1.1 INTRODUCTION

One of the major causes for memory loss in the world is Alzheimer’s disease (AD). The predominance of AD doubles every five years beyond 65.\(^\text{1}\) Scientists made considerable research on AD in the last few years; however, much is still unknown. AD mostly affects old age people above 75 years.

Alzheimer’s disease is brain disorder resulting in the death of brain cells. More or less Dementia is similar to AD, which results in loss of intellectual activities. Dementia is not a disease but brain disorder that accompany the symptoms of diseases which include changes in personality and behavior. A considerable number of people have been suffering with AD. It results in affecting the work and life long hobbies. Alzheimer’s disease first recognized as disease in Austria and recently in Europe and America.

The psychotic symptoms, like delusions and hallucinations are reported in most of the AD patients and there symptoms lead to early institutionalization.\(^\text{2}\)

The brain consists of billions of neurons and each neuron transfer the information to other neurons to form a network. The neurons can perform specific functions. In AD patients, the learning skills and memory power can decrease progressively.

The research on AD reveals that the associated anatomical and chemical changes occur. These changes include nerve cell degeneration and levels of acetylcholine in the brain of AD patients.\(^\text{3}\)
The AD is associated with advancing age and more prevalent among octogenarians. The poor and uneducated are more vulnerable to this disease than rich and educated.

It is expected that the AD patients increase substantially as the population ages. The scientists are trying to develop the methods of diagnosing the disease in the initial stages and ways to help the AD victims. The scientists and health care personnel are searching better ways to help the AD patients. It is projected that the number of Americans with AD may increase three times in the next 50 years that is from 4 millions to 14.3 millions.

1.1.1 Symptoms

The Alzheimer’s disease is classified as below:

a. Forgetfulness
b. Confusion
c. Dementia

a. Forgetfulness

This is diagnosed as temporary memory loss. The victims often forget names of kin and kith and misplace items regularly. This stage may include behavioral changes in addition to loss of spontaneity and social withdrawal.

b. Confusion

In this stage, the cognitive deterioration is prominent and there is pronounced memory loss. The victims frequently forget places and important dates.
The noticeable trait of this stage is poor judgment and change of individual’s personality.

c. Dementia

In this phase, there is a major loss of AD victims struggle to identify kin and kith finally they will become bedridden.\(^4\)

1.1.2 Diagnosis

It is important to understand different types of dementia related illness and easy to diagnose a patient with these kinds of symptoms. The dementia is categorized as:

1. Primary undifferentiated dementia,
2. Primary differentiated dementia and

The first group produces the dementia by affecting the brain directly, as those seen in Alzheimer’s. Both have similar symptoms and can not be differentiated by simple methods. The primary differentiated dementia includes loss of muscular control. The secondary dementia is due to temporary dysfunction of the brain and is curable, but accurate diagnosis is critical. Therefore, these three types of diseases cause diagnosis problems for the medical personnal.\(^5\)

The patients completely depend on the care takers during the last stage of AD. AD occurring in middle age or above, in the form of dementia which results in memory loss, confusion and emotional. Half of the affected people suffer from dementia and it is predominant in the aged
people\textsuperscript{6} above 85 and less than 50% of the victims are effected with Alzheimer’s disease.\textsuperscript{7}

1.1.3 Treatment

Tacrine 1, Physostigmine 2, (-)-Galanthamine 3, Memantine 4, Donepezil 5 and Rivastigmine 6 are used for the treatment of Alzheimer’s disease.\textsuperscript{8} Galanthamine is used as medication for acetyl cholinesterase inhibitors. It increases the amount of natural substance in the brain cells that is required for memory. In AD patients and also improve to think and rememberance.

**Tacrine (1)**

Tacrine 1 was first synthesized by Adrien Albert\textsuperscript{9} and used for the treatment of centrally acting and act as a histamine $N$-methyl transferase inhibitor.\textsuperscript{10}

\begin{center}
\textbf{Figure-1.1}: Tacrine (1)
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**Physostigmine (2)**

Physostigmine 2 (known as eserine) which is acts as a parasympathomimetic, which is a reversible cholinesteric inhibitor.\textsuperscript{11}
**Figure-1.2:** Physostigmine (2)

**(-)-Galanthamine (3)**

(-)-Galanthamine 3 is an alkaloid base which is isolated from the Caucasian snow-drop (Galanthus Woronowii) and from the bulbs of different species of the Amaryllidaceae family (commercially available as Reminyl). Reminyl is the most recently approved AChE inhibitor in USA and in Europe for the symptomatic treatment of AD patients.

![Chemical structure of (-)-Galanthamine (3)](image)

**Figure-1.3:** (-)-Galanthamine (3)

**Memantine (4)**

Memantine 4 is another active compound having anti Alzheimer's activity, which was synthesized by Eli Lilly. This is chemically known as 3,5-dimethyl adamantine-1-amine and used to treat AD victims.
Memantine (4) (marketed under the brands Axura and Namenda) acts on the glutamatergic system by blocking NMDA receptors.

![Chemical structure of Memantine](image1.png)

**Figure-1.4:** Memantine (4)

**Donepezil (5)**

Donepezil 5 is a centrally acting reversible acetyl cholinesterase inhibitor similar to physostigmine, which is mainly used to increase cortical acetyl choline, in the treatment of Alzheimer’s disease.

![Chemical structure of Donepezil](image2.png)

**Figure-1.5:** Donepezil (5)

The combination of Donepezil 5 with Memantine 4 results superior than Donepezil alone. Donepezil 5 was studied as newer agent for AD patients with mild cognitive (thinking and memory) impairment, used for the prevention of dementia, and can be used to improve speech in children.

**Rivastigmine (6)**

Rivastigmine 6 is used as drug for the treatment of dementia related to Parkinson’s disease.
Figure-1.6: Rivastigmine (6)

Rivastigmine is a cholinesterase inhibitor which inhibits both butynyl cholinesterase and acetyl cholinesterase whereas Donepezil selectively inhibits acetyl cholinesterase only.

1.2 CURRENT RESEARCH ON ALZHEIMER’S DISEASE

There are difficulties in diagnosing AD. The solution is for these difficulties are dealt in the article written by Douglas Gelb in the *Statistics in Medicine Journal*.\textsuperscript{12,13} The scientists are efforts to study the effects of different symptoms and their relation ship with the dementia patients.

In addition to these, many more areas of dementia and Alzheimer’s disease are being researched. The federal government has been spending huge amounts on Alzheimer’s disease.\textsuperscript{14,15}

Galanthamine 3, Memantine 4, Donepezil 5 and Rivastigmine 6 are the AChE inhibitors currently approved for symptomatic treatment of Alzheimer’s disease patients. Where as both, Donepezil and Galanthamine selectively and reversibly inhibit AChE. Moreover, Galanthamine is an allosteric modulator of nicotinic acetylcholine receptors (n Ach Rs) and
Donepazil inhibits Ach RS with a parallel desensitization effect of the receptor as per recent reports.

(-)-Galanthamine 3\textsuperscript{16} is a centrally acting reversible inhibitor of acetylcholinesterase (AChE), which enhances cognitive functions of Alzheimer’s patients.\textsuperscript{17} In the endeavor of searching for more potent inhibitors of AChE, there is considerable interest in derivatives which are based on (-) Galanthamine as a lead structure\textsuperscript{18}, since (-)-Galanthamine is less toxic than other AChE inhibitors, such as physostigmine and tacrine.\textsuperscript{19} Among them, (-)-Galanthamine derivatives\textsuperscript{20,21} and its iminium salt were found to be more potent than galanthamine in inhibiting AChE.

(-)-Galanthamine 3 had been isolated from the Caucasian snow-drop (\textit{Galanthis woronowii}) and also from the bulbs of different species of the \textit{Amaryllidaceaee family}.\textsuperscript{22} Some pharmacologist extracted Galanthamine in 1956 from the leaves of the plant Galanthis rivalist. It is commercially registered product in the form of hydrobromide salt under the trade name NIVALIN.\textsuperscript{23,24}

(-)-Galanthamine, commercially available as Razadyne, a Galanthamine hydro bromide, is the most recently approved AChE inhibitor.\textsuperscript{25} Owing to the scarce supply from threatened\textsuperscript{26} botanical sources\textsuperscript{27} and the high cost about $50 000 per kilogram) of its isolation from daffodils (0.1 – 2\% dry weight)\textsuperscript{28} several total syntheses have been reported to produce this drug.

Since the last reviews, of Marco-Contelles et al in 2006\textsuperscript{29} Oshino in 1998\textsuperscript{30} and Martin in 1987\textsuperscript{31} dedicated to the Amaryllidaceae family of
natural products, no review has been published on this subject. The extent of reports regarding Galanthamine has significantly increased in recent years.

Galanthamine 1, as an AChE inhibitor, an allosteric potentiator of neuronal nicotinic receptors for acetyl choline (nAChR), a modulator of neurotransmitter release, and also acts as an agent causing neuroprotection through an autiaprotic action. Hence now, we will try to place Galanthamine in the context of the treatment of dementia, both of vascular origin and of Alzheimer’s disease (AD) type.

In general, health care improves, and the proportion of elder people in the population increase and the number of AD patients is anticipated to increase dramatically.

1.3 PREVIOUS SYNTHETIC APPROACHES FOR GALANTHAMINE

Barton and Kirby revealed that Amaryllidaceae alkaloids, including Galanthamine, are derived from a common precursor, norbelladine 7 via intramolecular oxidative phenol coupling.
Norbelladine 7 was established as the biogenetic precursor for Galanthamine 3 bio synthesis, and further it was proven by the experiments using α-\(^{14}\)C-labelled Norbelladine derivatives.

Scheme-1.1

Narwedine 8 was assumed to be produced from dienol 9 via dienone 10 by intramolecular oxidative phenol coupling. Further studies have confirmed this assumption.\(^{36}\)

Scheme-1.2
Zenk reported\textsuperscript{37} the new inputs on this mechanism leading to Galanthamine by using radioactive and heavy isotope-labeled active precursors from parts of \textit{Leucojum aestivum} plants. A new process for the biosynthesis of Galanthamine 3 involves, oxidative intramolecular phenol coupling of 4'-O-methylnorbelladine 11 to a dienone 12, through intramolecular ring closing of the ether bridge results \textit{N}-desmethylnarwedine 13, in subsequent step which undergo stereoselective reduction and followed by \textit{N}-methylation (Scheme 1.2). Fuganti and Kirby\textsuperscript{38} laboratories have supported this hypothesis in further studies.

\textbf{Scheme-1.3}

Synthesis of Galanthamine, a significant effort, was done to prove synthetic feasibility of the above proposed biogenetic path way. Barton and Kirby\textsuperscript{39} have worked on this path and synthesized racemic Narwedine
from diphenolic amine 17 using potassium ferricyanide by the use of oxidative phenol coupling and later reduction of Narwedine 8 with LAH gives a mixture of racemic Galanthamine 3 and epi-galanthamine 18.

The synthesis of compound 17 was simple and straightforward (Scheme 1.2). When 4-hydroxy phenyl acetic acid 15 and O-benzyl isovanalline 19 were easily converted to acyl chloride 16 derivative and N-methyl amine 20, on condensation of 16 and 20 gave the target precursor 17 by the oxidative phenol coupling reaction.

Based on this the biomimetic synthesis of Galanthamine is represented, and the improved Barton synthesis is reported by several groups in subsequent years. Major modifications are

1. The promotion of target oxidative phenol coupling is done more efficiently by the protection of the para position.
2. The introduction of a third phenol functional group, to avoid the problems of regio-selectivity in the aromatic ring, a third phenol functional group is introduced.
3. The use of other oxidants like phenyliodine(III)-bis-(trifluoroacetate) (PIFA) and Mn(OAc)₃ that might afford products in higher yields and in mild conditions.
Kametani published a series of papers on the synthesis of Galanthamine and its derivatives in 1969.\textsuperscript{40} On the basis of previous synthetic works reported by Burchard\textsuperscript{41} and taking into account, the low yields of the oxidative phenol coupling reported by Barton,\textsuperscript{42} Kametani has proposed diphenolic amide 23 as the key precursor. The bromine atom is assumed to prevent the para coupling to the hydroxyl group and favor the ortho-coupling. This compound was easily prepared by routine transformations starting from \textit{p}-\textit{O}-benzylhydroxy amine 21.

The above proposal was fulfilled since the phenol oxidation of compound 23 afforded a narwedine-type compound 24 (35\% yield). Finally, treatment of compound 24 with lithium aluminum hydride (LAH) reduced the carbon-bromine bond, transformed the amide to an amine, and promoted the unselective reduction of the keto group to afford a mixture of Galanthamine 3 and epi-galanthamine 18.\textsuperscript{43}
Later on Kametani proposed an alternative total synthesis of racemic Galanthamine based on the oxidative phenol coupling of compound 24, an amide of the precursor 23 previously used by Barton. However, the key oxidative phenol coupling proceeded in a poor 5% yield, but the authors thought that this approach was simple and more efficient than their first alternative synthesis, since the synthesis of the required amide was easier. Eventually, the racemic N-norgalanthamine was synthesized by following similar protocols on bromine-containing intermediates.

Bulgarian researchers have also been worked on this topic. The synthesis of the tetracyclic ring system of galanthamine was studied by using the intramolecular para-ortho coupling of conveniently functionalized diarylethers by anodic oxidation. Later Vlahov and colleagues have reported the synthesis of the same compound previously prepared by Kametani and have submitted it to cyclization, but interestingly, they have found that under the same experimental conditions the yield was quite lower, about 15% only.

In view of the above, we discussed the eco-friendly and commercial viable process for synthesis of (-)-Galanthamine hydrobromide.

The first chapter of this thesis presents the Introduction about the Alzheimer’s disease and the developmental research work in the synthesis of Anti-Alzheimer’s drugs.

The second chapter of the thesis presents research work carried out in the synthesis of (-)-Galanthamine hydrobromide with increased yields which is the cost effective, viable and eco-friendly process.
The *third chapter* of the thesis discusses the impurity profile of (-)-Galanthamine hydrobromide. The Seven unknown impurities detected along with the known impurities were synthesized and characterized.

The *fourth chapter* of the thesis explores the polymorphism of (-)-Galanthamine hydrobromide. The two polymorphic forms have been synthesized and a comprehensive study has been under taken to synthesize the stable crystalline form of (-)-Galanthamine hydrobromide.

The *fifth chapter* of the thesis describes the synthesis and characterization of Memantine hydrochloride with a viable and cost-effective process by using non-hazardous chemicals.
1.4 REFERENCES


