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Synthesis characterization and antimicrobial activity of 6-nitro-*1H*-benzo[d] oxazol /thiazol-2-yl)methyl)-6-oxido-4,8-dihydro-*1H*-[1,3,2]dioxaphosphepino [5,6-c]pyrazole-6-yl)ureas/carboxamides

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ABSTRACT

*New novel derivatives of 1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxy phenyl /4-chlorophenyl) ureas (**8a-d as per scheme: I**) were Synthesized by condensation reaction of 1-((5-nitro benzo [d] oxazol-2-yl)methyl) -1H-pyraazole-4,5-diyl) dimethanol **(6)** and (phenyl carbamoyl) phosphoric acid dichlorides **7(a-d)**. The synthon **(6)** was obtained by deprotection of isopropilidine group of 6, 6-dimethyl-1-((5-nitrobenzo[d]oxazol-2-yl) methyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole **(5)**. The synthon **(5)** was obtained by condensation reaction between 2-(6, 6-dimethyl-4, 8-dihydro -1H-[1, 3] dioxepino [5, 6-c] pyrazole-1-yl) acetic acid **(3)** and 2-amino-nitrophenol. Similar procedures were adopted to prepare* N-(1-((5-nitrobenzo [d] oxazol -2-yl) methyl)-6-oxido-4, 8-dihydro-1H-[1, 3, 2] dioxaphospheno [5,6-c] pyrazol-6-yl) morpholine/piper dine/4-methyl piperazine carboxamides (***8e-g as per scheme: II***). *The synthesis of 1-(1-(benzo [d] thiazole-2-yl) methyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxyphenyl/4-chloro phenyl) ureas(**12a-d as depicted in scheme:III**) and N-(1-(benzo [d]thiazol-2-ylmethyl)-6-oxido-4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5.6-c] pyrazol-6-yl) morpholine / piperidine /4-methyl piperazinecarboxamides (**12e-g as depicted in scheme:IV**) were also carried out by the usage of similar synthetic procedures.*

Key words: (phenyl carbamoyl) phosphoric acid dichlorides, Pyrazole, Cyclizaton, Deprotection, Antibacterial and Antifungal activity.

INTRODUCTION

The chemistry of phosphorus heterocyclic compounds containing nitrogen plays an important role in the development of new pharmaceutical materials with novel properties [1, 2].The chemistry of organophosphorus compounds and their derivatives were found to be the highlight of study in lead compound discovery, biological screening and study of their various biological activities including its application in the field of Agriculture, Medicine and Industry [3, 4]. Organophosphorus compounds occupied a unique position in biological activities such as anti-bacterial [5], herbicides, insecticides, pesticides [6, 7], anti-fungal agents [8], anti-cancer [9], anti-HIV [10], anti-viral and anti-inflammatory [11].

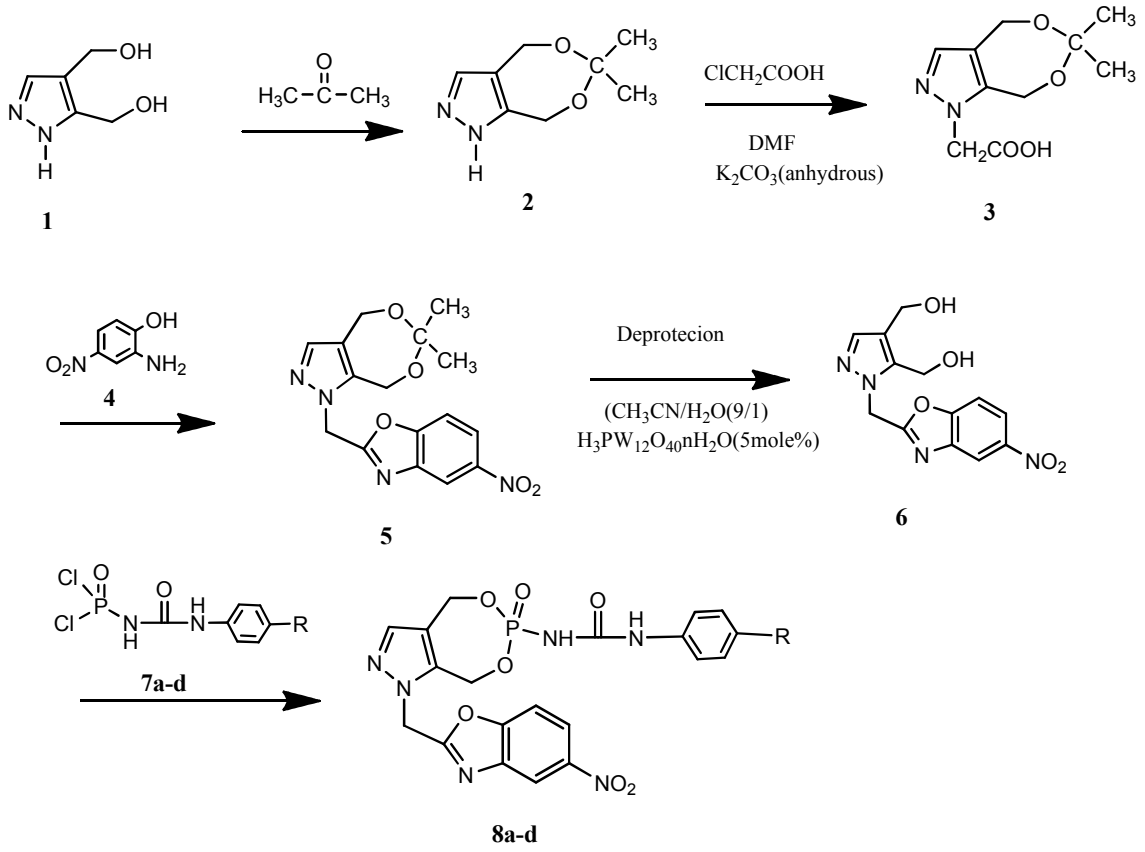
In support of our study pyrazoles and derivatives function as dyestuff, catalyst, polymerizing agents, drugs , herbicides and fungicides [12].they also possess various pharmacological activities such as anti-fungal activity [13], monoamineoxidase (MAO) inhibitory activity [14, 15], antiparkinson [16], anticonvulsant [17]. Pyrazole derivatives are valuable vasodialating and vasoconstructing drugs.

Benzoxazole and benzthiazoles nuclei are constituent of many of the bioactive heterocyclic compounds that exhibit antiangial, anti-ischemic, vasodilator, anti-diabetic, anti-microbial[18], cardiovascular, tranquilizer and virucidal activities [19-27].

A good deal of importance was given to dioxaphosphepino ureas/carboxamides and their derivatives [28] in the field of organophosphorus heterocyclic chemistry due to their unique biological applications [29,30].In view of the above observations, we synthesized Pyrazole derivatives possessing benzoxazole/benzthiazole moiety besides dioxaphosphepino ureas/carboxamides and screening for possible biological and pharmacological activities.

METERIALS AND METHODS

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals company, Inc. USA. And used without further purification. TLC was performed on aluminum sheet of silica gel $60F_{254}$, E-Merk, Germany using iodine as visualizing agent. Melting point was determined in open capillary tubes on Mel-Temp apparatus and is uncorrected. Column chromatography was performed on silica gel with different solvent systems as eluents to afford the pure compound. The IR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units, instruments. All H^1 and C^{13}-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHz for H^1-NMR and 75 MHz for C^{13}-NMR. P^{31}-NMR spectra were recorded on a Varian XL-spectrometer operating at 161.89MHz. The compounds were dissolved in DMSO-d_6 and Chemical shifts were referenced to TMS (H^1 and C^{13}-NMR) and 85% H_3PO_4 (P^{31}-NMR). Mass spectral data was recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis was recorded on a Carlo Erba 1108 elemental Analyzer, Central Drug Research Institute, Lucknow, India.



Scheme:I:synthetic route of 1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazole-6yl)-3(phenyl/p-tolyl/4-methoxy phenyl/4-chlorophenyl) ureas (8a-d).

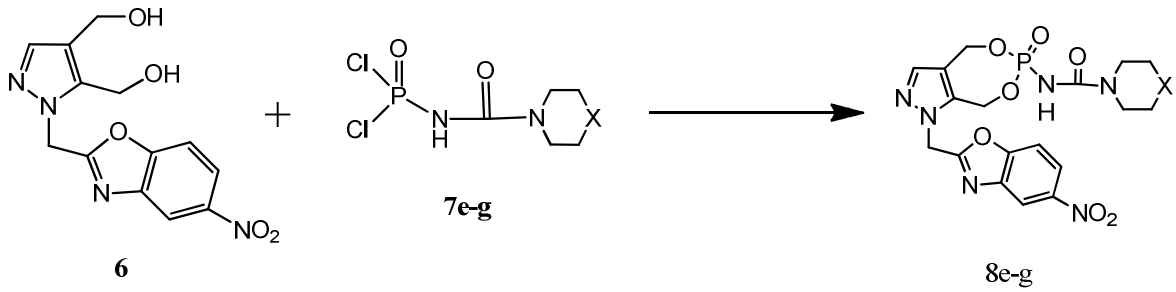
Compound 8	8*a*	8*b*	8*c*	8*d*
R	-H	-CH3	-OCH3	-Cl

Preparation of Intermediates:

(Phenyl carbamoyl) phosphoric acid dichloride (*7a-g*): [31, 32]

A solution of aniline (0.51g, 0.004mole) in dry toluene (25ml) was added drop wise to phosphide oxide (6, 0.64g, 0.004 mole) in dry toluene (30ml). After the addition, the temperature of the reaction mixture was maintained between -15 to - 5^0c for 30 minutes. Later the temperature of the mixture was raised to room temperature, with stirring for 30 minutes .Phenyl carbomido phosphoric acid dichloride being insoluble in toluene was separated out .It was collected by filtration and dried under reduced pressure.

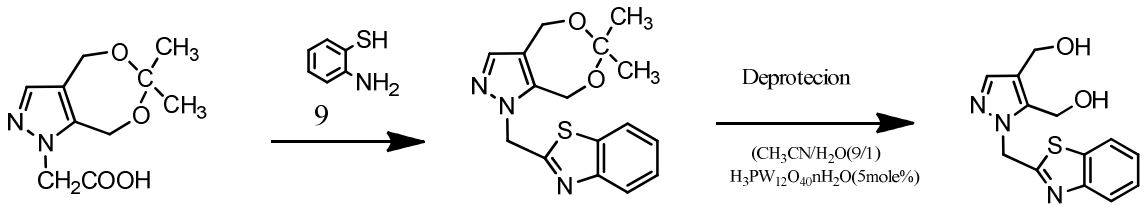
Similar treatment of 4-substituted Anilines / morpholine/piperidine/ N-methyl piperazine with dichloro isocyanato phosphine oxide in presence of dry toluene at -15 to -5^0c for 30 minutes offered the respective derivatives of 4-substituted Phenyl /marphonyl /piperidinyl/ N–methyl piperazenyl carbamido phosphoric acid dichloride.



6 8e-g

Scheme: II: Synthetic route of N-(1-((5-nitrobenzo [d] oxazol -2-yl) methyl)-6-oxido-4, 8-dihydro-1H - [1, 3, 2] dioxaphospheno [5,6-c] pyrazol-6-yl) morpholine/ piperadine /4-methyl piperazine carboxamides (8e-g).

Compound 8	*8e*	*8f*	*8g*
X	O	$-CH_2$	$-N-CH_3$



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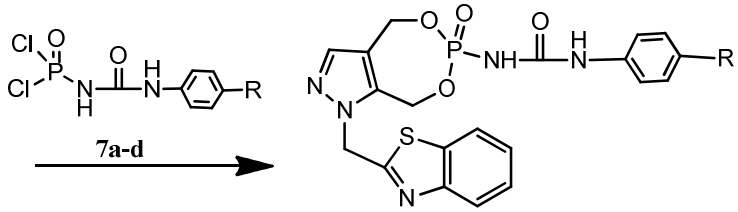
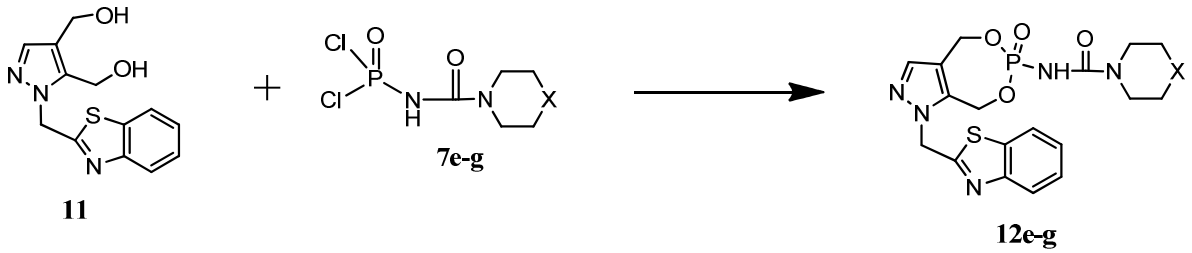


12a-d

Scheme :III: Synthetic route of 1-(1-(benzo [d] thiazole-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxy phenyl/4-chlorophenyl) ureas(12a-d) .

Compound 12	12a	12b	12c	12d
R	-H	$-CH_3$	$-OCH_3$	-Cl



Scheme:IV: Synthetic route of N-(1-benzo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxa phosphepino[5.6-c]pyrazol-6-yl) morpholine / piperidine /4-methylpiperazinecarboxamides (12e-g)

Compound 12	12e	12f	12g
X	O	$-CH_2$	$-N-CH_3$

RESULTS AND DISCUSSION

Typical Procedure for Synthesis of 2-(6, 6-dimethyl-4, and 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole-1-yl) acetic acid (*3*):

A suspension of 1-H-pyrazole-4, 5-dimethanol (1Mmole) **(*1*)** was dissolved in acetone (5ml) and 2, 2-dimethoxy propane (DMP, 2Mmole) solvent mixture. To the reaction mixture phosphotungstic acid (PTA, 5mole %) was added. The reaction mixture was stirred at room temperature for 4 hours under argon atmosphere until the 1-H-pyrazole-4; 5-dimethanol **(*1*)** had dissolved. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (9:1) solvent mixture as an eluent. After completion of the reaction, it was observed that the catalyst forms a gummy mass to stick on the wall inside the reaction flask. The solvent was decanted, dried under reduced pressure and the dried mass was re dissolved in dichloromethane (DCM).The dichloromethane solution was washed with water, dried with Na_2SO_4 and evaporated to get the crude product **(*2*)**, which was recrystallized by dissolving in boiling ether (5ml/g), cooling and then adding hexane (5ml/g) to give the pure product **(*2*)** [33].

A mixture of 6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole **(*2*)**, anhydrous K_2CO_3 chloro acetic acid and dimethyl formamide (DMF) was stirred at room temperature for 8 hours. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (7:3) solvent mixture as an eluent. The reaction mixture was diluted with ice cold water. The separated solid was identified as **(*3*)**. This was collected by filtration and recrystallized from ethanol.

Synthesis of 6,6 - dimethyl - 1 - ((5-nitrobenzo[d]oxazol -2 - yl)methyl - 4,8 - dihydro-1H-[1,3] dioxepino[5,6-c]pyrazole(*5*):[34,35]

A mixture of 0.1 mole 2-(6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole-1-yl) acetic acid **(*3*)** and 0.1 mole of 2-amino-nitrophenol **(*4*)** was heated under reflux for 1.5 hours with stirring at 150^{o}C. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (7:3) solvent mixture as an eluent. At the end of the reaction, the mixture was taken in a 30 ml dichloromethane and neutralized with 50 ml 1N NaOH solution. After neutralization the reaction mixture was extracted with CH_3Cl_2 (3×25 ml). The combined extract was dried on Na_2SO_4 . After filtration, the solvent was removed with rotary evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and $CHCl_3$ solvent was used as an eluent. Finally the product 6, 6-dimethyl-1-((5-nitrobenzo[d]oxazol-2-yl) methyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole **(*5*)** was recrystallised from aqueous dimethyl formamide.The structure of **(*5*)** was established by IR and ^{1}H-NMR and elemental analysis.

Synthesis of 1-((5-nitro benzo [d] oxazol-2-yl) methyl) -1H-pyraazole-4,5-diyl) dimethanol (*6*):

The isopropylidenation of 1, 2-diols was carried out by a procedure as reported in the literature[33].A suspension of the 6,6-dimethyl-1-((5-nitrobenzo[d]oxazol-2-yl)methyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazole **(*5*)** (1 m mol) in dry acetone and to this 5 mol % of phosphotungstic acid was added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 1 hour. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (7:3) solvent mixture as an eluent. After completion of the reaction, the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (3×20 ml) and water and the combined organic layer was dried with Na_2SO_4 and concentrated in vacuum to give the crude product. The crude product was purified by column chromatography on silica gel (60-120 mesh) with 15-30% ethyl acetate in cyclohexane as an eluent. The structure of **(*6*)** was established by IR, 1H-NMR and elemental analysis.

synthesis of 1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino[5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxyphenyl/4-chlorophenyl) ureas (*8a-d*):
A solution of (Phenyl carbamoyl) phosphoramidic dichloride (**7a**) (0.002 mole) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of Synthesis of 1-((5-nitro benzo [d] oxazol-2-yl) methyl) -1H-pyraazole-4, 5-diyl) dimethanol **(*6*)** (0.002mole) and triethylamine (0.004mole) in 30 ml of dry toluene and 10ml of tetrahydrofuran at 5^0c . After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 2 hours. Later the reaction mixture was heated to 50-60^{O}C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. After completion of the reaction the Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystallized from aqueous 2-propanol to get pure compound of 1-(1- ((5-benzo [d] oxazol-2-yl - methyl) -6-oxido -4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5, 6-c] pyrazole-6-yl)-3-phenylurea **(*8a*)**.

The similar procedure was adopted to synthesize 8b-d by the reaction of ***6*** with p-toylcarbamoyl phosphoramidic dichloride **(*7b*)**, 4-methoxy phenyl carbamoyl phosphoramidic dichloride ***(7c)***, and 4-chloro phenyl carbamoyl phosphoramidic dichloride **(*7d*)**. The structures of ***8a-d*** were established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental analysis.

synthesis of N-(1-((5-nitrobenzo [d] oxazol -2-yl) methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphospheno [5,6-c] pyrazol-6-yl) morpholine/piperadine/4-methyl piperazine carboxamides(*8e-g*):
A solution of Morpholino carbamoyl phosphoramidic dichloride**(*7e*)** (0.002 mole) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of a mixture of 1-(benzo [d] thiazol-2-yl) methyl) -1H-pyrazole-4,5-diyl) dimethanol**(*6*)** (0.002mole) and triethylamine (0.004mole) in 30 ml of dry toluene and 10ml of tetrahydrofuran at 5^0c . After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 3 hours. Later the reaction mixture was heated to 40-50^{O}C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. After completion of the reaction the Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystallized from aqueous 2-propanol to get pure compound of N-(1-(benzo[d]oxazole-2-ylmethyl)-6-oxido-4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5.6-c] pyrazol-6-yl) morpholine-4-carboxamide **(*8e*)** .yield (58%), m p 143-145^{O}C.

The similar procedure was adopted to synthesize **8f** and **8g** by the reaction of **6** with piperidene-1-carbamoyl phosphoramidic dichloride **(*7f*)** and 4-methyl piperazine-1- carbamoyl phosphoramidic dichloride **(*7g*)** respectively. The structure of ***8e-g*** was established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental.

Synthesis of 1 - (benzo [d] thiazole – 2 - ylmethyl) - 6,6 - dimethyl - 4,8 - dihydro - 1H-[1,3] dioxepino [5,6-c] pyrazole(*10*):[34,35]
A mixture of 0.1 mole 2-(6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-d] pyrazole-1-yl) acetic acid **(3)** and 0.1 mole of 2-aminobenzethiol (***9***) was heated under reflux for 1.5 hours with stirring at 150^{o}C. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (7:3) solvent mixture as an elutent. At the end of the reaction, the mixture was taken in a 30 ml dichloromethane and neutralized with 50 ml 1N NaOH solution. After neutralization the reaction mixture was extracted with CH_2Cl_2 (3×25 ml). The combined extract was dried on Na_2SO_4 . After filtration, the solvent was removed with rotary evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and $CHCl_3$ solvent was used as an elutent. Finally the product1-(benzo[d]thiazole-2-ylmethyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c] pyrazole**(*10*)**was recrystalised from aqueous dimethyl formamide. The structure of **(*10*)** was established by IR ^{1}H-NMR and elemental analysis.

Synthesis of 1-(benzo [d] thiazol-2-yl) methyl) -1H-pyrazole-4, 5-diyl) dimethanol (*11*):
The isopropylidenation of 1, 2-diols was carried out by a procedure as reported in the literature[33].A suspension of the 1-(benzo[d]thiazole-2-ylmethyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazole **(*10*)** (1 m mol) in dry acetone and to this 5 mol % of phosphotungstic acid was added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 1 hour. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (7:3) solvent mixture as an elutent. After completion of the reaction, the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (3×20 ml) and water and the combined organic layer was dried with Na_2SO_4 and concentrated in vacuum to give the crude product. The crude product was purified by column chromatography on silica gel (60-120 mesh) with 15-30% ethyl acetate in cyclohexane as an elutent. The structure of **(*11*)** was established by IR ^{1}H-NMR and elemental analysis.

Synthesis of 1 - (1 - (benzo [d] thiazole - 2 - yl) methyl) - 6 - oxido - 4,8 – dihydro - 1H - [1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxyphenyl/4-chloro phenyl) ureas(*12a-d*):
A solution of (Phenyl carbamoyl)phosphoramidic dichloride **(*7a*)** (0.002 mole) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of a mixture of 1-(benzo [d] thiazol-2-yl) methyl) -1H-pyrazole-4,5-diyl) dimethanol **(*11*)** (0.002mole) and triethylamine (0.004mole) in 30 ml of dry toluene and 10ml of tetrahydrofuran at 5^0c . After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 2 hours. Later the reaction mixture was heated to 50-60^{O}C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. After completion of the reaction the Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystalized from aqueous 2-propanol to get pure compound of 1-(1- (benzo [d] thiazol-2-yl - methyl) -6-oxido -4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5, 6-c] pyrazole-6-yl)-3-phenylurea **(*12a*)** .yield (58%), m p156-158^{O}C.

The similar procedure was adopted to synthesize ***12b-d*** by the reaction of ***11*** with p-toylcarbamoyl phosphoramidic dichloride **(*7b*)**, 4-methoxy phenyl carbamoyl phosphoramidicdichloride **(*7c*)** and 4-chloro phenyl carbamoyl phosphoramidic dichloride **(*7d*)**. The structure of **12a-d** was established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental analysis.

Synthesis of N - (1 - (benzo[d]thiazol - 2 - ylmethyl) - 6 - oxido - 4,8 - dihydro - 1H -[1,3,2] dioxaphosphepino[5,6-c]pyrazol-6-yl)morpholine/piperidine/4-methylpiperazine carboxamides (12e-g):
A solution of Morpholino carbamoyl phosphoramidic dichloride**(*7e*)** (0.002 mole) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of a mixture of 1-(benzo [d] thiazol-2-yl) methyl) -1H-pyrazole-4,5-diyl) dimethanol **(*11*)** (0.002mole) and triethylamine (0.004mole) in 30 ml of dry toluene and 10ml of tetrahydrofuran at 5^0c . After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 3 hours. Later the reaction mixture was heated to 40-50^{O}C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. After completion of the reaction the Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystalized from aqueous 2-propanol to get pure compound of N-(1-(benzo[d]thiazol-2-ylmethyl)-6-oxido-4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5, 6-c] pyrazol-6-yl) morpholine-4-carboxamide **(*12e*)** .yield (65%), m p 144-1462^{O}C.

The similar procedure was adopted to synthesize **12f** and **12g** by the reaction of ***11*** with piperidene-1-carbamoyl phosphoramidic dichloride **(*7f*)** respectively and 4-methyl piperazine-1- carbamoyl phosphoramidic dichloride **(*7g*).** The structure of ***12e-g*** was established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental analysis.

Physical, analytical and spectral data for the compounds
2-(6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole-1-yl) acetic acid (3): Yield:78%; M.p: 166-168OC;IR(KBr):2950cm-1(-OH),2940 and 2895 cm-1(Aliphatic γC-H), 1690 cm-1 (>C=O) , 1375-1487 cm-1 (pyrazole ring);H1-NMR(300Hz,DMSO-d6): δ 1.27 (s, 6H, two geminial CH3 groups) , 4.63 (s, 2H, two CH2 groups of acetals), 5.10 (s, 2H, -CH2 of –CH2COOH group), 7.30 (s, 1H, of pyrazole ring) and 11.0 (s, 1H, -COOH group); Anal. calcd (%) for C10H14N2O4 : C 53.09% , H 6.24% and N 12.38%.Found: C 52.29%, H 5.74% and N 11.78% .

6,6-dimethyl-1-((5-nitrobenzo[d]oxazol-2-yl) methyl-4,8-dihydro-1H-[1,3] dioxepino[5,6-c] pyrazole(5): Yield:70%; M.p: 144-146^{O}C ; IR(KBr): 3052 Cm^{-1} (Ar-H), 2940 & 2895 Cm^{-1} (Aliphatic γ_{C-H}), 1455 & 1390 Cm^{-1} (benzimidazole ring), 1395 & 1370 ((-C(CH_3)$_2$), 1375-1487 Cm^{-1} (pyrazole ring), 1355 & 1330 Cm^{-1} (–NO_2),1140 cm^1 (γ_{C-O});H^1-NMR(300Hz,DMSO-d6):δ 1.27 (s, 6H, two geminial CH_3 groups), 4.63 (s, 4H, two CH_2 groups of acetals), 4.99 (s, 2H, N-CH_2-benzoxazole ring), 7.30 (s, 1H, of pyrazole ring), 8.05-8.26(m, 3H, of benzoxazole ring); Anal.calcd(%) for $C_{16}H_{16}N_4O_5$: C 55.81%, H 4.68% , N 18.41% .Found : C 55.01% , H 4.18% and N 17.81%

1-((5-nitro benzo [d] oxazol-2-yl) methyl) -1H-pyraazole-4,5-diyl)dim ethanol(6):
Yield:70%; M.p: 126-128^{O}C ; IR(KBr): 3520(γ_{O-H}); 3050 (γ_{Ar-H}), 2940 & 2895 (Aliphatic γ_{C-H}), 1455 & 1390 (benzoxazole ring),1375-1487 (pyrazole ring),1355 & 1330 (-NO_2), 1140 cm^{-1} (γ_{C-O}); H^1-MR(300Hz,DMSO-d6):δ 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding) 4.73 (s, 4H, two CH_2 groups of dimethanol), 4.99 (s, 2H, N-CH_2-benzoxazole), 7.57 (s, 1H, of pyrazole ring), 7.39-7.74 (m, 3H, of benzoxazole ring); Anal.calcd(%) for $C_{13}H_{12}N_4O_5$: C 51.32% , H 3.98% , N 18.41% .Found : C 50.52% , H 3.48.% and N 17.81%.

1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6yl)-3-phenylurea(8a):
Yield:70%; M.p: 143-1450C; IR(KBr): 3160(γ P-NH), 3052(γAr-H), 2940&2895(Aliphatic γC-H), 1663 (NH-CO), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO2), 1300(C-O/δc-o)1250(P=O), 954 cm-1 (P-O); H1-MR(300Hz,DMSO-d6):δ 4.99 (s, 2H, -N-CH2-benzoxazole) 5.29 (s, 4H, two CH2 groups attached to phosphorus moiety), 6.15 (S,2H,-NH-CO-NH attached to phosphorus moiety),7.19-7.61(m, 5H , C6H5 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 8.05-8.26(m, 3H, of benzoxazol ring); 13C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 ,141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 152 , 139.4 , 121.6 , 128.9 and 128.0 corresponding to C1 , C2 , C3 , C4 , C5 , C6 , C7 , C8 , C9 , C10 , C11 , C12 , C13 , C14 , C15 , C16 & C20 , C17 & C19 andC18;^{31}PNMR(161.89MHz,DMSO-d6):δ -11.20 , 1.36 ; Anal.Calcd (%) For $C_{20}H_{17}N_6O_7P$: C 49.59%, H 3.54%, N 17.35%, P 6.39% Found: C 48.79%, H 3.04%, N 16.75% and P 5.69%.

1 - (1 - ((5 - nitrbenzo [d] oxazol - 2 - yl)methyl) - 6 - oxido - 4,8 - dihydro - 1H - [1,3,2] dioxaphosphepino[5,6-c]pyrazol-6yl)-3-(p-tolyl)urea(8b):
Yield: 75%; M.p: 164- 166^{0}C; IR(KBr): 3210 ($\gamma_{P\text{-}NH}$), 3055($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1668**(**NH-CO**),** 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1305($\gamma_{C\text{-}O}/\delta_{c\text{-}o}$)1245 (P=O**),** 950cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 2.34(s,3H,-$CH_3$of tolyloxy), 4.99 (s,2H,-N-CH_2-benzoxazole), 5.29 (s,4H,two CH_2 groups attached to phosphorus moiety), 6.15(S,2H,-NH-CO-NH attached to phosphorus moiety),7.21-7.56 (m, 4H,C_6H_4 ring attached to –NH –CO-NH-), 7.30 (s,1H,CH of pyrazole ring), 8.05-8.26 (m,4H,of benzoxazole ring); ^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 152.0 , 136.4 , 121.5 , 129.2 , 136.8 and 21.30 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} , C_{18} and C_{21} ;^{31}P NMR (161.89MHz, DMSO-d6): δ -11.53; Anal. Calcd (%) For $C_{21}H_{19}N_6O_7P$: C 50.61%, H 3.84 %, N 16.86%, P 6.21 % Found: C 49.81%, H 3.34 %, N 16.26% and P 5.51%.

1-(4-methoxy)-3-(1-((5-nitrbenzo[d]oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino[5,6-c] pyrazol-6yl)urea(8c):
Yield: 70%; M.p: 156-1580C; IR(KBr): 3230 (γ P-NH), 3065 (γAr-H), 2940&2895(Aliphatic$\gamma_{C\text{-}H}$),1665(NH-CO),1455&1390(benzoxazole ring) , 1375 &1487 (pyrazole ring), 1355& 1330(-NO2), 1310(γC-O/ δc-o) 1254 (P=O), 958cm-1 (P-O); H1-MR(300Hz,DMSO-d6):δ 3.83 (s,1H, -OCH3 of methoxy phenyl), 4.99 (s,2H,-N-CH2-benzoxazole), 5.29 (s,4H,two CH2 groups attached to phosphorus moiety),6.15(s,2H,-NH-CO-NH attached to phosphorus moiety), 6.97-7.51 (m, 4H,C6H4 ring attached to -NH –CO-NH-), 7.30 (s,1H,CH of pyrazole ring), 8.05-8.26 (m,3H,of benzoxazole ring); 13C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 152.0 , 131.7 , 119.8 , 114.5 , 158.9 and 55.8 corresponding to C1 , C2 , C3 , C4 , C5 , C6 , C7 , C8 , C9 , C10 , C11 , C12 , C13 , C14 , C15 , C16 & C20 , C17 & C19 , C18 and C21;31P NMR (161.89MHz, DMSO-d6): δ -11.48; Anal. Calcd (%) For C21H19N6O8P: C 49.03%, H 3.72%, N 16.34%, P 6.02% Found: C 48.28%, H 3.22%,N 15.74% and P 5.32%.

1-(4-chlorophenyl)-3-(-1((5-nitrobenzo[d]oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H- [1,3,2]dioxaphosphepino [5,6-c] pyrazol-6yl)urea(8d):
Yield: 70%; M.p: 172-174^{0}C; IR(KBr): 3215 ($\gamma_{P\text{-}NH}$), 3067 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1675 **(**NH-CO**),** 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1315($\gamma_{C\text{-}O}$/ $\delta_{c\text{-}o}$) 1259 (P=O**),** 959 (P-O**),**725 cm^{-1}(-Cl)**;** H^1-MR(300Hz,DMSO-d6):δ 4.99(s,2H,-N-CH_2-benzoxazole), 5.29 (s,4H,two CH_2 groups attached to phosphorus moiety), 6.15(S,2H,-NH-CO-NH attached to phosphorus moiety), 7.47-7.75 (m, 4H of C_6H_4 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 8.05-8.26(m, 3H of benzoxazol ring); ^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 ,120.5 , 115.2 , 142.4 , 156.1 , 152.0 , 137.5 , 120.8 , 129.0 , and 133.3 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} and C_{18} ;^{31}P NMR (161.89MHz, DMSO-d6): δ -9.23; Anal. Calcd (%)For $C_{20}H_{16}ClN_6O_7P$: C:46.30% , H 3.11 %, Cl 6.83%, N 16.20%, P 5.97% Found: C 45.50%, H 2.61%, Cl 6.13%, N 15.60% and P 5.27 %.

N - (1 - ((5 - nitrobenzo [d] oxazol - 2 - yl)methyl) - 6-oxido - 4,8 - dihydro - 1H - [1,3,2] dioxaphospheno [5,6 - c] pyrazol - 6 - yl) morpholine - 4 - carboxamide (8e):
Yield: 65%; M.p: 192-194^{0}C; IR(KBr): 3190 ($\gamma_{P\text{-}NH}$), 3068 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1678 (-CO-N=), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1310($\gamma_{C\text{-}O}/\delta_{c\text{-}o}$) 1250 (P=O**),** 954 (P-O**)**cm^{-1}**;** H^1-MR(300Hz,DMSO-d6):δ 3.31-3.65 (m, 8H of morpholine attached to –CO-NH-), 4.99 (s, 2H,-N-CH_2-benzoxazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15(s, 1H.-CO-NH attached to phosphorus moiety). 7.30(s, 1H, CH of pyrazole ring), 8.05-8.26(m, 3H of benzoxazol ring); ^{13}C-NMR (75MHz,

DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 158.5 , 46.3 and 65.7.corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} & C_{18} and C_{16} & C_{17} ;^{31}P NMR (161.89MHz, DMSO-d6): δ-7.15; Anal. Calcd (%) For $C_{18}H_{19}N_6O_8P$: C 45.20%, H 4.00 %, N 17.57%, P 6.48% Found: C 44.40%, H 3.50 %, N 16.97% and P 5.78%.

N -(1 - ((5 - nitrobenzo [d] oxazol - 2 - yl) methyl) - 6 -oxido - 4, 8 - dihydro - 1H - [1, 3, 2] dioxaphospheno [5,6 - c] pyrazol - 6 - yl) piperidine - 1 - carboxamide (8f):
Yield: 65%; M.p: 169-171^{0}C; IR(KBr): 3220 ($\gamma_{P\text{-}\underline{NH}}$), 3055 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1690 (-CO-N=**),** 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1310($\gamma_{C\text{-}O}/\delta_{c\text{-}o}$) 1245 (P=O**),** 950 (P-O**)**cm^{-1}**;** H^1-MR(300Hz,DMSO-d6):δ 1.53-3.77 (m, 10H of piperidine attached to –CO-NH-),4.99 (s,2H,-N-CH_2-benzoxazole), 5.29 (s,4H,two CH_2 groups attached to phosphorus moiety), 6.15(s,1H.-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 8.05-8.26(m, 3H of benzoxazol ring); ^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 156.5 , 49.0 , 24.9 and 23.8 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} & C_{19} , C_{16} & C_{18} and C_{17};^{31}P NMR (161.89MHz, DMSO-d6): δ-5.23; Anal.Calcd(%) For $C_{19}H_{21}N_6O_7P$: C 47.90%, H 4.44%, N 17.64%, P 6.50 % Found: C 47.10%, H 3.94 %, N 17.04% and P 5.80 %.

4 - methyl - N - (1 - ((5 - nitrobenzo[d] oxazol - 2 - yl)methyl) - 6 - oxido - 4,8 -dihydro -1H - [1,3,2] dioxaphospheno [5,6 - c] pyrazol - 6 - yl) piperazine - 1 - carboxamide (8g):
Yield: 70%; M.p: 178-180^{0}C; IR(KBr): 3217 ($\gamma_{P\text{-}\underline{NH}}$), 3070 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1680 (-CO-N=**),** 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1310($\gamma_{C\text{-}O}/\delta_{c\text{-}o}$) 1254 (P=O**),** 958 (P-O**)**cm^{-1}**;** H^1-MR(300Hz,DMSO-d6):δ 2.26 (s,3H,-CH3 group of 4-methyl piperazine),2.27-3.40 (m, 8H of 4-methyl piperazine attached to –CO-NH-) , 4.99 (s,2H,-N-CH_2-benzoxazole), 5.29 (s,4H,two CH_2 groups attached to phosphorus moiety), 6.15(s,1H.-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 8.05-8.26(m, 3H of benzoxazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 158.5 , 51.4 , 51.0 and 46.6 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} & C_{18} , C_{16} & C_{17} and C_{19} ;^{31}P NMR (161.89MHz, DMSO-d6): δ -8.2; Anal. Calcd (%) $C_{19}H_{22}N_7O_7P$: C 46.44%, H 4.51 %, N 19.95%, P 6.30% Found: C 45.64%, H 4.01%, N 19.35% and P 5.60.

1-(benzo[d]thiazole-2-ylmethyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c] pyrazole (10):
Yield: 70%; M.p: 145-147^{0}C; IR(KBr): 3052 (Ar-H), 2940 & 2895 (Aliphatic $\boldsymbol{\gamma}_{C\text{-}H}$), 1474, 1344,715 & 620 (benzthiazole ring), 1395 & 1370 ((-C(CH_3)$_2$), 1375-1487 Cm^{-1} (pyrazole ring), 1355 & 1330 Cm^{-1} (–NO_2),1140 cm^1 ($\boldsymbol{\gamma}_{C\text{-}O}$); H^1-NMR(300Hz,DMSO-d6):δ 1.27 (s, 6H, two geminial CH_3 groups), 4.63 (s, 4H, two CH_2 groups of acetals), 4.99 (s, 2H, N-CH_2-benzthiazole ring), 7.30 (s, 1H, of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazole ring); Anal.calcd(%) for $C_{16}H_{17}N_3O_2S$: C 60.93%, H 5.43 %, N 13.32 %, S 10.17% Found : C 60.13%, H 4.93%, N 12.62% and S 9.97%.

1- (benzo[d]thiazol - 2 - yl)methyl) - 1H-pyrazole - 4,5 - diyl) dimethanol(11):
Yield: 70%; M.p: 126-125^{o}C; IR(KBr): 3520($\nu_{O\text{-}H}$, intermolecular H-bonding),3052 ($\boldsymbol{\gamma}_{Ar\text{-}H}$), 2940 & 2895(Aliphatic $\boldsymbol{\gamma}_{C\text{-}H}$), 1474, 1344,715 & 620 (benzthazole ring) , 1375-1487 (pyazole ring) 1320 and 1040(ν_{OH} /$\nu_{C\text{-}O}$);H^1-NMR(300Hz,DMSO-d6):δ 3.65 (s, 2H, two –OH groups having Intermolecular H-bonding) 4.61(s,2H,-CH_2 groups of CH_2OH),4.79(s,2H,-CH_2 group of CH_2OH) 4.99 (s, 2H, N-CH_2-benthiazole), 7.30 (s, 1H, of pyrazole ring), 7.53-8.18 (m, 4H, of benzthiazole ring); Anal.calcd(%) for $C_{13}H_{13}N_3O_2S$: C 56.71% , H 4.76% , N 15.26% ,S 11.65% Found : C 57.91%, H 4.56%, N 14.56% and S 11.45% .

1-(1-(benzo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6-yl)-3-phenylurea (12a):
Yield: 58%; M.p: 156-158^{0}C; IR(KBr): 3317 ($\boldsymbol{\gamma}_{P\text{-}\underline{NH}}$), 3052 ($\boldsymbol{\gamma}_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1656 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1250 (P=O**),** 954 cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 1. 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15(S,2H,-NH-CO-NH attached to phosphorus moiety),7.19-7.43 (m, 5H of C_6H_5 ring attached to -NH -CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.13(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 152.0 , 139.4 , 121.6 , 128.9 , 128.0 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} , C_{18};^{31}P NMR (161.89MHz, DMSO-d6): δ -11.20, 1.36; Anal.Calcd (%) For $C_{20}H_{18}N_5O_4PS$: C 52.74%, H 3.98%, N 15.38%, P 6.80%, S 7.04% Found: C 51.94% , H 3.44%, N 14.78%, P 6.10% and S 6.84%.

1-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino [5,6-c]pyrazol-6yl)-3-(p-tolyl) urea(12b):

Yield: 65% ; M.p: 172-174 ^{o}C; IR(KBr): 3310 ($\gamma_{P\text{-}NH}$), 3055 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1660 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 245(P=O**),** 950 cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 2.34(s,3H,-$CH_3$of group),4.99(s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s,2H,-NH-CO-NH attached to phosphorus moiety), 7.21-7.56 m, 4H of C_6H_4 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR (75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 ,121.6, 152.8, 135.2 , 152.0 , 136.4 , 121.5 , 129.2 , 136.8 and 21. 3 corresponding to C1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17}& C_{19}, C_{18} and C_{21}; ^{31}P NMR (161.89MHz, DMSO-d6): δ -11.53; Anal. Calcd (%) For $C_{21}H_{20}N_5O_4PS$:C 53.73%, H 4.29%, N 14.92%, P 6.60 %, S 6.83%Found: C 52.93% ,H 3.79%, N 14.32%, P 5.90% and S 6.63%.

1-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3-(4-methoxy phenyl)urea(12c):

Yield: 65% ; M.p: 145-147 ^{o}C; IR(KBr): 3315 ($\gamma_{P\text{-}NH}$), 3065 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1665 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1254 (P=O**)**958 cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 3.83(s.3H,-OCH3 group),4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15(s,2H,-NH-CO-NH attached to phosphorus moiety),6.97-7.51 (m, 4H of C_6H_4 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR (75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 152.0 , 131.7 , 119.8 , 114.5 , 158.9 and 55.8. corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} , C_{18} and C_{21}; ^{31}P NMR (161.89MHz, DMSO-d6): δ -11.48; Anal. Calcd (%) For $C_{21}H_{20}N_5O_5PS$: C 51.96%, H 4.15 %, N 14.43%, P 6.38 %, S 6.61% Found: C 51.16%, H 3.65%, N13.83%, P 5.62% and S 6.41%.

1-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3-(4-chloro phenyl)urea(12d):

Yield: 60% ; M.p: 182-184 ^{o}C; IR(KBr): 3320 ($\gamma_{P\text{-}NH}$), 3067 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1670 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1256 (P=O**)**956 (P-O**),**725cm^{-1}(-Cl)**;** H^1-MR(300Hz,DMSO-d6):δ 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.0 (s,2H,-NH-CO-NH attached to phosphorus moiety), 7.47-7.75 (m, 4H of C_6H_4 ring attached to -NH -CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 ,118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 152.0 , 137.5 , 120.8 , 129.0 and 133.3 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} and C_{18}.;^{31}PNMR(161.89MHz,DMSO-d6):δ -9.23 ; Anal.Calcd (%) For $C_{20}H_{17}ClN_5O_4PS$: C 49.04%, H 3.50%, Cl 7.24%, N 14.30%, P 6.32%, S 6.55%Found: C 48.24% , H 3.00 %, Cl 6.54%, N 13.70%, P 5.62% and S 6.35%.

N-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-morpholine-4-carboxamide(12e):

Yield: 65% ; M.p: 194-196 ^{o}C; IR(KBr): 3325 ($\gamma_{P\text{-}NH}$), 3068 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$) , 1654 **(**-CO-N=**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1259 (P=O**)** 961 cm^{-1} (P-O**);**H^1-MR(300Hz,DMSO-d6):δ 3.31 (t, 4H –CH2- attached to Nitrogen of morpholine ring, J=7.1 Hz, H-2^{I}, H-3$^{I)}$, 3.60(t, 4H,-CH2- attached to oxygen of morpholine ring, J=7.1 Hz, H-3^{I}. H-2^{I}), 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s,1H,-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 158.5 , 46.3 and 65.7 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} & C_{28} and C_{16} & C_{17} ; ^{31}P NMR (161.89MHz,DMSO-d6):δ-7.15 ; Anal.Calcd (%) For $C_{18}H_{20}N_5O_5PS$: C 48.10%, H 4.49%, N 15.58%,P 6.89% , S 7.13%Found: C 47.30% , H 3.90%, N 14.98%, P 6.29% and S 6.93%.

N-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino [5,6-c]pyrazol-6yl)-piperidine-1-carboxamide(12f):

Yield: 65% ; M.p: 185-187 ^{o}C; IR(KBr): 3315 ($\gamma_{P\text{-}NH}$), 3055 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$) , 1658 **(**-CO-N=**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1259 (P=O**)** 963cm^{-1}(P-O**);**H^1-MR(300Hz,DMSO-d6):δ 1.53-3.77 (m, 10H of piperidine attached to –CO-NH-), 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s, 1H,-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18 (m, 4H, of benzthiazol ring).;^{13}C-NMR(75MHz,

DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 158.5 , 51.4 ,51.0 and 46.6 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} ,C_{14},C_{15} & C_{28}, C_{16} & C_{17} andC_{19}; ^{31}PNM(161.89MHz,DMSO-d6): δ-5.23; Anal.Calcd (%) For $C_{19}H_{22}N_5O_4PS$:C 51.00%, H 4.96%, N 15.65%, P 6.92%, S 7.17% Found: C 50.20, H 4.56%, N 14.95%, P 6.22% and S 6.97%.

N-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-4-methylpiperazine-1-carboxamide(12g):

Yield: 65% ; M.p: 165-167 ^oC; IR(KBr): 3320 ($\gamma_{P\text{-}NH}$), 3070 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$) , 1663**(**-CO-N=**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1246 (P=O**)** 951cm^{-1}(P-O**);**H^1-MR(300Hz,DMSO-d6):δ 2.26(s,3H.-CH3 group of 4-methyl piperazine), 2.27(t,4H, $-CH_2-N-CH_2-$ of piperazine attached to carbamido moiety, J=7.1 Hz , H-2^I,H-3^I), 3.40(t,4H,-CH2-N-CH2- of piperazine ring attached to carbmido moiety=7.1Hz , H-2^I and H-3^I) , 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s,1H,-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 156.5 , 49.0 , 24.9 and 23.8 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13},C_{14},C_{15}& C_{19} , C_{16}&C_{18} and C_{17}; Anal.Calcd(%) For $C_{19}H_{23}N_6O_4PS$: C 49.35%, H 5.01%, N 18.17%, P 6.70%,S 6.93% Found: C 48.55% , H 4.51%, N 17.57%,P 6.00% and S 6.73%.

Biological activity:

The antimicrobial activity [36] of chemical compound is influenced by physical and biological characteristics [37].It has been well established that physiological activity is a function of the chemical structure of compound [38].Heterocyclic organic compounds containing phosphorus, oxygen, nitrogen or sulfur in the ring system are expected to be more active due to the presence of hetero atoms [39-41].

In view of this, the synthesized new organophosphorus heterocyclic compounds have been tested for their antimicrobial activity.

Antibacterial activity:

The antibacterial activity [42] of final compounds ***8a-g*** synthesized was screened against the Staphylococcus aureus (gram positive), BacillusCerus**,** Escherichia coli (gram negative) and Pseudomonas aeruginosa organism. **8d-g** compounds exhibited high antibacterial activity against bacteria, while compounds ***8a-c*** compounds show low or no activity under given experimental conditions.The similar results were also noticed with thiazole compounds **12a-g**. The presence of chloro group in the structure has shown increased effect on their antibacterial activity. Amoxicillin and Cefaclor are tested as reference compounds to compare the activity.

Antibacterial activity of 1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxy phenyl/4-chlorophenyl) ureas (*8a-d*)and N-(1-((5-nitrobenzo [d] oxazol -2-yl) methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphospheno [5,6-c] pyrazol-6-yl) morpholine/piperadine/4-methyl piperazine carboxamides(*8e-g*):

COMPOUND (8)	R	X	Zone of inhibition (mm)			
			Staphylococcus aureus NCCS2079 250(µg/disc)	***Bacillus Cerus*** NCCS2106 250(µg/disc)	***Escherichia Coli*** NCCS2065 250(µg/disc)	***Pseudomonas aeruginosa*** NCCS2200 250(µg/disc)
8a	-H	-	8	6	7	5
8b	$-CH_3$	-	6	-	5	4
8c	$-OCH_3$	-	4	-	-	4
8d	-Cl	-	18	15	17	19
8e	-	O	17	16	17	15
8f	-	$-CH_2$	13	11	13	14
8g	-	$-N-CH_3$	16	13	15	14
8h	Amoxicillin	-	21	27	24	22
8i	Cefaclor	-	19	22	19	20

"_" indicates no activity

Antibacterial activity by disc diffusion methods for 1-(1-(benzo [d] thiazole-2-yl) methyl -6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3 (phenyl/p-tolyl/4-methoxy phenyl/4-chlorophenyl) ureas (*12a-d*) and N-(1-(benzo [d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5.6-c]pyrazol-6-yl)morpholine/ piperidine/4-methyl piperazine carboxamides (*12e-g*):

COMPOUND (12)	R	X	Zone of inhibition (mm)			
			Staphylococcus aureus NCCS2079 250(µg/disc)	*Bacillus Cerus* NCCS2106 250(µg/disc)	*Escherichia Coli* NCCS2065 250(µg/disc)	*Pseudomonas aeruginosa* NCCS2200 250(µg/disc)
12a	-H	-	9	7	8	6
12b	$-CH_3$	-	7	-	6	5
12c	$-OCH_3$	-	5	-	-	5
12d	-Cl	-	18	16	18	18
12e	-	O	16	17	18	16
12f	-	$-CH_2$	14	12	14	15
12g	-	$-N-CH_3$	17	14	16	15
12h	Amoxicillin	-	21	27	24	22
12i	Cefaclor	-	19	22	19	20

"_" indicates no activity

Antifungal activity:

The antifungal activity of final compounds 8a-g synthesized was screened against Aspergillusniger, Canadida albicans. Ketoconazole is tested as reference compound to compare the activity. The compounds ***8d-g*** exhibited more antifungal activity than the compounds ***8a-c.*** The similar results were also noticed with thiazole compounds **12a-g** under given experimental conditions.

Antifungal activity of 1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxy phenyl/4-chlorophenyl) ureas (*8a-d*) and N-(1-((5-nitrobenzo [d] oxazol -2-yl) methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphospheno [5,6-c] pyrazol-6-yl) morpholine/piperadine/4-methyl piperazine carboxamides(*8e-g*):

COMPOUND(8)	R	X	Zone of inhibition (mm)	
			Aspergillus niger NCCS 1196 250(µg/dsic)	*Canadida albicans* NCCS 3471 250(µg/dsic)
8a	-H	-	05	04
8b	$-CH_3$	-	04	-
8c	$-OCH_3$	-	04	-
8d	-Cl	-	14	13
8e	-	O	18	16
8f	-	$-CH_2$	12	11
8g	-	$-N-CH_3$	15	13
8h	Ketoconazole	-	22	25

"_" indicates no activity

Antifungal activity by disc diffusion method for 1-(1-(benzo [d] thiazole-2-yl) methyl) -6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6yl)-3(phenyl/p-tolyl/4-methoxy phenyl/4-chlorophenyl) ureas (*12a-d*) and N-(1-(benzo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5.6-c] pyrazol-6-yl) morpholine / piperidine /4-methyl piperazine carboxamides (*12e-g*):

COMPOUND(12)	R	X	Zone of inhibition (mm)	
			Aspergillus niger NCCS 1196 250(µg/dsic)	*Canadida albicans* NCCS 3471 250(µg/dsic)
12a	-H	-	06	05
12b	$-CH_3$	-	05	-
12c	$-OCH_3$	-	05	-
12d	-Cl	-	15	14
12e	-	O	19	17
12f	-	$-CH_2$	13	11
12g	-	$-N-CH_3$	16	14
12h	Ketoconazole	-	22	25

"_" indicates no activity

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