1.1. INTRODUCTION

Phosphorus (P) is a very widely distributed 12th most abundant element in the Earth’s crust. Phosphorus is an essential part of life and is found in our bones and teeth (hydroxyapatite). It is a necessary nutrient in our diet as ferric phosphate, and tricalcium phosphate. Phosphorus is present in plants and animals. There is over 454 grams of phosphorus in the human body. The first recorded isolation of phosphorus was by a German physician and alchemist Hennig Brand in 1669. Phosphorus is primarily obtained from phosphate rock.

Organophosphorus compounds have expanded so rapidly that they constitute now a major branch of chemistry, organic molecules containing phosphorous offer attractive possibilities for structural, synthetic and mechanistic study. A wide range of natural phosphorus based biologically active compounds which play an important roles as metabolic intermediates as common regulatory switches for proteins and as a backbone for the genetic information. The genetic information is coded in the sequence of nucleotides in a DNA molecule. Nucleotides and related compounds are also important “energy carrying” compounds. Among the ones commonly encountered are adenosine triphosphate (ATP) (I), and nicotinamide adenine dinucleotide dehydrogenase (NADH) (II).

Organophosphorus compounds have been made and used in very large quantities in agriculture, not only as insecticides but also later as herbicides and in other applications. The active compounds are normally esters, amides, or thiol derivatives of phosphoric or phosphonic acid.
1.2.APPLICATIONS OF ORGANOPHOSPHONATES

Organophosphonate molecules are an important class of active compounds and their synthesis and uses have received an increasing amount of attention. \(^5\) It has extensive applications in agriculture as insecticides (parathion (IV), malathion (V)), herbicides (glyphosate (VI)), and plant growth regulators. \(^6\) They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as eceothiopate used in the treatment of glaucoma. \(^7\) These compounds are very useful synthons for synthesizing organic compounds in the well-known reactions (Wittig, Mitsunobu, Staudinger, Organocatalysis etc.). \(^8\) The use of organophosphorus compounds as achiral or chiral ligands for transition metal catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production. \(^9\) Furthermore, organophosphorus compounds are frequently used as flame retardants for fabrics and plasticizing and stabilizing agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products, corrosion inhibitors, antifoaming agents and hydraulic fluids.

In medicine, a source of C-P compounds of natural origin was first recognized in 1969\(^{10}\) from the products in a fermentation broth of the bacterium, *Streptomyces fradiae*, a new phosphoric acid was isolated that had the properties of an antibiotic. Some organophosphorus compounds are act as active drugs for antibiotics (fosfomycin (VII)), anticancer (cyclophosphamide (VIII)) and anti HIV (foscarnet (IX)).
1.3. α-AMINOPHOSPHONATE DERIVATIVES

α-aminophosphonates have received enormous attention because they are considered to be structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis.\textsuperscript{11} Due to their structural analogy to α-amino acids, they function as inhibitors of enzymes involved in the metabolism of proteins and amino acids. For example, the phosphonic analogue of phenylalanine is an inhibitor of phenylalanyl-5-RNA-synthetase\textsuperscript{12} and phosphonodipeptide alafosfalin is an antimicrobial agent.\textsuperscript{13} The presence of stable and covalent carbon-phosphorus (C-P) bond exhibits several biological activities like antibacterial\textsuperscript{14}, antifungal\textsuperscript{15}, antiviral\textsuperscript{16}, herbicides,\textsuperscript{17} antitumor agents.\textsuperscript{18}

A K Bhattacharya \textit{et al.}\textsuperscript{19} developed an efficient and environmental benign method for the synthesis of α-aminophosphonates (XIII) by one pot reaction of aldehydes (X) with amines (XI) and diethyl phosphate (XII) in the presence of bismuth nitrate pentahydrate as a catalyst under microwave irradiation condition in good yields.

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\begin{align*}
\text{RCHO} + R'\text{NH}_2 + \text{HOP(OEt)}_2 & \xrightarrow{\text{BiNO}_3\cdot5\text{H}_2\text{O}, \text{r.t. or MWI}} \text{R}U\text{HNR}_1\text{PO(OEt)}_2 \\
\text{(X)} & \quad \text{(XI)} & \quad \text{(XII)} & \quad \text{(XIII)}
\end{align*}
\]

P Thirumurugan \textit{et al.}\textsuperscript{20} synthesized α-aminophosphonates (XVII) by the reaction of aromatic aldehydes (XIV), aromatic (or) aliphatic amines (XV), diethyl phosphite (XVI) using potassium hydrogen sulfate as a catalyst under neat conditions.

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\begin{align*}
\text{FeCHO} + \text{NH}_2 + \text{HPO(OEt)}_2 & \xrightarrow{\text{KHSO}_4 (10-40 \text{ mol }\%)} \text{FeNHPO(OEt)}_2 \\
\text{(XIV)} & \quad \text{(XV)} & \quad \text{(XVI)} & \quad \text{(XVII)}
\end{align*}
\]

B Kaboudin \textit{et al.}\textsuperscript{21} reported a simple method for synthesis of 1-aminoalkyl phosphonates (XXI) through a one-pot reaction of aldehydes (XVIII) with amines (XIX) and diethyl phosphate (XX) in the presence of acidic alumina under solvent-free conditions using microwave irradiation.
1.4. ABOUT HETEROCYCLICS

Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. A variety of atoms can be incorporated such as B, Se, P, Si into ring structures. Heterocyclic compounds play a vital role in biological processes and are widespread as natural products. Among the heterocycles, nitrogen heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. Indole is an important heterocyclic basic moiety in several drugs because it is built into proteins in the form of amino acid ‘tryptophan’ found in many natural products like alkaloids such as strychnine and lysergic acid diethylamide. Indole nucleus is the accepted pharmacophore in medicinal compounds has versatile biological activities.

Zheng et al. synthesized a series of indole derivatives and evaluated for their inhibitory activities against 5-LOX in rat peritoneal leukocytes by cell-based assays. All the compounds exhibited the most potent inhibitory activity compared to that of the reference drug, zileuton.

The piperazine moiety is a common pharmacophore found in many compounds of biological interest. For example, a piperazine core is found in indinavir, a potent HIV protease inhibitor that has been approved for use in man, clozapine is an
antipsychotic agent that blocks dopamine and 5HT$_2$A receptors. Quipazine and GR89696 are a 5HT$_3$ antagonist, and a potent selective $\kappa$-opioid receptor agonist respectively. These are only a few of the many examples in which the piperazine core has been used as a scaffold to generate biologically active molecules. Thus, it appears that the piperazine core acts as a privileged motif, because derivatives lead to biologically active compounds against enzyme and receptor targets.

1.5. SULFONYL DERIVATIVES

There is demand for novel chemotherapeutic antibacterial remains attractive in the field of medicinal chemistry. The discovery of sulfonamides as antibacterial in the early 1930s was the beginning of the most fascinating era of chemotherapeutic agents. Since the introduction of prontosil over 70 years ago, sulfa drugs have been widely used to treat a broad spectrum of microbial diseases. Sulfa drugs were introduced as protease inhibitors; therefore, they can be used as anticancer, anti-inflammatory and antiviral agents. Some of the sulfonamide derivatives with photodynamic activities were used against nasopharyngeal carcinoma cells and their antitumor and anti-angiogenesis activities in a dose dependent manner. They are commonly used in human and veterinary medicine for therapeutic and prophylactic purposes to fight common bacterial diseases. However, sulfonamides have more adverse reactions including nephrotoxicity, and so chemical modification of sulfonamides is necessary.

On other hand piperazine sulfonamide derivatives are known to exhibit wide range of pharmacological activities like antimicrobial, antiproliferative, anti-HIV, antifungal, antiprotozoal, anticonvulsant, anti-diabetic and sigma receptor ligands.

P W Finn et al. reported a series of novel sulfonamide derivatives (XXXII) synthesized from benzaldehyde (XXVI). All the synthesized compounds were evaluated for their ability to inhibit human histone deacetylase (HDAC).
Xiang Lu et al.\textsuperscript{47} reported a series of pyridine acyl sulfonamide derivatives (XXXIV) from coupling pyridine carboxylic acid (XXXIII), substituted benzenesulfonamides, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI.HCl) and 4-dimethylaminopyridine (DMAP) were dissolved in DCM at reflux temperature and were evaluated as potential cyclooxygenase-2 (COX-2) inhibitors.

A novel sulfonamide derivatives (XXXVII) were discovered\textsuperscript{48} as potent and selective inhibitors against human and mouse 11β-hydroxysteroid dehydrogenase type-1 by the reaction of (S) or (R)-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (XXXV) with cyclohexanamine to form tert-butyl 3-(cyclohexylcarbamoyl)piperidine-1-carboxylate (XXXVI) followed by treating with various benzene sulfonyl chlorides.
K Mahalakshmi Naidu et al. synthesized a series of twenty-four novel 3-(4-(substituted sulfonyl)piperazin-1-yl)benzo[d]isoxazole analogues (XLIII) and evaluated for their in vitro anti-tubercular activity against mycobacterium tuberculosis (MTB) H$_{37}$Rv strain.

Urea and thiourea derivatives are important oxygen, sulphur, and nitrogen containing compounds and they are useful substances in drug discovery. These are important building blocks in the synthesis of heterocycles.

1.6. UREA AND THIOUREA DERIVATIVES

Urea is a chief nitrogen-containing end product of protein metabolism and was first discovered in urine by Hilaire Rouelle in 1773. Urea and thiourea are important oxygen, sulphur, and nitrogen containing compounds and they are useful substances in drug discovery. These are important building blocks in the synthesis of heterocycles. Urea is a functional moiety that is commonly found in natural products and often displays a wide range of biological activities. Urea and thiourea compounds are known to possess antidiabetic and antimicrobial activities. It has been studied for the systematic control of tuberculosis also. A series of diaryl substituted heterocyclic urea which has been reported to inhibit cholesterol O-acyl transferase (ACAT) as hypocholesterolemic. N,N-disubstituted cyclic urea-3-benzamide was found to be HIV protease inhibitor in the treatment of AIDS. Some of the urea compounds are multistage glycation inhibitors with the highest post-Amadori activities. Some of these
inhibited AGE-proteins cross-linking including AGE-collagen cross-linking from the reaction of bovine serum albumin with glucose.\textsuperscript{57} Moreover, ureas and thioureas evaluate their plant growth-regulating activity mainly on the herbicidal, root growth inhibitory and stimulatory and cytokinin-like activities.\textsuperscript{58}

C.S. Shantharam \textit{et al}.\textsuperscript{59} reported a new series of urea/thiourea derivatives of Gly/Pro conjugated benzisoxazole (XLVIII) and screened for their \textit{in vitro} antiglycation activity.

M Liang Xiao \textit{et al}.\textsuperscript{60} synthesized a series of cinnamoyl thiourea derivatives (LI) from cinnamoyl isothiocyanate (XLIX) with substituted aniline (L) by using ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate BMIMBF\textsubscript{4} with significant enhancements in reactivity, reaction rate and yield.

A series of novel thiourea and urea derivatives were reported\textsuperscript{61} containing 1,2,4-triazole moieties (L\textsubscript{V} and L\textsubscript{VI}) from starting 2-(4-aminophenyl)acetic acid (L\textsubscript{II}) and evaluated for their antifungal and larvicidal activity.
Hassan M. Faidallah et al.\textsuperscript{62} reported some novel urea and thiourea derivatives of isoxazolo[4,5-d]pyridazine (LIX) from ethyl 5-acetyl-3-methyl-2,3-dihydroisoxazole-4-carboxylate (LVII) and structurally related thiazolo[4,5-d]pyridazine as antimicrobial agents.

In view of all the above versatile biological and pharmacological applications of organophosphonates, sulfonyl, urea and thiourea derivatives, we are encouraged to design, synthesize and structural characterization of new organophosphonates, sulfonyl, urea and thiourea compounds as well as for their antibacterial, antifungal and antioxidant activities evaluation.
REFERENCES


OBJECTIVES

- To synthesis some novel heterocyclic compounds.
- Synthesis of \( \alpha \)-aminophosphonate derivatives by using microwave irradiation method and evaluate their bioactivity.
- To study piperazine incorporated zafrulkast drug intermediate derivatives.
- To synthesize urea and thiourea derivatives of 2-aminodiphosphyl sulfide.
- Synthesis of \( N,N \)-dicyclohexyl-2-(piperazin-1-yl)acetamide derivatives.
- Structural characterization of the synthesized compounds by mass, LCMS, HRMS, \(^1\)H NMR, \(^{13}\)C NMR and IR spectral data.
- Evaluation of biological assay for all the synthesized compounds.