CHAPTER 1

INTRODUCTION

Cancer is an abnormal disease, which affect the normal cell growth inside the body. The cascade expression of multiple genes and protein paves complications to cure the disease. There are few important crucial proteins which are primary source for either inducing or suppressing the gene and protein expression. Currently kinases based proteins are taken as drug targets for treating the cancer because kinase signaling from one receptor to another receptor in cancer cell is more rapid and it leads to tremendous growth of the cancer cells in the body. The screening of lead compounds in vitro and in vivo studies takes more time and cost for screening the compounds are high. One of the approaches to analog-based drug discovery is the concept of ‘Bioisosteric Replacement’ in the design of novel pharmacological tools as well as new therapeutic agents with optimal pharmacological profile and improved pharmacokinetic properties. Benzothiazepines are seven member heterocyclic compounds that are bioisosters of benzodiazepines and contain a sulphur in place of nitrogen have received consideration in recent years. It is only that recent attention is being directed to a variety of synthetic methods due to its efficient therapeutic properties.

The synthesis of compounds containing sulfur atoms is of great interest in organic chemistry, for its use as a synthetic intermediate as well as for its biological potential. Instances of pharmacological applications include several compounds have been used as antibacterial agents, anti-HIV agents, anti-cancer and against various other diseases. Thus study of chemistry of 1, 5-benzothaizepines has attracted attention in recent years because of their wide application in organic synthesis.
Thiazepines are substituted thiepins, with nitrogen replacing a carbon in the seven-membered heterocyclic compounds.

(Figure 1.1) Thiepin

(Figure 1.2) Thiazepine

1,5-Benzothiazepines have single benzene attached to the Thiazepines.

(Figure 1.3) 1, 5 Benzothiazepine

1,5-Benzothiazepines is seven-membered ring heterocyclic compounds that possess many pharmacology activities and biological activities. For many years, their structure, synthetic methods and biological activities attracted extensive attentions.

The ring addition reaction of the C=N double bond had influenced chemists of the world with great interest, because this functional group carries on one of the main reactive position in chemical modification and derivatization. Therefore, synthesize and development of a series of the new 1,5-benzothiazepine derivatives
are of great interest. Similarly pyrazine, pyridine, furan and thiophen derivatives are also of good nature in pharmacophore. Therefore, we expect to realize reinforcement of many physiological activities of these compounds by means of combination of these groups with 1,5-benzothiazepine.

1,5-benzothiazepines: Versatile pharmacophore

1,5-Benzo-thiazepine moiety is a privileged class of pharamacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities. The high biological activity of these molecules prompted us to study the synthesis of novel molecules of these classes [1]. These compounds are widely used as

- Anticonvulsant [2]
- anti-HIV [3]
- CNS depressant [4]
- Ca++ channel blockers [5]
- Anti fungal [6]
- Hypnotic agents as well as anti-inflammatory agents
- Anticancer [7]
- Antimicrobial [8]

Dong et al reported that the discovery of tetra cyclic benzothiazepines (BTZs) as highly potent and selective antimalarial along with the identification of the Plasmodium falciparum cytochrome b, c (1) complex as the primary functional target this class of compounds [9]. Hence, Benzothiazepine function is quite stable and has wide biological activities, we inspired to synthesize new compounds possessing biological activities.
There are various benzothiazepines that earlier were synthesized and tested for biological activities. For examples, Diltiazem S (DTZ) is a 1,5-benzothiazepine calcium channel blocker synthesized in 1971. Nicardipine (a dihydropyridine derivative) reduces the three hyperactivities, verapamil (a diphenylalkylamine derivative) reduces only oxolinic acid hyperactivity and diltiazem (a benzothiazepine derivative) was active except in the MAOI-reserpine test. Levome-promazine used as a reference drug reduced the three hyperactivities. The renal effects of the calcium entry-blocking drugs diltiazem, nifedipine, verapamil and nitrendipine were reviewed. Although nifedipine stimulates plasma renin activity on a short-term basis, none of the calcium entry blockers produces a clinically significant sustained effect on any of the components of the reninangiotensin-aldosterone system.

Diltizem is a non-dihydropyridine (DHP) member of the group of drugs known as benzothiazepines. Benzothiazepines were considered as an important class of heterocyclic compounds in the field of drug and pharmaceutical research.

![Figure 1.4: Versatile pharmacophore nature of 1,5-benzothiazepines](image)
Table 1.1: Biological and pharmacological activities of some benzothiazepines

<table>
<thead>
<tr>
<th>S. NO</th>
<th>Structure</th>
<th>Pharmacological Activity</th>
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| 1     | ![Structure](image) | Antidepressive Activity, Coronary Vasodilating Activity.  

*US4590188  
US5002942  
Japan. J. Pharmacol. 23, 321-328 (1973).*
Motivation on 1, 5-Benzothiazepines

As mentioned on the above Table 1.1, Diltiazem, nifedipine, verapamil and nitrendipine has pharmacological activity of Antidepressive, Coronary Vasodilating and Anti-Brast Cancer activity respectively.

The present work focuses on pharmacological profile associated with 1,5- benzothiazepines. This work mainly covers the synthesis of novel seven member 1,5-benzothiazepines and study their pharmacological nature of cancer using in silico virtual screening.

Common synthetic methods

1,5-Benzothiazepines are commonly synthesized by the reaction of o-aminothiophenol with α, β-unsaturated carbonyl compounds, β-haloketones. There are various methods that had been reported for the preparation of 1,5-benzothiazepines using different solvents and inorganic solid supports such as
However, many of these reported procedures have one or more disadvantages such as use of expensive catalyst, low selectivity, harsh reaction conditions, low yield, relatively long reaction time and environmental concern.

In recent years replacement of hazardous-solvent with environmentally benign solvents is one of the major focus areas of green chemistry. The use of alternative reaction solvents such as following conditions are rapidly growing.

- Water [17]
- Ionic liquid [18]
- Fourous [19]
- Supercritical media [20]
- Polyethylene glycol (PEG) [21]

The application of microwave (MW) irradiation as a nonconventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry [22]. Many researchers have described accelerated organic reactions towards proving the synthetic utility of MW irradiation in routine organic synthesis [23].
Present study

Scheme: 1.1: Retro Synthetic route of 1, 5-benzothiazepines

This thesis involves to develop a simple convenient procedure for the synthesis of 1,5-benzothiazepines by using green methodology that are neat, solvent-free, microwave-assisted synthesis and uses eco friendly adsorbent. The structures of all newly synthesized compounds were established by IR, Mass spectral data, $^1$H NMR, and $^{13}$C NMR. More precisely, low costing in silico methods in combination with modern information technologies used to identify the potential new cures for cancer.

Besides that, to synthesis 1, 5-benzothiazepine, we need to synthesis the $\alpha$-oxoketene dithioacetals as an intermediate, we are synthesized these intermediates and characterized in the chapter 2.

Motivation for in Silico modeling in cancer research

Molecular docking is the in silico method provided for both protein and leads compounds to simulation using the various algorithms to check the binding
affinity between the active site amino acid residues and the leads. We motivated to screen the series of synthesized novel 1, 5-Benzothiazepine compounds for Lipinski’s rule of 5 using computational tools to check the drug likeness property for the leads compounds. The screened compounds are taken for receptor-ligand interaction to check the affinity between them. In this current study, 1,5-benzothiazepine derivatives were docked with mitogen-activated protein (MAP) kinases defied binding site co-ordinates using lib dock available through acclerys 2.5v and described in chapter 4.

References

22. S. Varma, Green Chemistry 1, 1999, 43.