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Synthesis, Characterization and Antimicrobial Evaluation of Novel Organo Phospho Carbamates Containing Imidazole Ureas/Carboxamides

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ABSTRACT

The novel Organo Phospho Carbamates containing imidazole ureas/ Carboxamides derivatives are an important class of organophosphorus heterocycles, having potential biological importance due to their unique features. The conversion of acid azide to urethanes (carbamates) through isocyanate involves Curtius rearrangement is an important synthetic method for the preparation of substituted ureido/carboxamide carbamates. They have multifacted applications as important pharmacophores in agriculture, pharmaceuticals, chemical synthesis and diverse other potential biological areas. The compounds electron withdrawing group at position 4 of ureido/carboxamide carbamates increased the activity against bacteria and fungus.

INTRODUCTION

The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry. Literature survey revealed that imidazole and its derivative are reported to have, antianthelmintic activity [1], cardiovascular activity [2], analgesic and anti-inflammatory activity [3], anti-neoplastic activity [4], anti-fungal activity [5], enzyme inhibition activity, anti-filarial agent, anti-viral activity and anti-ulcer activity [6].

The chemistry of phosphorus heterocyclic compounds containing nitrogen plays an important role in the development of new pharmaceutical materials with novel properties. The chemistry of organophosphorus compounds and their derivatives were found to be the highlight of study in lead compound discovery and biological screening and study of their various biological activities such as anti-bacterial [7], herbicides, insecticides, pesticides [8], anti-fungal agents [9], anti-HIV [10], anti-cancer [11], anti-viral and anti-inflammatory [12] including its application in the field of Agriculture, medicine and industry [13].

A good deal of importance was given to synthesized Imidazole possessing carbamate moiety besides dioxaphosphepino ureas/carboxamides screening for possible biological and pharmacological activities.

Solvents, reagents and conditions

(1-2) Isobutyl chloroformate, triethylamine stirred for 30 minutes and add NaN_3 stirred for 20 minutes at 0°C (2-4). The reaction mixture was refluxed for 16 hrs. (4(a-d)-5(a-d)) Dry acetone, PTA, the reaction mixture stirred at R.T., under nitrogen atm for 1 hr. (Step-1 and 2 [14]) Dry toluene, triethylamine, THF addition at 5°C, the reaction mixture slowly raised at R.T., stirred for 2 hrs and heated at 50-60°C and stirred for 4 hrs.

EXPERIMENTAL SECTION

2-(6,6-dimethyl-4,8-dihydro-^{1}H-[1,3]dioxepino[5,6-d]imidazole-1-yl) acetyl azide (2)

Yield 70%. m p: 94-96°C. IR (KBr): 2940 and 2895 (CH_2 and CH_3 of aliphatic-CH), 2400-2000 (N_3), 1395 (C $(CH_3)_2$ stretching

vibration), 1670, 1410 and 1285 cm^{-1} corresponding stretching vibrations of C=O, C-N of azide and C-O respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.27 (s, 6H, two geminial CH_3 groups), 4.57 (s, 4H, two CH_2 groups of acetals), 4.84 (s, 2H, N-CH_2-CO), 7.57 (s, 1H of imidazole ring). Anal.Calcd.For $C_{10}H_{13}N_5O_3$ C: 47.81, H: 5.22 and N: 27.87% Found: C: 47.01, H: 4.72 and N 27.27%.

Cyclohexyl ((6,6-dimethyl-4,8-dihydro-^{1}H-[1,3] dioxepino [5,6-d]imidazol-1-yl) methyl) carbamate (4a)

Yield 68%. m p: 140-142°C. IR (KBr): 3418-3384 (N-H), 3050 (stretching of Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1715 (C=O), 1618 (C=N), 1416 (C-N), 1395 (C $(CH_3)_2$ bending vibration) and 1320 cm^{-1} (C-O) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.27 (s, 6H two geminial CH_3 groups), 1.47-1.60 (m, 10H, CH_2 of cyclohexyl), 3.91 (m, 1H, O-CH of cyclohexyl) 4.57 (s, 4H two CH_2 groups of acetals), 5.40 (d, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). Anal.Calcd.For $C_{16}H_{25}N_3O_4$ C: 59.42, H: 7.79 and N 12.99% Found: C : 58.62, H: 7.29 and N: 12.39%.

Tetrahydro-2H-pyran-4-yl ((6,6-dimethyl-4,8-dihydro-^{1}H-[1,3] dioxepino [5,6-d]imidazol-1-yl) methyl) carbamate (4b)

Yield 68%. m p: 142-144°C. IR (KBr): 3420-3386 (N-H), 3052 (stretching of Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1715 (C=O), 1620 (C=N), 1418 (C-N), 1395 (C $(CH_3)_2$ bending vibration) and 1324 cm^{-1} (C-O) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.27 (s, 6H two geminial CH_3 groups), 1.47-1.60 (m, 10H, CH_2 of cyclohexyl), 3.91 (m, 1H, O-CH of cyclohexyl) 4.57 (s, 4H two CH_2 groups of acetals), 5.40 (d, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). Anal.Calcd.For $C_{15}H_{23}N_3O_5$ C: 55.37, H: 7.13 and N: 12.91% Found: C: 54.57, H: 6.63 and N 12.31%.

Tetrahydro-2H-thiopyran-4-yl ((6,6-trimethyl-4,8-dihydro-^{1}H-[1,3] dioxepino [5,6-d] imidazol-1-yl) methyl) carbamate (4c)

Yield 68%. m p: 144-146°C. IR (KBr): 3420-3390 (N-H), 3052 (stretching of Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1715 (C=O), 1620 (C=N), 1418 (C-N), 1395 (C$(CH_3)_2$ bending vibration), 1324 (C-O) and 715 cm^{-1} (C-S) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.27 (s, 6H two geminial CH_3 groups), 1.47-1.60 (m, 10H, CH_2 of cyclohexyl), 3.91 (m, 1H, O-CH of cyclohexyl) 4.57 (s, 4H two CH_2 groups of acetals), 5.40 (d, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). Anal.Calcd.For $C_{15}H_{23}N_3O_4S$ C: 52.77, H: 6.79, N: 12.31 and S: 9.39% Found: C: 51.97, H: 6.29, N: 11.71 and S: 9.19%

Perfluorophenyl ((6,6-dimethyl-4,8-dihydro-^{1}H-[1,3] dioxepino[5,6-d]imidazol-1-yl) methyl) carbamate (4d)

Yield 70%.m p: 142-144°C. IR (KBr): 3422-3392 (N-H), 3052 (stretching of Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1715 (C=O), 1620 (C=N), 1420 (C-N), 1395 (C $(CH_3)_2$ bending vibration), 1326 (C-O) and 1100 cm^{-1} (C-F) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.27(s, 6H two geminial CH_3 groups), 4.57 (s, 4H two CH_2 groups of acetals), 5.40 (s, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). Anal.Calcd.For $C_{16}H_{14}F_5N_3O_4$ C: 47.18, H: 3.46, N: 10.32 and F: 23.32% Found: C: 46.38, H: 2.96, N: 9.72 and F: 22.52%.

Cyclohexyl ((4, 5-bis (hydroxymethyl)-^{1}H-imidazol-1-yl) methyl) carbamate (5a)

Yield 60%. m p: 164-166°C. IR (KBr): 3520 (v_{O-H}, intramolecular H-bonding), 3020 (stretching of Ar-H), 3418-3384 (N-H), 2940 and 2895 (CH_2 of aliphatic C-H stretching), 1715 (C=O), 1618 (C=N), 1416 (C-N) and 1322 cm^{-1} (C-O) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.47-1.60 (m, 10H, CH_2 of cyclohexyl), 3.91 (m, 1H, O-CH of cyclohexyl)), 4.25 (s, 2H two –OH having intramolecular H-bonding), 4.73 (s, 4H two CH_2 groups of dimethanols), 5.40 (s, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). Anal.Calcd.For $C_{13}H_{21}N_3O_4$ C: 55.11, H: 7.47 and N: 14.83%. Found: C: 54.31, H: 6.97 and N: 14.23%.

Tetrahydro-2H-piran-4-yl ((4,5-bis (hydroxymethyl)-^{1}H -imidazol-1-yl) methyl) carbamate (5b)

Yield 65%. m p: 166-168°C. IR (KBr): 3520 (v_{O-H}, intramolecular H-bonding), 3030 (stretching of Ar-H), 3418-3386 (N-H), 2940 and 2895 (CH_2 of aliphatic C-H stretching), 1715 (C=O), 1620 (C=N), 1418 (C-N) and 1324 cm^{-1} (C-O) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.72-1.97 (m, 4H CH_2 of pyran), 3.55-3.65 (t, 4H, CH_2-O of pyran), 4.20 (s, 2H two –OH having intramolecular H-bonding), 4.07 (m, 1H, O-CH of pyran), 4.73 (s, 4H two CH_2 groups of dimethanols), 5.40 (s, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). For $C_{12}H_{19}N_3O_5$ C: 55.11, H: 7.47 and N: 14.83%. Found: C: 54.31, H: 6.97 and N: 14.23%.

Tetrahydro-2H-thiopiran-4-yl ((4,5-bis (hydroxymethyl)-^{1}H -imidazol-1-yl) methyl) carbamate (5c)

Yield 62%. m p: 165-168°C. IR (KBr): 3520 (v_{O-H}, intramolecular H-bonding), 3045 (stretching of Ar-H), 3418-3388 (N-H), 2940 and 2895 (CH_2 of aliphatic C-H stretching), 1715 (C=O), 1620 (C=N), 1418 (C-N), 1324 cm^{-1} (C-O) and 715 cm^{-1}(C-S) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.81-2.06 (m, 4H, CH_2 of thiopyran), 2.47-2.57 (t, 4H, -CH_2 –S of thiopyran), 4.20 (s, 2H two –OH having intramolecular H-bonding), 4.17 (m, 1H, O-CH of thiopyran), 4.73 (s, 4H two CH_2 groups of dimethanols), 5.40 (s, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). For $C_{12}H_{19}N_3O_4S$ C: 47.83, H: 6.35, N: 13.94 and S: 10.64%. Found: C: 47.03, H: 5.85, N: 13.34 and S: 10.44%.

Perfluorophenyl ((4, 5-bis(hydroxymethyl)-^{1}H-imidazol-1-yl) methyl) carbamate (5d)

Yield 75%. m p: 169-171°C. IR (KBr): 3520 (v_{O-H}, intramolecular H-bonding), 3035 (stretching of Ar-H), 3422-3390 (N-H), 2940 and 2895 (CH_2 of aliphatic C-H stretching), 1715 (C=O), 1620 (C=N), 1420 (C-N), 1326 cm^{-1} (C-O) and 1100 cm^{-1}(C-F) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 4.20 (s, 2H two –OH having intramolecular H-bonding), 4.73 (s, 4H two CH_2 groups of dimethanols), 5.40 (s, 2H, N-CH_2), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). For $C_{13}H_{10}F_5N_3O_4$ C: 42.52, H: 2.74, N: 11.44 and F: 25.87%. Found: C: 41.72, H: 2.24, N: 10.84 and F: 25.07%.

Cyclohexyl ((6-oxide-6-(3-phenylureido)-4,8-dihydro-H-[1,3,2] dioxaphosphepino[5,6-d] imidazole-1-yl) methyl) carbamate 7(a)

The obtained product of **7a** is 0.88 g, Yield 64%. m p: 149-151°C. IR (KBr): 3416-3382 (γ P-NH), 3040 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1675 (C=O of urea), 1618 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.47-1.60 (m, 10H, CH_2 of cyclohexyl), 3.91 (m, 1H, O-CH of cyclohexyl), 5.23 (s,4H, two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.19-7.61 (m, 5H, C_6H_5 attached to urea moiety),7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6): $_{PPM}$137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 76.8, 30.8, 24.1, 25.7, 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 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15}, C_{16} and C_{20}, C_{17} and C_{19} and $C_{18.}$ ^{31}P-NMR (161.89 MHz, DMSO-d_6): $_{PPM}$ -6.90, -6.45. For $C_{20}H_{26}N_5O_6P$ C: 51.83, H: 5.65, N: 15.11 and P: 6.68%. Found: C: 51.03, H: 5.15, N: 14.51 and P: 5.98%.

Tetrahydro-2H-pyran-4-yl ((6-oxide-6-(3-phenylureido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate 7(b)

The obtained product of **7b** is 0.93 g Yield 67%. m p: 150-152°C. IR (KBr): 3420-3384 (γ P-NH), 3040 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1675 (C=O of urea), 1618 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.72-1.97(m, 4H, CH_2 of pyran), 3.55-3.65 (t, 4H, CH_2-O of pyran), 4.07 (m, 1H, O-CH of pyran), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.19-7.61 (m, 5H, C_6H_5 attached to urea moiety),7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 72.5, 33.4, 63.2, 152.0, 139.4, 121.6, 128.9 and 128.0 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14}, C_{15} and C_{19}, C_{16} and C_{18} and C_{17}. ^{31}P-NMR (161.89 MHz, DMSO-d_6): $_{PPM}$ -6.95, -6.53. For $C_{19}H_{24}N_5O_7P$ C: 49.03, H: 5.20, N: 15.05 and P: 6.66%. Found: C: 48.23, H: 4.70, N: 14.45 and P: 5.96%.

Tetrahydro-2H-thiopyran-4-yl ((6-oxide-6-(3-phenylureido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate 7(c)

The obtained product of **7c** is 0.93 g Yield 65%. m p: 152-154°C. IR (KBr): 3425-3386 (γ P-NH), 3040 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1675 (C=O of urea), 1620 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250($\gamma_{P=O}$), 950 ($\gamma_{P\text{-}O}$) and 715 cm^{-1}(C-S) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.81-2.06 (m, 4H, CH_2 of thio pyran), 2.47-2.57 (t, 4H, CH_2-S of thiopyran), 4.17 (m, 1H, O-CH of thiopyran), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.19-7.61 (m, 5H, C_6H_5 attached to urea moiety),7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 69.5, 33.2, 25.5, 152.0, 139.4, 121.6, 128.9 and 128.0 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14}, C_{15} and C_{19}, C_{16} and C_{18} and C_{17}. ^{31}P-NMR (161.89 MHz, DMSO-d_6) $_{PPM}$ -7.04, -6.42. For $C_{19}H_{24}N_5O_6PS_c$: 47.40, H: 5.02, N: 14.55, P: 6.43 and S: 6.66%. Found: C: 46.60, H: 4.52, N: 13.95, P: 5.73 and S: 6.46%.

Perfluorophenyl ((6-oxide (3-phenylureido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7d)

The obtained product of **7d** is 0.95 g Yield 70%. m p: 156-158°C. IR (KBr): 3430-3388 (γ P-NH), 3040 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1675 (C=O of urea), 1622 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250($\gamma_{P=O}$), 1100 (C-F) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.19-7.61 (m, 5H, C_6H_5 attached to urea moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6): $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 155.0, 142.0, 139.3, 142.4, 140.1, 152.0, 139.4, 121.6, 128.9 and 128.0 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15}, C_{16} and C_{20}, C_{17} and C_{19} and $C_{18.}$ ^{31}P-NMR (161.89 MHz, DMSO-d_6) $_{PPM}$ -8.48. For $C_{20}H_{15}F_5N_5O_6P$ C: 43.89, H: 2.76, F: 17.36, N: 12.80 and P: 5.66%. Found: C: 43.09, H: 2.26, F: 16.56, N: 12.20 and P: 4.96%.

Cyclohexyl ((6-(3-(4-methoxyphenyl) ureido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate 7(e)

The obtained product of **7e** is 0.94 g Yield 64%. m p: 150-152°C. IR (KBr): 3416-3382 (γ P-NH), 3025 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1670 (C=O of urea), 1616 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.49-1.80 (m, 10H, CH_2 of cyclohexyl), 3.83 (s, 3H, CH_3 of methoxyphenyl), 3.91 (m, 1H, O-CH of cyclohexyl), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 6,97-7.51 (m, 4H, C_6H_4 attached to urea moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 76.8, 30.8, 24.1, 25.7, 152.0, 131.7, 119.8, 114.5, 158.9 and 56.8 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15}, C_{16} and C_{20}, C_{17} and C_{19}, C_{18} and C_{21}. ^{31}P-NMR (161.89 MHz, DMSO-d_6): $_{PPM}$ -6.08, -5.16. For $C_{21}H_{28}N_5O_7P$ C: 51.11, H: 5.72, N: 14.19 and P: 6.28%. Found: C: 50.31, H: 5.52, N: 13.59 and P: 5.58%.

Tetrahydro-2H-pyran-4-yl ((6-(3-(4-chlorophenyl)ureido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate 7(f)

The obtained product of **7f** is 1.01 g Yield 68%. m p: 152-154°C. IR (KBr): 3420-3384 (γ P-NH), 3027 (Ar-H), 2940 and 2895

(aliphatic C-H stretching), 1705 (C=O of ester group), 1680 (C=O of urea), 1618 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$), 950 ($\gamma_{P\text{-}O}$) and 730 cm^{-1} (C-Cl) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.72-1.97(m, 4H, CH_2 of pyran), 3.65 and 3.55 (t, 4H, CH_2-O of pyran), 4.07 (m, 1H, O-CH of pyran), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.47-7.57 (m, 4H, C_6H_4 attached to urea moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 72.5, 33.4, 63.2, 152.0, 139.4, 121.6, 128.9 and 128.0 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14}, C_{15} and C_{19}, C_{16} and C_{18} and C_{17}. ^{31}P-NMR (161.89 MHz, DMSO-d_6): $_{PPM}$ -8.32. For $C_{19}H_{23}ClN_5O_7P$ C: 45.66, H: 4.64, Cl: 7.09, N: 14.09 and P: 6.20%. Found: C: 44.86, H: 4.14, Cl: 6.29, N: 13.41 and P: 5.50%.

Tetrahydro-2H-thiopyran-4-yl ((6-(3-(4-bromophenyl)ureido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate 7(g)

The obtained product of **7g** is 1.12 g Yield 67%. m p: 154-156°C. IR (KBr): 3425-3386 (γ P-NH), 3029 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1680 (C=O of urea), 1618 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$), 950 ($\gamma_{P\text{-}O}$) and 715 cm^{-1} (C-S) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): $_{PPM}$ 1.81-2.06 (m, 4H, CH_2 of thio pyran), 2.57 and 2.47 (t, 4H, CH_2-S of thiopyran), 4.17 (m, 1H, O-CH of thiopyran), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.58-7.70 (m, 4H, C_6H_4 attached to urea moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6): $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 69.6, 32.2, 25.5, 152.0, 138.4, 121.9, 131.8 and 122.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14}, C_{15} and C_{19}, C_{16} and C_{18} and $C_{17.}$ ^{31}P-NMR (161.89 MHz, DMSO-d_6) $_{PPM}$ -10.45. For $C_{19}H_{23}BrN_5O_6PS$ C: 40.72, H: 4.14, Br: 14.26, N: 12.50, P: 5.53 and S: 5.72%. Found: C: 40.03, H: 3.69, Br: 13.66, N: 11.60, P: 4.93 and S: 5.52%.

Perfluorophenyl ((6-(3-(4-nitrophenyl) ureido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate 7(h)

The obtained product of **7h** is 1.06 g Yield72%. m p: 158-160^{0}C. IR (KBr): 3430-3388 (γ P-NH), 3030 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1705 (C=O of ester group), 1685 (C=O of urea), 1622 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$), 950 ($\gamma_{P\text{-}O}$) and 1100 cm^{-1} (C-F) respectively. ^{1}H-NMR (400 MHz, DMSO-d_6): δ $_{PPM}$: 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 2H, NH-of urea moiety), 7.82-8.24 (m, 4H, C_6H_4 attached to urea moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR(75 MHz, DMSO-d_6): $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 155.0, 142.0, 139.3, 142.4, 140.1, 152.0, 145.5, 119.9, 124.1 and 143.5 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15}, C_{16} and C_{20}, C_{17} and C_{19} and $C_{18.}$ ^{31}P-NMR (161.89 MHz, DMSO-d_6): $_{PPM}$ -7.85, -7.50. For $C_{20}H_{14}F_5N_6O_8P$ C: 40.55, H: 2.38, F: 16.04, N: 14.19 and P: 5.23%. Found: C: 39.75, H: 1.88, F: 15.84, N: 13.59 and P: 4.53%.

Cyclohexyl ((6-(morpholine-4-carboxamido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7i)

The obtained product of **7i** is 0.91 g. Yield : 67%. M p: 163-165°C. IR (KBr): 3416-3382 (γ P-NH), 3030 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1616 (C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H NMR (400 MHz, DMSO-d_6) δ $_{PPM}$: 1.49-1.80 (m, 10H, CH_2 of cyclohexyl), 3.31 (t, 4H, N-CH_2 of morpholine ring J=7.1Hz), 3.65 (t, 4H, -CH_2-O of morpholine ring J=7.1Hz), 4.30 (m, 1H, CH of cyclohexyl ring attached to oxygen), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR(75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 76.8, 30.8, 24.1, 25.7, 158.5, 139.4, 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 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15} and C_{18} and C_{16} and $C_{17.}$

^{31}P-NMR (161.89 MHz, DMSO-d_6) $_{PPM}$: -6.95.

Anal. Calcd(%) For $C_{18}H_{28}N_5O_7P$ C: 47.26, H: 6.17, N: 15.31 and P: 6.77%. Found: C: 46.66, H: 5.67, N: 14.71 and P: 6.77%.

Tetrahydro-2H-pyran-4-yl ((6-(morpholine-4-carboxamido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7j)

The obtained product of **7j** is 0.96 g, Yield : 70%.m p: 165-167°C. IR (KBr): 3420-3384 (γ P-NH), 3034 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1618(C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H NMR (400 MHz, DMSO-d_6) δ $_{PPM}$: 1.70-1.90 (m, 4H, CH_2 pyran of carbamate), 3.31 (t, 4H, N-CH_2 of morpholine ring), 3.65 (t, 4H, -CH_2-O of morpholine ring J=7.1Hz), 3.85 (t, 4H, CH_2-O pyran of carbamate J=7.1Hz), 4.17 (m, 1H, O-CH pyran of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 72.5, 33.4, 63.2, 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 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14} and C_{17} and C_{15} and C_{16}.

Anal.Calcd (%) For $C_{17}H_{26}N_5O_8P$ C: 44.45, H: 5.70, N: 15.24 and P: 6.74%. Found: C: 43.65, H: 5.20, N: 14.64 and P: 6.04%.

Tetrahydro-2H-thiopyran-4-yl ((6-(morpholine-4-carboxamido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7k)

The obtained product of **7k** is 0.98 g, Yield: 69%.m p: 167-169°C. IR (KBr): 3425-3386 (γ P-NH), 3010 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1618(C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$), 950 ($\gamma_{P\text{-}O}$) and 715 cm^{-1} (C-S) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.81-2.06 (m, 4H, CH_2 thio pyran of carbamate), 2.57 (t, 4H, CH_2-S thiopyran of carbamate), 3.31 (t, 4H, N-CH_2 of morpholine ring J=7.1Hz), 3.65(t, 4H, -CH_2-O of morpholine ring J=7.1Hz), 4.10 (m, 1H, O-CH thiopyran of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 69.5, 32.2, 25.5, 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 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14} and C_{17} and C_{15} and C_{16}.

Anal.Calcd (%) For $C_{17}H_{26}N_5O_7PS$ C: 42.94, H: 5.51, N: 14.73, P: 6.51 and S: 6.74%. Found: C: 42.14, H: 5.01, N: 14.13, P: 5.81 and S: 6.54%.

Perfluorophenyl ((6-(morpholine-4-carboxamido)-6-oxide-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7l)

The obtained product of **7l** is 1.01 g, Yield: 75%.m p: 169-171°C. IR (KBr): 3430-3388 (γ P-NH), 3020 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1618(C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$), 1100 (C-F) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 3.31 (t, 4H, N-CH_2 of morpholine ring J=7.1Hz), 3.65 (t, 4H, -CH_2-O of morpholine ring J=7.1Hz), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 155.0, 142.0, 139.3, 142.4, 140.1, 46.3, 65.7 and 46.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15} and C_{18} and C_{16} and $C_{17.}$

Anal.Calcd (%) For $C_{18}H_{17}F_5N_5O_7P$ C: 39.94, H: 3.17, F: 17.55, N: 12.94 and P: 5.72% Found: C: 39.14, H: 2.67, F: 16.75, N: 12.34 and P: 5.02%.

Cyclohexyl ((6-oxido-6-(piperidine-1-carboxamido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7m)

The obtained product of **7m** is 0.88 g, Yield: 65%. m p: 162-164°C. IR (KBr): 3416-3382 (γ P-NH), 3025 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1618(C=N), 1416 (C-N), 1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively. ^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.49-1.80 (m, 10H, CH_2 cyclohexyl of carbamate), 1.53-1.59 (m, 6H, CH_2 piperidine of carboxamide), 3.77 (t, 4H, N-CH_2 piperidine of carboxamide J=7.1Hz), 3.91 (m, 1H, O-CH cyclohexyl of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 76.8, 30.8, 24.1, 25.7, 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 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15} and C_{19}, C_{16} and C_{18} and C_{17}.

^{31}P-NMR (161.89 MHz, DMSO-d_6) $_{PPM}$: -5.05.

Anal.Calcd (%) For $C_{19}H_{30}N_5O_6P$ C: 50.11, H: 6.64, N: 15.38 and P: 6.80% Found: C: 49.31, H: 6.14, N: 14.78 and P: 6.10%.

Tetrahydro-2H-pyran-4-yl ((6-oxido-6-(piperidine-1-carboxamido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7n)

The obtained product of **7n** is 0.96 g, Yield: 70%. m p: 164-166°C. IR (KBr): 3420-3384 (γ P-NH), 3027 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1618(C=N), 1416 (C-N),1320 ($\gamma_{C\text{-}O}/\delta_{C\text{-}O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} ($\gamma_{P\text{-}O}$) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.53-1.59 (m, 6H, CH_2 piperidine of carboxamide), 1.72-1.97 (m, 4H, CH_2 pyran of carbamate), 3.77 (t, 4H, N-CH_2 piperidine of carboxamide J=7.1Hz), 3.55-3.65 (m, 4H, CH_2-O pyran of carbamate), 4.07 (m, 1H, O-CH pyran of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 72.5, 33.4, 63.2, 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 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14} and C_{18}, C_{15} and C_{17} and C_{16}.

Anal.Calcd (%) For $C_{18}H_{28}N_5O_7P$ C: 47.26, H: 6.17, N: 15.31 and P: 6.77%. Found: C: 46.46, H: 5.67, N: 14.71 and P: 6.07%.

Tetrahydro-2H-thiopyran-4-yl ((6-oxido-6-(piperidine-1-carboxamido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7o)

The obtained product of **7o** is 0.89 g, Yield: 63%.m p: 166-168°C. IR (KBr): 3425-3386 (γ P-NH), 3029 (Ar-H), 2940 and

2895 (aliphatic C-H stretching), 1650 (C=O), 1620 (C=N), 1416 (C-N), 1320 ($\gamma_{C-O}/\delta_{C-O}$), 1250 ($\gamma_{P=O}$), 950 ($\gamma_{P-O}$) and 715 cm^{-1} (C-S) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.53-1.59 (m, 6H, CH_2 piperidine of carboxamide), 1.81-2.06 (m, 4H, CH_2 thio pyran of carbamate), 2.57 (t, 4H, CH_2-S thio pyran of carbamate J=7.1Hz), 3.77 (t, 4H, N-CH_2 piperidine of carboxamide J=7.1Hz), 4.17 (m, 1H, O-CH thio pyran of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO). ^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 69.5, 32.2, 25.5, 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 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14} and C_{18}, C_{15} and C_{17} and C_{16}.

Anal.Calcd (%) For $C_{18}H_{28}N_5O_6PS$ C: 45.66, H: 5.96, N: 14.79, P: 6.54 and S: 6.77%. Found: C: 44.86, H: 5.46, N: 14.19, P: 5.84 and S: 6.57%.

Perfluorophenyl ((6-oxido-6-(piperidine-1-carboxamido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7p)

The obtained product of **7p** is 1.0 g, Yield: 75%. m p: 168-170°C. IR (KBr): 3430-3388 (γ P-NH), 3030 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1622 (C=N), 1416 (C-N), 1320 ($\gamma_{C-O}/\delta_{C-O}$), 1250 ($\gamma_{P=O}$), 1100 (C-F) and 950 cm^{-1} (γ_{P-O}) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.53-1.59 (m, 6H, CH_2 piperidine of carboxamide), 3.77 (t, 4H, N-CH_2 piperidine of carboxamide J=7.1Hz), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 155.0, 142.0, 139.3, 142.4, 140.1, 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 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15} and C_{19}, C_{16} and C_{18} and C_{17}.

Anal.Calcd (%) For $C_{19}H_{19}F_5N_5O_6P$ C: 42.51, H: 3.55, F: 17.61, N: 12.98 and P: 5.74% Found: C: 41.31, H: 3.05, F: 16.81, N: 12.38 and P: 5.04%.

Cyclohexyl ((6-(4-methylpiperazine-1-carboxamido)-6-oxido-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7q)

The obtained product of **7q** is 0.91 g, Yield: 65%. m p: 164-166°C. IR (KBr): 3416-3382 (γ P-NH), 3025 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1616 (C=N), 1416 (C-N),1320 ($\gamma_{C-O}/\delta_{C-O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} (γ_{P-O}) respectively. ^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.49-1.80 (m, 10H, CH_2 cyclohexyl of carbamate), 2.26 (s, 3H, N-CH_3), 2.27 (t, 4H, CH_2-N piperazine of carboxamide J=7.1Hz), 3.40 (t, 4H, N-CH_2 piperazine of carboxamide J=7.1Hz), 3.91 (m, 1H, O-CH of cyclohexyl of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 76.8, 30.8, 24.1, 25.7, 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 and C_{13}, C_{10} and C_{12}, C_{11}, C_{14}, C_{15} and C_{18}, C_{16} and C_{17} and C_{19}.

^{31}P-NMR (161.89 MHz, DMSO-d_6) $_{PPM}$: -7.10.

Anal.Calcd (%) For $C_{19}H_{31}N_6O_6P$ C: 48.51, H: 6.64, N: 17.86 and P: 6.58% Found: C: 47.71, H: 6.14, N: 17.26 and P: 5.88%.

Tetrahydro-2H-pyran-4-yl ((6-(4-methylpiperazine-1-carboxamido)-6-oxido-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7r)

The obtained product of **7r** is 0.9 g, Yield: 70%. m p: 166-168°C. IR (KBr): 3420-3384 (γ P-NH), 3027 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1618 (C=N), 1416 (C-N), 1320 ($\gamma_{C-O}/\delta_{C-O}$), 1250 ($\gamma_{P=O}$) and 950 cm^{-1} (γ_{P-O}) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.72-1.97(m, 4H, CH_2 pyran of carbamate), 2.26 (s, 3H, N-CH_3), 2.27 (t, 4H, CH_2-N piperazine of carboxamide J=7.1Hz), 3.40 (t, 4H, N-CH_2 piperazine of carboxamide J=7.1Hz), 3.85 (t, 4H, CH_2-O pyran of carbamate J=7.5Hz), 4.07 (m, 1H, O-CH pyran of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$ 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 72.5, 33.4, 63.2, 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 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14} and C_{17}, C_{15} and C_{16} and C_{18}.

Anal.Calcd (%) For $C_{18}H_{29}N_6O_7P$ C: 45.76, H: 6.19, N: 17.79 and P: 6.56%. Found: C: 44.96, H: 5.69, N: 17.19 and P: 5.86%.

Tetrahydro-2H-thiopyran-4-yl ((6-(4-methylpiperazine-1-carboxamido)-6-oxido-4,8-dihydro-^{1}H-[1,3,2]dioxaphosphepino[5,6-d] imidazole-1-yl) methyl) carbamate (7s)

The obtained product of **7s** is 0.98 g, Yield: 67%. m p: 168-170°C. IR (KBr): 3425-3386 (γ P-NH), 3029 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1620 (C=N), 1416 (C-N), 1320 ($\gamma_{C-O}/\delta_{C-O}$), 1250 ($\gamma_{P=O}$), 950 ($\gamma_{P-O}$) and 715 cm^{-1} (C-S) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 1.81-2.06 (m, 4H, CH_2 thio pyran of carbamate), 2.26 (s, 3H, N-CH_3), 2.27 (t, 4H, CH_2-N piperazine of carboxamide J=7.1Hz), 2.57 (t, 4H, CH_2-S thiopyran of carbamate J=7.1Hz), 3.40 (t, 4H, N-CH_2 piperazine of carboxamide J=7.5Hz), 4.17 (m, 1H, O-CH thiopyran of carbamate), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$: 137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 156.2, 69.5, 33.2, 25.5, 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 and C_{12}, C_{10} and C_{11}, C_{13}, C_{14} and C_{17}, C_{15} and C_{16} and C_{18}.

Anal.Calcd (%) For $C_{18}H_{29}N_6O_6PS$ C: 44.26, H: 5.98, N: 17.20, P: 6.34 and S: 6.56%. Found: C: 43.46, H: 5.48, N: 16.60, P: 5.64 and S: 6.36%.

Perfluorophenyl ((6-(4-methylpiperazine-1-carboxamido)-6-oxido-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (7t)

The obtained product of **7t** is 1.00 g, Yield: 73%. m p: 170-172°C.IR (KBr): 3430-3388 (γ P-NH), 3030 (Ar-H), 2940 and 2895 (aliphatic C-H stretching), 1650 (C=O), 1622 (C=N), 1416 (C-N), 1320 ($\gamma_{C-O}/\delta_{C-O}$), 1250 ($\gamma_{P=O}$), 1100 (C-F) and 950 cm^{-1} (γ_{P-O}) respectively.

^{1}H NMR (400 MHz, DMSO-d_6) δ_{PPM}: 2.26 (s, 3H, N-CH_3), 2.27 (t, 4H, CH_2-N piperazine of carboxamide J=7.1Hz), 3.40 (t, 4H, N-CH_2 piperazine of carboxamide J=7.1Hz), 5.23 (s, 4H two CH_2 groups attached to phosphorus moiety), 5.40 (s, 2H, N-CH_2), 6.0 (s, 1H, NH-of carboxamide moiety), 7.57 (s, 1H of imidazole ring) and 8.03 (s, 1H, NH-CO).

^{13}C-NMR (75 MHz, DMSO-d_6) $_{PPM}$137.3, 132.9, 127.7, 63.4, 60.6, 61.8, 155.0, 142.0, 139.3, 142.4, 140.1, 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 and C_{13}, C_{10} and C_{12}, C_{11}, $C_{14,}$ C_{15} and C_{18}, C_{16} and C_{17} and C_{19}.

Anal.Calcd (%) For $C_{19}H_{20}F_5N_6O_6P$ C: 41.16, H: 3.64, F: 17.14, N: 15.16 and P: 5.59% Found: C: 40.36, H: 3.14, F: 16.34, N: 14.56 and P: 4.89%.

RESULTS AND DISCUSSION

Synthesis of 2-(6,6-dimethyl-4,8-dihydro-^{1}H-[1,3] dioxepino[5,6-d] imidazole-1-yl) acetyl azide (2) [15]

To a solution of 2-(6,6-dimethyl-4,8-dihydro-1H-[1,3] dioxepino [5,6-d] imidazol-1-yl-acetic acid (4.5 g, 0.02 mol) **(1)** in acetone was added triethyl amine (0.50 ml) and stirred for 30 minutes. To the reaction mixture aqueous NaN_3 (0.6 mol) was added and stirred for 20 minutes at 0°C. After completion, reaction mixture was poured in ice cold water (20 ml), extracted with diethyl ether (10 ml). The organic layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give crude product. The crude product was purified by column chromatography (60-120 mesh silica gel, eluent: 10 % EtoAc-pet ether), to give pure acid azide (3.51 g) **(2).** This was collected by filtration and recrystallized from ethanol, mp 94-96°C, yield 70%.

Synthesis of Cylohexyl/tetrahydro-2H-pyran/tetrahydro-2H-thiopyran/perfluoro phenyl (6,6-dimethyl-4,8-dihydro-^{1}H-[1,3] dioxepino [5,6-d] imidazol-1-yl) methyl carbamates 4(a-d) [16]

To the solution if acid azide **(2)** (1.09 g 0.0039 mol), in Cyclohexanol (15 ml, 0.1 mol) **(3a)** was added and reaction mixture was refluxed for 16 hours. After completion of the reaction, solvent was evaporated under vacuum to give crude residue, which was purified by column chromatography (60-120 mesh silica gel). The reaction was monitored with TLC using hexane and ethylacetate (7:3) as an eluent. Ethylacetate and petroleum ether (3:7) solvent mixture was used as an eluent. Finally the product compound cyclohexyl ((6,6-dimethyl-4,8-dihydro-1H-[1,3] doxepin [5,6-d] imidazol-1-yl) methyl) carbamate (0.87 g) **(4a)** was purified from aqueous dimethyl formamide. Yield 68%, m p 140-142°C. The similar experimental procedure was adopted to synthesize **4(b-d)** (**4b**-0.88 g with 68%, **4c**-0.87 g with 68%, **4d**-0.79 g with 70%) from **2** and Tetrahydro-2H-pyron-4-ol **(3b**-1.5 ml, 0.0174 mol**)**, Tetrahydro-2H-pyron-4-ol (**3c**-1.5 ml, 0.0147 mol**)** and 2, 3, 4, 5, 6-pentafluorophenol **(3d**-1.5 ml, 0.0118 mol**)**.

Synthesis of Cyclohexyl/tetrahydro-2H-pyran-4-yl/tetrahydro-2H-thiopyran-4-yl/pefluorophenyl ((4, 5-bis (hydroxymethyl)-^{1}H-imidazol-1-yl) methyl) carbamates 5(a-d)

The isopropylidenation of 1, 2-diols was carried out by a procedure as reported in the literature. A suspension of the cyclohexyl ((6,6-dimethyl-4,8-dihydro-1H-[1,3] doxepin [5,6-d] imidazol-1-yl) methyl) carbamate (0.85 g, 0.0026 mol) **(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 eluent. After completion of the reaction, the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (3×20 ml) and water and the combined organic layer was dried with Na_2SO_4 and concentrated in vacuum to give the crude product **(5a)**. 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 (0.81 g) **(5a)** was 164-166°C with yield of 60%.

The similar procedure was adopted to synthesize **5(b-d)** (**5b**-0.84 g with 65%, **5c**-0.86 g with 62%, and **5d**-0.77 gr with 75%) from (**4b**-0.85 g, 0.0026 mol, **4c**-0.85 g, 0.0024 mol and **4d**-0.77 g, 0.0017 mol**).**

Synthesis of Cyclohexyl/terahydro-2H-pyran/tetrahydro-2H-thiopyran/perfluorophenyl ((6-oxide-6-(3-phenylureido)/(4-methoxyphenyl)/(4-chlorophenyl)/(4-bromophenyl)/(4-nitrophenyl) ureido)-4,8-dihydro-^{1}H-[1,3,2] dioxaphosphepino [5,6-d] imidazol-1-yl) methyl) carbamates 7(a-h)

A solution of (phenyl carbamoyl) phosphoramidic dichloride (5.0 g, 0.019 mol)[17] **(6a)** (2 mmol) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of Cyclohexyl ((4, 5-bis (hydroxymethyl)-1H-imidazol-1-yl) methyl) carbamate (0.80 g, 0.003 mol) **(5a)** and triethylamine in 30 ml of dry toluene and 10 ml of tetrahydrofuran at 5°C. After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 2 hours. Later on the reaction mixture was heated to 50-60°C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystallized from aqueous 2-propanol to get pure compound cyclohexyl ((6-oxide-6-(3-phenylureido)-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (0.80 g, 0.0019 mol) **(7a)**, yield 64%, m p 149-151°C. The similar procedure was adopted to synthesize **7(b-d)** (0.83 g-**7b**; 0.83 g-**7c**; 0.76 g-**7d**) by the reaction between 5(b-d) (0.83 g, 0.003 mol-5b; 0.85 g, 0.003 mol-5c; 0.75 g, 0.0025 mol-5d) with (phenyl carbamoyl) phosphoramidic dichloride (5.0 g, 0.019 mol) **(6a)**, **7(e-h)** (0.84 g-7e; 0.91 g-7f; 0.99 g-7g; 0.96 g-7h) were prepared by condensation of **5a** (0.84 g, 0.003 mol) + **6b** (5.0 g, 0.017 mol), **5b** (0.85 g, 0.003 mol) + **6c** (5.0 g, 0.017 mol), **5c** (0.90 g, 0.003 mol) + 6d (5.0 g, 0.015 mol) and **5d** (0.91 g, 0.0025 mol) + **6e** (5.0 g, 0.016 mol) respectively.

Synthesis of Cyclohexyl/tetrahydro-2H-pyran-4-yl/tetrahydro-2H-thiopyran-4-yl/perfluorophenyl ((6-(morpholine-4-carboxamido)/(piperidine-1-carboxamido)/(4-methylpiperazine-1-carboxamido)-6-oxide-4,8-dihydro-^{1}H -[1,3,2] dioxaphosphepino [5,6-d]imidazole-1-yl) methyl) carbamates 7(i-t)

A solution of morpholino carbamoyl phosphoramidic dichloride [18] **(6a)** (15 ml, 0.060 mole) in 25 ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of Cyclohexyl ((4, 5-bis (hydroxymethyl)-1H-imidazol-1-yl) methyl) carbamate (0.84 g, 0.003 mol) **(5a)** and triethylamine (6 ml, 0.004 mole) in 30 ml of dry toluene and 10 ml of tetrahydrofuran at 5°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°C and maintained for 4 hours with stirring. The completion of the reaction was monitored by TLC analysis. Triethyl amine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (60-120 mesh) with 30% of ethylacetate in cyclohexane as anelutent to afford Cyclohexyl ((6-(morpholine-4-carboxamido)-6-oxide-4,8-dihydro-1H-[1,3,2] dioxaphosphepino [5,6-d] imidazole-1-yl) methyl) carbamate (0.91 g) of (7i) with yield 67%, m p 163-165°C.

The similar procedure was adopted to synthesize **7(j-t)** by the reaction between **5(b-d)** (5b-0.85 g, 0.003 mol; **5c**-0.90 g, 0.003 mol; **5d**-0.91 g, 0.0025 mol) with morpholino carbamoyl phosphoramidic dichloride (15 ml, 0.06 mol) **(6a)**, **7(j-t)** (**7j**-0.96 g, 7k-0.98 g, 7l-1.01 g, 7m-0.88 g, 7n-0.96 g, 7o-0.89 g, 7p-1.0 g, 7q-0.91 g, 7r-0.99 g, 7s-0.98 g, 7t-1.0 g) were prepared by condensation of **5(a-d)** with (piperidene-1-carbonyl) phosphoramidic dichloride (15 ml, 0.061 mol) **(6b)** and 4-methylpiperazine-1-carbamoyl phosphoramidic dichloride (15 ml, 0.056 mol) **(6c).**

MICROBIOLOGY

The determine both the antibacterial and antifungal activity, these newly synthesized compounds was performed according to disc diffusion method, as recommended by the National Committee for Clinical Laboratory. The synthesized compounds were used at the concentration of 250µg/ml DMF as a solvent [18].

Antibacterial assay

The antibacterial activity of Carbamates containing imidazole ureas/caboxamides dioxaphosphepinoes **7(a-t)** were screened against the *Staphylococcus aureus* NCCS 2079 and *Bacillus cerus* NCCS 2106 (gram positive) and *Escherichia coli* NCCS 2065 Antifungal activity of Carbamates containing imidazole ureas/carboxamides dioxaphosphepinoes **7(a-t)** were screened against *Aspergillus niger* NCCS 1196 and *Candida albicans* NCCS 3471. Here Ketoconazole is tested as reference compound to compare the activity. and *Pseudomonasaeruginosa* NCCS 2200 (gram negative) organisms. Here Amoxicillin is tested as reference compound to compare the activity.

Antifungal assay

Most of the compounds exhibit good antibacterial and antifungal activity against both given microorganism. The presence of nitro, chloro and bromo were showed more activity than other substituted compounds.

The Anti-bactterial and anti-fungal activity of 7(a-t) was shown in **Table 1.**

Table 1. Anti-bacterial and anti-fungal activity of Carbamates containing imidazole ureas/carboxamides dioxaphosphepinoe 7(a-t).

S.NO	COMP	R	X	Zone of inhibition(mm) 250 (µg/disc)					
				Anti-bacterial activity[a]				Anti-fungal activity[b]	
				S.a	B.c	E.c	P.a	A.n	C.a

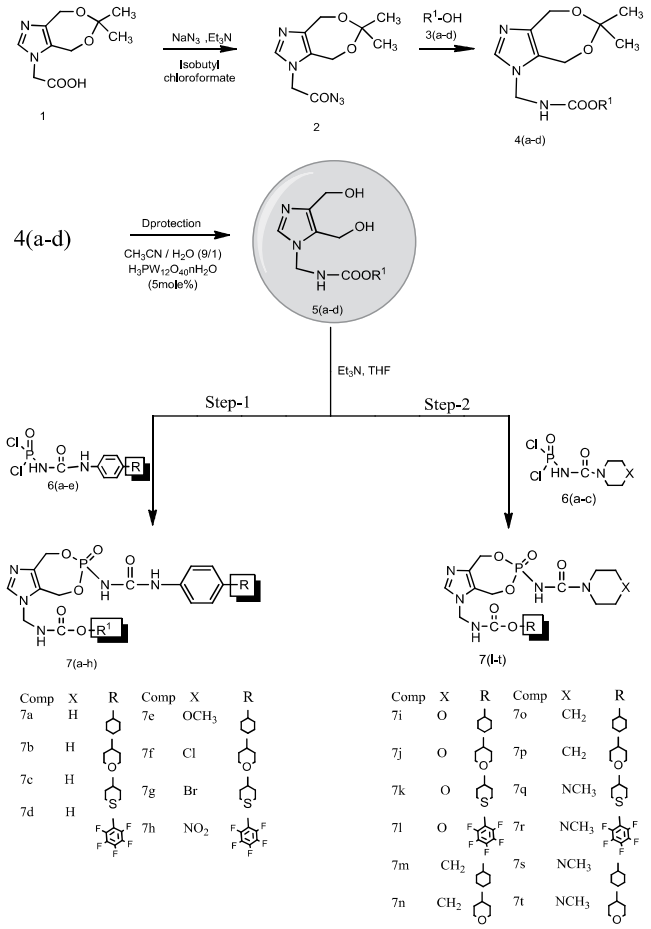
1	7a	H	-	8	7	9	10	10	8
2	7b	H	-	8	6	7	8	11	9
3	7c	H	-	7	5	6	7	8	6
4	7d	H	-	6	5	6	7	7	6
5	7e	OCH_3	-	15	14	13	15	15	16
6	7f	*Cl	-	19	18	19	17	19	18
7	7g	*Br	-	18	17	18	17	18	17
8	7h	*NO_2	-	20	21	19	20	20	22
9	7i	-	O	6	5	7	8	10	6
10	7j	-	O	7	4	5	6	11	7
11	7k	-	O	5	3	4	5	8	4
12	7l	-	O	4	3	4	5	7	4
13	7m	-	CH_2	15	16	15	13	15	17
14	7n	-	CH_2	13	12	13	12	14	16
15	7o	-	CH_2	13	15	12	14	17	20
16	7p	-	CH_2	10	9	7	8	13	14
17	7q	-	*NCH_3	17	18	17	15	18	16
18	7r	-	*NCH_3	15	14	15	14	17	15
19	7s	-	*NCH_3	18	20	18	17	20	18
20	7t	-	*NCH_3	15	17	16	14	15	13
Amoxicillin				21	27	24	22	-	-
Ketoconazole				-	-	-	-	22	25

[a]Abbreviations: S.a: Staphylococcus aureus, B.c: Bacillus cereus, E.c: Escherichia coli, P.a: Pseudomonas aeruginosa. [b] A.n: Aspergillus niger, C.a: Candida albicans

*Indicates more activity.

CONCLUSION

In conclusion, we have demonstrated the synthesis of Organo Phospho Carbamates containing imidazole ureas/Carboxamides of 7(a-t) involving the four more synthetic steps was required. In case of Organo phosphoimidazole derivatives which are proved to be having great potential for the different pharmacological activities (**Scheme 1).**



Scheme-1. Synthesis of organo phospho carbamates containing imidazole ureas/Carboxamides.

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REFERENCES

1. Lunt E (1987) Antitumor imidazotetrazines. 14. Synthesis and antitumor activity of 6- and 8-substituted imidazo[5,1-d]-1,2,3,5-tetrazinones and 8-substituted pyrazolo[5,1-d]-1,2,3,5-tetrazinones. J Med Chem 30: 357-366.
2. Robertson DW (1985) Structure-activity relationships of arylimidazopyridine cardiotonics: discovery and inotropic activity of 2-[2-methoxy-4-(methylsulfinyl)phenyl]-1H-imidazo[4,5-c]pyridine. J Med Chem 28: 717-727.
3. Suzuki M (1986) Boll chem farm 34: 3111-3120.
4. Johnson RA (1999) Inhibitory effect of 4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole on HCMV DNA replication and permissive infection. Anti viral research 41: 101-111.
5. Brewer MD (1987) Isothiourea derivatives of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole with broad-spectrum anthelmintic activity. J Med Chem 30: 1848- 853.
6. Nathanson JA (1985) Phenyliminoimidazolidines. Characterization of a class of potent agonists of octopamine-sensitive adenylate cyclase and their use in understanding the pharmacology of octopamine receptors. Mol Pharmacol 28: 254-268.
7. Breuer E (1996) The Chemistry of Organophosphorus Compounds, John Wiely and Sons Ltd, Newyork 4: 653.
8. Faraci WS (1995) Inhibition of Helicobacter pylori Urease by Phenyl Phosphorodiamidates: Mechanism of Action. Bioorg Med Chem 3: 605.
9. Fest C, Schmidt KJ (1982) The chemistry of organophosphorus pesticides Springer-Verlag, Berlin 12.
10. Nivarkar (2004) Tetrahedron Lett 45: 6863.
11. Haranadha Reddy Y (2012) Synthesis and Bioassay of α-aminophosphonates. Der chemica Sinica 3: 817-823.
12. Mehellou Y (2007) J Bioorg Med chem Lett 17: 3666.
13. Bouchareb F (2012) Efficient Method for the Synthesis of Diazaphospholidines: Toxicological Evaluation. American journal of organic chemistry 2: 14-17.
14. Kirsanov AV, Levchenko ES (1957) Chem Abstr 51: 2555.
15. (2010) Indian journal of chemistry 47B: 512-817.
16. Helene L, Leogane O (2005) Boc-Protected Amines via a Mild and Efficient One-Pot Curtius Rearrangement. Organic Letters 7: 4107-4110.
17. Vanladinpuia K, Bez G (2011) Useful methods for the synthesis of isopropylidenes and their chemoselective cleavage. Tetrahedron Letters 52: 3759-3764.
18. Bharadwaj S (2011) Scholar Research Library, Achieves of Applied Science Research 3: 558-567.