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

C. H. Lakshmi Praveena, V. Esther Rani, Y. N. Spoorthy and L. K. Ravindranath*

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ABSTRACT

New novel derivatives of 1-(1-((5-nitrobenzo[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-pyrazole-4,5-diyl) dimethanol (6) and (phenyl carbamoyl) phosphoric acid dichlorides 7(a-d). The synthon (6) was obtained by deprotection of isopropylidene 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] dioxaphosphepino [5,6-c] pyrazol-6yl) morpholine/piperine/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-6yl) 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 vasoconstricting 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.

MATERIALS 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 60F254, 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 H¹ and C¹³-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHz for H¹-NMR and 75 MHz for C¹³-NMR. P³¹-NMR spectra were recorded on a Varian XL-spectrometer operating at 161.89MHz. The compounds were dissolved in DMSO-d₆ and Chemical shifts were referenced to TMS (H¹ and C¹³-NMR) and 85% H₃PO₄ (P³¹-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 1: synthetic route of 1-(1-((5-nitrobenzo [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).

<table>
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<tr>
<th>Compound</th>
<th>8a</th>
<th>8b</th>
<th>8c</th>
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<tr>
<td>R</td>
<td>-H</td>
<td>-CH₃</td>
<td>-OCH₃</td>
<td>-Cl</td>
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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°C for 30 minutes. Later the temperature of the mixture was raised to room temperature, with stirring for 30 minutes. Phenyl carbamido 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°C for 30 minutes offered the respective derivatives of 4-substituted Phenyl /morpholonyl /piperidinyl/ N–methyl piperazenyl carbamido phosphoric acid dichloride.

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).

<table>
<thead>
<tr>
<th>Compound</th>
<th>8</th>
<th>8e</th>
<th>8f</th>
<th>8g</th>
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<tbody>
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<td>X</td>
<td>O</td>
<td>-CH₂</td>
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<td>-N-CH₃</td>
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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-6-yl]-3(phenylp-tolyl/4-methoxy phenyl/4-chlorophenyl) urea(12a-d).

<table>
<thead>
<tr>
<th>Compound</th>
<th>12a</th>
<th>12b</th>
<th>12c</th>
<th>12d</th>
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<td>R</td>
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Der Pharma Chemica, 2013, 5 (4):58-70


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-y1) acetate (3):
A suspension of 1-H-pyrazole-4, 5-dimethanol (1M mole) (I) was dissolved in acetone (5ml) and 2, 2-dimethoxypropane (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 (I) 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$_2$SO$_4$ 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$_2$CO$_3$ 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) acetate (3) and 0.1 mole of 2-amino-nitrophenol (4) was heated under reflux for 1.5 hours with stirring at 150°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$_2$Cl$_2$ (3×25 ml). The combined extract was dried on Na$_2$SO$_4$. 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 1H-NMR and elemental analysis.

Synthesis of 1-((5-nitro benzo [d] oxazol-2-yl) methyl) -1H-pyraazole-4,5-diy1) 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$_2$SO$_4$ 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.

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synthesis of 1-(1-((5-nitrobenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino[5,6-c]pyrazol-6-yl)-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-(benzo [d] thiazole-2-ylmethyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazole (7b), 4-methoxy phenyl carbamoyl phosphoramidic dichloride (7c), and 4-chloro phenyl carbamoyl phosphorinic dichloride (7d). The structures of 8a-d were established by IR, 1H-NMR, 13C-NMR, and elemental analysis. Elemental analysis.

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

synthesis of N-(1-((5-nitrobenzo [d] oxazol-2-yl) methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepin [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-((5-nitrobenzo [d] oxazol-2-yl) methyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphate[5,6-c]pyrazol-6-yl) morpholine-4-carboxamide (8e). Yield (58%), mp 143-145°C.

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

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-amino benzethiol (9) was heated under reflux for 1.5 hours with stirring at 150°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 30 mL 1N NaOH solution. After neutralization the reaction mixture was extracted with CH2Cl2 (3x25 mL). The combined extract was dried on Na2SO4. After filtration, the solvent was removed with rotary evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and CHCl3 solvent was used as an eluent. Finally the product1-(benzo[d]thiazole-2-ylmethyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c] pyrazole(10) was recrystallised from aqueous dimethyl formamide. The structure of (10) was established by IR 1H-NMR and elemental analysis.

Synthesis of 1-(benzo [d] thiazole-2-yl) methyl)-1H-pyrazole-4, 5-diyl dimethanol (11): The isopropylideneation 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 aceton 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 (3x20 mL) and water and the combined organic layer was dried with Na2SO4 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 (11) was established by IR 1H-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-6-yl) morpholine-4-carboxamide (12e-g):  
A solution of Morpholine 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] thiiazol-2-yl) methyl) -1H- pyrazole-4,5-diyl)dimethanol (11) (0.002 mole) and triethylamine (0.004 mole) in 30 ml of dry toluene and 10 ml of tetrahydrofuran at 5°C. 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°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- (benzo[d] thiiazol-2-yl) methyl) -6-oxido -4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5, 6-c] pyrazol-6-yl)-3-phenylurea (12a). Yield (75%), m p 144-146°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 phosphoramidic dichloride (7c) and 4-chloro phenyl carbamoyl phosphoramidic dichloride (7d). The structure of 12a-d was established by IR, 1H-NMR, 13C-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 (Phenyl carbamoyl )phosphoramidic dichloride (7f) (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] thiiazol-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°C. 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°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]thiazol-2-ylmethyl)- 6-oxido-4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepino [5, 6-c] pyrazol-6-yl)-3(phenyl /p-tolyl/4-methoxyphenyl/4-chloro phenyl ) ureas(12e-g). The structure of 12e-g was established by IR, 1H-NMR, 13C-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: 166-1680°C;IR(KBr):2950(-O-H),2940 & 2895 (Aliphatic C-H ), 1375-1487 cm-1 (pyrazole ring); H-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 8.05-8.26(m, 3H, of benzoxazole ring); Anal.calcd(%) for C32H38N2O3: C 52.59%, 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°C; IR(KBr): 3520(O-H), 3440 & 3350 (Aromatic OH ), 1537 (C=O); 1375 & 1380 cm-1 (pyrazole ring), 1355 & 1330 cm-1 ( –NO2),1140 cm-1 (γ(C=O)); 9.40-9.55 (H-NMR(300Hz,DMSO-d6)): δ 1.27 (s, 6H, two geminal CH3 groups), 4.63 (s, 4H, two CH2 groups of acetals), 4.99 (s, 2H, N-CH2-benzoxazole ring), 7.30 (s, 1H, of pyrazole ring), 8.05-8.26(m, 3H, of benzoxazole ring); Anal.calded(%) for C15H12N2O3: C 51.32%, H 3.98%, N 18.41%;Found: C 51.00%, H 4.18% and N 17.81%.

1-((5-nitro benzo[d] oxazol-2-yl) methyl)-1H-pyrazole-4,5-diyldimethanol(6): Yield:70%; M.p: 126-128°C; IR(KBr): 3520(γ(OH) ), 3050 (γ(C=O) ), 2940 & 2985 (Aliphatic γ(C=O) ), 1455 & 1390 (benzoxazole ring).1375-1487 (pyrazole ring).1355 & 1330 (-NO2), 1140 cm-1 (γ(C=O)); H-NMR(300Hz,DMSO-d6): δ 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding) 4.73 (s, 4H, two CH2 groups of dimethanol), 4.99 (s, 2H, N-CH2-benzoxazole), 7.57 (s, 1H, of pyrazole ring), 7.39-7.74 (m, 3H, of benzoxazole ring); Anal.calded(%) for C15H12N2O3: C 51.32%, H 3.98%, N 18.41%;Found: C 50.52%, H 3.48% and N 17.81%.
1-(1-((5-nitrobenz o[d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepin[5,6-c]pyrazol-6-yl)-3-phenylurea(8a):
Yield: 70%; M.p: 143-145°C; IR(KBr): 3215 (γ P-NH ), 3052(γ C=H ), 1663(NH-CO), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355&1330(-NO2), 1300(C=O-δC0 )1250(П=O), 954 cm-1 (П=O); H1-31MR(300MHz,DMSO-d6)-δ 4.99 ( s, 2H, -CH2-benzoxazole) 5.29 ( s, 4H, two CH2 groups attached to phosphorus moiety), 6.15(5,2H,-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 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 , 124.2 , 156.1 , 152.0 , 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 and C18; 131P NMR (161.89MHz, DMSO-d6)-δ -11.10, 1.36 ; Anal.Calcd (%) For C21H19N6O8P: 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 - (1- ((5-nitrobenz o[d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro -1H-[1,3,2] dioxaphosphepin[5,6-c]pyrazol-6-yl)-3-(p-toly l)urea(8c):
Yield: 75%; M.p: 164- 166°C; IR(KBr): 3210 (γ P-NH ), 3055(γ C=H ), 1668(NH-CO), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355&1330(-NO2), 1305(γC=O-δC0 )1245 (П=O), 950cm-1 (П=O); H1-MR(300MHz, DMSO-d6) δ 3.24(s,3H,CH3 of tolyloxy), 4.99 (s,2H,-N=CH2-benzoxazole), 5.29 (s,4H,two CH2 groups attached to phosphorus moiety), 6.15(5,2H,-NH-CO-NH attached to phosphorus moiety),7.21-7.56 (m, 6H,C6H5 ring attached to –NH –CO-NH- ), 7.30 (s,1H, CH of pyrazole ring). 8.05-8.26 (m,4H,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 , 124.2 , 156.1 , 152.0 , 139.5 , 124.3 , 121.5 , 129.8 , 136.8 and 21.20 corresponding to C1 ,  C2 ,  C3 ,  C4 ,  C5 ,  C6 ,  C7 ,  C8 ,  C9,  C10 ,  C11 ,  C12 ,  C13 ,  C14 ,  C15 ,  C16 & C20 ,  C17 & C19 and C18; 131P NMR (161.89MHz, DMSO-d6)-δ -11.53; Anal. Calcd (%) For C22H17N5O5P: C 56.11%, H 3.84 %, N 16.86 %, P 6.21% Found: C 49.91% , H 3.34 %, N 16.26 % and P 5.51 %.

1-(4-methoxy)-1-((5-nitrobenz o[d]oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepin[5,6-c]pyrazol-6-yl)morpholine-4-carboxamide (8e): N 16.34%, P 6.02% Found: C 48.28%, H 3.22%, N 15.74 % and P 5.32 %.

1-(4-chlorophenyl)-1-((5-nitrobenz o[d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepin[5,6-c]pyrazol-6-yl)morpholine-4-carboxamide (8e): N 16.34%, P 6.02% Found: C 48.28%, H 3.22%, N 15.74 % and P 5.32 %.

N - (1 - ((5-nitrobenz o[d] oxazol-2-yl)methyl) -6-oxido-4,8-dihydro -1H-[1,3,2] dioxaphospho[5,6-c] pyrazol-6-yl)morpholine-4-carboxamide (8e):
Yield: 65%; M.p: 192-194°C; IR(KBr): 3190 (γ P-NH ), 3068(γ C=H ), 1678 (-C=N-), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355&1330(-NO2), 1300(C=O-δC0 )1250(П=O), 954 (П=O)cm-1; H1-31MR(300MHz,DMSO-d6)-δ 3.31-3.65 (m, 8H of morpholine attached to –CO-NH-). 4.99 (s, 2H,-N=CH2-benzoxazole), 5.29 (s, 4H, two CH2 groups attached to phosphorus moiety), 6.15(s, 1H, CH of pyrazole ring). 7.30 (s, 1H, CH of pyrazole ring), 8.05-8.26 (m, 3H, of benzoxazole ring); 13C-NMR (75MHz,
N -((5 - nitrobenzo[d] oxazol - 2 - yl) methyl) - 6 - oxido - dihydro - IH -[1,3,2] dioxaphosphino[5,6-c]pyrazol - 6 - yl) pipеридине - 1 - карбоксамиде (8): Yield: 65%; M.p: 169-171°C; IR(KBr): 3220 (t(γNH)), 3055 (γCH). 2940&2985(Aliphatic γC-H ), 1690 (-CO-N=), 1455 & 1390(benzoxazole ring), 1375&1487(pyrazole ring), 1355& 1330(δC-δCδOδδ), 1245 (P=O), 950 (P-O) cm⁻¹; 1H-MR(300MHz,DMSO-d6): δ 1.53-3.77 (m, 10H of pipеридинеattached to -CO-NH), 4.99 (t,2H of benzoxazole), 5.29 (t,4H, two CH2 groups attached to phosphorus moiety). 5.61 (s,1H, CH of pyrazole ring), 7.30 (s, 1H, CH of pyrazole ring), 8.05-8.26 (m, 3H of benzoxazole ring). 13C-NMR(75MHz, DMSO-d6): 6.15 s, 1H of benzoxazole ring), 8.05-8.26 (m, 3H of benzoxazole ring). 13C-NMR(75MHz, DMSO-d6): δ 8.23; Anal.Calc(%) For C19H20N4O6P: 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 -((5 - nitrobenzo[d] oxazol - 2 - yl)methyl) - 6 - oxido - -dihydro - IH -[1,3,2] dioxaphosphino[5,6-c]pyrazol - 6 - yl) pipеридине - 1 - карбоксамиде (8g): Yield: 70%; M.p: 178-180°C; IR(KBr): 3217 (t(γNH)), 3070 (γCH). 2940&2985(Aliphatic γC-H ), 1680 (-CO-N=), 1455 & 1390(benzoxazole ring), 1375&1487(pyrazole ring), 1355& 1330(δC-δCδOδδ), 1257 (P=O), 958 (P-O) cm⁻¹; 1H-MR(300MHz,DMSO-d6): δ 2.26 (s, 3H-CH3 group of 4-methyl pipеридине), 4.99 (2H of benzoxazole), 5.29 (t,4H CH2 groups attached to phosphorus moiety). 6.15 (s, 1H, CH of benzoxazole ring), 7.30 (s, 1H, CH of pyrazole ring), 8.05-8.26 (m, 3H of benzoxazole ring). 13C-NMR(75MHz, DMSO-d6): δ 8.19; Anal. Calcd(%) For C19H20N4O6P: 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-IH-[1,3]dioxepino[5,6-c]pyrazol (10): Yield: 70%; M.p: 145-147°C; IR(KBr): 3052 (Ar-H), 2940 & 2985 (Aliphatic γC-H ), 1747, 1344,715 & 620 (benzothiazole ring), 1395 & 1370 ( t(C(CH3)3)), 1375-1487 Cm⁻¹ (pyrazole ring), 1355 & 1330 Cm⁻¹ ( -N=), 1140 cm⁻¹ (δC-O). 1H-NMR(300MHz,DMSO-d6): δ 1.27 (s, 6H, two geminal CH3 groups of acetyls), 4.63 (s, 4H, two CH2 groups of acetyls), 4.99 (s, 2H, N=CH2-benzothiazole), 7.30 (s, 1H of pyrazole ring), 7.53-8.18 ( m, 4H of benzothiazole ring). Anal.Calc(%) for C28H19N2O5S: 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°C; IR(KBr): 3520(γO-H, intermolecular H-bonding), 3052 (γCH). 2940 & 2895(Aliphatic γC-H ), 1747, 1344, 715 & 620 (benzothiazole ring), 1375-1487 (pyrazole ring) 1320 and 1040(νO-H/νC=O); 1H-NMR(300MHz,DMSO-d6): δ 3.65 (s, 2H, two -OH groups having Intermolecular H-bonding) 4.61(s,2H, CH2 groups of CH3OH,4.79(s,2H,-CH group of CH3OH) 4.99 (s, 2H, N=CH2-benzothiazole), 7.30 (s, 1H of pyrazole ring), 7.53-8.18 ( m, 4H of benzothiazole ring). Anal.Calc(%) for C28H19N2O5S: 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]-6-oxido-4,8-dihydro-IH-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6-yl)-3-pheny lurea (12a): Yield: 58%; M.p: 156-158°C; IR(KBr): 3317 (γP=O), 3052 (γCH). 2940&2895(Aliphatic γC-H ), 1656 (NH-CO) 1474,1344,715 &620 (benzothiazole ring), 1375&1487(pyrazole ring), 1250 (P=O), 954 cm⁻¹ (P-O); 1H-MR(300MHz,DMSO-d6): δ 1.49 (s, 2H, -NH-CH2-benzothiazole), 5.29 (t, 4H, two CH2 groups attached to phosphorus moiety), 6.15(S,2H-NH-CO-NH attached to phosphorus moiety), 7.19-7.43 (m, 5H of CH2 ring attached to -NH-CO-NH), 7.30 (s, 1H, CH of pyrazole ring), 7.53-8.13(m, 4H, of benzothiazole ring). 13C-NMR(75MHz, DMSO-d6): 135.2, 118.0, 141.0, 61.8, 60.7, 50.5, 163.5, 121.8, 124.5, 125.3, 121.6, 152.8, 152.4, 152.0, 139.4, 121.6, 128.9, 128.0 corresponding to C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C19, C18, 1H-NMR(161.89MHz, DMSO-d6): δ 11.20, 1.36; Anal.Calc(%) For C28H19N2O5P: 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%.
Yield: 65% ; M.p: 172-174 °C; IR(KBr): 3310 (γ(P=O)), 3055 (γ(C=H)), 1660 (N-H), 1474, 1434,715 & 620 (benzthiazole ring) ,1375&1487(pyrazole ring). 245(P=O), 950 cm⁻¹ (P=O); H¹-MR(300Hz,DMSO-d₆): δ 2.34(s,3H-CH₃ of group), 4.99(s, 2H, -N=CH₂-benzthiazole), 5.29 (s, 4H, two CH₂ groups attached to phosphorus moiety), 6.15 (s,2H-NH-CO-NH attached to phosphorus moiety). 7.21-7.56 m, 4H of C₆H₄ ring attached to -NH-CO-NH-), 7.30( s, 1H, CH of pyrazole ring), 7.53-8.18( m, 4H, of benzthiazol ring);¹³C-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, 158.8 and 55.8. corresponding to C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₁₀, C₁₁, C₁₂, C₁₃, C₁₄, C₁₅, C₁₆ & C₂₀, C₂₇ & C₁₉, C₁₈ and C₁₇;¹³P NMR (161.89MHz, DMSO-d₆): δ -11.48; Anal. Calcd (%) For C₄₁H₃₂N₂O₄P:S : 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-(benzo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepin-6-c[pyrazol-6-yl]-3-(4-methoxy phenyl)urea(12c):

Yield: 65% ; M.p: 182-184 °C; IR(KBr): 3320 (γ(P=O)), 3065 (γ(C=H)), 1670 (N-H), 1474, 1434,715 & 620 (benzthiazole ring) ,1375&1487(pyrazole ring). 1256 (P=O)956 cm⁻¹ (P=O); H¹-MR(300Hz,DMSO-d₆): δ 3.83(s,3H-CH₃ group), 4.99 ( s, 2H, -N=CH₂-benzthiazole ), 5.29 ( s, 4H, two CH₂ groups attached to phosphorus moiety), 6.15(s,2H-NH-CO-NH attached to phosphorus moiety).697-7.51 ( m, 4H of C₆H₄ ring attached to -NH-CO-NH-). 7.30( s, 1H, CH of pyrazole ring), 7.53-8.18( m, 4H, of benzthiazol ring);¹³C-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, 158.8 and 55.8. corresponding to C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₁₀, C₁₁, C₁₂, C₁₃, C₁₄, C₁₅, C₁₆ & C₂₀, C₂₇ & C₁₉, C₁₈ and C₁₇;¹³P NMR (161.89MHz, DMSO-d₆): δ -9.23; Anal. Calcd (%) For C₄₂H₃₄N₂O₄P:S : 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%.

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

Yield: 65% ; M.p: 194-196 °C; IR(KBr): 3325 (γ(P=O)), 3068 (γ(C=H)), 1654 (-C=O=N=), 1474,1434,715 & 620 (benzthiazole ring) ,1375&1487(pyrazole ring). 1259 (P=O) 961 cm⁻¹ (P=O);H¹-MR(300Hz,DMSO-d₆): δ 3.3 (t, 4H –CH₂- attached to Nitrogen of morphine ring, J=7.1 Hz, H-2¹, H-3²).3.60(t, 4H-CH₂- attached to oxygen of morphine ring, J=7.1 Hz, H-2¹, H-3²).4.99 (s, 2H, -N=CH₂-benzthiazole), 5.29 ( s, 4H, two CH₂ groups attached to phosphorus moiety). 6.15 (s,1H-C=O-NH attached to phosphorus moiety). 7.30( s, 1H, CH of pyrazole ring), 7.53-8.18( m, 4H, of benzthiazol ring);¹³C-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 C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₁₀, C₁₁, C₁₂, C₁₃, C₁₄, C₁₅, C₁₆ & C₂₀, C₂₇ & C₁₉ and C₁₈;¹³P NMR (161.89MHz,DMSO-d₆): δ -9.23; Anal. Calcd (%) For C₄₂H₃₄N₂O₄PS : 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]dioxaphosphepin-5,6-c[pyrazol-6-yl]-morpholine-4-carboxamide(12e):

Yield: 65% ; M.p: 185-187 °C; IR(KBr): 3315 (γ(P=O)), 3055 (γ(C=H)), 1658 (-C=O=N=), 1474,1434,715 & 620 (benzthiazole ring) ,1375&1487(pyrazole ring). 1259 (P=O) 963cm⁻¹ (P=O);H¹-MR(300Hz,DMSO-d₆): δ 1.53-3.77 (m, 10H of piperidine attached to -CO-NH-), 4.99 ( s, 2H, -N=CH₂-benzthiazole), 5.29 ( s, 4H, two CH₂ 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);¹³C-NMR(75MHz,
Yield: 65% ; M.p: 165-167

\[ \text{methylpiperazine-1-carboxamide(12g)} \]

51.4, 51.0 and 46.6 corresponding to C

\[ \text{MR(300Hz, DMSO-d}_6)\]

1474, 1344, 715 & 620 (benzthiazole ring) , 1375 & 1487 (pyrazole ring), 1246 (P=O & C

\[ \text{DMSO-d}_6)\]

\[ \text{δ}_{-\text{CH}_2-N-CH}_2- \text{attached to phosphorus moiety}, \text{5.29 ( s, 4H, two CH}_2 \text{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-}

\[ \text{8.18( m, 4H, of benzthiazol ring);} \]

\[ \text{121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 156.5 , 49.0 , 24.9 and 23.8 corresponding to C}\]

\[ \text{and C}_7\text{, C}_9\text{, C}_{10}\text{, C}_{11}\text{, C}_{12}\text{, C}_{13}\text{, C}_{14}\text{,C}_{15}\text{& C}_{19}\text{, C}_{16}\text{& C}_{17}; \text{Anal.Calcld(%) For C}_{19}\text{H}_{22}\text{N}_2\text{O}_5\text{PS: C} 49.35\%, \text{H} 5.01\%, \text{N} 18.17%, \text{P} 6.70%,\text{S} 6.93% \text{ Found: C} 48.55\%, \text{H} 4.51\%, \text{N} 17.57%,\text{P} 6.00%\text{ and S} 6.73%. \]

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 Cefactor are tested as reference compounds to compare the activity.

Antibacterial activity of 1-(1-(5-nitrobenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino [5,6-c]pyrazol-6yl)-4-
methylpiperazine-1-carboxamid(12g):

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<th>COMPOUND (8)</th>
<th>R</th>
<th>X</th>
<th>Staphylococcus aureus NCCS2079 250(µg/disc)</th>
<th>Bacillus Cerus NCCS2106 250(µg/disc)</th>
<th>Escherichia Coli NCCS2065 250(µg/disc)</th>
<th>Pseudomonas aeruginosa NCCS2200 250(µg/disc)</th>
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<tbody>
<tr>
<td>8a</td>
<td>-H</td>
<td>-</td>
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<td>6</td>
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<tr>
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<td>-</td>
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<tr>
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<td>-</td>
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<tr>
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<td>11</td>
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</tr>
<tr>
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<td>-N-CH3</td>
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<td>13</td>
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</tr>
<tr>
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<tr>
<td>8i</td>
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"-" 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-6-yl)-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):

<table>
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<tr>
<th>COMPOUND (12)</th>
<th>R</th>
<th>X</th>
<th>Zone of inhibition (mm)</th>
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<td></td>
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<td></td>
<td>Staphylococcus aureus NCCS2079 250(µg/disc)</td>
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<td>12a</td>
<td>-H</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>12b</td>
<td>-CH3</td>
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<td>-CH3</td>
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</tr>
<tr>
<td>12i</td>
<td>Cefaclor</td>
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"_" indicates no activity.

Antifungal activity:
The antifungal activity of final compounds 8a-g synthesized was screened against Aspergillus niger, Candida 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-nitrobenzo[d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5.6-c]pyrazol-6-yl)-3(phenyl/p-tolyl/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/piperidine/4-methyl piperazine carboxamides (8e-g):

<table>
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<th>COMPOUND (8)</th>
<th>R</th>
<th>X</th>
<th>Zone of inhibition (mm)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Aspergillus niger NCCS 1196 250(µg/disc)</td>
</tr>
<tr>
<td>8a</td>
<td>-H</td>
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<tr>
<td>8b</td>
<td>-CH3</td>
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<td>8c</td>
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<td>-N-CH2</td>
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<td>8h</td>
<td>Ketoconazole</td>
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"_" 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-6-yl)-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):

<table>
<thead>
<tr>
<th>COMPOUND (12)</th>
<th>R</th>
<th>X</th>
<th>Zone of inhibition (mm)</th>
</tr>
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<td></td>
<td></td>
<td>Aspergillus niger NCCS 1196 250(µg/disc)</td>
</tr>
<tr>
<td>12a</td>
<td>-H</td>
<td>-</td>
<td>06</td>
</tr>
<tr>
<td>12b</td>
<td>-CH3</td>
<td>-</td>
<td>05</td>
</tr>
<tr>
<td>12c</td>
<td>-OCH3</td>
<td>-</td>
<td>05</td>
</tr>
<tr>
<td>12d</td>
<td>-Cl</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>12e</td>
<td>-O</td>
<td>-</td>
<td>19</td>
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<tr>
<td>12f</td>
<td>-CH3</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>12g</td>
<td>-N-CH2</td>
<td>-</td>
<td>16</td>
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<tr>
<td>12h</td>
<td>Ketoconazole</td>
<td>-</td>
<td>22</td>
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"_" indicates no activity.

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