3. OBJECTIVES

3.1 OBJECTIVES OF THE PRESENT INVESTIGATION

- Development of feasible route for the synthesis of title compounds.
- Characterization of the newly synthesized compounds by FTIR, $^1$HNMR, $^{13}$C, FAB MASS and elemental analysis data.
- A preliminary docking study was initially carried out with the HEX-software for the designed compounds tried to dock with the antitubercular protein (2YES) from Protein Data Bank (PDB).
- To screen these newly synthesized compounds for Antitubercular activity by Microplate Alamar Blue Assay (MABA) method and Antimicrobial activity by Agar diffusion method.

3.2 NEED FOR THE STUDY

Research for the development of new therapeutic agent is becoming the major interest in many academic and industrial research laboratories all over the world with the aim to discover newer, more potent molecules, with higher specificity and reduced toxicity than the existing ones.

Tuberculosis is a common fatal infectious disease caused by strain of *M. Tuberculosis*. TB is normally affects the lungs and can also infect the other body parts. Most of the people is infected with this disease is increasing because of the growth of the population; the numbers of new cases are still increasing. In last year it was estimated that nearly 14 million of chronic cases, nearly 10 million of new cases were identified and nearly 2 million deaths annually mostly in countries which are developing. In addition more number of people in the developed country is infected with TB because of their immune system is compromised by immuno suppressive drugs, Aids or substance abuse. The distribution of TB is not same across the world because more than eighty percentage of the population growth in many African and Asian countries tests are +ve in the test of tuberculin (WHO, 2009; Kumar et al., 2007).

Tuberculosis disease is still a challenging problem of health in worldwide and *M. tuberculosis* remains one of the single most deadly human pathogens. The resurgence of
TB over last 15 years, in industrialized countries where it was almost eradicated, has been favored by the pathogenic synergy with human immunodeficiency virus infection. In fact, tuberculosis and other typical mycobacteriosis are now diseases frequently associated with AIDS; human immunodeficiency virus infection significantly increased the risk that new or latent TB infections will progress to active diseases. The incidence of tuberculosis is increasing worldwide, partly due to poverty and due to AIDS pandemic, which greatly raises the risk of this infectious cause (Grange et al., 2002). The increase in drug-resistant mycobacterium tuberculosis during recent years presents a therapeutic challenge to a pharmacist, scientist for selecting novel antituberculosis agents. Thus the development of new agents with potent antitubercular activity is urgently needed. The drug resistant to *M. tuberculosi* also has become a serious concern. Because of the concern of the resistance to most of the commonly used drugs by the mycobacteria (Culliton, 1992), our studies have been focused on the development of new potential therapeutic heterocyclic fused thiadiazole derivatives.

TB is a preliminary infectious cause of poverty along with Malaria and AIDS. Effective treatment of tuberculosis is difficult, because of the complicated structure and the cell wall composition of the mycobacteria. Because of this many drugs like antibiotics are not effective and inhibit the drug to enter into the cell wall. Drug resistant tuberculosis became a serious problem in current years. For ex: Isoniazid resistant tuberculosis is seen in many of the patients from Southeast Asia. The presence of isoniazid like substances in the cough syrup may play important role in causing the Isoniazid resistance. A massive increase in the frequency of tuberculosis occurred in the year of 1980’s because of persons infected with HIV and continued throughout the 1990’s. Increase in the tuberculosis infection occurred because of the suppression of the immune system of the body by HIV allowed tuberculosis (WHO, 2009; Migliore, 1995; Acharya and Goldman, 1970; Brennan and Nikaido, 1995; Obrien, 1994).

MDR-TB and XDR-TB are the types of tuberculosis disease which are affecting the public health seriously. Due to resistance, treatment of TB is difficult in patients because of poor compliances. In case of MDR TB, strains are resistant to two or more drugs of the firstline antituberculosis drugs such as INH, RIF, PZA, EMB and Streptomycin. (Bastian and Colebunders, 1999; Barry et al., 2000). There are two basic
approaches for the diagnosis of tuberculosis. The direct approach includes detection of mycobacterium and the indirect approach includes measurement of humoral and cellular responses of the host against tuberculosis. Immunizations against tuberculosis are being achieved through the Bacillus Calmette Guerin vaccination. Modern drugs have revolutionized the treatment of tuberculosis with the right course of treatment a cure of 100% can be achieved (Ramchandran and Paramasivan, 2003). Despite all the advances in the chemotherapy of tuberculosis, the treatment of the disease still continues to be challenging issue in the field of chemotherapy. The following factors render the management of this disease a complex and protracted procedure (Davis and Driver, 1957).

- Inadequate defense mechanism of the host.
- Metabolic character of the tubercle bacillus.
- Rapid development of the resistance by Mycobacterium tuberculosis to almost all of available antitubercular drugs, limited the ultimate value of these drugs.
- Persistence of dormant but viable tubercle bacilli in the tissues of the majority of patient’s inspite of extensive chemotherapy.
- Lack of bactericidal action of most of the antitubercular drugs.
- Marked toxicity of many of the drugs which prevent them from being administered in therapeutic doses.
- The economic condition of the underdeveloped countries does not permit the use of many of the drugs due to their high cost and longer duration of treatment required to eradicate mycobacterium tuberculosis. Considering the above factors, it is pertinent to mention here that a drug which can effectively eradicate tubercle bacilli within shorter duration of time is most desirable and progress in this area is the need of the hour, by considering above factors we have planned to synthesize the titled derivatives followed by its docking study and their antitubercular and other pharmacological activities.

It is a needed to synthesize new derivatives because of the following reasons

- Need of new active form of drug for the treatment of tuberculosis.
- Presence of drugs like Isoniazid in cough syrups may cause the INH resistance.
Emergence due to MDR TB and XDR TB.

Lengthy treatment.

In case of MDR tuberculosis and XDR tuberculosis, second line drugs are implemented, but there is also some limitations

- Some of the drugs are less active than the drugs of first line.
  Ex: P-amino salicylic acid
- Some of the drugs may show side effects.
  Ex: Cycloserine
- Some of the drugs are given by parenteral route.
  Ex: Streptomycin
- Drugs are not available in many developing countries. Ex: Fluoroquinolones

Literature survey clearly indicates that 1,3,4-thiadiazole can be considered as an important pharmacophore in the field of medicinal chemistry which can be used for conjugating it with other bioactive molecules such as Antifungal, Antibacterial, Anticonvulsant, Antitubercular, Anti-inflammatory etc. due to its potent pharmacological activity.

In literature review, several procedure have been described for the synthesis of Thiadiazole fused heterocycles, but most of the methods are very complicated, having longer reaction time and require very advanced synthetic technology. Also chemicals and reagents which are required for the synthesis are not easily available & expensive.

The purpose of this investigation is to synthesize different 1,3,4-thiadiazole fused different secondary amines, Schiff’s bases as well as azetidinone and thiazolidinone derivatives by efficient, cost effective, environmentally friendly & convenient method and to characterize them by melting point, TLC, elemental analysis, FTIR, $^1$HNMR, MASS, and $^{13}$C spectroscopic analysis. Prepared derivatives shall be docked by using HEX-software and pharmacologically screened for the activity of antitubercular activity against strain *M. Tuberculosis* by MABA procedure and also activity of antimicrobial against various fungal and bacterial strains by using agar diffusion method.
3.3 PLAN OF RESEARCH WORK

- Review of literature and introduction related to synthesis of different 1,3,4-thiadiazoles, Azetidinones, Thiazolidinone compounds and their pharmacological activities.
- All chemicals for subsequent steps are being procured.
- Development and standardization of feasible route for the synthesis of title compounds.
- Synthesis of some newer heterocyclic fused 1,3,4-thiadiazole derivatives.
- Synthesis of Schiff’s bases.
- Synthesis of novel Azetidinone derivatives.
- Synthesis of novel Thiazolidinone derivatives.
- Characterization of the newly prepared derivatives by IR, $^1$HNMR, $^{13}$C, MASS and elemental analysis data.
- Docking study with HEX-software for the designed compounds to dock with the antitubercular protein (2YES) from Protein Data Bank (PDB).
- To screen these newly synthesized compounds for *invitro* *M. Tuberculosis* using MABA method and antimicrobial activity by agar diffusion method.