ABSTRACT

The work described in the thesis entitled “Synthesis, characterisation and biological evaluation of heterocyclic compounds and their derivatives” can be abstracted as under.

CHAPTER-1

This chapter briefly introduces importance of heterocycles in the field of Drug development and discovery. General classification of active drugs based on their effect along with essential drug concept has been also explained. Brief introduction to drug development along with the relative literature review of the work done on 1,2,6-thiadiazine 1,1-dioxide, Thiadiazine and Sulfamide derivatives in past. This chapter further describes aims and objectives of the proposed research work.

CHAPTER-2

Esters are ubiquitous. Most naturally occurring fats and oils are the fatty acid esters of glycerol. Esters with low molecular weight are commonly used as fragrances and found in essential oils and pheromones. Phosphoesters form the backbone of DNA molecules. Nitrate esters, such as nitroglycerin, are known for their explosive properties, while polyesters are important plastics, with monomers linked by ester moieties. Esters are widespread in nature and are widely used in industry. Esters are responsible for the aroma of many fruits, including apples, pears, bananas, pineapples, and strawberries. Several billion kilograms of polyesters are produced industrially annually, important products being polyethylene terephthalate, acrylate esters and cellulose acetate.

Based on Ester functional group, synthesis of novel Alkyl 2-(3,5-Dimethyl-1,1-Dioxido-2H-1,2,6-Thiadiazin-4-yl) Benzoate by condensation of Sulfamide with 2-(2,4-dioxopentan-3-yl) benzoic acid in presence of dry HCl in different alcohols have been reported. In IR spectral data the characteristic bands of C-H aromatic stretching frequencies were observed between 3100-3000 cm\(^{-1}\), the stretching frequency of carbonyl (\(>\text{C}=\text{O}\)) of ester were at 1760-1670 cm\(^{-1}\). Vibrational frequency of N-H of Thiadiazine ring shows band around 3100-3500 cm\(^{-1}\). At 1153-1157 cm\(^{-1}\), 1317-1325 cm\(^{-1}\) >SO\(_2\) symetric and asymetric stretching frequency and at 1500-1550
cm⁻¹ >C=N vibrational frequency of thiadiazine ring has been observed. In 1H NMR the protons of the alkyl function of ester group shows their characteristic peaks between 1-3 δ ppm along with -O-R peak between 3-4 δ ppm with appropriate multiplicity. The two methyl groups attached ti thiadiazine ring shows their respective positions near 1.8-1.9 δ ppm.In the aromativ region of 7.0-8.0 δ ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.

The newly synthesized compounds Alkyl 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzoate, compound NB-4 and NB-6 were found to be active as antibacterial. In the study of antifungal activity compounds NB-6 and NB-7 were active against Aspergillus niger.

Single crystal XRD data of compound NB-2 Ethyl 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzoate have been also reported.

CHAPTER-3

Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins. Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs. For example, Atorvastatin the top selling drug worldwide since 2003, blocks the production of cholesterol and contains an amide bond as do Lisinopril (inhibitor of angiotensinconverting enzyme), Valsartan (blockade of angiotensin-II receptors), and Diltiazem (calcium channel blocker used in the treatment of angina and hypertension). Amide bonds are typically synthesised from the union of carboxylic acids and amines; however, the unification of these two functional groups does not occur spontaneously at ambient temperature, with the necessary elimination of water only taking place at high temperatures.

With keeping in mind the advantages of amide group here we synthesised various N-alkyl-2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzamide using Carbonyldiimidazole as a coupling agent and aliphatic and aromatic amines in THF. In IR spectrum the characteristic bands of C-H aromatic stretching frequencies were observed between 3100-3000 cm⁻¹, the stretching frequency of carbonyl (>C=O) of amide were at 1760-1670 cm⁻¹,-NH-stretching of –CONH-group lies between 3400-3500 cm⁻¹. Vibrational frequency
of N-H of Thiadiazine ring shows band around 3100-3500 cm\(^{-1}\). At 1130-1160, 1317-1325 cm\(^{-1}\) \(\text{>SO}_2\) symmetric and asymmetric stretching frequency and at 1500-1550 cm\(^{-1}\) \(\text{>C=N}\) vibrational frequency of thiadiazine ring has been observed. In 1H NMR study the protons of the alkyl function of amide group shows their characteristic peaks between 1-3 δ ppm along with -NH-R peak between 3-4 δ ppm with appropriate multiplicity. The two methyl groups attached to thiadiazine ring shows their respective positions near 1.8-1.9 δ ppm. In the aromatic region of 7.0-8.0 δ ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.

The newly synthesized compounds Alkyl 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzamide, compound NB-11 and NB-17 were found to be active as antibacterial. In the study of antifungal activity compound NB-20 was active against Aspergillus niger.

Single crystal XRD data of compound 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzoic acid have been also reported. Crystals of butyl 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzamide is under XRD Evaluation.

CHAPTER 4

A salt is the product generated upon the neutralisation of an acid or base. Pharmaceutical salts are important in the process of drug development, as converting an acidic or basic drug into a salt via a simple neutralisation reaction has the ability to change the physicochemical properties of a drug. Using different chemical species to neutralise the parent drug can produce a diverse series of compounds, and this process is traditionally used to improve drug solubility and drug dissolution rates. The type of salt is usually categorised by the bond between the neutralisation agent and the parent drug. Salts can be broadly classified into two groups, covalent and ionic. So in continuation of our work we synthesised various quaternary salts of 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoic acid using organic bases and inorganic alkali bases in Ethylacetate solvent. The characteristic bands of C-H aromatic stretching frequencies were observed between 3100-3000 cm\(^{-1}\). The stretching frequency of carbonyl (\(\text{>C=O}\)) of acid were at 1760-1670 cm\(^{-1}\). Vibrational frequency of N-H of Thiadiazine ring shows band around 3100-3500 cm\(^{-1}\). At 1153-1157, 1317-1325 cm\(^{-1}\) \(\text{>SO}_2\) symmetric and asymmetric stretching frequency and at 1500-1550 cm\(^{-1}\) \(\text{>C=N}\) vibrational frequency of thiadiazine ring has been observed. Also the
characteristic peak of quarternary salt around 2900 cm\(^{-1}\) has been observed. In \(^1\)H study the protons of the alkyl function of quarternary amide group shows their characteristic peaks between 1-3 \(\delta\) ppm with appropriate multiplicity. The two methyl groups attached to thiadiazine ring shows their respective positions near 1.8-1.9 \(\delta\) ppm. In the aromatic region of 7.0-8.0 \(\delta\) ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.

The newly synthesized compounds quarternary salts of 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoic acid, compound NB-21,NB-22,NB-23,NB-26,NB-27 were found to be active as antibacterial. In the study of antifungal activity compound NB-21, NB-23 was active against *Aspergillus niger*.

Crystals of Potassium salt, Sodium salt, Dicyclohexylamine salt, t-butylamine salt of 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzoic acid is under XRD Evaluation.

**CHAPTER-5**

In this chapter with keeping in mind the biological advantages of N-alkylated esters of thiadiazine ring from previous reference work we have reported the synthesis of novel Alkyl 2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoate by N-alkylation of 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoic acid using Methyl iodide in presence of K\(_2\)CO\(_3\) base which was further converted to different esters in presence of Thionyl chloride and alcohols. In IR spectrum the characteristic bands of C-H aromatic stretching frequencies were observed between 3100-3000 cm\(^{-1}\). The stretching frequency of carbonyl (\(>\text{C}=\text{O}\)) of ester were at 1760-1670 cm\(^{-1}\). Vibrational frequency of N-H of Thiadiazine ring shows band around 3100-3500 cm\(^{-1}\). At 1153-1157, 1317-1325 cm\(^{-1}\) \(>\text{SO}_2\) symetric and asymmetric stretching frequency and at 1500-1550 cm\(^{-1}\) \(>\text{C}=\text{N}\) vibrational frequency of thiadiazine ring has been observed. In 1H NMR study the protons of the alkyl function of ester group shows their characteristic peaks between 1-3 \(\delta\) ppm along with -O-R peak between 3-4 \(\delta\) ppm with appropriate multiplicity. The characteristic signal of methyl group attached with Nitrogen of thiadiazine ring shows their respective peak at 3.6-3.8 \(\delta\) ppm. The two methyl groups attached to thiadiazine ring shows their respective positions near 1.8-1.9 \(\delta\) ppm. In the aromatic region of 7.0-8.0 \(\delta\) ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.
The newly synthesized compounds Alkyl 2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoate, compound NB-32,NB-34,NB-36 were found to be active as antibacterial. In the study of antifungal activity compound NB-31 was active against Aspergillus niger.

Single crystal XRD data of Methyl 2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoate have been reported.

CHAPTER-6

Here we have reported the synthesis of N-Alkyl-2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl)benzamide using Carbonyldiimidazole as a coupling agent and aliphatic and aromatic amines in THF. In IR spectrum the characteristic bands of C-H aromatic stretching frequencies were observed between 3100-3000 cm\(^{-1}\). The stretching frequency of carbonyl (\(>C=O\)) of amide were at 1760-1670 cm\(^{-1}\). NH-stretching of \(-CONH\)-group lies between 3400-3500. At 1130-1160 cm\(^{-1}\), 1317-1325 cm\(^{-1}\) \(>SO_2\) symetric and asymmetric stretching frequency and at 1500-1550 cm\(^{-1}\) \(>C=N\) vibrational frequency of thiadiazine ring has been observed. In 1H NMR study the protons of the alkyl function of amide group shows their characteristic peaks between 1-3 \(\delta\) ppm along with -NH-R peak between 3-4 \(\delta\) ppm with appropriate multiplicity. The characteristic signal of Methyl group attached with Nitrogen of thiadiazine ring shows their respective peak at 3.6-3.8 \(\delta\) ppm. The two methyl groups attached ti thiadiazine ring shows their respective positions near 1.8-1.9 \(\delta\) ppm. In the aromativ region of 7.0-8.0 \(\delta\) ppm the four distinct peaks due to four aromatic protons of phenyl ring attached to Thiadiazine ring can be seen in the NMR.

The newly synthesized compounds Alkyl 2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoate, compound NB-41,NB-44 were found to be active against bacteria whereas all synthesised compounds were resistant against Aspergillus niger.

CHAPTER-7

Single crystal X-ray diffraction analysis of newly synthesised 1,2,6-thiadiazine 1,1-dioxide like 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoic acid, Ethyl2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoate, 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoic acid t-butyl amine salt, Methyl 2-(3,5-dimethyl-1,1-dioxido-2H-1,2,6-
thiadiazin-4-yl) benzoate, Methyl 2-(2,3,5-trimethyl-1,1-dioxido-2H-1,2,6-thiadiazin-4-yl) benzoate have been reported.