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Synthesis, characterization and biological evaluation of the novel benzodioxaphosphole-2-oxide derivatives with aryl substituted 2-azetidinone and 4-thiazolidinone system

P. Jagadeeswara Rao*, K. S. Bhavani Aishwarya, Y. N. Spoorthy,

D. Ishrath Begum and L. K. Ravindranath

Department of Chemistry, Sri Krishnadevaraya University, Anantapur–515005, INDIA

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Abstract: The reaction sequence leading to the formation of novel benzodioxaphosphole-2-oxide derivatives with aryl substituted azetidinone/thiazolidinone system were accomplished through facile condensation of aryloxy-1, 3, 2-benzodioxa phosphole-4-carbohydrazide-2-oxides **(4a-e)** with aromatic aldehydes to afford the corresponding the important intermediate N'-(4-substituted benzylidene)-2-(4-substituted phenoxy) benzo(1,3,2)dioxa phosphole-2-oxide-4-carbohydrazide**(5a-h)**. This intermediate **(5)** on one direction by subsequent reaction with chloroacetyl chloride and triethyl amine in dry 1,4-dioxane gives the title compounds with azetidinone system **(6 a-h)** and on the other direction on refluxing with mercapto acetic acid in dry 1,4-dioxane and anhydrous zinc chloride gives the title compounds with thiazolidinone system **(7 a-h)**. The structure of these newly synthesized compounds were established by their elemental analysis and spectral data (IR, H^1, $^{13}C$and ^{31}P-NMR).These compounds have been screened for their antimicrobial activity and all are showing significant anti bacterial and antifungal activity.

Keywords: Benzodioxaphosphole-2-oxide; azetidinone system; thiazolidinone system; anti bacterial; antifungal activity.

1. Introduction

An overview of organophosphorus chemistry[1] has proved it is of great importance in pharmaceutical[2], agricultural industry[3] and especially in the divisions of biochemistry[4] and molecular biology.[5] Because of assorted factors together with emerging infectious diseases and increasing number of multidrug resistant microbial pathogens organophosphorous derivatives particularly benzodioxaphosphole-2-oxide are being considered as an important source in new drug discoveries for treating various ailments related to bacterial and fungal infection.[6,7]

Small ring heterocyclic compounds especially 2-azetidinones and 4-thiazolidinone gained great importance since a long time in the therapeutic meadow due to their interaction with the active site residues of enzymes and control the catalysts.[8-10] The 2-azetidinone ring system is the common structural feature of broad range β-lactam antibiotics and exhibit powerful antibacterial[11], anti-inflammatory[12], anti-

* Corresponding author: E-mail: pjr.chem@gmail.com

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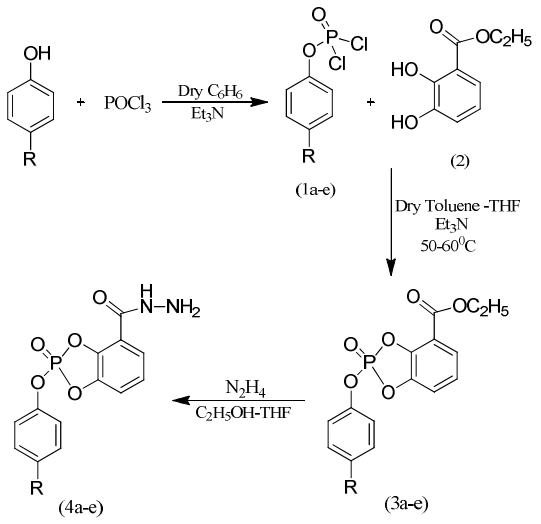
tubercular[13] and anti-tumor[14] activities. Moreover, compounds containing 4-thiazolidinone ring system compel diverse biological activities such as anti-viral, anti-convulsant, cyclooxygenase inhibitors, lipoxygenase inhibitors and inhibit the bacterial enzyme in the biosynthesis of polymers[15-17]. Hence these core structures are important class of chemotherapeutic agents in medicinal chemistry and have been incorporated into wide variety of drug candidates including analgesic, anti-histaminic, antagonist, anti-diabetic, anti-inflammatory, anti-parkinsonian and anti-HIV activities.[18-20]

In view of these observations, herein we report the synthesis and characterization of some novel benzodioxaphosphole-2-oxide derivatives with aryl substituted azetidinones and thiazolidinones to bring about a better antimicrobial activity.

2. Results and discussion

The synthetic itinerary for the preparation of the title compounds is accomplished in two stages. First stage involves the reaction of $POCl_3$ with freshly distilled 4-substituted phenol in dry benzene in the presence of triethylamine at room temperature and produces 4-substituted phenyl phosphorodichloridates[21] **1a-e.** The crucial cyclocondensation reaction[22] of 2,3-dihydroxy ethyl benzoate **(2)** with various aryl phosphorodichloridates **1a-e** occurred smoothly under heating and stirring conditions in dry toluene- tetrahydrofuran (THF) solvent mixture in presence of Et_3N to yield ethyl 2-(4-substituted phenoxy)-1, 3, 2-benzodioxa phosphole-4- carboxylate-2-oxides **(3a-e).** A solution of **3(a-e)** and hydrazine hydrate in absolute ethanol-THF (1:1) was refluxed[23] for obtaining 2-(4-substitutedphenoxy)-1, 3, 2-benzodioxaphosphole-4-carbohydrazide-2-oxides **(4a-e)** (Figure 1**).** During these stages, the course of progress of the reaction was monitored by TLC. The excess solvent was removed from the reaction mixture in rotaevaporator under reduced pressure. After recrystalization from hexane and chloroform (3:1) fairly pure and stable products were obtained. The compounds **(4a-e)** thus obtained were characterized by their elemental analysis and IR, ^{1}H-NMR, ^{31}P-NMR spectral data.

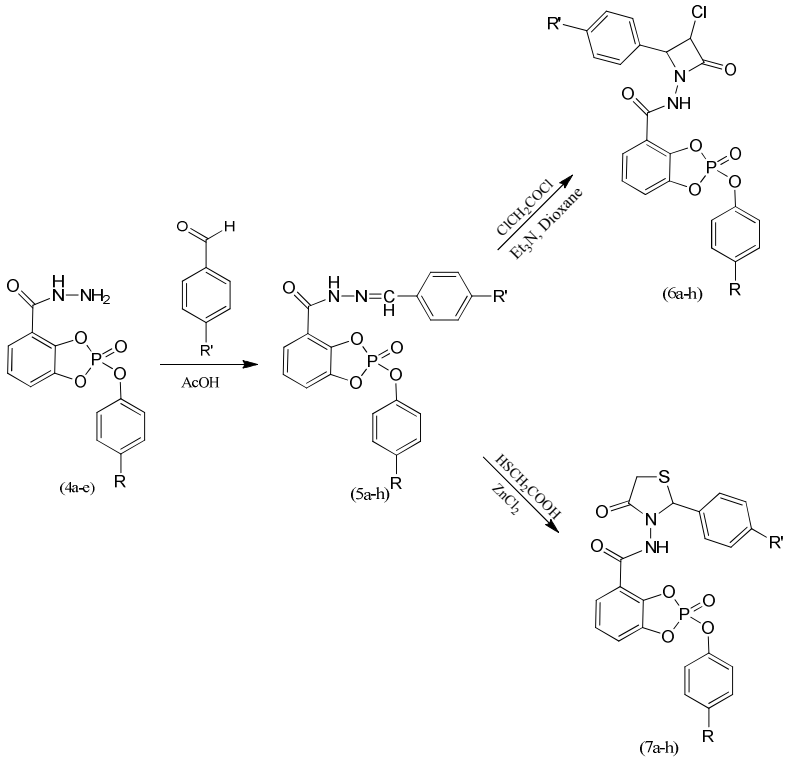


R = -H, - CH_3, -Cl, -Br, - NO_2

Figure 1. Synthesis of 2-(4-substitutedphenoxy)-1, 3, 2-benzodioxa phosphole-4-carbohydrazide-2-oxides

Preparation of Intermediate: N'-(4-substituted benzylidene)-2-(4-substituted phenoxy) benzo (1,3,2) dioxa phosphole-2-oxide-4-carbohydrazide (**5a-h**): A solution of 2- phenoxy-1,3,2-benzodioxa

phosphole-4-carbohydrazide-2-oxides **(4a)** and benzaldehyde was refluxed in absolute ethanol-tetrahydrofuran (1:1) solvent mixture containing a catalytic amount of sulfuric acid for 4 hours.[24] The course of progress of the reaction was monitored by TLC by using cyclohexane and ethyl acetate solvent mixture (7:3) as the eluent. After completion of the reaction, the solvent was removed in rotaevaporator, and the crude product was obtained as a gummy solid. The pure and stable product was obtained by the recrystalization of this gummy solid with 2-propanol and petroleum ether solvent mixture. Finally it forms N'-(benzylidene)-2-(phenoxy) benzo(1,3,2) dioxa phosphole-2-oxide-4-carbohydrazide **(5a)**. The other members of **5** were prepared by employing the same procedure between **(4a-e)** with 4-substituted benzaldehydes (**Figure 2**).



Comp	*6&7 a*	*6&7 b*	*6&7 c*	*6&7 d*	*6&7 e*	*6&7 f*	*6&7 g*	*6&7 h*
R	H	CH_3	Cl	Br	NO_2	H	H	H
R'	H	H	H	H	H	Cl	Br	NO_2

Figure 2. Synthesis of N-(2-(4-substituted phenyl)-3-chloro-4-oxoazetidin-1-yl-4-oxothiazolidin-3yl)- 2-(4-substituted phenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide

3. Experimental

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 alluminium sheet of silica gel 60F254, E-Merk, Germany using iodine as visualizing agent. Melting points were determined in open capillary tubes on Mel-Temp apparatus and are incorrected. 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 unit, Instrument. All ^{1}H and ^{13}CNMR spectra

were recorded on a Varian XL-300 spectrometer operating at 300MHz for ^{1}HNMR and 75.46 MHz for ^{13}CNMR. ^{31}PNMR spectra were recorded on a Varian XL-spectrometer operating at 161.89MHz. The compounds were dissolved in DMSO-d6 and Chemical shifts were referenced to TMS (^{1}H and ^{13}CNMR) and 85% H_3PO_4 (^{31}PNMR). Mass spectral data were recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analyses were recorded on a Carlo Erba 1108 Elemental Analyser, Central Drug Research Institute, Lucknow, India.

*3.1. Typical spectral data for the compounds **4a-e**:*

2-(Phenoxy)-1,3,2-benzodioxa phosphole-4-carbohydrazide-2-oxide (**4a**): Yield: 60%; M.p: 76-78 ºC; IR (KBr): 3457, 3413(-NH_2), 3220 (-NH), 1690(C=O), 1258 (P=O), 954, 1196 (P-O-C)cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 4.21(s, 2H, NH_2), 8.75(s,1H, NH), 6.73 -7.34 (m, 8H, C_6H_5 and C_6H_3); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -9.47 ppm Anal. Calcd.(%) for $C_{13}H_{11}N_2O_5P$: C 50.99, H 3.62,N 9.15; Found: C 50.92, H 3.58, N 9.07.

2-(4-Methyl-phenoxy)-1,3,2-benzodioxa phosphole-4-carbohydrazide-2-oxide (**4b**): Yield: 55%; M.p: 69-71 ºC; IR (KBr): 3452, 3439(-NH_2), 3206 (-NH), 1685(C=O), 1252 (P=O), 949, 1190 (P-O-C)cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 4.19(s, 2H, NH_2), 8.75(s, 1H, NH), 6.61-7.34 (m, 7H, C_6H_4 andC_6H_3), 3.10 ppm(S,3H,Ar-CH_3); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -7.79 ppm. Anal. Calcd.(%) for$C_{14}H_{13}N_2O_5P$: C 52.51, H 4.09, N 8.75; Found: C 52.43, H 4.02, N 8.69.

2-(4-Chloro-phenoxy)-1,3,2-benzodioxa phosphole-4-carbohydrazide-2-oxides (**4c**): Yield: 50%; M.p: 86-88 ºC; IR (KBr): 3464, 3454(-NH_2), 3209 (-NH), 1689(C=O), 1254 (P=O), 952, 1192 (P-O-C)cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 4.25(s, 2H, NH_2), 8.78(s, 1H, NH), 6.67-7.34(m, 7H, C_6H_4 and C_6H_3).; ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ-9.80 ppm. Anal. Calcd.(%) for $C_{13}H_{10}N_2O_5PCl$: C 45.83, H 2.96,N 8.22; Found: C 45.76, H 2.87, N 8.15.

2-(4-Bromo phenoxy)-1, 3, 2-benzodioxa phosphole-4-carbohydrazide-2-oxides (**4d**): Yield: 50%; M.p: 92-94 ºC; IR (KBr): 3464, 3454 (-NH_2), 3210 (-NH), 1685(C=O), 1260 (P=O), 954, 1194 (P-O-C)cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 4.28 (s, 2H, NH_2), 8.78(s, 1H, NH), 6.62-7.34(m, 7H, C_6H_4 and C_6H_3); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ-9.11 ppm. Anal. Calcd.(%) for $C_{13}H_{10}N_2O_5PBr$: C 40.54, H 2.62,N 7.27; Found: C 40.49, H 2.57, N 7.18.

*2-(4-nitrophenoxy)-1, 3, 2-benzodioxa phosphole-4-carbohydrazide-2-oxides (***4e**): Yield: 64%; M.p: 104-106 ºC; IR (KBr): 3468, 3455(-NH_2), 3214(-NH), 1684(C=O), 1268 (P=O), 960, 1204 (P-OC)cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 4.27(S.2H, NH_2), 8.80(S, 1H, NH), 6.99-8.02(m, 7H, C_6H_4 andC_6H_3); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -9.28 ppm. Anal. Calcd.(%) for $C_{13}H_{10}N_3O_7P$: C 44.46, H2.87, N 11.96; Found: C 44.35, H 2.74, N 11.89.

*N-(2-(4-substituted phenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(4-substituted phenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6a-h**):* A solution of N'-(benzylidene)-2-(phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carbohydrazide **(5a)** (0.025 mol) in dry 1,4-dioxane (20 ml) was added to a well stirred mixture of chloro acetyl chloride (0.025 mol) and triethylamine (0.025 mol) in dry 1,4-dioxane(20 ml) at 0-10^{o}C.[25,26].The reaction mixture was stirred for 8–10 hrs and kept for one day at room temperature. The progress of the reaction was monitored by TLC using cyclohexane –ethyl acetate (7:3) as an eluent. The triethylamine hydrochloride precipitate formed was filtered and washed several times with dry 1,4-dioxane. The solvent was removed in rotaevaporator from the filtrate and was concentrated under reduced pressure. The crude product was recrystalized from 2-propanol and petroleum ether (60-80^{0}C) solvent mixture to afford N-(2-(phenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(phenoxy)

benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide **(6a)(Figure 2)**. Similar procedure was adopted to synthesize **(6 b-h)** from **(5a-h)** and chloro acetyl chloride.

*N-(2-(phenyl)-3-chloro-4-oxoazetidin-1-yl)-2-(phenoxy)benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6a**):* Yield: 70%; M.p: 141-143 ºC; IR (KBr): 3352(NH), 1689(C=O), 1738(C=O azetidinone ring), 629(C-Cl azetidinone ring), 1252(P=O), 985& 1185(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.14(s, 1H, CO-NH-), 5.18(d, 1H, -CH-Ar of azetidinone ring), 5.58 (d, 1H, -CH-Cl of azetidinone ring), 7.03-7.42 (m, 13H, for C_6H_5,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 150.2(C-1),120.3(C-2&6),130.1 (C-3&5), 121.3(C-4) of ring A, 143.3(C-4'), 145.3(C-5'), 115.6(C-6'), 122.8(C-7'), 121.5(C-8'), 121.2(C-9'), 164.8(-CO) of ring B, 143.5(C-1"),126.9(C-2"&6"), 128.5(C-3"&5"),126.7(C-4") of ring C (phenyl group attached to azetidinone ring) and 67.4(C-2), 64.1(C-3), 163.5(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.51 ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_2O_6PCl$: C 56.12, H 3.43, N 5.95; Found: C 56.01, H 3.29, N 5.83.

*N-(2-(phenyl)-3-chloro-4-oxoazetidin-1-yl)-2-(4-methylphenoxy) benzo(1,3,2)dioxaphosphole -2-oxide-4-carboxamide (**6b**):* Yield: 65%; M.p: 152-154 ºC; IR (KBr): 3345(NH), 1676(C=O), 1725(C=O azetidinone ring), 627(C-Cl azetidinone ring), 1247(P=O), 959& 1167(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 3.18(s, 3H, Ar-CH_3), 9.10(s, 1H, CO-NH-), 5.20(d, 1H, -CH-Ar of azetidinone ring), 5.61(d, 1H, -CH-Cl of azetidinone ring), 6.83-7.45(m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 147.2(C-1),118.2(C-2&6),130.4(C-3&5), 131.0(C-4), 21.4(-CH_3) of ring A, 143.7(C-4'), 145.5(C-5'), 115.8(C-6'), 123.1(C-7'), 121.7(C-8'), 121.9(C-9'),164.1(-CO) of ring B, 143.9(C-1"), 126.1(C-2"&6"), 128.6(C-3"&5"),126.8(C-4") of ring C (phenyl group attached to azetidinone ring) and 67.0(C-2), 64.2(C-3), 163.3(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.92 ppm. Anal. Calcd.(%) for $C_{23}H_{18}N_2O_6PCl$: C 56.98, H 3.74, N 5.78; Found: C 56.85, H 3.61, N 5.69.

*N-(2-(phenyl)-3-chloro-4-oxoazetidin-1-yl) -2-(4-chlorophenoxy) benzo(1,3,2)dioxahosphole -2-oxide-4-carboxamide (**6c**):* Yield: 65%; M.p: 127-129 ºC; IR (KBr): 3357(NH), 1682(C=O), 1741(C=O azetidinone ring), 633(C-Cl azetidinone ring), 1261(P=O), 962& 1171(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.06(s, 1H, CO-NH-), 5.21(d, 1H, -CH-Ar of azetidinone ring), 5.48(d, 1H, -CH-Cl of azetidinone ring), 6.89-7.40 (m, 12H, for C_6H_4, C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 148.3(C-1), 125.7(C-2&6), 131.3(C-3&5), 126.9(C-4) of ring A, 143.7(C-4'), 145.1(C-5'), 115.0(C-6'), 122.7(C-7'), 121.3(C-8'), 121.8(C-9'), 164.5(-CO) of ring B, 143.2(C-1"), 126.4(C-2"&6"), 128.8(C-3"&5"), 126.5(C-4") of ring C (phenylgroupattachedtoazetidinonering) and 67.8(C-2), 64.5(C-3), 163.2(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -9.07ppm. Anal. Calcd.(%) for $C_{22}H_{15}N_2O_6PCl_2$: C 52.30, H 2.99, N 5.54; Found: C 52.16, H 2.87, N 5.43.

*N-(2-(phenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(4-bromophenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6d**):* Yield: 65%; M.p: 117-119 ºC; IR (KBr): 3363(NH), 1693(C=O), 1739(C=O azetidinone ring), 637(C-Cl azetidinone ring), 1269(P=O), 973& 1186(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.08(s, 1H, CO-NH-), 5.18(d, 1H, -CH-Ar of azetidinone ring), 5.53(d, 1H, -CH-Cl of azetidinone ring), 6.84-7.43 (m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 149.2(C-1), 123.3(C-2&6), 133.0(C-3&5), 115.7(C-4) of ring A, 143.5(C-4'), 145.3(C-5'), 115.9(C-6'), 122.4(C-7'), 122.1(C-8'), 121.7(C-9'), 165.8(-CO) of ring B, 143.9(C-1"), 125.6(C-2"&6"), 128.1(C-3"&5"),126.7(C-4") of ring C (phenyl group attached to azetidinone ring) and 66.9(C-2), 64.5(C-3), 163.9(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.64 ppm. Anal. Calcd.(%) for $C_{22}H_{15}N_2O_6PClBr$: C 48.07, H 2.75, N 5.10; Found: C 47.94, H 2.66, N 4.98.

*N-(2-(phenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(4-nitrophenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6e**):* Yield: 70%; M.p: 161-163 ºC; IR (KBr): 3358(NH), 1687(C=O), 1745(C=O azetidinone ring), 641(C-Cl azetidinone ring), 1257(P=O), 945& 1190(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.15(s, 1H, CO-NH-), 5.23(d, 1H, -CH-Ar of azetidinone ring), 5.58(d, 1H, -CH-Cl of azetidinone ring), 7.03-8.09(m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 156.3(C-1),121.9(C-2&6), 126.3(C-3&5), 140.5(C-4) of ring A, 144.3(C-4'), 146.0(C-5'), 115.9(C-6'), 123.1(C-7'), 121.8(C-8'), 121.5(C-9'),164.3(-CO) of ring B, 143.2(C-1"), 126.3(C-2"&6"), 128.5(C-3"&5"),126.7(C-4") of ring C (phenyl group attached to azetidinone ring) and 67.8(C-2), 64.3(C-3), 163.0(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -9.16 ppm. Anal. Calcd.(%) for $C_{22}H_{15}N_3O_8PCl$: C 51.23, H 2.93, N 8.15; Found: C 51.09, H 2.78, N 8.03.

*N-(2-(4-chloro phenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(phenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6f**):* Yield: 70%; M.p: 138-140 ºC; IR (KBr): 3367(NH), 1675(C=O), 1730(C=O azetidinone ring), 635(C-Cl azetidinone ring), 1246(P=O), 948& 1175(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.12 (s, 1H, CO-NH-), 5.10(d, 1H, -CH-Ar of azetidinone ring), 5.45(d, 1H, -CH-Cl of azetidinone ring), 7.03-7.48 (m, 12H, for C_6H_5, C_6H_3 and C_6H_4 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 150.7(C-1),120.9(C-2&6),130.3 (C-3&5), 121.6(C-4) of ring A, 143.1(C-4'), 145.8(C-5'), 115.3(C-6'), 122.5(C-7'), 121.1(C-8'), 121.5(C-9'),165.2(-CO) of ring B, 141.6(C-1"), 127.2(C-2"&6"), 128.8(C-3"&5"),132.3(C-4") of ring C (phenyl group attached to azetidinone ring) and 67.6(C-2), 64.4(C-3), 163.9(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.55ppm. Anal. Calcd.(%) for $C_{22}H_{15}N_2O_6PCl_2$: C 52.30, H 2.99, N 5.54; Found: C 52.15, H 2.86, N 5.38.

*N-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(phenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6g**):* Yield: 60%; M.p: 130-132 ºC; IR (KBr): 3363(NH), 1668(C=O), 1737(C=O azetidinone ring), 636 (C-Cl azetidinone ring), 1259(P=O), 964& 1169(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.07 (s, 1H, CO-NH-), 5.09(d, 1H, -CH-Ar of azetidinone ring), 5.46(d, 1H, -CH-Cl of azetidinone ring), 7.03-7.92 (m, 12H, for C_6H_5,C_6H_3 and C_6H_4 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 151.2(C-1),120.5(C-2&6),130.3 (C-3&5), 121.9(C-4) of ring A, 143.7(C-4'), 145.5(C-5'), 115.2(C-6'), 122.6(C-7'), 121.9(C-8'), 121.0(C-9'),165.0(-CO) of ring B, 142.5(C-1"), 127.2(C-2"&6"), 131.4(C-3"&5"),121.1(C-4") of ring C (phenyl group attached to azetidinone ring) and 67.9(C-2), 64.5(C-3), 163.7(-CO-) of ring D (azetidinonering); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.52 ppm. Anal. Calcd.(%) for $C_{22}H_{15}N_2O_6PClBr$: C 48.07, H 2.75, N 5.10; Found: C 47.91, H 2.63, N 4.94.

*N-(2-(4-nitrophenyl)-3-chloro-4-oxoazetidin-1-yl) - 2-(phenoxy) benzo(1,3,2)dioxaphosphole-2-oxide-4-carboxamide (**6h**):* Yield: 69%; M.p: 149-151 ºC; IR (KBr): 3360(NH), 1668(C=O), 1740(C=O azetidinone ring), 641(C-Cl azetidinone ring), 1255(P=O), 956& 1175(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.18 (s, 1H, CO-NH-), 5.12(d, 1H, -CH-Ar of azetidinone ring), 5.48(d, 1H, -CH-Cl of azetidinone ring), 7.03-8.21 (m, 12H, for C_6H_5,C_6H_3 and C_6H_4 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 151.2(C-1),120.6(C-2&6),130.5 (C-3&5), 121.7(C-4) of ring A, 144.3(C-4'), 145.7(C-5'), 115.3(C-6'), 122.5(C-7'), 122.5(C-8'), 121.8(C-9'),164.4(-CO) of ring B, 149.6(C-1"), 123.4(C-2"&6"), 123.7(C-3"&5"),145.9(C-4") of ring C (phenyl group attached to azetidinone ring) and 67.8(C-2), 64.3(C-3), 163.9(-CO-) of ring D (azetidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.95ppm. Anal. Calcd.(%) for $C_{22}H_{15}N_3O_8PCl$: C 51.23, H 2.93, N 8.15; Found: C 51.06, H 2.82, N 8.01.

Synthesis of N-(2-(4-substituted phenyl)-4-oxothiazolidin-3yl)-2-(4-substituted phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carboxamide (7a-h): A mixture of N'-(benzylidene)-2-(phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carbohydrazide **(5a)** (0.01mole) and mercapto acetic acid (0.01 mol) were dissolved in dry 1,4-dioxane (20 ml). A pinch of anhydrous zinc chloride was added and then refluxed

for 8hrs. The reaction[27, 28] progress of the reaction was monitored by TLC using cyclohexane –ethyl acetate (7:3) as an eluent. After the completion of the reaction the solvent was removed under reduced pressure in rotaevaporator to give solid. The residue was then treated by solution of sodium bicarbonate to remove excess of mercaptoacetic acid. The compound obtained was recrystallized from 2-propanol and petroleum ether (60-80^{0}C) solvent mixture to affordN-(2-(phenyl)-4-oxothiazolidin-3yl)-2-(phenoxy) benzo (1, 3, 2) dioxaphosphole-2-oxide-4-carboxamide **(7a).** Similar procedure was adopted to synthesize 7(b-h) from 5(a-e) and thio- aceticacid.

*N-(2-(phenyl)-4-oxothiazolidin-3yl)-2-(phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carboxamide (**7a**):* Yield: 70%; M.p: 144-146 ºC; IR (KBr): 3361(NH), 1652(C=O), 1765(C=O thiazolidinone ring), 690(C-Cl thiazolidinone ring), 1263(P=O), 978& 1164(P-O-C)cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.15(s, 1H, CO-NH-), 5.93(s, 1H, -CH-Ar of thiazolidinone ring), 3.85(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.97(d, 1H, H_b of CH_2 of thiazolidinone ring),7.05-7.45(m, 13H, for C_6H_5,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 150.2(C-1),120.3(C-2&6),130.1 (C-3&5), 121.3(C-4) of ring A, 144.5(C-4'), 144.9(C-5'), 115.6(C-6'), 122.8(C-7'), 121.5(C-8'), 121.2(C-9'), 164.7(-CO) of ring B, 138.2(C-1"), 130.7(C-2"&6"), 131.5(C-3"&5"),131.5(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 64.3(C-2), 35.6(C-4), 168.8(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.98 ppm. Anal. Calcd.(%) for $C_{22}H_{17}N_2O_6PS$: C 56.41, H 3.66, N 5.98; Found: C 56.27, H 3.54, N 5.86.

*N-(2-(phenyl)-4-oxothiazolidin-3yl)-2-(4-methyl phenoxy) benzo (1, 3, 2) dioxaphosphole-2-oxide-4-carboxamide (**7b**):* Yield: 65%; M.p: 156-158 ºC; IR (KBr): 3346(NH), 1643(C=O), 1758(C=O thiazolidinone ring), 689(C-Cl thiazolidinone ring), 1247(P=O), 961& 1157(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 3.21(s, 3H, Ar-CH_3), 9.12(s, 1H, CO-NH-), 5.97(s, 1H, -CH-Ar of thiazolidinone ring), 3.79(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.87(d, 1H, H_b of CH_2 of thiazolidinone ring), 6.85-7.47(m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 148.2(C-1),118.5(C-2&6),130.7(C-3&5), 131.9(C-4), 22.9(-CH_3) of ring A, 144.1(C-4'), 145.9(C-5'), 115.5(C-6'), 122.5(C-7'), 121.2(C-8'), 121.6(C-9'), 164.8(-CO) of ring B, 139.9(C-1"), 126.5(C-2"&6"), 128.1(C-3"&5"),127.8(C-4") ofring C (phenyl group attached to thiazolidinone ring) and 64.2(C-2), 34.9(C-4), 168.3(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.72 ppm. Anal. Calcd.(%) for $C_{23}H_{19}N_2O_6PS$: C 57.26, H 3.97, N 5.81; Found: C 57.15, H 3.88, N 5.65.

*N-(2-(phenyl)-4-oxothiazolidin-3yl)-2-(4-chlorophenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carboxamide (**7c**):* Yield: 65%; M.p: 131-133 ºC; IR (KBr): 3352(NH), 1654(C=O), 1755(C=O thiazolidinone ring), 691(C-Cl thiazolidinone ring), 1258(P=O), 964& 1162(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.08(s, 1H, CO-NH-), 5.95(s, 1H, -CH-Ar of thiazolidinone ring), 3.83(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.95(d, 1H, H_b of CH_2 of thiazolidinone ring), 6.91-7.42(m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 148.6(C-1),124.7(C-2&6),132.0(C-3&5), 127.2(C-4) of ring A, 143.1(C-4'), 144.5(C-5'), 114.7(C-6'), 122.6(C-7'), 121.5(C-8'), 122.0(C-9'), 164.9(-CO) of ring B, 139.2(C-1"), 125.4(C-2"&6"), 128.7(C-3"&5"),127.5(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 64.8(C-2), 34.5(C-4), 168.2(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.57 ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_2O_6PSCl$: C 52.55, H 3.21, N 5.57; Found: C 52.42, H 3.11, N 5.41.

*N-(2-(phenyl)-4-oxothiazolidin-3yl)-2-(4-bromo phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carboxamide (**7d**):* Yield: 65%; M.p: 121-123 ºC; IR (KBr): 3359(NH), 1661(C=O), 1762(C=O thiazolidinone ring), 694(C-Cl thiazolidinone ring), 1266(P=O), 973& 1170(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.11(s, 1H, CO-NH-), 5.91(s, 1H, -CH-Ar of thiazolidinone ring), 3.81(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.90(d, 1H, $H_b$of CH_2 of thiazolidinone ring), 6.84-7.45 (m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 148.2(C-1),124.3(C-

2&6),133.9(C-3&5), 116.7(C-4) of ring A, 143.1(C-4'), 145.6(C-5'), 115.3(C-6'), 122.8(C-7'), 121.7(C-8'), 122.1(C-9'), 165.1(-CO-) of ring B, 139.9(C-1"), 122.8(C-2"&6"), 128.5(C-3"&5"),128.0(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 64.1(C-2), 35.9(C-4), 169.5(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.73 ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_2O_6PSBr$: C 48.28, H 2.95, N 5.12; Found: C 48.16, H 2.83, N 4.98.

*N-(2-(phenyl)-4-oxothiazolidin-3yl)-2-(4-nitrophenoxy)benzo-(1,2,3)-dioxaphosphole-2-oxide-4-carboxamide (**7e**):* Yield: 72%; M.p: 167-169 ºC; IR (KBr): 3365(NH), 1658(C=O), 1770(C=O thiazolidinone ring), 693(C-Cl thiazolidinone ring), 1254(P=O), 968& 1168(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.13(s, 1H, CO-NH-), 5.94(s, 1H, -CH-Ar of thiazolidinone ring), 3.88(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.96(d, 1H, H_b of CH_2 of thiazolidinone ring), 7.01-8.08(m, 12H, for C_6H_4,C_6H_3 and C_6H_5 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 156.1(C-1),121.6(C-2&6), 126.8(C-3&5), 141.6(C-4) of ring A, 144.7(C-4'), 145.0(C-5'), 115.4(C-6'), 122.1(C-7'), 121.0(C-8'), 121.7(C-9'),164.8(-CO) of ring B, 140.0(C-1"), 126.9(C-2"&6"), 128.3(C-3"&5"),132.8(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 64.1(C-2), 35.5(C-4), 168.0(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -9.16 ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_3O_8PS$: C 51.34, H 3.14, N 8.18; Found: C 51.34, H 3.05, N 8.07.

*N-(2-(4-chloro phenyl)-4-oxothiazolidin-3yl)-2-(phenoxy) benzo (1, 3, 2) dioxaphosphole-2-oxide-4-carboxamide (**7f**):* Yield: 70%; MP: 142-144 ºC; IR (KBr): 3356(NH), 1650(C=O), 1759(C=O thiazolidinone ring), 695(C-Cl thiazolidinone ring), 1259(P=O), 970& 1158(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.17(s, 1H, CO-NH-), 5.96(s, 1H, -CH-Ar of thiazolidinone ring), 3.85(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.94 (d, 1H, H_b of CH_2 of thiazolidinone ring), 7.03-7.50 (m, 12H, for C_6H_5,C_6H_3 and C_6H_4 of three phenyl groups); C^{13}-NMR (75.46 MHz, DMSO-*d6*): δ 151.7(C-1),122.9(C-2&6),131.3 (C-3&5), 123.6(C-4) of ring A, 143.6(C-4'), 145.1(C-5'), 115.8(C-6'), 122.4(C-7'), 121.3(C-8'), 121.9(C-9'),164.2(-CO)ofring B, 137.6(C-1"), 130.2(C-2"&6"), 128.7(C-3"&5"),132.8(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 64.6(C-2), 35.4(C-4), 169.5(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.95ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_2O_6PSCl$: C 52.55, H 3.21, N 5.57; Found: C 52.39, H 3.08, N 5.43.

*N-(2-(4-bromo phenyl)-4-oxothiazolidin-3yl)-2-(phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carboxamide (**7g**):* Yield: 63%; M.p: 150-152 ºC; IR (KBr): 3349(NH), 1648(C=O), 1760(C=O thiazolidinone ring), 691(C-Cl thiazolidinone ring), 1259(P=O), 973& 1168(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.10(s, 1H, CO-NH-), 5.93(s,1H, -CH-Ar of thiazolidinone ring), 3.83(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.91(d, 1H, H_b of CH_2 of thiazolidinone ring),7.03-7.85 (m, 12H, for C_6H_5,C_6H_3 and C_6H_4 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 151.8(C-1),121.5(C-2&6),132.3 (C-3&5), 122.9(C-4) of ring A, 144.7(C-4'), 145.1(C-5'), 115.6(C-6'), 123.6(C-7'), 121.4(C-8'), 121.7(C-9'),164.9(-CO) of ring B, 138.5(C-1"), 130.2(C-2"&6"), 131.8(C-3"&5"),121.5(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 65.1(C-2), 35.5(C-4), 168.7(-CO-) of ring D (thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.83 ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_2O_6PSBr$: C 48.28, H 2.95, N 5.12; Found: C 48.14, H 2.73, N 5.04.

*N-(2-(4-nitro phenyl)-4-oxothiazolidin-3yl)-2-(phenoxy) benzo (1,3,2) dioxaphosphole-2-oxide-4-carboxamide (**7h**):* Yield: 65%; M.p: 161-163 ºC; IR (KBr): 3356(NH), 1653(C=O), 1758(C=O thiazolidinone ring), 697(C-Cl thiazolidinone ring), 1251(P=O), 970& 1165(P-O-C) cm^{-1}; ^{1}HNMR (300MHz, DMSO-*d6*): δ 9.18 (s, 1H, CO-NH-), 5.90(s, 1H, -CH-Ar of thiazolidinone ring), 3.85(d, 1H, H_a of CH_2 of thiazolidinone ring), 3.96(d, 1H, H_b of CH_2 of thiazolidinone ring), 7.05-8.18(m, 12H, for C_6H_5,C_6H_3 and C_6H_4 of three phenyl groups); ^{13}CNMR (75.46 MHz, DMSO-*d6*): δ 151.6(C-1),120.3(C-2&6),131.5 (C-3&5), 121.9(C-4) of ring A, 144.8(C-4'), 145.5(C-5'), 115.7(C-6'), 122.9(C-7'), 121.5(C-8'), 121.2(C-9'),164.9(-CO-) of ring B, 145.6(C-1"), 129.4(C-2"&6"), 123.7(C-3"&5"),146.9(C-4") of ring C (phenyl group attached to thiazolidinone ring) and 65.8(C-2), 35.9(C-4), 169.5(-CO-) of ring D

(thiazolidinone ring); ^{31}PNMR (161.89 MHz, DMSO-*d6*): δ -8.97ppm. Anal. Calcd.(%) for $C_{22}H_{16}N_3O_8PS$: C 51.47, H 3.14, N 8.18; Found: C 51.27, H 2.98, N 8.05.

2.2. Biological Activity:

All the newly synthesized titled compounds(**6&7a-h)** were tested for the antimicrobial activity by using the disc diffusion method,[29,30] and DMSO was used as the solvent at concentration level 250 µg/ml as recommended by NCCL. While Nutrient Agar Medium & Potato Dextrose Agar Medium was selected as growth media for bacterial & fungal growth respectively.

The antibacterial activity screened against the *Staphylococcus aureus* (gram positive) and *Escherichia coli* (gram negative) organisms. Penicillin and Streptomycin were used as reference compounds. The antifungal activity screened against *Aspergillusniger, Candida albicans.* Griseofulvin is used as the reference standard.[31] All the compounds exhibited good antibacterial and antifungal activity against both bacteria and fungi. But the significance is that azetidinone & thiazolidinone derivatives having the aromatic ring substituted with electron-withdrawing groups Cl, Br, NO_2 at the para-position exhibited higher antibacterial & antifungal activity close to the reference standards. Observations are shown in **Table 1**.

Table 1. Antimicrobial activities of synthesized compounds (**6&7a-h)**

Compound	**Antibacterial activity (zone of inhibition in mm)**		**Antifungal activity (zone of inhibition in mm)**	
	Staphylococcus aureus	***Escherichia coli***	***Aspergillusniger***	***Candida albicans***
6a	15	11	14	13
6b	11	9	9	11
6c	14	13	12	15
6d	17	11	15	12
6e	18	14	13	19
6f	21	17	19	20
6g	19	15	17	18
6h	24	18	25	22
7a	12	10	13	12
7b	10	9	11	10
7c	13	12	14	15
7d	11	11	17	13
7e	15	14	20	17
7f	21	17	22	19
7g	16	15	19	17
7h	23	19	24	21
Streptomycin*	27	21	-	-
Griseofulvin*	-	-	28	26

*Reference compounds

4. Conclusion

Herein we reported the resourceful process for synthesis of novel benzodioxaphosphole-2-oxide derivatives with aryl substituted azetidinone/ thiazolidinone system. The antimicrobial activity of these compounds were evaluated and compared with the reference standards. It was found that the compounds containing the chloro, bromo and nitro substitution along with the thiazolidine–or azetidinone systems

exhibited good antibacterial & antifungal activity. Hence these novel compounds may act as leads for further investigations.

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