ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis Characterization and Antimicrobial activity of 6 - oxido - 1 - ((5 -(4 - oxo - (2 - (pyridine - 3 - yl) thiazolidin - 3 - yl) 1,3,4 - thiadiazol - 2 - yl) methyl) - 4,8 - dihydro- 1H-[1,3,2] dioxaphosphepino [5,6-c] pyrazol - 6 - yl) carbamates.

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ABSTRACT

Novel derivatives of pyrazole dioxaphosphepino carbamates **(7a-e)** were synthesized from condensation reaction of dichlorophosphoryl carbamates ***(*6a – e*)*** and - bis (hydroxymethyl) derivative **(5),** which was obtained by deprotection of 6,6 - dimethyl - 4,8 - dihydro - dioxepino pyrazol derivative **(4)**, which in turn was synthesized by treatment of Schiff's base (**3**) with 2-mecaptoacetic acid in presence of $ZnCl_2$. The synthon **(3)** was obtained by condensation reaction between nicotinaldehyde **(2)** and amine **(1)**. The synthetic structures were established by spectral and microanalysis analysis, which were subjected to various biological activities viz., antimicrobial.

Keywords: Antibacterial; Antifungal; deprotection; dichloro phosphoryl carbamates; Pyrazole.

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ISSN: 0975-8585

INTRODUCTION

Carbamates of hetero cyclic compounds are important intermediates in the synthesis of compounds in pharmaceutical, medicinal, agrochemical and polymer chemistry, which possess biologically potent properties such as inhibitor of HIV, anti convulsants, antibacterials, antiepileptics and enzyme inhibitors [1-3].

Thiazolidinone moiety associated with broad spectrum of biological activities including anti-bacterial, anti-fungal, anti-inflomatory, hypotonic, anti-convulsant, anti -tubercular, anti-viral, antihistamic, cardiovascular, anthelmintic and anti- cancer. These can all so used as herbicides and insecticides [4 -6].

Organo phosphorus compounds consisting with 1, 3, 4 - Thiadiazole are versatile pharmacophores. These widely used as diuretic agents, CNS depressant, hypoglycemic agent, anti-inflammatory agent and anti microbial agent[7-10]. In support of our study pyrazoles and derivatives function as dyestuff, catalyst, polymerizing agents, drugs , herbicides and fungicides[11].they also possess various pharmacological activities such as anti-fungal activity[12], monoamineoxidase (MAO) inhibitory activity [12,13], antiparkinson[14], anticonvulsant[15]. Pyrazole derivatives are valuable vasodialating and vasoconstructing drugs.

In view of the numerous commercial applications of organophosphorus compounds, we synthesized pyrazole Organo phosphorus -Nitrogen heterocyclic carbamtes containing Thiazolidinone as core moiety, also they screening for possible biological and pharmacological activities.

EXPERIMENTAL

General Procedures

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 Bruker DRX500MHz 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.

5-((6,6-dimethyl-4,8-dihydro-1H-[1,3] dioxepino [5,6-c] pyrazol-1-yl) methyl)-1,3,4- thiadiazol - 2 - amine **(1) (M.p.)** and were prepared according to the reported procedure for their preparation in literature[**16-19**].

Preparation of Intermediates: [**16; 17**]

Reagents and reaction conditions: (i) Dry toluene, -15 to -5^{0}C, 30min, stirring.

Compound	R Name	Structure
a	Cyclopropyl	
b	Cyclohexyl	
c	Tetra hydro-2H-pyran	
c	Tetrahydro-2H-thiopyran	
d	perfluorophenyl	

Figure 1: Synthetic scheme of dichlorophosphoryl carbamates

ISSN: 0975-8585

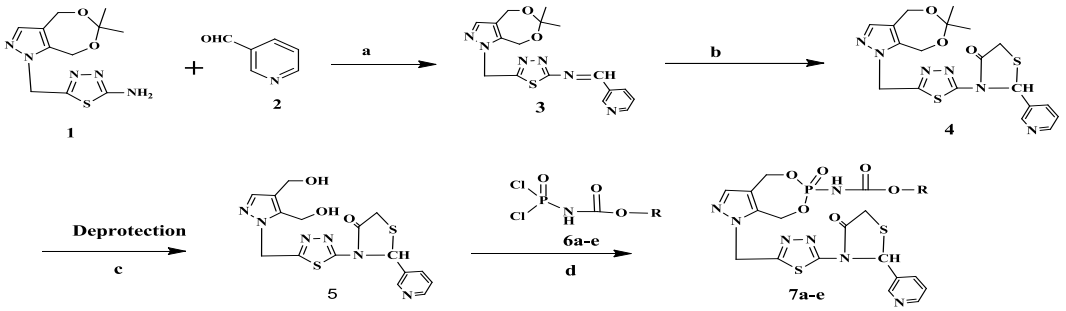
A solution of cyclopropyl alcohol (0.51g, 0.004mole) in dry toluene (25ml) was added drop wise to Phosphorisocyanatidic dichloride (6, 0.64g, 0.004 mole) in dry toluene (30ml). After the addition, the temperature of the reaction mixture was maintained between -15 to - 5^0c for 30 minutes. Later the temperature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

Similar treatment of Cyclohexyl alcohol/ Terahydro - 2H - pyran - 4 - yl alcohol / Tetrahydro-2H-thiopyran - 4 - yl alcohol/ 2,3,4,5,6-pentaflurophenol with Phosphor isocyanatidicdichloridein presence of dry toluene at -15 to -5^0c for 30 minutes offered the respective derivatives of Cyclohexyl / Terahydro - 2H - pyran - 4-yl / Tetrahydro - 2H - thiopyran - 4-yl/. Perflurophenyldichlorophosphoryl carbamates. These were confirmed by spectral and micro analysis.(table.1)

Table 1: Reaction time and details of the dichlorophosphoryl carbamates 6a-e

COMPOUND (*6*)	NAMEOFTHE DICLORIDATES	REACTION TIME (minutes)	mp (^{0}C / mm)	YIELD (%)
6a	Cyclopropyldichlrophosphoryl carbamate	30	138-140	50
6b	Cyclohexyldichlro phosphoryl Carbamate	45	149-151	44
6c	Tetrahydro-2H-pyran-4-yl dichlrophosphoryl carbamate	60	162-164	46
6d	Tetrahydro-2H-thiopyran-4-yldichlro phosphoryl carbamates	60	154-156	45
6e	Perfluorophrnyldichlro phosphoryl carbamate	60	169-171	43

Synthesis of 5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)-N-(pyridin-3-ylmethylene)-1,3,4-thiadiazol-2-amine (3):[18]



Reagents and conditions: **(a)** Absolute alcohol, acetic acid , 100°C, heated on steem bath for 5-6 hrs; **(b)** $HSCH_2COOH$, diaxane, anhydrous $ZnCl_2$, refluxed for 8 hrs ; **(c)** Dry acetone, CH_3CN/ H_2O (9/1), $H_3PW_{12}O_{40}$ nH_2O(5mol%), RT, rx^n mixture stirred 1 hr , inert atmosphere; **(d** Dry toluene, tri ethyl amine, THF, addition at 5°C kept at Rfor 2 hrs, rx^n mixture heated at 50-60°C for 4hrs.

Compound	R Name	Structure
a	Cyclopropyl	
b	Cyclohexyl	
c	Tetra hydro-2H-pyran	
c	Tetrahydro-2H-thiopyran	
d	perfluorophenyl	

Figure 2: synthetic scheme for the preparation of (**7a - e**).

Equimolar quantity of 5-**((**6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl**)** methyl**)** - 1,3,4-thiazol-2-amine **(1)** and Nicotinaldehydes **(2)** were dissolved in absolute alcohol, to this one a drop of acetic acid was added, then heated on a steam bath for 5-6 h at 100°C. After standing for 24 h at room

temperature. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (9:1) solvent mixture as an eluent. At the end of reaction product 5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)-N-(pyridin-3-ylmethylene)-1,3,4-thiadiazol-2-amine **(3)** was dried and recrystalised from warm absolute alcohol, (65%, M.P136-138^{0}C) IR (KBR)Cm^{-1} 3040 (Ar-H str), 2940 & 2895 (CH_2 and aliphatic C-H stretching), 1620(C=N str), 1375-1487(pyrazole ring str), 1140 (C-O str) ^{1}H NMR (400MHz, DMSO-d6) δ, ppm 1.27 (s, 6H, two geminial CH_3 groups), 4.63(s, 4H, two CH_2 group of acetal), 4.99(s, 2H,–CH2- flanked between pyrazole and 1, 3, 4-thiadiazole), 7.30 (s, 1H, of pyrazole), 7.50 (s,1H,N=CH-pyridine) and 7.58-9.07 (m, 4H, CH of pyridine). Anal.calcd (%) for $C_{17}H_{18}N_6O_2S$: C 55.12%, H 4.90%, N 22.69%, S 8.66%. Found: C 54.62%, H 4.40%, N 22.09%, S 8.46%.

Synthesis of 3-(5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c] pyrazol -1-yl) methyl)-1,3,4-thiadiazol- 2-yl)-2-(pyridin-3-yl)-thiazolidin-4-one(4)[19;20]

A mixture of Schiff's base (**3**) (0.01mol) and mercaptoacetic acid (0.01mol) dissolved in dioxane 20 ml), anhydrous zinc chloride (0.5 mg) was added and refluxed for 8 hrs. The progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate (7:3) solvent mixture as mobile phase .The reaction mixture was cooled and resulting solid was washed with sodium bicarbonate solution and recrystalised from absolute alcohol. (65%, M.P152-154^{o}C) IR (KBr) Cm^{-1} 3040(–Ar-H str), 2940 and 2895 (CH_2 and CH_3 aliphatic CH str), 1690(>C=O str), 1375-1487 (pyrazole str), 1188(C-S str)and 1140 (C-O, str) . ^{1}H NMR (400MHz, DMSO-d6) δ, ppm 1.27 (s, 6H, twogeminialCH_3 groups), 3.85&3.95 (s,2H,-CH_2- of thiazolidin-4-one),4.63(s, 4H, two -CH_2- groups of acetal), 4.99(s,2H,–CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 6.44(d,1H,-CH- of thiazolidin-4-one attached to pyridine ring), 7.30 (s, 1H, of pyrazole) and 7.38-8.59 (m, 4H, -CH- of pyridine). Anal.calcd (%) for $C_{19}H_{20}N_6O_3S_2$: C 51.34%, H 4.53%,N 18.91%, S 14.43%. Fou50.54%,H 4.53%, N 18.31%, S 14.23%.

Synthesis of 3-(5-((4,5bis (hydroxymethyl) - 1H - pyrazole - 1 - yl) methyl) - 1, 3, 4 - thiadiazol - 2 -yl) -2-(pyridine-3-yl) thiazolidin-4-one (5)

The isopropylidenation of 1, 2-diols was carried out by a procedure as reported in the literature[21].A suspension of 3-(5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)- 1,3,4-thiadiazol-2-yl)-2-(pyridin-3-yl)-thiazolidin-4-one **(4)** (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 mobile phase. After completion of the reaction, the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (3×20 ml) and water, the combined organic layer was dried with Na_2SO_4 and concentrated in vacuum to give the crude product. The crude product was purified by column chromatography on silica gel (60-120 mesh) with 15-30% ethyl acetate in cyclohexane as an eluent. (70%, M.P169-171^{O}C) IR (KBr)Cm^{-1} 3520 (ν_{O-H}, intermolecular H-bonding),3040 (Ar-H str), 2940 & 2895 (CH_2 and aliphatic C-H str), 1690(>C=O str),1620(C=N str), 1375-1487(pyrazole str), 1188(C-S str) and 1140 cm^{-1} (C-O, str). ^{1}H NMR (400MHz, DMSO-d6) δ, ppm3.65 (s, 2H, two –OH groups having Intramolecular H-bonding), 3.85 (s,1H_a,-CH_2- of thiazolidinone), 3.99 (d, 1H_b –CH_2 of thiazolidinone) 4.61 (s, 2H, - CH_2-group of dimethanol),4.79(s,2H,-CH_2 group of dimethanol), 4.99(s,2H,–CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 7.30 (s, 1H, of pyrazole) 6.44(s,1H,-CH- of thiazolidin-4-one attached to pyridine ring) and 7.38-8.59 (m, 4H, -CH- of pyridine). Anal.calcd (%) for $C_{17}H_{18}N_6O_2S$: C 47.51%, H 3.99%, N 20.78%, S 15.86%. Found: C 46.71%, H 3.99%, N 20.78%, S 15.66%.

Synthesis of Cyclopropyl/ cyclohexyl /terahydro-2H-pyran-4-yl/tetrahydro-2H-thiopyran-4-yl/ perfluorophenyl (6-oxido-1-((5-(4-oxo-(2-(pyridin-3-yl)thiazolidin-3-yl) 1,3,4-thiadiazol-2-yl) methyl) -4,8-dihydro- 1H-[1,3,2] dioxaphosphepino[5,6-c]pyrazol-6-yl) carbamates (7a-e)

A solution of Cyclopropyl dichlorophosphoryl carbamate **(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 3-(5-((4,5bis (hydroxymethyl)- 1H-pyrazole-1-yl)methyl)-1, 3, 4-thiadiazol-2-yl)-2- (pyridine-3-yl) thiazolidin-4-one**(5)** (0.002mole) and triethylamine (0.004mole) in 30 ml of dry toluene and 10ml of tetrahydrofuran at 5^{0}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^{O}C and maintained for 4 hours with stirring. The

ISSN: 0975-8585

completion of the reaction was monitored by TLC analysis. After the reactin Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystalized from aqueous 2-propanol to get pure compound of cyclopropyl(6-oxido-1-((5-(4-oxo-(2-(pyridin-3-yl)thiazolidin-3-yl)- 1,3,4-thiadiazol-2-yl) methyl) -4,8-dihydro- 1H-[1,3,2] dioxaphosphepino [5,6-c]pyrazol-6-yl) carbamate **(7a)**, yield 65% and mp 163-165^{O}C. The similar procedure was adopted to synthesize **7b-e** by the reaction between **(5)**with Cyclohexyl alcohol**(6b)**Terahydro-2H-pyran-4-yl alcohol **(6c)** Tetrahydro-2H-thiopyran-4-yl alcohol**(6d)** 2,3,4,5,6-pentaflurophenol**(6e)** respectively. The Structures of **7a-e** were established by IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis and respective data of these analyses were shown in tables.2-.8.

Physical, analytical and spectral data for the synthetic compounds 7a- e

Table 2: IR (KBr)) spectral data of (7a-e)

COMPOUND (*7*)	$\bar{\nu}/\delta$, cm^{-1}						
	P-NH	P=O	>C=O of Thiazolidinone	Carbamate carbonyl	Pyrazole	C-S	P-O-C
7a	3325	1240	1690	1680	1375-1487	1180	1190
7b	3323	1245	1695	1675	1370-1485	1185	1185
7c	3320	1248	1692	1683	1373-1490	1183	1191
7d	3328	1243	1693	1682	1380-1495	1187	1194
7e	3315	1230	1698	1685	1385-1495	1188	1197

Table 3: ^{1}H-NMR spectral data (7a-e)

Comp	^{1}H – NMR (DMSO – d_6)(δ_{ppm})
7a	0.34- 0.58 (m,4H, -CH_2 -of cyclopropyl) 2.69(m,1H,-CH- of cyclopropyl ring attached to carbamate moiety), 3.85(d,1Ha,-CH_2- of thiazolidinone), 3.95(d,1H_b,-CH_2- of thiazolidinone),4.99(s,2H,–CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.29 (s, 4H, two CH_2 group of acetal),5.44(d,1H,O=C-CH(Cl)-of 3-chloro azetidin-2-one), 6.44(s,1H,-CH- of thiazolidin-4-one attached to pyridine ring), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, CH of pyridine) and 8.0(s,1H,-NH- of carbamate moiety).
7b	1.47 – 1.80 (m, 10H, -CH_2- of cyclohexyl),3.91 (m, 1H, -CH- of cyclohexyl attached to carbamate moiety), 3.85(d,1Ha,-CH_2- of thiazolidinone), 3.95(d,1H_b,-CH_2- of thiazolidinone),4.99(s,2H,-CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.29 (s, 4H, two -CH_2- group of acetal),6.44(s,1H,-CH- of thiazolidin-4-one attached to pyridine ring), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.0(s,1H,-NH- of carbamate moiety).
7c	1.97 - 1.72 (m, 4H, -CH_2- of tetrahydro-2H-pyran), 3.65 (t, 4H, -CH_2-O-CH_2 of tetrahydro-2H-pyran, J=3.60Hz H-2^{I} and H-3^{I}), 3.85(d, 1Ha, -CH_2 - of thiazolidinone), 3.95(d,1H_b,-CH_2- of thiazolidinone),4.07 (m, 1H,-CH- of tetrahydro-2H-pyran attached to carbamate moiety), 4.99(s,2H,-CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.29 (s, 4H, two -CH_2- group of acetal),6.44(s,1H,-CH- of thiazolidin-4-one attached to pyridine ring), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.0(s,1H,-NH- of carbamate moiety).
7d	2.06 - 1.81 (m, 4H, -CH_2- of terahydro-2H-thiopyran),2.57 (t, 4H, -CH_2-S-CH_2 of tetrahydro-2H-thiopyran, J=2.52Hz H-2^{I} and H-3^{I}), 3.85(d,1Ha,-CH_2- of thiazolidinone), 3.95(d,1H_b,-CH_2- of thiazolidinone),4.17 (m, 1H, -CH of tetrahydro-2H- thiopyran attached to carbamate moiety), 4.99(s,2H,-CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.29 (s, 4H, two CH_2 group of acetal),6.44(d,1H,-CH- of thiazolidin-4-one attached to pyridine ring), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59(m, 4H, -CH- of pyridine) and 8.0(s,1H,-NH- of carbamate moiety)
7e	3.85(d,1Ha,-CH_2- of thiazolidinone), 3.95(d,1H_b,-CH_2-of thiazolidinone),4.99(s,2H,-CH_2- flanked between pyrazole and 1,3,4-thiadiazole),5.29 (s, 4H, two CH_2 group of acetal), 6.44(s,1H,-CH- of thiazolidin-4-one attached to pyridine ring), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.0(s,1H,-NH- of carbamate moiety).

ISSN: 0975-8585

Table 4: ^{13}C-NMR spectral data (7a-e)

Comp	^{13}C NMR (DMSO – d_6)(δ_{ppm})
7a	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 171.2 , 33.5 , 72.3 ,132.6 , 134.3, 123.0, 147.3,150.1, 150.1,157.6, 43.0 and 3.7 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_{18}, C_{15} , C_{17} ,C_{18} and C_{19}&C_{20}.
7b	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 171.2 , 33.5 , 72.3 ,132.6 , 134.3, 123.0, 147.3,150.1, 132.6, 157.6, 76.5, 30.82, 24.1 and 25.7corresponding 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_{17} ,C_{18} , C_{19}&C_{23}, C_{20}&C_{22} and C_{21}.
7c	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 171.2 , 33.5 , 72.3 ,132.6 , 134.3, 123.0, 147.3,150.1, 132.6, 157.6, 72.2, 33.4 and 63.2corresponding 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_{17} ,C_{18} , C_{19}&C_{22} and C_{20}&C_{21}.
7d	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 171.2 , 33.5 , 72.3 ,132.6 , 134.3, 123.0, 147.3,150.1, 132.6, 157.6, 69.3, 32.2 and 25.5 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_{16} , C_{17} ,C_{18} , C_{19}&C_{22} and C_{20}&C_{21}.
7e	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 171.2 , 33.5 , 72.3 ,132.6 , 134.3, 123.0, 147.3,150.1, 157.6, 142.0, 139.3, 142.4 and 140.1 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_{17} ,C_{18} , C_{19}&C_{23}, C_{20}&C_{22} and C_{21}.

Table 5:^{31}P-NMR spectra spectral data of 7a-e:

COMP (7)	^{31}P – NMR (DMSO – d_6) (δ_{ppm})
7a	-10.30, 0.55
7b	-11.50, 0.80
7c	-10.90,0.65
7d	-11.10, 0.70
7e	-9.50, 0.75

Table 6: Physical and Analytical data of 7a-e

COMPOUND	MOLECULAR FORMULA	mp (^{O}C)	YIELD (%)	ELEMENTAL ANALYSIS	
				FOUND	CALCULATED
7a	$C_{20}H_{20}N_7O_6P\,S_2$	163-165 ^{O}C	65%	C:42.91% H:3.17% N: 17.24% P:17.14% S:11.44%	C:43.71% H:3.67% N: 17.84% P:17.84% S:11.64%
7b	$C_{23}H_{26}N_7O_6P\,S_2$	139-141 ^{O}C	60%	C:45.89% H :3.93% N :15.97% P:4.54 % S:10.64%	C:46.69% H :4.43% N :16.57% P:5.24 % S:10.84%
	$C_{22}H_{24}N_7O_7P\,S_2$	183-185 ^{O}C	65%	C:43.72% H :3.58% N :15.92% P : 4.52% S:10.60%	C:44.52% H :4.08% N :16.52% P : 5.22% S:10.80%

ISSN: 0975-8585

	$C_{22}H_{24}N_7O_6P\,S_3$	141-143 ^oC	69%	C :42.54% H :3.47% N :15.48% P : 4.38% S:15.58%	C :43.34% H :3.97% N :16.08% P : 5.08% S:15.78%
	$C_{23}H_{15}\,F_5N_7O_6P\,S_2$	191-193 ^oC	75%	C:40.09% H :1.74% F:13.26 N:13.91% P : 3.89% S:9.29%	C:40.89% H :2.24% F:14.06 N :14.51% P : 4.59% S:9.49%

Biological studies

Condensed heterocyclic systems containing pyrazole, 1, 3, 4 - thiaiazole, thiazolidinone and dioxaphosphepino carbamates have attractive attention of chemist owing to these nuclei having been identified in the literature as the most active phormacores in drug design and synthesis. It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence in biological profiles of that molecule. All Synthesized compounds were screened for their anti-microbial activity by disc diffusion method. Antibacterial activity against *Staphylococus aureus* **(NCCS2079) ,** *Bacillus cerus* **(NCCS 2106),** *Escherichia Coli* **(NCCS 2065) ,** & *Pseudomonas areruginosa* **(NCCS2200)** at the concentration of 250µg/disc and antifungal activity against the *Aspergillus niger* (**NCCS 1196**) and *Candida albicans* (**NCCS 3471**) at the concentration of 250µg/disc. The zone of inhibition and activity index were determined in comparison of the standards drugs Amoxicillin and Ketoconazole. The outcome of this study is presented in tabular form in **table 7**. All these compounds were found to be active against the bacterial and fungal strains.

RESULT AND DISCUSSION

The antimicrobial activity [**22]** of chemical compound is influenced by physical and biological characteristics[**23]**.It has been well established that physiological activity is a function of the chemical structure of compound[**24]**. 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.

As a part of our endeavor to create novel pyrazole organophosohorus heterocyclic compounds of anticipated biological activity from easily accessible

starting materials, here in this paper we report , the preliminary results of our studies on the synthesis of pyrazole dioxaphosphepino carbamates containing 1,3,4 thiadiazol and thiazolidinone (**7a-e**). Compound **(5)** was obtained through a three step strategy on amine **(1)**. In the first step of this strategy involved the conversion of amine **(1)** in to Schiff's base (**3**) using literature procedure[**19].** In view of medicinal importance of Thiazolidinone derivatives, it was considered of interest to append this nucleus on to the N-(pyridin-3-ylmethylene function to form the Thiazolidinone derivative (4), which in the subsequent step was deprotected with CH_3CN/ H_2O (9/1), $H_3PW_{12}O_{40}\,nH_2O$(5mol%) in dry acetone to afford the compound **(5).** Compound **(5)** by treating With various dichlrophosphoryl carbamates (**6a-e**) in Dry toluene, and the presence of tri ethyl amine and THF yields of pyrazole dioxaphosphepino carbamates containing 1,3,4 thiadiazol and thiazolidinone (**7a-e**). All the Synthesized compounds gave satisfactory results of their microanalysis, IR, ^{1}H-NMR, ^{13}C NMR, ^{31}P NMR and MS spectral data which were found to be consistent to the assigned structures.

Organo phosphorus Pyrazole Carbamates containing thiazolidinone (**7a-e**) synthesized as per the Figure. 2 respectively were offered average antibacterial activity against the *Staphylococcus aureus* NCCS 2079, *BacillusCerus* NCCS 2106, *Escherichia coli* NCCS 2065 and *Pseudomonas aeruginosa* NCCS 2200 at the concentration of 250µg/disc. Organo phosphorus pyazole carbamate of Tetrahydro-2H-pyran (**7c)** and Tetrahydro-2H-thiopyran (**7d)** were exhibited more activity than other compounds of the series. The decreasing Oder of antibacterial activity of **7a-e** is as follows **"7c > 7d > 7b> 7e > 7a >".**

ISSN: 0975-8585

Table 7: Anti-bacterial and antifungal activity of compounds 7a-e

COMPOUND	Zone of nhibition (mm)					
	Staphylo cocus aureus NCCS 2079	**Bacillus Cerus NCCS 2106**	**Escherichia Coli NCCS 2065**	**Pseudomonas aeruginosa NCCS 2200**	***Aspergillus niger NCCS 1196***	***Canadida albicans NCCS 3471***
7a	08	11	10	09	09	12
7b	12	15	14	13	11	14
7c	16	19	18	17	13	16
7d	14	17	16	15	14	17
7e	10	13	12	11	15	18
Amoxicillin (std. Antibacterial)	21	27	24	22	-	-
Ketoconazole (std. Anti-fungal)	-	-	-	-	22	25

Organo phosphorus Pyrazole Carbamates containing thiazolidins (**7a-e**) as synthesized in **scheme** respectively of were offered average antifungal activity against the *Aspergillus niger* NCCS1196 and *Candida albicans* NCCS 3471 at the concentration of 250µg/disc. Organo phosphorus pyrazole carbamate system consisting of penta fluoro benzene (**7e)** Tetrahydro-2H-thiopyran (**7d)** and Tetrahydro-2H-pyran(**7c)** were exhibited more activity than other compounds of the series. The decreasing Oder of antifungal activity of 7**a-e**, is as follows **"7e > 7d > 7c > 7b > 7a".**

CONCLUSIONS

The newly synthesized compounds of Cyclopropyl / cyclohexyl / terahydro-2H -pyran -4-yl/tetrahydro-2H-thiopyran-4-yl/ perfluorophenyl(6- oxido-1- ((5 - (4 -oxo-(2-(pyridine-3-yl) thiazolidin -3- yl) -1,3,4 - thiadiazol -2- yl) methyl)- 4,8- dihydro-1H-[1,3,2] dioxaphosphepino [5,6-c] pyrazol-6-yl) carbamates (7a-e) were found to be active in the study of anti-bacterial and anti-fungal activity. It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel classes of antimicrobial agents.

ACKNOWLEDGEMENT

The authors (CH.L.P and V.E.R) 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.

REFERENCES

[1] P Tundo, CR McElory, F Arico, Syn Lett 2010;10: 1567-1571.
[2] JC jung, MA Avery, Tetrahedron Lett 2006; 47: 7969-7972.
[3] S Gattinoni, CD Simone, S Dallavalle, Bioorg Med Chem Lett 2010; 20: 4406-4411.
[4] Mhan.J, Chadha.V.K, Chaudhary.H.S, Sharma.B.D, Pujari.H.K, Mohapatra.L.N , Ind. J. Exp. Biol 1974 ; 17: 609.
[5] Srivastava.T, Gaikwad.A.K, Haq.W, Sinha.S, Katti.S. B, ARKIVOC 2005; 2: 120.
[6] (a) Ottana.R, Maccari.R, Barreca.M.L, Bruno.G, Rotondo.A, Rossi.A, Chiricosta.G, Paola.R.D, Sautebin.L, Cuzzocread.S, Vigorita.M.G, Bioorg.Med.Chem 2005; 13: 4243. (b) Gududuru.V, Bioorg.Med.Chem.Lett 2004; 14: 5289.
[7] (a) Roblin, R.-O. (Jr); Clapp, J.-W. J. Am. Chem. Soc 1950;72: 4890. (b) Vaughan, J.-R. (Jr); Eichler, J.-A.; Anderson, G.-W. J. Org.Chem1956; 21: 700.
[8] Maffii, G.; Testa, E.; Ettore, R.-H. Farmaco (Pavia) Ed. Sci 1958; 13: 187.
[9] Mhasalkar, M.-Y.; Shah, M.-H.; Pilankar, P.-D.; Nikam, S.-T.; Anantnarayan, K.-G.; Deliwala, C.-V. J. Med. Chem 1971; 14: 1000.
[10] Omar, A. M. M. E.; Wafa, O. M. A. J. Heterocycl. Chem 1986; 23: 1339.

[11] A R Katritzky, Comprehensive Heterocyclic Chemistry 1984; 5: 497-98.
[12] M Hareesh, B Srinivas Mahanti, Sailu, D Subramanyam, B Saidu Reddy Sakam, B Tara, B Balram, BVasudha and B Ram, Scholars Research Library, *Der Pharma Chemica*. 2012;4(4): 1637-1643.
[13] Manal M Kandeel, M Ali Sameha, Eman K A Abed ElALL, Mohamed A Abdelgawad, and Phoebe F Lamie,Scholars Research Library, *Der Pharma Chemica* 2012;4(4): 1704-1715.
[14] P k Naithani, V K Srivastava, J P Bharathwal, A K Saxena, T KGupta and K Shankhar, I*ndian J.Chem* 1989; 28B: 229
[15] M Verma, A K Chturvedi, A Chowdari and S S Paramar*, J PharmSci* 1974; 63: 1740.
[16] Ilkay Yildiz-Oren, Ismail Yalcin, Esin Aki-Sener*, Nejat Ucarturk; European Journal of Medicinal Chemistry 2004; 39: 291-298.
[17] Nobba Venkata Siva , Kumar , Sanjay Dashrath Viadya , Ramanatham Vinod Kumar , Shekhar Bhaskar Bhiruda , Ramchandra Bhimrao mane ; European Journal of Medicinal Chemistry 2006; 41: 599-604.
[18] ChhajedS.S, Upasani, Bastikar V.A, MahajanN.P, Journal of pharmacy research 2010; 3(6) :1192-1194.
[19] D.S.Mehta and V.H.Shah, Ind.j.Het.Chem 2001;11: 139-144.
[20] S.V.More, D.V.Dongarkhadekar, R.N.Chavam, W.N.Sadhav, S.R.Bhusare, R. pawar; J.Ins.Chem.Soc 2002;79: 768-769.
[21] Khiangte Vanladinpuia, Ghanashyam Bez* Tetrahedron Letters 2011; 52: 3759-3764.
[22] M Veera Narayana Reddy, A Bala Krishna and C Suresh Reddy, *Eur.J.Med.Chem* 2010; 45: 1828.
[23] D V Mangete, S P Deshmukh, D Bhokare and A Arti Deshpande, *Indian Pharma.SCI*; 2007; 69: 295.
[24] A C Brown and T Fracer, Trans Roy Soc Edinbrug 1968-69: 25, 151, 693.