THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

C H. Lakshmi praveena et al, The *Experiment*, *2015.,Vol. 30(3), 1991-2001*

Synthesis Characterization and Antimicrobial activity of (1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl)azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl) substituted carbamates

Abstract

New novel derivatives of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/perfluorophenyl(1-((5-(3-chloro-2-oxo - 4 - (pyridin - 3 - yl) azetadin - 1 - yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6 - c] pyrazol-6 - yl)carbamates (**7a-e** as depicted in scheme) were synthesized from condensation reaction of substituted dichlorophosphoryl carbamates **(6a – e)** and 1 - (5 - ((4, 5 - bis (hydroxymethyl) -1H - pyrazol - methyl) - 1, 3, 4 - thiadiazol - 2 - yl) - 3-chloro - 4 - (pyridine -3 - yl) azetidin- 2 - one**(5).** The Synthon **(5)**was obtained by deprotection of 3 - chloro -1 - (5 - ((6, 6 - dimethyl - 4, 8 - dihydro - 1H -[1, 3]dioxepino[5, 6 - c] pyrazol -1 - yl) -1, 3, 4 - thiadiazol - 2 - yl) - 4 - (pyidin - 3-yl) azetidin - 2 - one **(4).** Synthon **(4)** was prepared by the reaction between 5 - ((6, 6 - dimethyl - 4, 8 –dihydro - 1H - [1, 3] dioxepino [5, 6 - c] pyrazol - 1 - yl) methyl) - N - (pyridine - 3 - ylmethylene) - 1, 3, 4 - thiadiazol - 2 - amine **(3)** and chloro acetyl chloride in presence of Et_3N / Dioxane / $POCl_3$ on NaN_3 / THF conditions under the temperature 100^oC / 2-mecaptoacetic acid in presence of $ZnCl_2$. The synthon **(3)** was obtained by condensation reaction between nicotinaldehyde **(2)** 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 **(1)**. The products were characterized by spectral analysis (IR, ^1H-NMR,^{13}C- NMR, ^{31}P- NMR and elemental analysis). The newly synthesized compounds were subjected to various biological activities viz., antimicrobial.

Key Words: Antibacterial; Antifungal; deprotection; dichloro phosphoryl carbamates; Pyrazole.

INTRODUCTION

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

Azetidin-2-one, formally known as β-lactums, these are very important class of compounds possessing wide range of biological activities such as anti microbial, pesticidal, antitumor, antitubercular, anticancer, Cytotoxic, Chlosterol absorption inhibitors, elastase inhibitors and enzyme inhibitor[**4-8]**.

In support of our study pyrazoles and derivatives function as dyestuff, catalyst, polymerizing agents, drugs , herbicides and fungicides [**9**].they also possess various pharmacological activities such as anti-fungal activity [**10**], monoamineoxidase (MAO) inhibitory activity [**11, 12**], antiparkinson [**13**], anticonvulsant[**14**]. Pyrazole derivatives are valuable vasodialating and vasoconstructing drugs.

In view of the numerous commercial applications of organophosphorus compounds , we synthesized dichloro phosphoryl carbamates derivatives possesing Pyrazole moiety besides Azetidin-2-one derivatives, 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,

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY
ISSN-2319-2119
RESEARCH ARTICLE

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.

Preparation of Intermediates: [**15, 16]**

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. Dichlorophosphorylcarbamate 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 Phosphorisocyanatidic dichloride in 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 /.Perflurophenyl dichlorophosphoryl carbamates.

The structure of newly synthesized dichlorophosphoryl carbamates **(6*a-e*)** were established by IR, ^{1}HNMR and elemental analysis.

RESULT AND DISCUSSION

1. 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):[17]

The synthesis and characterization 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 **(1)** were carried out by reported in the literature[**18,19**].

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^{o}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)** as dried and recrystalised from warm absolute alcohol, mp136-138^{0}C and yield 65%. The structure of **(3)** was established by IR, ^{1}H-NMR and elemental analysis.

2. Synthesis of 3-chloro-1-5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c] pyrazol-1-yl)methyl)- 1,3,4-thiadiazol-2-yl)-4-pyridin-3-yl)azetidin-2-one(4):[20,21]

Monochloacetyl chloride (0.01 mol) was added drop wise to a mixture of Schiff's base **(3)** (0.01 mol) and tri ethyl amine (0.02 mol) in dioxine(25 ml) at room temperature. The mixture was stirred for 8 h and left at room temperature for 3 days. The progress of reaction was monitored by TLC using cyclohexane and ethyl acetate (9:1) solvent mixture as an mobile phase. Pour the content on crushed ice .The product 3-chloro-1-5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-pyridin-3-yl) azetidin-2-one**(4)** thus

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY
ISSN-2319-2119
RESEARCH ARTICLE

formed was filtered and washed with sodium bicarbonate solution . The dried product was recrystalised with absolute alcohol, mp155-157^{0}C and yield 70 %. The structure of **(4)** was established by IR, ^{1}H-NMR and elemental analysis.

3. Synthesis of 1-(5-((4, 5-bis (hydroxymethy) l-1H-pyrazol-1-yl) methyl) -1, 3, 4-thiadiazol-2-yl) -3-chloro-4-(pyridin-3-yl) azetidin-2-one (5)

The isopropylidenation of 1, 2-diols was carried out by a procedure reported in the literature [**22]**. A suspension of the 3-chloro-1-5-((6,6-dimethyl-4,8-dihydro-1H-[1,3]dioxepino[5,6-c]pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-4-pyridin-3-yl)azetidin-2-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. The m p of **(5)** was 141-143^{O}C with yield of 70%. The structure of **(5)** was established by IR, ^{1}H-NMR and elemental analysis.

Synthesis of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl)azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [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 1-(5-((4, 5-bis (hydroxymethy) l-1H-pyrazol-1-yl) methyl) -1, 3, 4-thiadiazol-2-yl) -3-chloro-4-(pyridin-3-yl) azetidin-2-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 completion of the reaction was monitored by TLC analysis. Triethylamine 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(1-((5-(3-chloro-2-oxo-4 - (pyridin- 3 - yl)azetadin - 1 - yl) - 1,3,4 - thiadiazol - 2 -yl) methyl)-6-oxido-4, 8-dihydro-1H-[1,3,2]dioxaphosphepino[5,6-c]pyrazol-6-yl)carbamate **(7a)**, yield 70.% and mp168-170^{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)** and 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. The IR, ^{1}H-NMR, ^{13}C-NMR physical and analytical data of compounds was shown in **Table.1 - Table.5**.

Biological activity:

The antimicrobial activity [**23**] of chemical compound is influenced by physical and biological characteristics [**24**].It has been well established that physiological activity is a function of the chemical structure of compound [**25]**.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 [**26,27**].

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

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

Antibacterial activity:

Organo phosphorus Pyrazole Carbamates containing azetadines **(7a-e)** reported in **scheme** respectively were offered average antimicrobial 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. Antibacterial data of **7a-7e** compounds were shown in **Table.6**

Antifungal activity

Organo phosphorus Pyrazole Carbamates containing azetadines **(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. Antibacterial data of **7a-7e** compounds were shown in **Table.7.**

Conclusions

The newly synthesized compounds of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl / perfluorophenyl (1 - ((5 - (3 - chloro - 2 - oxo - 4 - (pyridin - 3 - yl) azetadin - 1 - yl - 1,3,4 - thiadiazol - 2 - yl)methyl - 6 - oxido - 4,8 - dihydro-1H-[1,3,2]dioxa phosphepino [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

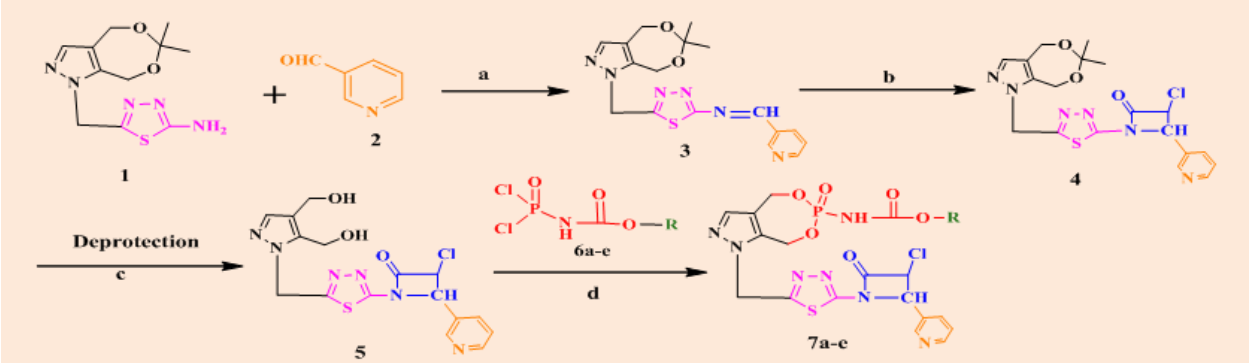
The authors (CH.L.P and V.E.R) thanks to U G C – S A P and U G C – B S R, New Delhi for financial assistance. They are also thankful to IICT Hyderabad and CDRI Lucknow for spectral and analytical data.

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

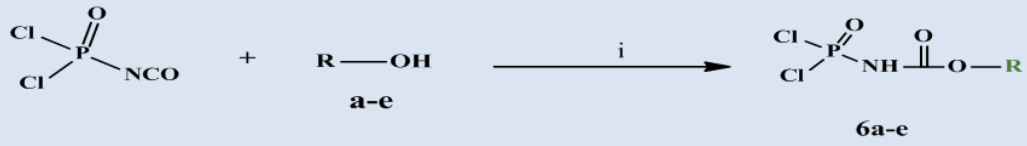
Tables and Figures



Reagents and conditions: (a) Absolute alcohol, acetic acid , 100°C, heated on steem bath for 5-6 hrs; **(b)** Mono chloro acetyl chloride, Et_3N/Dioxane, RT, stirred 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 RT for 2 hrs, rx^n mixture heated at 50-60°C for 4hrs.

Compound	R Name	Structure
Xa	Cyclopropyl	
Xb	Cyclohexyl	
Xc	Tetra hydro-2H-pyran	
Xc	Tetrahydro-2H-thiopyran	
Xd	perfluorophenyl	

***Fig-1: Proposed synthetic scheme for the preparation of* (*7a-e*)**



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

Compound	R Name	Structure
Xa	Cyclopropyl	
Xb	Cyclohexyl	
Xc	Tetra hydro-2H-pyran	
Xc	Tetrahydro-2H-thiopyran	
Xd	perfluorophenyl	

Fig-2: Synthetic Scheme Preparation of Intermediates

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

Spectral, Physical, Analytical data and antimicrobial data for the compounds:

Table.1: IR Spectral data of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl) azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):

COMPOUND (*7*)	R	$\bar{\nu}/\delta$, cm^{-1}					
		γ_{Ar-H}	P-NH	Pyrazole	Carbamate carbonyl	P=O	P-O-C
7a	Cyclo propyl	3040	3317	1375-1487	1675	1245	1194
7b	Cyclo hexyl	3045	3320	1370- 1485	1670	1240	1190
7c	Tetrahydro-2H-pyran	3035	3328	1373-1490	1678	1238	1193
7d	Tetrahydro-2H-thiopyran	3040	3310	1380-1495	1674	1243	1196
7e	Perfluoro phenyl	3040	3325	1385-1490	1680	1248	1198

Table.2:^{1}H-NMR Spectral data Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/ perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl)azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):

Comp	R	^{1}H – NMR (DMSO – d_6)(δ_{PPM})
7a	Cyclopropyl	0.34- 0.58 (m,4H, –CH_2 – of cyclopropyl) 2.69(m,1H,-CH- of cyclopropyl ring attached to carbamate moiety), 4.99(s,2H , CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.08(d,1H,CH of 3-chloro azetidin-2-one attached to pyridine ring), 5.29 (s, 4H, two CH_2 group of acetal),5.44(d,1H,O=C-CH(Cl)-of 3-chloro azetidin-2-one), 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	Cyclohexyl	1.49 - 1.80 (m, 10H, -CH_2- of cyclohexyl),3.91 (m, 1H, -CH- of cyclohexyl attached to carbamate moiety) ,4.99(s,2H,-CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.08(d,1H,-CH- of 3-chloro azetidin-2-one attached to pyridine ring),5.29 (s, 4H, two -CH_2- group of acetal),5.44(d,1H,O=C-CH(Cl)-of 3-chloro azetidin-2-one), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.10(s,1H,-NH- of carbamate moiety).
7c	Tetrahydro -2H-pyran	1.72 - 1. 97 (m, 4H, -CH_2- of tetrahydro-2H-pyran), 3.65 (t, 4H, -CH_2-O-CH_2 of tetrahydro-2H-pyran),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), 5.08 (d,1H,-CH- of 3-chloro azetidin-2-one attached to pyridine ring),5.29 (s, 4H, two -CH_2- group of acetal),5.44(d,1H,O=C-CH(Cl)-of 3-chloro azetidin-2-one), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.15(s,1H,-NH- of carbamate moiety).

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

7d	Tetrahydro -2H-thiopyran	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),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), 5.08(d,1H,-CH- of 3-chloro azetidin-2-one attached to pyridine ring),5.29 (s, 4H, two CH_2 group of acetal),5.44(d,1H,O=C-CH(Cl)-of 3-chloro azetidin-2-one), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.0 7(s,1H,-NH- of carbamate moiety).
7e	Perfluorophenyl	4.99(s,2H,-CH_2- flanked between pyrazole and 1,3,4-thiadiazole), 5.08(d,1H,-CH- of 3-chloro azetidin-2-one attached to pyridine ring),5.29 (s, 4H, two CH_2 group of acetal), 5.44(d,1H,O=C-CH(Cl)-of 3-chloro azetidin-2-one), 7.30 (s, 1H, of pyrazole ring) 7.38-8.59 (m, 4H, -CH- of pyridine) and 8.15(s,1H,-NH- of carbamate moiety).

Table.3: ^{13}C-NMR spectral data of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/ perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl)azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):

Comp	structure	^{13}C NMR (DMSO – d_6)(δ_{PPM})
7a	Cyclopropyl	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 162.2 , 62.0 , 67.8 , 140.8 , 133.5 , 123.4, 146.9, 148.4, 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_{15}, C_{16} , C_{17} ,C_{18} and C_{19}&C_{20}.
7b	Cyclohexyl	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 162.2 , 62.0 , 67.8 , 140.8 , 133.5 , 123.4, 146.9, 148.4, 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	Tetrahydro -2H-pyran	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 162.2 , 62.0 , 67.8 , 140.8, 133.5 , 123.4, 146.9, 148.4, 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	Tetrahydro -2H-thiopyran	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 162.2 , 62.0 , 67.8 , 140.8, 33.5 , 123.4, 146.9, 148.4, 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	Perfluorophenyl	135.2 , 118.0 ,141.0 , 62.2 , 61.1 , 47.6 , 168.0 , 163.4 , 162.2 , 62.0 , 67.8 , 140.8 , 133.5 , 123.4, 146.9, 148.4, 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}.

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

Table.4: ^{31}P-NMR spectral data of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl/ Tetrahydro-2H-thiopyran-4-yl/perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl) azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):

COMP (7)	STRUCTURE	^{31}P – NMR (DMSO – d_6) (δ_{PPM})
7a	Cyclopropyl	-9.50, 0.60
7b	Cyclohexyl	-10.80, 0.50
7c	Tetrahydro-2H-pyran	-9.70, 0.55
7d	Tetrahydro-2H-thiopyran	-9.78, 0.53
7e	Perfluorophenyl	-9.10, 0.70

Table .5: The Physical and Analytical data of compounds synthesized as per the schem

COMPOUND	MOLECULAR FORMULA	mp (^{O}C)	YIELD (%)	ELEMENTAL ANALYSIS	
				FOUND	CALCULATED
3	$C_{17}H_{18}N_6O_2S$	136-138^{O}C	65%	C:54.62% H:4.40% N: 22.09%. S:8.46%	C:55.12% H:4.90% N: 22.69%. S:8.66%
4	$C_{19}H_{19}ClN_6O_3S$	155-157 ^{O}C	70%	C:50.26% H :3.79% Cl:7.23% N :18.20% S:6.97%	C:51.06% H :4.29% Cl:7.93% N :18.80% S:7.17%
5	$C_{16}H_{15}ClN_6O_3S$	141-143 ^{O}C	70%	C:46.43% H :3.22% Cl:8.01% N :20.06% S:7.68%	C:47.23% H :3.72% Cl:8.71% N :20.66% S:7.88%
7a	$C_{20}H_{19}ClN_7O_6PS$	168-170 ^{O}C	70%	C:45.8% H : 2.97% Cl:5.72% N:17.17% P:4.91% S:5.61%	C:46.5% H : 3.47% Cl:6.42% N:17.77% P:5.61% S:5.81%

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

7b	$C_{23}H_{25}ClN_7O_6P\,S$	136-138 ^{O}**C**	60%	C:45.7% H : 3.74% Cl:5.27% N:15.91% S:5.20%	C:46.5% H : 4.24% Cl:5.97% N:16.51% S:5.40%
7c	$C_{22}H_{23}ClN_7O_7P\,S$	151-153 ^{O}**C**	68%	C:43.54% H :3.39% Cl:5.25% N:15.95% P:4.70% S:5.18%	C:44.34% H :3.89% Cl:5.95% N:16.45% P:5.20% S:5.38%
7d	$C_{22}H_{23}ClN_7O_6P\,S_2$	144-146 ^{O}**C**	65%	C:42.37% H :3.29% Cl:5.09% N:15.42% P : 4.36% S:10.28%	C:43.17% H :3.79% Cl:5.79% N:16.02% P : 5.06% S:10.48%
7e	$C_{23}H_{14}ClF_5N_7O_6P\,S$	184-186 ^{O}**C**	75%	C:39.95% H:1.58% Cl:4.53% F:13.21% N:13.86% P:.3.87% S:4.53%	C:40.75% H:2.08% Cl:5.23% F:14.01% N:14.46% P:.4.57% S:4.73%

Table.6:Antibacterial activity of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl)azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):
yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):

COMPOUND	**R**	**Zone of inhibition (mm)**			
		Staphylococus aureus NCCS2079 250(µg/ml)	**Bacillus Cerus NCCS2106 250(µg/ml**	**Escherichia Coli NCCS2065 250(µg/ml)**	**Pseudomonas aeruginosa NCCS2200 250(µg/ml)**
7a	Cyclopropyl	07	10	9	8
7b	Cyclohexyl	11	14	13	12
7c	Tetrahydro-2H-pyran	15	18	17	16
7d	Tetrahydro-2H-thiopyran	14	17	16	15
7e	Perfluorophenyl	11	14	13	12
Amoxicillin		21	27	24	22

THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

Table.7:Antifungal activity of Cyclopropyl/ Cyclohexyl Terahydro-2H-pyran-4-yl / Tetrahydro-2H-thiopyran-4-yl/perfluorophenyl(1-((5-(3-chloro-2-oxo-4-(pyridin-3-yl)azetadin-1-yl)-1,3,4-thiadiazol-2-yl)methyl-6-oxido-4,8-dihydro-1H-[1,3,2]dioxa phosphepino [5,6-c]pyrazol-6-yl)carbamates (7a-e):

COMPOUND	R	Zone of inhibition (mm)	
		Aspergillus niger NCCS 1196 250(µg/ml)	*Canadida albicans NCCS 3471 250(µg/ml)*
7a	Cyclopropyl	08	11
7b	Cyclohexyl	10	13
7c	Tetrahydro-2H-pyran	11	14
7d	Tetrahydro-2H-thiopyran	12	15
7e	Perfluorophenyl	13	16
Ketoconazole		22	25

REFERENCES

1. (a) P Tundo, CR McElory, F Arico, Syn Lett. 2010, 10, 1567-1571. (b) LR Morgan, RF Struck, WR Waud, Cancer Chemother.Pharmacol. 2009, 64, 829-835.
2. (a) J Deng, W Zhao, W Yang, React Funct Polym., 2006, 67, 828-835. (b) JC Jung, MA Avery, Tetrahedron Lett. 2006, 47, 7969-7972.
3. (a) S Gattinoni, CD Simone, S Dallavalle, Bioorg Med Chem Lett. 2010, 20,4406-4411. (b)J AO Meara, A Jakalina, S La Planate, Bioorg Med Chem Lett. 2007, 9 3362-3366. (c) M. R. Hema, M. Ramaiah, V.P. Vaidya, B.S.Shivakumar and G.S. Suresh J.Chem. Pharm.Res. 2013, 5(4), 47-51.
4. (a) Guner.V, Yildirir.S, Ozcelik.B, Abbasoglu.U, II Farmaco. 2000, 55, 497. (b) Singh.V.P, Saxsena.K.K, Bhati.S.K, Kumar.A; J.Global Pharma Tech. 2010, 2, 42.
5. (a) Veinberg.G, Shestakova. I, Vorona.M, Kanepe.I, Lukevics.E; Bioorg.Med. Chem. Lett. 2004, 14, 147. (b) Narute.A.S, Kheddekar.P.B, Bhusari.K.P, Ind. J. Chem. 2008, 47B,586.
6. (a) Banik.B.K, Becker.F.F, Banik.I; Bioorg.Med. Chem. 2004, 12, 2523. (b) Veinberg.G, Bokaldere.R, Dikovskaya.K, Vorona.m, Kanepe.I, Shestakova.I, Yashchenko.E.; Chem. Het.Comp. 2003, 39, 587.
7. Wang.Y, Zhang.H, Huang.W, Kong.J, Zhang B; Eur. J. Med. Chem. 2009, 44, 1638.
8. Wang.Y, Zhang.H, Huang.W, Kong.J, Zhou.J, Zhang B; Eur. J.Med. Chem., 44, 2009,1638.
9. A R Katritzky, Comprehensive Heterocyclic Chemistry. 1984, 5, 497-98.
10. Heohu and Hans US, 1981, 4273776, *chem.Abstr*. 1982, 96 , 6725.
11. 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.
12. 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.
13. P k Naithani, V K Srivastava, J P Bharathwal, A K Saxena, T KGupta and K Shankhar, I*ndianJ.Chem.*1989,28B,229.
14. M Verma, A K Chturvedi, A Chowdari and S S Paramar, *J PharmSci*. 1974, 63, 1740.
15. Ilkay Yildiz-Oren, Ismail Yalcin, Esin Aki-Sener*, Nejat Ucarturk; European Journal of Medicinal Chemistry. 2004, 39, 291-298.

16. 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.
17. ChhajedS.S, Upasani, Bastikar V.A, MahajanN.P. ,Journal of pharmacy research. 2010, 3(6),1192-1194.
18. C. H. Lakshmi Praveena, V. Esther Rani, Y. N. Spoorthy and L. K. Ravindranath* J. Chem. Pharm. Res., 2013, 5(5),280-292.
19. Pandey, V.-K.; Negi, H.-S.; Joshi, M.-N.; Bajpai, S.-K. *Indian.J. Chem.* 2003, *42B*, 206.
20. D.S.Mehta and V.H.Shah,Ind.j.Het.Chem. 2001, 11,139-144.
21. S.V.More,D.V.Dongarkhadekar,R.N.Chavam,W.N.Sadhav,S.R.Bhusare,R.p pawar; J.Ins.Chem.Soc. 2002, 79,768-769.
22. Khiangte Vanladinpuia, Ghanashyam Bez* Tetrahedron Letters. 2011, 52, 3759-3764.
N Bakthavatchala Reddy, B Siva Kumar, N J Reddy, p santhipriya and C Suresh Reddy, *j.chem.Pharm.Res.* 2010, 2(2) ,405-410.
23. M Veera Narayana Reddy, A Bala Krishna and C Suresh Reddy, *Eur.J.Med.Chem*, 2010, 45, 1828.
24. D V Mangete, S P Deshmukh, D D Bhokare and A Arti Deshpande, *Indian Pharma.SCI*, 2007, 69, 295.
25. A C Brown and T Fracer, Trans Roy Soc Edinbrug. 1968-69, 25, 151, 693.
26. B Siva Kumar and Y Haranadha Reddy, Scholars Research Library, *Der Pharma. Chemica*. 2011, 3(5), 29-34.
27. A BalaKrishna, S Annar, M VeeraNarayanaReddy, G chendraShekarReddy, C.SureshReddy and S K Nayak,*J.Chem. Pharma.Res.* 2009, 1(1), 256.

C H. Lakshmi praveena*, V.Esther Rani, and L.K .Ravindranath
Department of Chemistry, Sri Krishna Devaraya University,
Ananthapuramu, Andhrapradesh,
India, 515003.