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Synthesis Characterization and Antimicrobial Activity of N-((5-((6-OXIDO-6-(4 Substituted Phenoxy)-4,8-DIHYDRO-1H-[1,3,2] Dioxaphosphepino [5,6-C]Pyrazol-1-YL) Methyl)-1,3,4-Thiadiazol-2-YL)Carbamoyl) Substituted Benzene Sulfonamides

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Abstract: *New novel derivatives of* N-((5-((6-oxido-6-(4 substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-1-yl) methyl)-1,3,4-thiadiazol-2-yl)carbamoyl) substituted benzene sulfo namides **(*7a-o as depicted in scheme*)** w*ere Synthesized by condensation reaction of 4- substituted* Phenyl phosphorodichloridates **(6a-c)** *and* N-((5-((4,5-bis(hydroxymethyl)-1H-pyrazol-1-yi)methyl)- 1,3,4-thiadiazol-2-yl)carbamoyl) substituted benzene sulfonamides **(5a-e)**. *synthons **(5a-e)** were obtained by deprotection of isopropilidine group of* N-((5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)carbamoyl) substituted benzene sulfonamides **(4a-e)**.*These synthons **(4a-e)** were obtained by condensation reaction between* methyl (cyclopropyl/per fluoro phenyl /4-bromo phenyl/4-nitro phenyl) sulfonyl carbamates **(3a-e)**.*and* 5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-C]pyrazol-1-yl)methyl)-1,3,4-thia diazol-2-amine **(2).**

Key Words: Benzodioxaphospholes, Pyrazole, Cyclizaton, Deprotection, Antibacterial and Antifungal activity.

Introduction

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

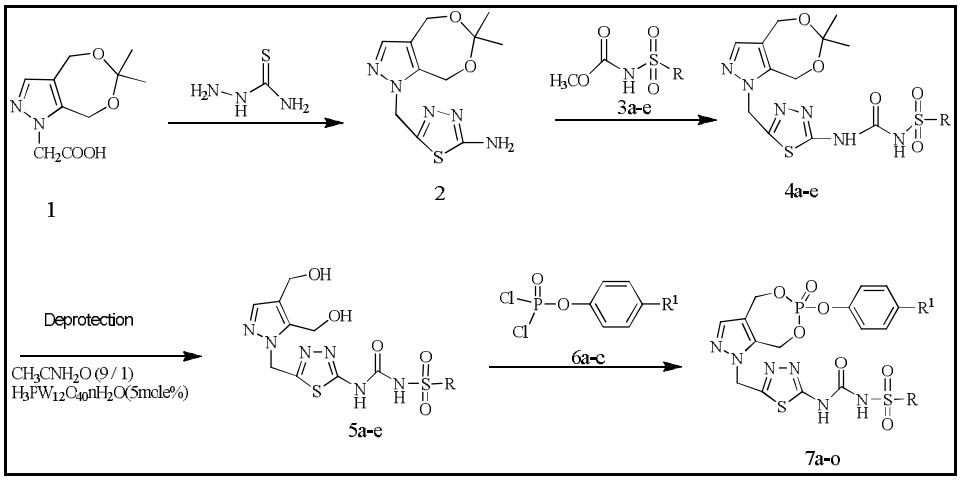
In support of our study pyrazoles and derivatives function as dyestuff, catalyst, polymerizing agents, drugs , herbicides and fungicides [12].they also possess various pharmacological activities such as anti-fungal activity [13], monoamineoxidase (MAO) inhibitory activity [14, 15], antiparkinson [16],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

A good deal of importance was given to 1, 3,2-Dioxaphospholane and their derivatives [28] in the field of organophosphorus heterocyclic chemistry due to their unique biological applications [29,30].In view of the numerous commercial applications of organophosphorus compounds , we synthesized sulfonamide derivatives possesing Pyrazole moiety besides 1, 3, 2-Dioxaphosphorinane and dioxaphospholanes, also they screening for possible biological and pharmacological activities.

Experimental Section

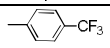
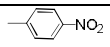
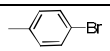
Meterials and Methods

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



***Scheme*: *Synthetic route of N-((5-((6-oxido-6-(4 substituted phenoxy)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-1-yl) methyl) -1,3,4-thiadiazol-2-yl) carbamoyl) cyclopropyl /(2,3,4,5,6-petafluoro/4-trifluoromethyl/4-nitro/ 4-bromo) benzene sulfonamides* (*7a-o*).**

Compound 7	R^1	R
7a	-H	
7b	-H	
7c	-H	
7d	-H	
7e	-H	
7f	-NO_2	
7g	-NO_2	
7h	-NO_2	
7i	-NO_2	
7j	-NO_2	
7k	-CF_3	

7l	$-CF_3$	
7m	$-CF_3$	
7n	$-CF_3$	
7o	$-CF_3$	

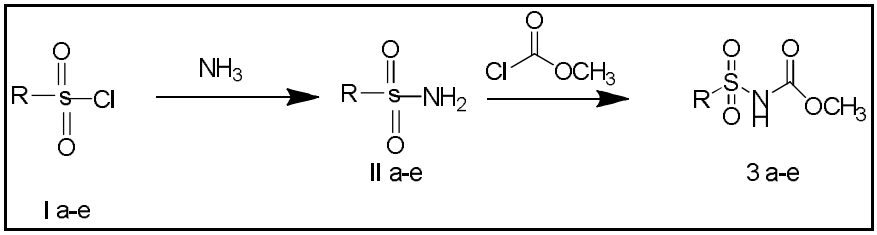
Preparation of Intermediates:

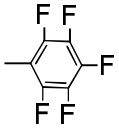
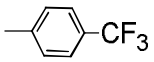
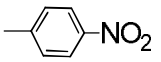
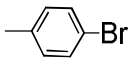
4-Substituted Phenyl Phosphorodichloridates (6a-C): [21, 22]

phosphorus oxy chloride (15.3 gr, 0.1 mole) in dry benzene (60ml) 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 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 (**6b-c**) were prepared by the same procedure [23 - 26] by reacting equimolar quantities of phosophorousoxychloride and respective substituted phenols in benzene in the presence of tri ethylamine.

Synthesis Of Methyl (Cyclopropyl /Per Fluoro Phenyl /4-Bromo Phenyl/4-Nitro Phenyl) Sulfonyl Carbamates(3a-e):



Compound	3 a	3b	3 c	3d	3 e
R					

The reaction was carried out in a 4 necked round bottom flask fitted with a reflux condenser, to this a mixture of cyclo propyl sulfonyl chloride **(*I a*)** and 20% aqueous solution of NH_3 were added. The reaction mixture was heated on water bath at 75-85 ^{0}c for 3 hrs. After completion of the reaction, the reaction mixture was maintained for 1hr at 15^{0}c . The solid that separated was filtered, washed with water and dried to obtain cyclopropyl sulfonamide **(*II a*)**.The similar procedure was adopted to synthesize other sulphonamides ***II b-e*** from ammonia and per fluorophenyl sulfonyl chloride **(*I b*)** /4-tri fluoro methyl sulfonyl chloride **(*I c*)** / 4-nitro phenyl sulfonyl chloride **(*I d*)** / 4-bromo phenyl sulfonyl chloride **(*I e*)** .The sulfonamides **(*II a-e*)** were immediately used for the synthesis of sulfonyl carbamates **(*3a-e*)** without any further purification.

In a typical experiment for the synthesis of methyl cyclo propyl sulfonyl carbamate **(*3a*)** , a mixture of cyclopropyl sulfonamide**(*II a*)** , ethyl methyl ketone (40ml) and potassium carbonate was taken in 4 necked round bottom flask and heated to 80 ^{0}c for 30 mins. To this reaction mixture methyl chloroformate was added drop wise by means of a dropping funnel by maintaining the temperature at 45 ^{0}c for one hour. The mixture was

then heated for 8h at 50^0c .The progress of the reaction was monitored by TLC using hexane and pet ether (7:3) solvent mixture as mobile phase. After the completion of reaction, the reaction mixture was poured on to ice water and extracted with ethyl acetate (to remove organic impurities).The P^H of the aqueous layer was adjusted to 2 to 3 by hydrochloric acid and again extracted with ethyl acetate .The organic layer was dried over anhydrous sodium sulfate and later concentred to dryness. The solid thus obtained was recrystalized from absolute ethanol with a yield of 60% and mp142-143^{o}C.The similar synthetic procedure was adopted to synthesize novel sulfonyl carbamates **(*3b-e*)** from the corresponding sulfonamides **(*II b-e*)** and methyl chloroformate.

The structure of newly synthesized sulfonyl carbamates **(*3a-e*)** was established by IR, ^{1}HNMR and elemental analysis.

Result and Discussion

Synthesis of 5 - ((6, 6 – DIMETHYL - 4, 8 – DIHYDRO - 1H - [1, 3] DIOXEPINO [5,6-c]PYRAZOL-1-YL) METHYL)-1,3,4-THIADIAZOL-2-AMINE(2):

A suspension of 1-H-pyrazole-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-pyrazole-4; 5-dimethanol 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 , which was recrystallized by dissolving in boiling ether (5ml/g), cooling and then adding hexane (5ml/g) to give the pure product 6, 6-dimethyl-4, 8-dihydro-1H-[1, 3] dioxepino [5, 6-c] pyrazole [27].

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

To a 3 neck round bottom flask fitted with a reflux condenser was added 2 - (6, 6-dimethyl - 4, 8 - dihydro - 1 H - [1, 3] dioxepino [5, 6 - c] pyrazole -1 - yl) acetic acid **(*1*)**,thio semicarbazide and conc.H_2SO_4 (15ml), the reaction mixture was cooled slowly at 0C^o.The resultant reaction mixture was refluxed on a water bath for 3hrs, then poured into crushed ice and neutralized with ammonia solution cautiously. A yellow coloured solid separates out. It was filtered off, washed with saturated sodium bicarbonate solution and water, dried and recrystalized from ethanol. The structure of **(*2*)** was established by IR, ^{1}H-NMR and elemental analysis.

Synthesis of N - ((5 - ((6, 6 - DIMETHYL - 4, 8 - DIHYDRO - 1H - [1, 3] DIOXEPINO [5, 6 -c] PYRAZOL - 1 - YL) METHYL) - 1, 3, 4 - THIADIAZOL - 2 - YL) CARBAMOYL) CYCLOPROPANE / (2, 3, 4, 5, 6 - PENTAFLURO / 4 - TRIFLUORO METHYL / 4-NITRO / 4 - BROMO) BENZENE SULFONAMIDES (4a- e) :

A mixture of methyl cyclopropyl sulfonyl carbamate **(3a)** (0.01 mol) and 5 - ((6, 6 -dimethyl - 4, 8 - dihydro - 1H - [1, 3] dioxepino[5, 6 - C] pyrazol -1 - yl) methyl) - 1, 3, 4 -thiadiazol - 2 - amine **(*2*)** (0.01 mol) in dry toluene (50 ml) was placed into a 3 neck round bottom flask fitted with a reflux condenser and a mechanical stirrer. The reaction mixture was refluxed and stirred for 4hrs. The progress of the reaction was monitored by TLC using hexane and ethyl acetate solvent mixture (7:3) as mobile phase. After the completion of the reaction the reaction mixture was cooled to room temperature and kept aside over night. The resulting solid was filtered off , dried and recrystalized from ethanol to obtain the desired synthon N - ((5 - 6, 6 - dimethyl - 4, 8 - dihydro -1 H - [1, 3] dioxepino [5, 6 - c] pyrazol - 1 - yl) methyl) - 1, 3, 4 - thiadiazol - 2 - yl) carbamoyl) cyclopropane sulfonamide**(4a)**.

The similar procedure was adopted for the synthesis of **4b-e** from synthon **(*2*)** and sulfonamides **(*3b-e*)**. The structures of ***4a-e*** were established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental analysis.

Synthesis of N- ((5 - ((4, 5 – BIS (HYDROXYMETHYL) - 1H – PYRAZOL – 1 - YL) METHYL) - 1, 3, 4 – THIADIAZOL – 2 - YL) CARBAMOYL) CYCLOPROPANE / (2, 3, 4, 5, 6 – PENTAFLURO /4 – TRIFLUOROMETHYL / 4 – NITRO / 4 – BROMO) BENZENE SULFONAMIDES (5a-e):

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

The similar procedure was adopted to synthesize **5b-e** by isopropylidenation of **4b-e**. The structures of **5a-e** were established by IR, ^{1}H-NMR and elemental analysis.

Synthesis of N- ((5 - ((6 - OXIDO - 6 - (4 - SUBSTITUTEDPHENOXY) - 4, 8 - DIHYDRO - 1H - [1, 3, 2] DIOXAPHOSPHEPINO [5, 6 - c] PYRAZOL - 1 - YL) METHYL) - 1, 3, 4 - THIADIAZOL - 2 - YL) CARBAMOYL)CYCLOPROPYL / (2, 3, 4, 5, 6 - PETAFLUORO / 4 - TRIFLUOROMETHYL/4 - NITRO/4 - BROMO) BENZENE SULFONAMIDES *(7a-o):*

A solution of phenylphosphorodichloridate **(*6a*)** (0.002 mole) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of N - ((5 - ((4, 5 – bis (hydroxymethyl) - 1H - pyrazol - 1 - yl) methyl) - 1, 3, 4 - thiadiazol - 2 - yl) carbamoyl) cyclo propane sulfonamide **(*5a*)** (0.002mole) and triethylamine (0.004mole) in 30 ml of dry toluene and 10ml of tetrahydrofuran at 5^{0}c. After 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 at 50-60^{O}C for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. Tri ethyl amine hydrochloride was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water, which was further purified by column chromatography over silicagel (60-120mesh),hexane and ethyl acetate (7:3) was used as an elutent to afford the compound N - ((5 - ((6 - oxido -6 - phenoxy - 4,8 - dihydro - 1H - [1, 3, 2] dioxaphospino [5, 6 - c] pyrazol -1 - yl) methyl) - 1, 3, 4 - thiadiazol - 2 - yl) carbamoyl) cyclopropanesulfonamide **(*7a*)**.

The similar reaction procedure was adopted to synthesize **7(b-e)** from **5(b-e)** with phenylphosphoro dichloridate **(*6a*).**In the same way the synthesis of ***7(f-j)*** and ***7(k-o)*** were also carried out by the reaction between ***5*(a-e)** and 4-nitro phenyl phosphorodichloridate **(6b)** and similarly **(*5a-e*)** with 4-(trifluoromethyl) phenyl phosphorodichloridate **(*6c*)** respectively.

. The structures of **7(a-o)** were established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis. .

Physical, Analytical and Spectral Data for the Compounds

Synthesis of 5- ((6,6-DIMETHYL-4,8- DIHYDRO-1H- [1,3] DIOXEPINO[5,6-c] PYRAZOL-1-YL) METHYL -1,3,4- THIADIAZOL-2-AMINE(2):

Yield:65%; M.p: 145-146^{O}C;IR(KBr): 3356 and 3263 (asymmetric and symmetric stretching of –NH_2 group), 3052 (stretching vibration of pyrazole ring - H), 2940 and 2895 of (CH_2 and CH_3 aliphatic –CH stretching), 1670 (stretching of C=N thiadiazole), 1375 -1 487 (stretching vibrations of pyrazole ring), 1395 (Geminal $C(CH_3)_2$ stretching vibration) and 695 Cm^{-1} (stretching of C-S-C of thiadizole); H^{1}-NMR(300Hz,DMSO-d6): δ, PPM. 1.27(s, 6H, two geminal CH_3 groups) , 4.63(S, 4H, two CH_2 groups of acetals) , 4.99 (s, 2H , -CH_2 - flanked between pyrazol and thiadizol ring), 6.99(s, 2H, -NH_2 group attached to thiadiazole ring) and 7.30 (s,

1H, of pyrazole ring) ;Anal. calcd (%) for $C_{11}H_{15}N_5O_2S$: C 46.16% , H 5.37% and N 24.89%.Found: C 46.16% , H 4.87% and N 24.69%.

Methyl cyclo propyl sulfonyl carbamate(3a):

Yield:60%; M.p: 142-143^{O}C ; IR(KBr): 3212 Cm^{-1} (-NH), 2915 & 2875 Cm^{-1} (Aliphatic γ_{C-H}), 1659 Cm^{-1} (C=O), 1342 & 1265 (SO_2), 1254 Cm^{-1} (C-O); H^1-NMR(300Hz,DMSO-d6):δ 0.79 (m,4H , $-CH_2-$ of cyclopropyl ring) , 1.75 (m,1H , -CH- of cyclo propyl ring attached to $-SO_2-$ group) , 3.67 (S,3H, $-OCOCH_3$) , 9.22(S ,1H , NH attached to SO_2 group); Anal.calcd(%) for $C_5H_9NO_4S$: C 33.51%, H 5.06% , N 7.82%, S 17.89% .Found :C 32.71% , H 4.56% , N 7.22%, S 17.69%.

Methyl (per fluoro phenyl) sulfonyl carbamate (3b):

Yield:65%; M.p: 128-129^{O}C ; IR(KBr): 3215Cm^{-1} (-NH), 2915 & 2875 Cm^{-1} (Aliphatic γ_{C-H}), 1667 Cm^{-1} (C=O), 1358 & 1279 (SO_2), 1269 Cm^{-1} (C-O); H^1-NMR(300Hz,DMSO-d6):δ 3.69 (s, 3H, $-CH_3$ of $OCOCH_3$), 9.22(s, 1H, NH attached to SO_2 group); Anal.calcd(%) for $C_8H_4F_5NO_4S$: C 31.49%, H 1.32% , F 31.13%, N 4.59%, S 10.51% .Found :C 30.69% , H 0.82% , F 30.33%, N 3.99%; S 10.31%.

Methyl (4- tri fluoro methyl) benzene (3c) Yield: 58%; M.p: 157-158 ^{O}C ; IR(KBr): 3213 Cm^{-1} (-NH), 2915 & 2875 Cm^{-1} (Aliphatic γ_{C-H}), 1663 Cm^{-1} (C=O), 1348 & 1270 (SO_2), 1265 Cm^{-1} (C-O); H^1-NMR(300Hz, DMSO-d63.68 (s, 3H,$-CH_3$ of $OCOCH_3$), 7.79-7.90(m,4H,C_6H_4 group); Anal.calcd(%) for $C_9H_8F_3NO_4S$: C 38.17%, H 2.85% , F 31.13%, N 4.95%, S 11.32% .Found :C 37.37% , H 2.35% , F 19.32%, N 4.35%, S 11.12% .

Methyl (4-nitro phenyl) sulfonyl carbamate (3d): Yield: 62%; M.p: 182-183 ^{O}C; IR(KBr): 3203 Cm^{-1} (-NH), 2915 & 2875 Cm^{-1} (Aliphatic γ_{C-H}), 1673 Cm^{-1} (C=O), 1349 & 1268 (SO_2), 1259 Cm^{-1} (C-O); H^1-NMR(300Hz,DMSO-d6 3.65 (s,3H, CH_3 of $OCOCH_3$), 8.21-8.41(m,4H,C_6H_4 group) , 8.97 (s ,1H, NH attached to SO_2 group); Anal.calcd(%) for $C_{/8}H_8N_2O_6S$: C 36.92%, H 3.10% , N 10.77%, S 12.32% .Found : C 36.12% , H 2.60% , N 10.17%, S 12.12% .

Methyl (4-bromo phenyl) sulfonyl carbamate (3e): Yield:65%; M.p: 174-175^{O}C ; IR(KBr): 3217Cm^{-1} (-NH), 2915 & 2875 Cm^{-1} (Aliphatic γ_{C-H}), 1680 Cm^{-1} (C=O), 1352& 1273 (SO_2), 1263 Cm^{-1} (C-O); H^1-NMR(300Hz,DMSO-d6):δ 3.59(s, 3H, CH_3 of $OCOCH_3$) , 7.77-7.87(m,4H, C_6H_4 group),8.89(s ,1H , NH attached to SO_2 group); Anal.calcd(%) for $C_{/8}H_8BrNO_4S$: C 32.67%, H 2.74% , Br 27.17%, N 4.76%, S 10.90% .Found : C 31.87% , H 2.24% , Br 26.57%, N 4.16%, S 10.70%.

N-((5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) carbamoyl) cyclopropane sulfonamide (4a): Yield:66%; M.p: 164-165^{O}C;IR(KBr): 3356 and 3263 (asymmetric and symmetric stretching of $-NH_2$ group), 3052 (stretching vibration of pyrazole ring - H), 2940 and 2895 of (CH_2 and CH_3 aliphatic –CH stretching), 1670 (stretching of C=N thiadiazole), 1375 -1 487 (stretching vibrations of pyrazole ring), 1395 (Geminal $C(CH_3)_2$ stretching vibration) and 695 Cm^{-1} (stretching of C-S-C of thiadizole); H^1-NMR(300Hz,DMSO-d6): δ, PPM. 1.27(s, 6H, two geminal CH_3 groups) , 4.63(S, 4H, two CH_2 groups of acetals) , 4.99 (s, 2H , $-CH_2$ - flanked between pyrazol and thiadizol ring), 6.99(s, 2H, $-NH_2$ group attached to thiadiazole ring) and 7.30 (s, 1H, of pyrazole ring) ;Anal. calcd (%) for $C_{11}H_{15}N_5O_2S$: C 46.16% , H 5.37% and N 24.89%.Found: C 46.16% , H 4.87% and N 24.69%.

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

1-(1-((5-nitrbenzo [d] oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6yl)-3-phenyl urea(8a): Yield:70%; M.p: 143-1450C; IR(KBr): 3160(γ P-NH), 3052(γAr-H), 2940&2895(Aliphatic γC-H), 1663 (NH-CO), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO2), 1300(C-O/δc-o) 1250(P=O), 954 cm-1 (P-O); H1-MR(300Hz,DMSO-d6):δ 4.99 (s, 2H, -N-CH2-benzoxazole) 5.29 (s, 4H, two CH2 groups attached to phosphorus moiety), 6.15 (S,2H,-NH-CO-NH attached to phosphorus moiety),7.19-7.61(m, 5H , C6H5 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of

pyrazole ring), 8.05-8.26(m, 3H, of benzoxazol ring); 13C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 ,141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 152 , 139.4 , 121.6 , 128.9 and 128.0 corresponding to C1 , C2 , C3 , C4 , C5 , C6 , C7 , C8 , C9 , C10 , C11 , C12 , C13 , C14 , C15 , C16 & C20 , C17 & C19 andC18;^{31}PNMR(161.89MHz,DMSO-d6):δ -11.20 , 1.36 ; Anal.Calcd (%) For $C_{20}H_{17}N_6O_7P$: C 49.59%, H 3.54%, N 17.35%, P 6.39% Found: C 48.79%, H 3.04%, N 16.75 %, P 5.69%.

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

1-(4-methoxy)-3-(1-((5-nitrbenzo[d]oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-1H-[1,3,2] dioxaphosphepino[5,6-c]pyrazol-6yl)urea(8c): Yield: 70%; M.p: 156-158^{0}C; IR(KBr): 3230 **(**$\gamma_{P\text{-}NH}$), 3065 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1665 **(**NH-CO**),** 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1310($\gamma_{C\text{-}O}$/ $\delta_{c\text{-}o}$) 1254 (P=O**),** 958cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 3.83 (s,1H, -OCH_3 of methoxyphenyl), 4.99 (s,2H,-N-CH_2-benzoxazole), 5.29 (s,4H,two CH_2 groups attached to phosphorus moiety),6.15(s,2H,-NH-CO-NH attached to phosphorus moiety), 6.97-7.51 (m, 4H,C_6H_4 ring attached to –NH –CO-NH-), 7.30 (s,1H,CH of pyrazole ring), 8.05-8.26 (m,3H,of benzoxazole ring); ^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 152.0 , 131.7 , 119.8 , 114.5 , 158.9 and 55.8 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} , C_{18} and C_{21};^{31}P NMR (161.89MHz, DMSO-d6): δ -11.48; Anal. Calcd (%) For $C_{21}H_{19}N_6O_8P$: C 49.03%, H 3.72%, N 16.34%, P 6.02% Found: C 48.28%, H 3.22%,N 15.74%, P 5.32%. *1-(4-chlorophenyl)-3-(-1((5-nitrobenzo[d]oxazol-2-yl)methyl)-6-oxido-4,8-dihydro-*

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

N-(1-((5-nitrobenzo [d] oxazol -2-yl)methyl)-6-oxido-4,8-dihydro-1H - [1,3,2]dioxaphospheno [5,6-c] pyrazol-6-yl) morpholine-4-carboxamide(8e): Yield: 65%; M.p: 192-194^{0}C; IR(KBr): 3190 ($\gamma_{P\text{-}NH}$), 3068 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$), 1678 (-CO-N=), 1455 & 1390(benzoxazole ring) ,1375&1487(pyrazole ring), 1355& 1330(-NO_2), 1310($\gamma_{C\text{-}O}/\delta_{c\text{-}o}$) 1250 (P=O**),** 954 (P-O**)**cm^{-1}**;** H^1-MR(300Hz,DMSO-d6):δ 3.31-3.65 (m, 8H of morpholine attached to –CO-NH-), 4.99 (s, 2H,-N-CH_2-benzoxazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15(s, 1H.-CO-NH attached to phosphorus moiety). 7.30(s, 1H, CH of pyrazole ring), 8.05-8.26(m, 3H of benzoxazol ring); ^{13}C-NMR (75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7, 56.3 , 152.6 , 111.5 , 121.7 , 120.5 , 115.2 , 142.4 , 156.1 , 158.5 , 46.3 and 65.7.corresponding to C_1 , C_2 , C_3, C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} & C_{18} and C_{16} & C_{17} ;^{31}P NMR (161.89MHz, DMSO-d6): δ-7.15; Anal. Calcd (%) For $C_{18}H_{19}N_6O_8P$: C 45.20%, H 4.00 %, N 17.57%, P 6.48% Found: C 44.40%, H 3.50 %, N 16.97%, P 5.78%.

*N-(1-((5-nitrobenzo [d] oxazol -2-yl) methyl)-6-oxido-4, 8-dihydro -1H - [1, 3, 2] dioxa phospheno [5,6-c] pyrazol-6-yl) piperidine-1-carboxamide(8f):*Yield: 65%; M.p: 169-171^{0}C; IR(KBr): 3220 ($\gamma_{P\text{-}NH}$), 3055 ($\gamma_{Ar\text{-}H}$),

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

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

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

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

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

1-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3-(p-tolyl)urea(12b): Yield: 65% ; M.p: 172-174 ^{o}C; IR(KBr): 3310 (γ_{P-NH}), 3055 (γ_{Ar-H}), 2940&2895(Aliphatic γ_{C-H}), 1660 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 245(P=O**),** 950 cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 2.34(s,3H,-$CH_3$of group),4.99(s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s,2H,-NH-CO-NH attached to phosphorus moiety), 7.21-7.56 m, 4H of C_6H_4 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR (75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 ,121.6, 152.8, 135.2 , 152.0 , 136.4 , 121.5 , 129.2 , 136.8 and 21. 3 corresponding to C1 , C_2 , C_3

, C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17}& C_{19}, C_{18} and C_{21}; ^{31}P NMR (161.89MHz, DMSO-d6): δ -11.53; Anal. Calcd (%) For $C_{21}H_{20}N_5O_4PS$: C 53.73%, H 4.29%, N 14.92%, P 6.60 %, S 6.83%Found: C 52.93% , H 3.79 %, N 14.32% , P 5.90%, S 6.63%.

*1-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3-(4-methoxyphenyl)urea(12c):*Yield: 65%; M.p: 145-147 ^oC; IR(KBr): 3315 ($\gamma_{P\text{-}\underline{NH}}$), 3065 ($\gamma_{Ar\text{-}H}$), 2940&2895 (Aliphatic $\gamma_{C\text{-}H}$), 1665 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1254 (P=O)958 cm^{-1} (P-O**);** H^1-MR(300Hz,DMSO-d6):δ 3.83(s.3H,-OCH3 group),4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15(s,2H,-NH-CO-NH attached to phosphorus moiety),6.97-7.51 (m, 4H of C_6H_4 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR (75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 152.0 , 131.7 , 119.8 , 114.5 , 158.9 and 55.8. corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19}, C_{18} and C_{21}; ^{31}P NMR (161.89MHz, DMSO-d6): δ -11.48; Anal. Calcd (%) For $C_{21}H_{20}N_5O_5PS$:C 51.96%, H 4.15 %, N 14.43%, P 6.38 %, S 6.61%Found: C 51.16%, H 3.65%, N13.83%, P 5.62%, S 6.41%.

*1-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-3-(4-chlorophenyl)urea(12d):*Yield: 60% ; M.p: 182-184 ^oC; IR(KBr): 3320 ($\gamma_{P\text{-}\underline{NH}}$), 3067 ($\gamma_{Ar\text{-}H}$), 2940&2895 (Aliphatic $\gamma_{C\text{-}H}$), 1670 **(**NH-CO**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1256 (P=O)956 (P-O**),**725cm^{-1}(-Cl**);** H^1-MR(300Hz,DMSO-d6):δ 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.0 (s,2H,-NH-CO-NH attached to phosphorus moiety), 7.47-7.75 (m, 4H of C_6H_4 ring attached to –NH –CO-NH-), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 ,118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 152.0 , 137.5 , 120.8 , 129.0 and 133.3 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} , C_{16} & C_{20} , C_{17} & C_{19} and C_{18}.;^{31}PNMR(161.89MHz,DMSO-d6):δ -9.23 ; Anal.Calcd (%) For $C_{20}H_{17}ClN_5O_4PS$: C 49.04%, H 3.50%, Cl 7.24%, N 14.30%, P 6.32%, S 6.55%Found: C 48.24% , H 3.00 %, Cl 6.54%, N 13.70%, P 5.62%, S 6.35%.

N-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino [5,6-c]pyrazol-6yl)-morpholine-4-carboxamide(12e): Yield: 65% ; M.p: 194-196 ^oC; IR(KBr): 3325 ($\gamma_{P\text{-}\underline{NH}}$), 3068 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$) , 1654 **(**-CO-N=**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1259 (P=O**)** 961 cm^{-1} (P-O**);**H^1-MR(300Hz,DMSO-d6):δ 3.31 (t, 4H –CH2- attached to Nitrogen of morpholine ring, J=7.1 Hz, H-2^I, H-$3^{I)}$, 3.60(t, 4H,-CH2- attached to oxygen of morpholine ring, J=7.1 Hz, H-3^I. H-2^I), 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s,1H,-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 158.5 , 46.3 and 65.7 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} , C_{14} , C_{15} & C_{28} and C_{16} & C_{17} ; ^{31}P NMR (161.89MHz,DMSO-d6):δ-7.15 ; Anal.Calcd (%) For $C_{18}H_{20}N_5O_5PS$: C 48.10%, H 4.49%, N 15.58%,P 6.89% , S 7.13%Found: C 47.30% , H 3.90%, N 14.98%, P 6.29%, S 6.93%.

N-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-piperidine-1-carboxamide(12f): Yield: 65% ; M.p: 185-187 ^oC; IR(KBr): 3315 ($\gamma_{P\text{-}\underline{NH}}$), 3055 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$) , 1658 **(**-CO-N=**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1259 (P=O**)** 963cm^{-1}(P-O**);**H^1-MR(300Hz,DMSO-d6):δ 1.53-3.77 (m, 10H of piperidine attached to –CO-NH-), 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s, 1H,-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18 (m, 4H, of benzthiazol ring).;^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 158.5 , 51.4 ,51.0 and 46.6 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13} ,C_{14},C_{15}&C_{28},C_{16}&C_{17}andC_{19}; ^{31}PNM(161.89MHz,DMSO-d6): δ-5.23; Anal.Calcd (%) For $C_{19}H_{22}N_5O_4PS$:C 51.00%, H 4.96%, N 15.65%, P 6.92%, S 7.17% Found: C 50.20, H 4.56%,N 14.95%, P 6.22%,S 6.97%.

N-(1-(bezo[d]thiazol-2-ylmethyl)-6-oxido-4,8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6yl)-4-methylpiperazine-1-carboxamide(12g): Yield: 65% ; M.p: 165-167 ^oC; IR(KBr): 3320 ($\gamma_{P\text{-}\underline{NH}}$), 3070 ($\gamma_{Ar\text{-}H}$), 2940&2895(Aliphatic $\gamma_{C\text{-}H}$) , 1663**(**-CO-N=**)** 1474,1344,715 &620 (benzthiazole ring) ,1375&1487(pyrazole ring), 1246 (P=O**)** 951cm^{-1}(P-O**);**H^1-MR(300Hz,DMSO-d6):δ 2.26(s,3H.-CH3 group of 4-methyl piperazine),

2.27(t,4H, $-CH_2-\underset{CH_3}{N}-CH_2-$ of piperazine attached to carbamido moiety, J=7.1 Hz , H-2^I,H-3^I), 3.40(t,4H,-CH2-N-CH2- of piperazine ring attached to carbmido moiety=7.1Hz , H-2^I and H-3^I) , 4.99 (s, 2H, -N-CH_2-benthiaazole), 5.29 (s, 4H, two CH_2 groups attached to phosphorus moiety), 6.15 (s,1H,-CO-NH attached to phosphorus moiety), 7.30(s, 1H, CH of pyrazole ring), 7.53-8.18(m, 4H, of benzthiazol ring);^{13}C-NMR(75MHz, DMSO-d6)δ 135.2 , 118.0 , 141.0 , 61.8 , 60.7 , 50.5 , 163.5 , 121.8 , 124.5 , 125.3 , 121.6 , 152.8 , 135.2 , 156.5 , 49.0 , 24.9 and 23.8 corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{12} , C_{13},C_{14},C_{15}& C_{19} , C_{16}&C_{18} and C_{17}; Anal.Calcd(%) For $C_{19}H_{23}N_6O_4PS$: C 49.35%, H 5.01%, N 18.17%, P 6.70%,S 6.93% Found: C 48.55% , H 4.51%, N 17.57%,P 6.00% ,S 6.73%.

Biological Activity:

The antimicrobial activity [37] of chemical compound is influenced by physical and biological characteristics [38].It has been well established that physiological activity is a function of the chemical structure of compound [39].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 [40-42].

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

Antibacterial Activity:

The antibacterial activity [43] of final compounds ***7a-o*** synthesized was screened against the Staphylococcus aureus (gram positive), BacillusCerus**,** Escherichia coli (gram negative) and Pseudomonas aeruginosa organism. In this series compounds consisting with two nitro groups **7i**, nitro group and 4-bromo benzene **7j**, nitro group & penta fluoro benzene **7g**, tri fluoro methyl group and 4-bromo benzene **7o** and nitro group & tri fluoro methyl group **7h** showed increased effect in their antimicrobial activity than other derivatives of the series. Amoxicillin and Cefaclor are tested as reference compounds to compare the activity.

Antibacterial Activity of N-((5-((6-OXIDO-6 - (4 SUBSTITUTED PHENOXY) - 4,8 - DIHYDRO-1H-[1,3,2] DIOXAPHOSPHEPINO [5,6-C] PYRAZOL-1-YL) METHYL) -1,3,4-THIADIAZOL-2 - YL) CARBAMOYL) CYCLO PROPYL / (2,3,4,5,6-PETAFLUORO / 4-TRIFLUOROMETHYL / 4-NITRO/ 4 - BROMO) BENZENE SULFONAMIDES (7a - o):

COMPOUND	**Zone of inhibition (mm)**			
	Staphylococus aureus NCCS2079 250(µg/disc)	**Bacillus Cerus NCCS2106 250(µg/disc)**	**Escherichia Coli NCCS2065 250(µg/disc)**	**Pseudomonas aeruginosa NCCS2200 250(µg/disc)**
7a	05	07	06	07
7b	07	09	08	09
7c	06	08	07	08
7d	10	12	11	12
7e	09	11	10	11
7f	08	10	09	10
7g	11	13	12	13
7h	10	12	11	12
7i	15	17	6	17
7j	13	15	14	15
7k	07	09	08	09
7l	10	12	11	12
7m	09	11	10	11
7n	13	15	14	15
7o	11	13	12	13
Amoxicillin	**21**	**27**	**24**	**22**
Cefaclor	**19**	**22**	**19**	**22**

Antifungal Activity

The antifungal activity of final compounds **7a-o** synthesized was screened against Aspergillusniger, Canadida albicans. Ketoconazole is tested as reference compound to compare the activity. In this series compounds bearing two nitro groups **7i**, nitro group and 4-bomo benzene **7j**, tri fluoro methyl group and 4-nitro group **7n**, nitro group & penta fluoro benzene **7g** and trifluoro methyl group & 4-bromo benzene **7o** were offered increased effect on their anti fungal activity than other derivatives.

Antifungal Activity of N-((5-((6-OXIDO-6 - (4 SUBSTITUTED PHENOXY) - 4,8 – DIHYDRO - 1H - [1,3,2] DIOXAPHOSPHEPINO [5,6-C] PYRAZOL – 1 –Y L) METHYL) - 1,3,4-THIADIAZOL-2 - YL) CARBAMOYL) CYCLO PROPYL / (2,3,4,5,6-PETAFLUORO / 4-TRIFLUOROMETHYL / 4-NITRO/ 4 - BROMO) BENZENE SULFONAMIDES (7a - o):

COMPOUND	Zone of inhibition (mm)	
	Aspergillus niger NCCS 1196 250(µg/dsic)	**Canadida albicans NCCS 3471 250 (µg/ dsic)**
7a	06	04
7b	09	07
7c	07	05
7d	12	10
7e	10	08
7f	09	07
7g	13	14
7h	11	09
7i	16	14
7j	14	12
7k	08	06
7l	11	09
7m	09	07
7n	14	12
7o	12	10
Ketoconazole	**22**	**25**

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