ORIGINAL ARTICLE

A C G publications

Org. Commun. 3:4 (2010) 98-105

organic communications

Synthesis and antibacterial activity studies of novel 2-substituted-1,3,2-oxazaphosphole-2-oxide derivatives of (S)-(+)-prolinol

B. Satheesh Krishna, A. Janardhan Rao, K. Reddi Mohan Naidu,

V. Koteswara Rao and C. Naga Raju *

Department of Chemistry, Sri Venkateswara University College of Sciences,

Sri Venkateswara University, Tirupati-517 502, INDIA

Abstract: The novel 2-substituted-1,3,2-oxazaphosphole-2-oxides of (S)-(+)-prolinol were synthesized by the cyclization of (S)-(+)-prolinol (**3**) with phosphorusoxychloride (**4**) followed by the treatment with various phenolic compounds, aminoacid esters and amine (**6a-l**) to obtain the title compounds (**7a-l**). Their structures are characterized by spectral, elemental analyses and evaluated their *in vitro* antibacterial activity against two gram positive and two gram negative bacteria. Three compounds exhibited very significant anti bacterial activity when compared with that of Ciprofloxacin.

Keywords: L–Prolinol; Phosphorus oxychloride; 1,3,2-Oxazaposphole-2-oxides; MIC.

1. Introduction

At the outset a wide range of pesticides, insecticides and antibiotics emanated from phosphorus compounds.[1] Specifically organophosphorus heterocycles bearing the P-N functionality exhibited anti-tumor, pesticidal and medicinal activity.[2-4] Optically active organophosphorus compounds, possessing a chiral centre at phosphorus are known to exhibit a variety of unique biological activities and hence they have a potential use as agricultural chemicals.[5] The synthesis of multi–ring phosphorus heterocycles were accomplished much importance as they find applications in medicine and industry.[6] Similarly the derivatives of aminoacids and phenolic compounds are also potential physiologically active compounds and also it is reported that the 1,3,2-oxazaphospholes are biologically important in the sense of its antimicrobial activity i.e., antifungal and antibacterial activity.[6] These aspects are driven to design and synthesis of title compounds as derivatives of (S)-(+)

* Corresponding author. E-Mail: rajuchamarthi10@gmail.com

The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 11/15/2010 EISSN:1307-6175

prolinol as a part of our research and evaluation of their antibacterial activity for the first time. More over, these proline based oxazaborolidines had been used as catalysts by Corey for the borane-mediated enantioselective reduction of prochiral ketones , a plethora of oxazaborolidines and related catalysts based on various chiral pool sources have been developed and their applications have been well studied.[7-10] Simillarly proline-based phosphorylated derivatives were used for borane mediated reduction of prochiral α-halo ketones to α-halo alcohols.[11] It is noted that phosphorus compounds with N-P=O structural frame work containing different amino and phenolic groups on phosphorus as substituents are used in borane-mediated asymmetric reduction of prochiral ketones with high enantiomeric purity, where the basic cyclic moiety controls the stereochemical course of the reaction, while the groups on the phosphorus have little significant role in directing the stereochemical course of the reaction.[11] Although we had studied the antibacterial activity of these compounds, we presume that these title compounds can control stereochemistry in organic synthesis as chiral catalysts in further studies.

2. Results and Discussion

2.1. Chemistry

2.1.1. Synthesis of 1,3,2-oxaza phosphole-2-oxides

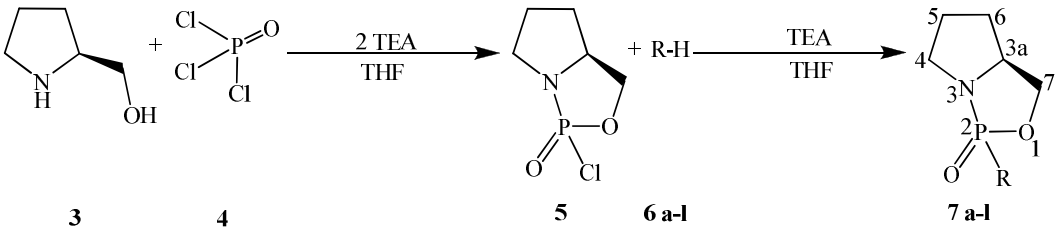
The synthesis of novel 2-substituted-1,3,2-oxazaphosphole-2-oxides of (S)-(+)-prolinol has accomplished in a two-step process. The (S)-(+)-prolinol (**3**) was treated with phosphorus oxychloride (**4**) in the presence of triethylamine in dry THF at -5 to 0 ^{o}C for one hour to yield 2-chloro-1,3,2-oxazaphosphole-2-oxide intermediate (**5**). To this intermediate (**5**) various phenols, aminoacid esters and amine (**6a-l**) were added in the presence of triethylamine in dry THF at 20 ^{o}C. Then the reaction temperature was increased to 40-50 ^{o}C and the reaction was continued for 5-6 hours to obtain the title compounds (**7a-l**).

The final product is obtained by removing the triethylammonium hydrochloride salt by filtration and evaporating the THF solvent in a rota-evaporator and finally purified by column chromatography and characterized by spectral and elemental analyses. The synthetic pathway is represented in Scheme- 1.

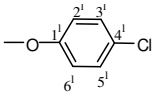
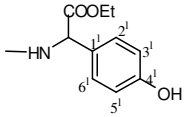
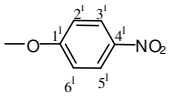
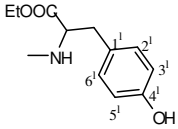
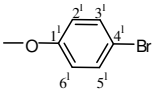
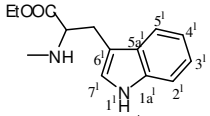
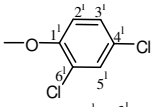
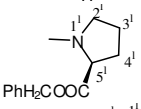
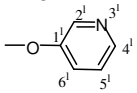
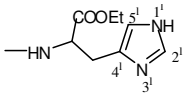
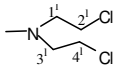
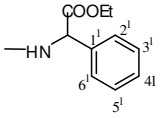
2.1.2. Synthesis of (S)-(+)-Prolinol (2)

The (S)-(+)-Prolinol (**3**), which is an α-aminoalcohol is prepared by the reduction of its α-amino acid L-proline (**1**) by converting to (S)-(+)-ethyl prolinate (**2**) which is its ester and then followed by reduction with lithium aluminium hydride at 0^{o}C in methanol. Further, it is characterized by determining its properties b.p. 54-56^{o}C, $[\alpha]_D^{25}$ +38.6. The synthetic path is represented in Scheme-2.

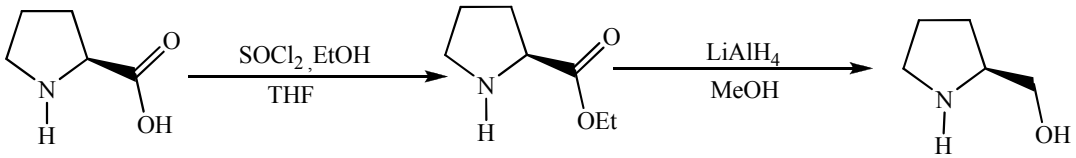
The chemical structures of all the title compounds **7a-l** were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR, mass spectral studies and elemental analyses and their data are presented in the experimental section. Characteristic IR stretching absorptions were observed in the regions 955-964 (P-O-C_{Ar}), 1208-1220 (P-O-C_{Ar}), 1225-1251 (P=O), 1730-1754 (C=O) and 3326-3394 cm^{-1} (N-H).[12] In ^{1}H NMR, the 3a proton resonated in the region 2.91- 3.20 as a multiplet.[13] In the ^{13}C NMR P-O-C-7 resonated as a singlet in the region δ 58.6-60.2. The α-carbon of the aminoacid ester group resonated at δ 59.8-52.6. The ^{31}P NMR chemical shifts are observed in the range of δ -22.28 to +24.53 ppm.[14,15]



3 **4** **5** **6 a-l** **7 a-l**

Compound	R	Compound	R
7a		**7g**	
7b		**7h**	
7c		**7i**	
7d		**7j**	
7e		**7k**	
7f		**7l**	

Scheme 1. Synthesis of 2-substituted-1,3,2-oxazaphosphole-2-oxide derivatives of (S)-(+)-prolinol



1 **2** **3**

Scheme 2. Synthesis of (S)-(+)-prolinol

2.2. Evaluation of Antibacterial Activity

The minimum inhibitory concentration of the test compounds (**7a-l**) was evaluated against two types of Gram Positive and Gram negative bacteria. The experiments were run in triplicates and the average results are included in Table.1. Most of the compounds were found to be effective against the microorganisms tested and these MICs were compared with the standard drug ciprofloxacin. The MIC values of the test compounds are almost as low as that of the standard drug.

Table 1. Minimum Inhibitory Concentrations (MIC in μg/mL) of the compounds **7a-l**

	R	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**	**7j**	**7k**	**7l**
BS	0.11	0.13	0.22	0.15	0.13	0.23	0.15	0.19	0.23	0.21	0.14	0.15	0.15
SA	0.16	0.21	0.42	0.29	0.21	0.25	0.49	0.76	1.00	0.81	0.29	0.22	0.72
KP	0.15	0.17	0.54	0.21	0.59	0.18	0.33	0.28	0.39	0.42	0.36	0.19	0.38
EC	0.22	0.24	0.51	0.35	0.26	0.25	0.55	0.46	0.61	0.44	0.34	0.26	0.62

R= *Ciprofloxacin*, SA= *Staphylococcus aureus*; BS= *Bacillus subtilis*;
KP= *Klebsiella pneumoniae*; EC= *Escherichia coli*;

3. Conclusion

In summary, a series of novel 2-substituted-1,3,2-oxazaphosphole-2-oxides (**7a-l**) were synthesized and their minimum inhibitory concentrations were evaluated.

4. Experimental

4.1. Chemistry

Chemicals were procured from Sigma-Aldrich, Merck and Lancaster, used as such without further purification. All solvents used for the spectroscopic and other physical studies were reagent grade and further purified by literature methods.[16] Melting points (m.p.) were determined using a calibrated thermometer by Guna Digital Melting Point apparatus, expressed in degrees centigrade (°C) and are uncorrected. Infrared Spectra (IR) were obtained on a Perkin-Elmer Model 281-B spectrophotometer. Samples were analyzed as potassium bromide (KBr) disks. Absorptions were reported in wave numbers (cm^{-1}). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 500 MHz spectrometer operating at 500 MHz for ^{1}H, 125 MHz for ^{13}C and 202 MHz for ^{31}P NMR. The ^{1}H and ^{13}C chemical shifts were expressed in parts per million (ppm) with reference to tetramethylsilane (TMS) and ^{31}P chemical shifts to 85 % H_3PO_4. LCMS mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer. Elemental analysis was performed on Thermo Finnigan Insturment at University of Hyderabad, Hyderabad, INDIA.

***(3aS)-2-(4^{l}-chlorophenoxy)perhydro-2λ^{5}-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-one (7a)*:** Yield: 72%; Mol.Wt: 273.5; m.p. 103-105 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 7.51 (d, 2H, *J*= 8.2 Hz, H-3^{l} & H-5^{l}), 7.10 (d, 2H, *J*= 8.5 Hz, H-2^{l} & H-6^{l}), 3.29-3.37 (m, 2H, H-7), 3.05-3.12 (m, 1H, H-3a),

2.80-2.87 (m, 2H, H-4), 1.42-1.63 (m, 4H, H-5 & H-6); ^{13}C NMR (125 MHz, DMSO-d_6) (δ ppm): 149.1 (C-1^{I}), 130.1 (C-4^{I}), 127.6 (C-3^{I} & C-5^{I}), 125.8 (C-2^{I} & C-6^{I}), 58.6 (C-7), 47.8 (C-3a), 44.5 (C-4), 33.2 (C-6), 27.1 (C-5); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): 20.40; IR (KBr) cm^{-1}: 1247 (P=O), 1208 (P-O-C_{Ar}), 961 (P-O-C_{Ar}); LCMS m/z (%): 275 [M+2] (27), 273[$M^{+\bullet}$] (80), 190 (54), 146 (37). Analysis (% calculated/ found) for $C_{11}H_{13}ClNO_3P$: C: 48.26/ 48.22, H: 4.75/ 4.72, N: 5.11/ 5.07.

(3aS)-2-(4^{I}-nitrophenoxy)perhydro-2λ^{5}-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-one (7b): Yield: 79%; Mol.Wt: 284; m.p. 125-127 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 7.90 (d, 2H, *J*= 8.4 Hz, H-3^{I} & H-5^{I}), 7.60 (d, 2H, *J*= 8.8 Hz, H-2^{I} & H-6^{I}), 3.32-3.39 (m, 2H, H-7), 3.06-3.12 (m, 1H, H-3a), 2.81-2.88 (m, 2H, H-4), 1.43-1.66 (m, 4H, H-5 & H-6); ^{13}C NMR (125 MHz, DMSO-d_6) (δ ppm): 148.3 (C-1^{I}), 144.4 (C-4^{I}), 135.5 (C-3^{I} & C-5^{I}), 129.3 (C-2^{I} & C-6^{I}), 58.6 (C-7), 47.8 (C-3a), 44.5 (C-4), 33.2 (C-6), 27.2 (C-5); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): 24.53; IR (KBr) cm^{-1}: 1251 (P=O), 1212 (P-O-C_{Ar}), 955 (P-O-C_{Ar}); LCMS m/z (%): 284[$M^{+\bullet}$] (72), 201(52), 146 (40). Analysis (% calculated/ found) for C11H13N2O$_5$P: C: 46.49/ 46.44, H: 4.61/ 4.55, N: 9.86/ 9.78.

(3aS)-2-(4-bromophenoxy)perhydro-2λ^{5}-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-one (7c): Yield: 75%; Mol.Wt: 318; m.p. 138-140 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 7.55 (d, 2H, *J*= 8.4 Hz, H-3^{I} & H-5^{I}), 7.18 (d, 2H, *J*= 8.8 Hz, H-2^{I} & H-6^{I}), 3.35-3.42 (m, 2H, H-7), 3.10-3.17 (m, 1H, H-3a), 2.84-2.89 (m, 2H, H-4), 1.45-1.66 (m, 4H, H-5 & H-6); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): 22.31; IR (KBr) cm^{-1}: 1253 (P=O), 1215 (P-O-C_{Ar}), 959 (P-O-C_{Ar}).

(3aS)-2-(2^{I},4^{I}-dichlorophenoxy)perhydro-2λ^{5}-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-one (7d): Yield: 79%; Mol.Wt: 308; m.p. 121-123 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 7.23 (s, 1H, H-3^{I}), 7.18 (d, 1H, *J*= 7.5 Hz, H-6^{I}), 7.13 (d, 1H, *J*= 7.8 Hz, H-5^{I}), 3.30-3.37 (m, 2H, H-7), 3.08-3.13 (m, 1H, H-3a), 2.82-2.90 (m, 2H, H-4), 1.45-1.62 (m, 4H, H-5 & H-6); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): 21.58; IR (KBr) cm^{-1}: 1243 (P=O), 1220 (P-O-C_{Ar}), 958 (P-O-C_{Ar}).

(3aS)-2-(3-pyridyloxy)perhydro-2λ^{5}-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-one (7e): Yield: 75%; Mol.Wt: 240; m.p. 127-129 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 7.24- 8.32 (m, 4H, Ar-H), 3.33-3.41 (m, 2H, H-7), 3.09-3.13 (m, 1H, H-3a), 2.81-2.92 (m, 2H, H-4), 1.46-1.64 (m, 4H, H-5 & H-6); ^{13}C NMR (125 MHz, DMSO-d_6) (δ ppm): 146.6 (C-1^{I}), 139.5 (C-2^{I}), 135.3 (C-4^{I}), 125.8 (C-6^{I}), 122.7 (C-5^{I}), 57.7 (C-7) 45.8 (C-3a), 42.4 (C-4), 32.2 (C-6), 26.9 (C-5); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): 20.51; IR (KBr) cm^{-1}: 1248 (P=O), 1218 (P-O-C_{Ar}), 964 (P-O-C_{Ar}); LCMS m/z (%): 240 [$M^{+\bullet}$] (76), 157(57), 146 (38); Analysis (% calculated/ found) for C10H13N2O$_3$P: C: 50.00/ 49.85, H: 5.46/ 5.42, N: 11.66/ 11.60.

(3aS)-N,N-bis(2-chloroethyl)octahydro-2λ^{5}-pyrrolo-[1,2-c][1,3,2]oxazaphosphol-2-one (7f): Yield: 80%; Mol.Wt: 287; m.p. 127-129 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 4.16 (t, 4H, NCH$_2$CH$_2$Cl *J* = 13.5 Hz), 3.30 (t, 4H, NCH$_2$CH$_2$-Cl, *J* = 13.5 Hz), 3.28-3.35 (m, 2H, H-7), 3.00-3.07 (m, 1H, H-3a), 2.80-2.87 (m, 2H, H-4), 1.46-1.64 (m, 4H, H-5 & H-6); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): 22.50; IR (KBr) cm^{-1}: 1231 (P=O), 1211 (P-O-C_{Ar}), 960 (P-O-C_{Ar}).

Ethyl 2-[(3aS)-1-oxoperhydro-2λ^{5}-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-yl]amino-2- (4-hydroxy phenyl) acetate (7g): Yield: 73%; Mol.Wt. 340; m.p. 135-137 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 9.90 (s, 1H, Ar-OH), 7.12 (d, 2H, *J*= 8.3 Hz, Ar-H), 6.76 (d, 2H, *J*= 9.0 Hz, Ar-H), 3.89 (d, 1H, *J*= 8.2 Hz, NH-CH-C=O), 3.80 (q, 2H, -OCH$_2$ *J*= 7.4 Hz), 3.32 (s, 1H, NH), 3.36-3.42 (m, 2H, H-7), 3.12-3.20 (m, 1H, H-3a), 2.85-2.92 (m, 2H, H-4), 1.34-1.58 (m, 4H, H-5 & H-6), 1.12-1.34 (3H, t, *J*= 7.4 Hz, -CH$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) (δ ppm): 168.7 (O=C-O), 152.9 (C-4^{I}), 131.7 (C-1^{I}), 125.2 (C-2^{I} & C-6^{I}), 120.6 (C-3^{I} & C-5^{I}), 63.6 (O-CH$_2$-CH$_3$), 60.4 (C-7), 55.0 (C-3a), 47.8 (NH-CH), 43.1 (C-4), 29.2 (C-6), 24.7 (C-5), 22.3 (O-CH$_2$-CH$_3$); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): -17.52; IR (KBr) cm^{-1}: 3354 (NH), 1728 (C=O), 1239 (P=O).

Ethyl 2-[(3aS)-1-oxoperhydro-2λ^5-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-yl]amino-3-(4-hydroxy phenyl)propanoate (7h): Yield: 78%; Mol.Wt: 354; m.p. 139-141 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 10.20 (s, 1H, Ar-OH), 7.10 (d, 2H, *J*= 9.0 Hz, Ar-H), 6.66 (d, 2H, *J*= 8.4 Hz, Ar-H), 4.02 (t, 1H, *J*= 8.1 Hz, NH-CH-CH_2), 3.88 (q, 2H, *J*= 7.6 Hz -OCH_2), 3.78-3.74 (m, 2H, NH-CH-CH_2), 3.32 (1H, s, NH), 3.34-3.39 (m, 2H, H-7), 3.09-3.17 (m, 1H, H-3a), 2.79-2.84 (m, 2H, H-4), 1.36-1.48 (m, 4H, H-5 & H-6), 1.12 (t, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) (δ ppm): 168.8 (O=C-O), 153.4 (C-4^1), 132.2 (C-1^1), 125.8 (C-2^1 & C-6^1), 121.0 (C-3^1 & C-5^1), 63.9 (O-CH_2-CH_3), 60.2 (C-7), 55.2 (C-3a), 47.3 (NH-CH), 43.4 (C-4), 36.4 (NH-CH-CH_2), 29.6 (C-6), 24.8 (C-5) 22.5 (O-CH_2-CH_3); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): -20.93; IR (KBr) cm^{-1}: 3365 (NH), 1735 (C=O), 1228 (P=O); LCMS *m/z* (%): 354 [$M^{+\bullet}$] (80), 309 (35), 146 (30); Analysis (% calculated/ found) for $C_{16}H_{23}N_2O_5P$: C: 54.23/ 54.18, H: 6.54/ 6.50, N: 7.91/ 7.87.

Methyl 2-[(3aS)-1-oxoperhydro-2λ^5-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-yl]amino-3- (1H-3-indolyl)propanoate (7i): Yield: 74%; Mol.Wt: 363; m.p. 129-131 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 10.85 (br s, 1H, NH), 7.20-7.01 (m, 5H, Ar-H), 3.92 (m, 1H, NH-CH-CH_2), 3.56 (q, 2H, OCH_2 *J*= 7.4 Hz), 3.35 (s, 1H, NH), 3.28-3.34 (m, 2H, H-7), 3.05-3.11 (m, 1H, H-3a), 2.80-2.85 (m, 2H, H-4), 1.34-1.58 (m, 4H, H-5 & H-6), 1.23 (t, 3H, OCH_2-CH_3 *J*= 7.4 Hz); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): -22.28; IR (KBr) cm^{-1}: 3326 (NH), 1742 (C=O), 1232 (P=O); Analysis (% calculated/ found) for $C_{17}H_{22}N_3O_4P$: C: 56.20/ 56.17, H: 6.10/ 6.06, N: 11.56/ 11.49.

Benzyl(2R)-1-[(3aS)-1-oxoperhydro-2λ^5-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-yl] tetrahydro -1H-2-pyrrolecarboxylate (7j): Yield: 73%; Mol.Wt: 350; m.p. 140-142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 7.52-7.35 (m, 5H, Ar-H), 5.28 (s, 2H, Ar-CH_2), 3.25-3.38 (m, 1H, N-CH-C=O), 3.22-3.36 (m, 2H, H-7), 3.12-3.18 (m, 1H, 3a), 2.85-2.94 (m, 4H, H-4 & H-5^1), 1.82-2.08 (m, 2H, H-3^1), 1.25-1.65 (m, 6H, H-5, H-6 & H-4^1); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): -19.56; IR (KBr) cm^{-1}: 3378 (NH),1758 (C=O), 1225 (P=O).

Ethyl2-[(3aS)-1-oxoperhydro-2λ^5-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-yl]amino-3-(1H--imidazoyl) propanoate (7k): Yield: 82%; Mol.Wt: 328; m.p. 145-147 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 11.20 (br s, 1H, NH), 8.73 (s, 1H, NH-CH=N-), 7.66 (s, 1H, NH-CH=C-), 5.02 (m, 1H , NH-CH-CH_2), 3.72 (t, 2H, O-CH_2-CH_3 *J*= 7.6 Hz), 3.28-3.34 (m, 2H, H-7), 3.16-3.24 (m, 1H, N-CH-C=O), 3.08 (d, 2H, *J*= 8.5 Hz, NH-CH-CH_2), 2.91-2.97 (m, 1H, H-3a), 2.65-2.72 (m, 2H, H-4), 1.34-1.58 (m, 4H, H-5 & H-6), 1.21 (t, 3H, O-CH_2-CH_3 *J*= 7.6 Hz); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): -20.51; IR (KBr) cm^{-1}: 3382 (NH), 1743 (C=O), 1239 (P=O).

Ethyl 2-[(3aS)-1-oxoperhydro-2λ^5-pyrrolo[1,2-c][1,3,2]oxazaphosphol-2-yl]amino -3-(phenyl) acetate (7l): Yield: 75%; Mol.Wt: 324; m.p. 127-129 °C; Anal: Calcd. for $C_{10}H_{13}N_2O_3P$: C, 50.00.20; H, 5.46; N, 11.66. Found: C, 49.75; H, 5.43; N, 11.60; ^{1}H NMR (500 MHz, DMSO-d_6) (δ ppm): 6.83- 7.12 (m, 5H, Ar-H), 4.61-4.69 (m, 1H, NH-CH-C=O), 3.45 (q, 2H, -OCH_2-CH_3, *J*=7.4 Hz), 3.35-3.41 (m, 2H, H-7), 3.32 (s, 1H, NH), 3.11-3.20 (m, 1H, H-3a), 2.84-2.92 (m, 2H, H-4), 1.34-1.58 (m, 4H, H-5 & H-6), 1.12 (t, 3H, -OCH_2-CH_3, *J*= 7.4 Hz); ^{31}P NMR (202 MHz, DMSO-d_6) (δ ppm): δ -21.31; IR (KBr) cm^{-1}: 3394 (NH), 1756 (C=O), 1248 (P=O); LCMS m/z (%): 324[$M^{+\bullet}$] (74), 279 (35), 148 (28).

4.2. Agar dilution method for MIC

The minimum inhibitory concentration (MIC) was evaluated by using agar dilution technique. Agar dilution MIC tests were performed according to standard method.[17] The lowest concentration of title compound showing no growth was read as the MIC. *Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniea* and *Escherichia coli* were included in each run.

Acknowledgements

The authors thank UGC, New Delhi, INDIA for sanctioning a major research project (F.No. 34-356/2008(SR)).

References

[1] Fest, C.; Schmidt, K. J. *The Chemistry of Organophosphorus Pesticides.* Springer-Verlag, Berlin 12, **1982**.

[2] Venugopal, M.; Sankar Reddy, B.; Devendranath Reddy, C.; Berlin, K. D. Synthesis and antimicrobial activity of 2-substituted-2,3-dihydro-5-propoxy-1*H*-1,3,2-enzodiazaphosphorle-2-oxides. *J. Heterocycl.Chem.***2001**,*38*,275-279.

[3] Katritzky, A.R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergmon Press: Oxford, U.K. **1996**.

[4] Reddy, P. V. G; Babu, Y. H.; Reddy, C. S.; Srinivasulu, D. Synthesis of 2-substituted-2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole 2-oxides/sulfides. *Heteroatom Chem.* **2002**, *13*, 340-345.

[5] Engel, R. *(Ed.), Handbook of Organophosphorus Chemistry*, Marcel Decker,. Inc., New York **1992.**

[6] Srinivasulu, K.; Kumar, M. A.; Raju, C. N.; Reddy, C. S. Synthesis and bioactivity of some new 2-substituted-3,4-dihydro-1-(9*H*- carbazol-4-yloxy)methyl- 3-[2-(2-methoxyphenoxy) ethyl]-1,3,2 λ^5-oxazaphosphole 2-oxides, sulfides and selenides. *Arkivoc.* **2007***, xiv,*100-109.

[7] Brown, H.C.; Jadhav, P. K.; Singaram, B. In *Modern Synthetic Methods*. Scheffold, R., Ed.; Springer-Verlag: Heidelberg, **1986,** *4*, 307-356.

[8] Corey, E. J.; Helal, C. J. Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: A new paradigm for enantioselective catalysis and a powerful new synthetic method. *Angew. Chem. Int. Ed.* **1998**, *37*, 1987-2012.

[9] Singh, V. K. Practical and useful methods for the enantioselective reduction of unsymmetrical ketones. *Synthesis.* **1992**, *7*, 605- 617.

[10] Deloux, L.; Srebnik, M. Asymmetric boron-catalyzed reactions**.** *Chem. Rev.* **1993**, *93*, 763-784.

[11] Basavaiah, D.; Reddy, G. J.; Chandrashekar V. A novel and effective chiral phosphoramide catalyst for the borane-mediated asymmetric reduction of prochiral α- halo ketones. *Tetrahedron: Asymmetry.* **2001**, *12*, 685-689.

[12] Thomas L.C., *Interpretation of the Infrared Spectra of Organophosphorus Compounds*, Hyden &Son Ltd. **1974**.

[13] Basavaiah, D.; Reddy, G.J.; Rao, K.V. Toward effective chiral catalysts containing the N-P=O structural frame work for the borane-mediated asymmetric reduction of prochiral ketones. *Tetrahedron:Asymmetry.* **2004**, *15*, 1881-1888.

[14] Khandazhinskaya, A.L.; Shirokova, E.A.; Skoblov, Y.S.; Victorova, L.S.; Goryunova, L. Y; Beabealashvilli, R. S.; Pronyaeva, T. R.; Fedyuk, N. V.; Zolin, V. V.; Pokrovsky, A. G.; Kukhanova, M .K. Carbocyclic dinucleoside polyphosphonates:Interaction with HIV reverse transcriptase and antiviral activity. *J. Med. Chem.,* **2002,** *45*, 1284–1291.

[15] Wang, R.; Harada, S.; Mitsuya, H.; Zemlicka, J. Inhibition of human immunodeficiency virus reverse transcriptase by synadenol triphosphate and its *E*- isomer. *J. Med. Chem.,* **2003,** *46*, 4799–4802.
[16] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th edn., Butterworth, Heinemann, Oxford, **1997**, *OX2,* 8DP.
[17] Jacobs, M. R.; Appelbaum. P. C. Antibiotic-resistant pneumococci. *Rev. Med.Microbiol.* **1995**, 6, 77–93.