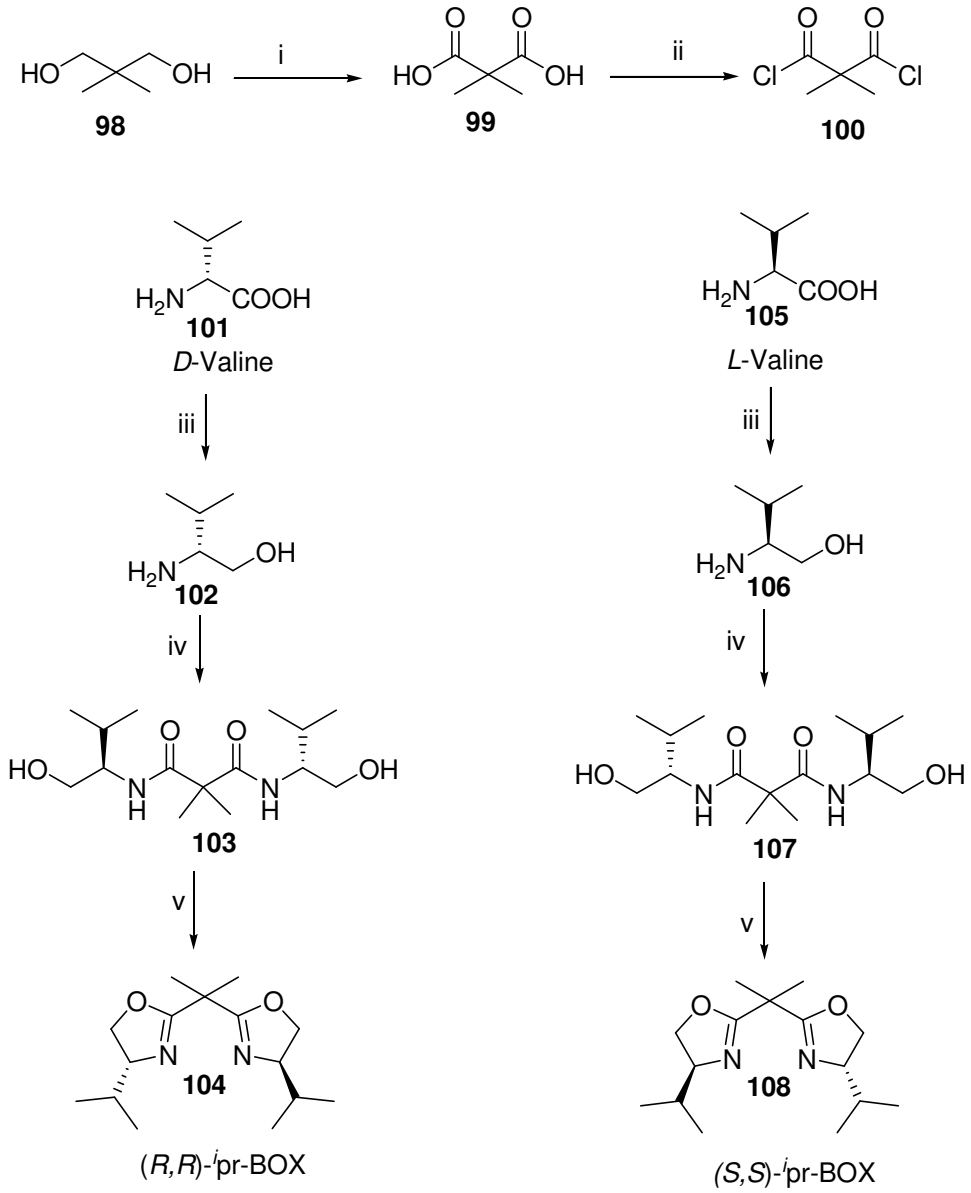
Reissig *et al.*[17-19] used cyclopropane derivatives such as (*rac*)-**90** for the synthesis of substituted (*rac*) γ-butyrolactones **93** (Scheme 2.6). *Vicinally* donor-acceptor-substituted cyclopropanes like **90** that serve as 1,3-dipolar synthon in **92** for many synthetically valuable transformations.[20] Since the two charges of synthon **92** are in 1,3-relationship, many reactions employing **91** may be regarded as processes involving a formal *umpolung of reactivity* and often provide products not easily available by alternative methods.[21] Deprotonation of D-A (donar-acceptor) substituted cyclopropanes such as (*rac*) - **90** with LDA at -78 °C, reacted with carbonyl compounds approaches the enolate exclusively, at the less hindered side giving the *cis* compound (*rac*) - **91** (aldol product). Deprotection and ring opening of aldol product **91** to γ-oxo esters (*rac*) - **92** can be accomplished under mild conditions with acids or fluoride sources. Similarly, crude hydroxyalkylated cyclopropanes are transformed to γ-lactols or its equivalents to the acyclic tautomers (*rac*) - **92** which under lactonization gave highly functionalized *(rac)* GBLs **93**. Reiser *et al* reported,[22-24] the synthesis of *anti* disubstituted γ-butyro- lactonaldehyde **97** with diastereo and enantioselectively, using copper (I)-catalyzed asymmetric cyclopropanation of furan-2-carboxylic ester, followed by ozonolysis, Sakurai allylation with allyltrimethylsilane and finally base mediated retroaldol-lactonization sequences. Cyclopropane carbaldehyde **94** can be synthesized by copper(I)-bis(oxazolines)-catalyzed cyclopropanation of furan-2-carboxylic esters followed by ozonolysis of cyclopropane ester. The selective nucleophilic addition of **94** which undergoes highly diastereoselective additions giving rise the Felkin-Anh adduct **95**. Base mediated retroaldol/lactonization cascades of **95** leads to γ-butyrolactone **97** with high

diastereoselectivity (95:5) (Scheme 2.6).[22-24] The advantage of this methodology is that γ-butyrolactones of either enantiomer can be achieved by copper(I)- bis(oxazolines)-catalyzed cyclopropanation of furan-2-carboxylic esters depending on the choice of chiral ligand (*R,R* or *S,S* bisoxazolines) used. Here it is note worthy to remember that both the analogues of **OUP-16** and **OUP-13** of the first selective H_4 receptor agonists can be achieved by both enantiomers of the γ-butyrolactones **55** and **64**.

2.2 Synthesis of chiral bis(oxazoline) ligands

Bis(oxizolines) have proved to be privileged structures because they promote a great number of metal-catalyzed transformations with extraordinary selectivity. Evans and coworkers discovered that *C2*-symmetric bis(oxazoline) copper complexes such as (box) Cu (I) & (II) both are effective promoters of enantioselective cyclopropanation, Diels-Alder, aldol, ene, Michael and amination reactions.[25,26] Chiral bis(oxazolines) were also used in our group extensively for the above mentioned asymmetric reactions.[26,27] Most commonly, bis(oxazolines) can be obtained from aminoalcohols by a two step condensation/cyclization sequence with acid chloride as described here.[27] Bis(4-isopropyloxazoline) available as either enantiomer from inexpensive *L*- or *D*- Valine, is an attractive alternative for large scale applications of enantioselective reactions.

Here synthesis of both (*R,R*) and (*S,S*)- ^{i}Pr-BOX ligands **(104 & 108)** is described. The (*R,R*)-^{i}Pr-BOX ligand **(104)** was derived from *D*-valine **(101)** and the (*S,S*)-^{i}Pr-BOX ligand **(108)** was prepared from the cheaper amino acid *L*-valine **(105).** 2,2-dimethylmalonyl dichloride **100** was prepared by oxidation of 2,2-dimethyl propane-1,3-diol (**98)** followed by oxalyl chloride treatment of corresponding 2,2-dimethyl malonic acid **99**. *D*-Valinol **102** was prepared from *D*-valine **101** and similarly *L*-valinol (**106**) was prepared from *L*-valine **105** by sodiumborohydride reduction in presence of iodine. These valinols **102** and **106** were coupled with **100** to obtain the corresponding C_2-symmetric diamides **103** and **107**. Tosylation of diamides **103** and **107** followed by their subsequent cyclization obtained the corresponding enantiomeric pure chiral bioxazoline ligands **104** and **108** (Scheme 2.7).[27]

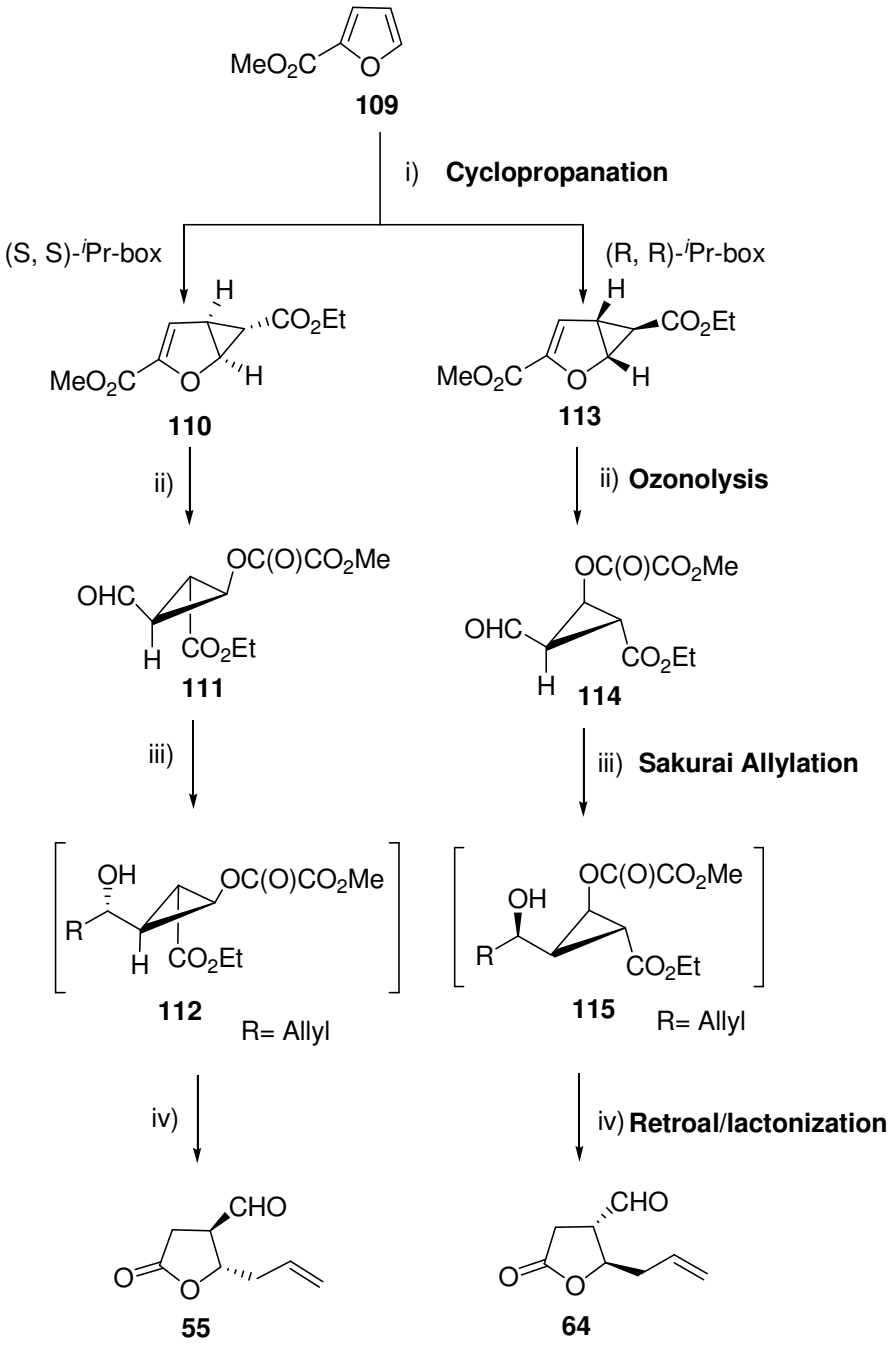


Reagents and conditions: i) HNO_3 ; ii) Oxalyl chloride, DMF, CH_2Cl_2; iii) $NaBH_4$, I_2, THF; iv) Et_3N, **100**, CH_2Cl_2 ; v) TsCl, Et_3N, DMAP, CH_2Cl_2

Scheme 2.7 Synthesis of chiral bis(oxazoline) ligands for asymmetric cyclopropanation

Following the synthetic strategy developed in our group the disubstituted γ-butyrolactones **55** and **64** can be obtained starting with the copper(I)-bis(oxazolines)-catalyzed cyclopropanation of furan-2-carboxylic ester **109** (Scheme 2.8). From the same starting material **109** the two enantiomers of cyclopropane esters **110** and **113** can be synthesized depending on the choice of chiral bis(oxazolines). The methodology was standardized up to 100 g scale with 99% ee. Ozonolysis of **110** followed by reductive workup leads to the aldehyde **111**, which undergoes highly diastereoselective additions with nucleophiles to **112** followed by a retroaldol/lactonization cascade to **55**. Similarly the other enantiomer of GBL **64** can be obtained from **113** (Scheme 2.8). The stereochemical outcome of the sequence of cyclopropanation, ozonolysis to the cyclopropylcarbaldehyde and subsequent

allylation/retroaldol-lactonization depends on the stereochemistry of the bis(oxazoline)-ligand (BOX) initially used for the cyclopropanation.



Reagents and conditions: i) $Cu(OTf)_2$, $PhNHNH_2$, ethyldiazoacetate, 0° C, 41%; ii) O_3, CH_2Cl_2, -78 °C, DMS, rt, 12h, 98%; iii) $BF_3.Et_2O$, allylTMS, CH_2Cl_2, -78 °C, 12h; iv) $Ba(OH)_2$ or Et_3N, MeOH, 0 °C, 50%

Scheme 2.8 Synthesis of *anti*-2,3-disubstituted γ-butyrolactones

There are four important reactions during the enantioselective synthesis of γ-butyrolactones.

1) Cyclopropanation

2) Ozonolysis

3) Sakurai Allylation

4) Lactonization

Each of those above reaction is described in detail.

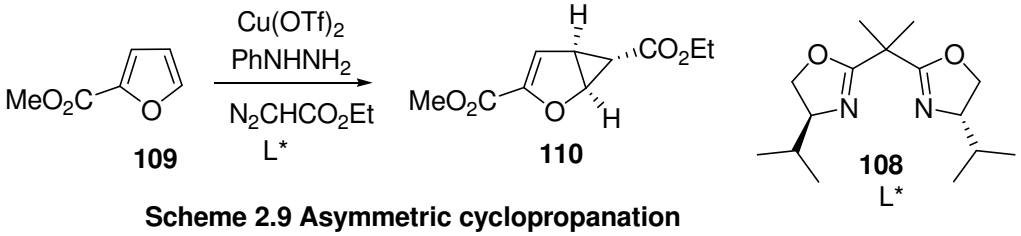
2.3 Cyclopropanation

W. H. Perkin reported the first synthesis of cyclopropane derivatives in 1884.[28] The cyclopropanation of olefins using the transition metal-catalyzed decomposition of α-diazoesters is one of the most extensively studied methods.[29] Both inter and intramolecular versions of this reaction have been developed. The nature of the starting diazo reagent as well as the type of the reaction (inter- or intramolecular) plays a key role in the appropriate selection of the most efficient catalyst for a given transformation. The simple α-diazoesters can be prepared on gram scale and reacted in presence of the metal catalyst and alkenes.[30] Cu, Rh, Ru and Os metal carbenes are known to react faster with electron rich alkenes among the wide range of catalysts, whereas Pd metal carbenes are optimal for electron-deficient alkenes. The mechanism of the transition metal-catalyzed decomposition of α-diazocarbonyl compounds is believed to proceed *via* formation of the metal carbene complex[31] in most cases. In 1966 Nozaki reported the first example of an enantioselective copper catalyzed intermolecular cyclopropanation.[32]

The copper (I) complex of bis(oxazoline) **104**, disclosed by Evans in the early 1990s, is still a standard to which new bis(oxazoline) ligands are compared.[33,34] In 1990 Wenkert *et al* reported the cyclopropanation of furan-2-methyl carboxylic ester with $Rh_2(OAc)_4$ leading to *exo*-cyclopropane furoic ester in 55% yield.[35] In difference to metal carbene complexes such as pybox ruthenium carbene and porphyrene-osmium carbene, the copper carbene complexes have not yet been characterized by X-ray crystallography. However the NMR study of copper-carbenes in solution was successfully carried out by Hofmann[36] *et al,* which is entirely consistent with Pfaltz's[37] mechanistic postulation for mono semicorrin copper (I) complex. According to Pfaltz's method the cyclopropanation is carried out using bis(semicarrinato) copper (II) complex as a precatalyst. Activation of this complex either by heating or addition of phenyl hydrazine in the presence of alkyl diazoacetate, the complex is reduced to loose one semicorrin ligand, and the resulting one reacts as an active catalyst for the cyclopropanation.

The regioselective cyclopropanation of furoic ester proceded only at the sterically less hindered double bond. This copper catalyzed cyclopropanation promoted highly enantio- and diastereoselectively in the presence of chiral bisoxazoline ligand, orienting the ester group exclusively on the convex face of the bicyclic frame work. The treatment of furoic ester **109** with ethyldiazoacetate in the presence of bisoxazoline **108** under above mentioned conditions (Scheme 2.9) leads to the cyclopropane carboxylate **110** obtained in pure form upon

crystallization (99% *ee*) in 41% yield up to 100g scale without loss of enantioselectivity in the course of scale up.



Scheme 2.9 Asymmetric cyclopropanation

The stereochemical outcome of the copper-bisoxazoline catalyzed cyclopropanation of furan-2-carboxylic methyl ester with ethyl diazoacetate can be explained by model studies of Pfaltz[37] and Andersson.[38]

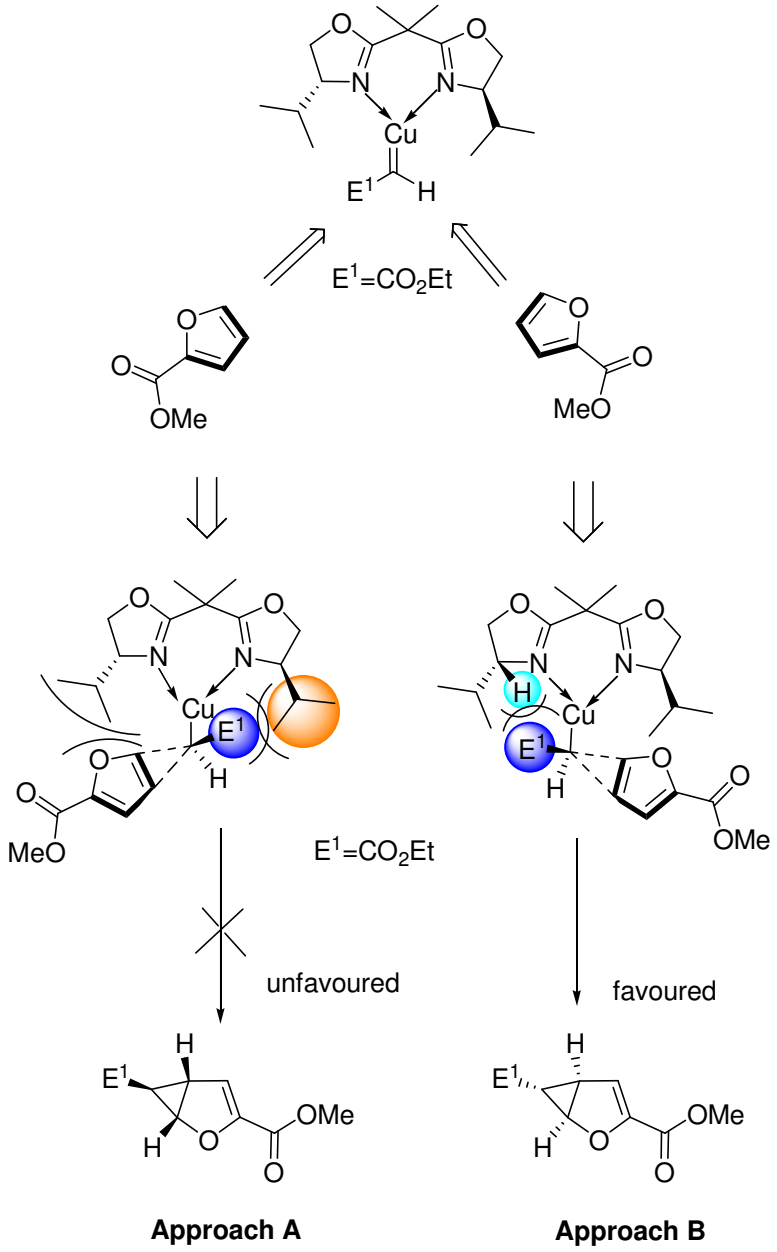


Figure 2.3 Visualization of asymmetric cyclopropanation using BOX(104) Cu(I) complex

The (bisoxazoline) copper (I) complex first reacts with the ethyl diazoacetate and forms a metal-carbene intermediate. Now there are two possibilities to interact the double bond of furoic ester either from bottom or from top side of this intermediate since it has trigonal planar geometry. Depending on the direction of attack, the ester group at the carbenoid center either moves forward or backward relative to the plane bisecting the bisoxazoline ligand. In the case of approach A, the repulsive steric interaction builds up larger between the ester group and the isopropyl group of the bisoxazoline ligand. However, the double bond of furan preferentially approaches from sterically less hindered side, where there is only a smaller repulsive interaction is present with hydrogen in case of approach B. Therefore, approach B is expected to be favoured over A (Figure 2.3).

2.4 Ozonolysis

The cleavage of an alkene or alkyne with ozone to form the organic compounds in which the carbon-carbon multiple bond has been replaced by a double bond to oxygen is called as ozonolysis. [39,40] The reaction outcome depends on the type of multiple bond being oxidized and also the work up conditions.

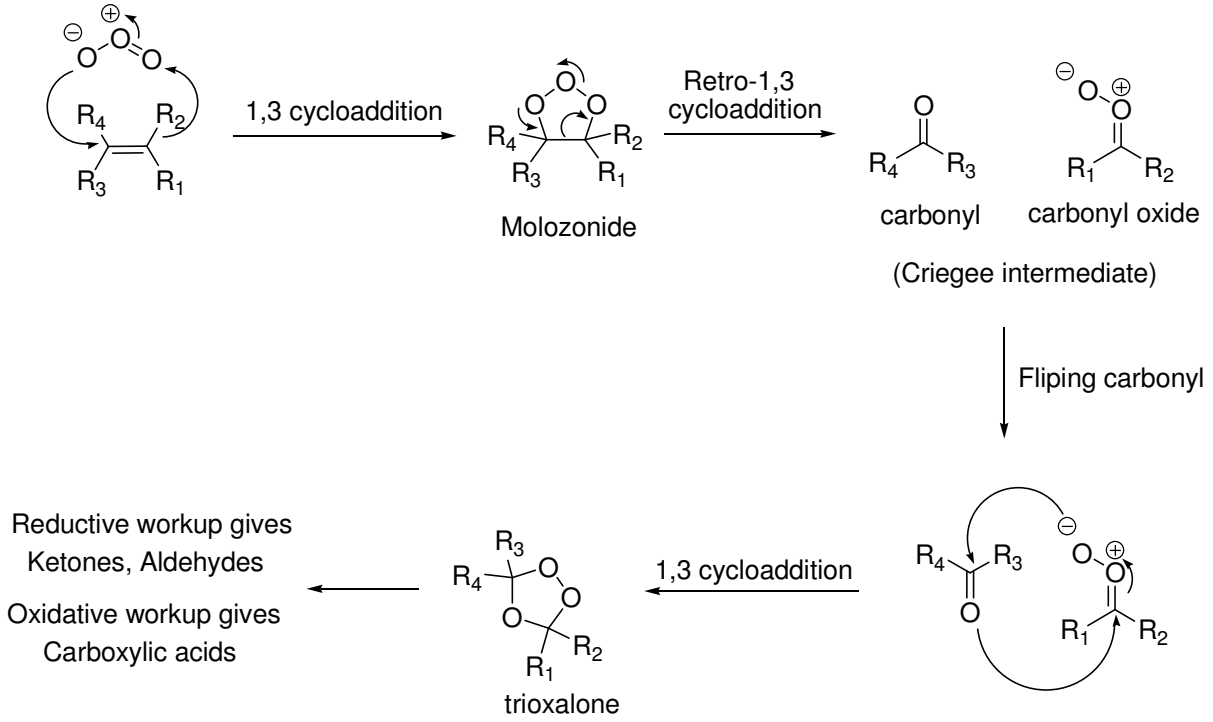
2.4.1 Ozonolysis of alkenes

In a typical procedure, ozone is bubbled through a solution of alkene in dichloromethane at -78 °C until the solution turns blue, indicating the consumption of olefin. The intermediate ozonide is converted to a carbonyl derivative by adding a reductive or oxidizing reagent depending on the choice of product. Reductive work up conditions are commonly used than oxidative conditions. Alkenes can be oxidized with ozone to form aldehydes, ketones, alcohols, or carboxylic acids. The use of dimethyl sulfide, triphenyl phosphine or zinc dust produces aldehydes or ketones, while the use of sodium borohydride produces alcohols. The use of hydrogen peroxide produces carboxylic acids. Recently, the use of amine *N*-oxides has been reported to produce aldehydes directly.[41] Dichloromethane is commonly used as solvent for this reaction. Methanol is often used as a 1:1 cosolvent to facilitate timely cleavage of the ozonide. In an industrial scale ozonolysis of oleic acid produces azelaic acid and pelargonic acids.

2.4.2 Mechanism of ozonolysis

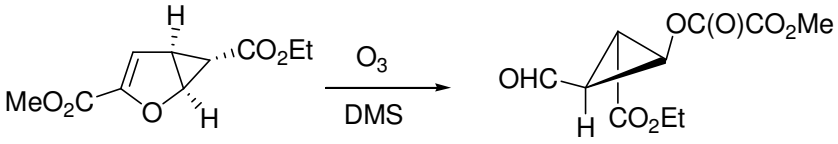
In the generally accepted mechanism proposed by Rudolf Criegee in 1953,[42] the alkene and ozone form an intermediate molozonide in a 1,3-dipolar cycloaddition. Then the molozonide reverts to its corresponding carbonyl oxide (also called as Criegee intermediate) and aldehyde or ketone in a retro-1,3-dipolar cycloaddition. The oxide and aldehyde or ketone react again in a 1,3-dipolar cycloaddition to produce a stable ozonide intermediate (a trioxolane). Evidence for this mechanism is found in isotopic labeling. When ^{17}O-labelled benzaldehyde reacts with

carbonyl oxides, the label ends up exclusively in the ether linkage of the ozonide (Scheme 2.10).[43]



Scheme 2.10 Plausible mechanism of ozonolysis

The reaction of bicyclohexene **110** with ozone in dichloromethane at -78 ºC, followed by reductive work up conditions in presence DMS gave rise to the highly functionalized cyclopropane carbaldehyde **111** in quantitative yield (Scheme 2.11).



110 **111**

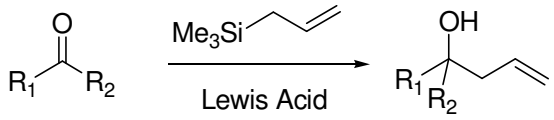
Scheme 2.11 Ozonolysis of cyclopropane ester

2.5 Sakurai Allylation

The Sakurai allylation also known as the Hosomi-Sakurai reaction[44] is the chemical reaction of carbon electrophiles such as aldehydes and ketones with allylsilanes catalyzed by a strong Lewis acid (LA). Lewis acid activation is essential for the completion of reaction. Strong Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$ and $AlCl(Et)_2$ are all effective in promoting this reaction. A wide variety of aliphatic, alicyclic and aromatic carbonyl compounds can undergo smoothly and a regiospecific transposition occurs in the allylic part. The reaction is a type of

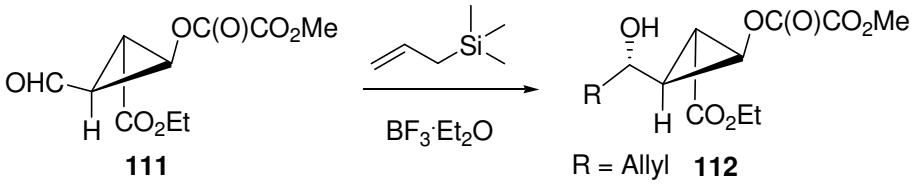
electrophilic allyl shift with the formation of an intermediate beta-silyl carbocation. Driving force is the stabilization of carbocation by the beta-silicon effect.

The high reactivity of allylsilane toward electrophiles has been explained by σ (Si-C)-π conjugation. The synthetic utility of this reaction is displayed by the regiospecific transformation of the allylic group to a carbonyl function, in which the carbon-carbon bond formation occurred exclusively at a γ-carbon of allylsilanes. The reaction mechanism involves a nucleophilic attack of the allylsilane to the carbonyl carbon polarized partially by LA through a cyclic process would be most favorable, because the regiospecificity and the *trans* preference in the stereochemistry of the products are observed actually (Scheme 2.12)



Scheme 2.12 Sakurai allylation with Lewis acids

Sakurai allylation of cyclopropane carbaldehyde **111** in the presence of Lewis acid $BF_3{\cdot}Et_2O$ gave the corresponding cyclopropane allyl alcohol **112** (Scheme 2.12).



Scheme 2.13 Sakurai allylation of cyclopropane carbaldehyde

2.5.1 Determination of Stereochemistry

The stereoselective addition of nucleophiles to a prochiral center will be influenced by an adjacent chiral centre. It is an important transformation in asymmetric synthesis of organic chemistry. The diastereoselective addition of nucleophiles to α chiral carbonyl compounds was postulated by D.J. Cram[45] and developed by Felkin and Anh.[46-49] According to Felkin-Anh model,[50] the carbonyl group orients orthogonally to the adjacent large group (L), therefore, two possible reactive conformations must be considered. Generally the priority of L group is determined by steric bulkiness. However in the Felkin-Anh model electron withdrawing substituents are considered as L for electronic reasons independent for their steric bulkiness.

Substituted cyclopropyl carbonyl compounds are most stable in bisected conformations for stereoelectronic reasons. Of the two possible bisected conformations, the s-*trans* conformation is favoured with respect to s-*cis* due to steric repulsion between carbonyl group and cyclopropyl moiety in the latter case. The addition of nucleophiles to the s-*cis*

conformation leads to the Felkin-Anh product and the conformation of s-*trans* leads to the *anti* Felkin-Anh product. Even though the s-*trans* conformation is favoured, when bulky nucleophiles approach the steric repulsion between the nucleophile and cyclopropyl group dominates its diastereoselectivity (Figure 2.4). [50]

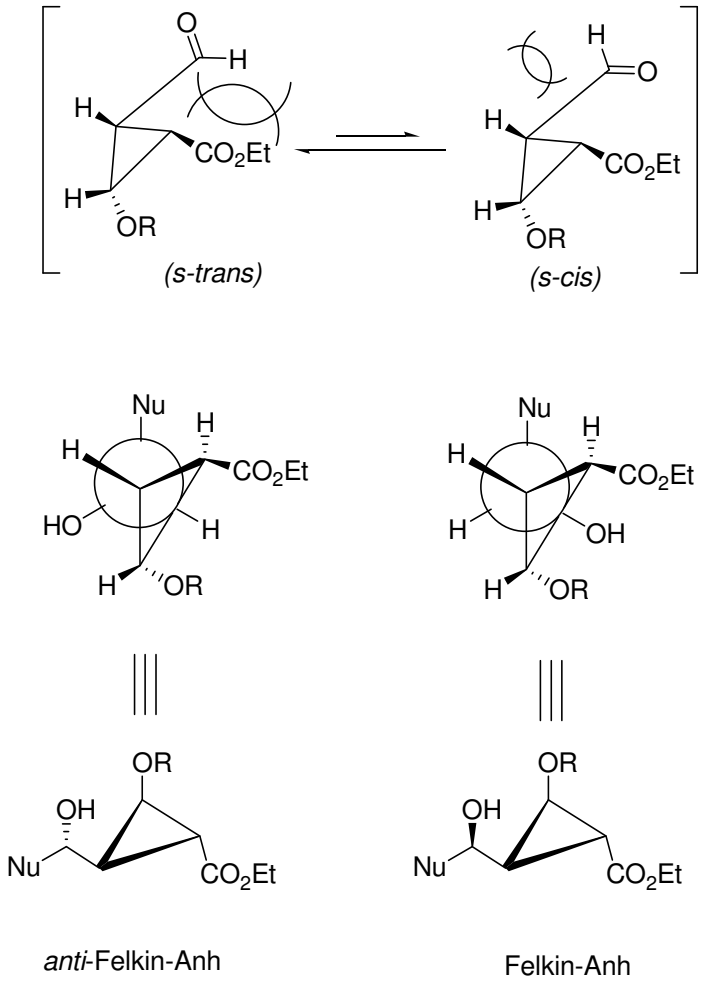
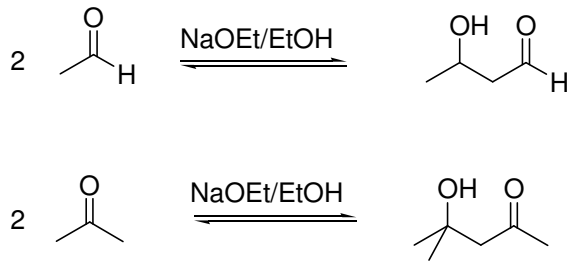


Figure 2. 4 Plausible nucleophilic attack on cyclopropane carbaldehyde

2.6 Retroaldol reaction

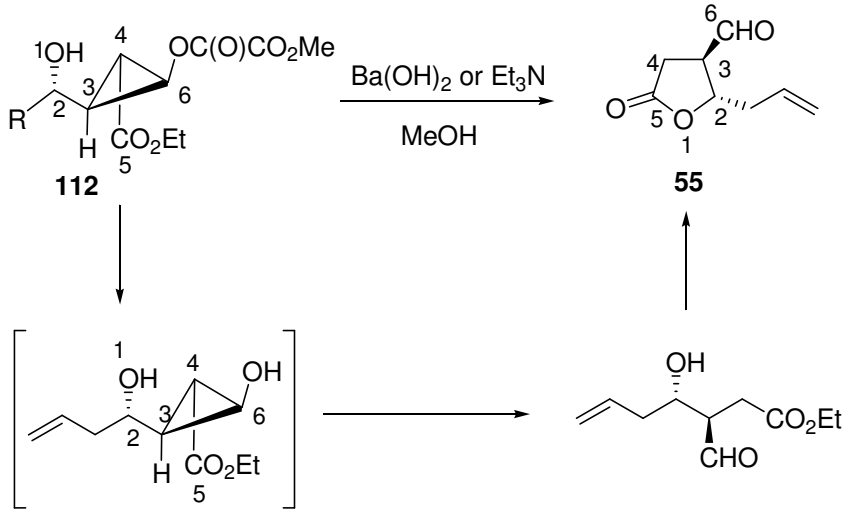
The aldol reaction is reversible, cleavage of a β-hydroxy carbonyl is called the reverse aldol or retro-aldol reaction.[51] Equlibrium between the β-hydroxylcarbonyl products and the carbonyl reactants lie toward the products with alkyl aldehydes and toward the reactants with alkyl and aryl ketones (Scheme 2.14).



Scheme 2.14 Retroaldol/lactonization

2.6.1 Formation of the *anti*-substituted lactones

The addition of allyl trimethyl silane to cyclopropyl carbaldehyde **(111)** gave the Felkin-Anh product **(112)** (Scheme 2.13). This cyclopropane derivative **(112)** has several properties that are useful for further synthetic transformations. The hydroxyl group at C-4 is located in a γ-position to the ester group at C-2 of the cyclopropane moiety, the vicinal donor-acceptor relationship between the hydroxyl group at C-1 and the ester group at C-2 could make feasible ring opening of cyclopropane. These two features made a possibility for the development of retroaldol/lactonization sequences of allyl cyclopropane to *trans*-disubstituted γ-butyrolactone. The base mediated Sakurai allylation product **112** either with $Ba(OH)_2$ or Et_3N upon retroaldol/lactonization sequence was afforded γ-butyrolactone **55** (Scheme 2.15).



Scheme 2. 15 Base mediated Lactonization

2.7 Introduction to tetrahydrofuran-imidazole based histamine H_3 and H_4 receptor agonists

Kurihara *et al* developed a series of chiral compounds related to aminomethyl tetrahydrofuran imidazoles (Figure 2.5), which have been examined *in vitro* for both the human histamine H_3 and H_4 receptors.[52] Among them, the (2*S*,5*S*)-isomer **54** showed approximately 300-fold higher selectivity at the H_3 receptor than the H_4 receptor. On the other hand, (2*R*,5*S*)- and (2*R*,5*R*)- cyanoguanidines **OUP-13** (**46)** and **OUP-16** (**45**) bound to the H_4 receptor had >40-fold selectivities over the H_3 receptor and they are the first selective H_4 receptor agonists. Thus the imidazole-tetrahydrofurane amines **116, 117, 35, 54** are H_3 agonists and their cyanoguanidine derivatives **118, 46, 45, 119** are H_4 receptor agonists.[52]

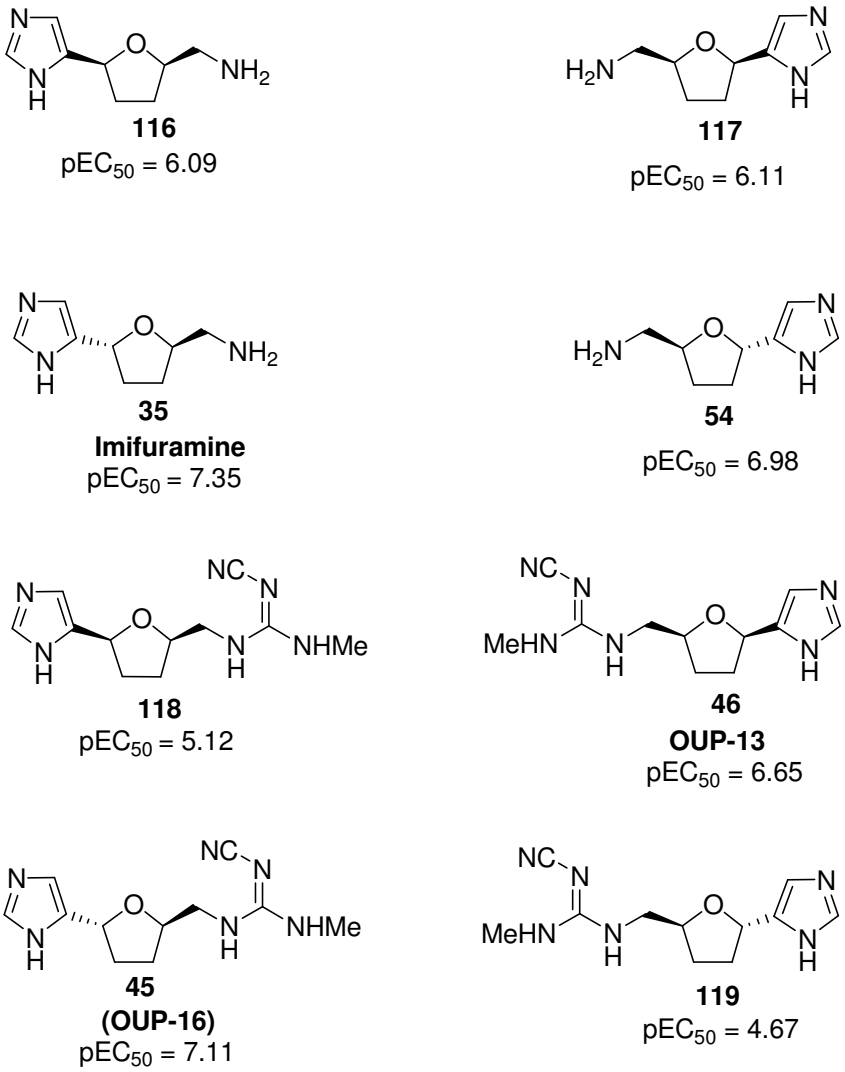


Figure 2.5 Histamine H_3 and H_4 receptor agonists developed by Kurihara *et al*

About the physiological and pathophysiological role of the H_4R is not much known. Recently, **OUP-16** has been described as a full agonist with moderate affinity and selectivity for the H_4 receptor. Furthermore, to investigate the possible physiological functions of the H_4 receptor, a more potent and selective ligands are required. Because of more sequence homology between

H_3 and H_4 receptor than any other subtypes of histamine receptors, most H_3 receptor ligands can bind to the H_4 receptor as well. For example, the classical "selective" H_3 receptor agonist, (*R*)-α-methylhistamine shows H_4 agonistic activity and thioperamide, the H_3 antagonist prototype, has moderate affinities for the H_4 receptor. Very few ligands have so far been reported that can selectively target the human H_4 receptor. Imifuramine was found as eutomer exhibiting H_3 agonistic activity.[52,53,54]

The competitive binding affinities (pK_i value) for the hH_3-receptor of the cyanoguanidines (**118, 46, 45, 119**) were significantly lower than that of the THF-amines (**116, 117, 35, 54**). (Table 1). The pK_i values of **35**, **54** for the binding to the hH_3 receptor were 10-fold higher than that of the other compounds and were 6.64 ± 0.12, 6.66 ± 0.14 respectively. The *trans*-isomers **(35**, **54)** of amino compounds exhibited about 10-fold higher affinity than their cis-isomers (**116**, **117**). In a functional H_3 receptor assay, the compounds **116**, **117**, **35** and **54** acted as full agonists ($0.9 < \alpha < 1.0$, Table1).[52]

Table 1. pEC_{50} values and affinity values of THF-imidazoles for human H_3 receptor[a]

Compound	configuration	Functional activity		binding pK_i
		pEC_{50}	efficacy(α)	
Histamine		8.39 ± 0.06	1.00	7.47 ± 0.11
(*R*)-α-methylhistamine		9.91 ± 0.05	0.85 ± 0.05	
116	2S,5R	6.09 ± 0.05	0.95 ± 0.04	5.77 ± 0.03
117	2R,5S	6.11 ± 0.08	1.06 ± 0.04	5.69 ± 0.05
35	2R,5R	7.35 ± 0.07	1.04 ± 0.05	6.64 ± 0.12
45	2S,5S	6.98 ± 0.05	0.91 ± 0.04	6.66 ± 0.14
118	2S,5R	NE	<0.1	5.09 ± 0.08
46	2R,5S	4.99 ± 0.08	0.43 ± 0.03	5.15 ± 0.17
45	2R,5R	5.50 ± 0.08	0.79 ± 0.06	5.66 ± 0.09
119	2S,5S	<4		4.73 ± 0.13

[a] The pEC_{50} values were determined by the inhibition of the forskolin-stimulated (1 μM) cAMP production, expressing the human H_3 receptor. All values shown are means ± SEM of at least four experiments. H_3 receptor competition binding was performed using [^{3}H] N^{α}-methylhistamine (1 nM).

Among them, **35** had the highest agonistic activity. As shown in Table 2, **35**, **46** and **45** competed for [^{3}H] histamine binding to the hH_4 receptor with pK_i values of 6.05 ± 0.04, 6.65 ± 0.06, and 6.90 ± 0.17 respectively. Moreover, **116**, **118**, **46**, **45**, and **119** all showed agonist

properties with high intrinsic activities (0.9 < α < 1.0). Among them, **45** most potently inhibited the 1 μM forskolinstimulated responses with an apparent pEC50 value of 7.11 ± 0.05 (Table 2). **35**, **54**, **46** and **45** exhibited receptor selectivity for either the hH_3 or hH_4 receptor. THF-Amine compounds **35**, **54** showed selective H_3 agonistic activity, which was approximately 45-, 300-, fold higher than for the H_4 receptor, respectively. In contrast, the cyanoguanidine analogues **46** and **119** exhibited full agonistic activities at the H_4 receptor with 45- and 41-fold higher potency than at the H_3 receptor, respectively.[52]

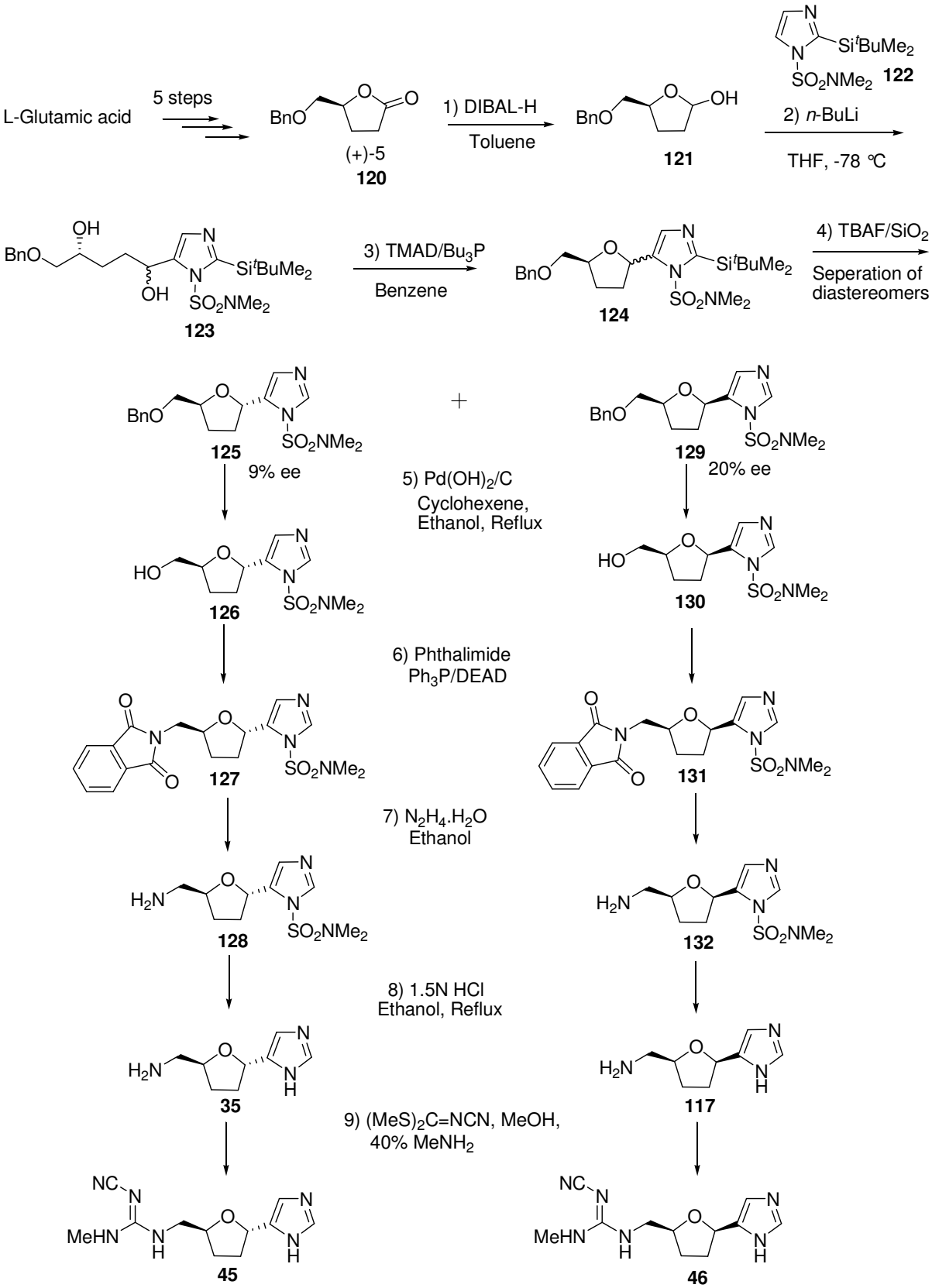
Table 2. pEC_{50} values and affinity values of THF-imidazoles for human H_4 receptor[a]

Compound	configuration	Functional activity		binding pK_i
		pEC_{50}	efficacy(α)	
Histamine		7.68 ± 0.05	1.00	
(*R*)-α-methylhistamine		6.26 ± 0.07	1.01 ± 0.01	
116	2S,5R	5.12 ± 0.05	1.02 ± 0.07	5.19 ± 0.07
117	2R,5S	5.26 ± 0.07	0.88 ± 0.06	5.60 ± 0.10
35	2R,5R	5.70 ± 0.05	0.70 ± 0.01	6.05 ± 0.04
54	2S,5S	4.51 ± 0.01	0.60 ± 0.04	4.89 ± 0.06
118	2S,5R	5.12 ± 0.06	1.07 ± 0.01	5.09 ± 0.07
46	2R,5S	6.65 ± 0.03	1.01 ± 0.01	6.65 ± 0.06
45	2R,5R	7.11 ± 0.05	0.99 ± 0.01	6.90 ± 0.17
119	2S,5S	4.67 ± 0.03	1 .06 ± 0.02	4.69 ± 0.12

[a] The pEC_{50} values were determined by the inhibition of the forskolin-stimulated (1 μM) cAMP production, expressing the human H_4 receptor. All values shown are means ± SEM of at least four experiments. H_4 receptor competition binding was performed using [^{3}H] histamine (10 nM).

The substitution of an amino group of tetrahydrofuranylimidazoles with a cyanoguanidine moiety led to a decrease in the agonistic activity at the H_3 receptor and an increase in the H_4 receptor selectivity. The **46** (**OUP-13**) and **45** (**OUP-16**), having the 2*R*-configuration, were highly selective compounds at the H_4 receptor. On the other hand, **54** having the 2*S*,5*S*-configuration, behaved as the most selective H_3 receptor agonist in THF-imidazole series. These results suggest that the stereochemistry of the tetrahydrofuranylimidazoles is useful for the investigation of selective ligands for hH_3 and hH_4 receptors.[52]

2.7.1 Synthesis of histamine H_3 and H_4 agonists by Kurihara and coworkers



Scheme 2.16 synthesis of histamine H_3 and H_4 receptor agonists by Kurihara *et al*

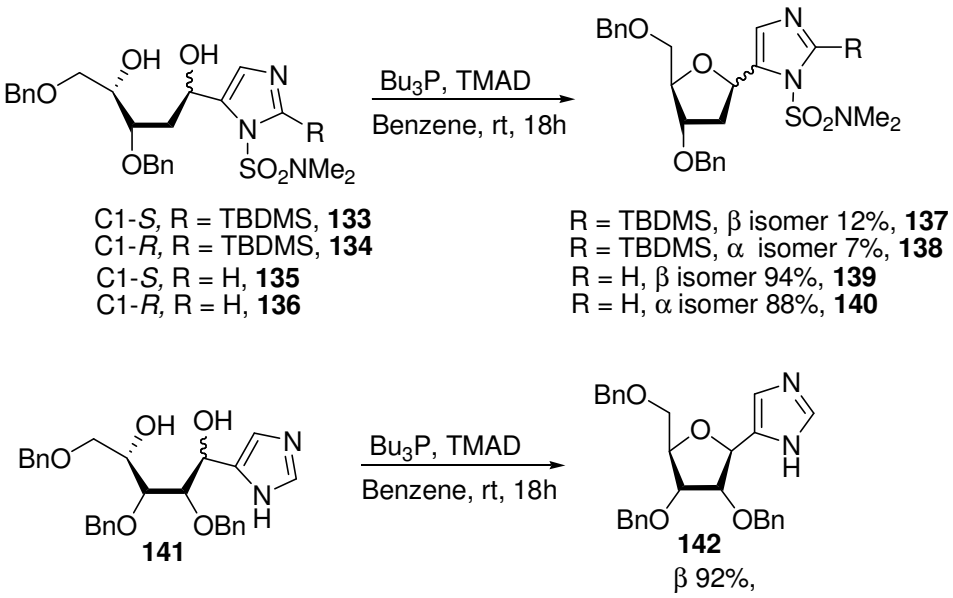
Kurihara *et al* reported the synthesis of *trans*- and *cis*-4(5)-(5-aminomethyltetrahydrofuranyl) imidazole [(+)-**35** and **117**], which was the clue to the development of H_3 or H_4 ligands, starting from L-glutamic acid.[53-56] Reduction of **120** with DIBAL-H followed by treatment of bisprotected imidazole **122** with **121** in presence of n-butyl lithium obtained **123** as 1:1 inseparable diastereomeric mixture (Scheme 2.16). The Mitsunobu cyclization of **123** using the expensive reagent TMAD obtained **124** as again 1:1 inseparable mixture of *trans* and *cis* cyclization product, due to indistinguishable activation between two hydroxy groups of a chiral 1,4-diol intermediate **123**. Deprotection of TBDMS with TBAF followed by flash chromatography afforded **125** and **129** whose NOE experiments did not show significant difference and relative configurations were not established at this stage. On the other hand optical rotation measurements did not show any variations. Latter stage using chiral HPLC proved that **125** and **129** was obtained with low optical purities of 1:1.2 (9% ee) and 1:1.5 (20% ee) (Scheme 2.16). Debenzylation of **125** and **129** using $Pd(OH)_2$/C furnished the primary alcohols **126** and **130**. Phthalimidation of **126** and **130** using DEAD-Ph_3P gave rise to **127** and **131** respectively. To determine the relative configuration at this stage phthalimide **127** was recrystalized and analyzed by X-ray crystallography as racemic mixture, and its configuration between C2 and C5 was found to be *trans*. Reductive cleavage of phthalimides **127** and **131** with hydrazine hydrate, followed by acidic hydrolysis using 1.5 N HCl produced amines **35** and **117**. Introduction of cyanoguanidine on **35** and **127** led to the histamine H_4 receptor agonists **45** (OUP-16) and **46** (OUP-13).[55]

The findings of imifuramine, and their cyanoguanidine derivatives **OUP-16** and **OUP-13** as important therapeutic targets of recently discovered histamine receptors and the synthetic drawbacks for the enantioselective version, encouraged us to synthesize *trans*- and *cis*-tetrahydrofuranylimidazole derivatives for improvement of more potent and receptor selective histamine H_3 and H_4 agonists using the γ-butyrolactone based enantioselective synthesis.

Kurihara and coworkers reported the efficient and β -stereoselective synthesis of 4(5) (2-deoxyribofuranosyl)imidazoles (**137-140**) and 4(5)-(β-D-ribofuranosyl) imidazole (**142**) where they have used Mitsunobu reaction as key step for the cyclization of diols **133-136,** and **141.** The cyclization of diols, **133** and **134** having bisprotected imidazoles (sulfonamide and TBDMS groups) using TMAD reagent on C1-*S* and C1-*R* diols gave only poor yields 12% and 7% and no enantioselectivity (Scheme 2.17).[57,58]

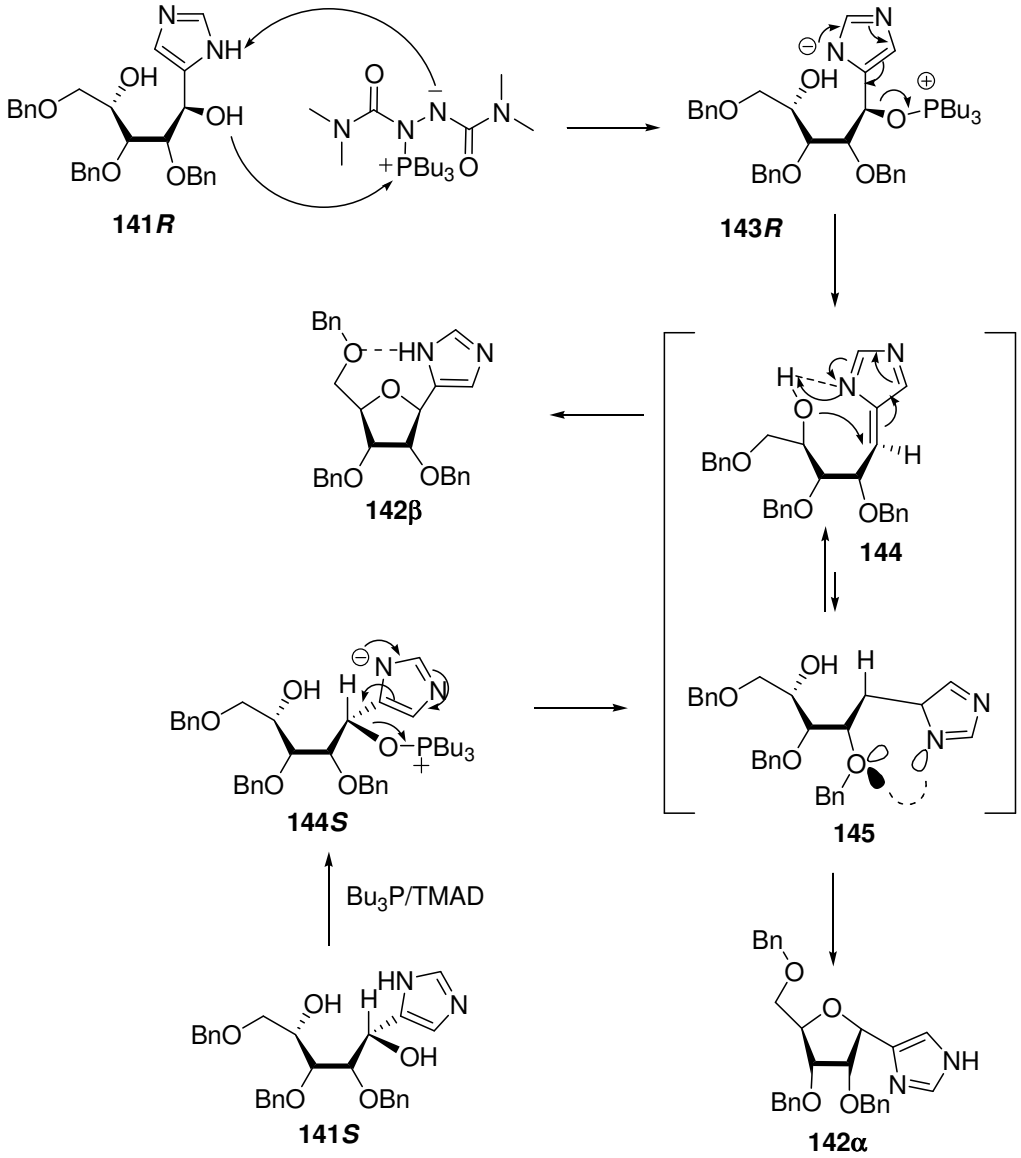
The cyclization of unsubstituted imidazole diol **141,** under Mitsunobu conditions (Bu_3P-TMAD) obtained **142** with β-stereo selectivity in 92% yields. The authors reported the feasible mechanism for the Mitsunobu cyclization (TMAD-Bu_3P system) of the diols bearing

an unsubstituted imidazoles (NH free imidazole diols) via diazafulvene intermediate (Scheme 2.18).[58] Mitsunobu cyclization of diols **133-136** bearing monosubstituted or disubstituted imidazole proceeded *via* a S_N2 process of the standard Mitsunobu reaction.



Scheme 2.17 Synthesis of ribofuranosyl imidazoles by Kurahira *et al*

The intact-imidazole moiety is thus shown to be indispensable for the exclusive formation of β-anomers. Intramolecular hydrogen bonding between the nitrogen in the imidazole and OH groups in the sugar moiety should be essential to the determination of the ratio of α- *vs* β-glycosylation. Epimerization between α and β-anomers did not take place under the present reaction conditions. From these results, β-selectivity may be explained as in Scheme 2.18.[58] Reaction of the TMAD-Bu_3P adduct with **141*R*** forms the zwitterion **143*R***. Preferential elimination of Bu_3PO from **143*R*** leads to isoimidazole **144**. Spontaneous cyclization assisted by a hydrogen bond gives the β-anomer (**142β**), which is stabilized by intramolecular hydrogen bonding. Although the *S*-isomer (**141*S***) similarly leads to the active species **145,** it exclusively gave the β-anomer *via* rotomer **144** which is thermodynamically more stable. The remarkable stereoselectivity (β/α ratio 26/1) of the ribofuranosylimidazoles **142** is facilitated by electronic repulsion in **145**. The somewhat low selectivity (α/β ratio 5.4/1) of the 2′-deoxy compounds **137-140** may be due to lack of the OBn group at C-2′.[58]

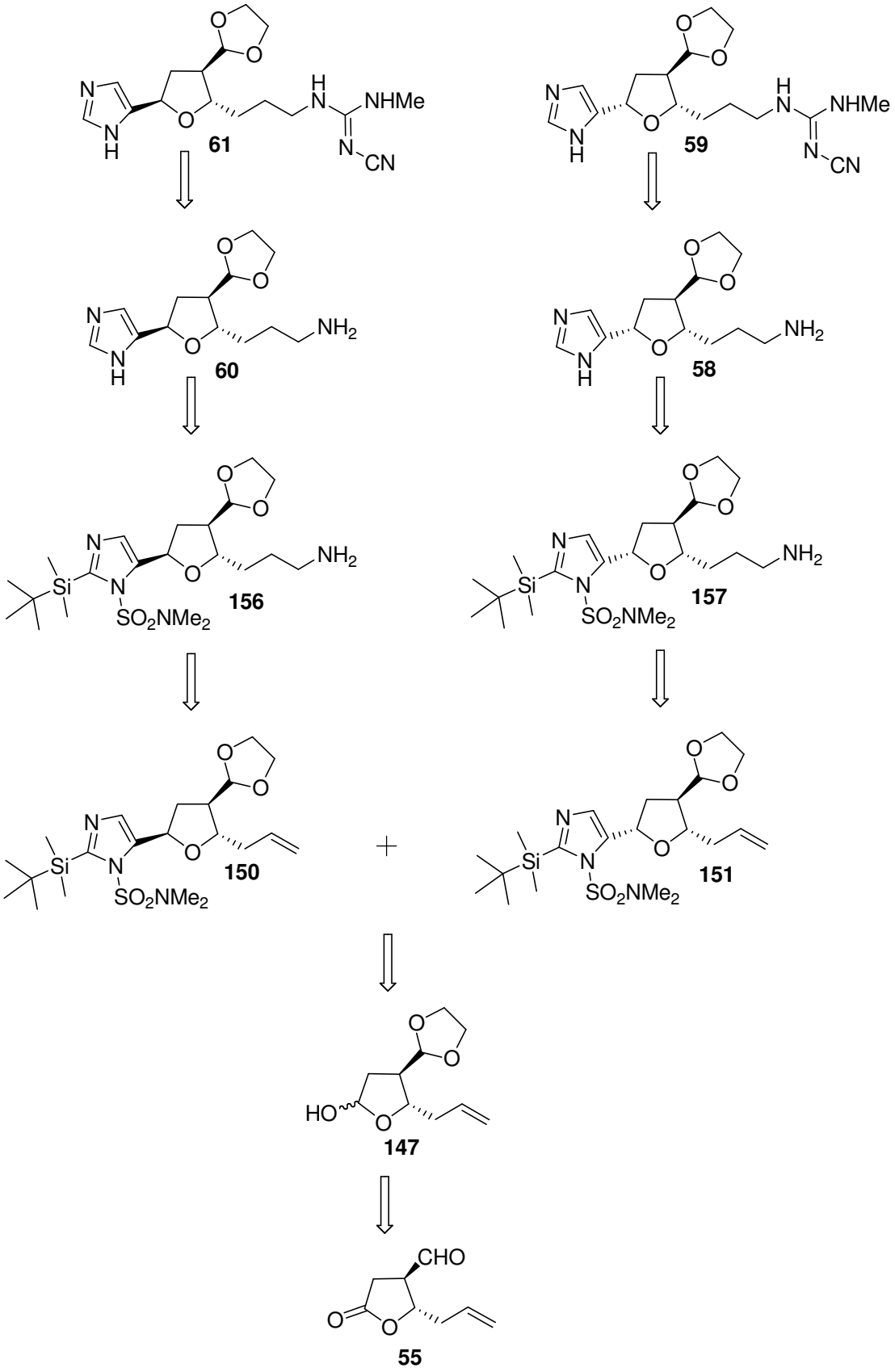


Scheme. 2.18 Mechanism of Mitsunobu cyclization via diazefulven intermediate by Kurihara *et al*

2.8 Enantioselective Synthesis of histamine H_3 and H_4 receptor potential agonists using γ-butyrolactone (GBL)-55

The retrosynthetic analysis for 'enantioselective synthesis of human histamine H_3 and H_4 receptor potential agonists' was briefly explained here based on γ-butyrolactone. The **OUP-16** analogue **61** can be obtained by introduction of cyanoguanidine on amine **60** and similarly **59** can be obtained from **58**. The amines **60** and **58** could be obtained by the deprotection of TBDMS and sulphonamide groups from **156** and **157** respectively. Synthesis of amines **156** and **157** would be possible from the corresponding building blocks **150** and **151** by hydroboration followed by phthalimidation and subsequent cleavage of phthalimide. Treatment of **147** with bisprotected imidazole **122** in presence of n-butyl lithium may obtain the diols as possibly diastereomers which can be cyclised by Mitsunobu reaction to afford the building blocks **150** and **151**. The lactol **147** can be obtained from the γ-butyrolactone **55** by

protection of aldehyde with ethylene glycol and followed by DIBAL-H reduction (Scheme 2.19).

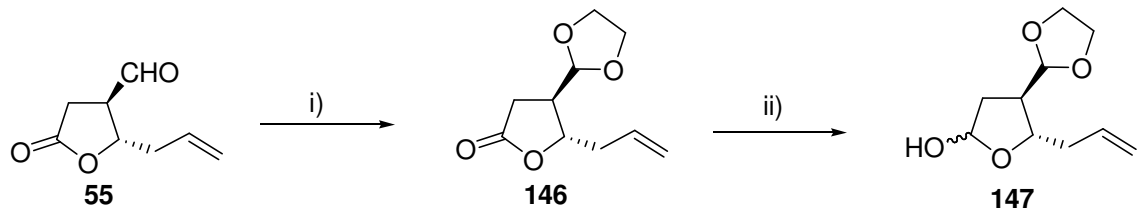


Scheme 2.19 Retrosynthetic analysis for histamine H_3 and H_4 receptor potential agonists based on γ-butyrolactone

2.8.1 Results and discussion

2.8.2 Synthesis of lactol

The aldehyde **55** was protected with ethylene glycol in the presence of catalytic amount of *para*-toluenesulfonic acid according to the known procedure.[59] Under the conditions mentioned below the aldehyde **55** gave **146** in 85% yield. DIBAL-H reduction of **146** at -78 °C for 2h, upon dilution with EA and the addition of saturated potassium sodium tartrate gave the corresponding lactol **147** in 90% yield (Scheme 2.20).[60]



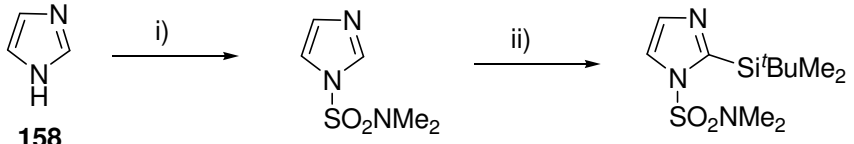
55 **146** **147**

Reagents and conditions: i) ethylene glycol (5 eq), *p*-TsOH (0.25 eq), benzene, 90 °C, 85%
ii)1.5 eq DIBAL-H (1M solution in DCM), -78 °C, 2h, 90%

Scheme 2.20 Synthesis of lactol

2.8.3 Synthesis of bisprotected imidazole

The bisprotected imidazole **122** was prepared in two steps according to the reported procedure by Chadwick and co-workers.[61] Treatment of imidazole **(158)** with *N,N*-dimethyl chlorosulfonamide and triethyl amine in benzene afforded the sulfonamide **159** in 80% yield. Further treatment of **159** with ^{n}BuLi at -70 °C in anhydrous THF gave the bisprotected imidazole **122** in 73% yield (scheme 2.21).[61,62]



158 **159** **122**

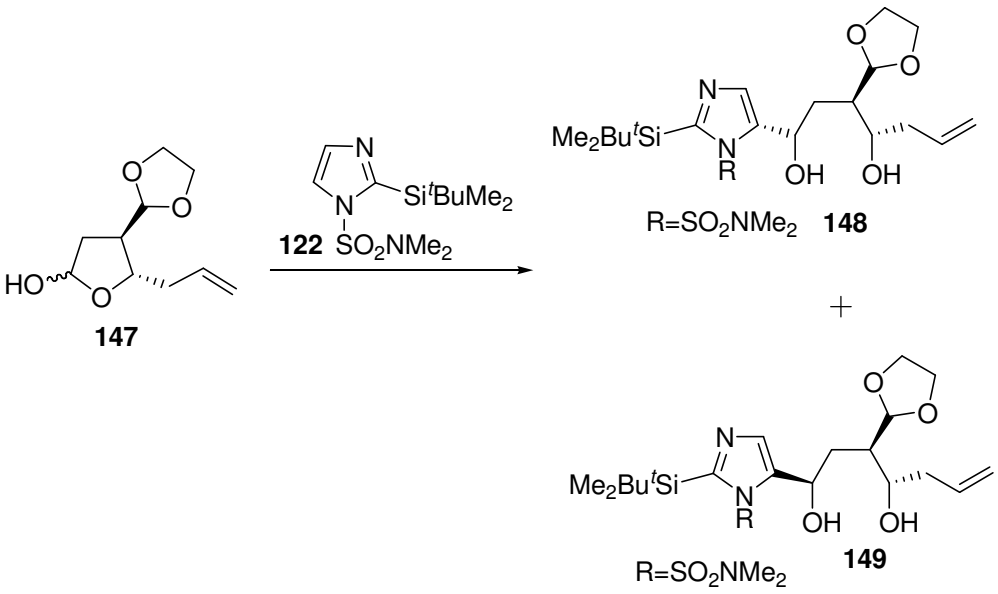
Reagents and conditions: i) Et_3N, N,N-Dimethyl sulfomoyl chloride, rt, 80%
benzene, rt 16h, ii) ^{n}BuLi, anhydrous THF, -70 °C, TBDMS-Cl, 1h, 73%

Scheme 2.21 Synthesis of Bisprotected imidazole

2.8.4 Synthesis of Imidazole-Diols

The bisprotected imidazole **122** was treated with ^{n}BuLi in THF at -70 °C to generate the anion which was subsequently reacted with lactol in THF to afford the diastereomers of the diols **148** and **149**. The anion generated at C-5 of bisprotected imidazole (**122**) was reacted on the anomeric carbon of the lactol **147** to form the C-C bond in diols **148** and **149**.[55] These diols were separated by silicagel column chromatography for further reactions to use single diastereomers (Scheme 2.22). The diols **148** and **149** were also used as mixture of

diastereomers for further synthetic transformation. Cyclization of these diols **148** and **149** was done under suitable Mitsunobu reaction conditions as explained broadly in section 2.8.5.

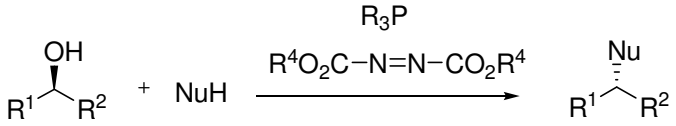


Reagents and conditions: **122** *n*-BuLi, THF, -70 °C, 1h, 90%

Scheme 2.22 Synthesis of Imidazole-diols

2.8.5 The Mitsunobu reaction

The Mitsunobu reaction is a redox combination of a trialkyl or triarylphosphine and a dialkyl azodicarboxylate for the substitution of primary or secondary alcohols with a broad range of nucleophiles.[63] Since its discovery in 1967 by Oyo Mitsunobu, this reaction is popularly known because of its versatility and effectiveness.[64,65] This mild reaction converts a hydroxyl group into a potent leaving group which can be displaced by a wide variety of nucleophiles. It has a privileged role in organic synthesis, particularly often used as a key step in natural product syntheses and medicinal chemistry because of its scope, stereospecificity.[63] This mild reaction converts a hydroxyl group into a potent leaving group which is able to displace by a wide variety of nucleophiles for the synthesis of broad range of compounds from esters, ethers, amines, azides, cyanides, thiocyanides, thioesters, and thioethers (Scheme 2.23).[63]



NuH = RC(O)OH, RC(O)SH, ArOH, ArSH, R_2NH, N_3H, NH_4SCN, etc

Scheme 2.23 Mitsunobu reaction with various nucleophiles

The Mitsunobu reaction has been proved to be a diverse, useful and practical method for C-O, C-N, C-C and C-X bond formation, among other uses in organic synthesis. It is also used for the inversion of asymmetric alcohols, formation of cyclic ethers, epoxides, amines, β-

lactams,[66,67] macrolactonization,[68] nucleosides synthesis,[69] dehydration[70] and carbon chain elongation.[71] Its mild reaction conditions and excellent stereoselectivity make it an excellent reaction that serves its purpose well. There is no doubt that it will continue to be an important synthetic tool for the practicing organic chemist. Some advantages and disadvantages about this reaction are described below.

Advantages

1) A mild, one-pot reaction 2) Typically gives good yields and high stereospecificity

3) Tolerates many functional groups 4) A wide range of nucleophiles are accepted.

Disadvantages

1) Byproducts are difficult to remove 2) Not very atom economical 3) Some of the reagents are expensive.

Here are some Mitsunobu reagents known in the literature as shown below (Figure 2.6).[72]

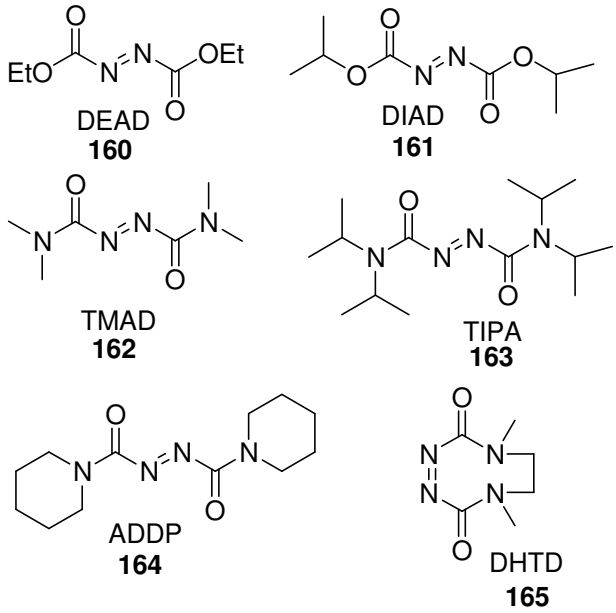


Figure 2.6 Mitsunobu reagents

Chiral secondary alcohols undergo a *complete inversion* of configuration unless they are sterically very congested.[73-75] The nucleophile is normally a relatively acidic compound containing an O-H, S-H, or an N-H group with p*K*a having less than or equal to 15, preferably below 11. The preferred phosphorus (III) component is triphenylphosphine (Ph_3P) or tributylphosphine (*n*-Bu_3P), both are inexpensive and commercially available. Generally, the Ph_3P-DEAD/DIAD system is useful for acidic nucleophiles with pK_a < 11. For those having a p*K*a > 11, more active coupling reagents such as 1,1-(azodicarbonyl)dipiperidine (ADDP), 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHDT) and *N*,*N*,*N*′,*N*′-tetramethylazo dicarboxamide (TMAD). Modification of the organic group on the

azodicarboxylate can afford these reagents. Recently Tsunoda and coworkers[76] have reported the above DEAD alternatives of increased basicity that allow carbon nucleophiles having higher pKa's to be used as nucleophiles.[77,78]

The mechanistic details of the Mitsunobu reaction, particularly at the intermediate stages, are still a subject of debate and intensive studies.[63,75,79,80] A feasible pathway of the esterification process is shown in Figure 2.7. The first step is the irreversible formation of the Morrison-Brunn-Huisgen (MBH) betaine intermediate **167** by phosphine and azodicarboxylate (**166**), the identity of betaine has been established by multinuclear NMR.[63] MBH **167** is able to deprotonate the nucleophile in step 2 and the resulting carboxylate anion deprotonates the alcohol forming an alkoxide which can attack the betaine at phosphorus eventually forming the pentacoordinated phosphorane **169** and oxyphosphonium ion **170** (step 3).[63] In step 4 the carboxylate anion participates in a bimolecular nucleophilic displacement of triphenylphosphine oxide which proceeds with inversion. It is generally accepted that the oxyphosphonium ion **170** is the active intermediate which undergoes S_N2 displacement. The other species probably play a spectator roles although **172** (acylphosphonium salt) may indeed be the active intermediate when the attempted inversion of hindered secondary alcohols yields esters with retained stereochemistry.[81] Finally the hydrazine $RO_2CNH\text{-}NHCO_2R$ and phosphine oxide $Ph_3P(O)$ are formed as byproducts in Mitsunobu reaction.

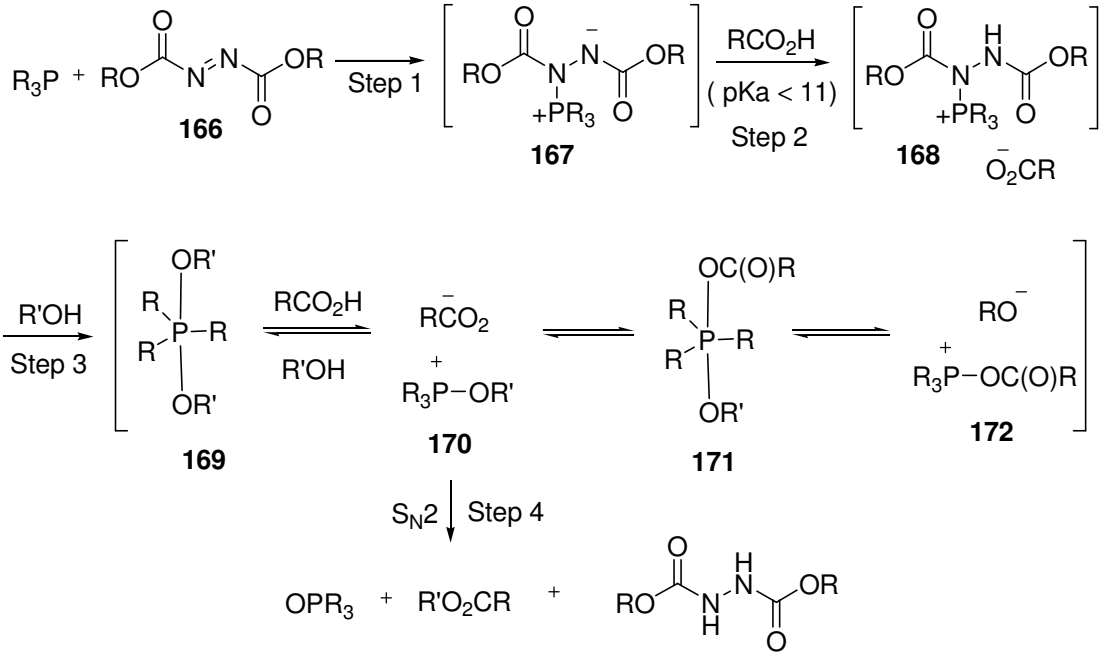


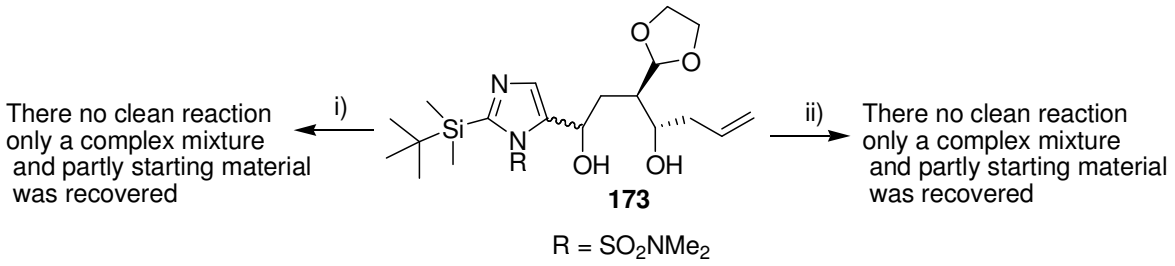
Figure 2.7 General mechanism of Mitsunobu esterification

Acids of lower pK_a have been shown to give higher yields of inverted products when the alcohol is sterically hindered. The proposed reason for this increased activity is the evidence that acids of lower pK_a tend to favor the oxyphosphonium intermediate **170** over the less

reactive phosphane **171**.[82,83] The intermolecular formation of aliphatic ethers is unfortunately hindered by the fact that the betaine intermediate is not basic enough to sufficiently deprotonate the weakly acidic hydroxyl group. However, formation of cyclic ethers via intramolecular condensation proceeds in good yields.[84,85]

The difficulty with the Mitsunobu reaction is that the isolation and purification of the desired product requires separation from phosphine oxide and hydrazinedicarboxylate byproducts. Various ways of addressing this problem have been developed by modifying triphenylphosphine or azo dicarboxylate reagents to facilitate isolation and purification of the products. Few methodologies are established with their own limitations, including acidic or basic aqueous workup, applying novel ring opening metathesis (ROM) protocols, post reaction sequestration (solution or solid-phase reaction), and polymer assisted phase-switching or solid phase immobilization.[86,87] The use of polystyryldiphenylphosphine resin can circumvent the problem of removal of triphenylphosphine oxide because the resulting phosphine oxide is also anchored to the polymer and it can be readily filtered off.[63] Reduction of the phosphine oxide back to reusable resin can be effected by treating it with trichlorosilane.[63,88] Polymer-supported triphenylphosphine prepared from bromopolystyrene has also been used for esterification reactions.[89,90]

Zaragoza and Stephensen have reported that fmoc protected amino acids esterified with Wang resin reacted with aliphatic alcohols in the presence of *n*-Bu_3P-ADDP/*i*-Pr_2NEt or Et_3N to yield *O*-alkyl carbamates that are suitable for robotic synthesizers.[63,91] Here the substrate was polymer bound, but not the reagents.[63] They also noted that primary alcohols gave good results, but yields using secondary alcohols were not satisfactory.[63] Peroxisome proliferator-activated receptors (PPARs) have great potential as pharmaceutical targets for many applications.[63] Humphries *et al* have disclosed a method for the synthesis of PPAR agonists using the PS-PPh_3-ADDP reagent system.[63,92] A solid phase synthesis of AChE inhibitors was developed by Leonetti *et al*.[93] where they used *n*-Bu_3P-ADDP in CH_2Cl_2. Recently, a polymer bound azodicarboxylate and anthracene tagged phosphine for the Mitsunobu reaction leading to phthalimides, esters, as well as ethers has been reported by Lan *et al*.[94] The authors pointed out that the azodicarboxylate and its corresponding hydrazine product could be readily separated from the desired products by simple filtration.[63] Curran and co-workers have been developed new approaches to circumvent the problem of separation by using new fluorous tagged azodicarboxylate reagents, and fluorous phosphine in the Mitsunobu reaction.[95,96] The byproducts could be separated either by fluorous flash chromatography or fluorous solid-phase separation.[63,95]



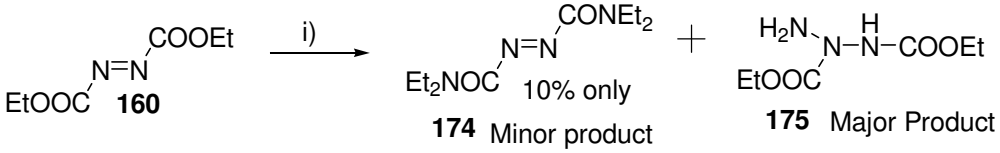
173

$R = SO_2NMe_2$

Reagents and conditions: i) DEAD, Ph_3P, benzene, rt, 18h; ii) DIAD, Ph_3P, benzene, rt, 18h

Scheme 2.24 Mitsunobu cyclization of diastereomeric diol

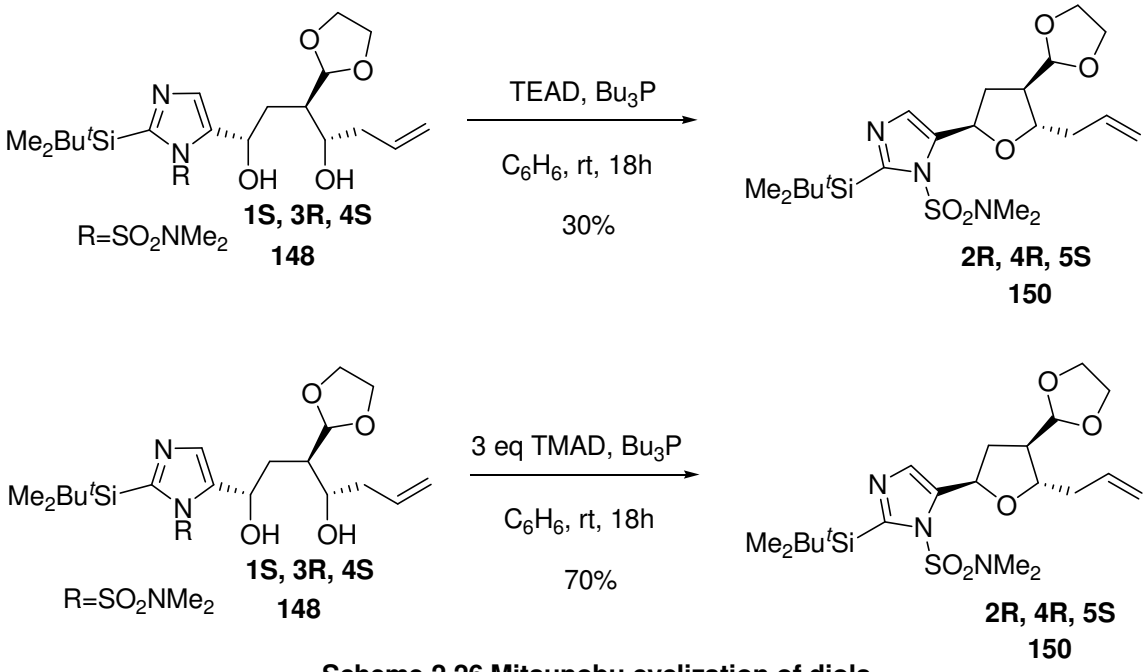
In our case, the Mitsunobu cyclization was first carried out under standard Mitsunobu conditions by using Diethylazodicarboxylate (DEAD) and triphenylphosphine (PPh_3). The expected product was not formed, but only a complex mixture of reagents and starting material was observed (Figure 2.24). The reaction also did not work with DIAD (diisopropyl azodicarboxylate) and tributylphosphine. To investigate this problem the reaction was studied in detail to achieve the target product with desired stereochemistry. The search for a suitable Mitsunobu reagent revealed tetraethyl azodicarboxylate (TEAD) **174** as an alternative to tetramethyl azodicarboxylate (TMAD) **162** and azodicarboxylate dipyrrolidine **176** as an alternative to azodicarboxylate dipiperidine (ADDP) **164**. When DEAD was treated with diethyl amine at 0 °C in ether, TEAD was formed as minor product only about 10% yield. The major product was isolated as hydrazine derivative. This can be explained by addition of diethyl amine to nitrogen of the azo centre rather then the ester carbonyl (Scheme 2.25).[97]



Reagents and conditions: i) Diethyl amine, anhydrous ether, 0 °C, 2h

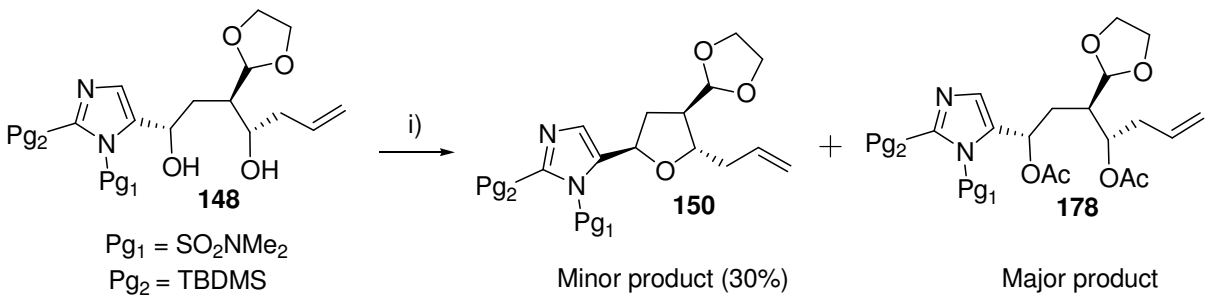
Scheme 2.25 Preparation of N,N,N′,N′ tetraethylazodicarboxylate (TEAD)

The cyclization of the diols was done with the above prepared TEAD reagent but the product was formed with very low yield. To overcome all these problems the reaction was tested with tetramethylazodicarboxylate (TMAD). The diol was treated with 3 eq of TMAD in presence of tributylphosphine in benzene at room temperature to obtain the cyclized product in about 70% yield (Scheme 2.26). The same condition was applied to convert diol **149** to **151** *cis* isomer which gave little bit lower yield compare to *trans* isomer.



Scheme 2.26 Mitsunobu cyclization of diols

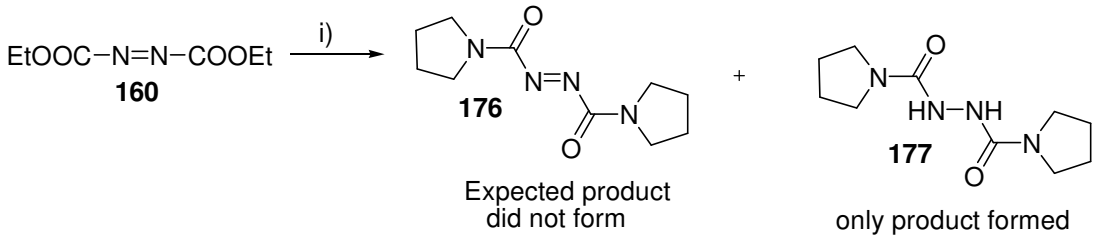
Toy and co-workers have introduced $PhI(OAc)_2$, an additional component to use only a catalytic amount (10 mol %) of the expensive azodicarboxylate reagents.[98] This methodology was applied here to convert **148** to **150** by using 10 mol % of TMAD, 3 equivalents of tributylphosphine and 3 equivalents of $PhI(OAc)_2$ however, only 30% yield of **150** was observed under these conditions and as the major product the undesired **178** was isolated (Scheme 2.27). $PhI(OAc)_2$ converts hydrazine byproducts back to the azodicarboxylate but acetic acid is a byproduct which may interfere in the expected reaction. As long as acetic acid does not interfere in the expected reaction, this methodology could be a very useful one. This idea of "organocatalytic" cycle is quite novel and needs further exploration to view the scope of this reaction to avoid the stoichiometric use of expensive azodicarboxylate reagents.



Reagents and conditions: i) TMAD (10 mol%), Bu_3P, $PhI(OAc)_2$, benzene, rt, 18h

Scheme 2.27 Mitsunobu cyclization with 10 mol% TMAD

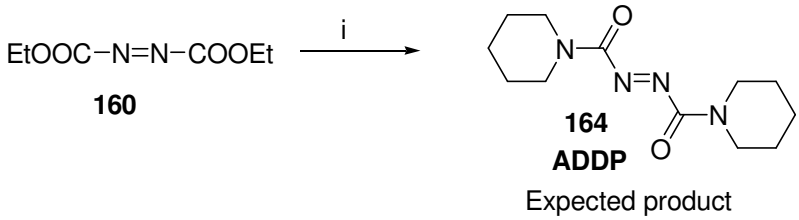
The treatment of DEAD (**160)** with pyrrolidine at 0 °C in anhydrous ether did not give the expected product **176** even as minor product, instead only the hydrazine by product **177** was observed (Scheme 2.28).



Reagents and conditions i) Pyrrolidine, dry Et_2O, 0 °C, 2h

Scheme 2.28 Preparation of pyrrolidine based Mitsunobu reagent

The final attempt for the suitable Mitsunobu reagent was investigated by treating DEAD (**160**) with piperidine at 0 °C in ether to form the corresponding reagent azodicarbonyl dipepiredine (ADDP) which was successful and the product **164** was obtained in good yield (Scheme 2.29).[97]



Reagents and conditions: i) Piperidine, dry ether, 0 °C, 2h, 74%

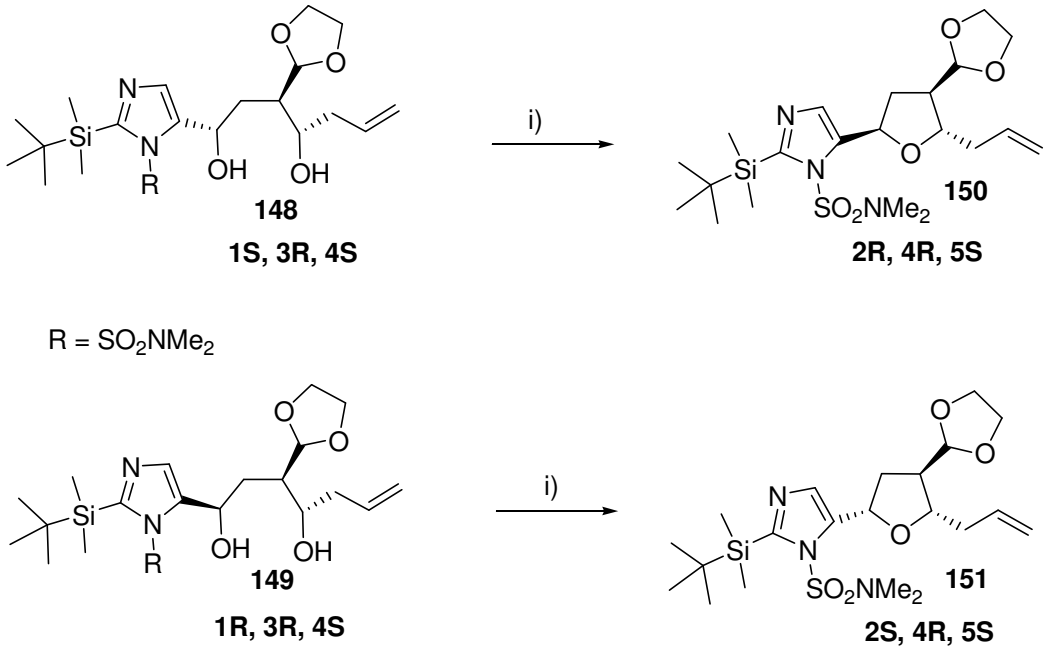
Scheme 2.29 Preparation of Azodicarbonyldipepiredine (ADDP)

Tsunoda *et al.*[78] reported 1,1′-(azodicarbonyl)-dipiperidine (ADDP)-Bu_3P and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)-Bu_3P as new reagent systems for the Mitsunobu reaction, and Kurihara *et al.* applied these methods to the cyclization of unsubstituted imidazole diols.[55] Treatment of the mixture with ADDP-Bu_3P afforded the β-anomer having an unsubstituted imidazole in modest yield. The authors also reported that (TMAD)-Bu_3P system obtained the products in good to excellent yield.

As mentioned in scheme 2.26 when TMAD-Bu_3P system used as Mitsunobu conditions the cyclization of substituted imidazole diols (**148** and **149**) afforded the products (**150** and **151**) in about 70% yield. Interestingly when ADDP-Bu_3P system used as Mitsunobu conditions the cyclization of substituted imidazole diols (**148** and **149**) afforded the products (**150** and **151**) in about 80% yield as shown in scheme 2.30. These results clearly suggested us that use of inexpensive reagent ADDP gave more yield than expensive TMAD in our case.

Yokoyama *et al.*[99] reported synthesis of *C*-ribonucleosides having typical aromatic heterocycles, in which the cyclization of the corresponding diols proceeds through intramolecular S_N2 reaction under Mitsunobu conditions. The orientation of the glycosidic linkage is controlled by the C1 configuration of the substrate: one isomer (1*R*) affords an α-anomer and the other isomer (1*S*) gave β-anomer.[55,58] Thus, Mitsunobu cyclizations of **148**

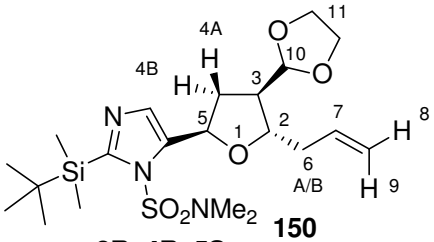
(1*S*) and its diastereomer **149** (1*R*) are required selective formations of C1-oxyphosphonium intermediates to obtain products with high optical purities.[55]



Reagents and conditions: i) ADDP (3 eq), Bu_3P, benzene, rt,18h, 80%

Scheme 2.30 Mitsunobu cyclization of diols with ADDP

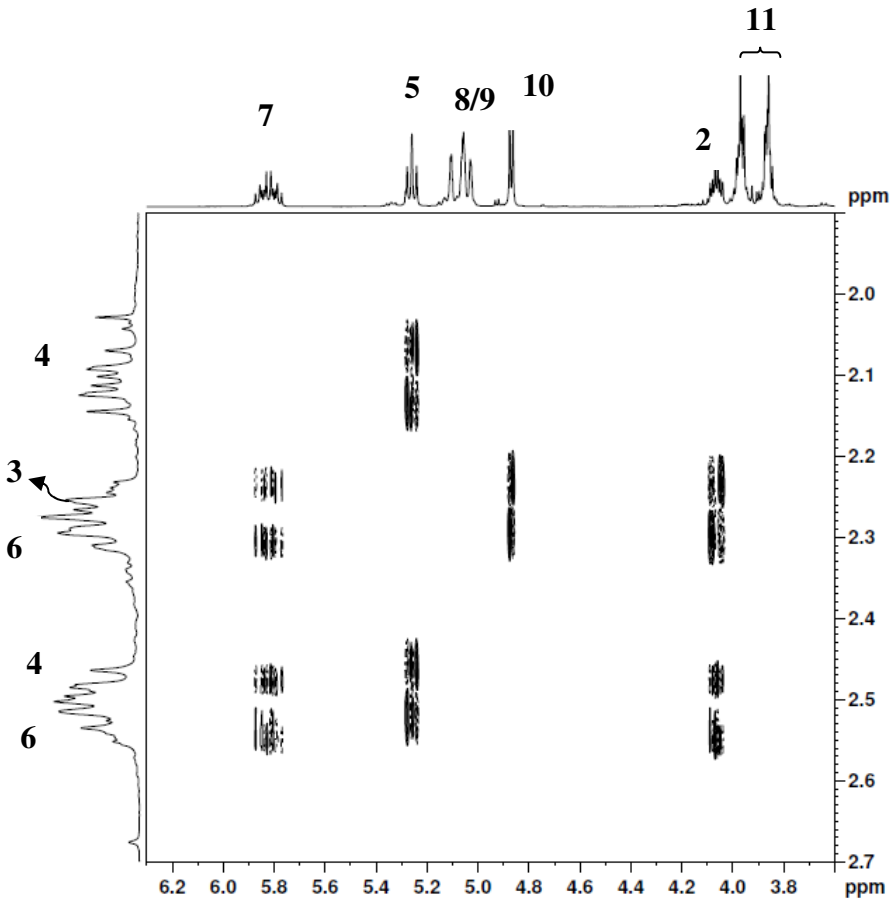
The cyclization of **148** and **149** proceded under Mitsunobu condition (ADDP-Bu_3P) is stereoselective intramolecular S_N2 reaction as reported by Yokoyama *et al*.[99] The orientation of the glycosidation is controlled by the C1 configuration of the substrates **148** and **149**, thus one isomer **148** (1*S*) gave β-anomer **150** (2*R*) and the other isomer **149** (1*R*) affords an α-anomer **151** (2*S*) as shown in scheme 2.30.[55] The stereochemistry of both **150** and **151** were determined by COSY and NOE experiments which supports that the configuration in **150** as 2*R* and in **151** as 2*S*. The high optical purity of these products were confirmed by optical rotation and chiral HPLC, which shows that, this strategy is enantioselective for the synthesis of analogues of histamine H_3 and H_4 receptor agonists. The Optical purity of **150** was determined as $[\alpha]_D^{24}$ – 49.5 (c 1.0, $CHCl_3$) and **151** as $[\alpha]_D^{24}$ + 15.7 (c 1.0, $CHCl_3$).

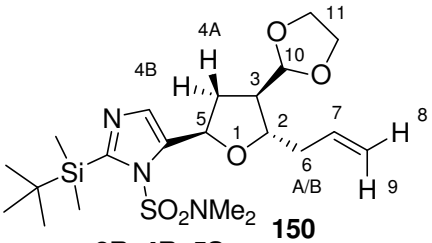


150

2R, 4R, 5S

COSY Spectrum

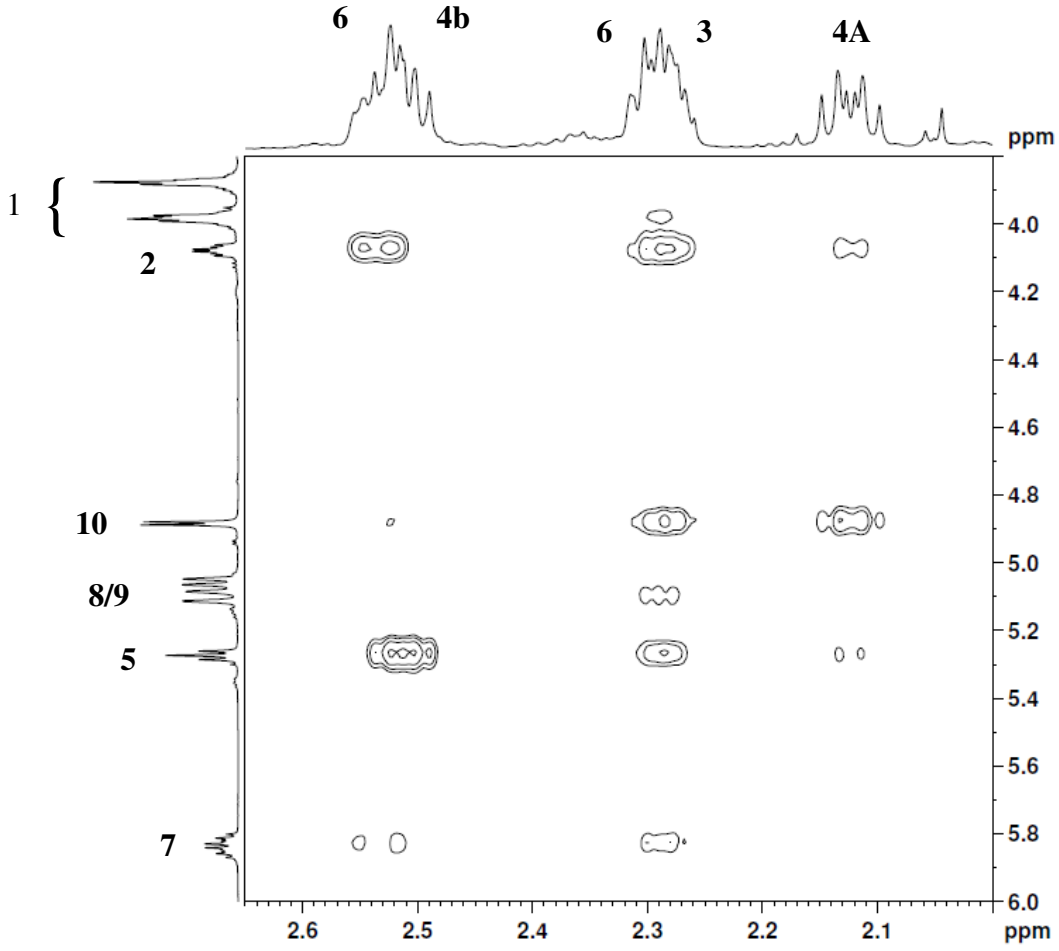


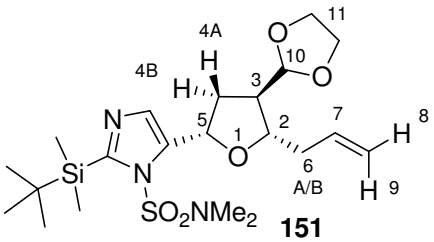


150

2R, 4R, 5S

NOESY Spectrum

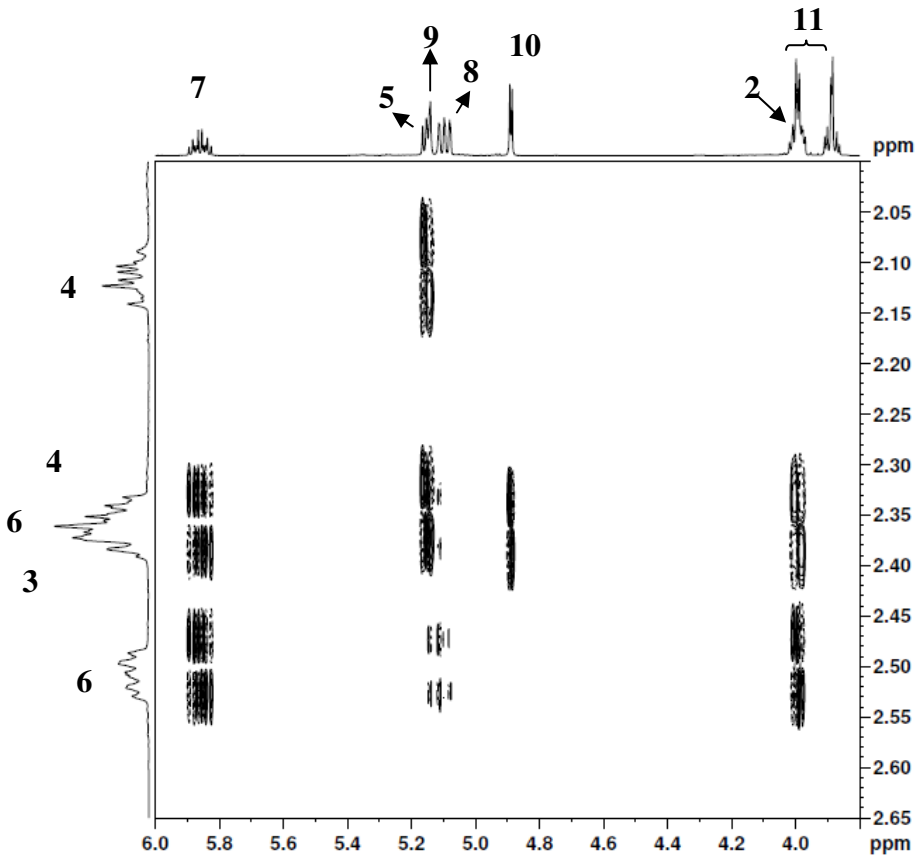


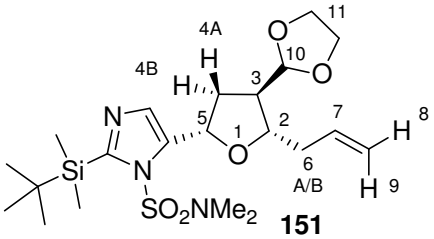


151

2S, 4R, 5S

COSY spectrum

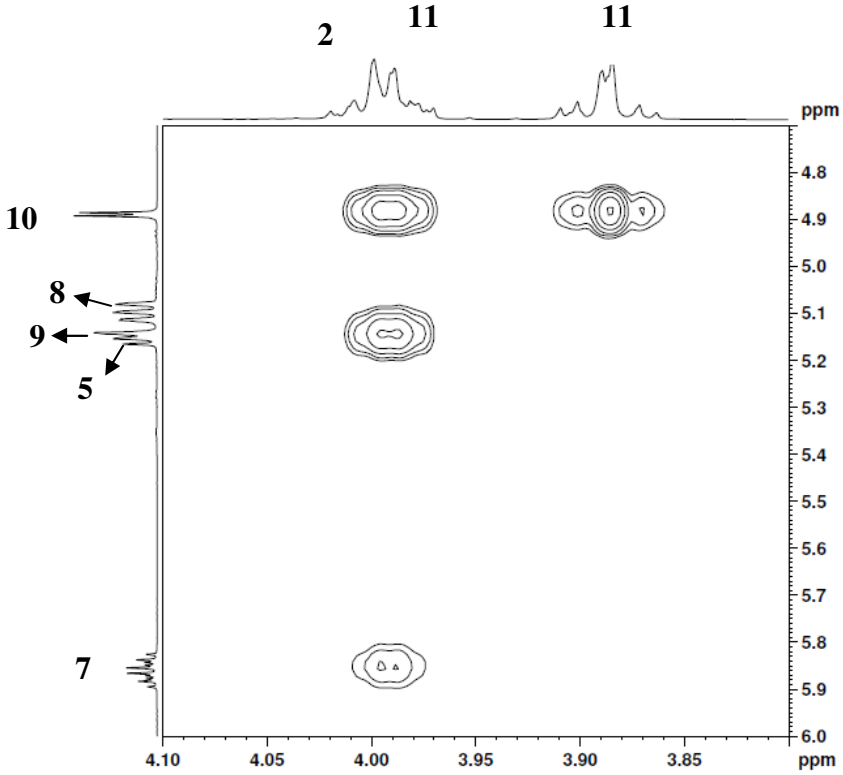




151

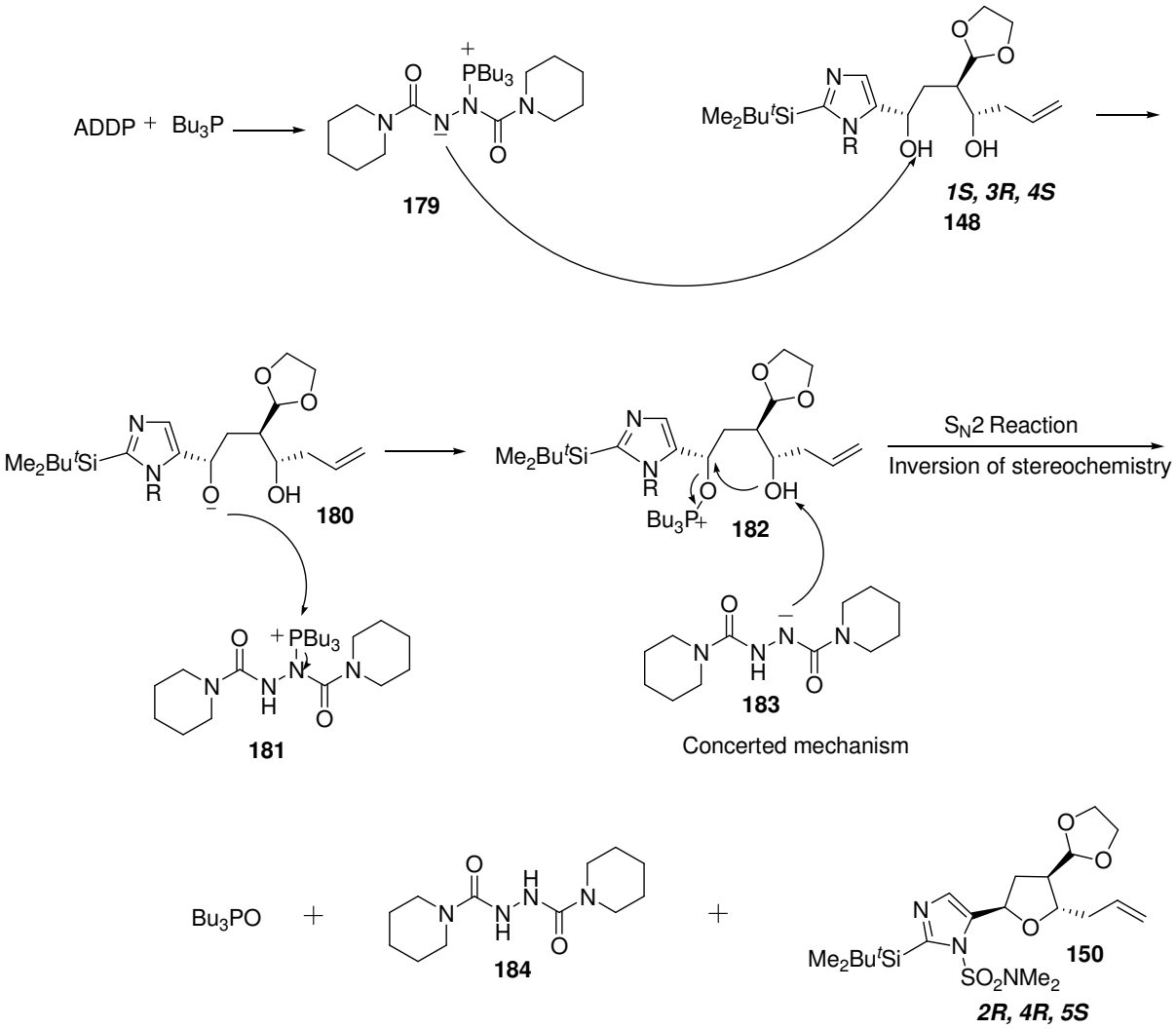
2S, 4R, 5S

NOESY spectrum



The plausible mechanism for the cyclization of diols **148** and **149** was explained incontrast to diazafulvene intermediate and according to stereoselective cyclization of Mitsunobu reaction as reported by Yokoyama *et al*.[99] This plausible mechanism also supports the Mitsunobu cyclization of diols bearing monosubstituted or disubstituted imidazole proceeds via a S_N2 process of standard Mitsunobu reaction as mentioned by Kurihara *et al*.[58] In our case the diols **148** and **149** having bisprotected imidazoles (sulfonamide and TBDMS protecting groups) are electron deficient aromatic rings (since sulfonamide is electron withdrawing group) which do not favour to undergo diazafulvene rearrangement (see Scheme 2.18). The feasible mechanism is suggested in scheme 2.31. ADDP and tributyl phosphin forms betain intermediate (MBH) **179** which can pick up a proton from 1-hydroxy group of *1S* diol **148** and affords alkoxide anion **180.** This alkoxide anion can attack on phosphorous of **181** eventually lead to the oxyphosphonium intermediate **182**. This oxyphosphonium intermediate can undergo stereospecific S_N2 type cyclization by concerted mechanism to obtain the

required product **150** and delivers the byproducts tributyl phosphine and hydrazine derivative **184** (Scheme 2.31). Similarly diol **149** undergo same mechanism to furnish **151**. It is believed that the cyclization of diols **148** and **149** proceeds through normal intramolecular S_N2 mechanism as shown in scheme 2.31 which supports the stereoselective cyclization of Mitsunobu reaction as reported by Yokoyama *et al*.[99]



Scheme 2.31 Plausible mechanism of Mitsunobu cyclization of Imidazole diols

Hydroboration of **150** and **151** did not work with catecholborane, 9-BBN and acetoxyborohydride. The hydroboration was studied in detailed to overcome the problem of reactions with **150** and **151**.

2.8.6 Hydroboration

In 1936 diborane, B_2H_6, a rare substance, prepared in less than gram quantities in only two laboratories, that of Alfred Stock at Karlsruhe, Germany and of H. I. Schlesinger, at the University of Chicago, USA.[100] The existence of simplest hydrogen compound of boron, not as BH_3, but as B_2H_6, was considered to constitute a serious problem for the electronic theory

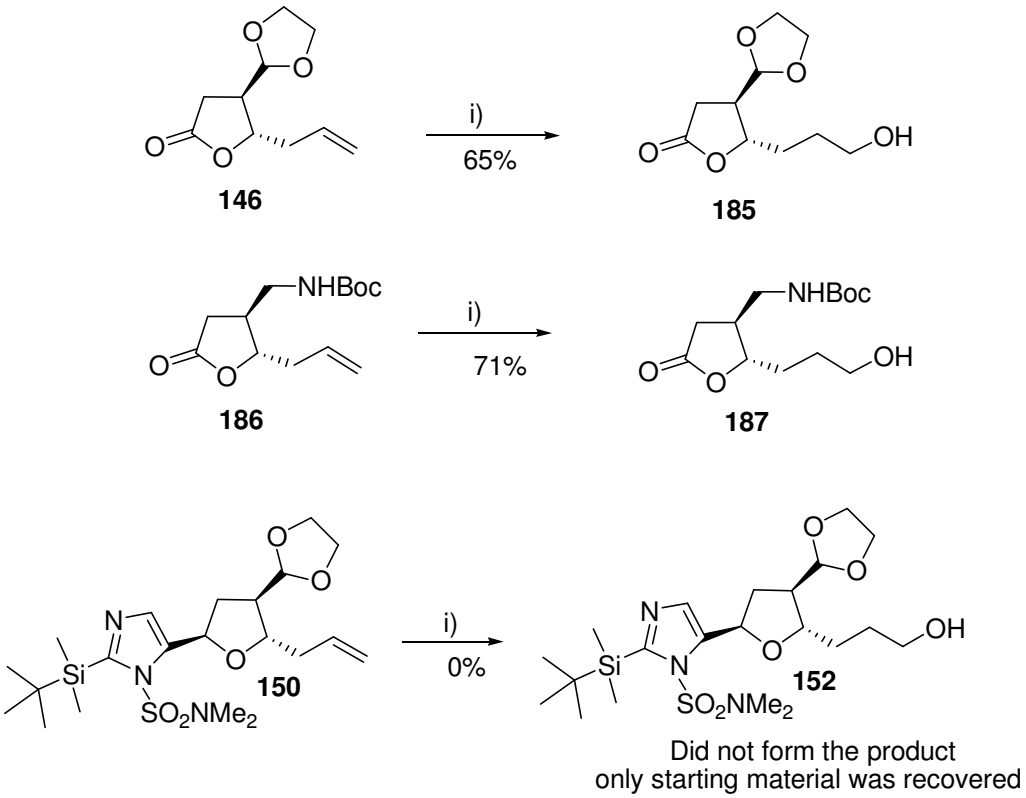
of G. N. Lewis.[101] The reactions of diborane were under study at the University of Chicago by H. I. Schlesinger and Anton B. Burg, in the hope that a knowledge of the chemistry would aid in resolving the structural problem.

Investigation of selective reductions by Brown and coworkers, a minor anomaly resulted in the discovery of hydroboration.[102] Brown's coworker, B. C. Subba Rao, was examining the reducing characteristics of sodium borohydride in diglyme catalyzed by aluminum chloride.[103] Investigation soon established that the reagent was adding an H-B, bond to the carbon-carbon double bond to form the corresponding organoborane.[104,105] The process of producing organoboranes by the addition of a compound with a B-H bond to an unsaturated hydrocarbon is called as hydroboration. Subba Rao established that oxidation of such organoboranes, in situ, with alkaline hydrogen peroxide, proceeds quantitatively, producing alcohols.[105-107]

It was soon established that the addition proceeds in an anti-Markovnikov manner. The reaction involves a *cis*-addition of the H-B bond. The addition takes place preferentially from the less hindered side of the double bond. No rearrangement of the carbon skeleton was observed, even in the molecules as labile as α-pinene. Most functional groups can tolerate hydroboration. The hydroboration of a simple olefines generally proceeds directly to the formation of the trialkylborane. However, in a number of instances it has been possible to control the hydroboration to achieve the synthesis of monoalkyl boranes, dialkylboranes, and cyclic, bicyclic boranes. Many of these reagents such as thexylborane, disiamylborane, dipinylborane (IPC_2BH) and 9-borabicyclo-(3.3.1)-nonane (9-BBN) have proven to be valuable in overcoming problems encountered with the use of diborane itself.[102,108,109]

2.8.7 Hydroboration of cyclic buiding blocks

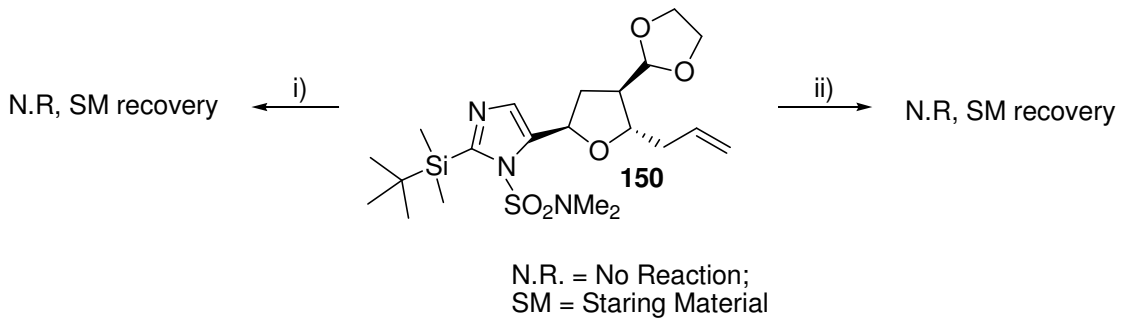
The transition metal catalyzed hydroboration of olefins represent conventional approaches towards regioselective synthesis of alcohols. There are few methods available efficiently for the rhodium-catalyzed olefin addition reactions.[110] This method has been used in our research group for the conversion of allylic double bond of γ-butyrolactone derived olefins to the corresponding primary alcohols using catecholborane in presence of Wilkinson catalyst.[111] When olefins **146** and **186** were treated with catecholborane in presence of Wilkinson catalyst, obtained the primary alcohols **185**[112] and **187**[113] in 65% and 71% respectively. But under the same conditions olefin **150** did not proceed to obtain the alcohol **152** and only starting material was recovered quantitatively (Scheme 2.32). The reason may be due to the imidazole moiety in olefin **150,** the catalyst may not be active enough to form the oxidative addition species to proceed the reaction.



Reagents and conditions: i) $Rh(PPh_3)_3Cl$, Catechol borane, THF, H_2O_2, 0 °C-rt, 12h

Scheme 2.32 Hydroboration with catechol borane

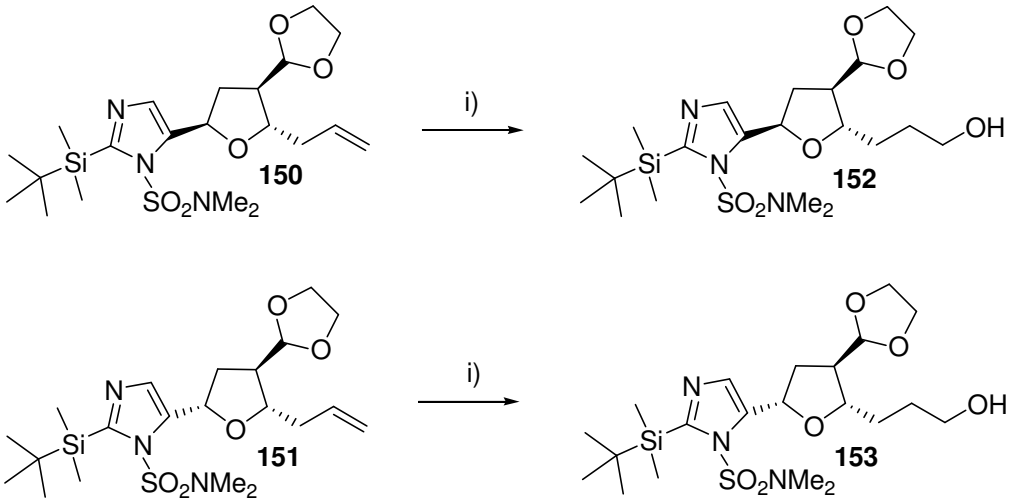
Periasamy and coworkers reported the conversion of olefins to alcohols by using acetoxyborohydride method.[114,115] Simple addition of sodium borohydride to acetic acid could generate acetoxyborohydride in situ which can react with variety of olefins to obtain the alcohols. When olefin **150** was treated with acetoxyborohydride which was generated by addition of sodium borohydride to acetic acid, unfortunately this reaction did not work even after stirring the reaction mixture from 0 °C to room temperature for 24 hours. Under these conditions only the starting material was recovered quantitatively. Then the hydroboration of **150** was done with 9-BBN but again only the starting material was recovered. It may be because of sterically bulky borane hydride not able to react with olefin **150** (Scheme 2.32).



Reagents and conditions: i) $AcOH/NaBH_4$,THF, 0 ℃-rt, 24h ii) 9-BBN, THF, H_2O_2, rt,12h

Scheme 2.33 Hydroboration on cyclic building block

Knochel *et al.* reported the remote C-H activation of phenyl substituted alkenes by using BH_3.THF.[116] The authors used diborane at 50 °C to obtain the alcohols in 24 hours. Under these conditions when olefin **150** was subjected to diborane the starting material was completely disappeared with in 8h at 50 °C, further addition of 2M NaOH followed by oxidation with hydrogen peroxide obtained the alcohol in very good yield. Later the reaction was standardized without heating and only at room temperature with additional stirring of 2-3 hours. Olefin **150** was treated with diborane at room temperature for 12 hours and further oxidation of organoborane with hydrogen peroxide obtained the alcohol **152** in 80% yield (Scheme 2.34). Under the same conditions olefin **151** furnished the alcohol **153**.

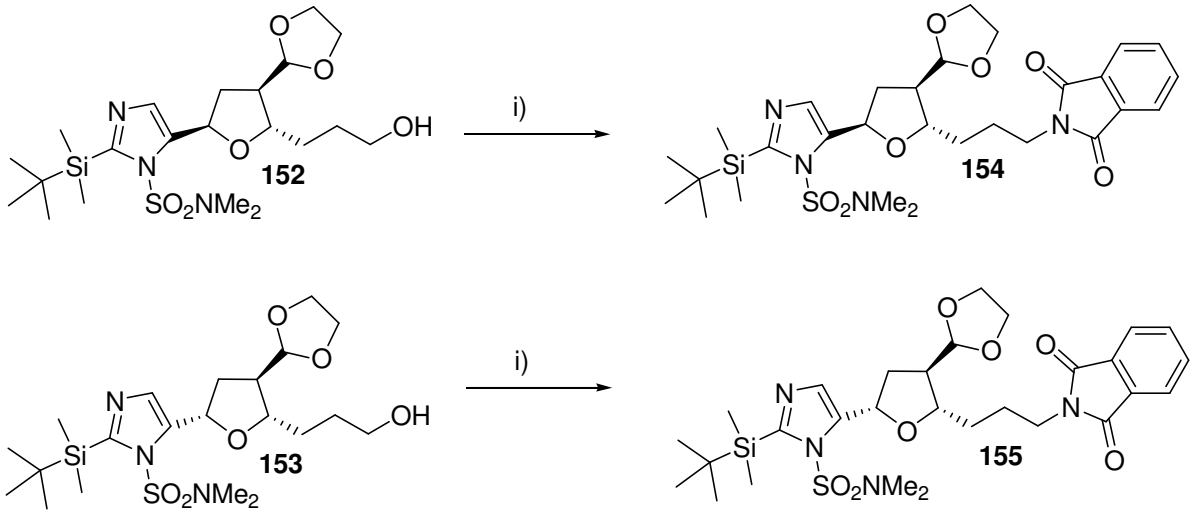


Reagents and conditions: i) BH_3.THF, THF, rt, 12h, 2M NaOH/H_2O_2, 5h, 80%.

Scheme 2.34 Hydroboration with diborane

2.8.8 Phthalimidation

In 1972, Mitsunobu reported the formation of amines from alcohols via phthalimide and subsequent reduction with hydrazine.[117] Amines are also accessible via Staudinger reductions of azides which are formed in excellent yields using HN_3 under Mitsunobu conditions.[118] The primary alcohols **152** and **153** were subjected to phthalimidation using phthalimide, diethylazodicarboxylate and triphenylphosphine under standard Mitsunobu phthalimidation conditions to get the phthalimides **154** and **155** as C-N bond forming reactions in 65% yield (Scheme 2.34).

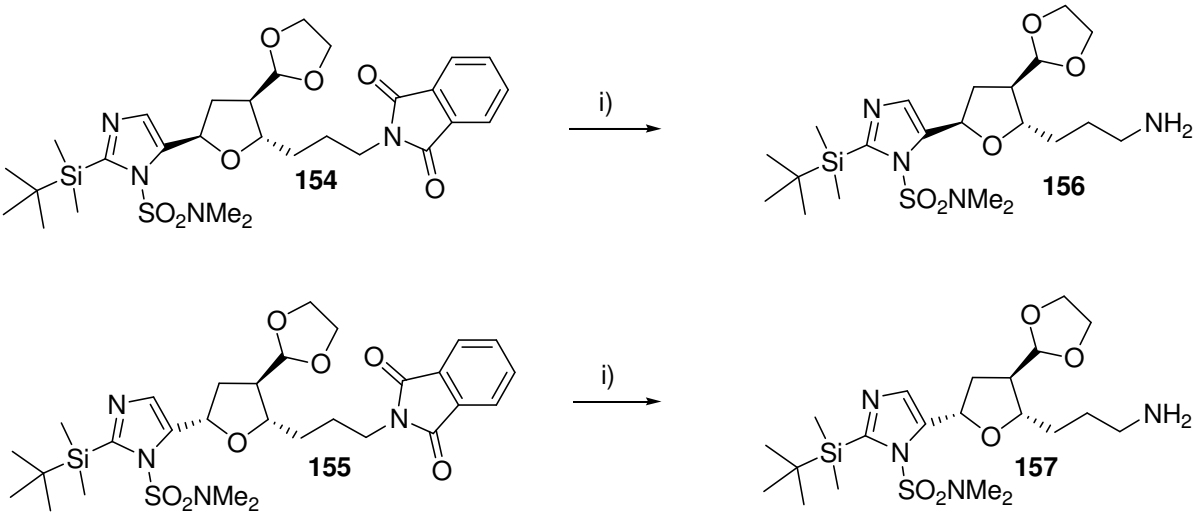


Reagents and conditions: Phthalimide, PPh_3, DEAD, rt, 12h, 65%

Scheme 2.34 Synthesis of phthalimides

2.8.9 Synthesis of amines

The reductive cleavage of phthalimides was done under basic hydrolysis conditions.[117] Phthalimides **154** and **155** were treated with hydrazine hydrate in ethanol at room temperature obtained the primary amines **156** and **157** in 76% yield (Scheme 2.35).



Reagents and conditions: i) $N_2H_4.H_2O$, EtOH, rt, 12h, 76%

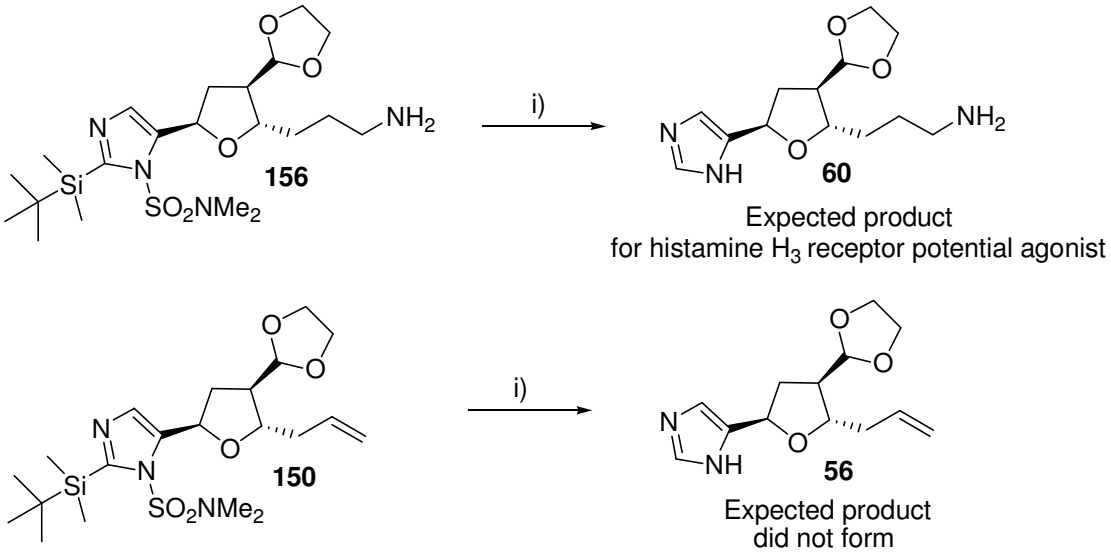
Scheme 2.35 Synthesis of amines

2.9.0 Deprotection of TBDMS and Sulfonamide groups

The deprotection of sulfonamide was done under acidic conditions using HCl as reported by Kurihara *et al.*[53-56] Using HCl under the conditions mentioned by Kurihara *et al* when **156** and **150** were subjected to acidic hydrolysis, only TBDMS was deprotected and sulfonamide did not deprotect. The reaction was done with 1.5 N HCl, there was only starting material left even after refluxing for 24h. Then the concentration was increased to 3N and 6N even after

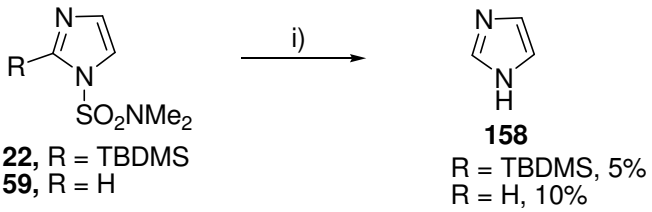
refluxing 24h there is no product formation. Only starting material was recovered. The deprotection was also done with TFA[119] and sulfuric acid[120] but in both the cases only starting material was recovered. The deprotection of sulfonamide was done under basic conditions with KOH[121] and also with K_2CO_3/thiophenol[122] in both cases only starting material was recovered. The deprotection was also done with Na/liq ammonia,[123] Na/Naphthalene,[124] Na-Hg[125] in all three cases either starting material was recovered or only a complex mixture was observed. Then the reaction was done by using most of the known methods in the literature for the deprotection of sulfonamide like, TBAF,[126] TMSI,[127] 1,3-diaminopropane in microwave,[128] Mg in methanol[129] and SmI_2 in THF[130] to get the target molecule. But in all the cases deprotection was not successful.

The reaction was carried out on final target molecule, later on when it was not successful then the model studies were done on the cyclic building block and also on imidazole sulfonamide none of them were successful. The deprotection on simple imidazole sulfonamide gave very low yield (10%) with HCl (Schemes 2.36 and 2.37). The reaction profile was illustrated in the table 3. Deprotection of sulfonamide was not successful with various reagents and different reaction conditions as shown in the table 3.



Reagents and conditions: i) 1.5 N HCl, Ethanol, reflux, 12h

Scheme 2.36 Deprotection of TBDMS and sulfonamide



Reagents and conditions: i) 1.5 N HCl, Ethanol, reflux, 12h

Scheme 2.37 Deprotection of sulfonamide on model substrate

Table 3. Deprotection of sulfonamide under different reaction conditions

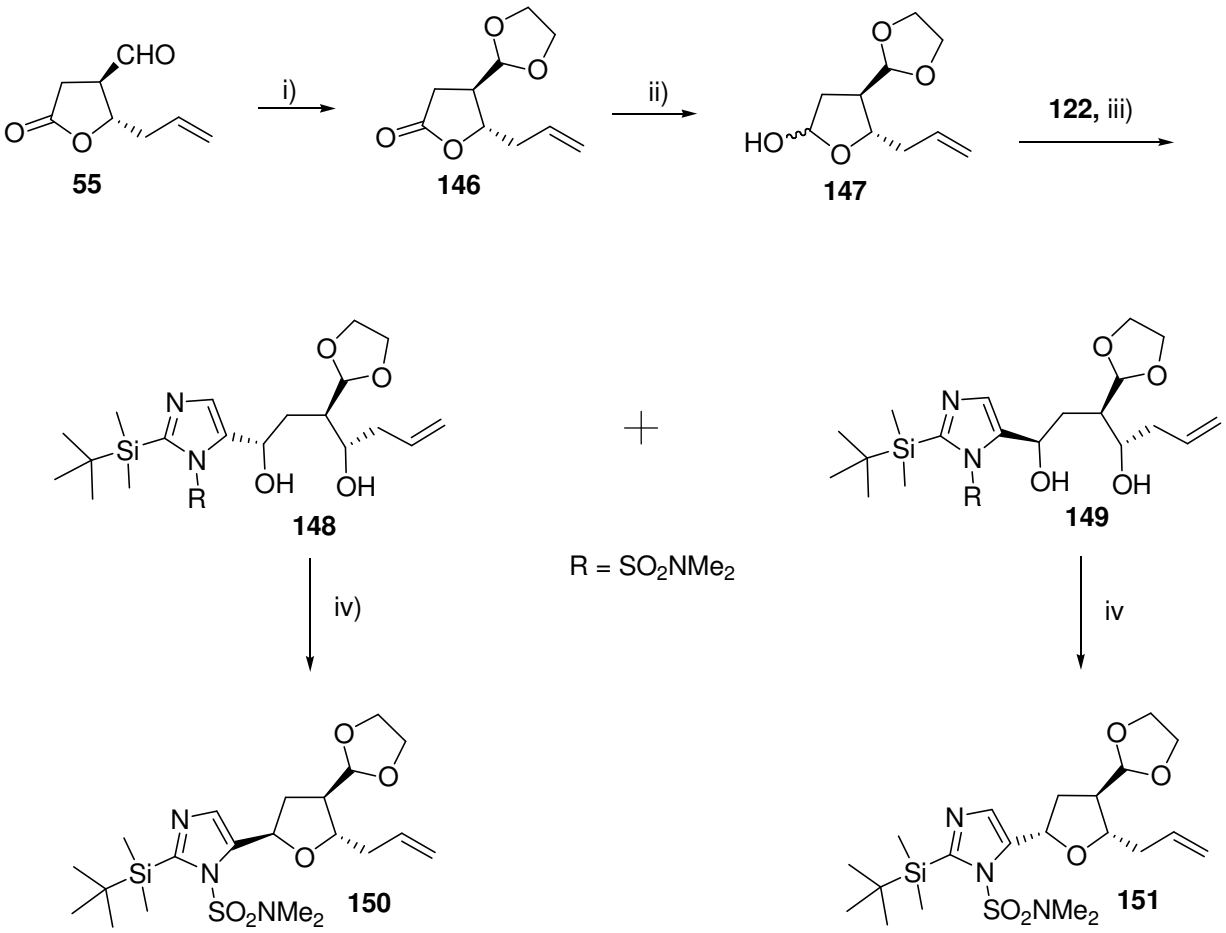
Reagent	Solvent	Temperature	Product obtained
1N, 3N, 6N, conc HCl	THF	0 °C, RT, Reflux	Only TBDMS deprotection
1N, 3N, 6N, conc HCl	Ethanol	0 °C, RT, Reflux	Only TBDMS deprotection
TFA	DCM	0 °C, RT	Only TBDMS deprotection
Na/liq. NH_3	Anhyd. THF	-78 °C	NMR is not clean
Na-Hg (1.5% Na)	Methanol	reflux	Starting material recovery
Na/naphthalene	1,2-dimethoxy ethane	RT	Traces of amount converted
TMSCl/NaI	Acetonitrile	reflux	Only SM
1,3-diamino propane	DMF	140 °C, Microwave	Complex mixture
Thiophenol/K_2CO_3	DMF	RT	SM recovery
5% KOH	Methanol	RT	Only TBDMS deprotection
Mg (5eq)	Methanol	RT	SM recovery
SmI_2	THF	RT	SM recovery
TBAF	THF	RT	Complex mixture

2.9.1 Summary

2.9.2 Synthesis of cyclic building blocks for the human histamine H_3 and H_4 receptor potential agonists from GBL-55

Protection of **55** with ethylene glycol followed by DIBAL-H reduction gave **147** as anomeric mixture (1:1) in 90% yield. Treatment of **147** with bisprotected imidazole **122** in the presence of *n*-butyl lithium afforded diols **148** and **149** in 90% yield. Diastereomers of these diols were separated by silica gel column chromatography. Treatment of these diols **148** and **149** with ADDP-Bu_3P obtained the cyclized products **150** and **151** respectively (Scheme 2.38).

Preparation of suitable Mitsunobu reagents and analysis of stereochemistry of cyclic building blocks was achieved.

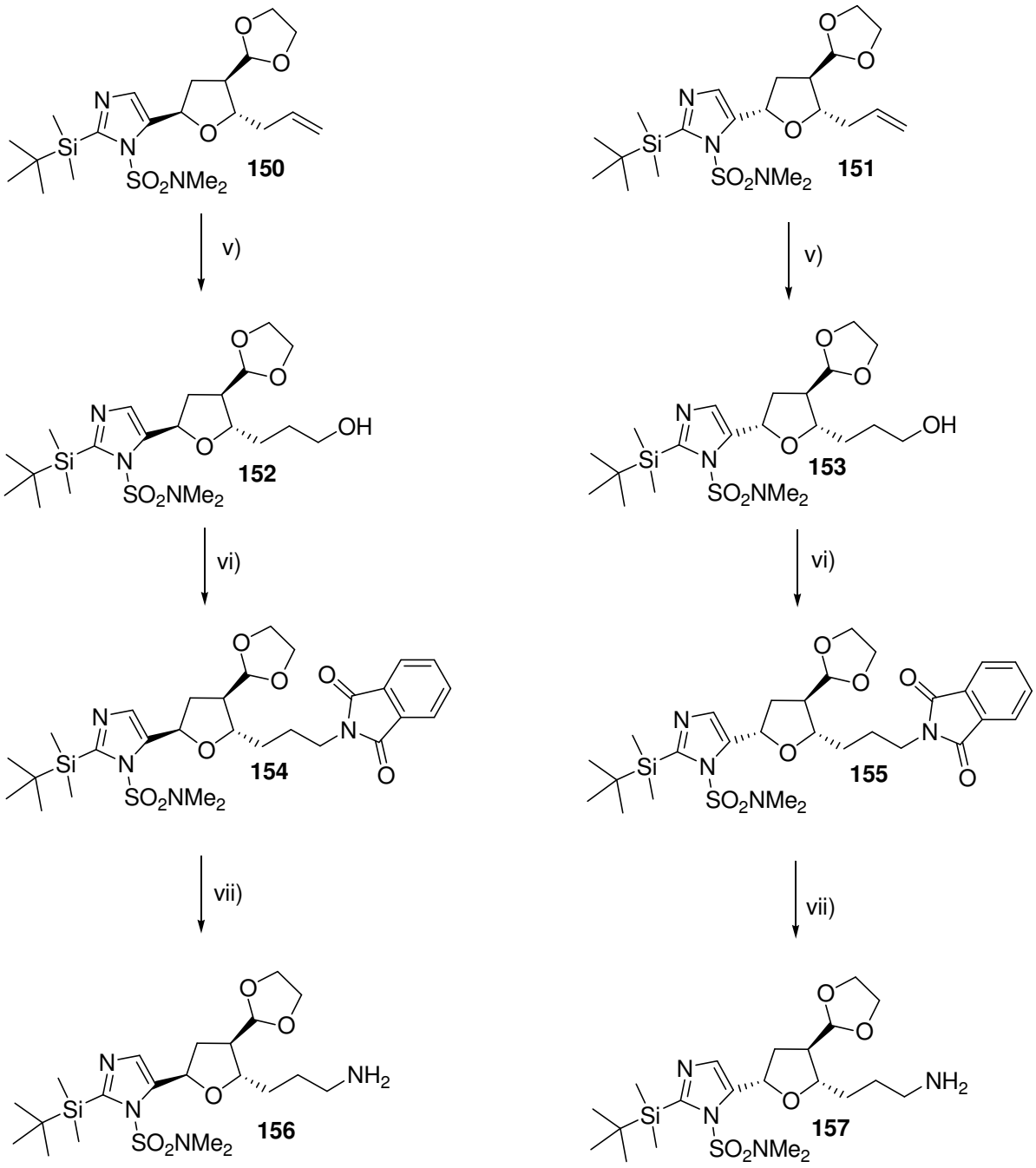


Reagents and conditions: i) ethylene glycol, TsOH, benzene, reflux, 85%; ii) DIBAL-H, CH_2Cl_2 -78°C, 90%; iii) BuLi, THF -78°C, 90%; iv) TMAD, Bu_3P, benzene, RT, 70% or ADDP, Bu_3P, benzene, RT, 80%

Scheme 2.38 Synthesis of building blocks for THF-Imidazole based H_3&H_4-receptors agonists

2.9.3 Towards the synthesis of human histamine H_3 and H_4 receptor potential agonists

The forward synthesis having imidazole, tetrahydrofuran and amine side chain (linker, spacer and lipohilic groups) for the synthesis of histamine H_3 and H_4 receptor potential agonists was established by hydroboration of the cyclic building blocks **150** and **151** and subsequent phthalimidation and dephthalimidation**.**

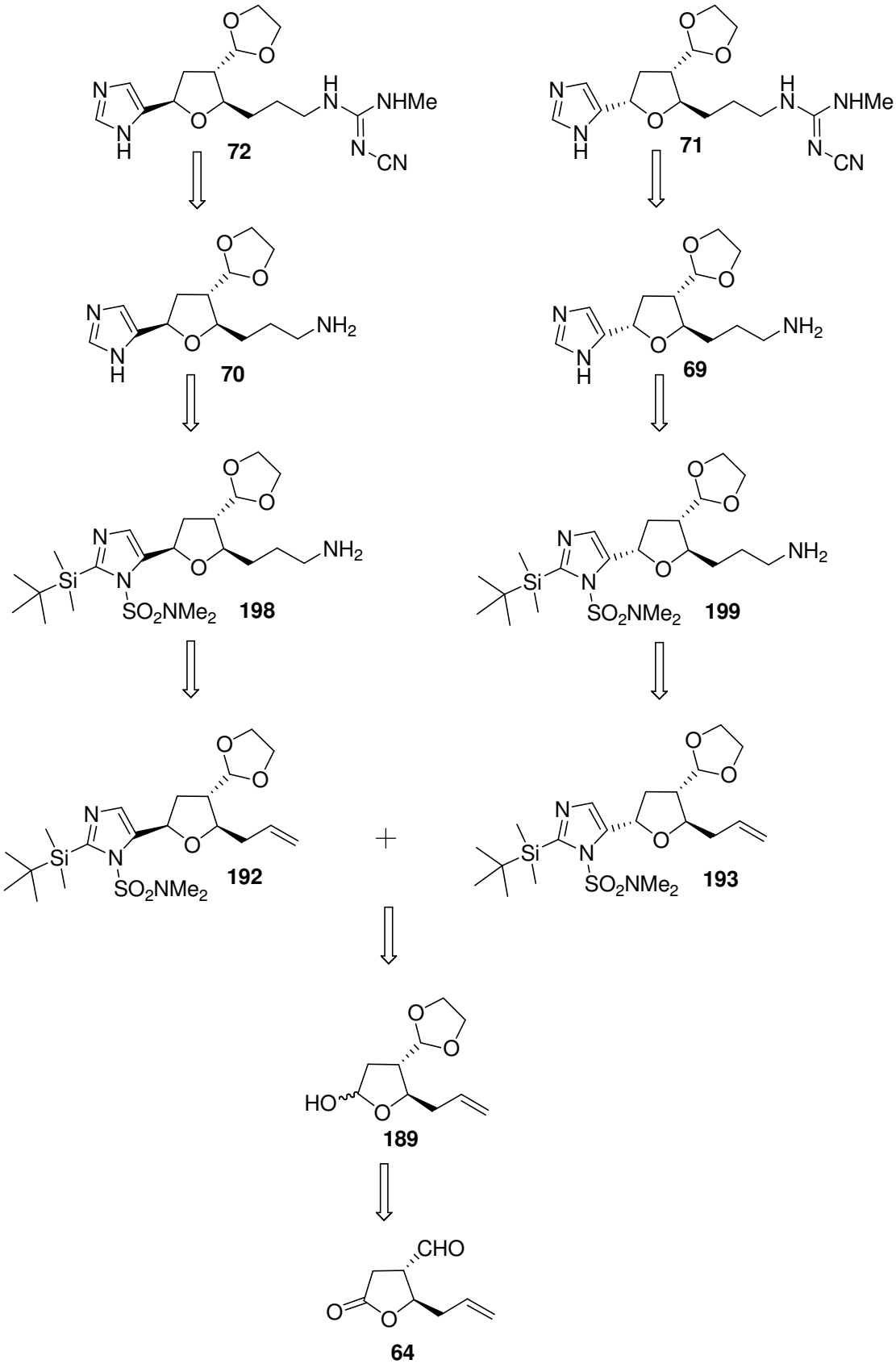


Reagents and conditions: v) BH_3.THF, THF, rt, 12h, 2M NaOH/H_2O_2, 5h, 80%
vi) Phthalimide, PPh_3, DEAD, rt, 12h, 65% vii) N_2H_4.H_2O, EtOH, rt 12h 76%.

Scheme 2.39 Towards the synthesis of histamine H_3 and H_4 receptors potential agonists

Hydroboration of **150** and **151** with BH_3.THF to furnished the primary alcohols **152** and **153** in good yields (80%). The primary alcohols **152** and **153** were subjected to phthalimidation using phthalimide, DEAD and PPh_3 to get phthalimides **154** and **155** in 65% yield. Deprotection of phthalimides using hydrazine hydrate afforded the primary amines **156** and **157** in 76% (Scheme 2.39).

2.9.4 Synthesis of OUP-13 analogues from γ-butyrolactone GBL-64

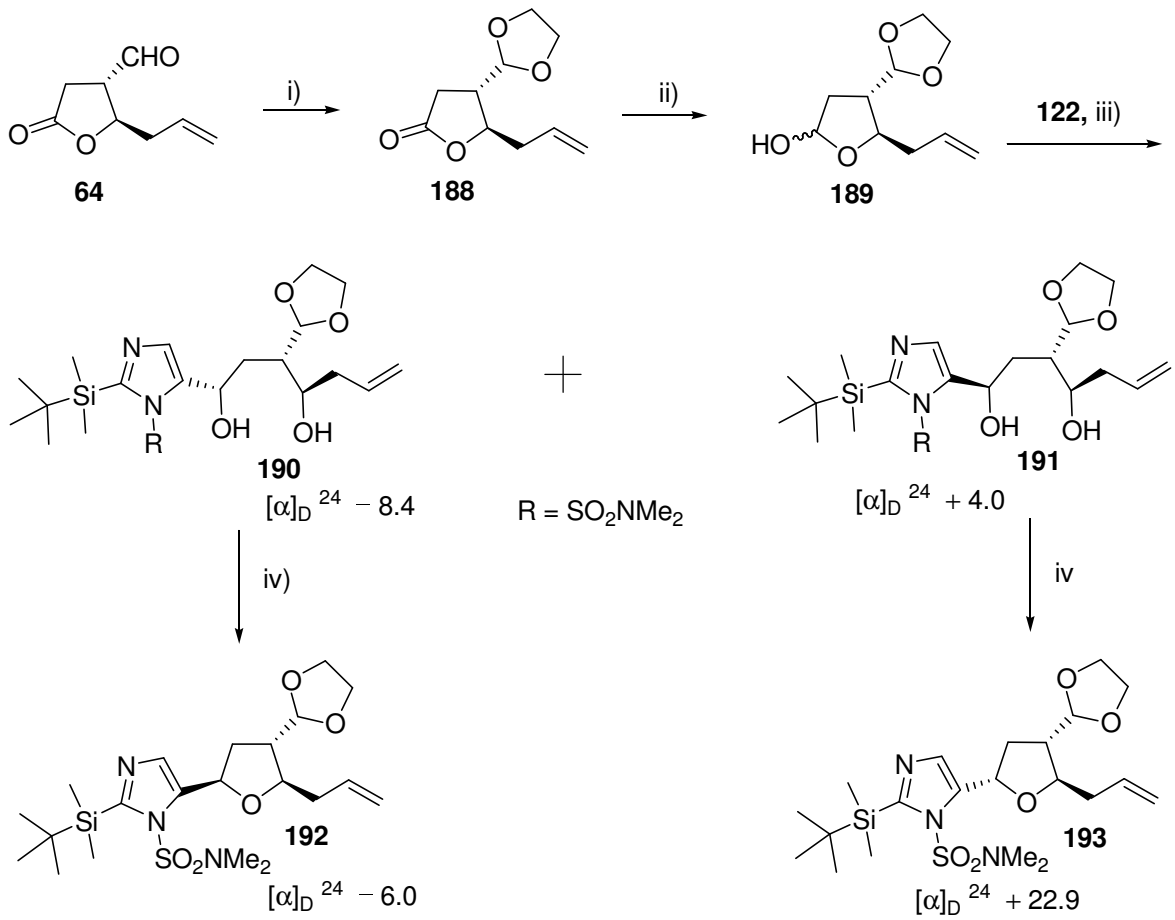


Scheme 2.40 Retrosynthetic analysis for histamine H_3 and H_4 receptor potential agonists based on γ-butyrolactone

The **OUP-13** analogue **72** can be synthesized from the corresponding amine **70** by introduction of cyanoguanidine**.** The amine **70** could be obtained by the deprotection of TBDMS and sulphonamide groups from **198**. Hydroboration of **192** and subsequent Mitsunobu phthalimidation followed by reductive cleavage of phthalimide may afford **198**. Aldehyde protection of **GBL-64** with ethylene glycol followed DIBAL-H reduction of lactone would give the corresponding lactol **189**. Treatment of this lactol with bis protected imidazole could provide diols as possible diastereomers which can be cyclized under Mitsunobu conditions to obtain two cyclic building blocks **192** and **193** (Scheme 2.40).The cyanoguanidine derivative of imidazole tetrahydrofuran **71** can be obtained from **193** by following the same sequence of **192** to **72**.

2.9.5 Synthesis of cyclic building blocks for the human histamine H_3 and H_4 receptor potential agonists from GBL-64

As explained in the section 2.8 earlier, following the same methodology by using the GBL **64** the cyclic building blocks were synthesized.



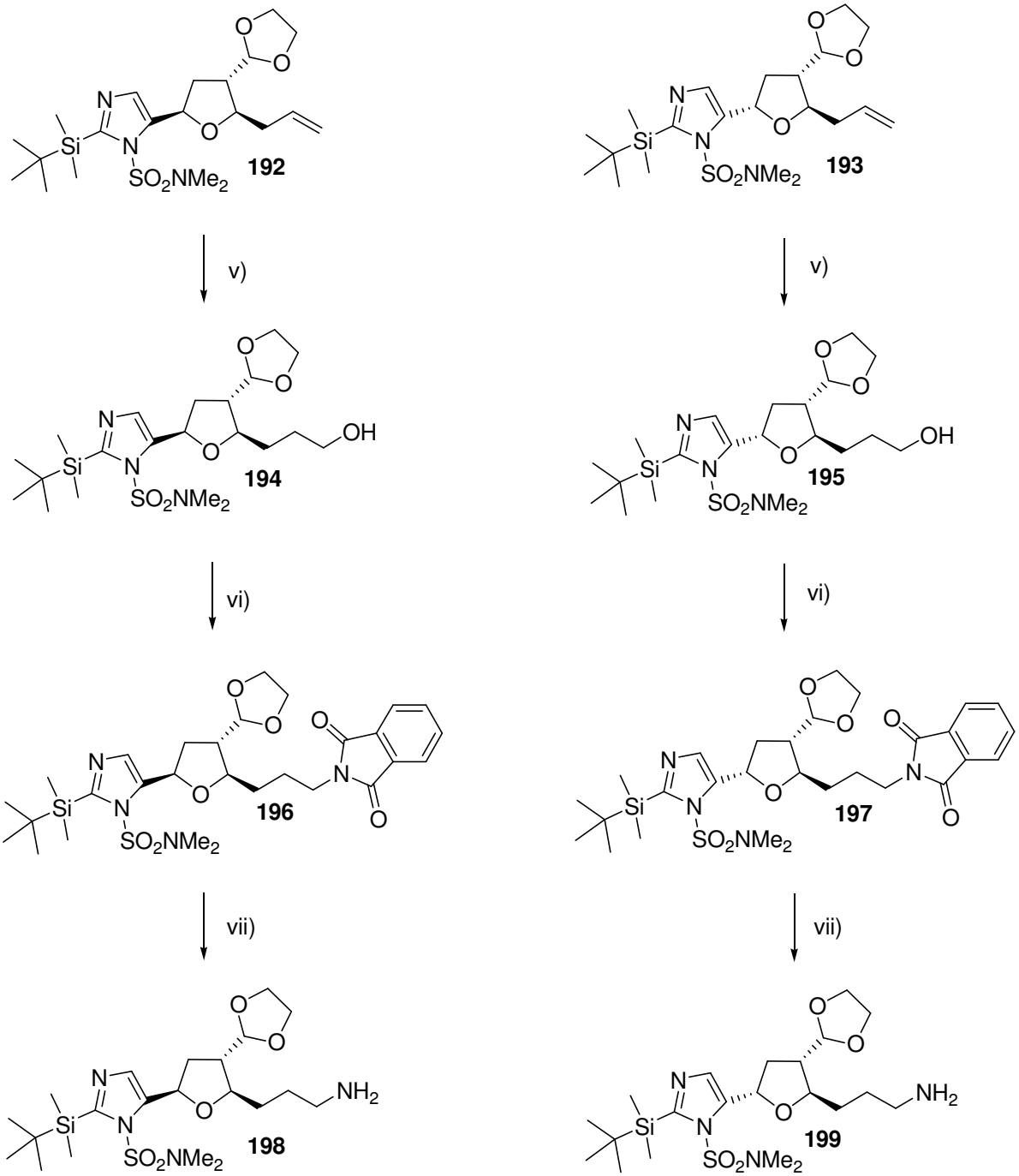
Reagents and conditions: i) ethylene glycol, TsOH, benzene, reflux, 85%, ii) DIBAL-H, CH_2Cl_2 -78℃, 90%, iii) *n*-BuLi, THF, -78℃, 85%; iv) TMAD, Bu_3P, benzene, rt, 68% or ADDP, Bu_3P, benzene, rt, 78%

Scheme 2.41 Synthesis of building blocks for THF-Imidazole based H_3&H_4-receptors agonists

Protection of **64** with ethylene glycol followed by DIBAL-H reduction gave **189** as anomeric mixture (1:1) in very good yield (90%). Bis protected imidazole **122** was prepared in two steps according to literature procedure. Treatment of **189** with bisprotected imidazole **122** in the presence of butyl lithium afforded diols **190** and **191** in 85% yield. Diastereomers of diols **190** and **191** were separated by silica gel column chromatography. Treatment of these diols **190** and **191** with ADDP/Bu_3P as Mitsunobu conditions obtained the cyclized products **192** and **193** (Scheme 2.41). Diastereomers of the chiral diols **190** $[\alpha]_D^{24}$ – 8.4 (c 1.0, $CHCl_3$) and **191** $[\alpha]_D^{24}$ + 4.0 (c 1.0, $CHCl_3$) were separable by column chromatography in high optical purities. Cyclization of chiral diols **190** and **191** proceeded via stereoselective S_N2 Mitsunobu reaction by using inexpensive ADDP reagent to afford cyclized products **192** $[\alpha]_D^{24}$ – 6.0 (c 1.0, $CHCl_3$) and **193** $[\alpha]_D^{24}$ + 22.9 (c 1.0, $CHCl_3$) . The stereochemistry was analyzed in early stage on cyclic building blocks by COSY and NOESY experiments comparing with Kurihara's method.

2.9.6 Towards the synthesis of human histamine H_3 and H_4 receptor potential agonists from GBL-64 cyclic building blocks

As explained in the section 2.82, following the same strategy the amines **198** and **199** were prepared. Hydroboration of the cyclic building blocks **192, 193** with BH_3·THF followed by oxidation obtained the primary alcohols **194** and **195** in good yields (76%). The primary alcohols **194** and **195** were subjected to phthalimidation using phthalimide, DEAD and PPh_3 to obtain the phthalimides **196** and **197** in 62% yield. Deprotection of phthalimides using hydrazine hydrate afforded the primary amines **198** and **199** in 72% yield (Scheme 2.42).



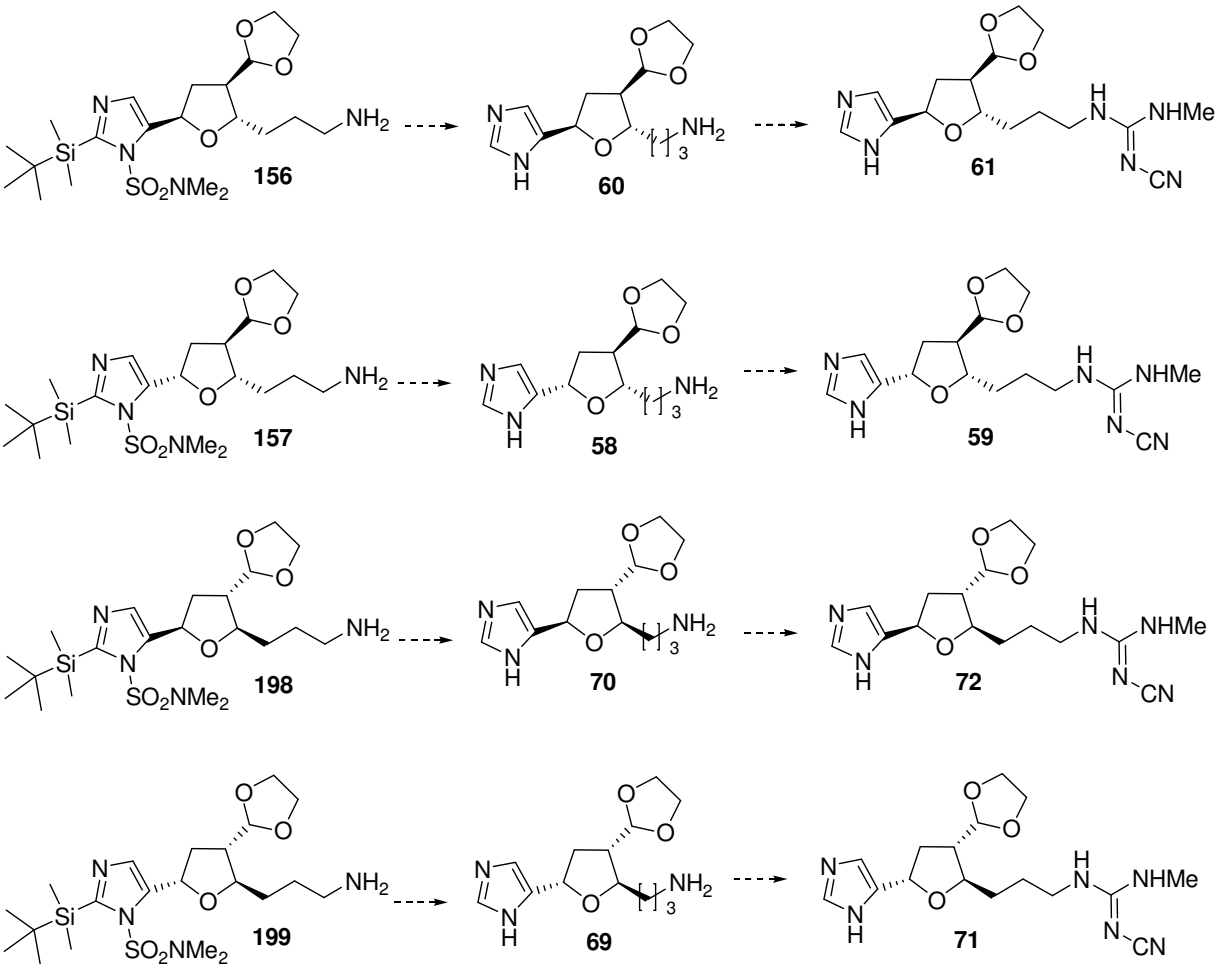
Reagents and conditions: v) BH_3.THF, THF, rt, 12h, 2M NaOH/H_2O_2, 5h,76%;
vi) Phthalimide, PPh_3, DEAD, rt, 12h,62%; vii) N_2H_4.H_2O, EtOH, rt, 12h, 72%

Scheme 2.42 Toward the synthesis of histamine H_3 and H_4 receptors potential agonists

2.9.7 Final steps towards the synthesis of histamine H_3 and H_4 receptor potential agonists

Deprotection of sulfonamides **156, 157, 198, 199** would give the corresponding imidazole (NH free) amines **60, 58, 70** and **69** which are analogues to the imifuramine, and can be interesting to see the structure activity relationship. Upon introduction of cyanoguanidine groups on these amines **60, 58, 70** and **69** would lead to histamine H_4 receptor agonists **61, 59,**

72 and **71.** In this way we can get a small library of molecules for histamine H_3 as well as H_4 receptor agonists. This would be the first application of enantioselective GBLs to the histamine H_3 and H_4 receptor agonists as chiral drugs (Scheme 2.43).



Scheme 2.43 Proposed synthesis of histamine H_3 and H_4 receptor analogues

2.9.8 Conclusion

Application of γ-butyrolactones **GBL-55** and **GBL-64** for the enantioselective synthesis of tetrahydrofuran imidazole based histamine H_3 and H_4 receptor potential agonists were achieved for the first time. Deprotection of TBDMS and sulfonamides **156, 157, 198** and **199** would supply variety of analogues for the histamine H_3 receptor agonists (**60, 58, 70** and **69**). By introducing cyanoguanidine on these amines leads to H_4 receoptor agonists **61, 59, 72** and **71**. This synthetic approach afforded analogues of both *cis* and *trans* tetrahydrofurane-imidazoles, for example imifuramine, its enantiomer, **OUP-16** and **OUP-13** analogues for the histamine H_3 and H_4 receptor potential agonists.

References

1) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725.

2) Fukuzawa, S-I.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997,** *119,* 1482.

3) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**,*34*, 1449.

4) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem*. **1994**, *59*, 365.

5) Midland, M. M.; Nguyen, N. H. *J. Org. Chem*. **1981**, *46*, 4108.

6) Sakamoto, S.; Yamamoto, Y.; Oda, J. *J. Am. Chem. Soc*. **1987**, *109*, 7188.

7) Hajra, S.; Giri, A. K.; Karmakar, A.; Khatua, S. *Chem. Comm.* **2007,** 2408.

8) Hajra, S.; Giri, A. K.; Karmakar, A. *Tetrahedran Lett*. **2008,** *49*, 3625

9) Hajra, S.; Giri, A. K. *J. Org. Chem.* **2008,** *73,* 3935.

10) Zimmerman, H.E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

11) Hoffmann, R. W.; Wolff, J. J. *Chem. Ber.* **1991**, *124*, 563.

12) Özlügedik, M.; Kristensen, J.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Eur. J. Org. Chem.* **2002**, 414.

13) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2282.

14) Weisenberg, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218.

15) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422.

16) Hanko, R.; Rabe, K.; Dally, R.; Hoppe, D. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1690.

17) Reissig, H-U.; Christiane, B. *J. Org. Chem.* **1988**, *53*, 2440.

18) Reissig, H-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

19) Reissig, H.-U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, **1987**; Chapter 8, pp 375-443.

20) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.

21) Seebach D. *Angew. Chem, Int. Ed. Engl.* **1979**, *18*, 239

22) Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955.

23) Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315.

24) R.B. Chhor.; B. Nosse.; S. Sörgel.; C. Böhm.; M. Seitz.; O. Reiser. *Chem. Eur. J.* **2003**, *9*,120.

25) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000,** *33,* 325.

26) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett,* **2001,** *3,* 4259.

27) Evans, D.A.; Woerpel, K.A.; Nosse, B.; Schall, A.; Shinde, Y.; Jezek, E.; Mahbubul Haque, M.; Chhor, R.B.; Reiser, O. *Organic Synthesis* **2006**, *83*, 97.

28) Perkin, Jr. W.H. *Berichte der Deutschen Chemischen Gesellschaft* **1884**, *17*, 54.

29) Lebel, J.-F. H.; Marcoux, C. M.; Andre, B. C. *Chem Rev* **2003**, *103*, 977.

30) Ryan, P. W.; Andre, B.C. *Org. Lett,* **2002**, *4*, 4531.

31) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Editors, *Comprehensive Asymmetric Catalysis I-III, Volume 2*, **1999**.

32) Nozaki, H.; Moriuti, S.; Takaya, H.; Nayori, R. *Tetrahedron Lett* **1966,** *7,* 5239.

33) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed. Engl*. **1992,** *31,* 430.

34) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc,* **1991**, *113*, 726

35) Wenkert, E.; Guo, M.; Lavilla, T.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem* **1990,** *55,* 6203.

36) Straub, B. F.; Hofmann, P. *Angew. Chem. Int. Ed. Engl.* **2001,** *40,* 1288.

37) Fritschi, H.;Leutenegger, U.; Pfaltz, A. *Helv Chim Acta* **1988,** *71,* 1553.

38) Temme, O.; Taj, S. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007.

39) Claus, R. E.; Schreiber, S. L. *Org. Syn., Coll. Vol.* **1990,** *7,* 168

40) Tietze, L. F.; Bratz, M. *Org. Syn.*, *Coll. Vol.* **1998,** *9,* 314

41) Schwartz, C.; Raible, J.; Mott, K.; Dussault P. H. *Org Lett,* **2006,** *8,* 3199.

42) Criegee, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *87*, 745.

43) Berger, S. *Eur. J. Org. Chem.* **1998**, 1625.

44) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17,* 1295.

45) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963,** *85,* 1245.

46) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199.

47) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

48) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

49) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *3*, 155.

50) Mengel, A.; Reiser, O. *Chem. Rev.***1999**, *99*, 1191.

51) Augustine, R. L. Techniques and applications in organic synthesis, **1979,** *1*, pp1-84

52) Hashimoto, T.; Harusawa, S.; Araki, L.; Zuiderveld, O. P.; Smit, M. J.; Imazu, T.; Takashima, S.; Yamamoto, Y.; Sakamoto, Y.; Kurihara,T.; Leurs, R.; Bakker, R. A.; Yamatodani, A. *J. Med. Chem.* **2003,** *46,* 3162.

53) Harusawa, S.; Imazu, T.; Takashima, S.; Araki, L.; Ohishi, H.; Kurihara,T.; Sakamoto, Y.; Yamamoto, Y.; Yamatodani, A. *J. Org. Chem.* **1999,** *64,* 8608.

54) Harusawa, S.; Imazu, T.; Takashima S.; Araki, L.; Ohishi, H.; Kurihara, T.; Yamamoto, Y.; Yamatodani, A. *Tetrahedron Lett.* **1999**, *40*, 2561.

55) Harusawa, S.; Araki, L.; Imazu, T.; Ohishi, H.; Sakamoto, Y.; Kurihara, T. *Chem. Pharma. Bull.* **2003,** *51,* 325.

56) Harusawa, S.; Araki, L.; Terashima, H.; Kawamura, M.; Takashima, S.; Sakamoto, Y.; Hashimoto, T.; Yamamoto, Y.; Yamatodani, A.; Kurihara,T. *Chem. Pharma. Bull.* **2003,** *51,* 832.

57) Harusawa S., Murai Y., Moriyama H., Ohishi H., Yoneda R., Kurihara T. *Tetrahedron Lett.*, **1995,** *36,* 3165.

58) Harusawa, S.; Murai, Y.; Moriyama, H.; Imazu, T.; Ohishi, H.; Yoneda, R.; Kurihara, T. *J. Org. Chem.* **1996,** *61,* 4405.

59) Tetsuji, K.; Suzuki, T.; Masahiro, N.; Etsuko, S.; Katsuo, U. *Heterocycles,***1982,** *19,* 205.

60) Pilli, R. A.; Riatto, V. B. *Tetrahydron: Asymmetry* **2000,** *11,* 3675.

61) Chadwick D. J.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1,* **1984,** 481.

62) Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1,* **1990**, 1645.

63) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E; Pavan Kumar, K.V. P. *Chem. Rev.* **2009,** *109,* 2551.

64) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

65) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935.

66) Mattingly, P. G. K., Jr. J. F.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983.

67) Brain, C. T. C., A.; Nelson, A.; Tanikkul, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 1247.

68) a) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.
b) Butera, J.; Rini, J.; Helquist, P. *J. Org. Chem.* **1985**, *50*, 3676.
c) Liu, L.; Tanke, R. S.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 5332.

69) Chong, Y. G., G.; Chu, C. K. *Tetrahedron: Asymmetry* **2000**, *11*, 4853.

70) Goundry, W. R. F.; Lee, V.; Baldwin, J. E. *Synlett* **2006**, 2407.

71) Lai, J.-Y. Y., J.; Hawkins, D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691.

72) Tsunoda, T.; Kaku, H.; Ito, S. July, **2005,** TCIMAIL, number 123 (http://www.tci-asiapacific.com/tcimail/backnumber/article/123drE.pdf)

73) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.

74) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751

75) Guanti, G.; Banfi, L.; Basso, A.; Bevilacqua, E.; Bondanza, L.; Riva, R. *Tetrahedron: Asymmetry* **2004**, *15*, 2889.

76) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahydron Lett.* **1993,** *34,* 1639.

77) Tsunoda, T.; Kaku, H. N, N, N', N'-Tetramethyl-azodicarboxamide. ''Electronic Encyclopedia of Reagents for Organic Synthesis'' eds, by L. A. Paquette, *et al.,* Wiley, 15 October 2003.

78) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett* **1994,** 539.

79) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 1176.

80) Shi, J. Y.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 3609.

81) Grynkiewicz, G. *Rocz. Chem.* **1976**, *50*, 1449.

82) Camp, D. J., I. D. *J. Org. Chem* **1989**, *54*, 3045.

83) Camp, D. J., I. D. *J. Org. Chem* **1989**, *54*, 3049.

84) Carlock, J. T. M., M. P. *Tetrahedron Lett.* **1978**, *19*, 5153.

85) Guianvarc′h, D. B., R.; Fourrey, J.-L. *Tetrahedron Lett.* **2001**, *42*, 647.

86) Nam, N.-H.; Sardari, S.; Parang, K. *J. Comb. Chem.* **2003**, *5*, 479

87) Tunoori, A. R.; Dutta, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, *39*, 8751.

88) Amos, R. A.; Emblidge, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598.

89) Thomas, G. L.; Ladlow, M.; Spring, D. R. *Org. Biomol. Chem.* **2004**, *2*, 1679.

90) Thomas, G. L.; Bo¨hner, C.; Ladlow, M.; Spring, D. R. *Tetrahedron* **2005**, *61*, 12153

91) Zaragoza, F.; Stephensen, H. *Tetrahedron Lett.* **2000**, *41*, 2015.

92) Humphries, P. S.; Do, Q.-Q. T.; Wilhite, D. M. *Beilstein J. Org. Chem.* **2006**, *2*, 21.

93) Leonetti, F.; Cappa, A.; Maccallini, C.; Carotti, A. *Arki Voc* **2004**, 272.

94) Lan, P.; Porco, J. A., Jr.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5*, 660.

95) Dandapani, S.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 8751.

96) Curran, D. P.; Wang, X.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 3716

97) Smissman, E. E.; Makriyannis, A. *J. Org. Chem.,* **1973,** *38,* 1652

98) But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 9636.

99) Yokoyama, M.; Toyoshima, A.; Akiba, T.; Togo, H.; *Chem. Lett.,* **1994,** 265.

100) Mehrotra, R. C.; Singh, A. *Organomettalic Chemistry***,** A Unified Approach, Second Edition, **2000,** PP 552

101) Stock, A. *Hydrides of Boron and Silicon*, **1933,** Cornell University Press, Ithaca, New York

102) Nobel Lecture, 8 December, 1979 by H. C. Brown (http://nobelprize.org/nobel_prizes/chemistry/laureates/1979/brown-lecture.pdf)

103) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956,** *78,* 2582.

104) Brown, H. C**.** *Hydroboration,* W. A. Benjamin, New York, 1962.

105) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956,** *78,* 5694.

106) Brown, H. C.; Subba Rao, B. C. *J. Org. Chem.* **1957,** *22,* 1136.

107) Brown, H. C. *Boranes in Organic Chemistry* **, 1972,** Cornell University Press, Ithaca, New York.

108) Negishi, E.; Brown, H. C. *Synthesis,* **1974,** 77.

109) Brown, H. C.; Lane, C. F. *Heterocycles,* **1977,** *7,* 454.

110) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679.

111) Brewer, M.; Rich, D. H. *Org. Lett.* **2001,** *3,* 945.

112) Chinna A.K. Reiser, O. unpublished results.

113) Mohammad Mahbubul Haque, Ph.D thesis 2005, University of Regensburg

114) Narayana, C.; Periasamy, M. *Tetrahydron Lett.* **1985,** 26, 1757.

115) Narayana, C.; Periasamy, M. *Chem. Commun,* **1987,** 1857.

116) Varela, J.A.; Pena, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* **2001,** *3,* 2395.

117) Mitsunobu, O. W., M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679-680.

118) Loibner, v. H. Z., E. *Helv. Chim. Acta.* **1976**, *59*, 2100-2113

119) Guianvarc'h, D.; Fourrey, J-L.; Maurisse, R.; Sun, J-S.; Benhida. R. *Org. Lett.,* **2002,** *4,* 4209

120) Witt, O.; Truttwin, H. *ibid.,* **1914,** *47,* 2788

121) Sundberg, R. J.; Laurino, J. P. *J. Org. Chem.,* **1984,** *49,* 249.

122) Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett,* **1998,** *39,* 6613

123) Iserloh, U.; Dudkin, V.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2002,** 43, 7027.

124) Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999,** *40,* 6181.

125) Forshee, P. B.; Seibert, J. W. *Synthesis,* **2006,** 756.

126) Yasuhara, S.; Sakamoto, T. *Tetrahedron Lett.* **1998,** *39,* 595.

127) Sabitha, G.; Subba Reddy, B. V.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999,** *40,* 1569.

128) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G. Feringa, B. L.; Minnaard, A.J. *Angew. Chem. Int. Ed.* **2006,** *45,* 2789.

129) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem Commun,* **1997,** 1017.

130) Ankner, T.; Hilmersson, G. *Org. Lett,* **2009,** *11,* 503.

Aim of the work

The application of furan methyl carboxylate **109** and acetyl furan **248** towards the histamine H_3 and H_4 receptor agonists (Figure 3.2) was shown in Figure 3.1. As explained in schemes 3.6 and 3.16, Cu-(I)-(bisoxazoline) catalyzed asymmetric cyclopropanation and *N*-bromosuccinimide (NBS) mediated ring opening of cyclopropane derivatives upon functional group transformation can afford compounds **244, 246, 247, 256, 273-276**. By changing the position of amino methyl group, keeping the methoxy group and extending the spacer length between tetrahydrofuran and imidazole for the synthesis of derivates of histamine H_3 and H_4 receptor potential agonists was shown (Figure 3.1 and 3.2).

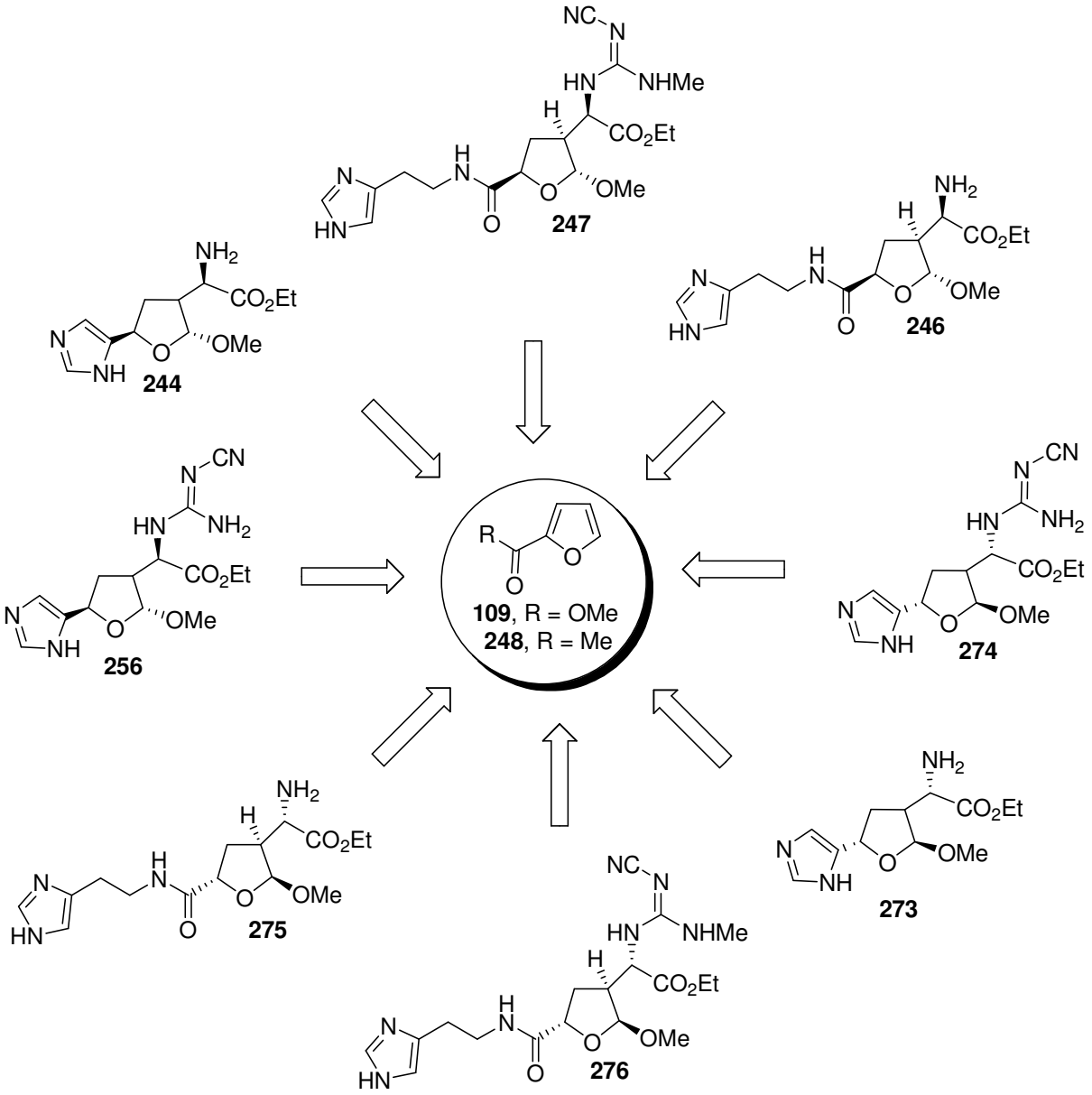


Figure 3.1 Tetrahydrofuran-imidazole based histamine H3 and H4 receptor potential agonists by cyclopropane ring opening methodology

Compounds **35, 45, 46, 54, 116-119** can be synthesized from imidazole aldehyde **258** (Figure 3.2)**.** Protection of NH followed by Grignard reaction with butenyl bromide can afford the olefin having alcohol functionality. Sharpless asymmetric dihydroxylation followed by Mitsunobu cyclization may give the corresponding cyclic building blocks. Upon functional group transformation of olefins to amines followed by introduction of cyanoguanidine would furnish the histamine H_3 and H_4 receptor agonists as shown in scheme 3.20.

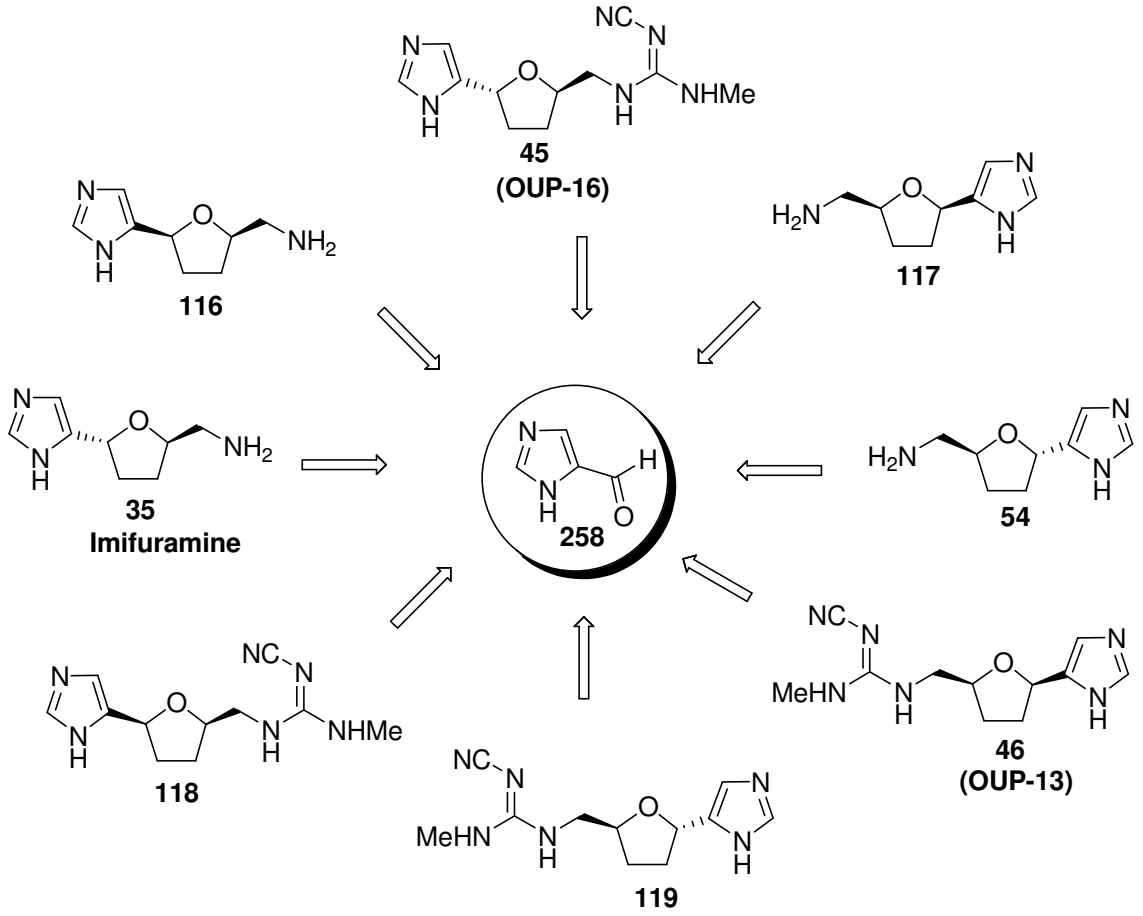


Figure 3.2 Synthesis of Imifuramine and OUP-16 based on imidazole aldehyde an alternative route to Kurihara's synthesis

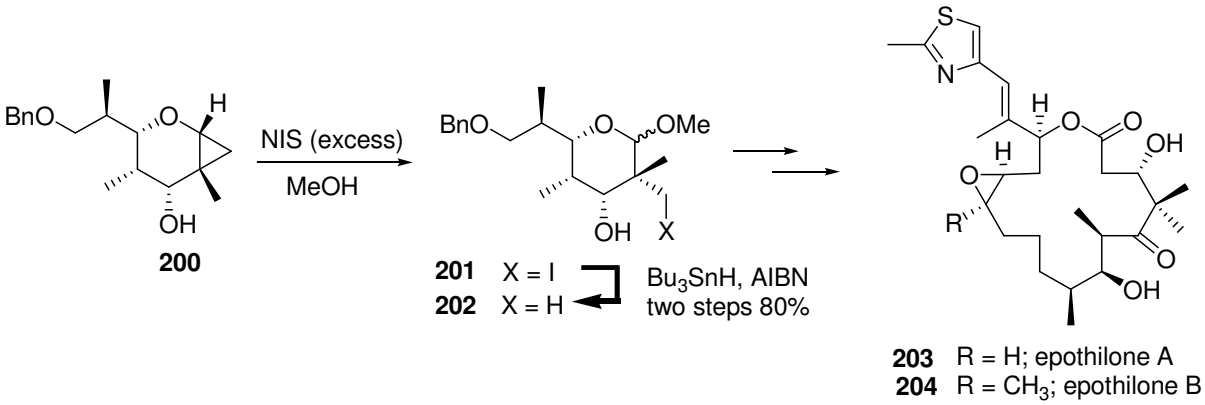
Chapter 3

3. Synthesis of histamine H_3 and H_4 receptor potential agonists by NBS mediated cyclopropane ring opening methodology

3.1.1 Introduction to cyclopropane ring opening methodology

1,2-Cyclopropanated sugar derivatives undergo ring opening reactions to give 2-C branched sugars when subjected to solvolysis in the presence of stoichiometric or catalytic amount of metal salts (Hg or Pt),[1] strong acids,[2] or halonium ions.[3] Among them halonium ion mediated ring opening reactions can proceed under mild conditions (NIS or NBS) and leads to useful biologically active compounds such as natural products, unnatural amino acids and carbohydrate derivatives. Several applications and modifications to the NIS strategy have been reported.[4-6] Compared with the organomercury intermediates, the halomethylene appendage obtained directly from the NIS/NBS protocol opened a window for more environmentally responsible elaboration.[7]

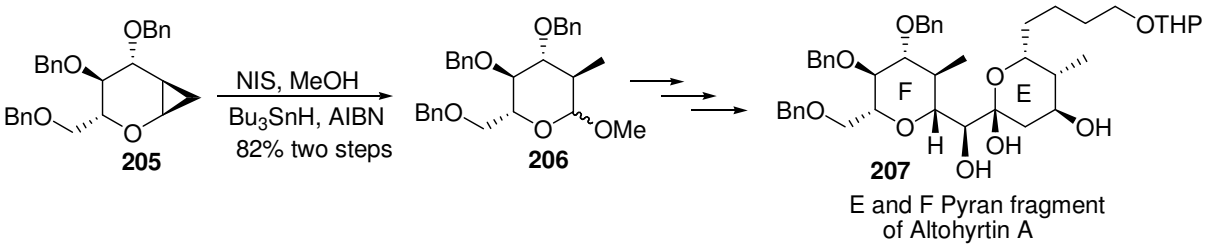
The development of a novel cyclopropane solvolysis strategy for incorporating the geminal methyl groups of the epothilones A and B, has been reported by Danishefsky and co-workers using *N*-iodosuccinimide (NIS).[8] The important key intermediate **202** for the synthesis of epothilones A (**203**) and B (**204**) was efficiently prepared by NIS mediated ring opening of cyclopropane **200** in methanol. The methyl glycoside **201** underwent reductive deiodination to afford the geminal methyl groups of artificial glycoside **202** (Scheme 3.1).



Scheme 3.1 Cyclopropane ring opening with NIS, a key intermediate 3.59 for the total synthesis of epothilones A and B by Danishefsky *et al*

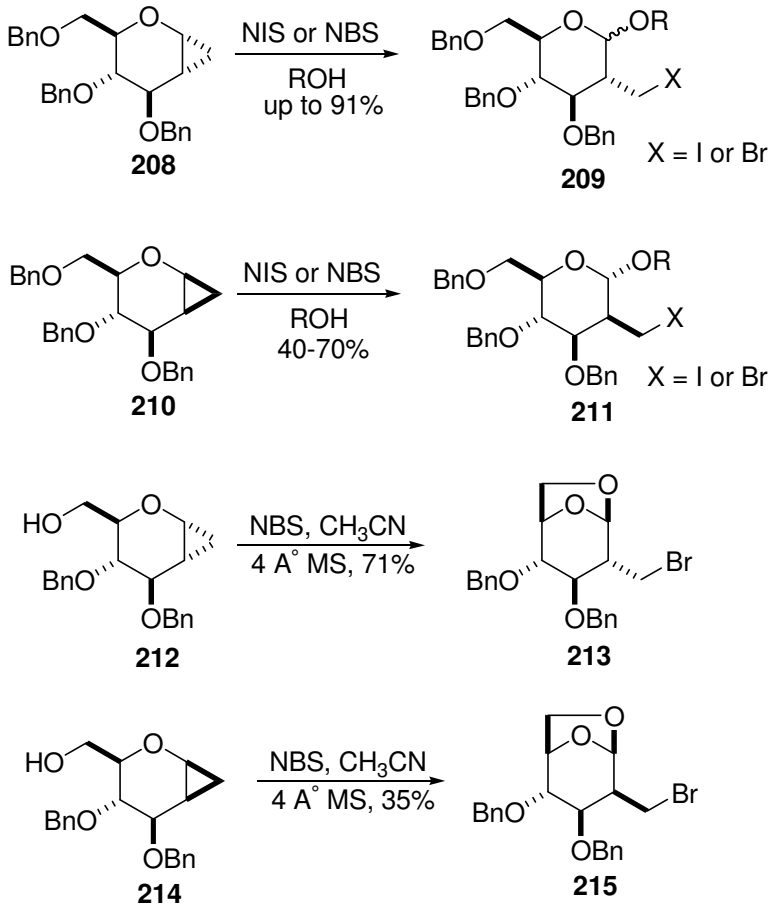
The cyclopropane **205** (Scheme 3.2) was obtained from reductive dehalogenation of corresponding dichlorocyclopropane derivative. Several attempts by Ley and co-workers to open either the dichlorocyclopropane or the analogous dehalogenated cyclopropane with carbon nucleophiles proved unsuccessful.[9] Finally cyclopropane ring opening of **205** was achieved with *N*-iodosuccinimide (NIS) and methanol to furnish **206** as anomeric mixture

after reduction of the iodide in 82% yield (in 2 steps). The synthesis of the highly substituted E and F pyran fragment **207** of altohyrtin A from tri-*O*-benzyl-D-glucal is achieved by cyclopropanation and NIS ring opening methodology (Scheme 3.2).[9]



Scheme 3.2 NIS opening of cyclopropane for the synthesis of E and F pyran fragment 3.63 by Ley *et al*

Nagarajan *et al*[10] discovered a different cyclopropane reactivity between diastereomers **208** and **210** (Scheme 3.3). Reaction of α-cyclopropane **208** with either NIS or NBS occurred rapidly and provided an anomeric mixture of **209** in 91% yield.

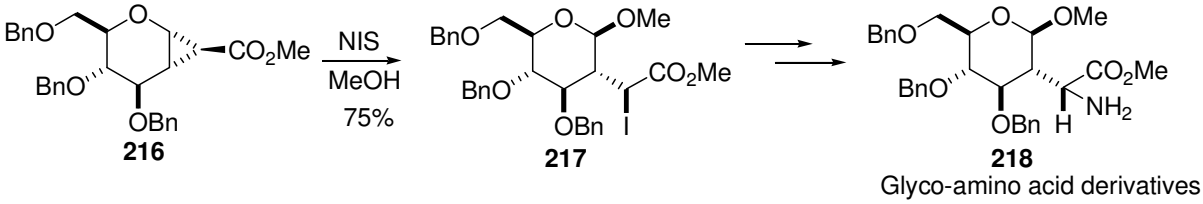


Scheme 3.3 NIS or NBS ring opening of cyclopropane sugar derivatives by Nagarajan *et al*

In contrast, reaction under identical conditions with β-cyclopropane **210** results in slower formation of **211** with pronounced anomeric selectivity. The same trend in reactivity was also observed on diastereomeric substrates **212** and **214** in which the free C(6) hydroxyl group is available to participate in an intramolecular nucleophilic attack to furnish **213** and **215**

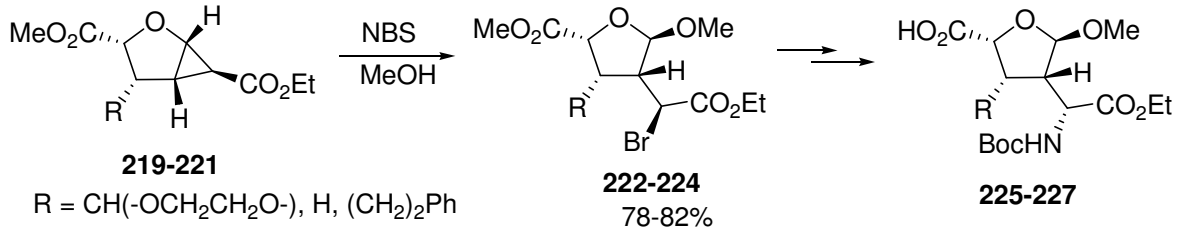
(Scheme 3.3). The authors extended the methodology to the formation of halogenated 2-C disaccharides by inclusion of sugar alcohols in the reaction.[11]

Very recently, an efficient method for the synthesis of C(2) branched glycolamino acid derivatives **218** has been developed by Chandrasekaran and co-workers through direct NIS mediated ring opening in methanol (Scheme 3.4).[12] D-glucal derived cyclopropane **216** afforded the iodosugar **217** as a single diastereomer in 75% yield upon treatment with NIS/MeOH. The S_N2 reaction of this iodosugar with NaN_3 in DMF followed by reduction of sugar azide gave rise the glycoamino acid derivative **218** (Scheme 3.4). Furthermore the authors extended this methodology for efficient synthesis of fused perhydrofuro[2,3-b]pyrans (and furans)[13] and also to nucleosides synthesis.[14]



Scheme: 3.4 General strategy for the synthesis of glycoamino acids by Chandrasekaran *et al*

Following the above synthetic methodology Reiser and co-workers also synthesized unnatural amino acid derivatives of substituted tetrahydrofuran by NBS mediated cyclopropane ring opening reactions.[15,16] When furan cyclopropane derivatives **219-221** were treated with NBS in methanol, the tetrahydrofuran-bromo compounds **222-224** were obtained in 78-82%. This methodology was applied for the synthesis of unnatural amino acid derivatives **225-227** (Scheme 3.5).

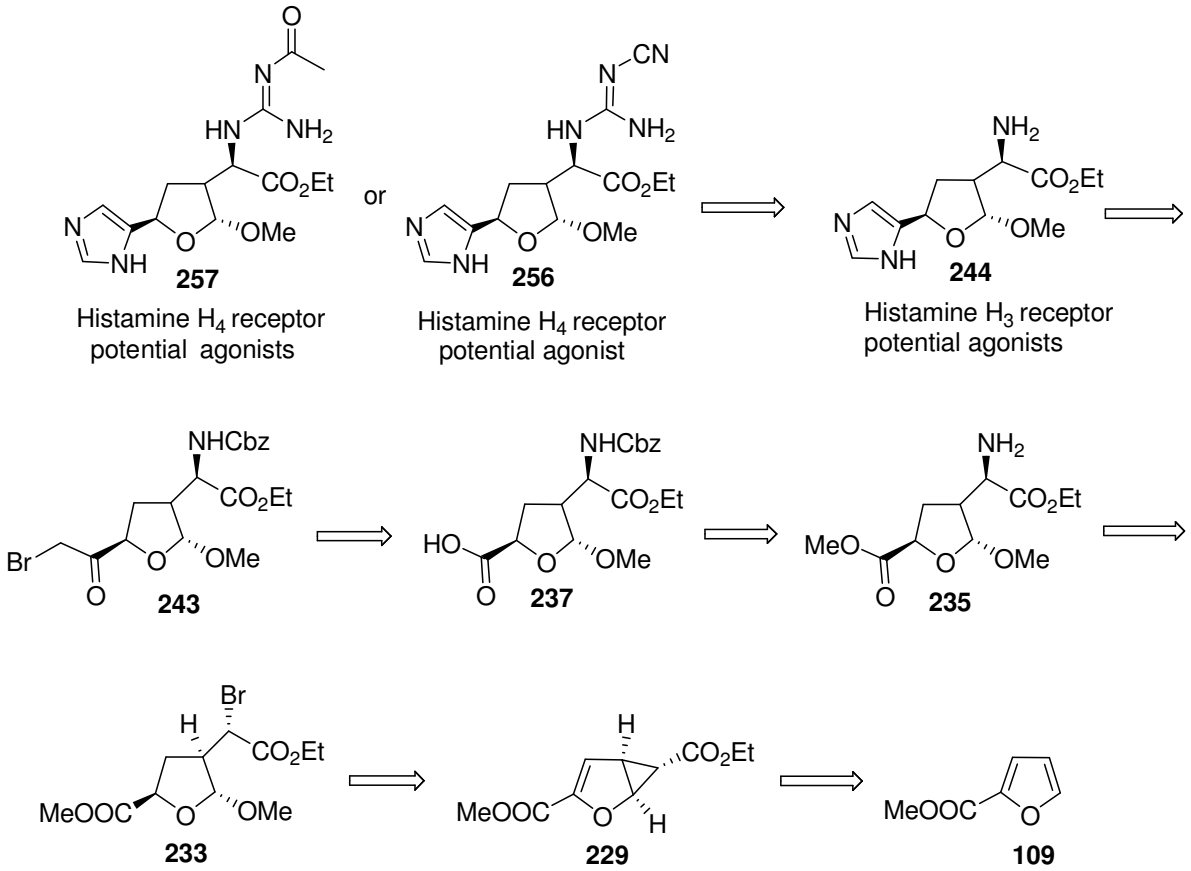


Scheme 3.5 Cyclopropane ring opening with NBS for the synthesis of unnatural amino acid derivatives by Reiser *et al*

3.1.2 Enantioselective synthesis of histamine H_3 and H_4 receptor potential agonists by furan cyclopropane ring opening methodology.

3.1.3 Retrosynthetic analysis based on cyclopropanation of furan

Introduction of acyl or cyanoguanidine groups into **244** can furnish potential histamine H_4 receptor agonists **257** or **256**. Treatment of **243** with formamidine acetate in presence of ammonia (7N in methanol) may afford **244** by formation of imidazole ring and subsequent deprotection of Cbz group. This bromomethyl ketone **243** could be obtained from the corresponding acid **237** upon treatment with acid chloride, followed by diazomethane and HBr.



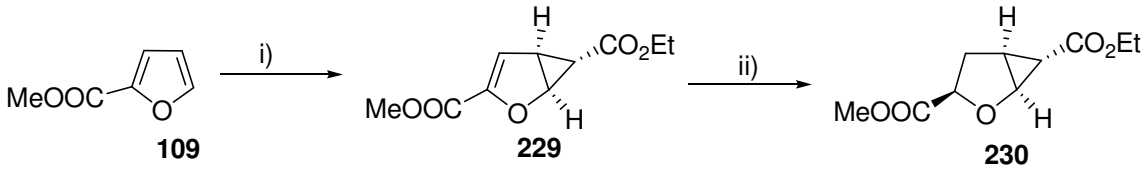
Scheme 3.6 Retrosynthetic analysis for histamine H_3 and H_4 receptor potential agonists based on cyclopropane ring opening metholodogy

Protection of amine **235** with Cbz chloride followed by selective hydrolysis of methyl ester can afford **237**. The S_N2 reaction of **233** with sodium azide and subsequent reduction with Pd/C may afford amine **235** as possible precursor for histamine H_3 receptor agonist. Hydrogenation of **229** with Pd/C followed by NBS opening of cyclopropane ring in methanol could furnish the cyclopropane ring opening product **233**. The cyclopropane ester **229** can be

obtained from the copper(I)-bis(oxazolines) catalyzed cyclopropanation of furan-2-carboxylic ester **109** (Scheme 3.6).

3.1.4 Asymmetric cyclopropanation and hydrogenation

Cu(I)bisoxazoline catalyzed asymmetric cyclopropanation of methylfuran carboxyalte **109** at 0 °C gave the cyclopropane carboxylate **229** in 41% yield (Scheme 3.7). The hydrogenation of **229** was done by using 10% Pd/C in ethyl acetate at room temperature under balloon pressure to afford product **230** in moderate yields up to 50%**.** Change of solvents and Pd/C (5% Pd/C in ethylacetate, methanol) did not improve the yield of **229**. Within 15 minutes it was observed by TLC analysis that at least three byproducts were forming in addition to remaining starting material **229** and the desired product **230**. Continuation of the reaction for more than 15 minutes, increased the amounts of unwanted side products.

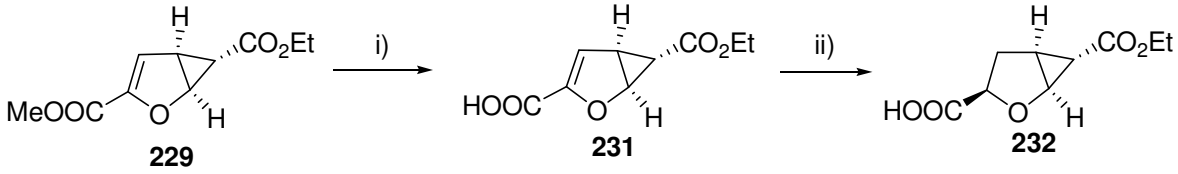


109 **229** **230**

Reagents and conditions: i) (*R,R*)-^{i}Pr(bisoxazoline), $Cu(OTf)_2$, $PhNHNH_2$, EDA, 41%, ii) H_2, 10% Pd/C, EtOAc, rt, 30 min, 50%

Scheme 3.7 Asymmetric cyclopropanation and hydrogenation

To overcome the above problem, the methyl ester of **229** was selectively hydrolyzed by using 1 equivalent of lithium hydroxide to the corresponding carboxylic acid **231** in excellent yield. Upon treatment of acid **231** under the same reaction conditions (10% Pd/C, H_2, EtOAc) used for **229** to **230** with longer reaction time gave the hydrogenation product **232** in quantitative yield with no side products being observed (Scheme 3.8).



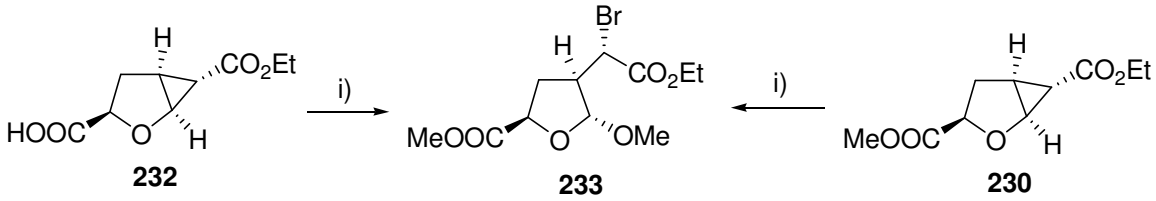
229 **231** **232**

Reagents and conditions: i) LiOH (1 eq), THF, H_2O, 0 °C, rt, 12h, 96%, ii) H_2, 10% Pd/C, EtOAc, rt, 12h, 98%

Scheme 3.8 Selective hydrolysis of methyl ester and hydrogenation on acid

3.1.5 NBS mediated cyclopropane ring opening reactions

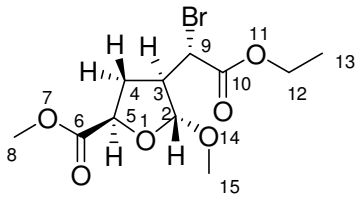
By following the cyclopropane ring opening methodology, treatment of **232** or **230** with NBS in methanol gave the corresponding cyclopropane ring opening product **233** in good yield. Under these conditions it was observed that the free acid **232** was converted to its methyl ester in **233** (Scheme 3.9). Stereochemistry of **233** was analyzed by NOESY and COSY spectrum.



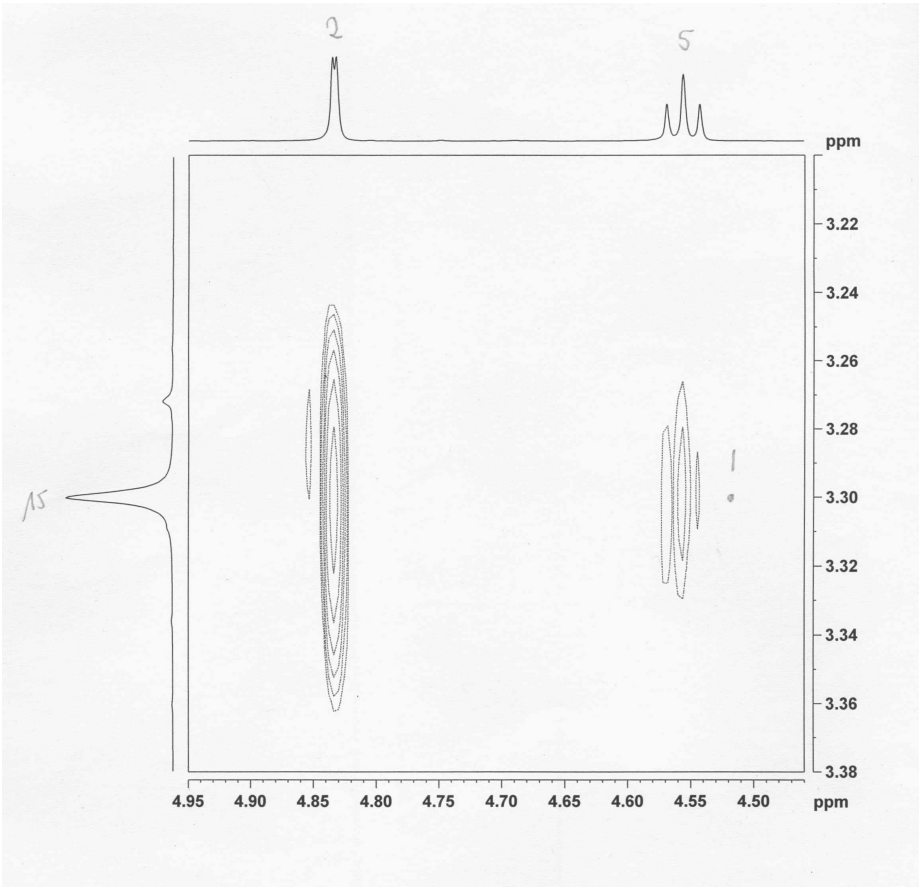
Reagents and conditions: i) NBS, MeOH, 0 ℃-rt, 36h, 80%

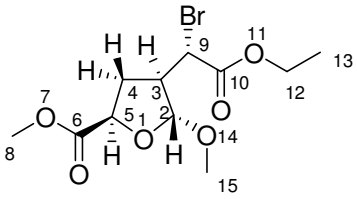
Scheme 3.9 Cyclopropane ring opening methodology

The S_N2 reaction of **233** with sodium azide in DMF at room temperature yielded the corresponding azide **234** in quantitative yield. The reduction of azide was done in presence of H_2 by using 10% Pd/C in ethyl acetate at room temperature gave the amine **235** with excellent yield (Scheme 3.10).

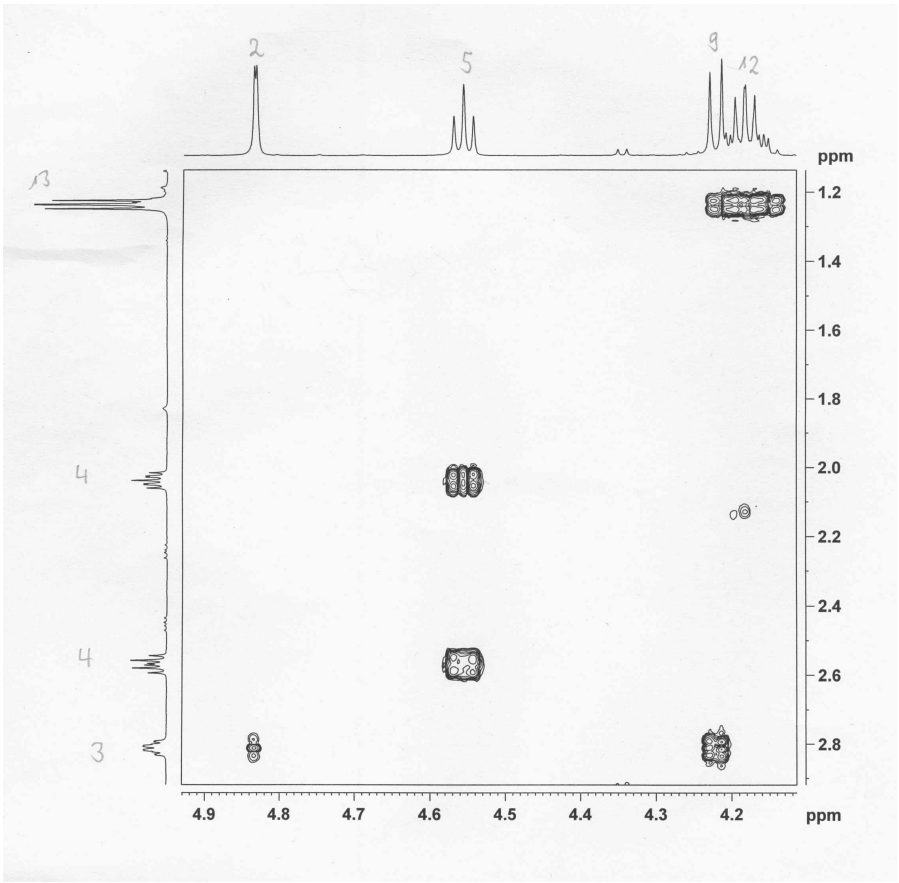


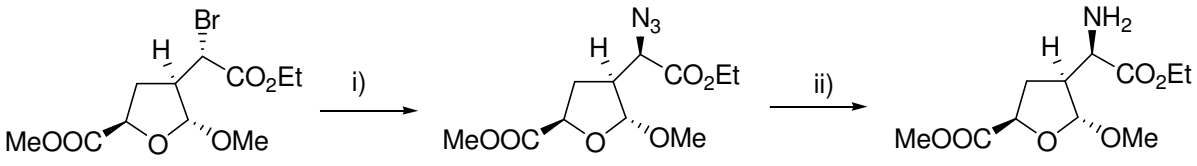
NOESY spectrum





COSY spectrum





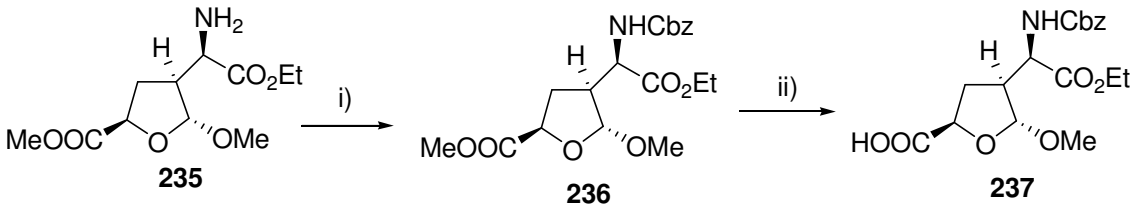
233 **234** **235**

Reagents and conditions: i) NaN_3, DMF, 15h, 97%, ii) H_2, Pd/C, EtOAc, rt, 12h, 95%

Scheme 3.10 Synthesis of α-aminoester

3.1.6 Protection of amine and selective hydrolysis of methyl ester

Protection of amine **235** with Cbz-chloride in presence of triethylamine in dichloromethane gave **236** in good yield. Once again the selective hydrolysis of methylester **236** was done with 1 equivalent of lithium hydroxide to get the corresponding acid **237** in excellent yield (Scheme 3.11).[17]

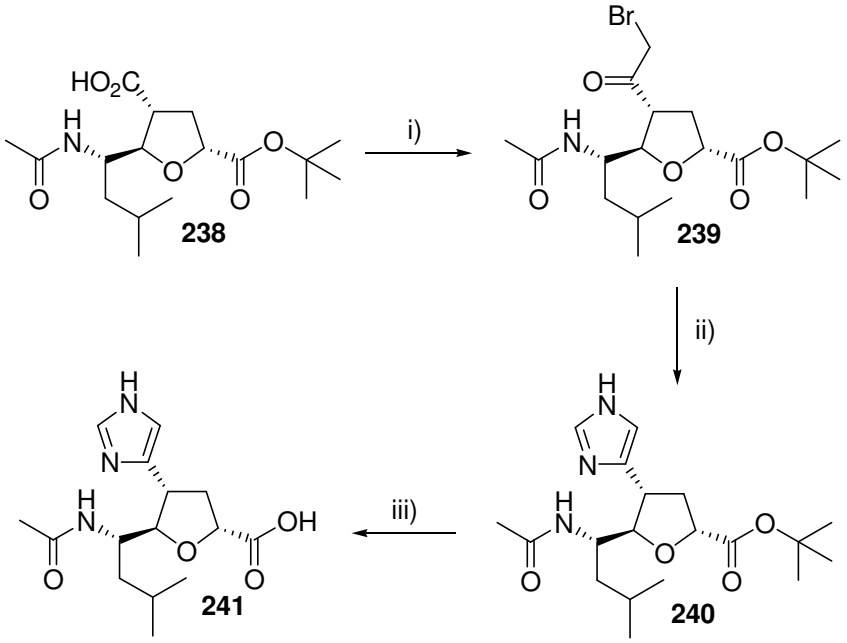


Reagents and conditions: i) CbzCl, Et_3N, DCM, rt, 85%, ii) LiOH (1eq), THF, H_2O, rt, 12h, 95%

Scheme 3.11 Protection of amine and hydrolysis of methyl ester

3.1.7 Synthesis of neuraminidase (NA) NA B inhibitor by Wang *et al*

Next it was envisioned to convert the carboxylic acid group of **237** into an imidazole ring via bromomethyl ketone intermediate following the method reported by Wang *et al.*



(i) *i*-BuOCOCl, CH_2N_2, then HBr, 60.0%; (ii) formamidine, NH_3, 45 °C, over night, 20.0%; (iii) 6N HCl, 4h, 95.8%.

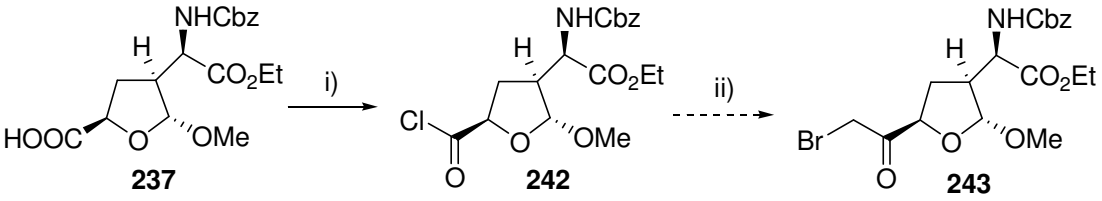
Scheme 3.12 Synthesis of influenza neuraminidase (NA) B inhibitor by Wang *et al*

Recently, Wang *et al* synthesized 2,3-disubstituted tetrahydrofuran-5-carboxylic acids as inhibitors of influenza neuraminidase (NA) NA A (IC_{50} = 0.5μM) and NA B (IC_{50} = 1.0μM). The 3-carboxylate of **238** was converted into the bromomethyl ketone moiety via diazomethyl ketone giving compound **239**. Condensation of **239** with formamidine in liquid ammonia in a sealed tube gave the imidazole derivative **240**, which, upon acid hydrolysis of *tert*-butyl ester, afforded the desired compound NA B (**241**) (Scheme 3.12).[17]

3.1.8 Synthesis of key intermediate bromomethyl ketone by Arndt-Eistert elongation

Treatment of the acid **237** with oxalylchloride in dichloromethane gave the corresponding acid chloride **242** and this acid chloride was directly subjected to diazomethane and HBr to

obtain bromomethyl ketone **243** as reported by Wang *et al* (Scheme 3.12)[17] but unfortunately the reaction failed to furnish product **243** (Scheme 3.13).

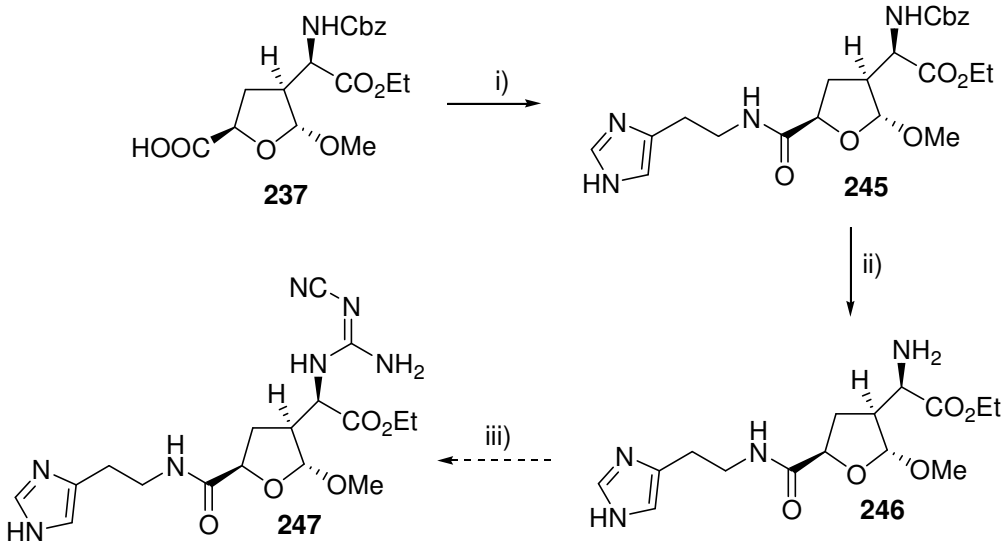


Reagents and conditions: i) oxalylchloride, DCM, rt, 70%,
ii) CH_2N_2, ether, HBr, 0 °C, over two steps

Scheme 3.13 Synthesis of bromomethyl ketone-tetrahydrofuran derivative

3.1.9 Synthesis of histamine H_3 and H_4 receptor agonists by increasing the spacer length between imidazole and THF ring.

Having the intermediate **237** in hand, it was coupled with histamine under standard reaction conditions (EDC, HOBt, NEt_3)[18] to obtain amide **245** for the synthesis of potential H_3 receptor agonist. The deprotection of Cbz by using Pd/C under H_2 atmosphere at room temperature gave the corresponding free amine **246** in good yield. This compound **246** was tested for the histamine H_3 and H_4 receptor agonist and it is only a very weak agonist for histamine H_3 receptor.[19] Introduction of cyanoguanidine may obtain histamine H_4 receptor potential agonist **247** (Scheme 3.15).



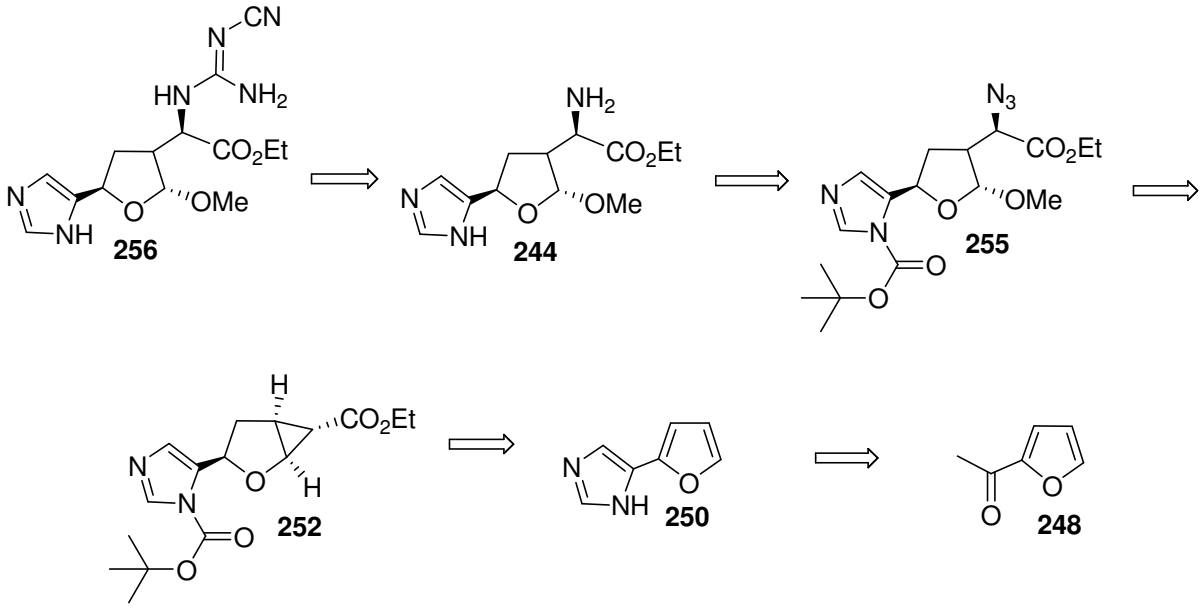
Reagents and conditions: i) Histamine, EDC, HOBt, NEt_3, DMF, rt, 70%, ii) H_2, Pd/C, EtOAc, 80% iii) $(MeS)_2C{=}NCN$, MeOH, 40% $MeNH_2$

Scheme 3.15 Synthesis of histamine-furane derivatives for H_3 and H_4 agonists

3.2 Enantioselective synthesis of histamine H_3 and H_4 receptor potential agonists by imidazole-furan cyclopropane ring opening methodology.

3.2.1 Retrosynthetic analysis for the Histamine H_3 and H_4 receptor agonists based on Imidazole-Furan.

The possible histamine H_4 receptor agonist **256** can be synthesized by the introduction of cyanoguanidine on amine **244**. Amine **244** would be possible to obtain from **255** by reduction of azide followed by deprotection of Boc.

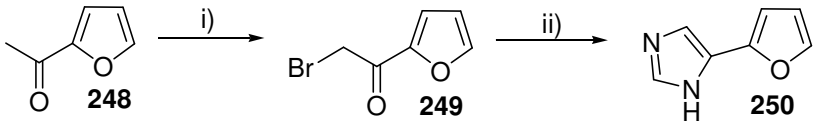


Scheme 3.16 Retrosynthetic analysis based on imidazole-furane cyclopropane to histamine H_3 and H_4 receptor agonists

NBS mediated ring opening cyclopropane **252** in methanol and subsequent S_N2 reaction with sodium azide may furnish **255**. Protection of **250** with Boc and subsequent asymmetric cyclopropanation followed by hydrogenation may give **252**. Bromination of acetyl furane **248** to the corresponding bromoacetyl furan and subsequent treatment with formamidine acetate in liq. ammonia can afford furan-imidazole **250** (Scheme 3.16).

3.2.2 Preparation of furan-imidazole

Bromination of acetylfuran **248** with 1 eq of bromine furnished bromoacetylfuran **249** with excellent yield.[20] The treatment of bromoacetylfuran **249** with formamidine acetate in the presence of 7N ammonia at 45 °C, after 12 h stirring in an autoclave gave the corresponding imidazole furan **250** in 65% yield (Scheme 3.17) following Wang's method.[17]

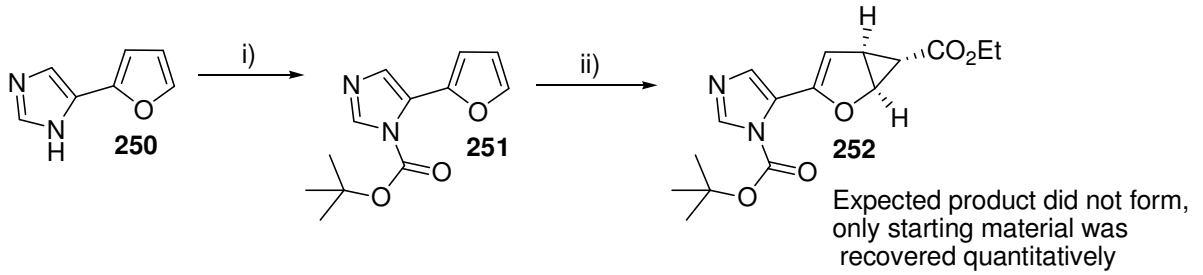


Reagents and conditions: Br_2 (1 eq), Et_2O, rt, 30 min, 90%,
ii) Formamidine acetate, liq. NH_3, 45 °C, 12 h, 65%

Scheme 3.17 Synthesis of furane-imidazole

3.2.3 Synthesis of cyclopropane dihydrofuran-imidazole

The NH protection of imidazole-furan was done by treating **250** with Boc anhydride and triethylamine in chloroform to obtain **251** in good yields. Subsequently, to obtain the desired product **252** the Cu (I) bisoxazoline catalyzed asymmetric cyclopropanation was tested under several conditions.



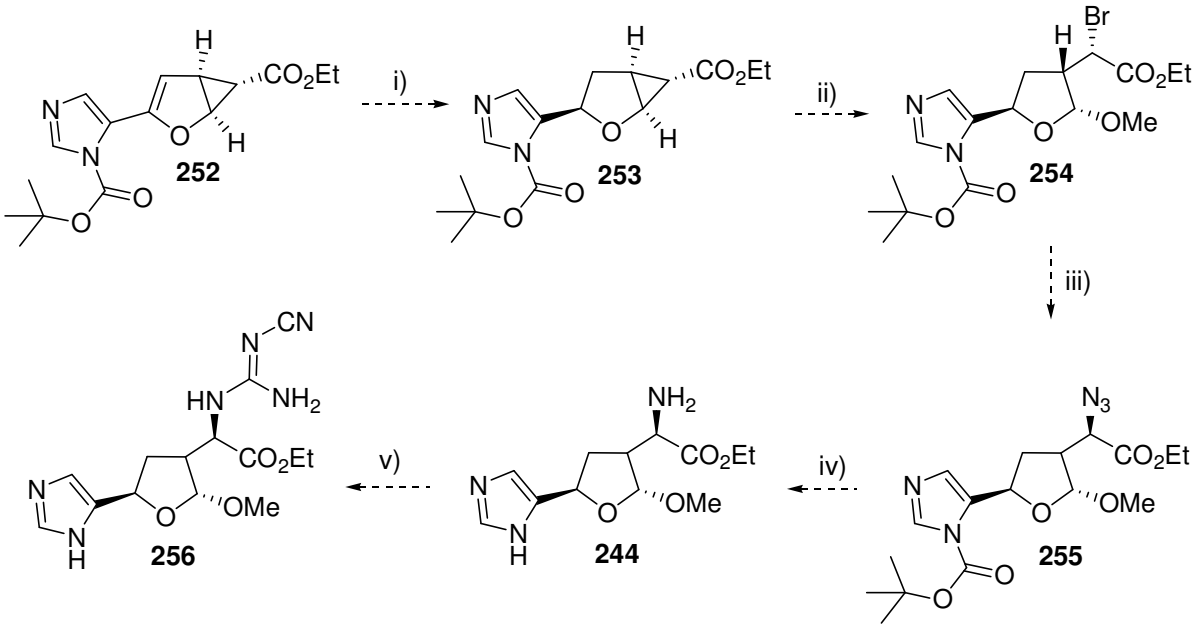
Reagents and conditions: i) $(Boc)_2O$, NEt_3, $CHCl_3$, rt, 85%, ii) (*S,S*)-^{i}Pr-Box, $Cu(OTf)_2$, $PhNHNH_2$, $N_2CHCOOEt$, 0 °C,

Scheme 3.18 Synthesis of cyclopropane-dihydrofurane-imidazole

When **251** was treated with (*S,S*)-isopropyl bisoxazoline, copper triflate, phenyl hydrazine and ethyl diazoacetate at 0 °C up to reaction timed of 3 days only the starting material was recovered along with dimerized products stemming from ethyl diazoacetate. The cyclopropanation of **251** was also done without using a chiral ligand just by addition of copper triflate, phenyl hydrazine and ethyldiazoacetate to see the racemic version of the reaction but even under these conditions the reaction did not work, neither at 0 °C nor at room temperature. Finally the cyclopropanation was also tested with dirhodiumtetraacetate as an alternative to the copper catalysts previously employed. In this case also only starting material was recovered (Scheme 3.18).

3.2.4 Proposed synthesis of histamine H_3 and H_4 receptor potential agonists

Hydrogenation of the double bond in **252** can be done with Pd/C under H_2 atmosphere in ethylacetate to afford **253**. Upon treatment of **253** with NBS in methanol may give **254** which can undergo S_N2 reaction with NaN_3 to obtain **255**. Reduction of **255** with Pd/C in presence of hydrogen followed by deprotection of Boc in the presence of acid would furnish **244**. Introduction of cyanoguanidine on **244** may afford **256** as possible H_4 receptor agonist (Scheme 3.19).

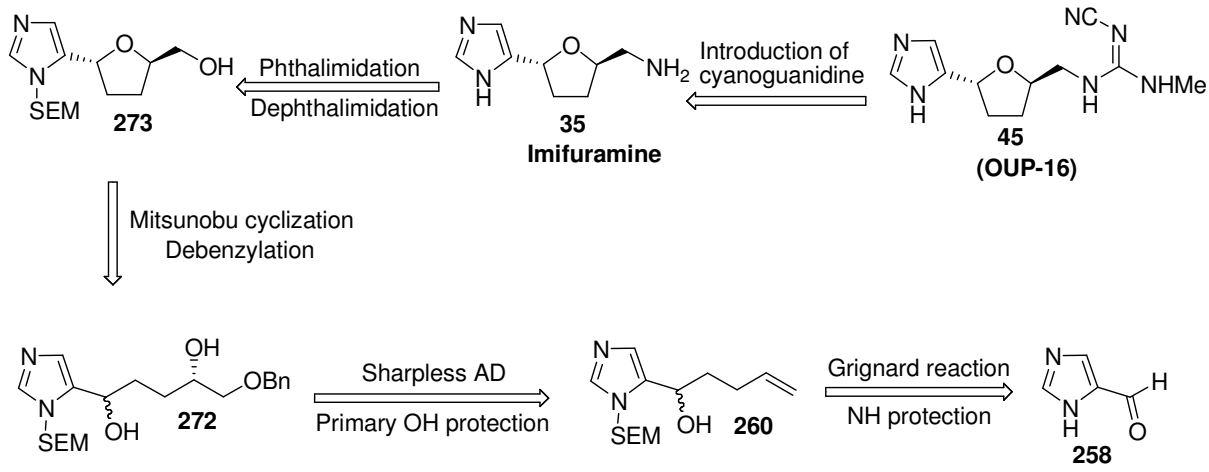


Reagents and conditions: i) H_2, Pd/C, EtOAc, rt ii) NBS, MeOH, rt iii) NaN_3, DMF, rt iv) H_2, Pd/C, EtOAc, 3N HCl, v) $(MeS)_2C{=}NCN$, MeOH, 40% $MeNH_2$

Scheme 3.19 Proposed synthesis of histamine H_3 and H_4 receptor potential agonists

3.3 Synthesis of Imifuramine and OUP-16 as an alternative route to Kurihara's synthesis[21]

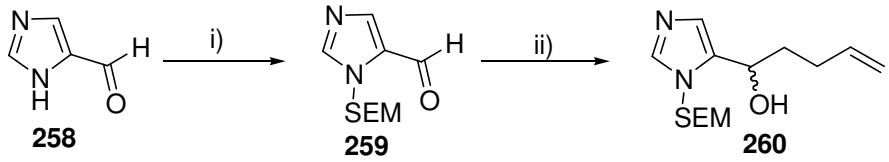
The histamine H_4 receptor agonist (OUP-16) **45** can be obtained by introduction of cyanoguanidine on amine **35**. In turn, it should be possible to obtain imifuramine **35** from **273** by phthalimidation and dephthalimidation. Mitsunobu cyclization of **272** followed by debenzylation may afford the cyclized product **273**. Sharpless asymmetric dihydroxylation of **260** with AD-mix-α and subsequent benzylation of the primary hydroxyl group can furnish the corresponding diol **272**. Protection of aldehyde **258** followed by Grignard reaction with butenyl bromide would furnish **260** (Scheme 3.20).



Scheme 3.20 Retrosynthetic analysis for imifuramine (H_3 agonist) and OUP-16 (H_4 agonist)

3.3.1 NH protection and Grignard reaction of imidazole aldehyde

The NH protection of imidazole aldehyde **258** was done with SEM-Cl in presence of triethyl amine in dichloromethane for 12 h to furnish **259** in good yield.[22] The Grignard reaction of **259** using butenyl magnesium bromide, (prepared in situ by addition of butenyl bromide to Mg in THF at 0 °C upon stirring for 30 minutes) from 0 °C to room temperature for 12 h furnished the alcohol **260** in 60% yield (Scheme 3.21).



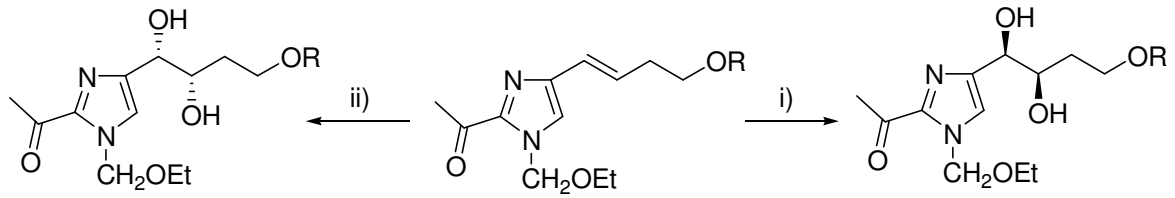
Reagents and conditions: i) SEM-Cl, Et_3N, DCM, 70%
ii) Butenylbromide, Mg, THF, 30 min at 0 °C,12h at rt, 60%

Scheme 3.21 SEM protection and Grignard reaction with butenylbromide

3.3.2 Sharpless asymmetric dihydroxylation

In the 1980s, Sharpless discovered a combination of reagents that oxidize the C=C to almost pure single enantiomers of 1,2-diols.[23] The oxidizing agent is osmium tetroxide (OsO_4) in the presence of a reoxidizing agent, potassium ferricyanide ($K_3Fe(CN)_6$), a base such as potassium carbonate (K_2CO_3), and a chiral ligand that binds to OsO_4 and directs the attack of OsO_4 to either the top (β) face or bottom (α) face of C=C. These reagents are commercially available and are called AD-mix-α and AD-mix-β. Using $(DHQD)_2$-PHAL as the chiral ligand, AD-mix-β directs attack of the OH groups to the β face of C=C. Using $(DHQ)_2$-PHAL as the chiral ligand, AD-mix-α directs attack of the OH groups to the α face.[24]

Pyne and coworkers (Scheme 3.22) reported the Sharpless asymmetric dihydroxylation on imidazole derived internal olefin as an important contribution.[25-27] Catalytic asymmetric dihydroxylation (AD) of **261** at 0 °C for 4 days using commercially available AD mix-α or AD mix-β gave the syn-l,2-diols (*1'S,2'S*)-**265** or (*1'R,2'R*)-**263**, respectively, in moderate yields. The enantiomeric purities of **265** and **263** were 98 and 99% respectively, as determined by ^{1}H NMR analysis of their Mosher diester. Catalytic AD of the alcohol **262** with AD mix-β or AD mix-α gave triols **264** or **266**, respectively, in good yield but in 95 and 90 % enantiomeric purities as determined by ^{1}H NMR analysis of their respective tri-Mosher esters (Scheme 3.22).[25]



265 R = TBDMS (56% ee 98%)
266 R = H (76% ee 90%)

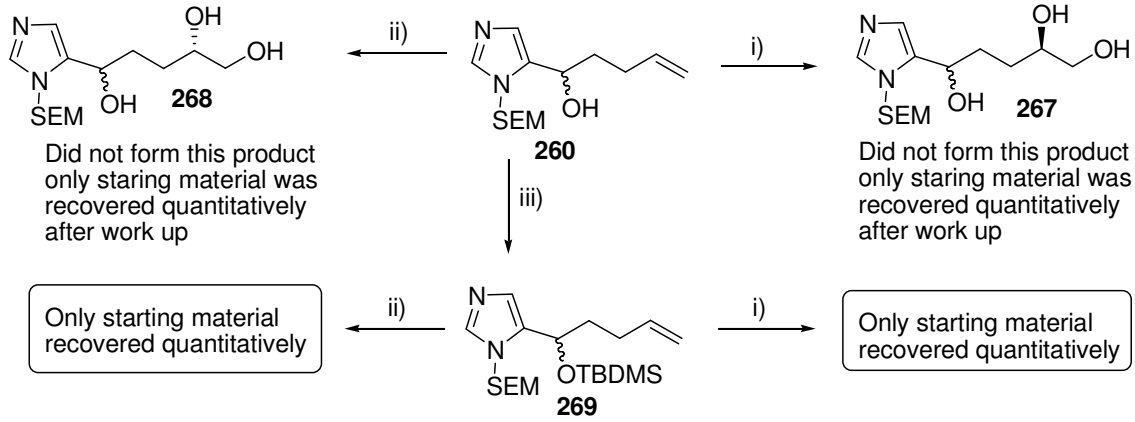
261 R = TBDMS
262 R = H

263 R = TBDMS (65%, ee 99%)
264 R = H (79%, ee 95%)

Reagents and conditions: i) AD-mix-β, $(DHQD)_2PHAL$, H_2O/*t*-BuOH, 0 °C, 3 days
ii) AD-mix-α, $(DHQ)_2PHAL$, H_2O/*t*-BuOH, 0 °C, 3 days

Scheme 3.22 Asymmetric synthesis of Imidazole triols by Pyne *et al*

Following the methodology developed by Pyne *et al*, the imidazole olefin **260** was aimed to be converted to the imidazole β-hydroxy triol **267** or imidazole α-hydroxy triol **268**. However, the Sharpless asymmetric dihydroxylation (AD) using readily available AD-mix-β in *tert*-butanol : water mixture (1:1) at 0 °C for 3 days did not afford the expected product **267**. Under these conditions only the starting material was recovered. Likewise, Sharpless asymmetric dihydroxylation with AD-mix-α under the same conditions mentioned above did not proceed to obtain the product **268**. Also in this case the starting material was recovered quantitatively. It was originally reported by Sharpless *et al*[28] that an asymmetric dihydroxylation of olefins which are sluggish at 0 °C can be performed at room temperature as well. Nevertheless, when **260** was treated with AD-mix- α or AD-mix-β at rt for 3-5 days the imidazole α-hydroxy triol **268** or imidazole β-hydroxy triol **267** could still not be obtained. The free OH in **260** was protected with TBDMS to afford **269** and the asymmetric dihydroxylation was performed with both AD-mix-α and AD-mix-β at 0 °C as well as at room temperature, unfortunately in both cases the reaction did not proceed even after stirring for 5 days, only starting material was recovered quantitatively (Scheme 3.23).

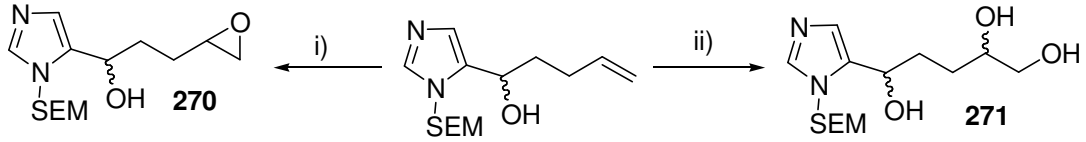


Reagents and conditions: i) AD-mix-β, *t*-BuOH/H_2O (1:1), 0 °C, 3days, ii) AD-mix-α, *t*-BuOH/H_2O (1:1), 0 °C, 3days, iii) TBDMS-Cl, imidazole, DMF, 70%

Scheme 3.23 Sharpless asymmetric dihydroxylation

3.3.3 Epoxidation and racemic dihydroxylation

Since the asymmetric dihydroxylation of **260** or **269** failed, it was decided to try routes that would install the diol unselectively either by direct dihydroxylation or via epoxide formation and subsequent opening with hydroxide. When **260** was treated with osmium tetroxide in presence of NMO at rt for 7 days the expected product **271** was not obtained and only the starting material was recovered. Treatment of **260** with *m*-CPBA in dichloromethane at rt for 3 days also did not furnish either epoxide **270** or triol **271**, only starting material was recovered (Scheme 3.24).



Did not form epoxide nither diol only starting material was recovered quantitatively

Did not form this product only staring material was recovered quantitatively after work up

Reagents and conditions: i) *m*-CPBA, DCM, 0 °C-rt, 3days ii) $K_2OsO_4.2H_2O$, NMO, *t*-BuOH/H_2O (1:1), rt, 7 days

Scheme 3.24 Epoxidation and racemic dihydroxylation

Conclusion

The lower yield of hydrogenation of cyclopropane ester **229** was solved by hydrolyzing methyl ester to the acid **231**, which underwent hydrogenation of its double bond in quantitative yield. The cyclopropane ring opening methodology was tried to apply towards the synthesis of histamine H_3 and H_4 receptor potential agonists with increased spacer length (Scheme 3.15) to give **245** and **246**, which were found to be very weak agonists. Acetyl furan **248** was converted to imidazole furan **250** in two steps (Scheme 3.17) and it may be a useful model study for the conversion of **243** to **244** (Scheme 3.14) as possible histamine H_3 and H_4 receptor agonists. All attempts for asymmetric cyclopropanation of imidazole furan failed. An alternative synthesis for imifuramine (**35**) and OUP-16 (**45**) was tried by Grignard reaction to **259** and Sharpless asymmetric dihydroxylation on **260**.

References

1) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res*. **1996**, *291*, 205.

2) a) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett*. **1999**, *1*, 1295.

b) Hoberg, J. O.; Lcaffey, D. J. *Tetrahedron Lett*. **1996**, *37*, 2533.

3) Ramana, C. V.; Nagarajan, M. *Carbohydr. Lett*. **1998**, *3*, 117.

4) Ramana, C. V.; Nagarajan, M. *Synlett* **1997**, 763.

5) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem*. **1996**, *61*, 8000.

6) Boechman, R.; Charette, A.; Asberom, T.; Johnston, B. *J. Am. Chem. Soc.* **1991,** *113,* 5337.

7) Yu, M.; Pagenkopf, B. L. *Tetrahedron,* **2005,** *61,* 321.

8) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997,** *119,* 10073.

9) Fernandez-Megia, E.; Gourlaouen, S.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998,** 991.

10) Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1995,** 217.

11) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997,** *62,* 7694.

12) Sridhar, P.R.; Ashalu, K. C.; Chandrasekaran, S. *Org. Lett.,* **2004,** *6,* 1777.

13) Haveli, S. D.; Sridhar, P. R.; Suguna, P.; Chandrasekaran, S. *Org. Lett.,* **2007,** *9,* 1331.

14) Haveli, S. D.; Roy, S.; Chandrasekaran, S. *Synlett,* **2009,** *20,* 451.

15) Yogesh Shinde, Ph.D thesis 2007, University of Regensburg.

16) Roland Weisser, Ph.D thesis 2007, University of Regensburg.

17) Wang, G. T.; Wang,S.; Gentles,R.; Sowin, T.; Maring, C. J.; Kempf, D. J.; Kati, W. M.; Stoll,V.; Kent D. Stewart, K. D.; Laver, B. *Bioorg. Med. Chem. Lett.* **2005,** *15,* 125.

18) Lee, D. Y. W.; He, M.; Kondaveti, L.; Liu-Chen, L. Y.; Ma, Z.; Wang, Y.; Chen, Y.; Li, J-G.; Beguin, C.; Carlezon, W. A.; Cohend, B. *Bioorg. Med. Chem. Lett.* **2005,** *15,* 4169.

19) See table 4 for pharmacological activity.

20) Rho, T.; Lankin, C. M.; Lankin, M. E.; Shih, D. H. *Synth. Commun.* **1997,** *27*, 4315.

21) Harusawa, S.; Araki, L.; Imazu, T.; Ohishi, H.; Sakamoto, Y.; Kurihara, T. *Chem. Pharma. Bull.* **2003,** *51,* 325.

22) Bhaumik, J.; Yao, Z.; Borbas, K. E.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 8807.

23) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.,* **1988,** *110,* 1968.

24) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

25) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1995,** *60,* 2378.

26) Cliff, M. D.; Pyne, S. G. *Tetrahedron Lett.* **1995,** *36,* 5969.

27) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1997,** *62,* 1023.

28) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H-L.; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang. X-L. *J. Org. Chem.* **1992**, *57*, 2768.

Chapter 4

4. Pharmacology

4.1 Determination of histamine receptor agonism and antagonism in GTPase assays

4.1.1 Generation of recombinant baculoviruses, cell culture and membrane preparation

Receptors were N-terminally tagged with the FLAG epitope and C-terminally tagged with a hexahistidine tag. The cDNA of the human H_3R was kindly provided by Dr. Robin Thurmond (Johnson & Johnson Research and Development, La Jolla, CA), and the cDNA of the human H_4R was from the UMR cDNA Resource Center at the University of Missouri-Rolla (Rolla, MO). Baculoviruses for the human H_3R and a fusion protein of the human H_4R with the RGS-protein GAIP were prepared in analogy to the procedures for the H_1R and the H_2R-$G_{s\alpha S}$ fusion protein using the BaculoGOLD transfection kit (BDPharmingen, San Diego, CA) according to the manufacturer's instructions.[1,2]

Sf9 cells were cultured in 250- or 500-mL disposable Erlenmeyer flasks at 28 °C under rotation at 150 rpm in SF 900 II medium (Invitrogen, Carlsbad, CA) supplemented with 5 % (v/v) fetal calf serum (Biochrom, Berlin, Germany) and 0.1 mg/mL gentamicin (Cambrex Bio Science, Walkersville, MD). Cells were maintained at a density of 0.5 – 6.0 x 10^6 cells/mL. After initial transfection, high-titer virus stocks were generated by two sequential virus amplifications. In the first amplification, cells were seeded at 2.0 x 10^6 cells/mL and infected with 1:100 dilution of the supernatant from the initial transfection. Cells were cultured for 7 days, resulting in the death of virtually the entire cell population. The supernatant fluid of this infection was harvested and stored under light protection at 4 °C. In a second amplification, cells were seeded at 3.0 x 10^6 cells/mL and infected with 1:20 dilution of the supernatant fluid from the first amplification. Cells were cultured for 48 h, and the supernatant fluid was harvested. After the 48 h culture period, the majority of cells showed signs of infections (e.g. altered morphology, viral inclusion bodies), but most of the cells were still intact. The supernatant fluid from the second amplification was stored under light protection at 4 °C and used as routine virus stock for membrane preparations.

In infections for membrane preparation, cells were sedimented by centrifugation and suspended in fresh medium at 3.0 x 10^6 cells/mL. Cells were infected with 1:100 dilutions of high-titer baculovirus stocks encoding the histamine H_3 and H_4 receptors, histamine receptor fusion proteins, G-protein subunits and RGS proteins. Cells were cultured for 48 h before

membrane preparation. Sf9 membranes were prepared as described,[2] using 1 mM EDTA, 0.2 mM phenylmethylsulfonyl fluoride, 10 µg/mL benzamidine and 10 µg/mL leupeptin as protease inhibitors. Membranes were suspended in binding buffer (12.5 mM $MgCl_2$, 1 mM EDTA and 75 mM Tris/HCl, pH 7.4) and stored at -80 °C until use. Protein concentrations were determined using the DC protein assay kit (Bio-Rad, Hercules, CA).

4.1.2 Synthesis of [γ-^{32}P]GTP. [γ-^{32}P]GTP was synthesized by enzymatic phosphorylation of GDP according to a previously described procedure.[3] [^{32}P]P_i (8,500-9,100 Ci/mmol orthophosphoric acid) was from PerkinElmer Life Sciences (Boston, MA, USA). All unlabeled nucleotides, glycerol-3-phosphate dehydrogenase, triose phosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase, and lactate dehydrogenase were from Roche (Mannheim, Germany). 3-Phosphoglycerate kinase and Lglycerol-3-phosphate was from Sigma.

4.1.3 Steady-state GTPase activity assay with Sf9 insect cell membranes expressing histamine H_3 and H_4 receptors

H_3R-regulated GTP hydrolysis was determined with membranes co-expressing human H_3R, mammalian $Gi_{\alpha 2}$, $G_{\beta 1\gamma 2}$ and RGS4. Human H_4R activity was measured with membranes co-expressing an H_4R-RGS19 fusion protein with $Gi_{\alpha 2}$ and $G_{\beta 1\gamma 2}$. Assay tubes contained Sf9 membranes (10-20 µg of protein/tube), $MgCl_2$ (H_1R, H_2R: 1.0 mM; H_3R, H_4R: 5.0 mM), 100 µM EDTA, 100 µM ATP, 100 nM GTP, 100 µM adenylyl imidodiphosphate, 5 mM creatine phosphate, 40 µg creatine kinase and 0.2 % (w/v) bovine serum albumin in 50 mM Tris/HCl, pH 7.4, as well as ligands at various concentrations. In H_4R assays, NaCl (final concentration of 100 mM) was included. Reaction mixtures (80 µL) were incubated for 2 min at 25 °C before the addition of 20 µL [γ-^{32}P]GTP (0.1 µCi/tube). Reactions were conducted for 20 min at 25 °C and terminated by the addition of 900 µL of slurry consisting of 5% (w/v) activated charcoal suspended in 50 mM NaH_2PO_4, pH 2.0. Charcoal absorbs nucleotides but not P_i. Charcoal-quenched reaction mixtures were centrifuged for 7 min at room temperature at 15.000 *g*. 600 µL of the supernatant fluid were removed, and $^{32}P_i$ was determined by liquid scintillation counting. Enzyme activities were corrected for spontaneous degradation of [γ-^{32}P]GTP. Spontaneous [γ-^{32}P]GTP degradation was determined in tubes containing all components described above, plus a high concentration of unlabeled GTP (1 mM) that, by competition with [γ-^{32}P]GTP, prevents [γ-^{32}P]GTP hydrolysis by enzymatic activities present in Sf9 membranes. Spontaneous [γ-^{32}P]GTP degradation was <1 % of the total amount of radioactivity added. The experimental conditions chosen ensured that not more than 10% of the total amount of [γ-^{32}P]GTP added was converted to $^{32}P_i$. All experimental data were

analyzed by non-linear regression with the Prism 4 program (GraphPad Software, San Diego, CA).[3,4]

4.1.4 Pharmacology activity for human histamine H_3 and H_4 receptor agonists

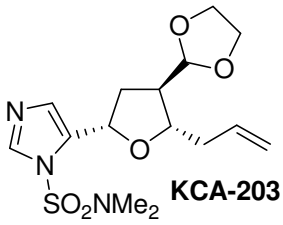
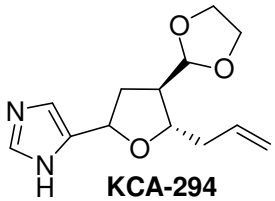
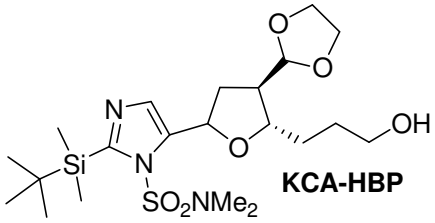
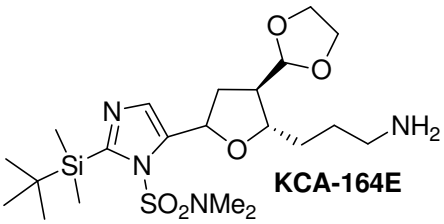
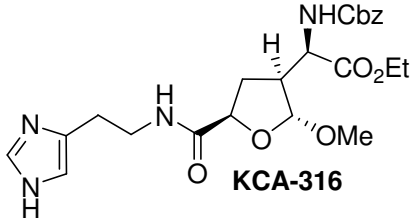
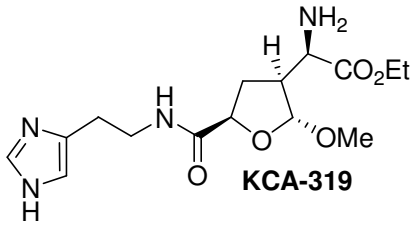
Agonist potencies and efficacies of KCA-compounds at hH_3R and hH_4R in the GTPase assay. Steady-state GTPase activity in Sf9 membranes expressing hH_3R and hH_4R was determined as described in section 4.1.3. Reaction mixtures contained ligands at concentrations from 1 nM to 100 µM as appropriate to generate saturated concentration-response curves. Data were analyzed by nonlinear regression and were best fit to sigmoid concentration-response curves. Typical basal GTPase activities ranged between 2 and 4 pmol/mg/min, and the maximal stimulatory effect of HA (10 µM) amounted to 50 to 80% above basal. The efficacy (*E*max) of histamine was determined by nonlinear regression and was set at 1.00. The *E*max values of other agonists were referred to this value. Data shown are the means ± S.E.M. of a representative experiment each performed in duplicate (Table 4).

4.1.5 Graphs.

Representative dose/response curves of KCA-compounds tested in the steady-state GTPase assay.

GTPase activity in Sf9 membranes expressing hH_3R was determined as described in chapter 4 and section 4.1.3. Reaction mixtures contained HA, KCA-compounds or THIO at the concentrations indicated on the abscissa to generate saturated concentration/response curves as far as possible. Data were analyzed by nonlinear regression and were best fit to sigmoid concentration/response curves. Data points are the means ± S.E.M. of a representative experiment performed in duplicates. A summary of the results of experiments with other KCA-compounds is shown in Table 4.

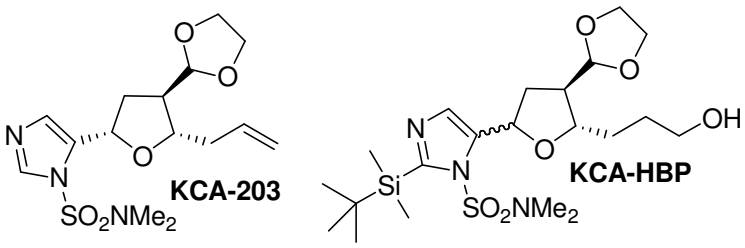
Table:4

Compound	$hH_3R + G\alpha_{i2} + \beta_1\gamma + RGS4$			$hH_4R\text{-}GAIP + G\alpha_{i2} + \beta_1\gamma_2$		
	E_{max}	EC_{50}/K_B (nM)	N*	E_{max}	EC_{50}/K_B (nM)	N*
 **KCA-203**	n. a.	n. a.	1	n. a.	n. a.	1
 **KCA-294**	n. a.	n. a.	1	n. a.	n. a.	1
 **KCA-HBP**	n. a.	n. a.	1	n. a.	n. a.	1
 **KCA-164E**	n. a.	n. a.	1	n. a.	n. a.	1
 **KCA-316**	0.80	11810	1	n. a.	n. a.	1
 **KCA-319**	0.20	27840	1	n.a.	n.a.	1

* Number of independent experiments, n. a. : not active

Figure 4.1: Concentration/response curves of HA, THIO, KCA-203 and KCA-HBP on GTPase activity in Sf9 cell membranes expressing hH_3R, $G\alpha_{i2}$, $G\beta_1\gamma_2$ and RGS4.

GTPase activity in Sf9 membranes was determined as described in chapter 4 and section 4.1.3. Reaction mixtures containing membranes (10 µg of protein/tube) and ligands at concentrations indicated on the abscissa. Data shown are the means ± S.E.M. of a representative experiment performed in duplicates. Data were analyzed by nonlinear regression and were best fitted to sigmoidal concentration/response curves.



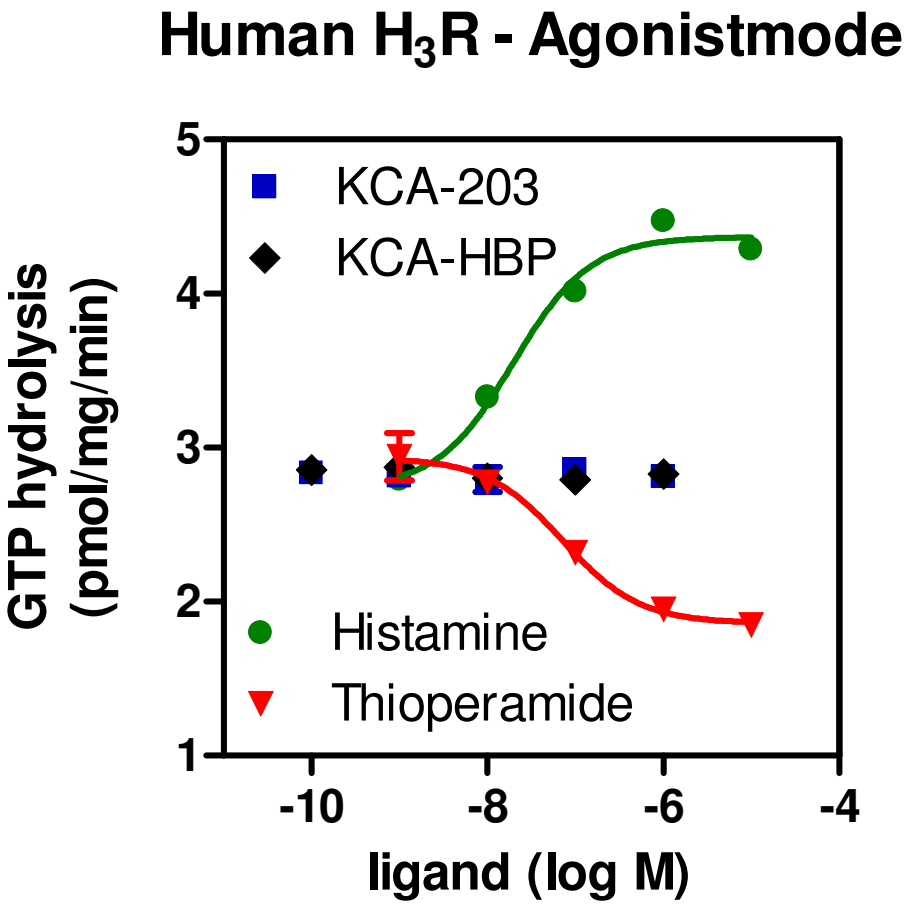
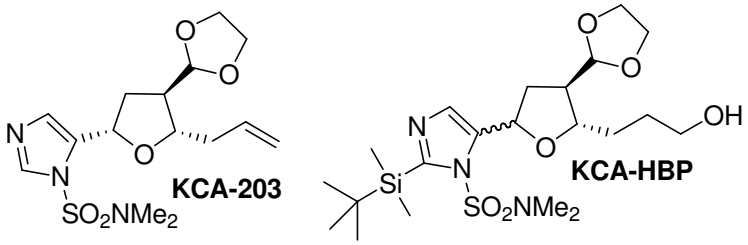


Figure 4.1 Pharmacology activity of KCA-203 and KCA-HBP for hH_3R agonist mode

Figure 4.2: Inhibition curves of THIO, KCA-203 and KCA-HBP on HA pre-stimulated GTPase activity in Sf9 cell membranes expressing hH_3R, $G\alpha_{i2}$, $G\beta_1\gamma_2$ and RGS4.

GTPase activity in Sf9 membranes was determined as described in chapter 4 and section 4.1.3. Reaction mixtures containing membranes (10 µg of protein/tube), HA (100 nM) and ligands at concentrations indicated on the abscissa. Data shown are the means ± S.E.M. of a representative experiment performed in duplicates. Data were analyzed by nonlinear regression and were best fitted to sigmoidal inhibition curves.



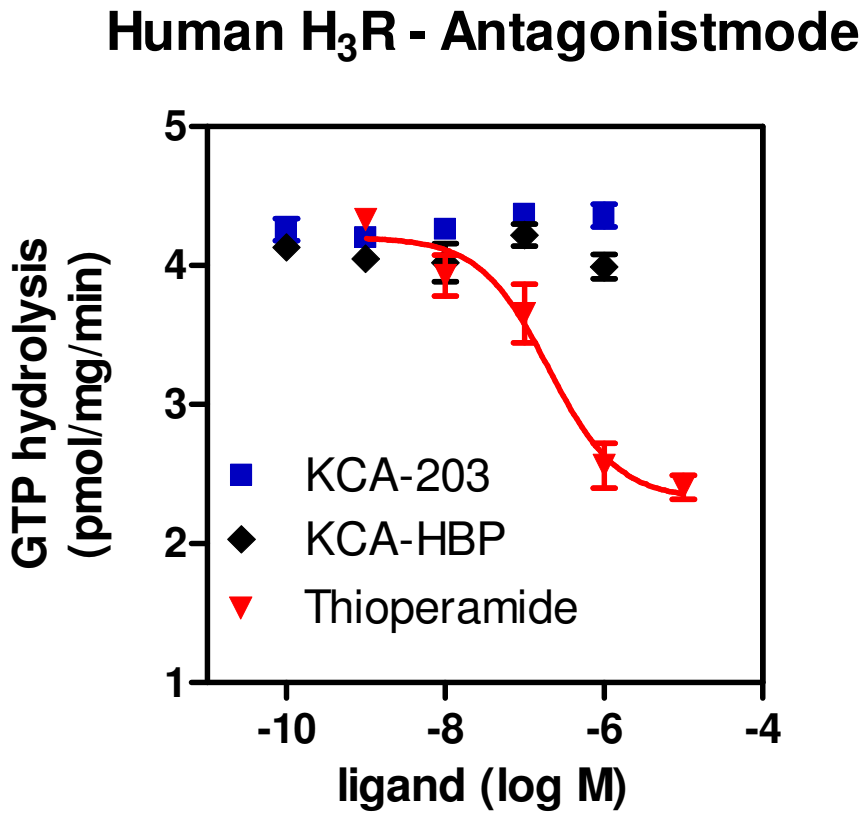
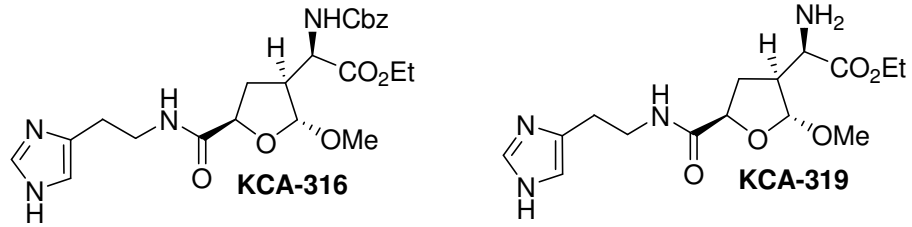


Figure 4.2 Pharmacology activity of KCA-203 and KCA-HBP for hH_3R antagonist mode

Figure 4.3: Effects of KCA-316 and KCA-319 on GTPase activity in Sf9 cell membranes expressing hH_3R, $G\alpha_{i2}$, $G\beta_1\gamma_2$ and RGS4.

Data are expressed as percentage change in GTPase activity induced by KCA-316 and KCA-319 compared to the GTPase activities stimulated by HA or inhibited by THIO. Basal GTPase activity was set to 0% and the maximal stimulation of GTPase activity by HA (10 μM) was defined to be 100%. All other values were referred to HA. Data shown are the means ± S.E.M. of a representative experiment performed in duplicates.



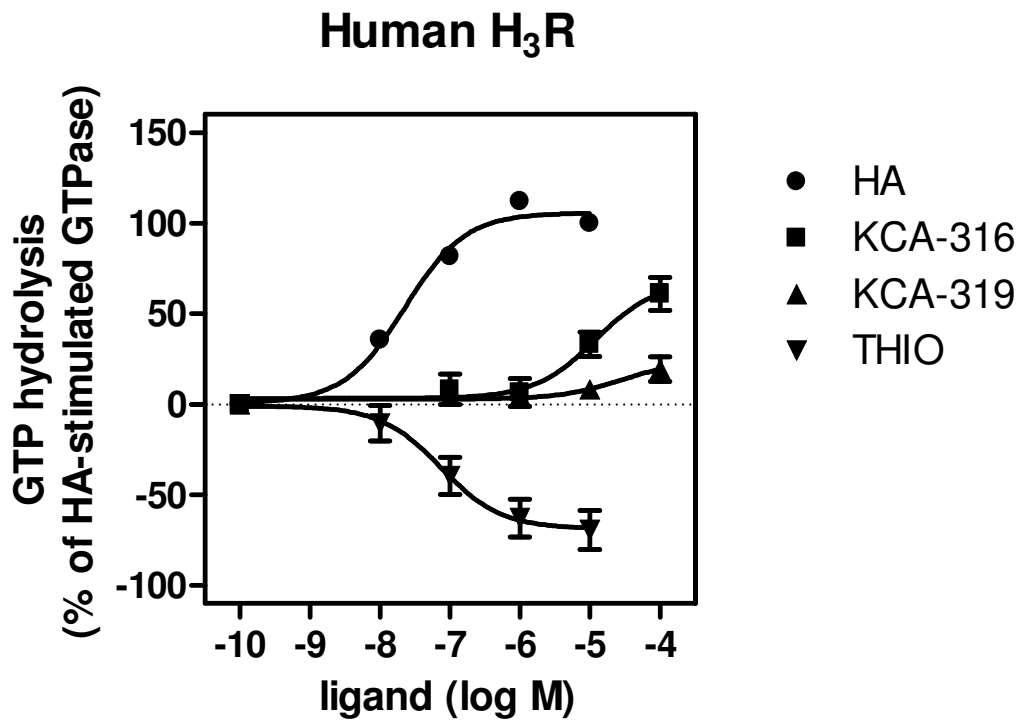


Figure 4.3 Pharmacology activity of KCA-316 and KCA-319 for hH_3R

References

1) Kelley, M. T.; Burckstummer, T.; Wenzel-Seifert, K.; Dove, S.; Buschauer, A.; Seifert, R. *Mol Pharmacol* **2001,** *60,*1210.

2) Houston, C.; Wenzel-Seifert, K.; Burckstummer, T.; Seifert, R. *J Neurochem* **2002,** *80,* 678.

3) Stark, H.; Purand, K.; Hüls, A.; Ligneau, X.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1996**, *39,* 1220.

4) Ghorai, P.; Kraus, A.; Keller, M.; Go¨tte, C.; Igel, P.; Schneider, E.; Schnell, D.; Bernhardt, G.; Dove, S.; Zabel, M.; Elz, S.; Seifert, R.; Buschauer, A. *J. Med. Chem.* **2008,** *51,* 7193.

Experimental Part

Instruments and general techniques used

^{1}H NMR-Spectra were recorded Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz). The chemical shifts are reported in δ (ppm) relative to all deuterated solvents chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d_6, 2.49 ppm), methanol-d_4, (CD_3OD, 3.34 ppm) and tetramethylsilane (TMS, 0.00 ppm) as an internal standard. The spectra were analysed by first order, the coupling constants (*J*) are reported in Hertz (Hz). Characterization of signals: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bm = broad multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, integration is determined as the relative number of atoms. Diastereomeric ratios were determined by comparing the integrals of corresponding protons in the ^{1}H NMR spectra.

^{13}C NMR-Spectra were recorded on Bruker Avance 300 (75.5 MHz), Bruker Avance 400 (100.6 MHz) and Bruker Avance 600 (150.9 MHz). The chemical shifts are reported in δ (ppm) relative to chloroform ($CDCl_3$, 77.0 ppm), dimethylsulfoxide (DMSO-d_6, 39.52 ppm), methanol-d_4 (CD_3OD, 49.0 ppm) and tetramethylsilane (TMS, 0.00 ppm) as an internal standard.

2D-NMR-Spectra (COSY, NOESY, HMBC and HSQC) were recorded on Bruker Avance 400 (400 MHz), Bruker Avance 600 (600 MHz).

IR-Spectra were recorded with an AT1 Mattson Genesis Series FT-IR or a Bio-Rad Excalibur series FT-IR.

MS-Spectra were recorded in Finnigan MAT 95, Varian MAT 311A, Finnigan TSQ 7000 and Micromass Q TOF.

Optical Rotations were measured on a Perkin-Elmer-Polarimeter 241 with sodium lamp at 589 nm and also with KRUSS OPTRONIC GERMANY in the specified solvent.

HPCL and GC Chiral HPLC (335 UV detector) was performed on a Kontron Instruments 325 System. Chiracel OD/OD-H, AS and OJ columns were used (50x4.6 mm, 10 "m,) at the mentioned flowed rate and wavelength. Gas chromatography (GC) was measured on Fisons Instruments GC 8000 series (Data Jet Integrator, CP-chiralsil-DEX-CP column).

Ozonolysis experiments were carried out using FISCHER process technology ozone generator. Microwave assisted reaction was done using Discover CEM.

Thin layer chromatography (TLC) was performed on aluminum plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Visualisation was accomplished by

UV-light (wavelength λ = 254 nm), Mostain, Molybdatophosphoric acid and a vanillin/sulphuric acid solution.

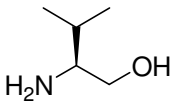
Column chromatography was performed on silica gel (Merck Geduran 60, 0.063-0.0200 mm mesh) and flash-silica gel 60 (0.040-0.063 mm mesh).

Solvents: Dry solvents were prepared by following the standard methods. THF and toluene were distilled over sodium/benzophenone and stored over sodium wire. Dichloromethane and DMF were distilled over calcium hydride. Ethanol and methanol were distilled over magnesium and stored under nitrogen over 4 Å MS. HPLC grade solvents were used without further purification directly from MBRAUN MB SPS solvent purifier.

All reactions with oxygen or moisture sensitive reactant were performed under nitrogen/Argon atmosphere.

Synthesis of bis(oxazolines)

(*S*-amino-3-methylbutan-1-ol (106))-2

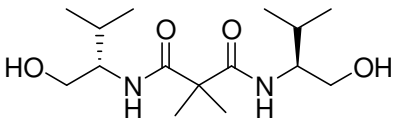


10 g (85.3 mmol) of *L*-Valine **105** and 8.1 g (214 mmol) of sodium borohydride were taken in 150 mL of anhydrous THF under nitrogen. 21.6 g (85.3 mmol) of iodine was taken in 60 mL of anhydrous THF and added dropwise to the above reaction mixturte at 0 °C slowly over a period of 1h, resulting in evolution of hydrogen gas. Then the reaction was refluxed for 20h and cooled to room temperature, then methanol was added cautiously until the stirred solution become clear. The reaction mixture was stirred for additional 30 minutes and solvent was evaporated under reduced pressure. This crude mixture was dissolved in 60 mL of 20% KOH and stirred for 4 hours and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure which obtained valinol as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (dd, *J* = 6.8, 4.2 Hz, 6H), 1.55 (dq, *J* = 13.5, 6.7 Hz, 1H), 2.54 (ddd, *J* = 8.8, 6.4, 4.0 Hz, 1H), 3.27 (dd, *J* = 10.5, 8.8 Hz, 1H), 3.63 (dd, *J* = 10.5, 4.0 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.46, 19.36, 31.68, 58.52, 64.79

***N,N′*-bis((*S*)-1-hydroxy-3-methylbutan-2-yl)-2,2-dimethylmalonamide (107)**



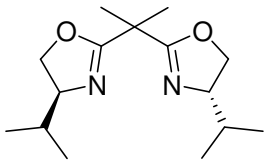
13 g of *L*-Valinol **106** (126.09 mmol) was taken in 130 mL of anhydrous dichloromethane and to this was added triethyl amine (44 mL, 5 eq) at 0 °C. 2,2-Dimethyl melonyl chloride (8.45 mL, 1 eq) in dichloromethane was added dropwise to the above reaction mixture. The reaction mixture was stirred for 3h at room temperature. The reaction mixture was washed with 1N HCl, and the aqueous layer was extracted with dichloromethane, the combined organic layers are washed with saturated sodium bicarbonate, brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the product was recrystallized in ethyl acetate.

R_f = 0.25 (EtOAc: MeOH, 95:5), $[\alpha]_D^{24}$ –6.0 (c 0.50, CH_2Cl_2), Mp 98-99 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.8 Hz, 6H), 1.50 (s, 6H), 1.82 (oct, 2H, *J* = 6.8 Hz), 2.66 (bs, 2H), 3.52 (m, 2H), 3.69-3.86 (m, 4H), 6.41 (d, *J* = 8.6 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.81, 19.63, 23.72, 29.13, 50.20, 57.13, 63.52, 174.50

(*S*)-4,5-dihydro-2-(2-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)propan-2-yl)-4-isopropyloxazole (108)



To a mixture of (–)-(*S,S*)-*N,N'*-Bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethyl-malonamide (**107**, 18.76 g, 620.0 mmol, 1.0 eq) and 4-dimethylamino pyridine (0.75 g, 6.2 mmol, 0.1 equiv.) in dry CH_2Cl_2 (400 mL) was slowly added triethyl amine (37.6 mL, 270.0 mmol, 4.4 equiv.) over 15 min. Subsequently a solution of tosyl chloride (23.65 g, 124.0 mmol, 2.0 equiv.) in dry CH_2Cl_2 (50 mL) was added dropwise *via* the addition funnel. The reaction mixture was stirred for additional 48 h at room temperature where the color changed to yellow and cloudy precipitate occurred. The precipitate was dissolved in CH_2Cl_2 (150 mL). The reaction mixture was then washed with saturated NH_4Cl (250 mL) followed by water (150 mL) and saturated $NaHCO_3$ (200 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and concentration in vacuo the residue was purified by hot *n*-pentane extraction to afford **108** (7.466 g, 44% yield) as a colorless oil.

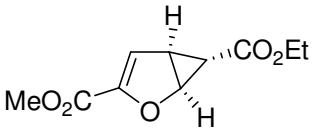
R_f = 0.25 (CH_2Cl_2: MeOH, 19:1), $[\alpha]_D^{24}$ –107.5 (c = 1.0, CH_2Cl_2)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, 6H, *J* = 6.8 Hz), 0.91 (d, 6H, *J* = 6.8 Hz), 1.51 (s, 6H), 1.88-1.73 (m, 2H), 3.93-4.06 (m, 4H), 4.15-4.26 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.30, 18.50, 24.41, 32.23, 38.52, 69.90, 71.54, 168.70

Synthesis of γ-butyrolactones.

6-Ethyl 3-methyl (1*S*,5*S*,6*S*)-(−)-2-Oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate (110)



100 g (793.65 mmol) of methylfuroic ester (**109**) was taken in 2L, (3 neck) round bottom flask and cooled to 0 ºC under nitrogen. To this, 1.74 g (6.5 mmol) of bisoxazoline ligand (**108**), 1.895 g (5.2 mmol) copper triflate, 0.65 mL (6.5 mmol) phenyl hydrazine were added sequentially to the neat stirred methylfuroic ester. To the above mixture 1952 g (1.952 kg) of 14% ethyl diazoacetate was added slowly dropwise with a special dropping funnel over a period of 16 days at 0 ºC. The reaction mixture was filtered through a pad of basic alumina and eluted with DCM until clearness of the eluent. Removing the solvent under reduced pressure afforded the crude product as yellow-brown oil. Crude product was devided into two parts for the column chromatography. Silica gel column chromatography (2 batches) of the crude product with 5% EA/PE obtained 69 g of cyclopropane ester **110** (41% yield). Crystallization in pentane/DCM mixture obtained **110** with 99% ee.

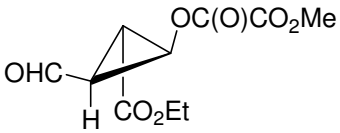
R_f (SiO_2, EA:PE 1:9, Moistain) = 0.35, Mp. 42 °C, $[\alpha]_D^{20}$ = –272 (c = 1.0, CH_2Cl_2)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (dd, 1H, *J* = 2.7, 1.1 Hz), 1.23 (t, 3H, *J* = 7.1 Hz), 2.87 (ddd, 1H, *J* = 5.3, 2.9, 2.7 Hz), 3.78 (s, 3 H), 4.12 (q, 2H, *J* = 7.1 Hz), 4.97 (dd, *J* = 5.3, 1.1 Hz, 1H), 6.39 (d, *J* = 2.9 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.20, 21.50, 31.90, 52.10, 61.00, 67.50, 116.00, 149.30, 159.50, 171.70

IR (KBr): = 3118, 2956, 1720, 1617, 1428, 1380, 1297, 1166, 1124, 1041, 954, 831, 725 cm^{-1}

(2*S*,3*R*)-ethyl 2-((methoxycarbonyl)formoyloxy)-3-formylcyclopropanecarboxylate (111)



17.88 g (84.33 mmol) of cyclopropane ester **110** was taken in 250 mL of anhydrous dichloromethane and cooled to -78 °C, ozone was passed the through controlled ozone generator till the blue colour solution was appeared (about 30-45 minutes). Then the excess ozone was expelled by passing oxygen through $CaCl_2$ and KOH guard tubes for 15 minutes. To this 25 mL of DMS was added and the reaction was stirred for 24h. The reaction mixture was washed with sodium bicarbonate (25×4), dried over anhydrous sodium sulfate. The

solvent was removed under reduced pressure and the product obtained in quantitatively was crystallized in ether at -30 °C.

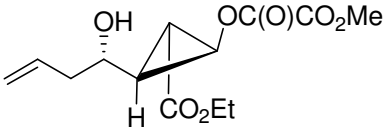
Mp. 52 °C. $[\alpha]_D^{20} = -37.7$ (c = 1.0, CH_2Cl_2)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* =7.1 Hz, 3H), 2.79 (ddd, *J* = 7.3, 6.0, 4.0 Hz, 1H), 2.90 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.91 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 2H) 4.83 (dd, *J* = 7.3, 3.6 Hz, 1H), 9.45 (d, *J* = 4.0 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.10, 26.40, 34.90, 54.00, 58.9, 62.00, 156.60, 156.90, 168.10, 192.70

IR (KBr): = 3066, 3015, 2963, 2892, 1785, 1751, 1735, 1706, 1445, 1345, 1313, 1210, 1167, 1086, 1011, 963, 867, 790, 715, 613, 495 cm^{-1}

(2*S*,3*S*)-ethyl 2-((methoxycarbonyl)formoyloxy)-3-((*S*)-1-hydroxybut-3-enyl) cyclopropanecarboxylate (112)

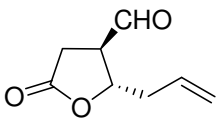


14 g (57.33 mmol) of cyclopropane carbaldehyde **111** was taken in 220 mL of anhydrous dichloromethane at -78 °C, to this 8.64 mL (68.79 mmol) of $BF_3.Et_2O$ was added slowly. After 5 minutes, 13.7 mL (86 mmol) of allyl trimethylsilane was added dropwise and the reaction was stirred for 12h at -78 °C. Saturated sodium bicarbonate was added to the reaction mixture and allowed to room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×25 mL). The combined organic layers washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure obtained the cyclopropane allyl alcohol **112** in quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3H), 1.81– 1.92 (m, 1H), 2.15 (dd, *J* = 6.2, 2.7 Hz, 1H), 2.31 – 2.51 (m, 4 H), 3.70 (ddd, *J* = 7.3, 7.3, 5.4 Hz, 1H), 3.88 (s, 3 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 4.72 (dd, *J* = 7.5, 2.8 Hz, 1H), 5.14 – 5.22 (m, 2 H), 5.76 – 5.93 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 24.7, 31.3, 41.7, 53.8, 58.8, 61.3, 67.8, 118.8, 133.4, 157.2, 157.2, 170.6

(2*S*,3*R*)-2-allyl-tetrahydro-5-oxofuran-3-carbaldehyde (55)



16.4 g (61.194 mmol) of cyclopropane allyl alcohol **112** was taken in 260 mL of methanol and to this 9.65 g (30.6 mmol) of $Ba(OH)_2$ in 310 mL of methanol was added dropwise at 0 °C. The reaction was stirred for 6 hours and the solvent was removed under reduced pressure.

The crude mixture was diluted with dichloromethane and water. The layers were separated after long time. The separation of organic and aqueous layers was easy when Et_3N was used as base instead of $Ba(OH)_2$. The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by column chromatography (1:1 EA/PE) to obtain **55** in 50% yield.

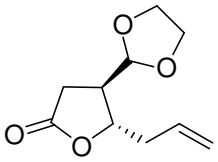
TLC R*f* (SiO_2, EA:PE 1:1, Moistain) = 0.35

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 – 2.59 (m, 2H), 2.71 (dd, *J* = 18.2, 9.9 Hz, 1H), 2.89 (dd, *J* = 18.2, 7.5 Hz, 1H), 3.19 (dddd, *J* = 10.0, 7.3, 6.0, 1.2 Hz, 1H), 4.74 (dd, *J* = 11.9, 6.2 Hz, 1H), 5.10 – 5.27 (m, 2 H), 5.75 (dddd, *J* = 17.3, 10.0, 7.0, 3.5 Hz, 1H), 9.69 (d, *J* = 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8, 39.2, 51.2, 78.0, 120.4, 130.9, 174.2, 197.4

Synthesis of histamine H_3 and H_4 receptor potential agonists based on γ-butyrolactones.

(5*S*,4*R*)-5-Allyl-4[1,3] dioxolan-2-yl-dihydro-furan-2-one (146)



The aldehyde **55** (3.9 g, 25.32 mmol) was dissolved in 120 mL of benzene and to this 7.05 mL (126.6 mmol) of ethylene glycol and (0.962 g , 5.06 mmol) *p*-Toluene sulfonic acid were added under nitrogen.The reaction mixture was refluxed with Dean Stark apparatus for 24h. Then the reaction mixture was cooled to rt and diluted with diethyl ether and washed with $NaHCO_3$ and brine. The aqueous layer was extracted with ether (3 × 40 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography using EA/PE (20:80) as eluent to obtain **146** (4.25 g, yield 85%).

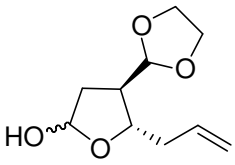
TLC R_f (EA:PE 1:1, Mostain) = 0.70

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32-2.60 (m, 5H), 3.80-4.0 (m, 4H), 4.47-4.54 (m, 1H), 4.85 (d, 1H, *J* = 3.29), 5.10-5.20 (m, 2H), 5.68-5.84 (m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.55, 39.20, 42.38, 65.41, 65.58, 79.66, 103.46, 119.25, 132.03, 175.93

HRMS: Reiser *et al*, *Chem. Eur.J.* **2003**, *9,* 260

(2*R/S*,4*R*,5*S*)-5-Allyl-4-[1,3]dioxolan-2-yl-tetrahydro-furan-2-ol (147)



3.0 g (15.14 mmol) of **146** was dissolved in 160 mL of anhydrous dichloromethane under nitrogen and cooled to -78 °C. To this 22.7 mL (22.7 mmol) of DIBAL-H (1M solution in DCM) was added slowly drop wise. Then the reaction was stirred for 2 h. The reaction was quenched by the addition of ethyl acetate and warmed to room temperature. Then saturated solution of sodium potassium tartarate was added and the mixture was stirred for another 2 h. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulphate. Then the solvent was removed under reduced pressure to obtain lactol as anomeric mixture. A filter column (EA/PE 22:78) was done to get the pure product **147** in excellent yield (2.74 g, 90%).

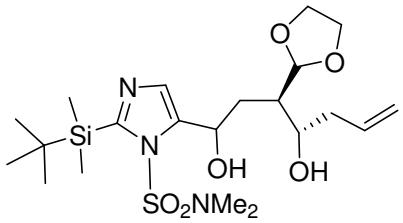
TLC R_f (EA:PE 1:1, Mostain) = 0.65

^{1}H NMR (300 MHz, $CDCl_3$) (from KCA-95): 1.92-2.05 (m, 1H), 2.10-2.22 (m, 1H), 2.25-2.55 (m, 3H), 3.80-4.08 (m, 4H), 4.15-4.23 (m, 1H), 5.01-5.15 (m, 2H), 5.34-5.49 (m, 1H), 5.70-5.95 (m, 1H)

^{13}C NMR (from KCA-95) (75 MHz, $CDCl_3$): δ = 34.65, 35.59, 40.07, 41.38, 44.48, 45.33, 64.90, 65.00, 65.10, 65.24, 65.38, 80.35, 98.34, 104.42, 105.07, 116.99, 117.62, 134.08, 135.22

HRMS calcd for $C_{10}H_{16}O_4Na$ (M+Na) 223.0946, found 223.0921

(1*R/S*, 3*R*, 4*S*)-2-(tert-Butyl-dimethyl-silanyl)-5-(3-[1,3]dioxolan-2-yl-1,4-dihydroxy-hept-6-enyl) imidazole-1-sulfonic acid dimethylamide (148,149)



The bis protected imidazole **122** (prepared according to literature procedure)[61,62] 9.77 g, (33.75 mmol) was dissolved in 100 mL of anhydrous THF and cooled it to -70 °C. To this 21.1 mL (33.75 mmol) of 1.6 M BuLi-hexane was added dropwise, then the resulting mixture was stirred for 30 min at -50 °C to precipitate the lithium salt. The reaction mixture was again cooled back to -70 °C and the THF solution of lactol **147** (2.5 g, 12.5 mmol in 50 mL) was added slowly. The dry ice bath was removed and the reaction mixture was stirred at rt for 1 h. Then the reaction was quenched with water and THF was removed under reduced

pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with water and brine. The solvent was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was separated in quantitative yield by column chromatography using EA:PE 55:45 to 65:35 as eluent to obtain 90% (5.55 g) of diols.

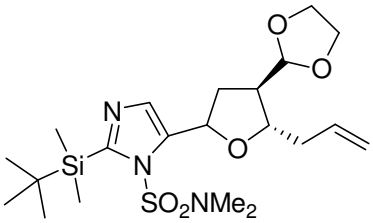
TLC R_f (EA:PE 7:3, Mostain) = 0.56, 0.46

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.37 (s, 6H), 0.98 (s, 9H), 2.01-2.08 (m, 2H), 2.10-2.32 (m, 3H), 2.83 (s, 6H), 3.82-4.13 (m, 5H), 4.96 (d, 1H, *J* = 3.84), 5.06-5.16 (m, 3H), 5.74-5.89 (m, 1H), 7.25 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = -3.59, -3.55, 18.42, 27.21, 30.03, 37.74, 38.88, 42.22, 63.18, 64.70, 65.09, 70.77, 76.63, 105.86, 177.79, 130.05, 134.96, 137.50, 156.20

HRMS: calcd for $C_{15}H_{26}N_3O_6S$ (M+H) 376.1542, found 376.1539

(2*R*/*S*,4*R*,5*S*)-5-(5-Allyl-4-[1,3]dioxolan-2-yl-tetrahydro-furan-2-yl)-2-(tert-butyl dimethyl -silanyl)-imadazole-1-sulfonic acid dimethylamide (150,151)



The diol **(148,149)** (3.55 g, 7.24 mmol) was taken in 310 mL of benzene and to this tributyl phosphine 5.38 mL (21.74 mmol) and 5.48 g (21.74 mmol) of ADDP were added at rt under nitrogen atmosphere. Then the reaction was stirred over night (12h) at rt. Benzene was removed under reduced pressure and the residue was diluted (dissolved) with ethyl acetate from this the insoluble hydrazine by product was filtered through celite pad. The ethyl acetate layer was washed with water and brine. Then the solvent was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The product was purified by column chromatography using (EA: PE 25:75) to obtain the cyclised product 2.67 g in 78% yield. The same reaction was done by using TMAD which gave only 68% yield.

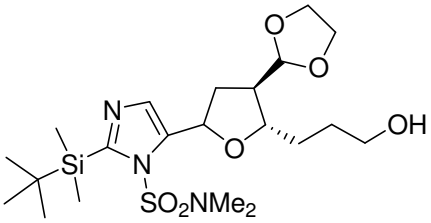
TLC R_f (EA:PE 3:7, Mostain) = 0.70

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.33 (s, 6H), 0.96 (s, 9H), 2.00-2.12 (m, 1H), 2.25-2.36 (m, 3H), 2.41-2.51 (m, 1H), 2.82 (s, 6H), 3.79-3.99 (m, 5H), 4.83 (d, 1H, *J* = 4.11), 5.00-5.13 (m, 3H), 5.73-5.88 (m, 1H), 7.20 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = -3.42, -3.63, 18.44, 27.30, 34.37, 34.45, 39.78, 46.51, 65.06, 65.23, 71.16, 79.81, 104.71, 117.45, 130.10, 134.65, 135.02, 156.17

HRMS: calcd for $C_{21}H_{36}N_3O_5SSi$ (M-H) 470.2145: found 470.2137

(2*R*/S,4*R*,5*S*)-2-(tert-Butyl-dimethyl-silanyl)-5-[4-[1,3]dioxolan-2-yl-5-(3-hydroxy-propyl)-tetrahydro-furan-2-yl]-imidazole-1-sulfonic acid dimethylamide (152,153)



The diastereomeric mixture of olefin **(150,151)** (1 g, 21.23 mmol) was dissolved in 100 mL of anhydrous THF and to this 12.7 mL (12.7 mmol) of BH_3.THF (1 M solution in THF) was added slowly drop wise under nitrogen atmosphere. Then the reaction was stirred over night at rt. The reaction was quenched with 2M NaOH and H_2O_2 and stirred it for another 4 h. The product was purified by column chromatography using EA:PE (80:20). The isolated product was 0.83 g, 80% yield as diastereomeric mixture having **152** and **153**.

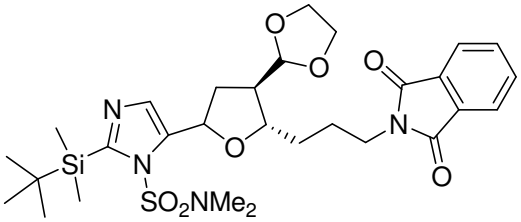
TLC R_f (EA:PE 100:0, Mostain) = 0.30

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.34 (s, 6H), 0.93 (s, 9H), 1.15-1.17 (m, 3H), 1.75-1.85 (m, 1H), 2.13-2.33 (m, 2H), 2.38-2.53 (m, 1H), 2.80 (s, 6H), 3.51-3.63 (m, 2H), 3.78-3.94 (m, 4H), 4.76-4.86 (m, 1H), 7.23 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = -3.64, -3.47, -3.42, 18.42, 27.28, 29.69, 31.54, 32.49, 34.60, 34.97, 37.47, 37.54, 47.38, 48.72, 62.62, 65.03, 65.23, 70.13, 71.18, 77.27, 79.69, 80.56, 104.55, 104.69, 130.21, 130.48, 134.89, 135.38, 156.22, 156.30

HRMS: calcd for (M+H) $C_{21}H_{40}N_3O_6SSi$ 490.2407, found 490.2401

(2*R*/*S*,4*R*,5*S*)-2-(tert-butyl-dimethyl-silanyl)-5-{5-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl) -propyl]-4-[1,3]dioxolan-2-yl-tetrahydro-furan-2-yl}-imidazole-1-sulfonic acid dimethyl amide (154,155)



The diastereomeric alcohol (**152,153)** (200 mg, 0.409 mmol) was disolved in 20 mL of anhydrous THF and to this 90 mg (0.61 mmol) of phthalimide, 214 mg (0.81 mmol) of triphenyl phosphene were added under nitrogen. To the above reaction mixture, 0.128 mL (0.81 mmol) of DEAD was added drop wise. Then the reaction was stirred overnight at rt. The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried over

anhydrous sodium sulphate and concentrated to give the crude product which was purified by column chromatography using EA: PE (30:70) as eluent. The isolated product is 165 mg, 65% yield as diastereomeric mixture having **154** and **155**.

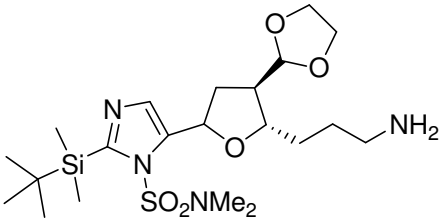
TLC R_f (EA:PE 1:1, Mostain) = 0.55

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.35 (s, 6H), 0.98 (s, 9H), 1.60-1.90 (m, 4H), 2.04-2.2 (m, 1H), 2.23-2.34 (m,1H), 2.41-2.54 (m, 1H),2.85 (s, 6H), 3.60-3.73 (m, 3H), 3.80-4.0 (m, 5H), 4.80-4.86 (m, 1H), 7.26 (s, 1H), 7.65-7.72 (m, 2H), 7.79-7.83 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = -3.66, -3.64, -3.44, -3.39, 14.32, 14.42, 18.43, 25.34, 25.56, 27.30, 29.69, 32.22, 32.93, 34.35, 34.74, 37.39, 37.41, 47.32, 48.59, 65.12, 65.20, 69.81, 70.77, 79.05, 79.79, 104.53, 104.70, 123.19, 130.23, 130.47, 132.11, 132.13, 133.75, 133.91, 133.94, 134.24, 134.60, 135.09, 156.21, 156.34, 168.37

HRMS: calcd for (M+H) $C_{29}H_{43}N_4O_7SSi$ 619.2622 found: 619.2613

(2*R*/S,4*R*,5*S*)-5-[5-(3-amino-propyl)-4-[1,3]dioxolan-2-yl-tetrahydro-furan-2-yl]-2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide (156,157)



The diastereomeric phthalimide (**154,155)** (130 mg, 0.21 mmol) was dissolved in 15 mL of ethanol and to this 0.066 mL (1.36 mmol) of hydrazine hydrate was added drop wise. Then the reaction was stirred over night at rt. Ethanol was concentrated under reduced pressure and the residue was diluted with ethyl acetate and washed with minimum amount of water and brine. The highly polar product was purified by column chromatography using ethyl acetate and then methanol as eluent. The isolated product was 78 mg, 76% yield having diastereomeric mixture **156** and **157**.

TLC R_f (EA:PE 100:0, Ninhydrin) = 0.01, (MeOH:$CHCl_3$ 1:9) = 0.15

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.38 (s, 6H), 1.00 (s, 9H), 1.45-1.80 (m, 5H), 2.00-2.38 (m, 3H), 2.45-2.58 (m, 1H), 2.64-2.74(m, 2H), 2.87 (s, 6H), 3.43-3.51 (m, 2H), 3.56-3.74 (m, 6H), 3.83-4.03(m, 5H), 4.83-4.92 (m, 1H), 7.3(s, 1H)

^{13}C NMR (75 MHz, CD_3Cl_3): δ = -3.65, -3.45, -3.40, 14.13, 18.44, 22.70, 26.08, 29.36, 29.50, 29.63, 29.68, 30.44, 30.52, 31.93, 32.24, 33.09, 34.50, 34.84, 37.46, 42.00, 47.42, 62.92, 65.01, 65.04, 65.18, 65.24, 70.01, 70.57, 71.03, 72.53, 76.61, 79.57, 80.44, 104.68, 104.80, 130.17, 130.43, 135.04, 135.50, 156.20

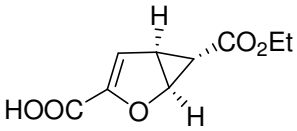
^{1}H NMR (300 MHz, CD_3OD): δ = 0.38 (s, 6H), 0.96 (s, 9H), 1.5-1.83 (m, 5H), 1.99-2.16 (m, 1H), 2.24- 2.40(m, 2H), 2.452.58 (m, 1H), 2.62-2.78 (m, 2H), 2.89 (s, 6H), 3.81-4.06 (m, 5H), 5.12- 5.33(m, 1H), 7.28 (s, 1H)

^{13}C NMR (75 MHz, CD_3OD): δ = -3.66, -3.64, -3.44, -3.39, 14.32, 14.42, 19.20, 23.79, 28.05, 30.67, 30.80, 33.12, 33.38, 34.27, 35.72, 36.25, 37.93, 37.97, 42.35, 63.06, 66.11, 66.26, 66.37, 71.22, 71.62, 72.41, 81.09, 81.47, 105.82, 106.05, 130.85, 131.10, 136.95, 137.54, 157.35.

HRMS: calcd for (M+H) $C_{21}H_{41}N_4O_5SSi$ 489.2567; found: 489.2559

Synthesis of histamine H_3 and H_4 receptor potential agonists by furan cyclopropane ring opening methodology.

(1*S*,5*S*,6*S*)-6-(ethoxycarbonyl)-2-oxa-bicyclo[3.1.0]hex-3-ene-3-carboxylicacid (231)



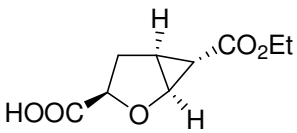
11.60 g (54.71 mmol) of compound **229** was taken and dissolved in 150 mL of THF and cooled to 0 °C. To this 1.57 g of (65.66 mmol) lithium hydroxide in 100 mL of water was added slowly drop wise. Then the reaction was stirred over night. Completion of the reaction was checked by TLC and the reaction mixture was acidified to 2-3 pH with 1N HCl. Then the reaction mixture was diluted with ethyl acetate and separated the organic layer. The aqueous layer was extracted with EA (5 × 20 mL) and the combined organic layer was dried under anhydrous sodium sulfate. Removal of the solvent under reduced pressure followed by crystallization in chloroform/n-hexane (1:10) gave the pure product **231** in 96% yield.

TLC R_f (EA:PE 100:0, $KMnO_4$) = 0.10

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17-1.20 (m, 1H), 1.26 (t, 3H, *J* = 7.13) 2.84-2.92 (m, 1H), 4.15 (q, 2H, *J* = 7.13), 4.97 (dd, 1H, *J1* = 1.09, *J2* = 5.21), 6.52 (d, 1H, *J* = 3.01), 11.17-11.21 (bs, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.20, 21.49, 32.19, 61.34, 67.78, 118.74, 148.58, 163.70, 171.93

(1*S*,3*R*,5*S*,6*S*)-6-(ethoxycarbonyl)-2-oxa-bicyclo[3.1.0]hexane-3-carboxylicacid (232)



4.6 g (23.23 mmol) of compound **231** was taken in 250 mL of ethylacetate and to this 460 mg of Pd/C (10%) was added. Then hydrogen balloon was kept and the reaction was stirred at room temperature over night. The reaction mixture was passed through the celite and the

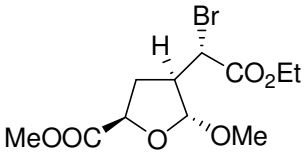
solvent was removed under reduced pressure obtained **232** in 98% yield. The NMR of this product **232** is very clean without purification and there were no starting material and side products observed.

TLC R_f (EA:PE 100:0, Mostain) = 0.10

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, 3H, *J* = 7.13), 1.8-1.88 (s, 1H), 2.13-2.38 (m, 2H), 2.60-2.777 (m, 1H), 4.04 (q, 2H, *J1* = 7.04, *J2* = 14.27), 4.32 (d, 1H, *J* = 5.76), 4.79 (dd, 1H, *J1* = 3.84, *J2* = 10.70), 9.5-10.5 (bs, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.15, 25.62, 28.10, 34.09, 60.82, 67.45, 78.61, 170.68, 177.45

(2*R*,4*R*,5*R*)-methyl 4-((S)-(ethoxycarbonyl)bromomethyl)-tetrahydro-5-methoxyfuran-2-carboxylate (233)



4.8 g (24.00 mmol) of compound **232** was taken in 200 mL of anhydrous methanol and to this 6.4 g (36 mmol) of NBS was added at 0 °C and the reaction was stirred for 36 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography in 5% EA/PE as eluent to obtain **233** in 80 % yield.

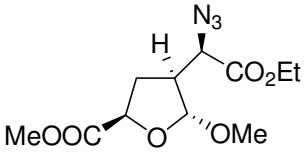
TLC R_f (EA:PE 1:9, Mostain) = 0.35

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, 3H, *J* = 7.13), 1.98-2.10 (m, 1H), 2.51-2.64 (m, 1H), 2.76-2.87 (m, 1H), 3.28-3.32 (s, 3H), 3.71-3.75 (s, 3H), 4.12-4.25 (m, 3H), 4.56 (t, 1H, *J* = 7.68), 4.83 (d, 1H, *J* = 1.92)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.87, 32.80, 46.64, 49.31, 52.37, 55.50, 62.33, 75.31, 107.33, 168.66, 171.84

HRMS: calcd for $C_{11}H_{17}BrO_6Na$ (M+Na) = 349.0106; found: 349.0104

(2*R*,4*R*,5*R*)-methyl 4-((*R*)-(ethoxycarbonyl)azidomethyl)-tetrahydro-5-methoxyfuran-2-carboxylate (234)



3.6 g (11.11 mmol) of compound **233** was taken in 35 mL of analytical grade DMF and to this 2.16 g (33.33 mmol) of sodium azide was added at room temperature under nitrogen. The reaction was stirred overnight and then the reaction mixture was quenched with water and

extracted with ethylacetate (5 × 20 mL). The solvent was removed under reduced pressure and the pure product was isolated by filtered column chromatography to obtain **234** in 97 % yield.

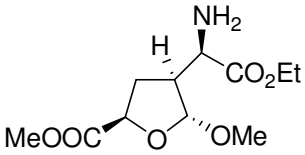
TLC R_f (EA:PE 1:9, Mostain) = 0.30

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3H, *J* = 7.13), 1.94-2.08 (m, 1H), 2.20-2.33 (m, 1H), 2.39-2.54 (m, 1H), 3.37-3.42 (s, 3H), 3.67-3.72 (s, 3H), 3.98 (d, 1H, *J* = 10.97), 4.18 (q, 2H, *J1* = 7.13, *J2* = 14.27), 4.56 (t, 1H, J = 8.23), 4.96 (d, 1H, *J* = 4.11)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.15, 30.03, 46.07, 52.18, 54.81, 61.85, 61.96, 76.63, 104.21, 169.37, 172.63

HRMS: calcd for $C_{11}H_{17}N_3O_6Na$ (M+Na) = 310.1015; found 310.1006

(2*R*,4*S*,5*R*)-methyl 4-((*R*)-(ethoxycarbonyl)(amino)methyl)-tetrahydro-5-methoxyfyran-2-carboxylate (235)



2.06 g (7.17 mmol) of compound **234** was taken and dissolved in 150 mL of distilled ethyl acetate and to this 200 mg of Pd/C (10%) was added at room temperature. Then the reaction was stirred under hydrogen atmosphere (balloon pressure) overnight. The completion of the reaction was checked by TLC. The reaction mixture was passed through celite and the solvent was removed under reduced pressure obtained **234** in 95 % yield. The product **235** was pure enough to proceed to the next step.

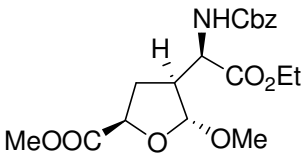
TLC R_f (EA:PE 100:0, Ninhydrin) = 0.25

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, 3H, *J* = 7.13), 2.00-2.40 (m, 3H), 3.38 (s, 3H), 3.69 (s, 3H), 4.12 (q, 2H, *J1* = 7.13, *J2* = 14.27), 4.53 (t, 1H, J = 7.95), 4.98 (d, 1H, *J* = 3.84)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.21, 30.46, 48.69, 52.07, 54.79, 60.78, 61.01, 76.75, 105.02, 172.97, 174.74

HRMS: calcd for $C_{11}H_{19}NO_6Na$ (M+Na) = 284.1110, found: 284.1106

(2*R*,4*S*,5*R*)-methyl 4-((*R*))-1-(benzyloxycarbonylamino)-2-ethoxy-2-oxoethyl)-5-methoxytetrahydrofuran-2-carboxylate (236)



1.83 g (7.01 mmol) of **235** was taken in 120 mL of anhydrous THF and to this 1.45 mL (10.51 mmol) of triethylamine was added under nitrogen atmosphere. To the above reaction mixture

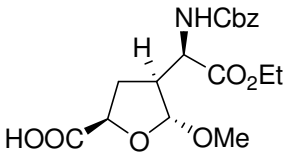
1.2 mL (9.11 mmol) of carboxybenzoylchloride was added drop wise and the reaction was stirred at room temperature for 12 h. Then the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 25 mL). The organic layer was washed sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product **236** was separated by column chromatography as 25% EA/PE as eluent in 85% yield.

TLC R_f (EA:PE 1:1, Mostain) = 0.50

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (m, 3H), 2.14-2.40 (m, 2H), 2.76-2.92 (m, 1H), 3.38 (s, 3H), 3.74 (s, 3H), 4.07-4.27 (m, 2H), 4.59 (m, 2H), 5.12 (s. 2H), 5.82(d, 2H, *J* = 10.15) 7.27-7.43 (m, 5H)

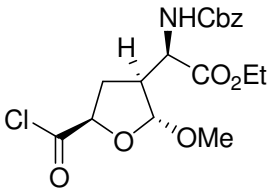
^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.11, 29.28, 44.45, 46.28, 52.20, 55.10, 61.58, 67.08, 75.53, 105.34, 128.20, 128.74, 136.30, 137.49, 156.56, 171.16, 172.61

(2*R*,4*S*,5*R*)-4-((*R*)-1-(benzyloxycarbonylamino)-2-ethoxy-2-oxoethyl)-5-methoxytetrahydrofuran-2-carboxylic acid (237)



1.5 g (3.79 mmol) of compound **236** was taken in 30 mL of THF and to this 100 mg (4.17) of lithium hydroxide in 100 mL of water was added at 0 °C. The reaction was stirred for 12 h and completion of the reaction was checked by TLC. Then the reaction mixture was acidified to 2-3 pH with 1N HCl. The reaction mixture was diluted with ethyl acetate and separated the organic layer. The aqueous layer was extracted with EA (5 × 15 mL) and the combined organic layer was dried over anhydrous sodium sulfate which obtained **237** in 95% yield.

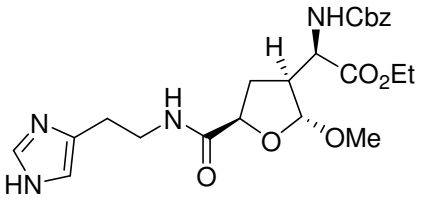
benzyl(*R*)-((2*R*,3*S*,5*R*)-5-(chlorocarbonyl)-tetrahydro-2-methoxyfuran-3-yl) (ethoxycarbonyl)methylcarbamate (242)



291 mg (0.763 mmol) of compound **237** was taken in 40 mL of anhydrous DCM and to this two drops of DMF was added at 0 °C under nitrogen. To the above reaction mixture 0.2 mL (2.29 mmol) of oxalyl chloride was added and the reaction was stirred for 12 h. The reaction mixture was quenched with water and extracted with ethyl acetate (4 × 10 mL). The organic layer was washed with sodium bicarbonate and brine. Removal of the solvent under reduced

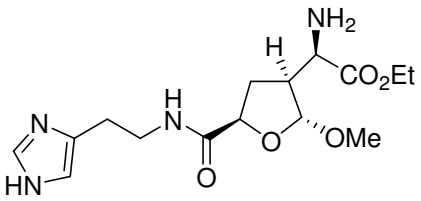
pressure gave the acid chloride **242** in good yield. The next step was done with this product without purification.

benzyl(*R*)-((2*R*,3*S*,5*R*)-5-(2-(1*H*-imidazol-4-yl)ethylcarbamoyl)-tetrahydro-2-methoxyfuran-3-yl)(ethoxycarbonyl)methylcarbamate (245)



30 mg (0.078 mmol) of **237** was taken in 5 mL of DMF and to this 0.012 mL (0.0866 mmol) of triethyl amine, 10.5 mg (0.094 mmol) of histamine, 11.70 mg (0.086 mmol) of HOBt and 16.60 mg (0.086 mmol) of EDC were added sequentially and the reaction was stirred at room temperature 3 h. Then the reaction was quenched with water and extracted with ethyl acetate (5 × 10 mL) and the organic layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure obtained **245** in 70% yiled.

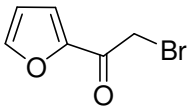
(*R*)-ethyl 2-((2*R*,3*S*,5*R*)-5-(2-(1*H*-imidazol-4-yl)ethylcarbamoyl)-tetrahydro-2-methoxyfuran-3-yl)-2-aminoacetate (246)



30 mg (0.065 mmol) of **245** was taken in 4:1 mixture of ethylacetate and ethanol then treated with 5 mg of Pd/C (10%). The reaction was stirred under hydrogen atmosphere at room temperature for 8 h. The reaction mixture was passed through a small pad of celite and the solvent was removed under reduced pressure to obtain **246** in 80% yiled.

Synthesis of histamine H_3 and H_4 receptor potential agonists by imidazole-furan cyclopropane ring opening methodology.

2-bromo-1-(furan-2-yl)ethanone (249)



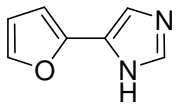
1.0 g (9.00 mmol) of 2-acetyl furan was taken in 5 mL of anhydrous ether and to this 0.46 mL (9.00 mmol) of bromine was added drop wise at 0 °C and the reaction was stirred for 30 min. The reaction mixture was poured in to ice cold water and extracted with ether (4 × 20 mL) and dried over anhydrous sodium sulfate. The removal of the organic solvent and purification by column chromatography using 6% EA/PE gave **249** in 90% yield.

TLC R_f (EA:PE 1:9, Mostain) = 0.50

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30 (s, 2H), 6.58, (q, 1H, *J1* = 1.64, *J2* = 3.56), 7.32 (dd, 1H, *J1* = 0.54, *J2* = 3.56), 7.63 (dd, *J1* = 0.54, *J2* = 1.64)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.11, 112.89, 119.20, 147.36, 150.29, 180.34

5-(furan-2-yl)-1*H*-imidazole (250)



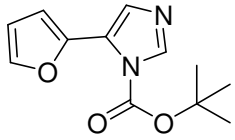
1.0 g (5.31 mmol) of **249** was taken in 40 mL of 7M liquid ammonia and to this 4.2 g (40.3 mmol) of formamidine acetate was added and the reaction set up had put it in autoclave without any external pressure. The reaction was stirred over night at 45 °C in an oil bath. The solvent was evaporated slowly in a fume hood and the residue was removed by rotavapour. The crude product was purified by a filter column eluting with ethyl acetate gave the pure product **250** in 65% yield.

TLC R_f (MeOH:$CHCl_3$ 1:9) = 0.15

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.49-6.41 (m, 1H), 6.51-6.54 (m, 1H), 7.34 (s, 1H), 7.38 (d, 1H, *J* = 1.09), 7.72 (s, 1H), 12.53 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.30, 111.35, 114.75, 131.55, 135.72, 141.07, 149.04

tert-butyl 5-(furan-2-yl)-1*H*-imidazole-1-carboxylate (251)



270 mg (2.01 mmol) of compound **250** was taken in 15 mL of chloroform and to this 0.41 mL (3.01 mmol) of triethyl amine was added. In 5 mL of chloroform 571 mg (2.60 mmol) of Boc anhydride was dissolved and added to the above reaction mixture slowly drop wise. The reaction was stirred at room temperature for 4 h. Then the reaction was quenched with water and the organic layer was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and the removal of solvent was done under reduced pressure. The crude product was purified by column chromatography eluting in 25% EA/PE to obtain **251** in 85% yield.

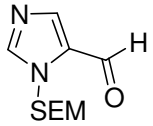
TLC R_f (EA:PE 4:6, Mostain) = 0.55

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 9H), 6.41-6.46 (m, 1H), 6.69 (d, 1H, *J* = 3.01), 7.37-7.40 (m, 1H), 7.51 (d, 1H, *J* = 1.09), 8.06 (d, 1H, *J* = 1.09)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.88, 85.89, 106.11, 111.36, 111.55, 135.35, 137.36, 141.72, 146.88, 148.70

Synthesis of histamine H_3 and H_4 receptor potential agonists based on imidazole aldehyde.

1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-5-carbaldehyde (259)



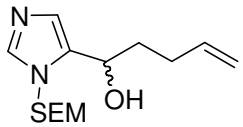
1.0 g (10.4 mmol) of **258** was dissolved in 50 mL of anhydrous dichloromethane and to this 1.73 mL (12.5 mmol) of triethyl amine was added drop wise. To this 2.2 mL (12.5 mmol) of SEMCl was added slowly drop wise under nitrogen and the reaction mixture was stirred for 12 h. The reaction mixture was washed with water and extracted with dichloromethane (3 × 15 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography eluting with 40% EA/PE to obtain **259** in 70% yield.

TLC R_f (EA:PE 100:0, Mostain) = 0.50

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.03 (s, 9H), 0.85-0.96 (m, 2H), 3.48-3.62 (m, 2H), 5.7 (s, 2H), 7.83 (s, 1H), 7.88 (s, 1H), 9.79 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = -0.35, 19.26, 68.60, 94.74, 145.20, 180.82, 187.71

1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pent-4-en-1-ol (260)

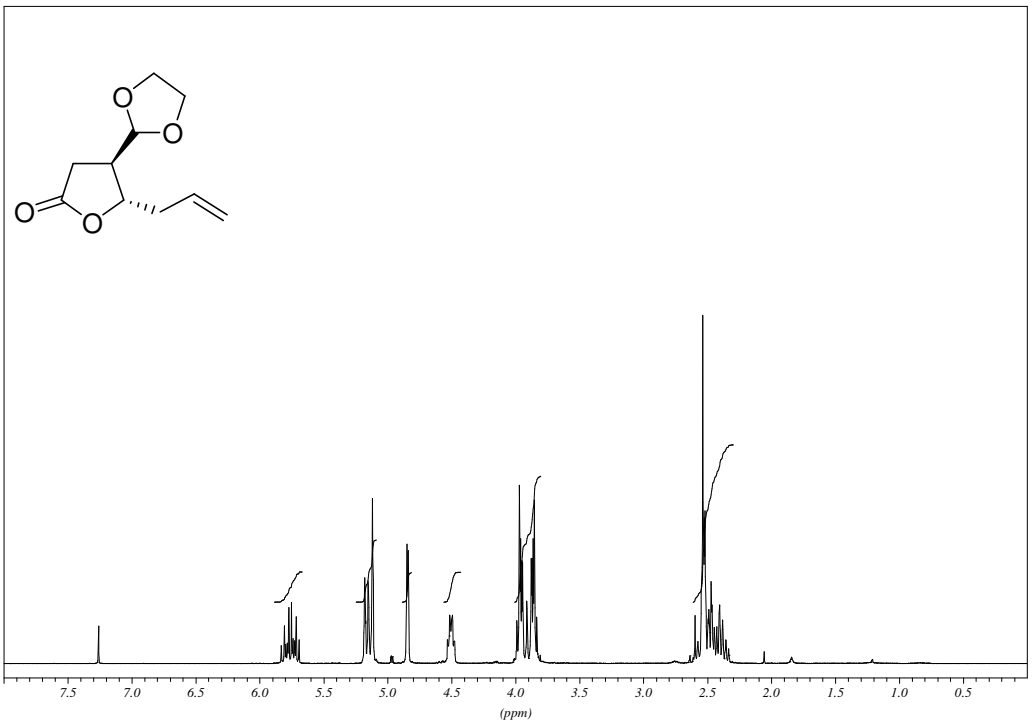


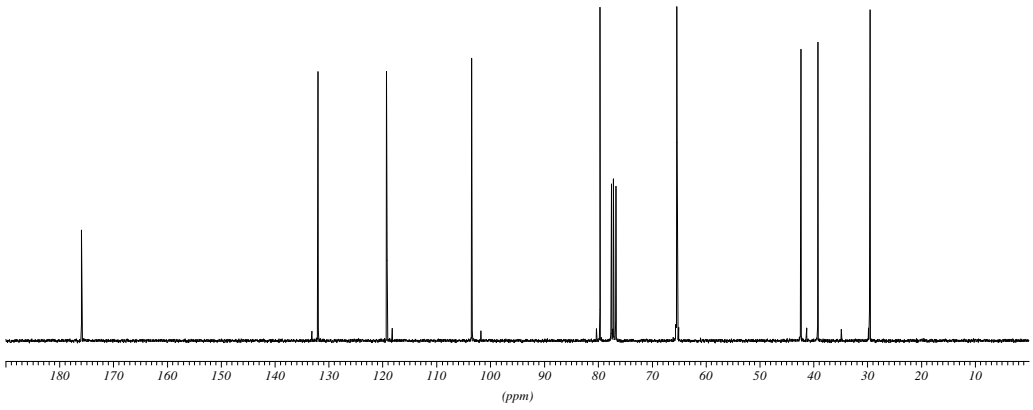
49.20 mg (2.050 mmol) of Mg was taken in two neck RB was fitted with76.95, cooling condenser at and rubber septum under nitrogen and to this a pinch of iodine was added at 0 °C. This mixture was stirred in 2 mL of anhydrous ether and 0.195 mL (1.921 mmol) of butynly bromide was added slowly drop wise. The reaction mixture was stirred for 30 min until the Grignard reagent is formed. To the above Grignard reagent 290 mg (1.281 mmol) of **259** was added slowly drop wise in 20 mL of ether. When the addition is over immediately a white precipitate is formed then the cooling bath was removed and the reaction was stirred overnight at rt. The reaction mixture was quenched with saturated ammonium chloride and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethylacetate (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was isolated by column chromatography eluting with 60% EA/PE gave **260** in 60% yield.

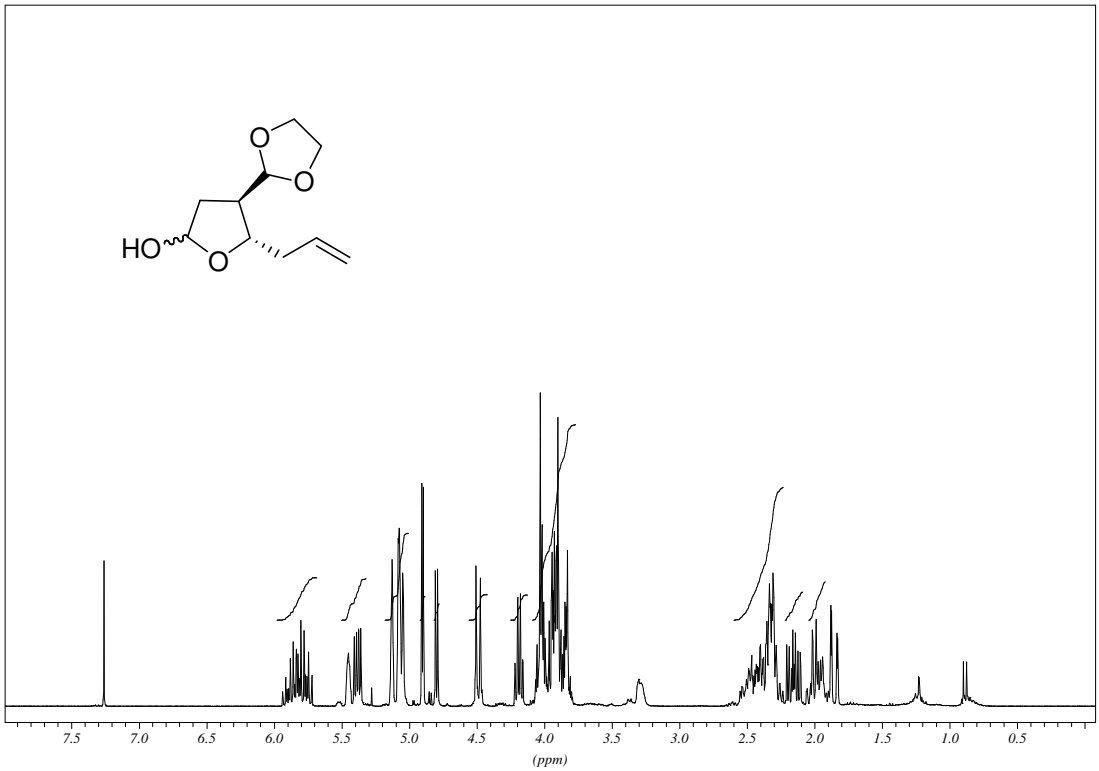
TLC R_f (EA:PE 100:0, Mostain) = 0.10 or R_f (MeOH:$CHCl_3$ 1:9, Mostain) = 0.4

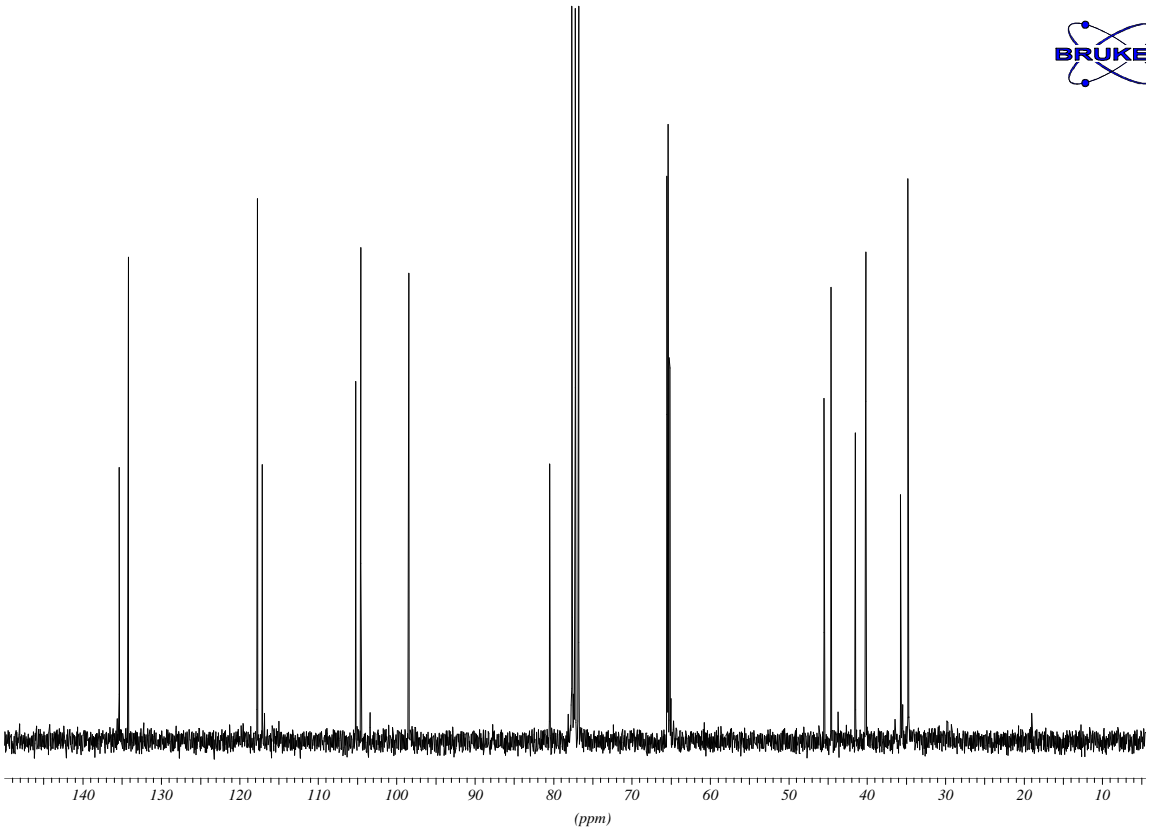
^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.09 (s, 9H), 0.86-1.0 (m, 2H), 1.90-2.10 (m, 2H), 2.15-2.35 (m, 2H), 3.45-3.60 (m, 2H), 4.62-4.82 (m, 2H), 4.94-5.15 (m, 2H), 5.36 (s, 2H), 5.80-5.95 (m, 1H), 6.92-7.01 (bs, 1H), 7.49-7.55 (bs, 1H)

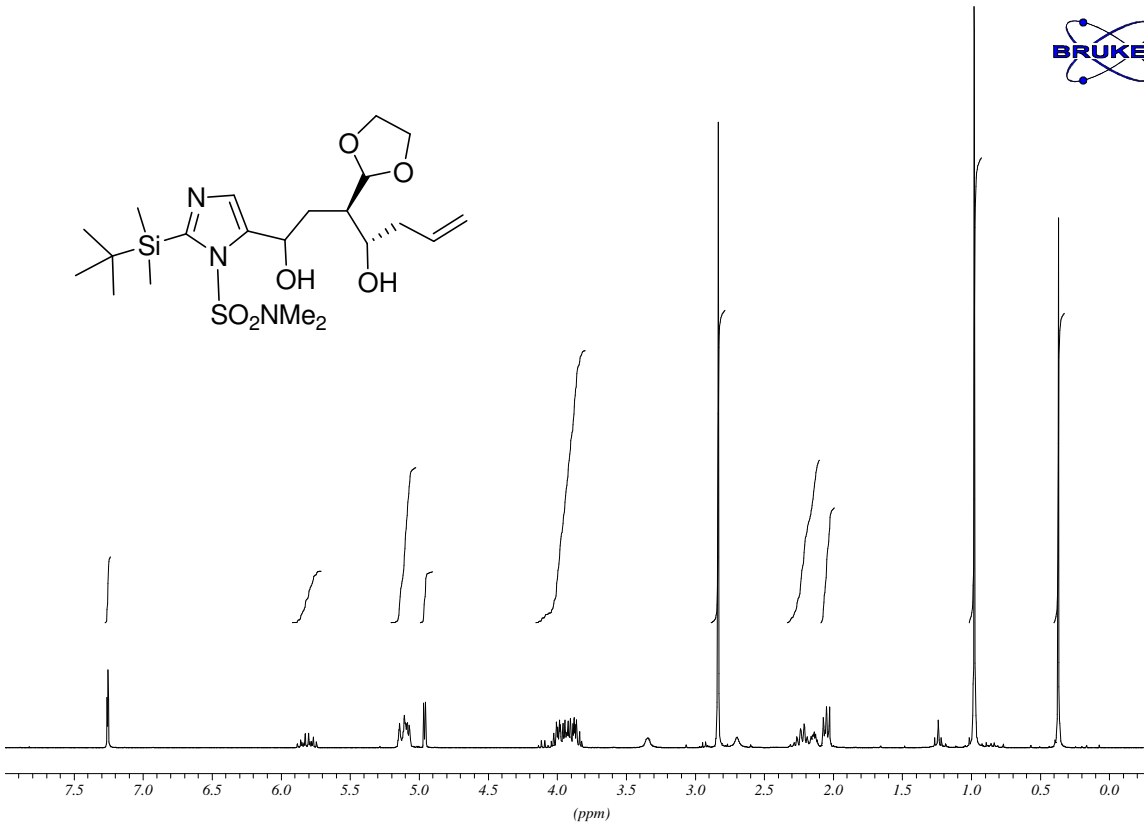
^{13}C NMR (75 MHz, $CDCl_3$): δ = -0.34, 19.14, 31.66, 35.68, 37.53, 65.28, 67.60, 75.87, 116.75, 128.79, 135.69, 139.84

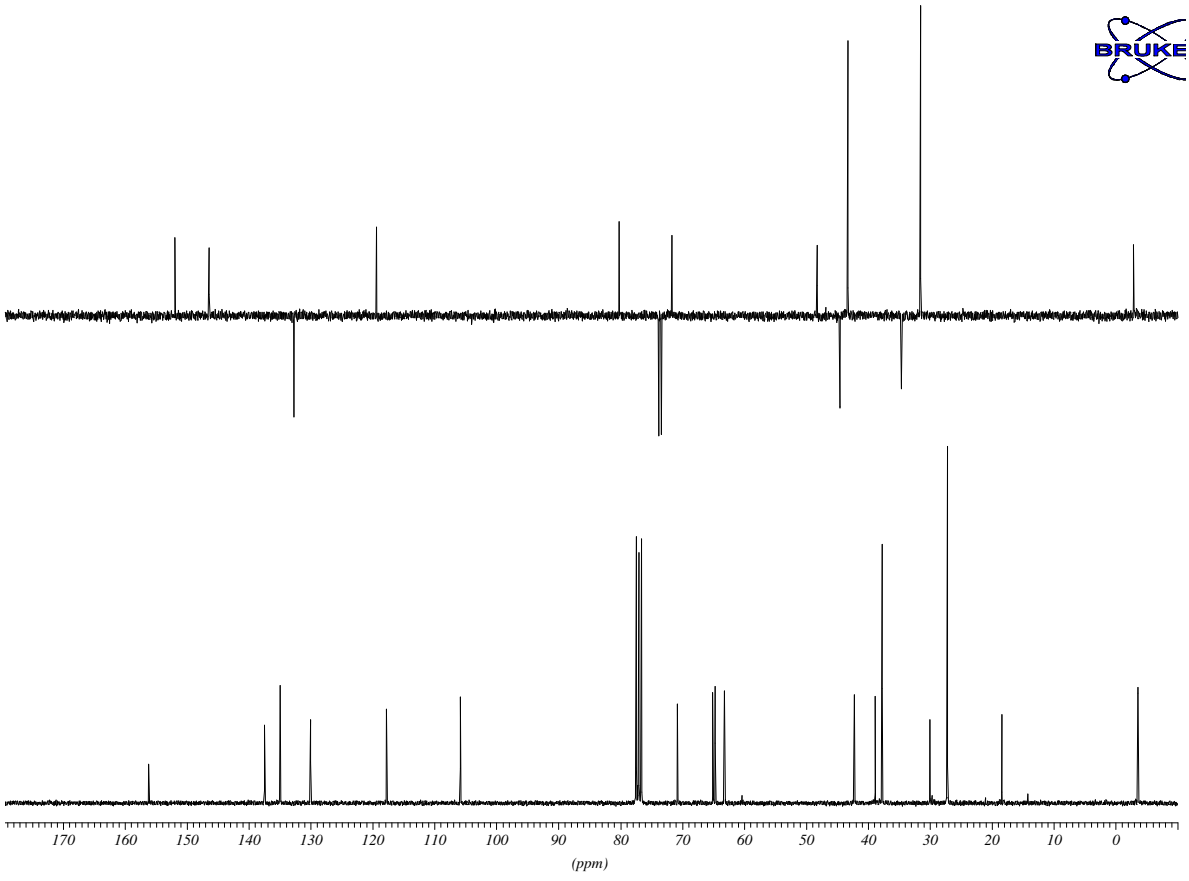

O
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

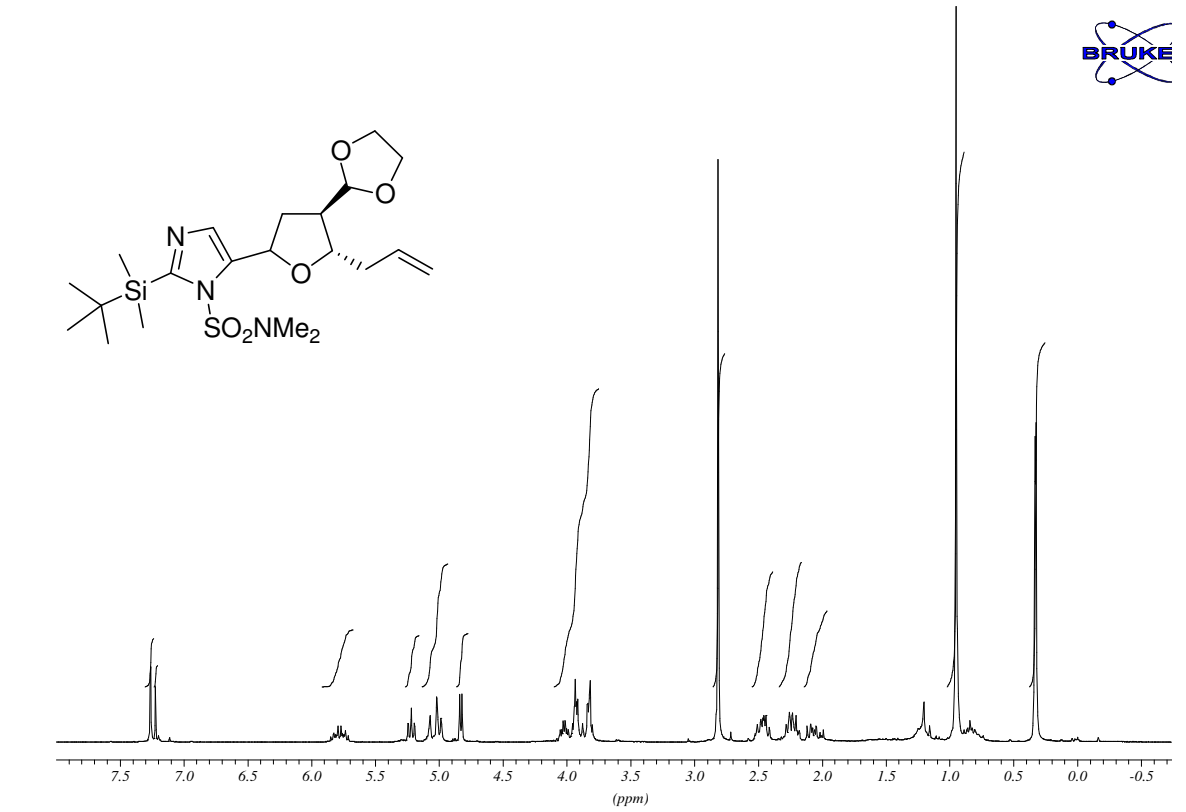

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

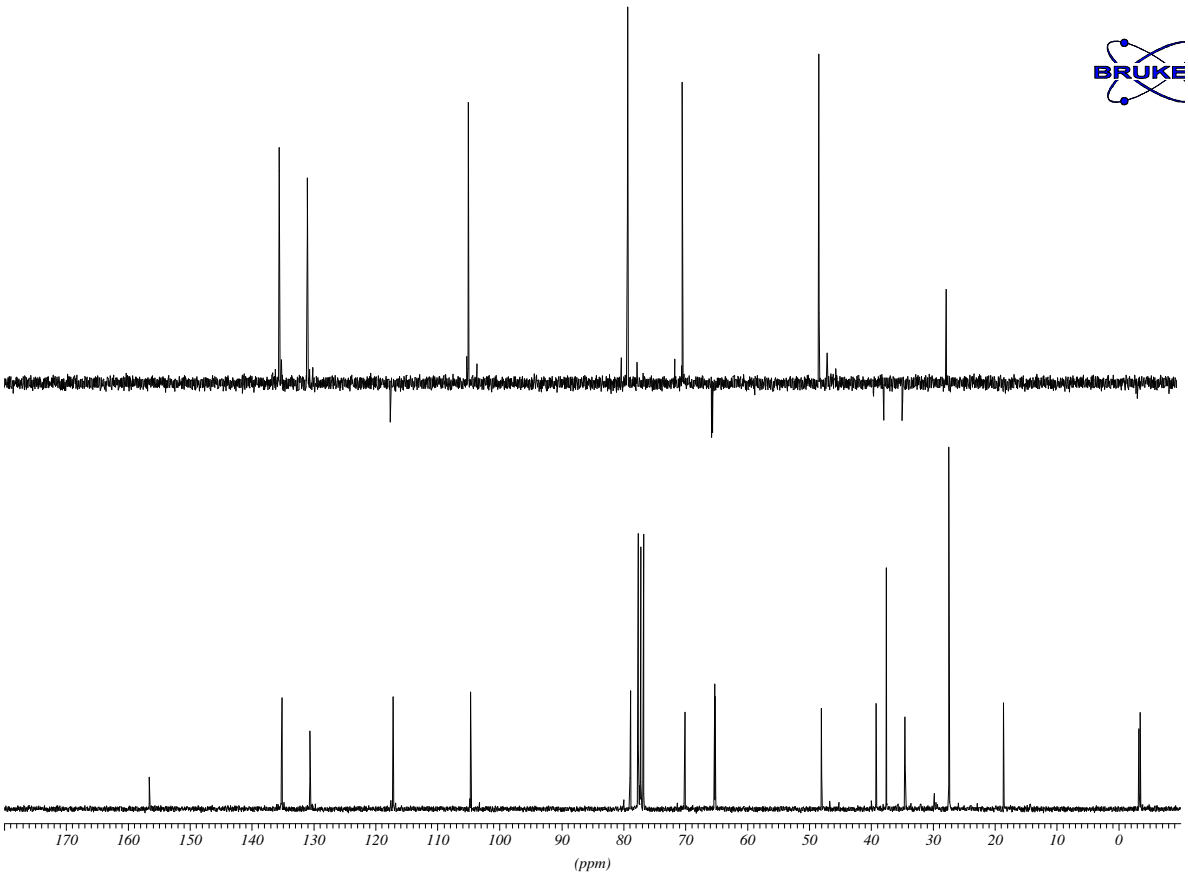

HO
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

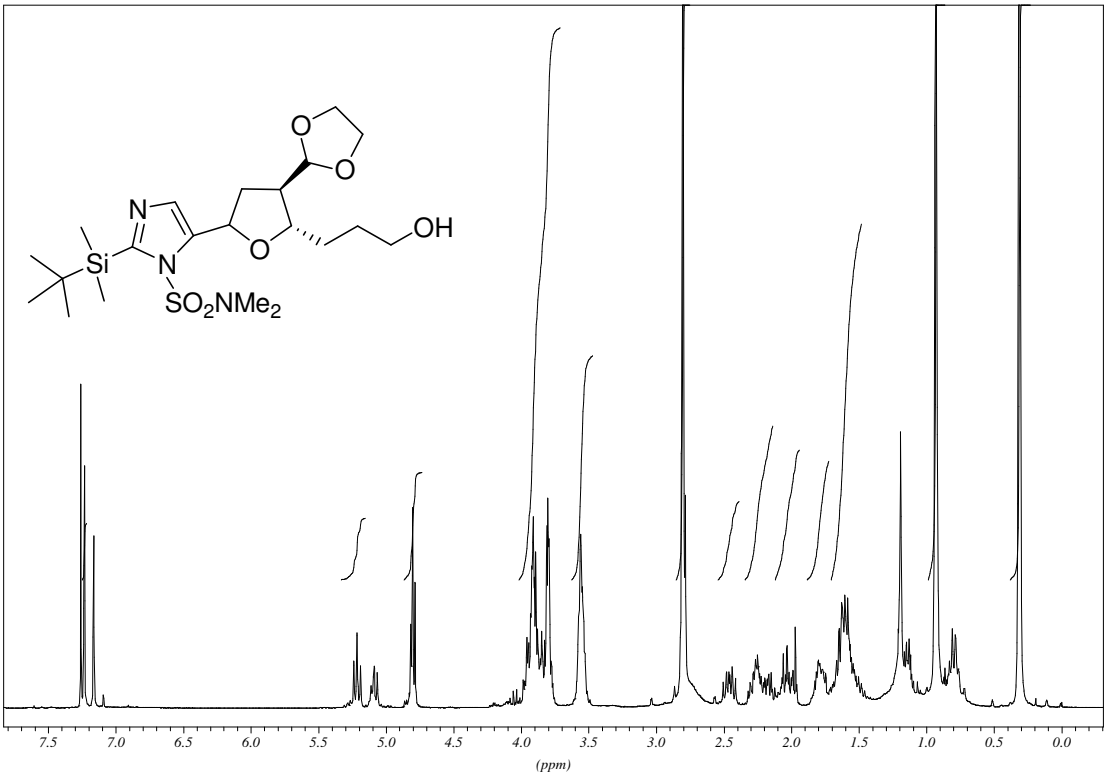

140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

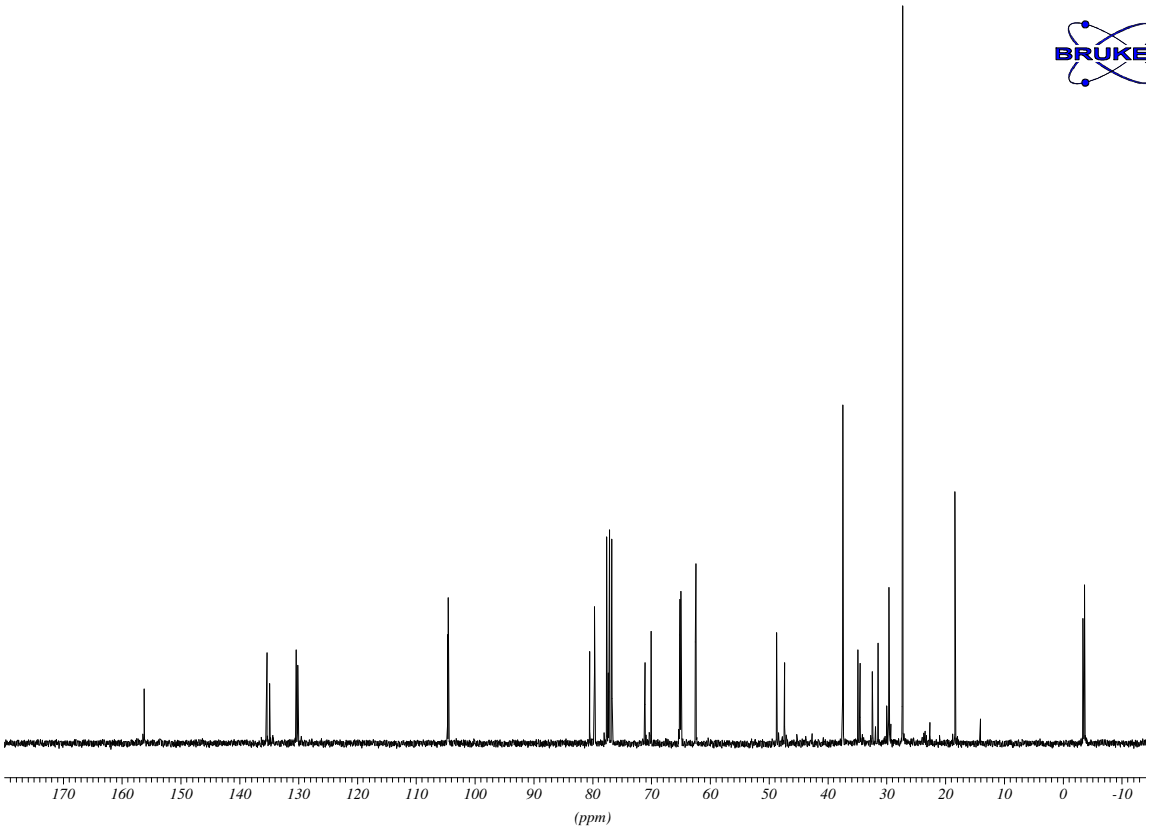

O
O
N
Si
N
OH
OH
SO2NMe2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

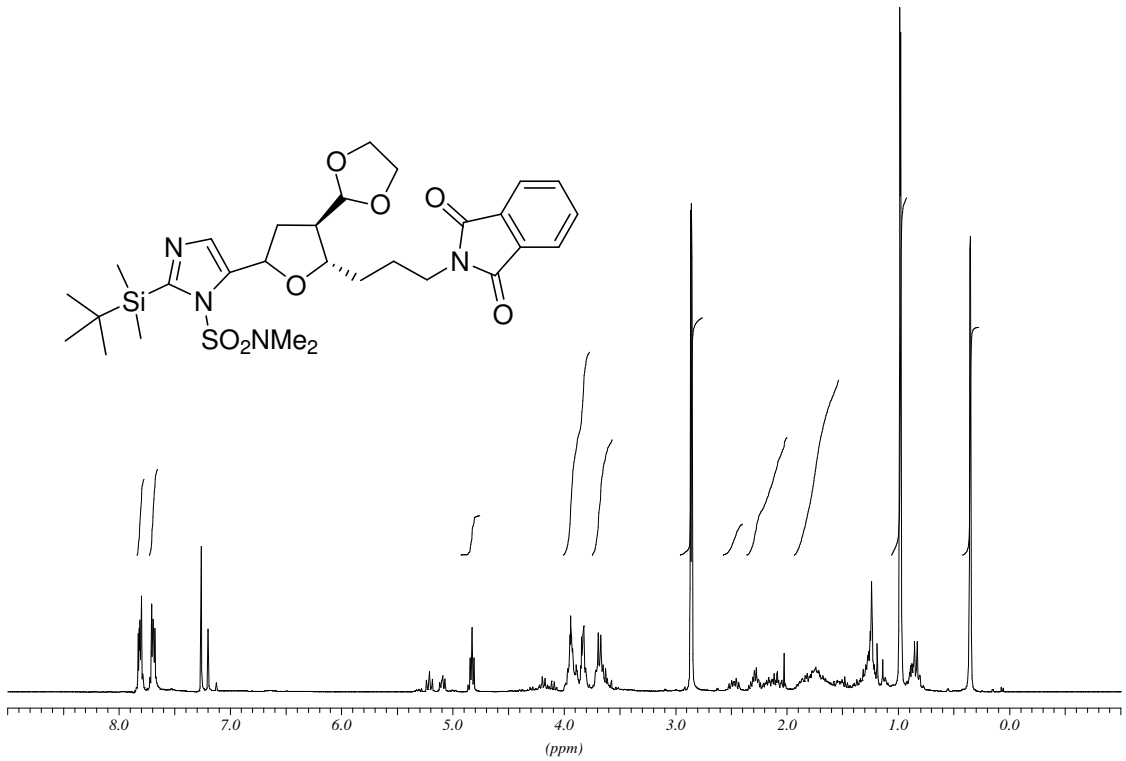

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

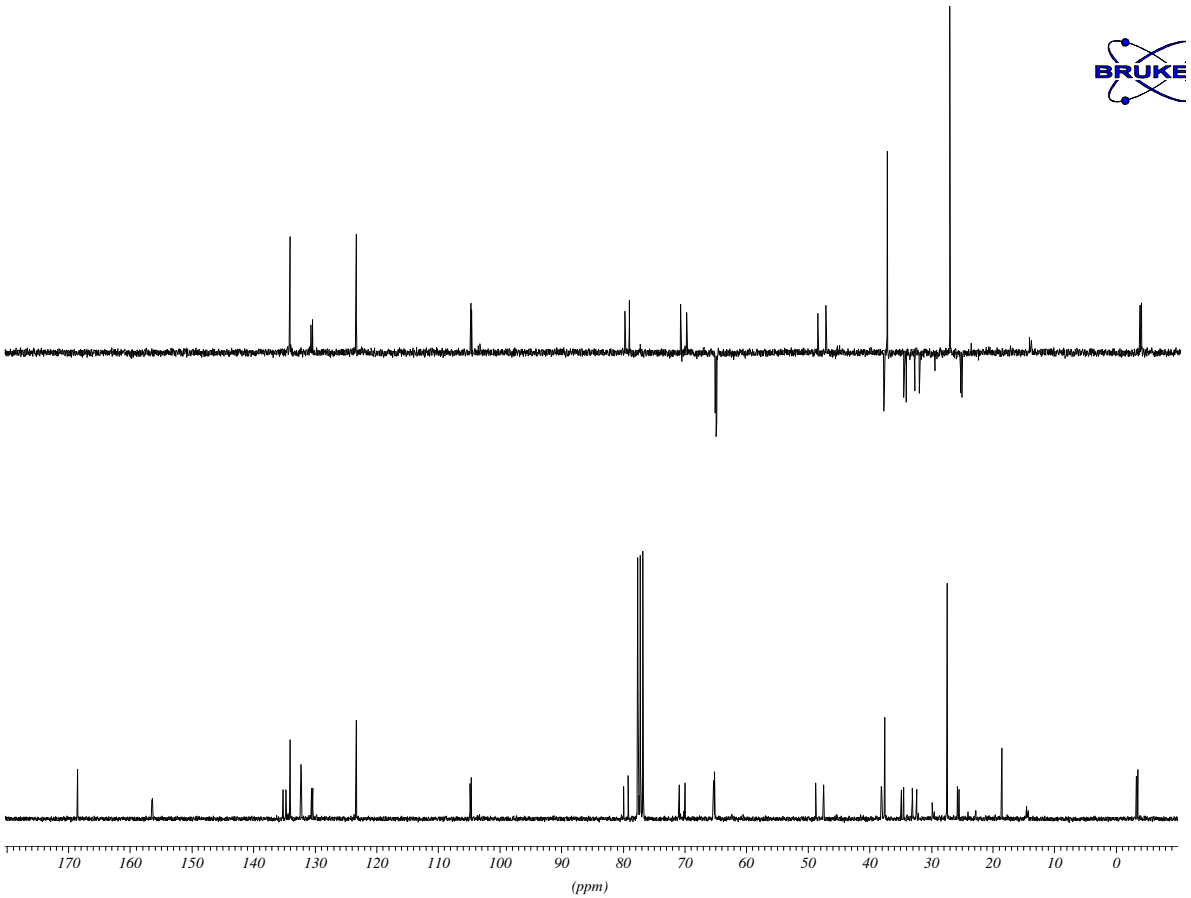

O
O
N
Si
N
O
SO2NMe2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

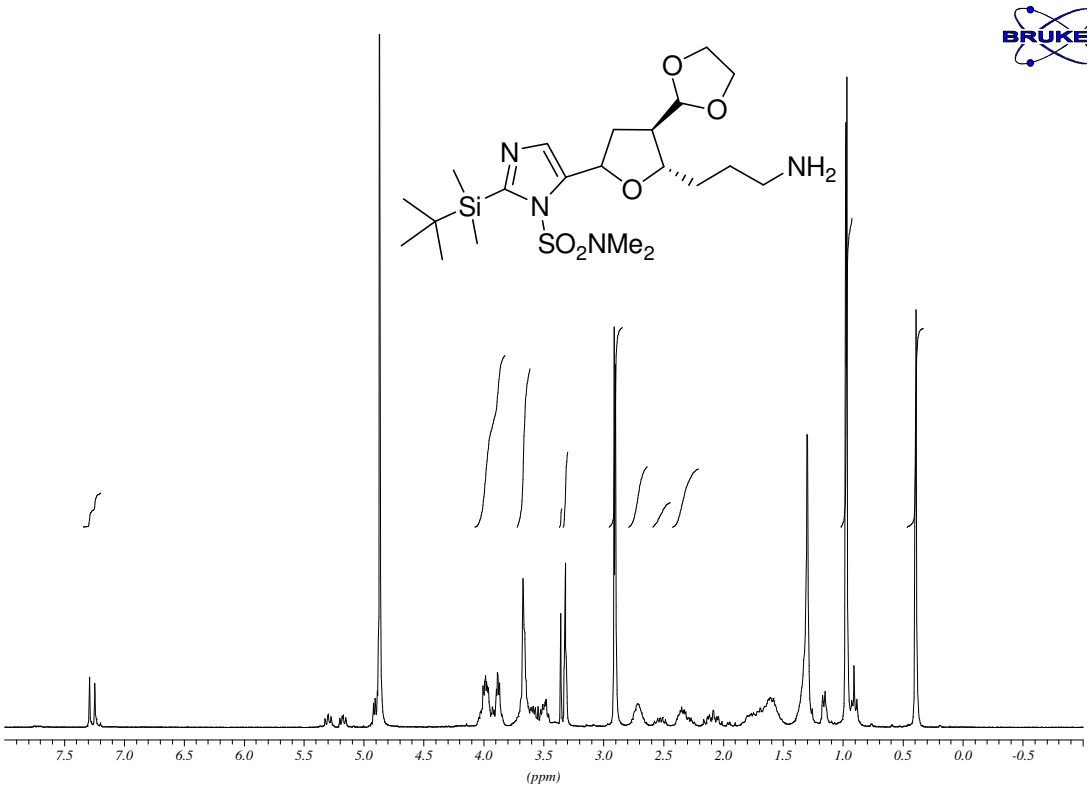

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

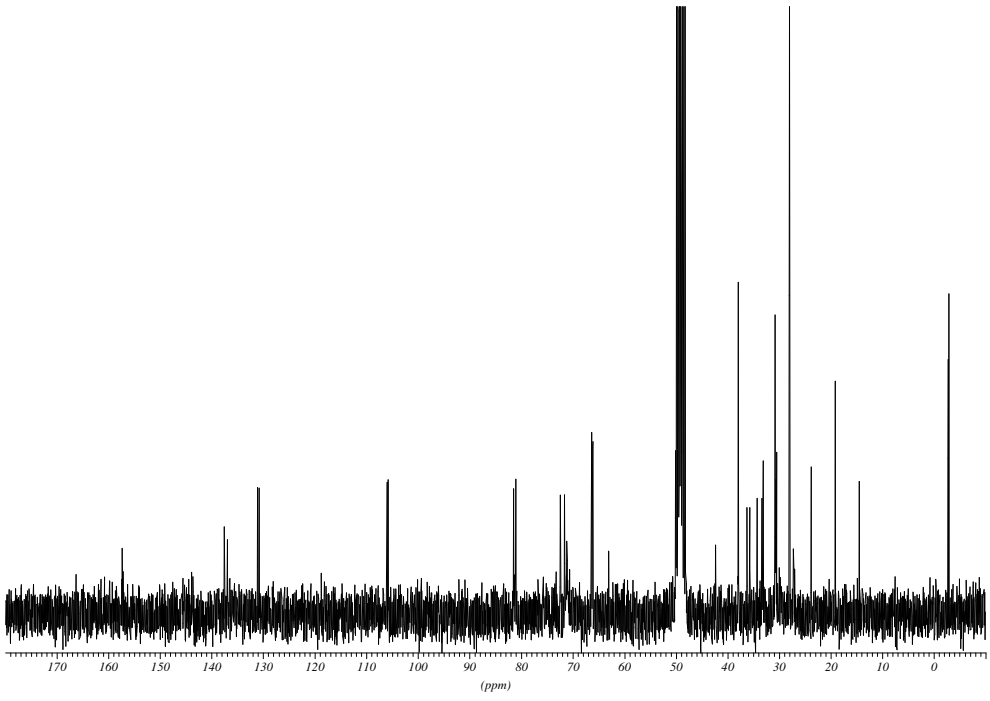

O
O
N
OH
Si
N
O
SO2NMe2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

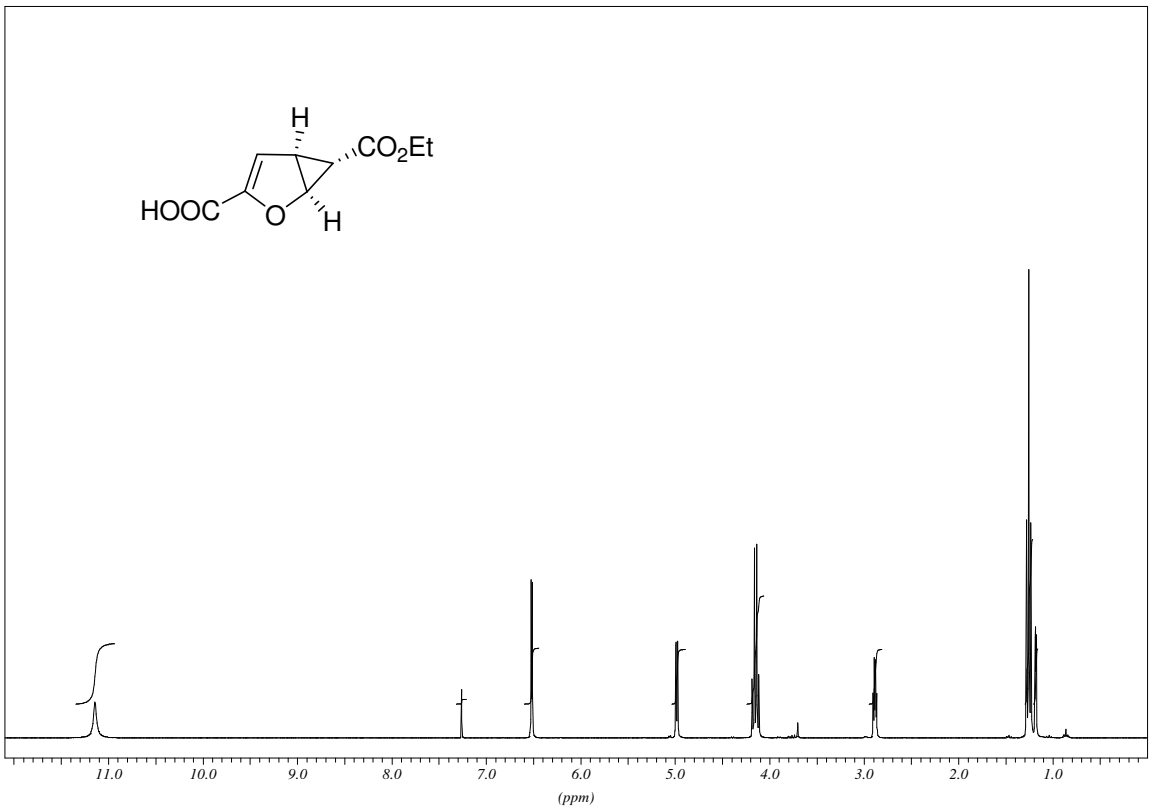

BRUKE
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

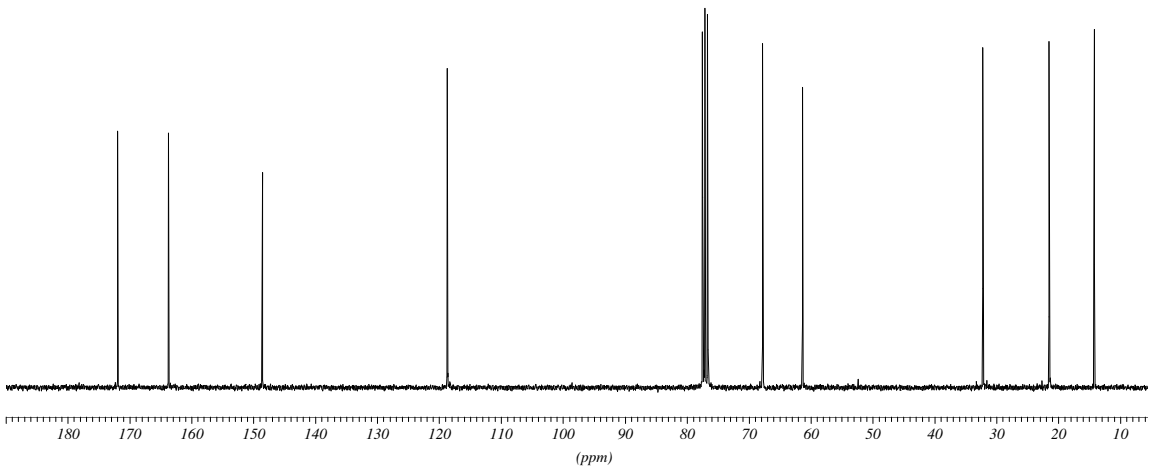

O
O
O
N
N
O
N
Si
N
SO2NMe2
O
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

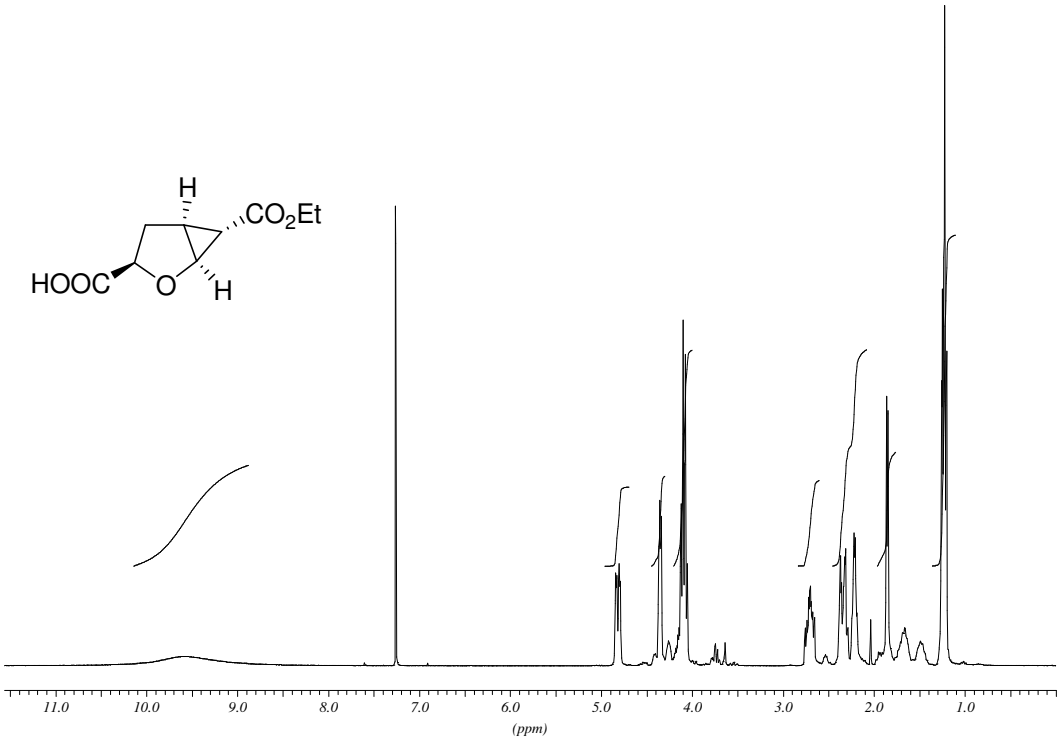

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

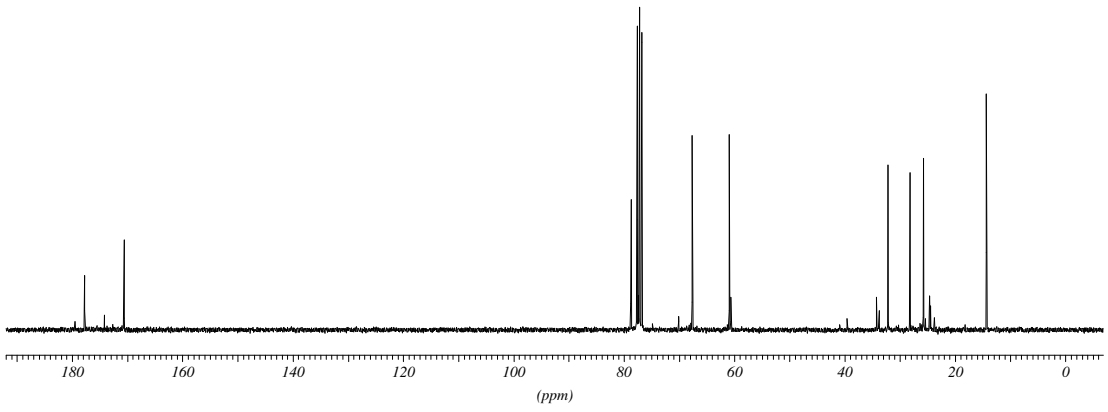

O
O
N
NH2
O
Si
N
SO2NMe2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

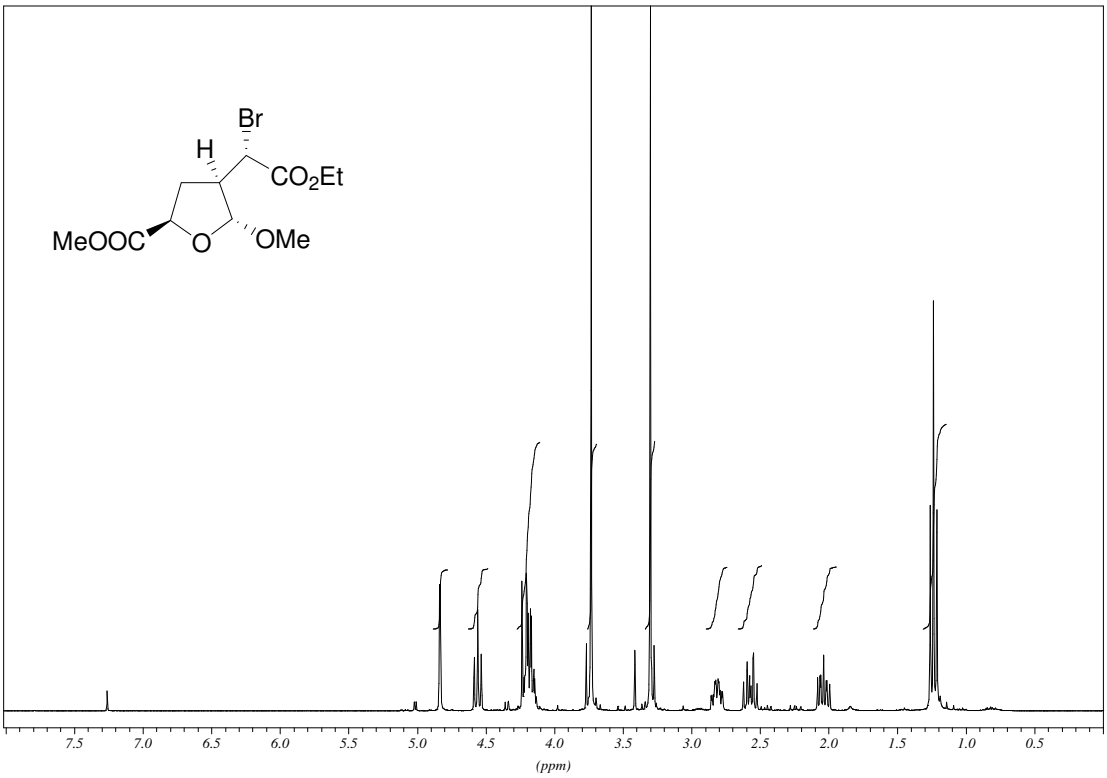

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

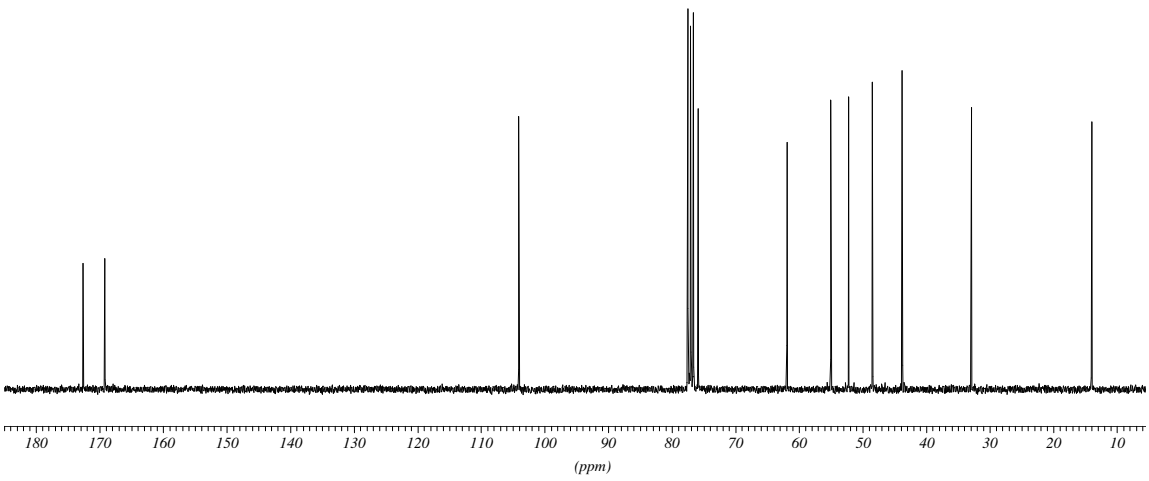

H
CO2Et
HOOC
O
H
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

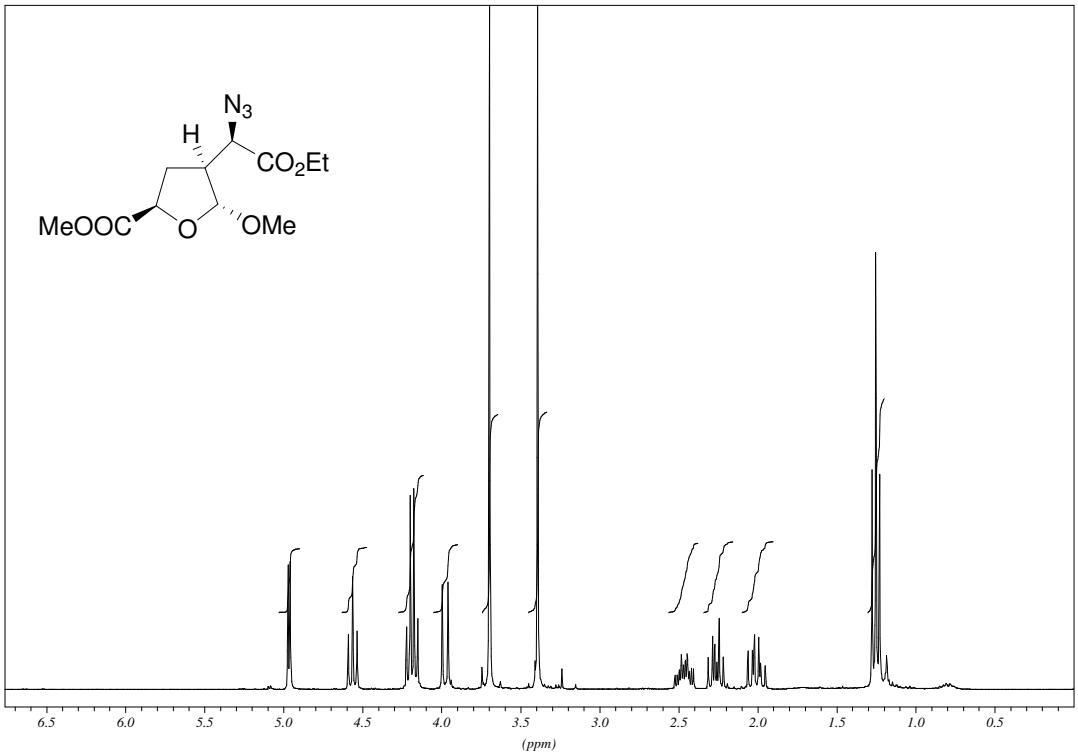

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

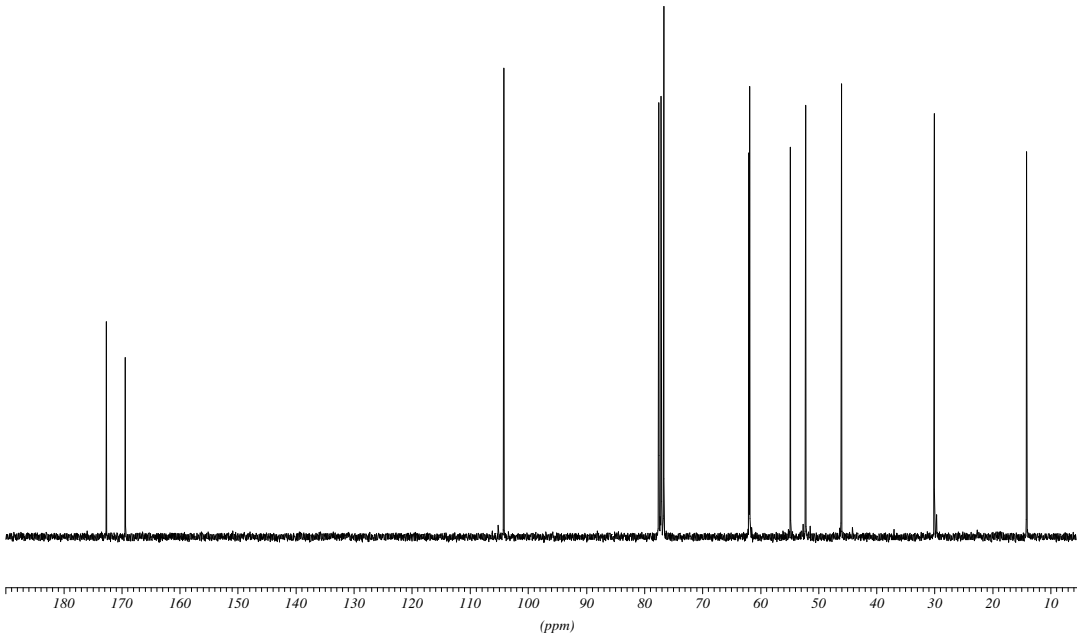

H
CO2Et
HOOC
O
H
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

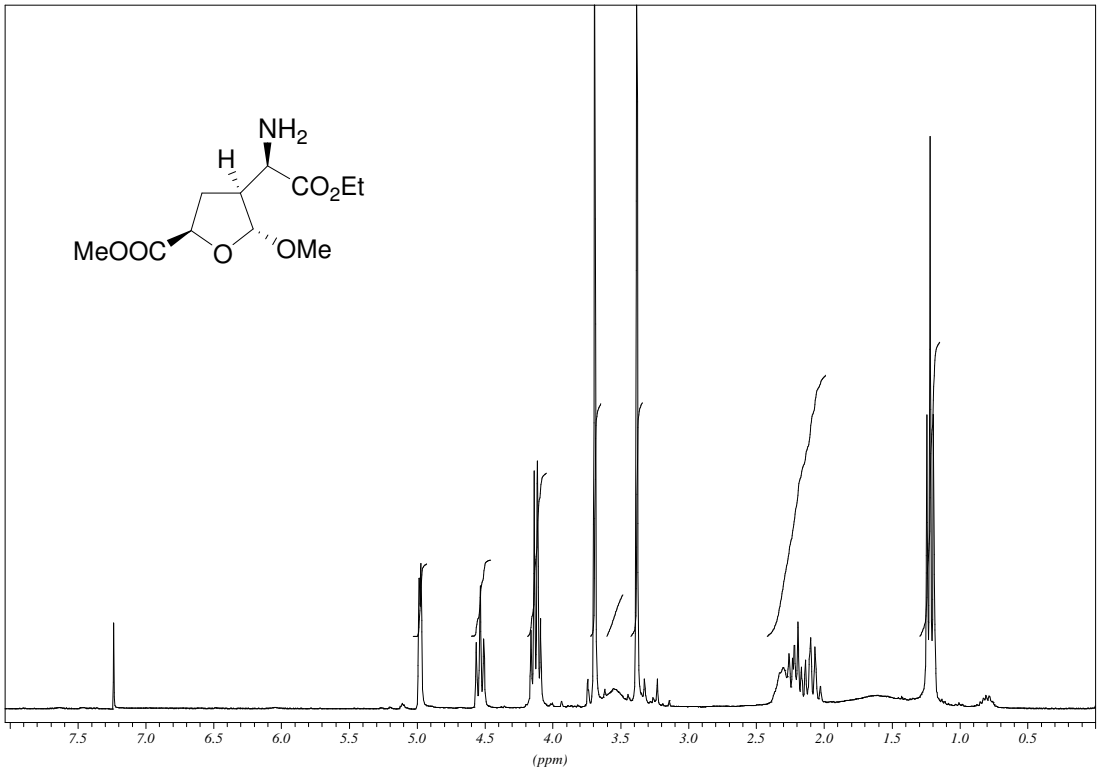

180
160
140
120
100
80
60
40
20
0
(ppm)

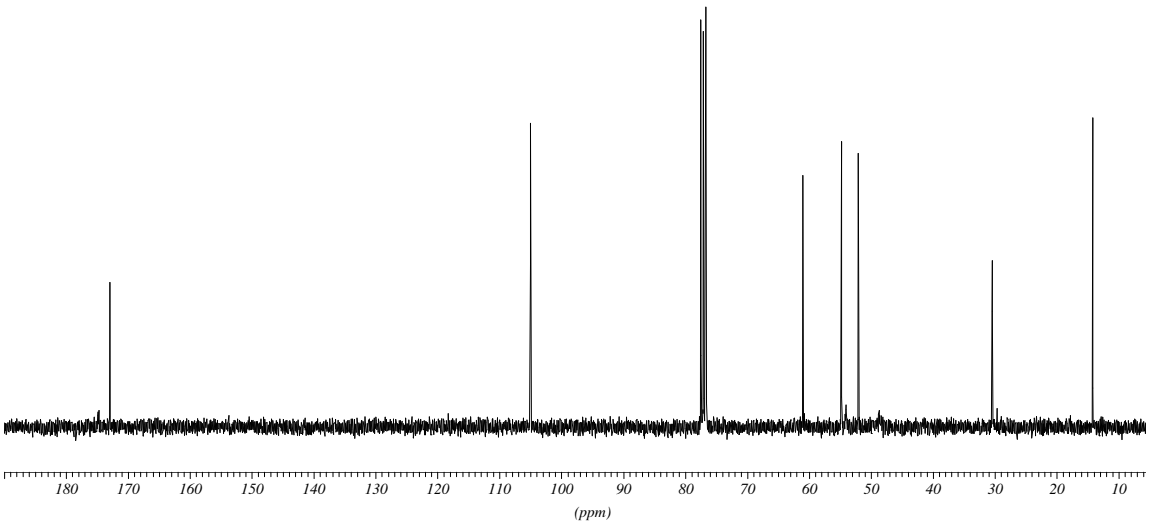

Br
H
CO2Et
MeOOC
O
OMe
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

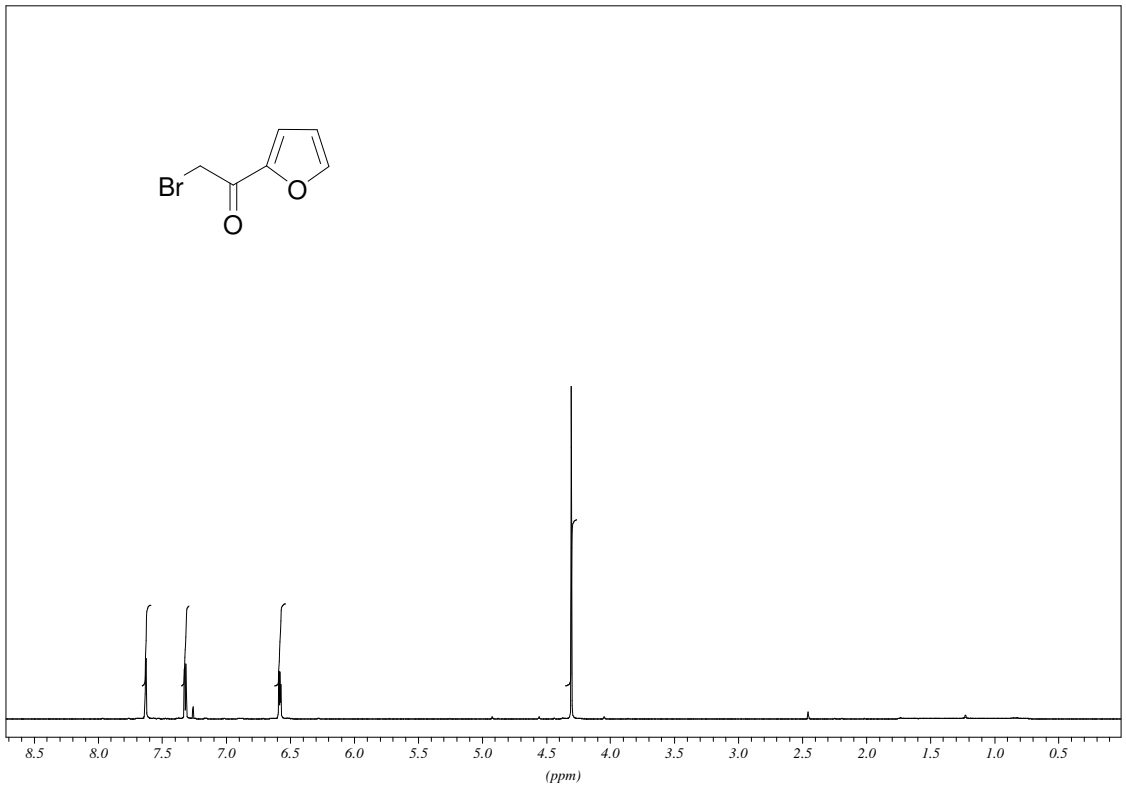

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

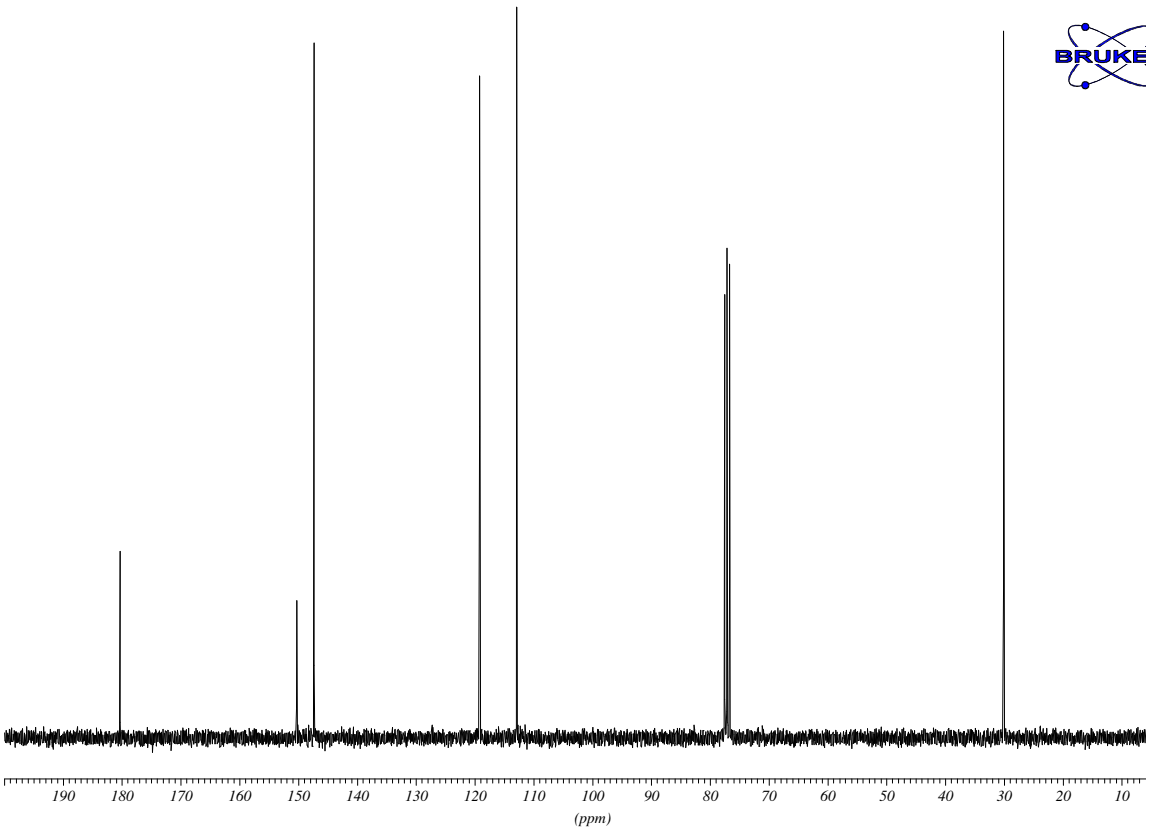

N3
H
CO2Et
MeOOC
O
OMe
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

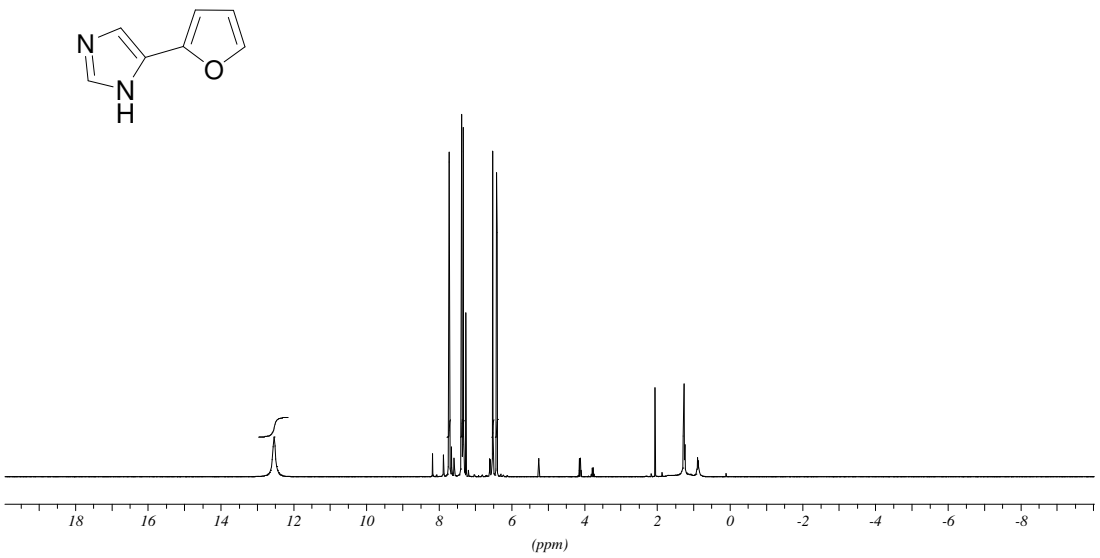

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

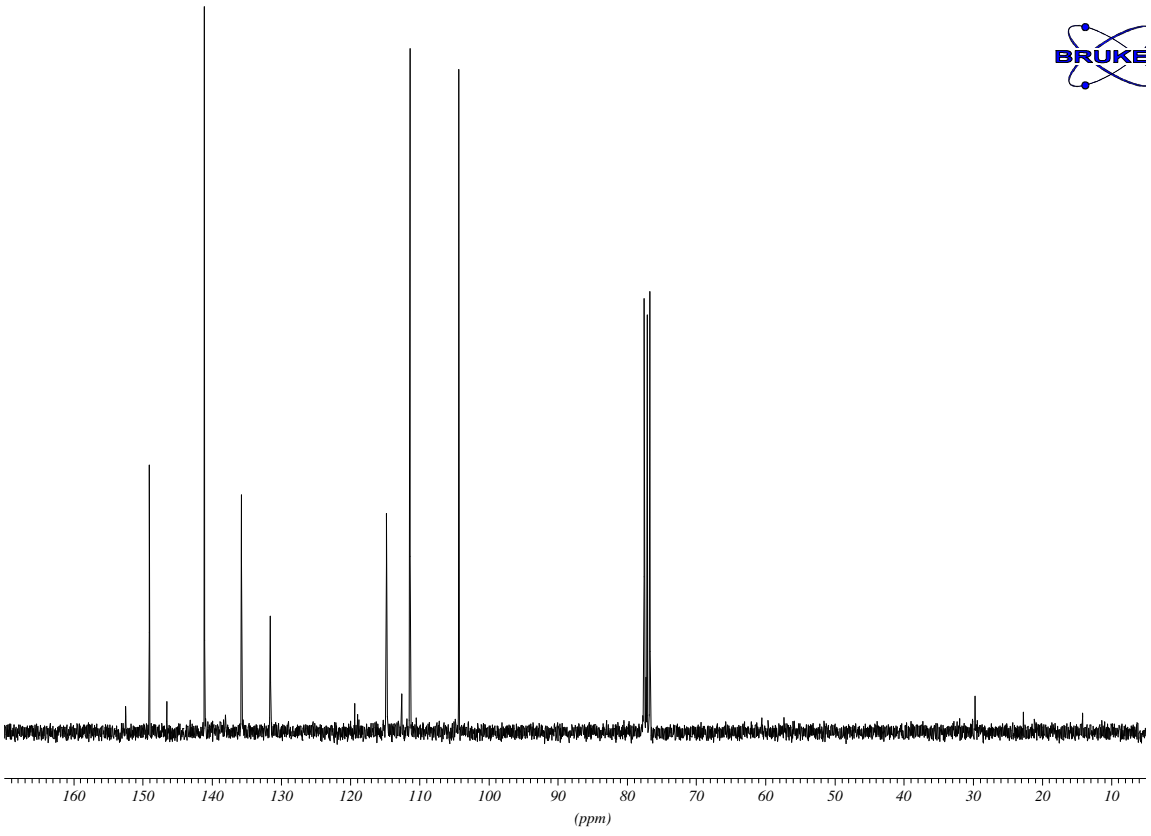

NH2
H
CO2Et
MeOOC
O
OMe
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

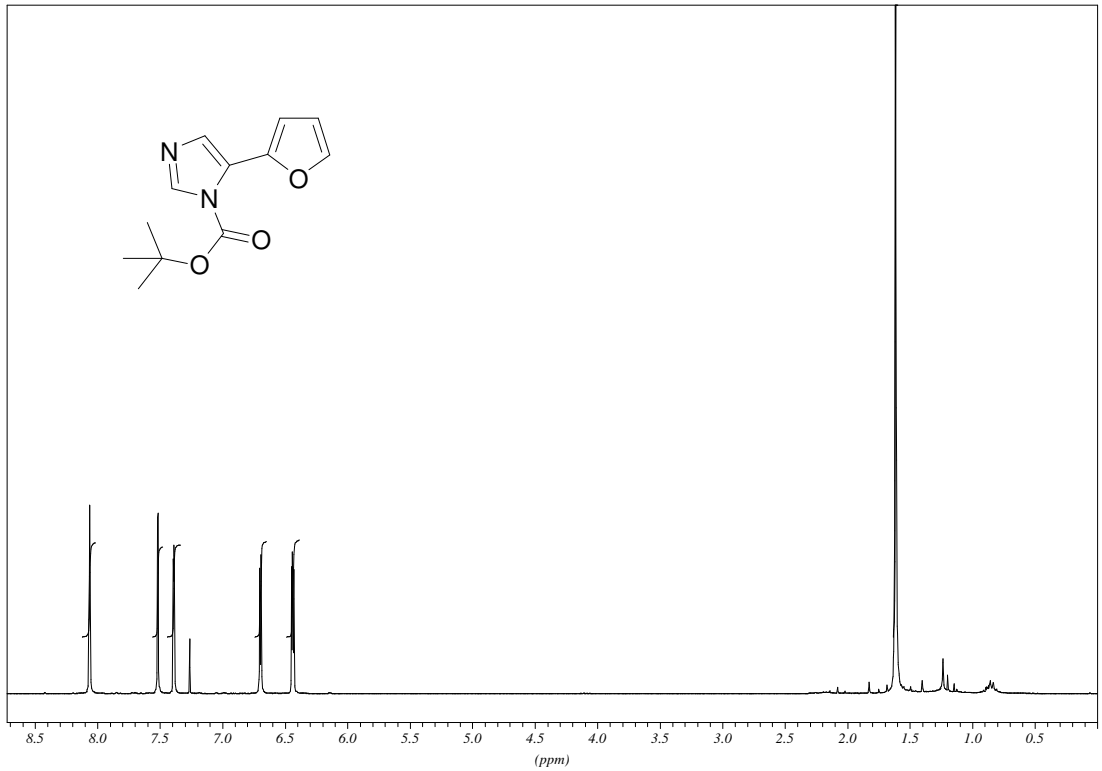

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

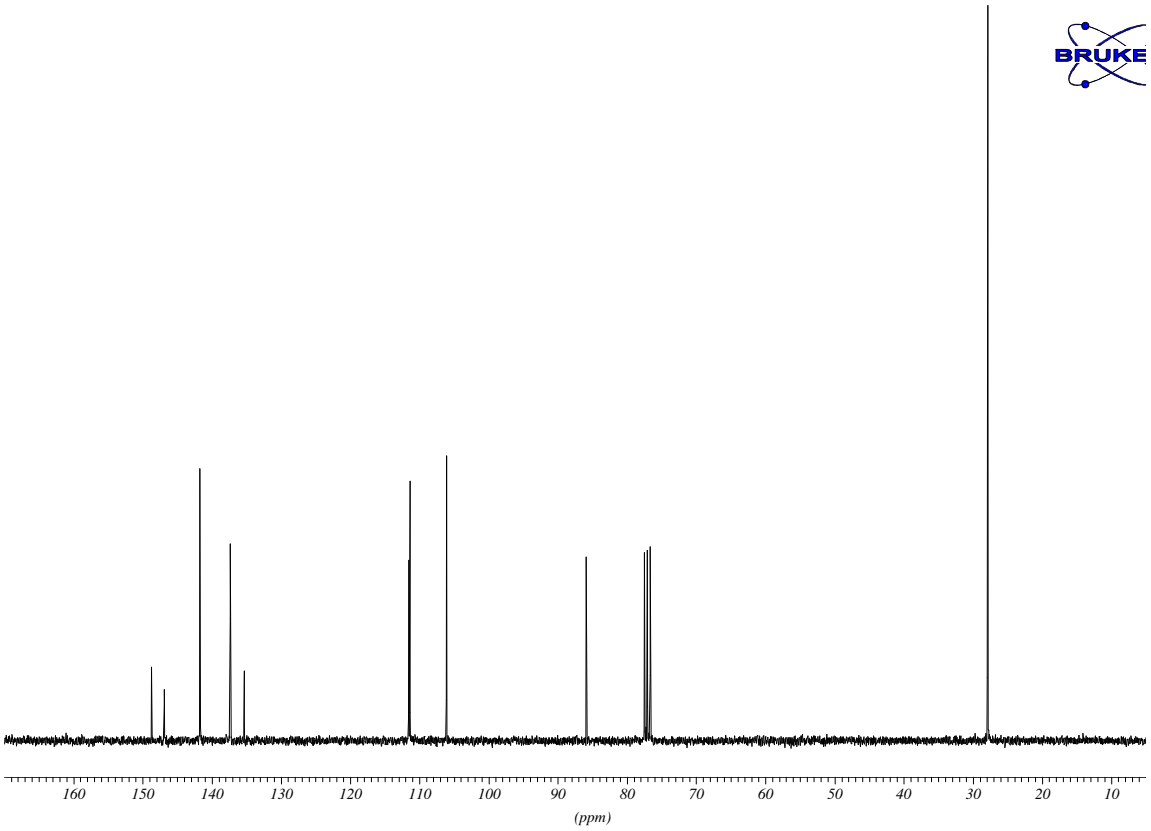

Br
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

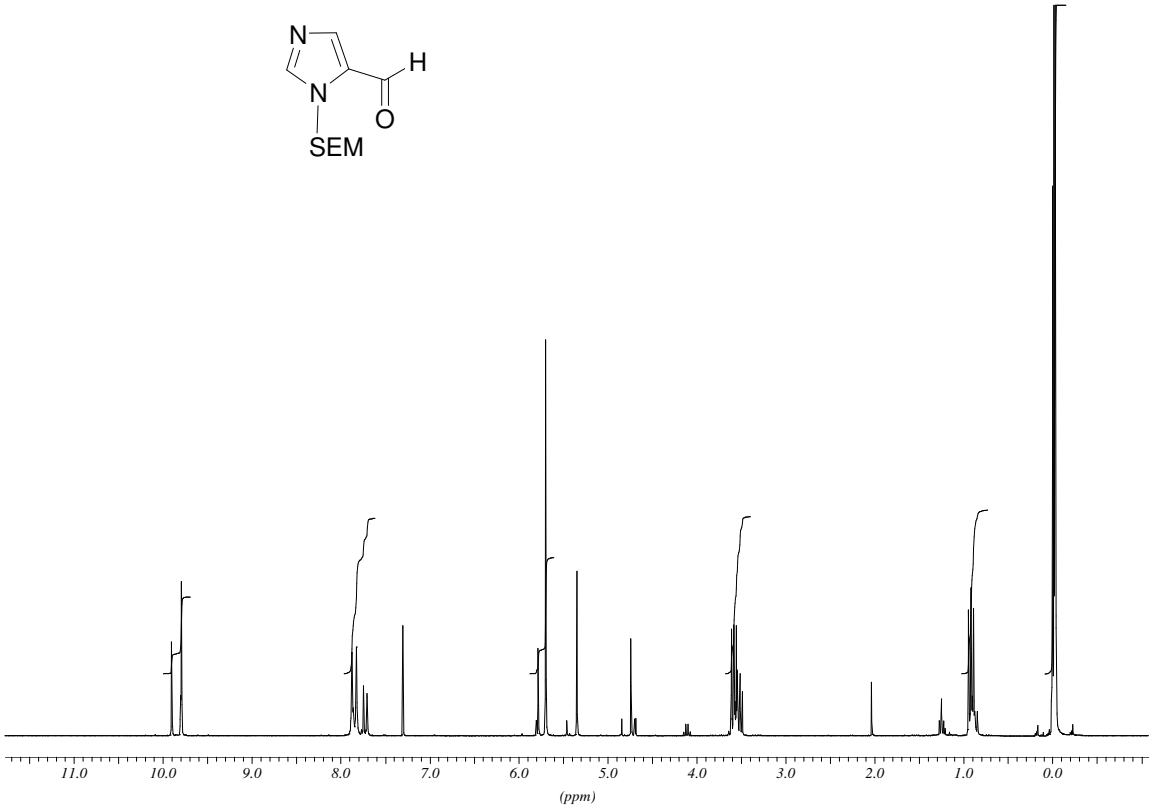

BRUKER
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

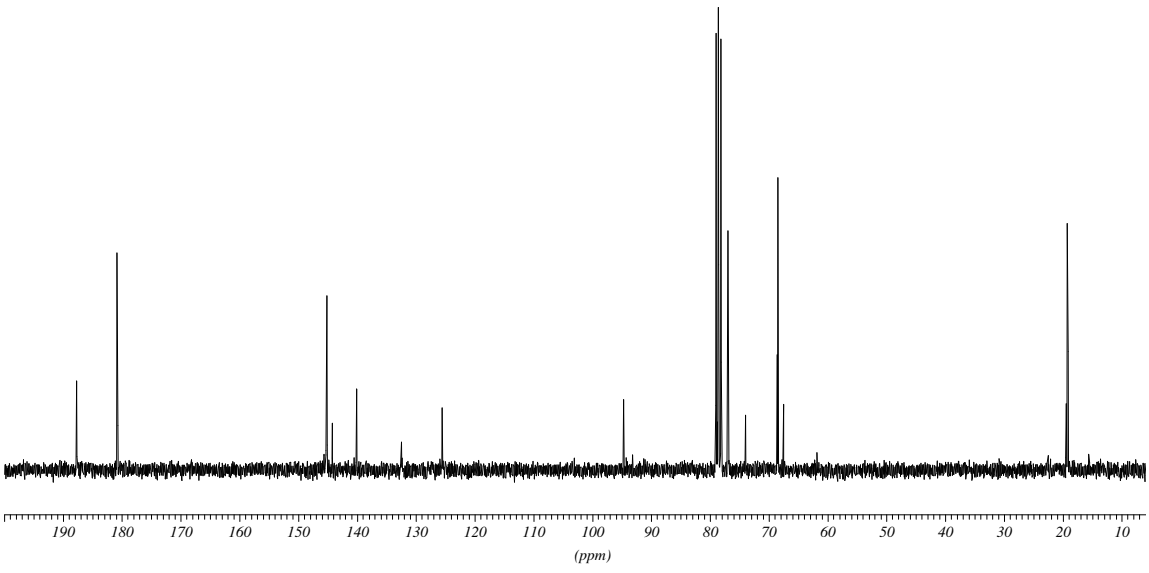

N
N
H
O
18
16
14
12
10
8
6
4
2
0
-2
-4
-6
-8
(ppm)

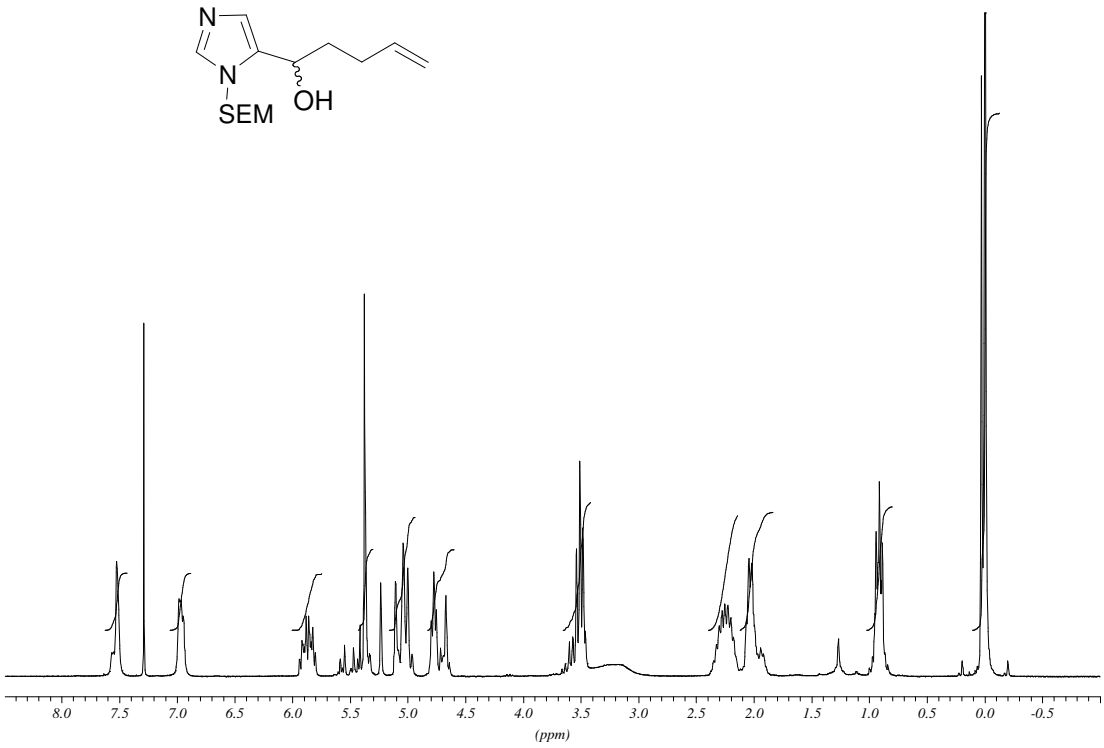

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

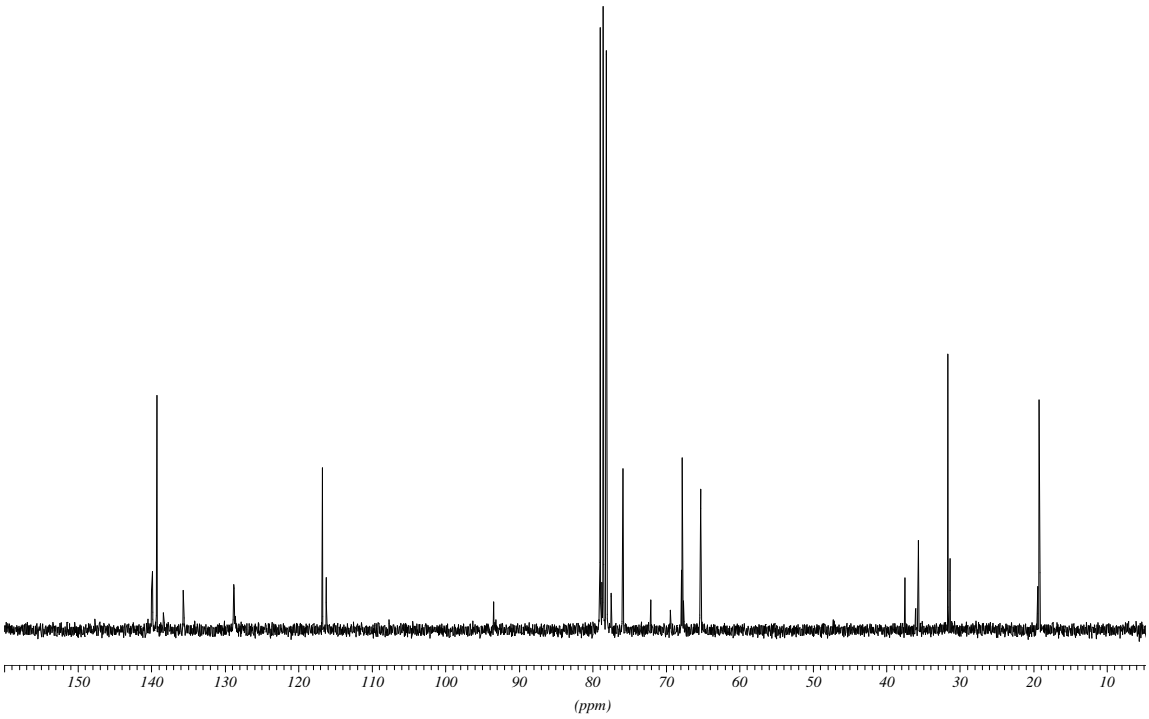

N
O
N
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N
H
N
O
SEM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


N
N
SEM
OH
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

Acknowledgements

It's a great pleasure to express my sincere gratitude to my research guide Prof. Dr. Oliver Reiser, who gave me an opportunity to pursue my Ph.D. in Germany and for introducing me to an exciting area of enantioselective synthesis towards medicinal chemistry. His constructive support, suggestions and freedom made me to motivate and progress further in research.

I am very much thankful to Prof. Dr. Roland Seifert for carrying out pharmacology experiments of my compounds personally and also for his valuable suggestions. I am grateful to Prof. Dr. Armin Bushauer, chairman of GRK (Graduiertenkolleg) 760 for providing me not only financial support, funded by Deutsche Forschungsgemeinschaft (DFG)) during the graduate college period but also for introducing me to learn interdisciplinary science in GRK.

I would like to thank to Prof. Dr. Burkhard König and Prof. Dr. Sigurd Elz for the scientific discussion and for being the examiners of my Ph.D viva voce. I thank Prof. Dr. Buschauer for being chairman of the committee in my Ph.D exam. I would like to thank all the faculty of Institute of Organic Chemistry and Pharmacy, University of Regensburg for their kind nature and help in all aspects of scientific discussion.

I wish to express my sincere gratitude to Prof. S. Chandrasekaran, Department of Organic Chemistry, Indian Institute of Science (IISc), Bangalore, India, who introduced me to the research world and for his continues encouragement to grow as a chemist.

My sincere thanks to Prof. M. V. Rajasekaran (School of Chemistry, University of Hyderabad) who was my project supervisor during my master′s project, for his constant encouragement towards research career.

I deeply acknowledge Prof. M. Periasamy and Prof. D. Basavaiah, School of Chemistry, University of Hyderabad, for their advanced teaching, in Organic Chemistry, during my master of science in chemistry and their encouragement towards research. I am also thankful to all the faculty, School of Chemistry, University of Hyderabad for their advanced teaching in general chemistry. I am very much thankful to my friend Dr. P. Ramu Sridhar, Assistant Professor, School of Chemistry, University of Hyderabad, who gave me the intial training, (when he was a Ph.D student at IISc Bangalore) how to work in research labs and also for staying longer hours in lab.

I am thankful to Dr. Anjaneyulu, lecturer, C.K.M College, Warangal, A.P. for his excellent teaching of Organic Chemistry in Bachelor of Science, by whom I inspired to choose chemistry for my career. I also thankful to Mr. Anjaiah for teaching me, mechanisms of organic reactions during my B.Sc.

I would like to thank to Dr. Peter Kreitmeier for his help to all the technical problems in the lab through out my stay in our research group. A special thanks to Mrs. Rotermund, Ms. Ohli for their constant help in all the administrative work. I had a great help from Dr. Hirtreiter for my early settlement in Regensburg.

I thank to Dr. Thomas Burgermeister, for his kind help in the structural assignment of few complicated spectra especially COSY and NOESY. I also thank Annette Schramm, Fritz Kastner, and Georgina Stühler for recording few 2D-NMR spectra. I am thankful to technicians, Mr. Georg Adolin, Mr. Klaus Döring and Ms. Andrea Roithmeier, for their technical support during my PhD tenure. I would like to thank to Zentrale Analytik, University of Regensburg for their help in recording mass spectra. I thank to the Department of Organic Chemistry, IISc Bangalore, India for recording few HRMS samples.

I would like to thank to European Science Foundation (ESF) for inviting me with full financial support, to ESF-COST international conference on 'natural products chemistry, biology and medicine' at Acquafredda di Maratea, Italy. My special thanks to Prof. K.C. Nicoloau for his suggestions during the poster session in this conference. I am also thankful to Prof. Shibasakhi with whom I had opportunity to talk during this conference.

I am happy to express my sincere thanks to my German friends who are in GRK for their advice and discussion during the conference sessions, poster and oral presentation. I am very glad to Dr. Erich Schneider, Dr. Patric Igel and Mr. David Schnell for correcting my introduction part of thesis, and for their valuable suggestion. I would like to thank to Dr. Max Keller, Dr. Martin Miminger, Dr. Jens Geduhn, Ms. Natali for their friendly atmosphere during the graduate college tenure.

I thank all my lab colleagues Dr. Ai Matsuno, Dr. Alexandru Georghe, Dr. Erick Cuevas-Yanez, Ms. Liu Meina, Mrs. Danfeng and Tapan for their friendly atmosphere. I also would like to thank the former members of Reiser group, Dr. Wom boo Jeong, Dr. Silvia De Pol, Dr. Patil, Dr. Yogesh, Dr. Mohammed, Dr. Sindhu, Dr. Suman, Dr. Valerio D'Elia, Dr. Worluk for their help. Though I cannot name all I am thankful to present and past research group of Prof. Reiser during my stay for translating documents German to English and their help in all aspects.

I wold like to thank all my Indian friends Pranthik Maity for making delicious Bengali and other Indian dishes, Srinivas Kalidindi for arranging trips all over Europe during the holidays though I joined rarely, Ramesh Rasappan for helping me in software, Anu Naik for arranging Pizza parties, Tamil Selvi for giving Sambar a typical south Indian dish, Tapan Maji for saying hundreds of jokes and making fun. I am thankful to Sushma for inviting week end

parties. I am very much thankful to all my present Indian friends who are working in Institute of Organic Chemistry and Pharmacy for correcting my thesis. I am very much thankful to Dr. Senthil Kumar, Dr. Amilan, Dr. Anand, Ms. Mochumi and Dr. Ananta, Ms. Sudipta, Mahesh, Kumaran and Kiran for their help.

I thank Dr. Ashu Kumar Bansal and Mrs. Shika for their suggestions and north Indian special food during the festivals. I am very much thankful to Dr. Reji Varghese for his valuable suggestions and help. I thank all Indigo students Sai Sudheer, Raju Mane, Praveen and Sangram for providing me an amicable atmosphere.I would like to thank Dr.Narsaiah, Prof. Dilip D. Dhavale and Prof. Saumen Hajra for their valuable suggestions.

I would like to express many thanks to my Indian engineering friends who are working in Siemens Regensburg, for inviting me during the Indian festivals and also for playing cricket in holydays, to name few, Srikanth, Pavan, Mrs. Aishwarya, Aravind & Padma, Suraj & Megha, Pramod, Avinash, Chandra and Jignesh for their friendly atmosphere.

I am very much thankful to my IISc friends and labmates Dr.Suresh & Mrs. Radhika, Dr. Saravanan, Mr. Srinivasa Murthy for their suggestions and fun. I am thankful to all the labmates of Prof. SCN group who helped me during my stay in IISc.

I am very much thankful to my HCU friends, seniors, classmates and juniors to name few, Prasad, Jaya Prakash, B.V.N. Murthy, Shiva, Bhuvan, DK, KK. Special thanks to my best friend Dr. Karunakar anna, who is helping me a lot and for his valuable suggestions. I am also very much thankful to my senior HCU friends Dr. Prabhakar, Dr. Lincon & Dr. Sawthi, Mr. Lenin for their suggestions and help.

Being in abroad, thinking of my family members gave me pleasure in many ways. My special thanks to my mother whom I can't acknowledge just in one phrase, for her affection, love and patience for my longer stay in abroad. I thank all my sisters, brother-in-laws, nieces and nephews for taking care of my mother in my absence and their help in all regards.

CURRICULUM VITAE

Mr. Chinna Ashalu Kashamalla

Present Address
Research Scholar
C/o Prof. Dr. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany.

Tel.: +49-9419434633

Fax: +49-9419434121

chinna.kashamalla@chemie.uni-regensburg.de

Permanent Address
Ramanna gudem
Nellikudur
Warangal-506368
Andhra Pradesh
India.

Ph: +919908425767

chinna.kashamalla@gmail.com

ACADEMIC RECORDS:

August 2005- September 2009	Ph. D (Doctoral Degree) Organic and Medicinal Chemistry	Institute of Organic Chemistry, University of Regensburg, D-93053 Regensburg Germany.
April 2002	Master of Science (General Chemistry) First Division	School of Chemistry University of Hyderabad* (A Central University) Hyderabad-500046 India.
April 1998	Bachelor of Science (Chemistry and Biology)	Kakatiya University Warangal-506009 India.

***** *University of Hyderabad gained a grade* 5* *- the highest level in the quality and level of research by Universities with Potential for Excellence (UPE) ranking, University Grants Commission, Government of India*

AFFILIATIONS AND AWARDS

August 2005-July 2008

A member of Graduate College (GRK 760) Research Training Group Medicinal Chemistry funded by DFG (German Chemical Society).

2004

Selected for Graduate School Doctoral program, to the Institute of Chemistry and Chemical Engineering, EPFL Switzerland.

Qualified national level entrance examination for the research training programme to the department of Organic Chemistry, Indian Institute of Science, Bangalore, India.

2003

Qualified Graduate Aptitude Test in Engineering (GATE). It is an all India examination conducted by national coordinating board to identify meritorious and motivated candidates for admission to Engineering, Technology and Pharmacy.

2002

Qualified National Eligibility Test (NET). The University Grants Commission (UGC) conducts a national level test for determining the eligibility of Indian Nationals for the award of Junior Research Fellowship and for appointment of lecturers.

2001

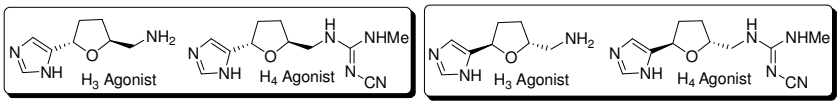
Qualified National Eligibility Test (NET). The University Grants Commission (UGC) conducts a national level test for determining the eligibility of Indian Nationals for the award of Junior Research Fellowship and for appointment of lecturers.

RESEARCH INTEREST: Design and synthesis of biologically active compounds and it´s application towards medicinal chemistry.

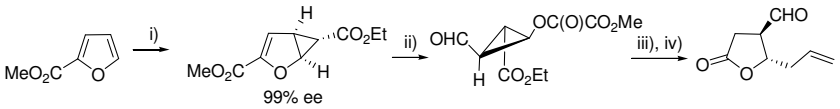
The histamine H_4 receptor has been characterized through homology searching of the genomic data base in 2000. The H_4 receptor was found to have a similar amino acid sequence and pharmacological characteristics as the histamine H_3 receptor. It has been suggested that the H_4-receptor plays a role in the treatment of autoimmune, inflammatory and allergic disorders. Imifuramines and their cyanoguanidine derivatives have been identified as promising lead structures for the development of H_3 and H_4 receptor agonists. We herein describe the enantioselective synthesis of different functionalized terahydrofuran-imidazloe derivatives as potential histamine H_3 and H_4 receptor agonists based on a route for the enantioselective synthesis of γ-butyrolactones that has been developed in our group. We have synthesised some analogues of imifuramine by keeping an additional functional group at 4^{th} position of tetrahydrofuran ring and also extending the side chain of aminomethyl group to gain insight in to the structure activity relationship. On the other hand we are also synthesising some analogues by cyclopropane ring opening methodology to change the position of aminomethyl and cyanoguanidine groups for the histamine H_3 and H_4 receptor agonists.

RESEARCH ABSTRACT:

Synthesis of Histamine H_3 and H_4 receptor agonists

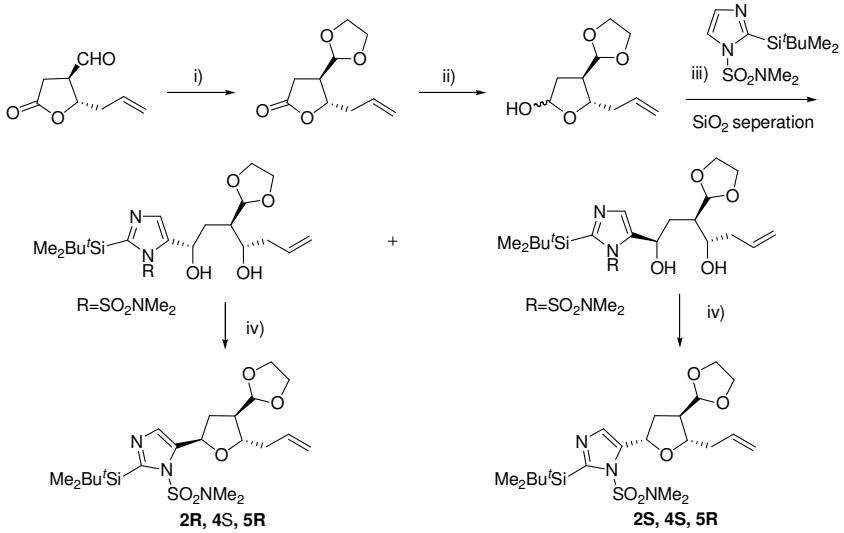


Enantioselective Synthesis of γ-butyrolactones



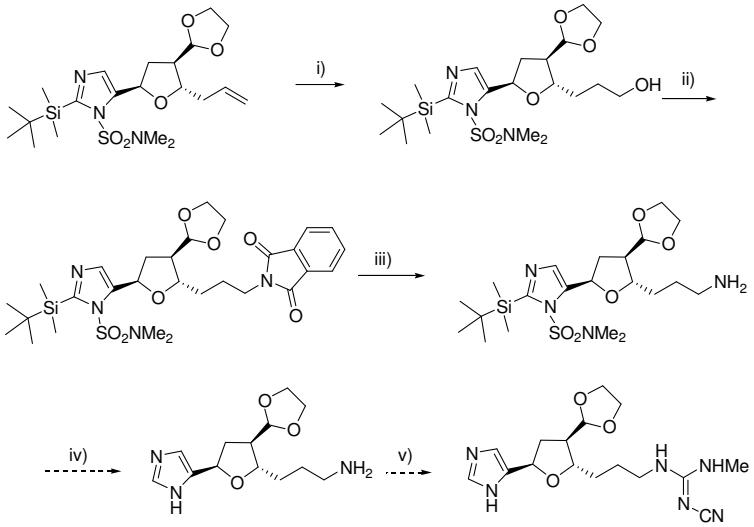
Reagents and conditions: i) (S,S)- isopropyl Bisoxazoline, $Cu(OTf)_2$, $PhNHNH_2$, ethyldiazoacetate, 0℃, 41%; ii) O_3, DCM, -78℃, DMS, rt, 12h, 98%; iii) $BF_3.Et_2O$, allylTMS, DCM -78℃, 12h; iv) $Ba(OH)_2$, MeOH, 0℃ 50%

Synthesis of Tetrahydrofuron-imidazole based building blocks for Histamine H_3 and H_4 receptor agonists



Reagents and conditions: i) ethylene glycol, TsOH, benzene, reflux, 85%; ii) DIBAL-H, CH_2Cl_2 -78℃, 90%; iii) BuLi, THF -78℃, 90%; iv) a) TMAD, Bu_3P, benzene, RT, 70% or b) ADDP, Bu_3P, benzene, RT, 80%

Towards the synthesis of histamine H_3 and H_4 receptor agonists



Reagents and conditions:i) BH_3.THF, THF, rt 12h, 2M $NaOH/H_2O_2$, 5h, 80%; ii) Phthalimide, PPh_3, DEAD, rt 12h, 65%; iii) $N_2H_4.H_2O$, EtOH, rt 12h, 76%; iv) Na/Naphthalene, dimethoxy ethane, rt; v) $(MeS)_2C{=}NCN$, MeOH, 40% $MeNH_2$

RESEARCH EXPERIENCE:

August 2005- September 2009	Ph. D thesis	Thesis supervisor: **Prof. Dr. Oliver Reiser** Institute of Organic Chemistry, University of Regensburg Germany.

Enantioselective Synthesis of Tetrahydrofuran-Imidazole based Human Histamine H_3 and H_4 Receptor Agonists

December 2004- May 2005	Senior Chemist	Medicinal Chemistry Division G.V.K. Biosciences ICICI Knowledge Park Thurkapally, R.R Dist Andhra Pradesh, India.

Synthesis of spiro and fused hetero cycles from aromatic aldehydes/acids

September 2002- November 2004	Project Assistant	Prof. S. Chandrasekaran Department of Organic Chemistry, Indian Institute of Science Bangalore, India.

Efficient Methodology for the Synthesis of 2-C-Branched Glyco-amino Acids by Ring Opening of 1, 2 - Cyclopropanecarboxylated Sugars.

January –April 2002	Master's thesis	Prof. M. V. Rajasekaran University of Hyderabad Hyderabad, India.

A Cambridge crystallographic data search on sulfur-phenyl non-bonding interactions

Experimental Skills:

Designing and performing multistep organic synthesis.

Extensive experience in performing reactions from mg to multi gram scale.

Have a sound practical knowledge in handling dry, air sensitive reagents and performing reactions in inert atmosphere.

Instrumentation:

Handled NMR (Automatic Shimming), IR, UV-Visible Spectrometers,
Polarimeter, HPLC and GC during my research career.

Have sufficient knowledge on analyzing NMR, Mass, IR and UV spectral data.

Publications:

1. Efficient Methodology for the Synthesis of 2-C-Branched Glyco-amino Acids by Ring Opening of 1,2-Cyclopropanecarboxylated Sugars.

Perali Ramu Sridhar**, K. Chinna Ashalu,** and S. Chandrasekaran*****

Org. Lett., **2004,** *6,* 1777-1779.

Manuscript under preparation:

2. Enantioselective Synthesis of Tetrahydrofuran-Imidazole based Human histamine H_3 and H_4 Receptor Potential Agonists

Chinna Ashalu. K, Buschauer, A., Seifert, R., Reiser, O.*

3. Asymmetric synthesis of human histamine H_3 and H_4 receptor agonists by cyclopropane ring opening methodology

Chinna Ashalu. K, Buschauer, A., Seifert, R., Reiser, O.*

Participated International Conferences:

Poster Presentations:

Enantioselective Synthesis of Tetrahydrofuran-Imidazole based H_3&H_4 Receptor Potential Agonists

Kashamalla, C.A., Buschauer, A., Seifert, R., Reiser, O.*

1) 3rd Summer School Medicinal Chemistry, September 25-27, 2006. University of Regensburg, Germany.

2) Frontiers in Medicinal Chemistry Annul meeting March 2-5, 2008. University of Regensburg, Germany.

3) ESF-COST High-Level Research Conference Natural Products Chemistry, Biology and Medicine, May 18-23, 2008. Acquafredda di Maratea, Italy. (Chair: Prof. K. C. Nicolaou)

4) 4th Summer School Medicinal Chemistry September 29 - October 1, 2008. University of Regensburg, Germany.

Personal Details:

Date of Birth: 16-03-1977
Gender: Male
Nationality: Indian
Marital status: Single

References:

Prof. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434631 (4630)
Fax: +49-9419434121
Email: oliver.reiser@chemie.uni-regensburg.de

Prof. S. Chandrasekaran (Chairman, Division of Chemical Sciences)
Department of Organic Chemistry,
Indian Institute of Science, Bangalore – 560 012. India. Phone: +91-80-293-2404
Fax: +91-80-2360-0529
Email: scn@iisc.orgchem.ernet.in

Prof. M.V. Rajasekharan
School of Chemistry
University of Hyderabad
Central University P.O.,
Hyderabad – 500 046, India.
Phone: 091-40-23134857
E-mail: mvrsc@uohyd.ernet.in

Prof. Dr. Burkhard König
Institute of Organic Chemistry
University of Regensburg
D-93053, Regensburg, Germany
Tel.: +49-9419434575
Fax: +49-9419431717
Email: burkhard.koenig@chemie.uni-regensburg.de