SUMMARY

The thesis entitled "Synthesis, Spectral Characterisation and Biological Activity of Organophosphorus Heterocyclic Compounds" describes the synthesis, spectral analysis and antimicrobial studies of novel phosphorus heterocycles with five, six and eight-membered rings possessing oxygen and nitrogen as hetero atoms and bio-active aryloxy, O-2-chloroethyl, alkylcarbamate, thiocarbamate, urea, 2-chloroethyl, allyl, benzyl, amino acid esters and bis-(2-chloroethyl) amine moieties as substituents.

CHAPTER I

A review of literature is made to have a comprehensive picture on the present status of the chemistry of organophosphorus compounds. The mechanism of action of phosphorus toxins and anticholinesterase agents is also discussed.

CHAPTER II

Objectives of our present study on phosphorus heterocycles are given.

CHAPTER III

The experimental techniques utilised for the synthesis of organophosphorus compounds and information about spectral instruments (IR, $^1$H, $^{13}$C and $^{31}$P NMR and Mass spectra) is furnished. Procurement of solvents and synthesis of some starting materials and reagents is described.
CHAPTER IV

Synthesis, spectral characterization and biological activity of some new five membered heterocyclic compounds, 2-substituted-2,3-dihydro-5-benzoyl-1H-1,3,2-benzodiazaphosphole 2-oxides/sulfides (16a-k) is reported. They are prepared by reactions of equimolar quantities of 3,4-diaminobenzophenone (1) with various aryl phosphorodichloridates (2a-g), O-2-chloroethylphosphoryl dichloride (3), and aryl phosphorothioic dichlorides (4a-c) in dry toluene-tetrahydrofuran mixture (3:1) in the presence of triethylamine at 50-60°C. Their structures are confirmed by IR, $^1$H, $^{13}$C and $^{31}$P and mass spectral studies. Most of the compounds possess significant activity against both bacteria and fungi.

\[
\text{Compd} \quad \text{R} \quad \text{Compd} \quad \text{R}
\]
\[
16a \quad \text{OC}_6\text{H}_5 \quad 16i \quad \text{OC}_6\text{H}_5
\]
\[
16b \quad \text{OC}_6\text{H}_4-\text{CH}_3(2''') \quad 16j \quad \text{OC}_6\text{H}_4-\text{CH}_3(4''')
\]
\[
16c \quad \text{OC}_6\text{H}_4-\text{CH}_3(4'') \quad 16k \quad \text{OC}_6\text{H}_4-\text{Cl}(4'')
\]
\[
16d \quad \text{OC}_6\text{H}_4-(\text{CH}_3)_2(2'',3'') \quad 16f \quad \text{OC}_6\text{H}_4-\text{Cl}(2'')
\]
\[
16e \quad \text{OC}_6\text{H}_4-(\text{CH}_3)_2(2'',6'') \quad 16g \quad \text{OC}_6\text{H}_4-\text{Cl}(4'')
\]
\[
16h \quad \text{OCH}_2\text{CH}_2\text{Cl}
\]

CHAPTER V

Section A

Synthesis, spectral analysis and antimicrobial activity of 2-alkylcarbamato/alkenylcarbamato/thiocarbamato-2,3-dihydro-5-benzoyl-1H-1,3,2-benzodiazaphosphole 2-oxides (18a-j) is described. Their preparation is accomplished by the addition reaction of dichloroisocyanato phosphine oxide
(6) with alcohols / thiol at -10°C under inert atmosphere and anhydrous conditions in dry toluene-tetrahydrofuran mixture (1:1) to afford the corresponding dichlorophosphinyl carbamates/thiocarbamates (17), which is subsequently condensed in situ with 3, 4-diaminobenzophenone (1) in the presence of triethylamine at 45-50°C. Only one product 2-amino-2,3-dihydro-5-benzoyl-1H-1,3,2-benzodiazaphosphole 2-oxide (19) is obtained on pyrolysis of 18a-j. The IR, 1H, 13C and 31P NMR and mass spectral data are discussed.

\[
\begin{align*}
\text{Compd.} & \quad \text{XR} & \quad \text{Compd.} & \quad \text{XR} \\
18a & \quad \text{OCH}_3 & 18f & \quad \text{OCH}_2\text{CH}=\text{CH}_2 \\
18b & \quad \text{OCH}_2\text{CH}_3 & 18g & \quad \text{OC}_2\text{H}_11 \\
18c & \quad \text{OCH}_2\text{CH}_2\text{Cl} & 18h & \quad \text{OCH}_2\text{C}_6\text{H}_5 \\
18d & \quad \text{OCH}(\text{CH}_3)_2 & 18i & \quad \text{OCH}_2\text{CH}_2\text{C}_6\text{H}_5 \\
18e & \quad \text{OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2 & 18j & \quad \text{SCH}_2\text{CH}_2\text{CH}_3 \\
\end{align*}
\]

Section B

Synthesis of \(N\)-substituted-\(N'\)-(2,3-dihydro-2-oxido-5-benzoyl-1H-1,3,2-benzodiazaphosphole 2-yl) ureas (21a-i) were accomplished through a two step process. The synthetic route involves the reaction of equimolar quantities of the reactants. The amines added to the dichloro isocyanatophosphine oxide (6) at -15°C to -5°C under inert anhydrous condition in dry toluene with the formation of carbamidophosphoric acid dichlorides (20a-i).
Cyclisation of 20a-i with 3,4-diaminobenzophenone (1) in the presence of triethylamine in dry toluene-tetrahydrofuran (1:1) mixture at 40-45°C afforded 21a-i. IR, NMR (1H, 13C and 31P) and mass spectral data were discussed for them in detail.

The compounds 18a-c, 18h-j and 21a-i were screened for their antibacterial activity against Staphylococcus aureus and Escherichia coli. Vancomycin and Gentamycin were used as standard antibiotics. Antifungal activity was evaluated against Fusarium solani and Aspergillus niger. Nystatin is used as a standard. The title compounds are active against tested fungi and bacteria.

![Diagram of cyclization reaction](image)

<table>
<thead>
<tr>
<th>Compd.</th>
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<th>Compd.</th>
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</tr>
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<tbody>
<tr>
<td>21a</td>
<td></td>
<td>21f</td>
<td>HN-CH2-</td>
</tr>
<tr>
<td>21b</td>
<td>Cl</td>
<td>21g</td>
<td>HN-</td>
</tr>
<tr>
<td>21c</td>
<td>Br</td>
<td>21h</td>
<td>HN-</td>
</tr>
<tr>
<td>21d</td>
<td>CH3</td>
<td>21i</td>
<td></td>
</tr>
<tr>
<td>21e</td>
<td></td>
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</table>

CHAPTER VI

Section A

Synthesis of N-(substituted)-N'(5-bromo-5-nitro-2-oxide-1,3,2-dioxaphosphorinane 2-yl) ureas (22a-h) were synthesized by the condensation of
equimolar quantities of carbamidophosphoric acid dichlorides (20a-h) with 2-bromo-2-nitro-1,3-propane diol (5) in the presence of triethylamine in dry toluene-tetrahydrofuran mixture (1:1) at room temperature. Their structures were confirmed by IR, $^1$H, $^{13}$C and $^{31}$P NMR and mass spectral studies.

$$
\text{(20a-h)} + \begin{array}{c}
\text{Br} \\
\text{O}_2\text{N} \\
\text{OH} \\
\text{OH}
\end{array} \xrightarrow{\text{Toluene-THF, Et3N, RT}} \begin{array}{c}
\text{Br} \\
\text{O} \\
\text{OH} \\
\text{O} \\
\text{NH} \\
\text{C} \\
\text{NH} \\
\text{N} \\
\text{R}
\end{array}
$$

<table>
<thead>
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<th>Compd.</th>
<th>R</th>
<th>Compd.</th>
<th>R</th>
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</thead>
<tbody>
<tr>
<td>22a</td>
<td>C$_6$H$_5$</td>
<td>22e</td>
<td>C$_6$H$_3$-(CH$_3$)$_2$(2',4')</td>
</tr>
<tr>
<td>22b</td>
<td>C$_6$H$_4$-Cl(4')</td>
<td>22f</td>
<td>C$<em>6$H$</em>{11}$</td>
</tr>
<tr>
<td>22c</td>
<td>C$_6$H$_4$-Br(4')</td>
<td>22g</td>
<td>CH$_2$-C$_6$H$_4$-(Cl)(2')</td>
</tr>
<tr>
<td>22d</td>
<td>C$_6$H$_4$-CH$_3$(4')</td>
<td>22h</td>
<td>C$_{10}$H$_8$(1')</td>
</tr>
</tbody>
</table>

Section B

$N$-(Substituted)-$N'$-[6-methyl-2-oxido-4H-1,3,2-dioxaphosphorino (5,4-b) pyridine 2-yl] ureas (23a-j) were synthesized by the reaction between 3-hydroxy-6-methyl-2-pyridine methanol (lutidine diol) (7) and the substituted carbamidophosphoric acid dichlorides (20a-j) in dry toluene-tetrahydrofuran mixture (1:1) in the presence of triethylamine at 45-50°C. The structures of products were confirmed by IR, $^1$H, $^{13}$C and $^{31}$P NMR data as well as mass spectral analysis.

The title compounds 22a-h and 23a-j exhibited moderate antimicrobial activities against the growth of bacteria *Staphylococcus aureus*, *Escherichia coli* and fungi *Aspergillus niger* and *Helminthosporium oryzae*. 
Several new class of phosphorus heterocyclic compounds containing exocyclic P-C link such as 6-(2'-chloroethyl)/(allyl)/(benzyl)-1,2,4,8,10,11-hexachloro-12H-dibenzo[d,g][1,3,2]dioxaphosphorin 6-oxides (24a-e), 2-(2''-chloroethyl)/(allyl)-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2H-1,3,2-benzoxazaphosphorin 2-oxides (25a, 25b), 2-(2''-chloroethyl)-2,3-dihydro-3-(4'-bromophenyl)-1H-naphth[1,2-e][1,3,2]oxazaphosphorin 2-oxide (26), 2-(2''-chloroethyl)/(allyl)-2,3-dihydro-5-benzoyl-1H-1,3,2-benzodiazaphosphole 2-oxides (27a, 27b), 4-phenyl-2-(2''-chloroethyl)-1H-1,3,3a,5,6-pentaza-2-phosphapentalene 2-oxide (28) and 4-benzyl-2-(2''-chloroethyl)-1H-1,3,3a,5,6-pentaza-2-phosphapentalene 2-oxide (29) were synthesized by reacting equimolar quantities of corresponding hexachlorophene (9), 2-cyclohexylaminomethyl-4-tert-butylphenol (11), 1-(4'-bromoanilinomethyl)-2-naphthol (10), 3,4-diaminobenzophenone (1), 5-phenyl-1,2-diamino-1,3,4-triazole (12) and 3-benzyl-4,5-diamino-1,2,4-triazole (13) with respective phosphonyldichlorides (8a-e) in dry toluene/toluene-tetrahydrofuran.
mixture (1:1)/pyridine in the presence of triethylamine at various temperatures. Their structures have been established by IR, NMR (\(^1\)H, \(^{13}\)C and \(^{31}\)P) and mass spectral data. The compounds have been screened for their expected antibacterial and antifungal activities.

\[
\begin{align*}
\text{Compd.} & \quad R \\
\text{24a.} & \quad \text{CH}_2\text{-CH}_2\text{-Cl} \\
\text{24b.} & \quad \text{CH}_2\text{-CH=CH}_2 \\
\text{24c.} & \quad \text{CH}_2\text{-C}_6\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{Compd.} & \quad R \\
\text{25a.} & \quad \text{CH}_2\text{-CH}_2\text{-Cl} \\
\text{25b.} & \quad \text{CH}_2\text{-CH=CH}_2
\end{align*}
\]
\[ \text{(10)} \quad \text{Toluene, Et}_3\text{N, 50-55°C} \quad \rightarrow \quad \text{(26)} \]

\[ \text{(1)} \quad \text{8a-b, Toluene-THF, Et}_3\text{N, 50-55°C} \quad \rightarrow \quad \text{(27a-b)} \]

Compd. R

27a. CH\(_2\)-CH\(_2\)-Cl

27b. CH\(_2\)-CH=CH\(_2\)

\[ \text{(12)} \quad \text{(8a), Pyridine, Et}_3\text{N, 55-60°C} \quad \rightarrow \quad \text{(28)} \]

\[ \text{(13)} \quad \text{(8a), Pyridine, Et}_3\text{N, 55-60°C} \quad \rightarrow \quad \text{(29)} \]
Synthesis of 2-(amino acid ester)-6-(1,1-dimethylethyl)-3-cyclohexyl-3, 4-dihydro-2H-1,3,2-benzoxazaphosphorin 2-sulfides/oxides (31a-j) were accomplished through a two step process. This involved the prior preparation of the monochloride as 2-chloro-6-(1,1-dimethylethyl)-3-cyclohexyl-3,4-dihydro-2H-1,3,2-benzoxazaphosphorin 2-sulfide (30) and its subsequent reaction with the glycine methyl ester hydrochloride (14a), L-alanine methyl ester hydrochloride (14b), L-leucine methyl ester hydrochloride (14c), L-isoleucine methyl ester hydrochloride (14d), anthranilic acid methyl ester hydrochloride (14e), and glycine ethyl ester hydrochloride (14f) in dry tetrahydrofuran in the presence of triethylamine at various temperatures. The IR, $^1$H, $^{13}$C and $^{31}$P NMR and mass spectral data are discussed.
Section B

2-[[Amino acid ester]bis-(2-chloroethylamino)-6-methyl-4H-1,3,2-dioxaphosphorino (5,4-b) pyridine 2-sulfides (33a-e) have been synthesized through a two step process. This involved the prior preparation of the monochloride as 2-chloro-6-methyl-4H-1,3,2-dioxaphosphorino(5,4-b)pyridine 2-sulfide (32) and its subsequent reaction with the glycine methyl ester hydrochloride (14a), L-alanine methyl ester hydrochloride (14b), anthranilic acid methyl ester hydrochloride (14e), glycine ethyl ester hydrochloride (14f) and bis-(2-chloroethyl)amine hydrochloride in dry tetrahydrofuran in the presence of triethylamine at various temperatures. The compounds were characterized by physical and spectral parameters like IR, $^1$H, $^{13}$C and $^{31}$P NMR and mass spectroscopy.
LIST OF PUBLICATIONS