Synthesis, characterization and antimicrobial evaluation of novel compounds
1(-benzo[d]oxazol/thiazol-2-yl)-methyl-6-phenoxy-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide

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ABSTRACT

New novel derivatives of 1-(5/6-mono substituted or 5,6-disubstituted benzo [d] oxazol-2-yl) methyl)-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino [5,6-d] imidazole-6-oxide (8a-f as per Scheme-1) were prepared by condensation of 4-substituted phenyl phosphorodichloridates (7a-f) with 1-(5/6-mono substituted or 5,6-disubstituted benzo [d] oxazol-2-yl)methyl -1H-imidazole-4,5-diyl dimethanol (6a-f). The synthons (6a-f) obtained by deprotection of isopropylidene of 1-(5/6-mono substituted or 5,6-disubstituted benzo [d] oxazol-2-yl) methyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (5a-f). The synthons (5a-f) were obtained by the reaction of 2-(6,6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole-1-yl) acetic acid (3) with 4/5 mono substituted or 4,5-di substituted 2-amino phenols (4a-f). Similar procedure was adapted to prepare 1-(benzo [d] thiazol-2-yl) methyl )-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (12a-f according to Scheme-2).

Key words: Benzodioxaphospholes, imidazole, cyclization, 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 and 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-HIV [9], anti-cancer [10], anti-viral and anti-inflammatory [11].

Benzoxazole and benzthiazoles nuclei are constituent of many of the bioactive heterocyclic compounds that exhibit antiangial, antiischaemic, vasodilator, anti-diabetic, anti-microbial, cardiovascular, tranquilizer and virucidal activities [12-21].

In support of our study, imidazoles are also an interesting group of compounds, many of which possess anti-fungal activity [22], anti-bacterial, monoamine oxidase (MAO) inhibitory activity [23], antiparkinson [24], anticonvulsant [25], it also function as dyestuff, catalyst, polymerizing agents, drugs, herbicides and fungicides [26]. Imidazole derivatives are valuable vasodialating and vasoconstrcuting drugs.

A good deal of importance was given to 1, 3, 2-Dioxaphosphorinane and dioxaphospholane derivatives [27] in the field of organophosphorus heterocyclic chemistry due to their unique stereo chemical futures and diverse potential biological applications [28]. In view of the above observations, we have synthesized imidazole derivatives
possessing Benzoxazole / Benzthiazole moiety besides 1, 3, 2-Dioxaphosphorinane and dioxaphospholanes and screening for possible biological and pharmacological activities.

EXPERIMENTAL SECTION

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 aluminium sheet of silica gel 60F_{254}, E-Merk, Germany using iodine as visualizing agent. Melting point were determined in open capillary tubes on Mel-Temp apparatus and are 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 1H and 13C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHz for 1H-NMR and 75 MHz for 13C-NMR. 31P-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 (1H and 13C-NMR) and 85% H_{3}PO_{4} (31P-NMR). Mass spectral data was recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis were recorded on a Carlo Erba 1108 elemental Analyser, Central Drug Research Institute, Lucknow, India.

Preparation of Intermediates:

4-substituted phenyl phosphorodichloridates (7a-f) [29, 30]:

Phosphorus oxy chloride (15.3 gr, 0.1mole) in dry benzene (60 ml) was taken in to three-necked flask (500 ml) equipped with dropping funnel and reflux condenser fitted with a calcium chloride guard tube. The flask was heated under reflux for 1.5 hours with stirring at 140°C. This was collected by filtration and recrystallized from ethanol. The structure of (2) was established by IR, 1H-NMR and elemental analysis

Typical procedure for the synthesis of 2-(6, 6-dimethyl-4,8-dihydro -1H-[1,3] dioxepino [5,6-d] imidazole-1-yl) acetic acid (3):

A suspension of 1-H-Imidazole-4, 5-dimethanol (1Mmole) 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-Imidazole-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_{2}SO_{4} and evaporated to get the crude product (2) [35], which was recrystallized by dissolving in boiling ether(5ml/g), cooling and then adding hexaner(5ml/g) to give the pure product (2). The structure of (2) was established by IR, 1H-NMR and elemental analysis

A mixture of 6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-d] imidazole (2), anhydrous K_{2}CO_{3} chloroacetic 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 2-(6, 6-dimethyl-4,8-dihydro-1H-[1,3] dioxepino [5,6-d] imidazole-1-yl) acetic acid (3). This was collected by filtration and recrystallized from ethanol. The structure of (3) was established by IR, 1H-NMR and elemental analysis.

Typical procedure for 1- (5/6- mono substituted or 5,6-di substituted benzo[d] oxazol-2-yl-methyl)-6,6-dimethyl-4,8-dihydro -1H-[1,3] dioxepino [5,6-d] imidazol [36-38](5a-f):

A mixture of 0.1 mole 2-(6,6-dimethyl-4,8-dihydro-1H-[1,3] dioxepino[5,6-d] imidazole-1-yl) acetic acid (1) and 0.1 mole of 2-aminophenol (4a) was heated under reflux for 1.5 hours with stirring at 140°C. The progress of the
reaction was monitored by TLC using cyclohexane and ethylacetate (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. The organic layer was separated and aqueous solution extracted with CHCl$_2$ (3×25 ml). The combined extracted were dried on Na$_2$SO$_4$. After filtration, the solvent was removed with rota 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 1-(benzo [d] oxazol-2-yl-methyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (5a) was recrystallised from aqueous dimethyl formamide.

The similar procedure was employed for the synthesis of 1-(5/6-mono substituted or 5,6-di substituted benzo [d] oxazol-2-yl-methyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (5b-f), by condensing 2-(5,6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole-1-yl) acetic acid (3) with 5-nitro aminophenol (4b) / 6-nitro aminophenol (4c) / 5,6-dinitro aminophenol (4d) / 5-chloro aminophenol (4e) / 5-chloro,6-nitro aminophenol (4f). The structure of (5a-f) was established by IR, $^1$H-NMR and elemental analysis.

**Typical procedure for the synthesis of 1-(5/6-mono substituted or 5,6-di substituted -1H-benzo [d] oxazol-2-yl methyl) -1H-imidazole-4, 5-diyli dimethanol (6a-f):**

The isopropylidenation of 1,2-diols was carried out by a procedure as reported in the literature [39]. A suspension of the 1-(1H-benzo[d] oxazol-2-yl) methyl)-6, 6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (5a) (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. At the end of 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 (6a). 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 similar procedure was adopted to synthesise (6b-f) from (5b-f). The structure of (6a-f) was established by IR, $^1$H-NMR and elemental analysis.

**Typical procedure for the synthesis of 1-(5/6-mono substituted or 5,6-di substituted benzo [d] oxazol-2-yl methyl)-6-(4-sulfamoylphenoxy)-4,8-dihdyro-1H-[1,3,2] dioxaphosphino[5,6-d] imidazole-6-oxide (8a-f):**

A solution of phenylphosphorodichloridate (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 1-(benzo [d] oxazol-2-yl) methyl)-1H- imidazole-4,5-diyl) dimethanol (6a) (0.002 mole) and triethylamine (0.004 mole) 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 2 hours. Later the reaction mixture was heated to 50-60°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 [40] of 1(benzo [d] oxazol-2-yl - methyl) - 6- phenoxy-4,8-dihydro-1H-[1,3]- dioxepino [5,6-d] imidazole (8a).

The similar procedure was adopted to synthesise (8b-f) by the reaction between (6b-f) with 4-methyl phenyl phosphorodichloridate (7b), 4-methoxy phenyl phosphorodichloridate (7c), 4-chloro phenyl phosphorodichloridate (7d), 4-bromo phenyl phosphorodichloridate (7e), 4-nitro phenyl phosphorodichloridate (7f).

The structures of these newly synthesized compounds (8a-f) were characterized by their elemental analysis and spectral data (IR, $^1$H-NMR, $^{13}$C-NMR, $^{31}$P-NMR and Mass).

**Typical procedure for the synthesis of 1- (benzo[d] thiazol-2-yl-methyl)-6,6-dimethyl-4,8-dihydro -1H-[1,3] dioxepino [5,6-d] imidazol (10):**

A mixture of 0.1 mole 2-(6, 6-dimethyl-4,8-dihydro-1H-[1, 3] dioxepino[5,6-d] imidazole-1-yl) acetic acid (3) and 0.1 mole of 2-aminobenzenethiol (9) was heated under reflux for 1.5 hours with stirring at 140°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. The organic layer was separated and aqueous solution extracted with CHCl$_3$ (3×25 ml). The combined extracted were 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 1-(benzo [d] thiazol-2-yl-methyl)-6, 6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (10) [36-
Typical procedure for the synthesis of 1-(benzo [d] thiazol-2-yl methyl) -1H-imidazole-4,5-diyl) dimethanol (11):
The isopropylidenation of 1, 2-diols was carried out by a procedure as reported in the literature [39]. A suspension of the 1-(benzo[d] thiazol-2-yl) methyl)-6,6-dimethyl-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (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 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 (11) was established by IR, 1H-NMR and elemental analysis.

Typical procedure for the synthesis of 1-(benzo [d] thiazol-2-yl -methyl) - 6-(4-substituted-phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (12a-f):
A solution of phenylphosphorodichloridate (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 1-(benzo [d] thiazol-2-yl ) methyl) -1H- imidazole-4,5-diy1 ) 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 2 hours. Later the reaction mixture was heated to 50-60°C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. 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(benzo [d] thiazol-2-yl - methyl) - 6-(4-substituted) phenoxy-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (12a) [40].

The similar procedure was adopted to synthesis (12b-f) by the reaction between (11) with 4-methyl phenyl phosphorodichloridate (7b), 4-methoxy phenyl phosphorodichloridate (7e), 4-chloro phenyl phosphorodichloridate (7d), 4-bromo phenyl phosphorodichloridate (7e), 4-nitro phenyl phosphorodichloridate (7f).

The structures of these newly synthesized compounds (12a-f) were characterized by their elemental analysis and spectral data (IR, 1H-NMR, 13C-NMR, 31P-NMR and Mass).
Physical, analytical and spectral data for the compounds:

2-(6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-d] imidazole-1-yl) acetic acid (3):
Yield: 78%; M p: 174\(^{\circ}\)C; IR (KBr): 2950 (OH stretching of COOH), 2940 and 2895 (CH\(_2\) and CH\(_3\) aliphatic –CH stretching), 1690 (carbonyl group of COOH), 1478 & 1366 (characteristic of imidazole ring), 1360 & 1380 (bending vibration of C (CH\(_3\)) and 1140 \(cm^{-1}\) C-O, stretching vibrations). \(^1\)H NMR (400MHz, DMSO-d6): \(\delta\) 1.27 (s, 6H, two geminal CH\(_3\) groups), 4.57 (s, 2H, two CH\(_2\) of –CH\(_2\)COOH group), 7.57 (s, 1H of imidazole ring) and 11.0 (s, 1H, –COOH group). Anal.Calcd.For C\(_{10}\)H\(_9\)N\(_2\)O\(_3\): C 56.68%, H 7.13% and N 11.02%; Found: C 55.88%, H 6.63% and N 10.42%.

1-(benzo [d] oxazol-2-yl) methyl]-6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] - dioxepino [5, 6-d] imidazole (5a):
Yield: 70%; M p: 158-160\(^{\circ}\)C; IR (KBr): 3052 (Ar-H stretching), 2940 & 2895 (CH\(_2\) and CH\(_3\) aliphatic C-H stretching), 1478 & 1366 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoazole), 1360 & 1380 (bending vibration of C (CH\(_3\)) and 1140 \(cm^{-1}\) C-O stretching). \(^1\)H NMR (400MHz, DMSO-d6): \(\delta\) 1.27 (s, 6H, two geminal CH\(_3\) groups), 4.57 (s, 4H, two CH\(_2\) groups of acetals), 4.99 (s, 2H, N-CH\(_2\)-benzoazole ), 7.57 (s, 1H of imidazole ring) and 7.39-7.74 ( m, 4H of benzoazole ring). Anal.Calcd.For C\(_{16}\)H\(_{17}\)N\(_2\)O\(_3\): C 64.24%, H 5.7% and N 14.04%; Found: C 63.44%, H 5.2% and N 13.44%.

6, 6-dimethyl-1-(6-nitro benzo [d] oxazol-2-yl) methyl]-4, 8-dihydro-1H-[1, 3] - dioxepino [5, 6-d] imidazole (5b):
Yield: 75%; M p: 182-184\(^{\circ}\)C; IR (KBr): 3020 (Ar-H stretching), 2940 & 2895 (CH\(_2\) and CH\(_3\) aliphatic C-H stretching), 1470 & 1360 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoazole), 1360 & 1380 (bending vibration of C (CH\(_3\)) and 1355-1330 (NO\(_2\) stretching) and 1145 \(cm^{-1}\) (C-O stretching). \(^1\)H NMR (400MHz, DMSO-d6): \(\delta\) 1.27 (s, 6H, two geminal CH\(_3\) groups), 4.57 (s, 2H, two CH\(_2\) groups of acetals), 4.99 (s, 2H, N-CH\(_2\)-benzoazole), 7.57 (s, 1H of imidazole ring) and 7.88-8.43 (m, 3H of benzoxazole ring). Anal.Calcd.For C\(_{16}\)H\(_{16}\)N\(_4\)O\(_5\): C 55.81%, H 4.6% and N 16.27% Found; C 55.01%, H 4.1% and N 15.67%.
6, 6-dimethyl-1-((5-nitro benzo [d] oxazol-2-yl) methyl) -4, 8-dihydro-1H-[1, 3]- dioxepino [5, 6-d] imidazole (5c):
Yield: 75%; M p: 172-174°C; IR (KBr): 3035 (Ar-H stretching), 2940 & 2895 (CH₂ and CH₃ aliphatic C-H stretching), 1472 & 1365(bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole), 1360 & 1380 (bending vibration of C (CH₂)₃), 1355-1330 (NO₂ stretching) and 1145 cm⁻¹ (C-O stretching). ¹H NMR (400MHz, DMSO-d₆): δ 2.17 (s, 6H, two geminal CH₂ groups), 4.57 (s, 2H, CH₂ groups of acetals), 4.99 (s, 2H, N-CH₂-benzoxazole), 7.57 (s, 1H of imidazole ring) and 8.05-8.26(m, 3H of benzoxazole ring). Anal.Calcd.For C₁₆H₁₆N₂O₅: C 55.81%, H 4.6% and N 16.27% Found; C 55.01%, H 4.1% and N 15.67%.

6, 6-dimethyl-1-(5, 6-dinitro benzo [d] oxazol-2-yl) methyl) -4, 8-dihydro-1H-[1, 3]- dioxepino [5, 6-d] imidazole (5d):
Yield: 80%; M p: 204-206°C; IR (KBr): 3045 (Ar-H stretching), 2940 & 2895 (CH₂ and CH₃ aliphatic C-H stretching), 1488 & 1375(bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole), 1360 & 1380 (bending vibration of C (CH₂)₃), 1355-1330 (NO₂ stretching) and 1148 cm⁻¹ (C-O stretching). ¹H NMR (400MHz, DMSO-d₆): δ 1.27 (s, 6H, two geminal CH₂ groups), 4.58 (s, 2H, CH₂ groups of acetals), 4.99 (s, 2H, N-CH₂-benzoxazole), 7.57 (s, 1H of imidazole ring) and 8.35-8.45 (m, 2H of benzoxazole ring). Anal.Calcd.For C₁₆H₁₆N₂O₅: C 49.36%, H 3.8% and N 17.99% Found; C 48.56%, H 3.3% and N 17.39%.

6, 6-dimethyl-1-((5-chloro benzo [d] oxazol-2-yl) methyl) -4, 8-dihydro-1H-[1, 3]- dioxepino [5, 6-d] imidazole (5f):
Yield: 70%; M p: 158-160°C; IR (KBr): 3045 (Ar-H stretching), 2940 & 2895 (CH₂ and CH₃ aliphatic C-H stretching), 1472& 1365 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole), 1360 & 1380 (bending vibration of C (CH₂)₃), 1146 (C-O stretching) and 725 cm⁻¹ (Cl stretching). ¹H NMR (400MHz, DMSO-d₆): δ 1.27 (s, 6H, two geminal CH₂ groups), 4.57 (s, 2H, two CH₂ groups of acetals), 4.99 (s, 2H, N-CH₂-benzoxazole), 7.57 (s, 1H of imidazole ring) and 7.49-7.81 (m, 3H of benzoxazole ring). Anal.Calcd.For C₁₆H₁₂ClN₂O₅: C 57.58%, H 4.8%, Cl 10.62%, and N 12% Found; C 56.78%, H 4.3% and Cl 9.62.

6, 6-dimethyl-1-((5-chloro 6-nitro benzo [d] oxazol-2-yl) methyl) -4, 8-dihydro-1H-[1, 3]- dioxepino [5, 6-d] imidazole (5g):
Yield: 75%; M p: 158-160°C; IR (KBr): 3055 (Ar-H stretching), 2940 & 2895 (CH₂ and CH₃ aliphatic C-H stretching), 1472 & 1365 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole), 1360 & 1380 (bending vibration of C (CH₂)₃), 1355 & 1330 (NO₂ stretching) and 1145 cm⁻¹ (C-O stretching). ¹H NMR (400MHz, DMSO-d₆): δ 1.27 (s, 6H, two geminal CH₂ groups), 4.56 (s, 2H, two CH₂ groups of acetals), 4.99 (s, 2H, N-CH₂-benzoxazole), 7.57 (s, 1H of imidazole ring) and 8.05-8.13(m, 2H of benzoxazole ring). Anal.Calcd.For C₁₆H₁₂ClN₂O₅: C 50.74%, H 3.9%, Cl 9.36% and N 14.7% Found; C 49.9% Cl 8.56% and N 14.1%.

(1-benzo [d] oxazol-2-yl methyl)-1H-imidazole-4, 5-diyl) dimethanol (6a):
Yield: 76%; M p: 178-180°C; IR (KBr): 3520 (υO-H, intramolecular H-bonding), 3052 (Ar-H stretching), 2940 & 2895 (CH₂ aliphatic C-H stretching), 1478 & 1366 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole ring) and 1140 cm⁻¹ (C-O stretching). ¹H NMR (400MHz, DMSO-d₆): δ 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding) 4.73 (s, 4H, two CH₂ groups of dimethanols), 4.99 (s, 2H, N-CH₂-benzoxazole), 7.57 (s, 1H of imidazole ring) and 7.89-8.43 (m, 3H of benzoxazole ring). Anal.Calcd.For C₁₆H₁₆N₂O₅: C 60.22%, H 5.0% and N 16.21% Found; C 59.82%, H 4.4% and N 15.61%.

(1-((6-nitro benzo [d] oxazol-2-yl) methyl)-1H-imidazole-4, 5-diyl) dimethanol (6b):
Yield: 75%; M p: 183-185°C; IR (KBr): 3515 (υO-H, intramolecular H-bonding), 3015 (Ar-H stretching), 2940 & 2895 (CH₂ aliphatic C-H stretching), 1470 & 1360 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole ring), 1355 & 1330 (NO₂ stretching) and 1145 cm⁻¹ (C-O stretching). ¹H NMR (400MHz, DMSO-d₆): δ 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding) 4.73 (s, 4H, two CH₂ groups of dimethanols), 4.99 (s, 2H, N-CH₂-benzoxazole), 7.57 (s, 1H, of imidazole ring) and 7.89-8.43 (m, 3H of benzoxazole ring). Anal.Calcd.For C₁₆H₁₂N₂O₅: C 51.2%, H 3.98% and N 18.41% Found; C 50.4%, H 3.48% and N 17.81%.

(1-((5-nitro benzo [d] oxazol-2-yl) methyl)-1H-imidazole-4, 5-diyl) dimethanol (6c):
Yield: 75%; M p: 172-174°C; IR (KBr): 3525 (υO-H, intramolecular H-bonding), 3030 (Ar-H stretching), 2940 & 2895 (CH₂ aliphatic C-H stretching), 1473 & 1365 (bending vibrations, characteristic of imidazole ring), 1455 &
Yield: 70%; M p: 173-175°C; IR (KBr): 3530 (νO-H, intramolecular H-bonding), 3030 (Ar-H stretching), 2940 & 2895 (CH2 aliphatic C-H stretching), 1473 & 1365 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole ring), 1148 (C-O stretching) and 725 cm⁻¹ (Cl stretching).

1H NMR (400MHz, DMSO-d6): δ 4.99 (s, 2H, N-CH2-benzoxazole), 7.57 (s, 1H of imidazole ring) and 7.49-7.81 (m, 3H of benzoxazole ring).

Anal.Calcd. For C19H15ClN3O4: C 52.64%, H 3.75%, N 12.28% and P 6.7%.

Yield: 75%; M p: 155-157°C; IR (KBr): 3052 (Ar-H stretching), 2940 & 2895 (CH2 aliphatic C-H stretching), 1475 & 1360 (bending vibrations, characteristic of benzoxazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole ring), 1550 & 1330 (NO2 stretching), 1305 (γC=O / δC=O), 1245 (γP=O) and 950 cm⁻¹(γP=O;C=arom).1H NMR (400MHz, DMSO-d6): δ 4.99 (s, 2H, N-CH2-benzoxazole), 5.23 (s, 4H, two CH2 groups attached to phosphorus moiety), 7.18-7.28 (m, 5H of benzoxazole ring), 7.39-7.74(m, 4H of benzoxazole ring).

Anal.Calcd. For C19H15NO4P: C 56.64%, H 3.55%, N 9.98% and P 6.38% Found; C 57.44%, H 4.0%, N 10.58% and P 7.0%.

Yield: 75%; M p: 142-144°C; IR (KBr): 3065 (Ar-H stretching), 2940 & 2895 (CH2 aliphatic C-H stretching), 1478 & 1366 (bending vibrations, characteristic of benzoxazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole ring), 1550 & 1330 (NO2 stretching), 1305 (γC=O / δC=O), 1245 (γP=O) and 950 cm⁻¹(γP=O;C=arom).1H NMR (400MHz, DMSO-d6): δ 4.99 (s, 2H, N-CH2-benzoxazole), 5.23 (s, 4H, two CH2 groups attached to phosphorus moiety), 6.83-7.06 (m, 4H of phenoxy group), 7.57 (s, 1H, CH of benzoxazole ring) and 7.88-8.34 (m, 3H of benzoxazole ring).

Anal.Calcd. For C31H17N5O5P: C 51.84%, H: 3.25%, N 11.68% and P 6.09% Found; C 52.64, H 3.75%, N 12.28% and P 6.7%.
6-((4-chloro phenoxy)-1-(6-(5-chloro benzo[d]oxazol-2-yl)methyl)-4,8-dihydro-1H-[1,3,2]dioxaphosphepin [5,6-d]imidazole-6-oxide (8e):

Yield: 70%; M p 144-146°C; IR (KBr): 3052 (C-O stretching), 1740 & 1356 (bending vibrations, characteristic of benzoxazole ring), 1550 & 1330 (NO\textsubscript{2} stretching). \textsuperscript{1}H NMR (400MHz, DMSO-d\textsubscript{6}): δ 4.99 (s, 2H, -N-CH\textsubscript{2} groups attached to phosphorus moiety), 6.89-7.32 (m, 4H of phenoxy group), 7.57 (s, 1H, CH of imidazole ring) and 8.35-8.45 (m, 2H, of benzoxazole ring). Anal.Calcd.For C\textsubscript{19}H\textsubscript{14}ClBrN\textsubscript{2}O\textsubscript{5}: C 43.74%, H 2.51%, Cl 6.79%, N 12.7% and P 5.94%. Found: C 43.74%, H 2.5%, Cl 6.79%, N 12.7% and P 5.94%.

6-((5,6-dinitro benzo[d]oxazol-2-yl)methyl)-4,8-dihydro-1H-[1,3,2]dioxaphosphepin [5,6-d]imidazole-6-oxide (8f):

Yield: 70%; M p 132-134°C; IR (KBr): 3052 (C-O stretching), 1740 & 1356 (bending vibrations, characteristic of benzoxazole ring), 1550 & 1330 (NO\textsubscript{2} stretching). \textsuperscript{1}H NMR (400MHz, DMSO-d\textsubscript{6}): δ 4.99 (s, 2H, -N-CH\textsubscript{2} groups attached to phosphorus moiety), 6.89-7.43 (m, 4H of phenoxy group), 7.57 (s, 1H, CH of imidazole ring) and 7.49-7.81 (m, 2H of benzoxazole ring). Anal.Calcd.For C\textsubscript{19}H\textsubscript{14}ClN\textsubscript{2}O\textsubscript{6}: C 43.89%, H 2.26%, Cl 6.1%, N 7.63% and P 5.37%. Found: C 44.69%, H 2.7%, Br 15.65%, N 6.9% and P 6.07%.

1-((5-chloro benzyl) methyl) -1H-imidazole-4,5-diyl) dimethanol (11):

Yield: 70%; M p 153-155°C; IR (KBr): 3052 (Ar-H stretching), 1471& 1536 (bending vibrations, characteristic of imidazole ring), 1455 & 1390 (bending vibrations, characteristic of benzoxazole ring), 1310 (ν\textsubscript{C=O} / δ\textsubscript{C-O}), 1241 (γ\textsubscript{C-O(Carom)}), 961 (γ\textsubscript{P-O(Carom)}) and 725 cm\textsuperscript{-1} (Cl stretching). \textsuperscript{1}H NMR (400MHz, DMSO-d\textsubscript{6}): δ 4.49 (s, 2H, N-CH\textsubscript{2} groups having Intramolecular H-bonding), 4.73 (s, 4H, two CH\textsubscript{2} groups of acetals), 4.99 (s, 2H, N-CH\textsubscript{2}benzthiazole), 5.75 (s, 1H, CH of imidazole ring) and 7.53-8.18 (m, 4H of benzthiazole ring). Anal.Calcd.For C\textsubscript{16}H\textsubscript{18}ClN\textsubscript{2}O\textsubscript{2}: C 60.93%, H 5.43%, N 13.32% and S 10.1% Found: C 60.13%, H 4.93%, N 12.8% and S 9.97%.

1-(benzo[d]thiazol-2-yl) methyl)-1H-imidazole-4,5-diyl dimethanol (11):

Yield: 70%; M p 155-157°C; IR (KBr): 3520 (Ar-H stretching), 1748 & 1366 (bending vibrations, characteristic of imidazole ring), 1474, 1344, 715 & 620 (bending vibrations, characteristic of benzothiazole), 1360 & 1380 (bending vibration of CH\textsubscript{2} groups of dimethanols), 4.99 (s, 2H, -NCH\textsubscript{2}benzthiazole), 5.75 (s, 1H, CH of imidazole ring) and 7.53-8.18 (m, 4H of benzthiazole ring). Anal.Calcd.For C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}: C 60.13%, H 4.93%, N 13.12% and S 9.97%.

1-(benzo[d]thiazol-2-yl) methyl)-1H-imidazole-4,5-diyl dimethanol (11):

Yield: 70%; M p 155-157°C; IR (KBr): 3520 (ν\textsubscript{O-H}, intramolecular H-bonding), 3052 (Ar-H stretching), 2940 & 2895 (CH\textsubscript{2} aliphatic C-H stretching), 1478 & 1366 (bending vibrations, characteristic of imidazole ring), 1474 , 1344, 715 & 620 (bending vibrations, characteristic of benzothiazole), 1360 & 1380 (bending vibration of CH\textsubscript{2} groups of dimethanols), 4.99 (s, 2H, -NCH\textsubscript{2}benzthiazole), 5.75 (s, 1H, CH of imidazole ring) and 7.53-8.18 (m, 4H of benzthiazole ring). Anal.Calcd.For C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}: C 56.71%, H 4.76%, N 15.26% and S 11.6% Found: C 55.91%, H 4.26%, N14.66% and S11.45%.
Yield: 65%; M p 157-158°C; IR (KBr): around 3051 (Ar-H stretching), 1480 & 1369 (bending vibrations, characteristic of imidazole ring), 1474 , 1344, 715 & 620 (bending vibrations, characteristic of benzthiazole), 1300 ( δ C=O / δ C-O), 1241(γ P=O) and 861 cm⁻¹(γ P-O-C(arom)). ¹H NMR (400MHz, DMSO-d6): δ 4.99 (s, 2H, N-CH₂-benzthiazole), 5.23 (s, 4H, two CH₂ groups attached to phosphorus moiety), 6.84-7.53 (m, 4H of phenoxy group), 7.47(s, 1H, CH of imidazole ring) and 7.53-8.18 (m, 4H of benzthiazol). Anal.Calcd.For C₁₉H₁₉BrN₂O₂PS: C 46.36%, H 3.07%, Br 16.23%, N 8.54%, P 6.29% and S 6.51% Found; C 45.56%, H 2.57%, Br 15.63%, N 7.94%, P 5.59% and S 6.31%.

1-(benzo[d]thiazol-2-yl) methyl -6-(4-nitrophenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepine [5, 6-d] imidazole-6-oxide (12d): Yield: 65%; M p 124-126°C; IR (KBr): around 3068 (Ar-H stretching), 1471 & 1356 (bending vibrations,characteristic of imidazole ring), 1474 , 1344, 715 & 620 (bending vibrations, characterestic of benzthiazole), 1550 &1330 (NO₂ stretching), 1300 (γ C=O / δ C-O), 1245(γ P=O) and 950 cm⁻¹(γ P-O-C(arom)). ¹H NMR (400MHz, DMSO-d6): δ 4.99 (s, 2H, N-CH₂-benzthiazole), 5.23 (s, 4H, two CH₂ groups attached to phosphorus moiety), 7.57(s, 1H, CH of imidazole ring) and 7.47-8.09 (m, 4H of phenoxy group) and 7.53-8.18(m,4H of benzthiazol). Anal.Calcd.For C₁₉H₁₇N₂O₂PS: C 49.78%, H 3.30%, N 12.22%, P 5.94% and S 7.00% Found; C 48.98%, H 2.80%, N 11.62%, P 5.24% and S 6.80%.

**Biological activity**

The antimicrobial activity [41] of these newly synthesized compounds was performed according to disc diffusion method, as recommended by the National Committee for Clinical Laboratory [42]. The synthesised compounds were used at the concentration of 250µg/ml DMF as a solvent [43].
Antibacterial activity
The antibacterial activity [44] of 1(5/6- mono substituted or 5,6-di substituted benzo [d] oxazol-2-yl - methyl ) - 6-(4- substituted-phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepinolo [5,6-d] imidazole-6-oxide (8a-f) were screened against the Staphylococcus aureus (gram positive), Bacillus cereus, Escherichia coli (gram negative) and Pseudomonos aeruginosa organisms. The benzo[d]-oxazoles (8d-f) shown more activity, while (8a-c) exhibited low activity. The antibacterial activity of (8a-f) was shown in the (Table 1).

The similar results were also noticed with the benzo[d]-thiazole possessing chloro (12d), bromo (12e) and nitro (12f) exhibit high anti-bacterial activity, when compared to compounds (12a-c). Here Amoxicillin and Cefaclor are tested as reference compounds to compare the activity. The antibacterial activity of benzo[d]-thiazole (12a-f) was shown in the (Table 2).

Table 1: Antibacterial activity of 1-(5/6- mono substituted or 5,6-disubstituted benz [d] oxazol-2-yl methyl) - 6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepinolo [5,6-d] imidazole-6-oxide (8a-f)

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Table 2: Antibacterial activity of 1-(benzo [d] thiazol-2-yl) methyl)-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepinolo [5,6-d] imidazole-6-oxide (12a-f)

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Antifungal activity
Antifungal activity of final compounds 1- (5/6-mono substituted or 5,6-disubstituted benz [d] oxazol-2-y1 ) methyl)- 6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepinolo [5,6-d] imidazole-6-oxide (8a-f) were screened against Aspergillus niger, Helminthosporium Oryzae. The compounds (8d-f) showed more fungal activity, while (8a-c) exhibited low activity. The fungal activity of benzo[d]-oxazole (8a-f) was shown in the (Table 3). The similar results were also noticed with 1-( benzo [d] thiazol-2-yl ) methyl ) - 6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepinolo [5,6-d] imidazole-6-oxide (12a-f) under given experimental conditions. The fungal activity of (12a-f) was shown in the (Table 4). Here Griseofulvin [45-47] is tested as reference compound to compare the activity.

Table 3: Antifungal activity of 1-(5/6-mono substituted or 5,6-disubstituted benz [d] oxazol-2-y1 ) methyl)- 6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepinolo [5,6-d] imidazole-6-oxide (8a-f)

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Table 4: Antifungal activity of 1-(benzo [d] thiazol-2-yl) methyl) -6-(4-substituted phenoxy)-4, 8-dihydro-1H-[1, 3, 2] dioxaphosphepin [5, 6-d] imidazole-6-oxide (12a-f)

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Acknowledgement
The authors (V.E.R and CH.L.P) thanks to U G C – S A P and U G C – B S R , New Delhi for financial assistance. They are also thankful to IICT Hyderabad and CDRI Lucknow for spectral and analytical data.

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