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Synthesis, characterization and antimicrobial evaluation of novel compounds 6-nitro-*1H*-benzo[*d*]imidazol-2-yl)-methyl-6-phenoxy-4,8-dihydro-*1H*-[1,3,2] dioxaphosphepino[5,6-*d*]-imidazole-6-oxide-Mannich bases

V. Esther Rani, CH Lakshmi Praveena, Y. N. Spoorthi and L. K. Ravindhranath*

Department of Chemistry, S. K. University, Anantapur

ABSTRACT

New novelnderivatives of 1-((1 (piperidine-1-yl-methyl) /(morpholinomethyl) / (4-methylpiperazin-1-yl-methyl)-6-nitro- 1H-benzo [d] imidazol-2-yl) methyl -6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (9a-h) were prepared by condensation of 4-substituted of phenyl phosphorodichloridates (8a-f) with 1-((1- (piperidin-1-ylmethyl) / (morpholinomethyl) / (4-methylpiperazin-1-ylmethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl) 1H-imidazole-4,5-diyl)dimethanol(7a-c). The synthons (7a-c) was obtained by deprotection of isopropylidene of 6,6-dimethyl-1-((6-nitro-1-((1-(piperidin-1-ylmethyl) / (morpholinomethyl) / (4-methylpiperazin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole (6a-c). The synthons (6a-c) was obtained by the reaction of mannich reaction of 6,6-dimethyl-1-((6-nitro-1H-benzo [d] imidazol-2-yl) methyl) -4,8-dihydro - 1H - [1,3] - dioxepino[5,6-d] imidazole (5) with secondary heterocyclic amines and formaldehyde in DMF. The synthon (5) was obtained by the condensation of 2-(6,6-dimethyl-4,8-dihydro-1H-[1,3] dioxepino [5,6-d] imidazole-1-yl) acetic acid (3) with 4-nitro benzene 1,2-diamine(4).

Key words: Benzodioxaphospholes, imidazole, cyclization, deprotection, Antibacterial and Antifungal activity.

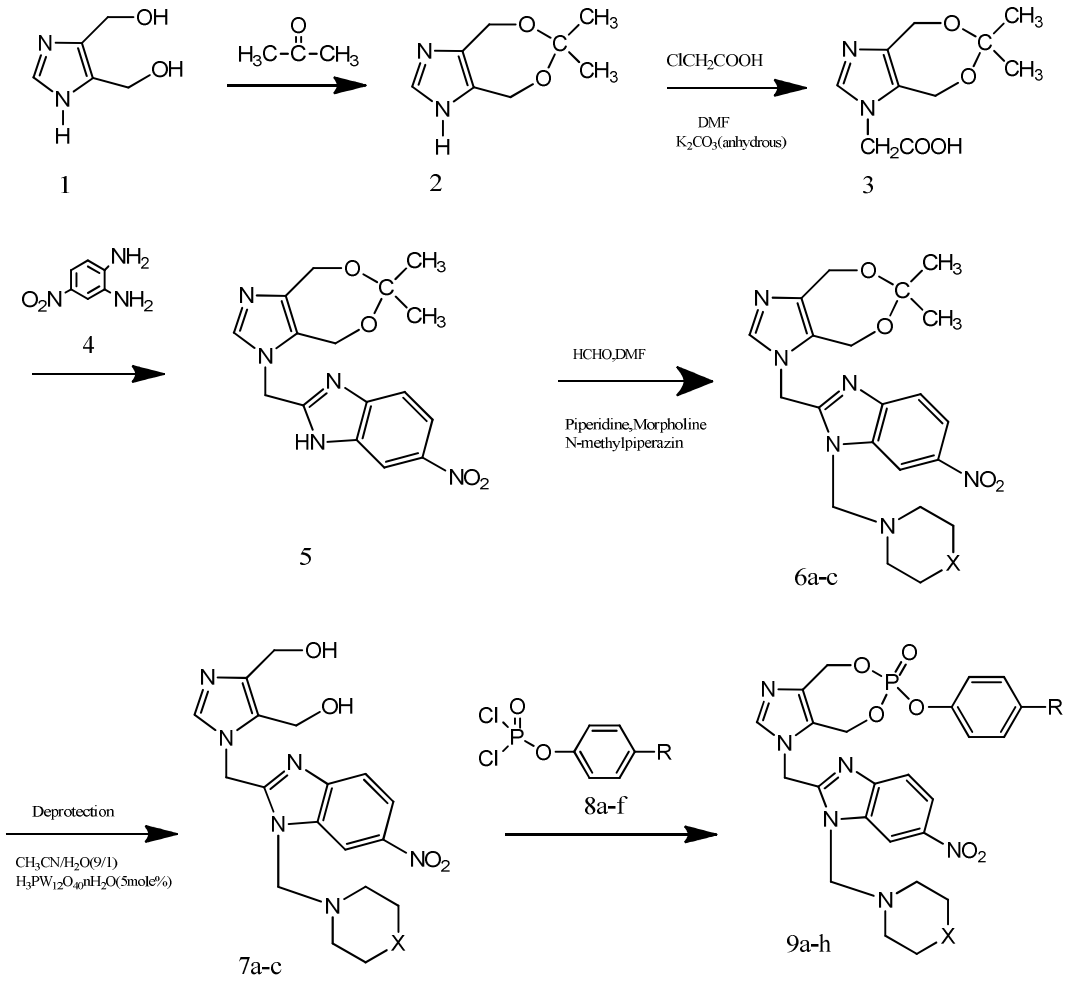
INTRODUCTION

Imidazole derivetives possess a broad spectrum of pharmalogical activities such as anticonvulsant [1], antiparkinson[2], monoamine oxidase (MAO) inihibitory activity [3], anti-bacterial, anti-fungul activity [4], it also function as dyestuff, catalyst, polymerizing agents, drugs, herbicides and fungicides [5]. Imidazole derivatives are valuable vasodialating and vasoconstructing drugs.

Benzimidazoles, benzoxazole and benzthiazoles nuclei are constituent of many of the bioactive heterocyclic compounds that exhibit antiangialantiischaemic, vasodilator, anti-diabetic, anti-microbial, cardiovascular, tranquilizer and virucidal activities [6-15].

The chemistry of phosphorus heterocyclic compounds containing nitrogen has pioneered the application of combinatorial techniques to the development of new pharmaceutical materials with novel properties [16]. Organophosphorus compounds possess significant biological activity against broad spectrum of bacteria, pets, virus, fungicides and plant growth regulators. The organophosphorus heterocyclic compounds chemistry received much attention of chemists in past two decades due to their wide range of applications in the field of the Agriculture, medicine and industry [17,18]. Some organophosphorus compounds have been described in the literature as inhibitors of bacterial [19] , herbicides, insecticides, pesticides [20,21], anti-fungal agents [22], anti-HIV [23], anti-cancer [24], anti-viral and anti-inflammatory [25] .

A good deal of importance was given to 1, 3, 2-Dioxaphosphorinane and dioxaphospholane derivatives [26] in the field of organophosphorus heterocyclic chemistry due to their unique stereochemical futures and diverse potential biological applications [27,28]. In view of the numerous commercial applications of organophosphorus compounds. It appeared of interest to synthesize imidazole derivatives possessing Benzazole moiety besides 1, 3, 2-Dioxaphosphorinane and dioxaphospholanes.



Scheme II.1 : 1-((1 (piperidine-1-yl-methyl) /(morpholinomethyl) / (4-methylpiperazin-1-yl-methyl)-6-nitro- 1H-benzo [d] imidazol-2-yl) methyl -6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (9a-h)

COMP	6a	6b	6c
X	$-CH_2$	O	$N-CH_3$

COMP	7a	7b	7c
X	$-CH_2$	O	$N-CH_3$

COMP	9a	9b	9c	9d	9e	9f	9g	9h
R	H	H	CH_3	OCH_3	Cl	Br	NO_2	H
X	CH_2	O	O	O	O	O	O	$N-CH_3$

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 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 ^{13}C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHz for ^1H -NMR and 75 MHz for ^{13}C-NMR. ^{31}P-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 ^{13}C-NMR) and 85% H_3PO_4 (^{31}P-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 [29, 30] (8a-f):

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 and stirred by means of hot plate –cum –magnetic stirrer. To this dry triethyl amine (10.1 gr, 0.1 mole) and dry benzene (50 ml) were added slowly and the reaction mixture was stirred for 30 minutes. To this mixture, freshly distilled phenol (9.4 gr, 0.1 mole) in dry benzene (60 ml) was added drop wise through the dropping funnel. The addition took about thirty minutes and whole reaction mixture was refluxed with vigorous stirring for 10 hours. The reaction mixture was cooled and the solid tri ethylamine -hydrochloride was filtered off. The solvent from the filtrate was removed under reduced pressure in a rota evaporator. The dark brown liquid remained, was subjected to fractional distillation and the major product distilling at 118-124^{0}C / 11mm was collected as colourless glassy viscous liquid (8.3 gr, 40%).

Other substituted phenyl phosphorodichlorates**(8a-f)** were prepared by the same procedure [31-34] by reacting equimolar quantities of phosophorousoxychloride and respective substituted phenols in benzene in the presence of tri ethylamine.

RESULTS AND DISCUSSION

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)**(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-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_2SO_4 and evaporated to get the crude product **(2)** [35], which was recrystallized by dissolving in boiling ether(5ml/g), cooling and then adding hexane(5ml/g) to give the pure product **(2)** . The structure of **(2)** was established by IR, ^{1}H- NMR and elemental analysis

A mixture of 6,6-dimethyl-4,8-dihydro-1H-[1,3] dioxepino [5,6-d] imidazole **(2)**, anhydrous K_2CO_3 chloroacetic acid and dimethyl formamide (DMF) was stirred at room tempareture for 8 hours. The progress of the reaction was monitored by TLC using cyclohexane and ethylacetate (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. The structure of **(3)** was established by IR, ^{1}H-NMR and elemental analysis.

6,6-dimethyl-1-((6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole [36-38] (5)

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 4-nitrobenzene1,2-diamine **(4)** was heated under reflux for 1.5 hours with stirring at 140^{o}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 period, the mixture was taken in a 30 ml dichloromethane and neutralized with 50 ml 1N NaOH solution, after neutralization the mixture was extracted with CH_2Cl_2 (3×25 ml). The combined extracted were 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 product 6,6-dimethyl-1-((6-nitro-1H-benzo[d]imidazol-2-yl) methyl)-4,8-dihydro-1H-[1,3]-dioxepino [5,6-d] imidazole **(5)** was purified from aqueous dimethyl formamide. The structure of (**5)** was established by IR , ^{1}H-NMR and elemental analysis.

6,6-dimethyl-1-((6-nitro-1-((1-(piperidin-1-ylmethyl) / (morpholinomethyl) / (4-methylpiperazin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl) methyl)-4,8-dihydro-1H-[1,3] dioxepino [5,6-d] imidazole [39] (6a-c)

A mixture of 0.1 mole 6,6-dimethyl-1-((6-nitro-1H-benzo[d]imidazol-2-yl)methyl-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole **(5)**, piperidine (0.15 mol) and water 20 ml was stirred to obtained a clear solution. To this solution, HCHO (0.05 mol) and DMF were added in ice cold condition and stirred for 2 hours in an ice bath and left over night at room temperature. 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, after neutralization the mixture was extracted with CH_2Cl_2 (3×25 ml). The combined extract were dried on Na_2SO_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 compound 6,6- dimethyl-1- ((6-nitro-1-((1-(piperidin-1-ylmethy) l-1H-benzo [d] imidazol-2-yl) methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole **(6a)** was purified from aqueous dimethyl formamide.

The similar procedure was adopted to synthesise **(6b & 6c)** by condensing 6,6-dimethyl-1-((6-nitro-1H-benzo[d]imidazol-2-yl)methyl-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole **(5)** with morpholine and N-methyl piperazine respectively. The structure of **(6a-c)** was established by IR , ^{1}H-NMR and elemental analysis.

Synthesis of 1-((1- (piperidin-1-ylmethyl) / (morpholinomethyl) / (4-methylpiperazin-1-ylmethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-1H-imidazole-4,5-diyl)dimethanol (7a-c)

The isopropylidenation of 1, 2-diols was carried out by a procedure as reported in the literature [40]. A suspension of the 6,6- dimethyl-1- ((6-nitro-1-((1-(piperidin-1-ylmethy) l-1H-benzo [d] imidazol-2-yl) methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole **(6a)** (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 ethylacetate (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% ethylacetate in cyclohexane as an eluent. The similar procedure was adopted to synthesise **(7b & 7c)** from **(6b & 6c)**. The structure of **(7a-c)** was established by IR, ^{1}H-NMR and elemental analysis.

Synthesis of 1-((1-(piperidine-1-yl-methyl) / (morpholinomethyl) / (4-methylpiperazin-1-yl-methyl)-6-nitro-1H-benzo [d] imidazol-2-yl) methyl -6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (9a-h)

A solution of phenyl phosphorodichloridate (8a) (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-((1- (piperidin-1-ylmethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,5-diyl)dimethanol **(7a)** (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. 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 [41] of 1-((1(piperidine-1-yl-methyl)-6-nitro-1H-benzo [d] imidazol-2-yl) methyl – 6 – phenoxy-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole – 6-oxide **(9a)**.

The similar procedure was adopted to synthesise **(9b-h)** by the reaction between**(7b-c)** with 4-methyl phenyl phosphoro dichloridate**(8b),** 4-methoxy phenyl phosphoro dichloridate**(8c),** 4-chloro phenyl phosphoro dichloridate**(8d),** 4-bromo phenyl phosphorodichloridate**(8e),** 4-nitro phenyl phosphorodichloridate**(8f).**

The structures of these newly synthesized compounds **(9a-h)** were characterized by their elemental analysis and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-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^{O}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 $(CH_3)_2$) and 1140 cm^1 (C-O, stretching vibrations). ^{1}H NMR (400MHz, DMSO-d6): δ 1.27 (s,6H,two geminial CH_3 groups), 4.57 (s, 2H, two CH_2 groups of acetals), 4.67 (s, 2H, CH_2 of –CH_2COOH group), 7.57 (s, 1H, of imidazole ring) and 11.0 (s,1H, -COOH group). Anal.Calcd.For $C_{10}H_{14}N_2O_4$ C 56.68% , H 7.13% and N 11.02%. Found: C 55.88% , H 6.63% and N 10.42%.

*6,6-dimethyl-1-((6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d] imidazole **(5):***

Yield 70%, m p 147^{0}C: IR (KBr): 3460 (stretching of -NH- of benzimidazole), 3052 (stretching of Ar-H), 2940 & 2895 (CH_2 and CH_3 aliphatic C-H stretching), 1478 & 1366 (characteristic of imidazole ring), 1390 & 1365 (characteristic of benzimidazole ring), 1360 & 1380 (bending vibration of $C(CH_3)_2$), 1355 & 1330 (stretching of –NO_2) and 1140 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 1.27 (s, 6H, two geminial CH_3 groups) , 4.57 (s, 2H, two CH_2 groups of acetals), 4.99 (s, 2H,- N-CH_2-benzimidazole), 5.0 (s, 1H, NH of benzimidazole

ring), 7.57 (s, 1H, of imidazole ring) and 7.22-7.59 (m, 4H, of benzimidazole ring). Anal.Calcd. For $C_{16}H_{17}N_5O_4$ C 55.97%, H 4.99% and N 20.40%. Found: C 55.17%, H 4.49% and N 19.80%.

6,6-dimethyl-1-((6-nitro-1-(piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d]imidazole ***(6a):***
Yield 70%, m p 162-164^{0}C: IR (KBr): 3052 (stretching of Ar-H), 2940 & 2895 (CH_2 and CH_3 aliphatic C-H stretching), 1478 & 1366 (characteristic of imidazole ring), 1390 & 1365 (characteristic of benzimidazole ring), 1395& 1370 (bending vibration of C $(CH_3)_2$), 1355 & 1330(stretching of $–NO_2$) and 1140 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 1.27 (s, 6H, two geminial CH_3 groups) ,1.53-2.45 (m, 10H, $(CH_2)_5$ of piperidine ring), 4.57 (s, 2H, two CH_2 groups of acetals), 4.80 (s, 2H, -N-CH_2-N- of piperidine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). Anal.Calcd.For $C_{22}H_{28}N_6O_4$ C 59.99% H 6.41% N 19.08%. Found: C 59.19%, H 5.91% N 18.68%.

6,6-dimethyl-1-((6-nitro-1-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d]imidazole ***(6b):***
Yield 75%, m p 148-150^{0}C: IR (KBr): 3040(stretching of Ar-H), 2940 & 2895 (CH_2 and CH_3 aliphatic C-H stretching), 1470& 1360 (characteristic of imidazole ring), 1385& 1365 (characteristic of benzimidazole ring), 1395& 1370 (bending vibration of C$(CH_3)_2$), 1355 & 1330(stretching of $–NO_2$) and 1145 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 1.27 (s, 6H, two geminial CH_3 groups) ,2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.57 (s, 2H, two CH_2 groups of acetals), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). Anal.Calcd. For $C_{21}H_{26}N_6O_5$ C 57.00% H 5.92% N 18.99% Found: C 56.20% H 5.42% N 18.39%.

6,6-dimethyl-1-((6-nitro-1-(4-piperazin-1-yl)methyl)-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3]-dioxepino[5,6-d]imidazole **(6c):**
Yield 70%, m p 172-174^{0}C: IR (KBr): 3035(stretching of Ar-H), 2940 & 2895 (CH_2 and CH_3 aliphatic C-H stretching), 1472& 1365 (characteristic of imidazole ring), 1398& 1370 (characteristic of benzimidazole ring), 1395 & 1370 (bending vibration of C$(CH_3)_2$), 1355 & 1330(stretching of $–NO_2$) and 1148 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 1.27 (s, 6H, two geminial CH_3 groups) , 2.26 (s, 3H, CH_3 group attached to piperazine ring), 2.35-2.45 (m, 8H, $(CH_2)_4$ of piperazine ring), 4.57 (s, 2H, two CH_2 groups of acetals), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 4.80 (s, 2H, -N-CH_2-N- of piperazine ring), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). Anal. Calcd. For $C_{22}H_{29}N_7O_4$ C 58.01% H 6.42% N 21.52% Found: C 57.21% H 5.92% N 20.92%.

1-((1-(piperidin-1-ylmethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,5-diyl)dimethanol ***(7a):***
Yield 75%, m p 145-147^{0}C: IR (KBr): 3520 (ν_{O-H}, intramolecular H-bonding), 3052 (stretching of Ar-H), 2940 & 2895 (CH_2 aliphatic C-H stretching), 1478 & 1366 (characteristic of imidazole), 1390 & 1365 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $–NO_2$) and 1140 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 1.53-2.45 (m, 10H, $(CH_2)_5$ of piperidine ring), 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding), 4.73 (s, 4H, two CH_2 groups of dimethanols), 4.80 (s, 2H, -N-CH_2-N- of piperidine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). Anal. Calcd. For $C_{19}H_{24}N_6O_4$ C 56.99% H 6.04% N 20.99% Found : C56.18% H 5.54% N 20.39%.

1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,5-diyl)dimethano **(7b):**
Yield 65%, m p 134-136^{0}C: IR (KBr): 3520 (ν_{O-H}, intramolecular H-bonding), 3020 (stretching of Ar-H), 2940 & 2895 (CH_2 aliphatic C-H stretching), 1470& 1360(characteristic of imidazole), 1385 & 1365 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $–NO_2$) and 1145 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J= 7.1 Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J= 7.1 Hz H-3',H-2'), 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding), 4.73 (s, 4H, two CH_2 groups of dimethanols), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). Anal. Calcd. For $C_{18}H_{22}N_6O_5$ C 53.73% H 5.51% N 20.88% Found: C52.93% H 5.01% N 20.28%.

1-((1-((4methylpiperazin-1-yl)methyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,5-diyl) dimethanol **(7c):**
Yield 70%, m p 154-156^{0}C: IR (KBr): 3520 (ν_{O-H}, intramolecular H-bonding), 3035 (stretching of Ar-H), 2940 & 2895 (CH_2 aliphatic C-H stretching), 1472& 1365(characteristic of imidazole), 1398& 1370 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $–NO_2$) and 1148 cm^1 (C-O stretching). ^{1}H NMR (400MHz, DMSO-d6): δ 2.35-2.45 (m, 8H, $(CH_2)_4$ of piperazine ring), 3.65 (s, 2H, two –OH groups having Intramolecular H-bonding), 4.73 (s, 4H, two CH_2 groups of dimethanols), 4.80 (s, 2H, -N-CH_2-N- of piprazine ring), 4.99 (s, 2H, -

N-CH_2-benzimidazole ring), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). Anal.Calcd. For $C_{19}H_{25}N_7O_4$ C 55.76% H 6.01% N 23.60% Found:C 54.13% H 5.57% N 23.00%.

1-((6-nitro-1-(piperidin-1-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl-6-phenoxy-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9a):**
Yield 70%, m p 177-179^{0}C: IR (KBr): 3052 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1478 & 1366 (characteristic of imidazole ring), 1390 & 1365 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of –NO_2) , 1140 cm^1 (C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1250 ($\gamma_{P=O}$) and 954 cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 1.53-2.45 (m, 10H, $(CH_2)_5$ of piperidine ring), 4.80 (s, 2H, -N-CH_2-N- of piperidine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring),5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 7.57 (s, 1H, of imidazole ring) 7.18-7.28 (m, 5H, of phenoxy group) and 7.66 -8.19 (m, 3H, of benzimidazole ring).^{13}C-NMR(75MHz, DMSO-d6): δ 137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 54.5, 25.6, 24.5, 150.2, 120.3, 130.1and 121.3 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_{19}, C_{16}& C_{18}, C_{17}, C_{20}, C_{21}& C_{25}, C_{22}& C_{24} and C_{23} . ^{31}P NMR (161.89MHz, DMSO-d6): δ-5.90, -5.45 ppm. Anal. Calcd. For $C_{25}H_{27}N_6O_6P$ C 55.76% H 5.0% N 15.61% P 5.7%Found : C 54.96% H 4.55% N 15.01% P 5.05%.

1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl-6-phenoxy-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9b):**
Yield 75%, m p 163-165^{0}C: IR (KBr): 3055 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1475& 1360 (characteristic of imidazole ring), 1392& 1367 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of –NO_2) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1245 ($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 7.57 (s, 1H, of imidazole ring) 7.18-7.28 (m, 5H, of phenoxy group) and 7.66 -8.19 (m, 3H, of benzimidazole ring).^{13}C -NMR(75MHz, DMSO-d6): δ 137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 53.5, 66.4, 150.2, 120.3, 130.1and 121.3 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_{18}, C_{16}& C_{17}, C_{19}, C_{20}& C_{24}, C_{21}& C_{23} and C_{22} . ^{31}P NMR (161.89MHz, DMSO-d6): δ-5.95, -5.53ppm. Anal. Calcd. For $C_{24}H_{25}N_6O_7P$ C 53.33% H 4.6% N 15.55% P 5.7% Found : C 52.53% H 4.16% N 14.95% P 5.03%.

1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl-6-(p-tolyloxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9c):**
Yield 75%, m p 184-186^{0}C: IR (KBr): 3065 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1478& 1364 (characteristic of imidazole ring), 1394& 1366 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of –NO_2) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1254 ($\gamma_{P=O}$) and 958 cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 2.34 (s, 3H ,CH_3 group attached to phenoxy group), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.83-7.06 (m, 4H, of phenoxy group), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). ^{13}C -NMR(75MHz, DMSO-d6): δ 137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 53.5, 66.4, 147.2, 118.2, 130.4, 131.0 and 21.3 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_{18}, C_{16}& C_{17}, C_{19}, C_{20}& C_{24}, C_{21}& C_{23} , C_{22}, and C_{25} . ^{31}P NMR (161.89MHz, DMSO-d6): δ-6.04, -5.42ppm. Anal. Calcd. For $C_{25}H_{27}N_6O_7P$ C 54.15% H 4.9% N 15.16% P 5.5% Found: C 53.35% H 4.41% N 14.56% P 4.89%.

6-(4-methoxyphenoxy)-1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9d):**
Yield 70%, m p 192-194^{0}C: IR (KBr): 3067 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1480& 1369 (characteristic of imidazole ring), 1396& 1370 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of –NO_2) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1256 ($\gamma_{P=O}$) and 956 cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 3.83 (s, 3H , methoxy group attached to phenoxy group), 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.82-6.84 (m, 4H, of phenoxy group), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). ^{13}C -NMR(75MHz, DMSO-d6): δ137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 53.5, 66.4, 142.5, 116.9, 115.7, 153.2 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_{18}, C_{16}& C_{17}, C_{19}, C_{20}& C_{24}, C_{21}& C_{23} , C_{22}, and C_{25} . ^{31}P NMR

(161.89MHz, DMSO-d6): δ-11.48ppm. Anal. Calcd. For $C_{25}H_{27}N_6O_8P$ C 52.63% H 4.7% N 14.73% P 5.4% Found : C 51.83% H 4.27% N 14.13% P 4.73%.

6-(4-chlorophenoxy)-1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9e):**
Yield 70%, m p 203-205^{0}C: IR (KBr): 3069 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1482 & 1362 (characteristic of imidazole ring), 1401& 1370 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $-NO_2$) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1259($\gamma_{P=O}$) and 961cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.89-7.32 (m, 4H, of phenoxy group), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). ^{13}C -NMR(75MHz, DMSO-d6): δ137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 53.5, 66.4, 148.3, 125.7, 131.3 and 126.9 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}, C_{19}, C_{20}& C_{24}, C_{21}& C_{23} and C_{22} . ^{31}P NMR (161.89MHz, DMSO-d6): δ-6.08, -5.16ppm. Anal. Calcd. For $C_{24}H_{24}ClN_6O_7P$ C 50.14% H 4.2%Cl 6.17% N 14.6% P 5.39% Found : C 49.34% H 3.71%Cl 5.37% N 14.02% P 4.69%.

6-(4-bromophenoxy)-1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9f):**
Yield 70%, m p 156-158^{0}C: IR (KBr): 3070 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1480& 1369 (characteristic of imidazole ring), 1402& 1372 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $-NO_2$) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1256($\gamma_{P=O}$) and 964cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.84-7.43 (m, 4H, of phenoxy group), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). ^{13}C -NMR(75MHz, DMSO-d6): δ 137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 53.5, 66.4, 149.2, 123.0, 133.0 and 115.7 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}, C_{16}& C_{17}, C_{19}, C_{20}& C_{24}, C_{21}& C_{23} and C_{22} . ^{31}P NMR (161.89MHz, DMSO-d6): δ-8.32ppm. Anal. Calcd. For $C_{24}H_{24}BrN_6O_7P$ C 46.54% H 3.9% Br 12.90% N 13.57% P 5.00% Found: C 45.74% H 3.41% Br 12.30% N 12.97% P 4.30%.

1-((1-(morpholinomethyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-6-(4-nitrophenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide **(9g):**
Yield 75%, m p 142-144^{0}C: IR (KBr): 3075 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1486 & 1370 (characteristic of imidazole ring), 1406& 1374 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $-NO_2$) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1258 ($\gamma_{P=O}$) and 966 cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 2.50 (t, 4H, -CH_2-N-CH_2 of morpholine ring J=7.1Hz H-2',H-3'), 3.65 (t, 4H, -CH_2-O-CH_2 of morpholine ring J=7.1Hz H-3',H-2'), 4.80 (s, 2H, -N-CH_2-N- of morpholine ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 7.34-8.09 (m, 4H, of phenoxy group), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring). ^{13}C -NMR(75MHz, DMSO-d6): δ 137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 53.5, 66.4, 158.3, 121.9, 128.3 and 140.5 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}, C_{19}, C_{20}& C_{24}, C_{21}& C_{23} and C_{22} . ^{31}P NMR (161.89MHz, DMSO-d6): δ-12.45ppm. Anal. Calcd. For $C_{24}H_{24}N_7O_9P$ C 49.24% H 4.1% N 16.75% P 5.2% Found : C 48.44% H 3.63% N 16.15% P 4.59%.

1-((1-((4-methylpiperazin-1-yl)methyl)-6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-6-phenoxy-4,8 – dihydro-1H-[1,3,2] dioxaphosphepino[5,6-d]imidazole-6-oxide **(9h):**
Yield 70%, m p 165-167^{0}C: IR (KBr): 3062 (stretching of Ar-H), 2940 & 2895(CH_2 aliphatic C-H stretching), 1480& 1372 (characteristic of imidazole ring), 1390& 1365 (characteristic of benzimidazole ring), 1355 & 1330 (stretching of $-NO_2$) , 1140(C-O stretching), 1300 (γ_{C-O} / δ_{C-O}), 1254 ($\gamma_{P=O}$) and 968 cm^{-1} ($\gamma_{P-O-C(aromatic)}$). ^{1}H NMR (400MHz, DMSO-d6): δ 2.26 (s, 3H, CH_3 attached to piperazne ring), 2.35-2.45 (m, 8H, $(CH_2)_4$ of piprazine ring), 4.80 (s, 2H, -N-CH_2-N- of piperazne ring), 4.99 (s, 2H, -N-CH_2-benzimidazole ring), 5.23 (s, 4H, two CH_2 groups attached to phosphorus moiety), 7.18-7.28 (m, 5H, of phenoxy group), 7.57 (s, 1H, of imidazole ring) and 7.66 -8.19 (m, 3H, of benzimidazole ring).^{13}C -NMR(75MHz, DMSO-d6): δ137.3, 132.9, 127.7, 63.0, 60.5, 48.3, 145.9, 116.1, 118.6, 144.3, 106.7, 135.1, 148.3, 75.7, 52.5, 57.3, 46.6, 150.2, 120.3, 130.1 and 121.3 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_{18}, C_{16}& C_{17}, C_{19}, C_{20} C_{21}& C_{25}, C_{22} & C_{24} and C_{23} . ^{31}P

NMR (161.89MHz, DMSO-d6): δ -5.85, -5.50 ppm. Anal. Calcd. For $C_{25}H_{27}N_8O_8P$ C 50.17% H 4.5% N 18.72% P 5.1% Found : C 49.37% H 4.05% N 18.16% P 4.48%.

Biological activity

The antimicrobial activity [42-44] of these newly synthesized compounds was performed according to disc diffusion method, as recommended by the National Committee for Clinical Laboratory [45]. The synthesised compounds were used at the concentration of 250µg/ml DMF as a solvent [46].

Antibacterial activity

The antibacterial activity of 1-((1(piperidine-1-yl-methyl)/(morpholinomethyl)/(4-methylpiperazin-1-yl-methyl)-6-nitro- 1H-benzo [d] imidazol-2-yl) methyl -6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-6-oxide (9a-h) were screened against the Staphylococcus aureus (gram positive) and Escherichia coli (gram negative) organisms. Most of the compounds exhibited good antibacterial activity against both bacteria. The presence of chloro and nitro in the structure has shown increased effect on their antibacterial activity [47, 48].

Antibacterial activity of 1-((1(piperidine-1-yl-methyl)/(morpholinomethyl)/(4-methylpiperazine-1-yl-methyl)-6-nitro-1H-benzo [d] imidazol-2-yl) methyl-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide (9a-h)

S.NO	COMPOUND	R	X	Zone of inhibition(mm)			
				Staphylococcus aureus NCCS 2079 250 µg/ disc	*Bacillus cereus NCCS 2106 250 µg/ disc*	*Escherichia coli NCCS 2065 250µg/ disc*	*Pseudomonas aeruginosa NCCS 2200 250 µg/ disc*
1	9a	H	CH_2	6	5	7	8
2	9b	H	O	7	4	5	6
3	9c	CH_3	O	5	3	4	5
4	9d	OCH_3	O	4	3	4	5
5	9e	Cl	O	15	16	15	13
6	9f	Br	O	13	12	13	12
7	9g	NO_2	O	16	18	17	15
8	9h	H	N-CH_3	10	9	7	8
9	Amoxycillin			21	27	24	22
10	Cefaclor			19	22	19	20

Antifungal activity

Antifungal activity of 1-((1(piperidine-1-yl-methyl)/(morpholinomethyl)/(4-methylpiperazine-1-yl-methyl)-6-nitro-1H-benzo [d] imidazol-2-yl) methyl-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide (9a-h) were screened against Aspergillus niger, Candida albicans [49].

Antifungal activity of 1-((1(piperidine-1-yl-methyl)/(morpholinomethyl)/(4-methylpiperazine-1-yl-methyl)-6-nitro-1H-benzo [d] imidazol-2-yl) methyl-6-(4-substituted phenoxy)-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-d]imidazole-6-oxide (9a-h)

S.NO	COMPOUND	R	X	Zone of inhibition (mm)	
				Aspergillus niger NCCS 1196 250(µg/disc)	*Candida albicans NCCS 3471 250(µg/disc)*
1	9a	H	CH_2	8	6
2	9b	H	O	9	7
3	9c	CH_3	O	6	4
4	9d	OCH_3	O	5	4
5	9e	Cl	O	16	17
6	9f	Br	O	15	16
7	9g	NO_2	O	18	20
8	9h	H	N-CH_3	13	14
9	Ketoconazole			22	25

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