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Synthesis, Characterization, Docking and antimicrobial evaluation of novel compounds of 2-phenoxy-1,3,2-benzodioxaphosphole-2-oxide-oxo azetidin and pyrazol-5-one-Mannich bases

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ABSTRACT

The synthetic route of new mannich bases of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy)[d][1,3,2]dioxaphosphole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(tri fluoromethyl)-1H-pyrazole-5(4H)-one(8a-f) was depicted in scheme:1. The mannich bases (8a-f) were prepared by condensation reaction between 4-(3-chloro-1-(3,4–dihydroxyphenyl)-4-oxaazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(6) and 4-Substituted-PhenylPhosphorodichlori date (7a-f). The synthon (6) was obtained by hydrolysis of 4-(3-chloro-1-(3,4-dimethoxyphenyl)-4-oxo azetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one(5). The synthon (5) was obtained by condensation reaction between 4-(((3,4-dimethoxyphenyl)imino)methyl)-1-(morpholinomethyl)-3-(trifluoro methyl)-1H-pyrazol-5-(4H)-one(4) and chloroacetyl chloride. The synthon (4) was obtained by Mannic reaction between 4-(((3,4-dimethoxy phenyl)imino)methyl)-3-(trifluoromethyl)-1-1H-pyrazol-5-(4H)-one(3) with formaldehyde and morpholine. The synthon (3) was obtained by condensation between 5-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-4-carbaldehyde (1) and 3-4-dimethoxy aniline(2).

The structures of newly synthesized compounds (8a-f) were established by IR, 1HNMR, 13C-NMR, 31P-NMR, Mass spectral studies and Elemental analysis.

Keywords: Benzodioxaphospholes, Azetidone, Antimicrobial activity and Docking studies.

INTRODUCTION

Heterocyclic compounds represent an important class of biologically active molecules especially, those containing the pyrazolone nucleus have been shown to possess high biological activities [1-8] such as anticancer [9], antischenic effects [10], anti-inflammatory[11], antifungal[12], antipyretic[13], antitubercular[14], antihypertensive[15], antiviral[16] and antimicrobial[17]. The derivatives of pyrazolones are an important class of antipyretic and analgesic compounds. Organophosphorus compounds have attracted the attention of researches because of their multifaceted applications in industrial [18,19], agricultural [20], biochemical [21], and medicinal areas [22,23]. Organophosphorus esters are being used as pesticides [24, 25] and insecticides [20]. It is an established fact that compounds containing four-membered and five-membered heterocyclic ring systems exhibit potent biological effects like antimicrobial [17], anticonvulsant, anti-inflammatory [11], anti-cancer [9], antitubercular[14], antiviral[16] activities. With reference to azetidine-2-ones, these are important class of structural moieties having four-membered heterocyclic systems that present in antibiotics [26] such as penicillins and cephalosporins.

Some substituted pyrazolines and their derivatives are used as antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular and insecticidal agents, some of these compounds have also anti-inflammatory, anti-diabetic, and anesthetic properties [27, 28]. Prompted by the above multi dimension observations, a research project was undertaken to synthesize a series of organophosphorous heterocycles baring azetadine-2-one, pyrazolone and Mannich base moieties in the same carbon skeleton structure.

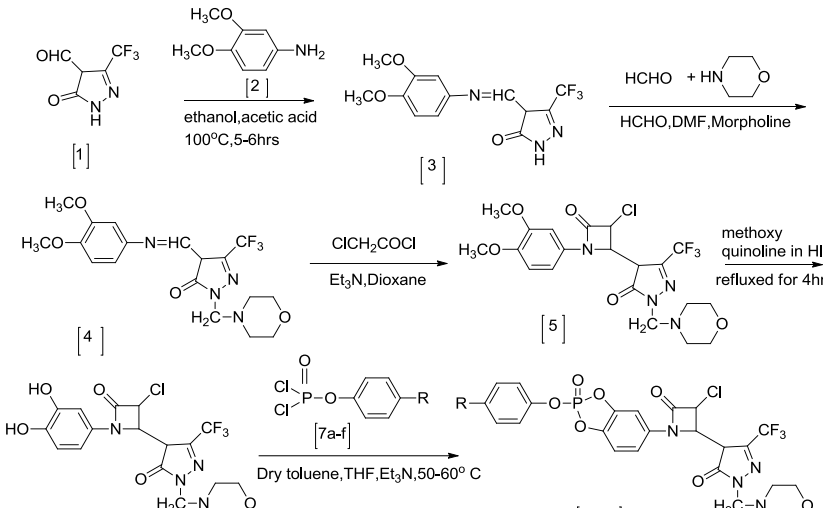


Figure: Scheme.1.4-(3-chloro-1-(2-(4-substitutedphenoxy)-2-oxidobenzo[d][1,3,2]dioxaphosphole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-ones(8a-f).

Compound No	7a	7b	7c	7d	7e	7f
	8a	8b	8c	8d	8e	8f
R	-H	$-CH_3$	$-OCH_3$	-Cl	-Br	$-CF_3$

MATERIALS AND METHODS

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals Company, Inc.USA and used without further purification. TLC was performed on aluminium sheet of silica gel 60F254, E-Merk,Germany using iodine as visualizing agent. Melting point were determined in open capillary tubes on Mel-Tempapparatus and are uncorrected. Column chromatography was performed on silica gel with different solvent systems as eluents to afford the pure compound. The IR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units,instruments. All 1H and 13C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHzfor 1H -NMR and 75 MHz for 13C-NMR. 31P-NMR spectra was recorded on a Varian XL-spectrometer operating at161.89MHz. The compounds were dissolved in DMSO-d6 and Chemical shifts were referenced to TMS (1H and13C-NMR) and 85% H3PO4 (31P-NMR). Mass spectral data was recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis were recorded on a Carlo Erba 1108 elemental Analyser, Central DrugResearch Institute, Lucknow, India.

Preparation of Intermediates

4-substituted phenyl phosphorodichloridates [29,30] (7a-f): Phosphorous oxychloride (15.3gm,0.1mole) in dry benzene (60ml) was taken into three-necked flasks (500ml) equipped with a dropping funnel and reflux condenser fitted with a calcium chloride guard tube. The flask was heated and stirred by means of a hot plate-cum-magnetic stirrer. To this, dry triethylamine (10.1gm, 0.1mole) and dry benzene (50ml) was added slowly and the reaction mixture was stirred for 30mits. To this mixture, freshly distilled phenol (9.4gms, 0.1mole) in dry benzene (60ml) was added dropwise through the dropping funnel. The addition took about thirty minutes and the whole reaction mixture was refluxed with vigorous stirring for 10hrs. The reaction mixture was cooled and solid triethylamine-hydrochloride was filtered off. The solvent from the filtrate was removed under reduced pressure in a rota evaporator. The dark brown liquid remained, was subjected to fractional distillation and the major product distilling at 118-124˚/11mm was collected as a colorless glassy viscous liquid(8.3gms,40%). The other substituted phenylphosphorodichlorates (7a-f) were prepared by the same procedure [31-34] by reacting equimolar quantities of phosphorous oxychloride and respectively substituted phenols in dry benzene in the presence of triethylamine.

RESULTS AND DISCUSSION

Synthesis of schiff's base [35] 4-(((3,4–dimethoxyphenyl)imino)methyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one (3)

A mixture of 5-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-4-carbaldehyde(1,3.6gms, 0.02mol),anhydrous K2CO3,3-4-dimethoxyaniline and DMF(50ml) was stirred at room temperature for 8hrs. The reaction mixture was diluted with ice-cold water. The separated solid was identified as 4-(((3,4-dimethoxyphenyl)imino)methyl)-3-(trifluoromethyl)-1-1H-pyrazol-5-(4H)-one(3).The light yellow precipitate (3) was filtered off under vacuum and recrystallized from dimethylformamide, with a melting point of 146-148˚c, with a yield of (3,4.2gms, 0.133mol,75%).

Synthesis of Mannich base [36, 37] 4-(((3,4–dimethoxyphenyl)imino)methyl)-1-(morpholino methyl)-3-(tri fluoromethyl)-1H-pyrazol-5(4H)-one(4)

Equimolar quantity of formaldehyde(1.2gms.0.04mol) and morpholine (3.5gms, 0.04mol) and 4-(((4-(((3,4-dimethoxyphenyl)imino)methyl)-3-(trifluoromethyl)-1-1H-pyrazol-5-(4H)-one(3, 6.3gms,0.02mol) were dissolved in absolute alcohol, to this three drops of acetic acid is added

then heated on a steam bath for 5-6hrs at 100˚c. After standing for 24hrs at room temperature, the product was dried and recrystallized from warm absolute alcohol. The separated solid was identified as 4-(((3,4-dimethoxyphenyl)imino)methyl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one(4,5.8gms,0.014mol). The melting point of (4) was found to be 126-128˚c, with a yield of 70%.

Synthesis [38, 39] of 4-(3-chloro-1-(3,4-dimethoxyphenyl)-4-oxoazetidin-2-yl)-1-(morpholino methyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one(5)

Monochloroacetylchloride (1.7gms, 0.015mol) was added dropwise to the compound 4-(((3,4-dimethoxyphenyl)imino)methyl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one(4, 4.2gms,0.01mol) and trimethylamine (0.02 mol) in dioxane (25ml) at room temperature. The mixture was stirred for 8hrs and left at room temperature for 3days. Pour the contents on crushed ice to afford 4-(3-chloro-1-(3,4-dimethoxyphenyl)-4-oxoazetidin-2-yl)-1-(morpho linomethyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one(5). The product thus formed was filtered and washed with sodium bicarbonate solution. The dried product was recrystalised with absolute alcohol. The separated solid was identified as 4-(3-chloro-1-(3,4-dimethoxyphenyl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one(5,3.4gms,0.0075mol). The melting point of (5) was found to be 168-170˚c, with a yield of 75%.

Synthesis [40] of 4-(3-chloro-1-(3,4–dihydroxylphenyl)-4-oxaazetidin-2-yl)-1-(morpholino methyl)-3-(tri fluoromethyl)-1H-pyrazol-5(4H)-one (6).

A solution of hydroiodic acid (5%) was refluxed in glass joined apparatus for 3-4hrs. The phenolic base 4-(3-chloro-1-(3,4–dihydroxyphenyl)-4-oxaazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoro methyl)-1H-pyrazol-5(4H)-one(6) was liberated from the viscous hydroiodic acid by adding approximately the calculated amount of sodium carbonate solution, after neutralization, the reaction mixture was distilled under reduced pressure to afford crystallised product 4-(3-chloro-1-(3,4–dihydroxyphenyl)-4-oxaazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5 (4H)-one(6,3.0gms,0.007mol). The melting point of (6) was found to be 184-186˚c, with a yield of 70%.

Synthesis [41] of 4-(3-chloro-1-(2-(4-substituted phenoxy)-2-oxido-benzo[d][1,3,2]dioxophos phole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoro methyl)-1H-pyrazol-5(4H)-one(8a-f).

A solution of phenylphosphorodichloridate(7a)(0.42gms,0.002mol) in 25ml of dry toluene was added dropwise over a period of 20mints to a stirred solution 4-(3-chloro-1-(3,4–dihydroxyphenyl)-4-oxaazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(6,0.85gms, 0.002mol) and triethylamine (0.404gms, 0.004mol) in 30ml of dry toluene and 10ml of tetrahydro furan at 5˚c,after completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 2hrs. The reaction mixture was later heated to 50˚-60˚c and maintained for 4hrs with stirring. The completion of the reaction was monitored by TLC analysis using n-hexane + ethyl acetate (7:3) as an elutent. Triethylamine 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 of 4-(3-chloro-1-(2-oxido-2-phenoxybenzene[d][1,3,2]dioxaphosphole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholino methyl)-3-(tri fluoromethyl)-1H-pyrazol-5(4H)-one (8a,0.63gms, 0.001mol), yield-52%, m.p 132-134˚c. The similar procedure was adopted to synthesis (8a-f) from the reaction between (6) with p-tolylphosphorodichloridate(7b)/4-methoxyphenylphosphorodichloridate(7c)/4-chlorophenylphosphorodichloridate(7d)/4 bromophenylphosphorodichloridate (7e)/4-trifluorophenylphosphorodi chloridate(7f). The structures of these newly synthesized compounds (8a-f) were characterized their elemental analysis and spectral data (IR, 1HNMR, 13C NMR, p31 NMR and Mass).

Physical, analytical and spectral data for the compounds:

4-(((3,4–dimethoxyphenyl)imino)methyl)-3-(trifluoromethyl)-1H-pyrazol-5-(4H)-one (3):

IR (KBr)(ῡmax,cm-1): 3225 cm-1 (-N-H str. of pyrazoline-5-one),3040cm-1(Ar-H str.),1657cm-1 (>C=O str. of pyrazoline-5-one),1620cm-1 (exocyclic azomethine >C=N-H str),1500,1430,1375cm-1 (str characteristic bands of pyrazoline-5-one ring),1340cm-1(C-F str band of CF3) and 1240cm-1(Ar-O-CH3 str). 1H NMR (400MHz, DMSO-d6):δ 2.20(d,1H,J=7.50,-CH of pyrazoline-5-one ring), 2.7(s,1H,-NH-of pyrazoline-5-one ring), 3.40 (s, 6H,two –OCH3 groups),6.9-7.2(m,3H of aromatic ring) and 8.4(d, 1H, J=7.50, >CH=N- exocyclic). Anal.Calcd.For C13H12N303F3 C 49.52%, H 3.80%, N, 13.33%. Found: C 48.8%, H 3.73%, N 12.95%.

4-(((3,4–dimethoxyphenyl)imino)methyl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(4):

IR (KBr)(ῡmax, cm-1): 3040cm-1(Ar-H str.),2960,2870cm-1(str. of –CH2 group), 2500,1500,1000, 500cm-1 (characteristic absorption of morpholine ring),1657 cm-1 (>C=O str. of pyrazoline-5-one), 1620cm-1(exocyclic azomethine >C=N-H str) 1500, 1430,1375cm-1(str. characteristic bands of pyrazoline-5-one ring),1340cm-1(C-F str. band of CF3),1240cm-1(Ar-O-CH3 str).1H NMR spectra (400MHz, DMSO-d6):δ2.20(d,1H,J=7.50,-CH of pyrazoline-5-one ring),2.45(t,4H,CH2 adj. N of morpholine), 3.65 (t,4H, CH2 adj.O- of morpholine), 3.40(s,6H,two –OCH3 groups),4.05(s,2H,N-CH2-N)6.9-7.2(m,3H of aromatic ring) and 8.4(d,1H,J=7.50,>CH=N- exocyclic). Anal.Calcd.For C18H21N4O4F3 C 52.17%, H 5.07%, N 13.52%. Found: C 51.5%, H 4.95%, N 13.09%.

4-(3-chloro-1-(3,4-dimethoxyphenyl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoro methyl)-1H-pyrazol-5-(4H)-one(5):

IR (KBr)(ῡmax, cm-1)3040cm-1(Ar-H str.),2960,2870cm-1(str. of –CH2 group),2500,1500,1000, 500cm-1 (characteristic absorption of morpholine ring) ,1697cm-1, 1330cm-1, 651cm-1 (>C=O,C-N, C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1 (>C=O str. of pyrazoline-5-one), 1500,1430, 1375cm-1(str. of characteristic of pyrazoline-5-one ring),1340cm-1(C-F str. band of CF3),1240cm-1(Ar-O-CH3 str).1H NMR spectra (400MHz, DMSO-d6) δ2.20(d,1H,J=7.50,-CH of pyrazoline-5-one ring),2.45(t,4H,N-Adj–CH2of morpholine),3.65 (t,4H, O-Adj –CH2 of morpholine), 3.40(s,6H,two –OCH3 groups),3.85(d,1H,-CH of azetidinone), 4.05(s,2H,N-CH2-N), 5.05(d,1H,-CH-Cl of azetidinone ring),6.9-7.2(m,3H of aromatic ring).Anal.Calcd.For C20H21N4O5F3 C 52.74%, H 4.83%, N 12.30%. Found: C 51.45%, H 4.68%, N 11.89%.

4-(3-chloro-1-(3,4–dihydroxylphenyl)-4-oxaazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoro methyl)-1H-pyrazol-5(4H)-one (6):

IR (KBr)(ῡmax, cm-1) 3350cm-1(str. of intramolecular –OH band) 3040cm-1(Ar-H str.),2960, 2870cm-1(str. of –CH2 group),2500,1500,1000,500 cm-1 (characteristic absorption of morpholine ring),1697cm-1, 1330cm-1,651cm-1(>C=O,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657 cm-1 (>C=O str. of pyrazoline-5-one), 1500,1430, 1375cm-1(str. of characteristic of pyrazoline-5-one

ring),1340cm-1(C-F str. band of CF3).1H NMR spectra (400MHz, DMSO-d6) δ 2.20(d,1H,J=7.50,-CH of pyrazoline-5-one ring), 2.45(t,4H,N-Adj–CH2 of morpholine),3.65 (t, 4H,O-Adj –CH2 of morpholine), 3.85(d,1H,-CH of azetidinone one ring),4.05(s,2H,N-CH2-N),4.6 (s,2H,two phenolic –OH groups), 5.05(d,1H,-CH-Cl of azetidine one ring),6.9-7.2 (m,3H of aromatic ring). Anal.Calcd.For C18H18N4O5F3 C 50.5%, H 4.2%, N 13.1%. Found: C 49.4%, H 4.09%, N 12.76%.

4-(3-chloro-1-(2-oxido-2-phenoxybenzene[d][1,3,2]dioxaphosphole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(8a):

IR (KBr)(ῡmax, cm-1)3040cm-1(Ar-H str.),2960,2870cm-1 (str.of–CH2 group),2500, 1500,1000, 500 (characteristic absorption of morpholine ring), 1697cm-1,1330cm-1,651cm-1(>C=O ,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1(>C=O str. of pyrazoline-5-one), 1500,1430,1375(str. of characteristic Pyrazoline-5-one),1340cm-1(C-F str. band of CF3)1255 cm-1 (P=O str. vibrations),954cm-1 (P-O str. vibration of P-O-C aromatic ring),1196 cm-1 (Caromatic-O str. vibration of Caromatic-O-P group). 1H NMR spectra (400MHz, DMSO-d6):δ2.20(d,1H,J=7.50Hz,-CH of pyrazoline-5-one),2.45(t,4H,N-Adj,-CH2 of morpholine),3.65 (t,4H,O-Adj,-CH2 of morpholine), 3.85(d,1H,-CH azetidinone ring), 4.05(s,2H,N-CH2-N),5.05(d,1H,CH-Cl of azetidinone ring), 6.9-7.20(m,8H, C6H5 and C6H3 rings). 13C NMR (75 MHz, DMSO-d6):δ 155.6,23.0,175.9,56.6,56.8, 161.9,135.7,107.7,145.4,140.8,117.5,115.6,150.2,120.3,130.1,121.3,130.1,120.3,70.3,53.2,66.4, 66.4,53.2,125.8, corresponding to C1,C2,C3,C4,C5,C6,C7,C8,C9,C10,C11,C12,C13,C14,C15,C16,C17, C18, C19,C20,C21,C22,C23,C24. 31P –NMR (161.89MHz, DMSO-d6): δ -8.15 ppm. Anal.Calcd. For C24H21N4O7PClF3 C 47.88%, H 3.49%, N 9.31%. Found: C 47.28%, H 3.36%, N 8.99%.

4-(3-chloro-1-(2-oxido-2-(p-tolyloxy)benzo[d][1,3,2]dioxaphosphole-5-yl)-4-oxoazetidin-2-yl)-1-(morpho linomethyl)-3-(tri fluoro methyl)-1H-pyrazol-5(4H)-one(8b):

IR (KBr)(ῡmax, cm-1) 3040cm-1(Ar-H str.),2960,2870cm-1 (str.of–CH2 group),2500,1500,1000,500 (characteristic absorption of morpholine ring), 1697cm-1,1330cm-1,651cm-1(>C=O ,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1(>C=O str. of pyrazoline-5-one),1500, 1430,1375(str. of characteristic Pyrazoline-5-one),1340cm-1(C-F str. band of CF3)1239 cm-1(P=O str. vibrations),960cm-1 (P-O str. vibration of P-O-C aromatic ring),1192 cm-1 (Caromatic-O str. vibration of Caromatic-O-P group). 1H NMR spectra (400MHz, DMSO-d6): δ 2.20(d,1H,J=7.50Hz,-CH of pyrazoline-5-one),2.45(t,4H,N-Adj,-CH2 of morpholine),3.65(t,4H,O-Adj,-CH2 of morpholine),3.85(unequal quartet, 1H,-CH of azetidinone ring),4.05(s,2H,N-CH2-N),5.05 (d, 1H, J=8.5Hz, CH-Cl of azetidinone ring), 6.9-7.10(m,7H, C6H4 and C6H3 rings),2.34(s, 3H,-CH3). 13C NMR (75 MHz, DMSO-d6):δ 155.6,23.0,175.9,56.6,56.8,161.9,135.7,107.7,145.4,140.8,117.5, 115.6,150.2,120.3,130.1,121.3,130.1,120.3,70.3,53.2,66.4,66.4,53.2,125.8,21.3 correspond ing to C1,C2,C3,C4,C5, C6,C7,C8, C9,C10,C11, C12, C13, C14,C15, C16,C17,C18,C19,C20,C21, C22,C23,C24, C25. 31P –NMR (161.89MHz, DMSO-d6): δ -8.48 ppm. Anal.Calcd.For C25H23N4O7PClF3 C 48.7%, H 3.73%, N 9.09%. Found: C 48.1%, H 3.63%, N 8.89%.

4-(3-chloro-1-(2-(4-methoxyphenoxy)-2-oxidobenzo[d][1,3,2]dioxaphosphol-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(triflоromethyl)-1H-pyrazol-5-(4H)-one(8c):

IR (KBr)(ῡmax, cm-1) 3040cm-1(Ar-H str.),2960,2870cm-1 (str.of–CH2 group),2500, 1500,1000,500 (characteristic absorption of morpholine ring), 1697cm-1,1330cm-1,651cm-1(>C=O ,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1(>C=O str. of pyrazoline-5-one),1500, 1430,1375(str. of characteristic Pyrazoline-5-one),1340cm-1(C-F str. band of CF3)1245 cm-1(P=O str. vibrations),944cm-1 (P-O str. vibration of P-O-C aromatic ring),1184 cm-1 (Caromatic-O str. vibration of Caromatic-O-P group). 1H NMR spectra (400MHz, DMSO-d6): δ 2.20(d,1H,J=7.50Hz,-CH of pyrazoline-5-one),2.45(t,4H,N-Adj,-CH2 of morpholine), 3.65(t,4H,O-Adj,-CH2 of morpholine),3.85(unequal quartet, 1H,-CH of azetidinone ring),4.05(s,2H,N-CH2-N),5.05 (d,1H, J=8.5Hz, CH-Cl of azetidinone ring), 6.8-7.0 (m,7H,C6H4 and C6H3 rings),3.4(s, 3H,-OCH3). 13C NMR (75 MHz, DMSO-d6): δ 155.6, 23.0, 175.9, 56.6, 56.8, 161.9, 135.7, 107.7, 145.4, 140.8, 117.5, 115.6, 142.5, 116.9, 115.7, 153.2, 115.7, 116.9, 70.3, 53.2, 66.4, 66.4, 53.2, 125.8, 55.8 corresponding to C1,C2,C3,C4,C5,C6,C7,C8,C9,C10,C11,C12,C13,C14,C15,C16,C17,C18,C19,C20,C21,C22,C23,C24,C25.31PNMR (161.89MHz, DMSO-d6): δ -8.92ppm. Anal. Calcd. For C25H23N4O8PClF3 C 47.50%, H 3.64%, N 8.86%. Found: C 46.9%, H 3.56%, N 8.63%.

4-(3-chloro-1-(2-(4-chlorophenoxy)-2-oxidobenzo[d][1,3,2]dioxaphosphol-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(tri fluoromethyl)-1H-pyrazol-5(4H)-one(8d):

IR (KBr)(ῡmax, cm-1) 3040cm-1(Ar-H str.),2960,2870cm-1 (str.of–CH2 group),2500, 1500,1000,500 (characteristic absorption of morpholine ring), 1697cm-1,1330cm-1,651cm-1(>C=O ,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1(>C=O str. of pyrazoline-5-one),1500, 1430,1375(str. of characteristic Pyrazoline-5-one),1340cm-1(C-F str. band of CF3)1270 cm-1(P=O str. vibrations),969cm-1 (P-O str. vibration of P-O-C aromatic ring),1210 cm-1 (Caromatic-O str. vibration of Caromatic-O-P group). 1H NMR spectra (400MHz, DMSO-d6): δ 2.20(d,1H,J=7.50Hz,-CH of pyrazoline-5-one),2.45(t,4H,N-Adj,-CH2 of morpholine),3.65(t,4H,O-Adj,-CH2 of morpholine),3.85(unequal quartet, 1H,-CH of azetidinone ring), 4.05(s,2H,N-CH2-N),5.05(d,1H, J=8.5Hz, CH-Cl of azetidinone ring), 7.20-7.40(m,7H,C6H4 and C6H3 rings). 13C NMR (75 MHz, DMSO-d6):δ155.6,23.0,175.9,56.6,56.8,161.9,135.7,107.7,145.4,140.8,117.5,115.6,142.5,116.9, 115.7,153.2,115.7,116.9,70.3,53.2,66.4,66.4,53.2,125.8 corresponding to C1,C2,C3,C4,C5, C6,C7,C8, C9,C10,C11,C12,C13,C14,C15,C16,C17,C18,C19,C20,C21,C22,C23,C24. 31P–NMR (161.89MHz, DMSO-d6): δ -7.75ppm. Anal. Calcd. For C24H21N4O7PCl2F3 C 45.2%, H 3.29%, N 8.79%. Found: C 44.6%, H 3.19%, N 8.56%.

4-(1-(2-(4-bromophenoxy)2-oxidobenzo[d][1,3,2]dioxaphosphol-5-yl)-3-chloro-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3 (trifluoromethyl)-1H-pyrazol-5(4H)-one(8e):

IR (KBr)(ῡmax, cm-1) 3040cm-1(Ar-H str.),2960,2870cm-1 (str.of–CH2 group),2500, 1500,1000,500 (characteristic absorption of morpholine ring), 1697cm-1,1330cm-1,651cm-1(>C=O ,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1(>C=O str. of pyrazoline-5-one), 1500,1430,1375(str. of characteristic Pyrazoline-5-one),1340cm-1(C-F str. band of CF3)1265 cm-1 (P=O str. vibrations),963cm-1 (P-O str. vibration of P-O-C aromatic ring),1203 cm-1 (Caromatic-O str. vibration of Caromatic-O-P group). 1H NMR spectra (400MHz, DMSO-d6): δ 2.20 (d,1H,J=7.50Hz,-CH of pyrazoline-5-one),2.45(t,4H,N-Adj,-CH2 of morpholine),3.65(t,4H,O-Adj,-CH2 of morpholine),3.85(unequal quartet, 1H,-CH of azetidinone ring),4.05(s,2H,N-CH2-N),5.05(d,1H, J=8.5Hz, CH-Cl of azetidinone ring), 7.10-7.30(m,7H, C6H4 and C6H3 rings). 13C NMR (75 MHz, DMSO-d6):δ155.6,23.0,175.9,56.6,56.8,161.9,135.7,107.7,145.4,140.8,117.5,115.6,142.5,116.9, 115.7,153.2,115.7,116.9, 70.3,53.2,66.4,66.4,53.2,125.8 corresponding to C1, C2, C3, C4, C5, C6, C7,

C8,C9,C10,C11,C12,C13,C14,C15,C16,C17,C18,C19,C20,C21,C22,C23,C24. 31P–NMR (161.89MHz, DMSO-d6): δ -8.10 ppm. Anal.Calcd.For C24H21N4O7PClF3Br C 42.32%, H 3.08%, N 8.22%. Found: C 41.72%, H 2.99%, N 7.99%.

4-(3-chloro-1-(2-oxido-2-(4-(trifluoromethyl) phenoxy)benzo[d][1,3,2]dioxaphosphol-5-yl)-4-oxoazetidin-2-yl)-1-(morpho linomethyl)-3-(trifluoro methyl)-1H-pyrazol-5-(4H)-one(8f):

IR (KBr)(ῡmax, cm-1) 3040cm-1(Ar-H str.),2960,2870cm-1 (str.of–CH2 group),2500, 1500,1000,500 (characteristic absorption of morpholine ring), 1697cm-1,1330cm-1,651cm-1(>C=O ,C-N,C-Cl characteristic frequencies of 4-oxoazetidin ring),1657cm-1(>C=O str. of pyrazoline-5-one), 1500, 1430,1375(str. of characteristic Pyrazoline-5-one),1340cm-1(C-F str. band of CF3)1276 cm-1 (P=O str. vibrations),975cm-1 (P-O str. vibration of P-O-C aromatic ring),1213 cm-1 (Caromatic-O str. vibration of Caromatic-O-P group). 1H NMR spectra (400MHz, DMSO-d6): δ 2.20(d,1H,J=7.50Hz,-CH of pyrazoline-5-one),2.45(t,4H,N-Adj,-CH2 of morpholine),3.65(t,4H,O-Adj,-CH2 of morpholine),3.85(unequal quartet, 1H,-CH of azetidinone ring),4.05(s,2H,N-CH2-N),5.05(d,1H, J=8.5Hz, CH-Cl of azetidinone ring),6.9-7.2(M,3H,aromatic ring),7.30-7.50(M,7H of C6H3 and C6H4 rings). 13C NMR (75 MHz, DMSO-d6):δ 155.6,23.0,175.9,56.6,56.8,161.9,135.7,107.7, 145.4,140.8,117.5,115.6,142.5,116.9,115.7,153.2,115.7,116.9,70.3,53.2,66.4,66.4,53.2,155.8, 124.1 corresponding to C1,C2,C3,C4,C5,C6,C7,C8,C9,C10,C11,C12,C13,C14,C15,C16,C17,C18,C19,C20,C21,C22, C23,C24,C25. 31P–NMR (161.89MHz, DMSO-d6): δ -7.56ppm. Anal.Calcd.For C25H20N4O7PClF6 C 44.80%, H 2.98%, N 8.36%. Found: C 44.2%, H 2.88%, N 8.15%.

Biological activity

The antimicrobial activity [42-44] of these newly synthesized compounds was performed according to disc diffusionmethod, as recommended by the National Committee for Clinical Laboratory [45]. The synthesised compoundswere used at the concentration of 250μg/ml DMF as a solvent [46].

Antibacterial activity

The antibacterial activity of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy) [d] [1,3,2]di oxaphosphole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5 (4H)-one(8a-f) were screened against the staphylococcus aureus NCCS 2079(SA), Bacillus cereus NCCS 2106(BC)(gram positive) and Escherichia coli NCCS 2065(EC), and Pseudomonas aeruginosa NCCS 2200(PA)(gram negative) organisms. Most of the compounds exhibit moderate antibacterial activity against both bacteria. The presence of –CF3 (8f), chloro (-Cl, 8d) and bromo (-Br, 8e) showed more activity than other substituted compounds. The order of antibacterial activity is 8f>8d>8e>8c>8b>8a.

Antibacterial activity of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy)[d][1,3,2]dioxaphos phole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(8a-f).

S.NO	COMPOUND	R	Zone of inhibition(mm)			
			staphylococcus aureus NCCS 2079 250 μg/ disc	*Bacillus cereus NCCS 2106 250 μg/ disc*	*Escherichia coli NCCS 2065 250 μg/ disc*	*Pseudomonas aeruginosa NCCS 2200 250 μg/ disc*
1	8a	H	11	12	10	11
2	8b	CH_3	9	11	7	9
3	8c	OCH_3	17	18	16	17
4	8d	Cl	15	16	13	14
5	8e	Br	16	17	14	15
6	8f	CF_3	14	13	12	12
Amoxicillin			22	25	21	23

Antifungal activity

The antifungal activity of 4-(3-chloro-1-(2-oxido-2(4-substituted phenoxy)[d][1,3,2]dioxaphos phole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (8a-f) were screened against the Aspergillus niger NCCS 1196 (AN) and candied albicans NCCS 3471(CA) organisms. Most of the compounds exhibit moderate antifungal activity against both fungi. The presence of -CF3(8f), chloro(8d) and bromo(8e) showed more activity than other substituted compounds. The order of antifungal activity is 8f>8d>8e>8c>8b>8a.

Antifungal activity of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy)[d][1,3,2]dioxaphos phole-5-yl)-4-oxoazetidin-2-yl)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(8a-f).

S.NO	COMPOUND	R	Zone of inhibition(mm)	
			Aspergillus niger NCCS 1196 250 μg/ disc	*candied albicans NCCS 3471 250 μg/ disc*
1	8a	H	12	11

2	8b	CH_3	10	09
3	8c	OCH_3	20	18
4	8d	Cl	15	15
5	8e	Br	17	17
6	8f	CF_3	13	11
Ketaconazole			22	25

Docking studies

Docking studies of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy) [d][1,3,2]dioxaphosphol-5-yl)-4-oxo azetidin-2-yl)1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(8a-f) with Sortase A Enzyme

The docking studies of 8a, 8b, 8c, 8d, 8e, 8f were carried out as model compounds on sortase-A enzyme. The docking ligands were found to have some interactions between an oxygen atom of the ligands and sortase-A enzyme. The results pertaining to antimicrobial docking studies were shown in the Table 1-2 and fig 1. Moreover, these docked conformations form hydrogen bond interactions with the active site of the enzyme. The common hydrogen bonding interactions were formed between all the docked ligands and ILE57PDB:1H, TYR54H, THR77H. Except 8e, the remaining Mannich bases show two hydrogen bonds with sortase-A enzyme. The order of enzyme-ligand hydrogen bond energy (S(Hb_ext)) is 8b>8f>8e>8d>8a=8c. The vanderwaals interactions between ligand-enzyme were also noticed. The order of enzyme-ligand vanderwaals score of interaction was found to be 8d>8f>8e>8c>8a>8b. However the ligands fail to exhibit intramolecular hydrogen bonding with the enzyme. The ligands exhibit minimum intramolecular strain. Finally, all the ligands exhibit moderate to good antibacterial activity with Sortase-A enzyme. The order of gold score fitness value of the ligands is 8e>8c>8f>8d>8a>8b. According to gold score fitness value ligand 8e exhibits high binding activity with the enzyme and ligand 8b showed leads binding activity with the enzyme.

Table 1: Docking results of ligands (8a-f) with Sortase A enzyme.

Comp	**R**	**Fitness**	**S(Hb_ex)**	**S(vdw_ex)**	**S(Hb_int)**	**S(vdw_in)**
8a	H	31.29	0.86	32.05	0.00	-13.63
8b	CH_3	27.07	2.18	30.08	0.00	-16.47
8c	OCH_3	31.97	0.86	32.24	0.00	-13.22
8d	Cl	31.92	1.01	32.93	0.00	-14.37
8e	-Br	33.11	1.03	32.55	0.00	-12.69
8f	$-CF_3$	31.94	1.04	32.87	0.00	-14.29

Table 2: Hydrogen bonding interactions of compounds with Sortase A enzyme

Comp No	**R**	**No of 'H' bonds**	**Compounds**		**Bond Length (Ao)**	**Fitness**
			Protein	Atoms		
8a	H	2	ILE57:PDB:1H TYR54:H	O:26 O:29	1.976 2.716	31.29
8b	$-CH_3$	2	YHR77:H TYR54:H	O:30 O:29	2.270 1.905	27.07
8c	$-OCH_3$	2	TYR54:H TYR54:H	O:26 P:27	1.852 2.635	31.97
8d	-Cl	2	TYR54:H TYR54:H	O:26 O:29	1.880 2.610	31.92
8e	-Br	1	TYR54:H	O:26	1.987	33.11
8f	$-CF_3$	2	TYR54:H TYR54:H	O:26 P:27	1.867 2.595	31.94

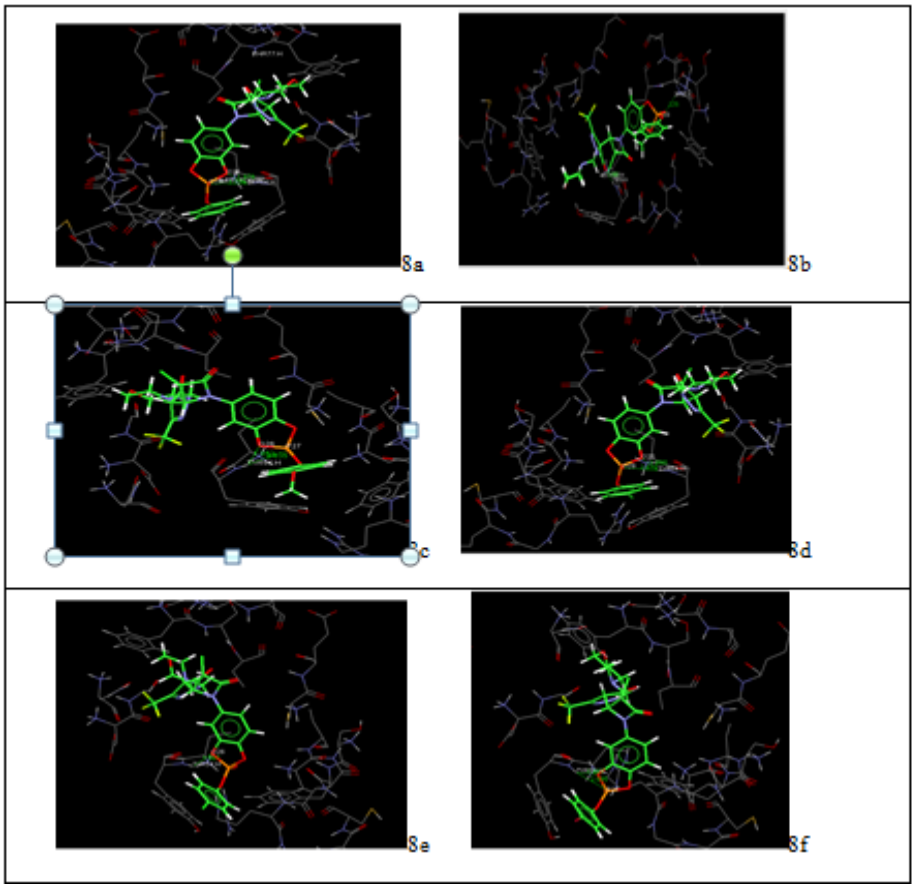
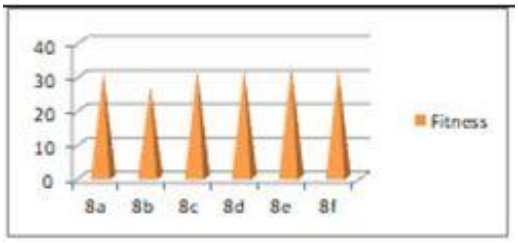


Figure 1: Anti-bacterial Docking studies of (8a-f) with Sortase-A enzyme**.**



Comparative Gold score fitness values for compounds (8a-f)

Docking studies of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy) [d][1,3,2]dioxaphosphol-5-yl)-4-oxo azetidin-2-yl)1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(8a-f) with Ferulic Acid Esterase

The docking studies of (8a-f) were carried out on Ferulic Acid Esterase from Aspergillus Niger. The docking ligands were found to have some interactions between an oxygen atom of the ligands and Ferulic Acid Esterase enzyme. The results pertaining to antifungal docking studies were shown in the Table 3-4 and fig 2. Moreover, these docked conformations form hydrogen bond interactions with the active site of the enzyme. Bind pocket and common hydrogen bonding interactions were formed between all the docked ligands and TYR54: H, ILE53:PDB1H, THR77:H. The order of enzyme-ligand hydrogen bond score is 8a>8b>8c> 8f>8d=8e. Besides hydrogen bond interaction between ligand-enzyme, the vanderwaals forces of interactions between ligand-enzyme were also noticed. The order of enzyme-ligand vanderwaals forces of interactions 8e>8c>8a>8d>8b>8f with the enzyme. However, the ligands fail to exhibit intramolecular hydrogen bonding and the ligands exhibit minimum intramolecular strain. Finally, all the ligands exhibit moderate to good antifungal activity found to be with Ferulic Acid Esterase enzyme. The gold score fitness value of the ligand is 8b>8a>8f>8c>8e>8d. According to gold score fitness value of ligand 8b exhibits high binding activity with the enzyme and ligand 8d shows least binding activity with the enzyme.

Table 3: Docking studies of (8a-f) on Ferulic Acid Esterase derived from Aspergillus Niger.

Comp	R	Fitness	S(Hb_ex)	S(vdw_et)	S(Hb_in)	S(vdw_it)
8a	-H	21.84	11.93	13.63	0.00	-8.84
8b	$-CH_3$	26.31	6.85	12.67	0.00	-50.57
8c	$-OCH_3$	11.53	6.10	16.44	0.00	-17.18
8d	-Cl	3.64	0.00	13.51	0.00	-14.93
8e	-Br	8.38	0.00	19.58	0.00	-18.54
8f	$-CF_3$	20.88	4.97	11.14	0.00	-41.16

Table 4: Hydrogen bonding interactions of compounds with Ferulic Acid Esterase.

Comp No	R	No of 'H' bonds	Compounds		Bond Length (Ao)	Fitness
			Protein	Atoms		
8a	H	2	TYR54:H ILE53:PDB1H	O:26 O:26	1.929 1.669	21.84
8b	$-CH_3$	2	THR77:H TYR54:H	O:30 O:26	2.540 1.615	26.31
8c	$-OCH_3$	2	THR77:H TYR54:H	O:30 O:29	2.575 1.018	11.53
8d	-Cl	2	TYR54:H TYR54:H	P:27 O:26	2.610 1.880	3.64
8e	-Br	1	TYR54:H	O:26	1.958	8.38
8f	$-CF_3$	2	TYR54:H TYR54:H	O:29 O:26	2.558 1.540	20.88

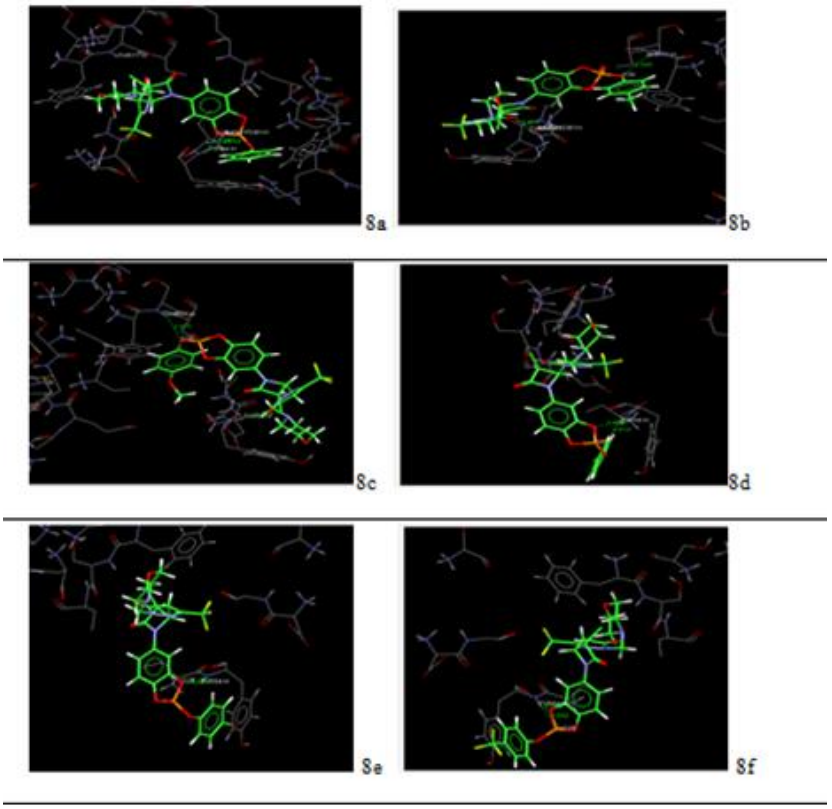
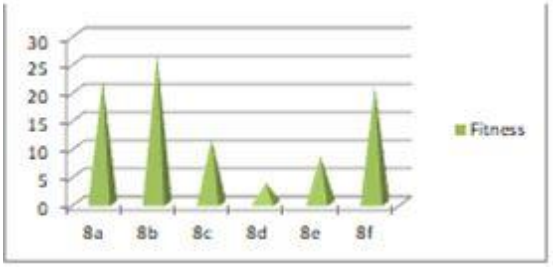


Figure 2: Antifungal docking studies of (8a-f) with ferulic acid esterase.



Comparative Gold score fitness values for compounds (8a-f)

Docking studies of 4-(3-chloro-1-(2-oxido-2-(4-substituted phenoxy) [d][1,3,2]dioxaphosphol-5-yl)-4-oxo azetidin-2-yl)1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(8a-f) with BCL-2

The docking studies of (8a-f) were carried out on BCL-2 (PDB ID: 1G5M). The results pertaining to anticancer docking studies were shown in the Table 5-6 and Figure 3. The docking ligands were found to have some interactions between an oxygen atom of the ligands and B-Cell Lymphoma-2 protein. Moreover, these docked conformations formed were due to hydrogen bond interactions with the active site of the protein. Bind pocket, and common hydrogen bonding interactions. The docked conformations were formed between all the docked ligands and amino acid moiety of the protein such as TYR54: H, ILE53:PDB2H. The order of protein-ligand hydrogen bond score is 8b>8c>8f>8e>8d>8a. Besides hydrogen bonding interaction between ligand-protein, the vanderwalls forces of interactions between ligand-protein were also noticed. The order of protien-ligand vanderwaals forces of interactions 8d>8f>8e>8c>8a>8b with the protien. However, the ligand fails to exhibit intramolecular hydrogen bonding its own molecule. The ligands exhibit minimum intra molecular strain. Finally, all the ligands exhibit moderate to good anticancer activity with B-Cell Lymphoma-2 protein. The order of gold score fitness value of the ligands is 8e>8c>8f> 8d>8a>8b. According to gold score fitness value ligand 8e exhibits high binding activity with the protein and ligand 8b showed least binding activity with the protein.

Table 5: Docking studies of (8a-f) on BCL-2 (B-cell lymphoma 2).

Comp	R	Fitness	S(Hb_ex)	S(vdw_et)	S(Hb_in)	S(vdw_it)
8a	H	21.29	1.86	22.05	0.00	-13.63
8b	$-CH_3$	17.07	4.18	20.08	0.00	-16.47
8c	$-OCH_3$	21.97	2.86	22.24	0.00	-13.22
8d	-Cl	21.92	2.01	22.93	0.00	-14.37
8e	-Br	23.11	2.03	22.55	0.00	-12.69
8f	$-CF_3$	21.94	2.04	22.87	0.00	-14.29

Table 6: Hydrogen bonding interactions of compounds wih BCL-2 (B-cell lymphoma 2).

Comp No	R	No of 'H' bonds	Compounds		Bond Length (Ao)	Fitness
			Protein	Atoms		
8a	H	1	TYR54:H	O29	1.861	21.29
8b	$-CH_3$	1	ILE53:PDB2H	N4	1.972	17.07
8c	$-OCH_3$	1	TYR54:H	O26	2.017	21.97
8d	-Cl	1	TYR54:H	O26	1.870	21.92
8e	-Br	2	TYR54:H TYR54:H	O29 O29	2.691 1.917	23.11
8f	$-CF_3$	2	TYR54:H TYR54:H	O26 O29	2.658 1.852	21.94

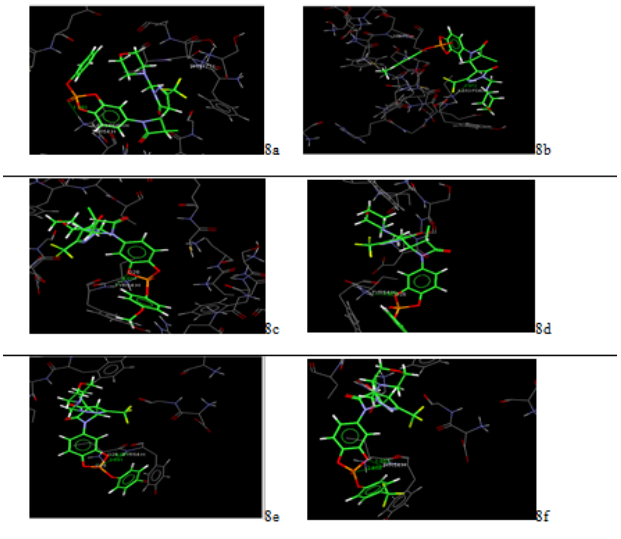
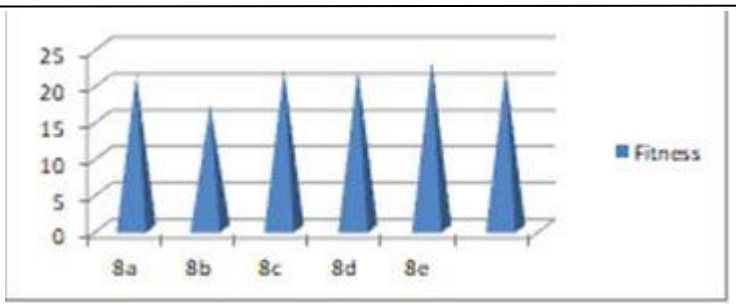


Figure 3: Anticancer docking studies of (8a-f) with BCL-2.



Comparative Gold score fitness values for compounds (8a-f)

CONCLUSION

In the present investigations, we report herein synthesis of novel benzodioxaphosphole-2-oxide derivatives containing structurally varied heterocycles. The salient observations noticed in the experimental results and structural elucidations were briefly described in this research paper. This research article gives information about abstract of work done besides highlights in the results and discussion. The spectral data (IR, 1H NMR, 13C NMR, P31-NMR and Mass), antimicrobial profile and docking studies were presented in this research paper. The piece of novel work on "Synthesis, Characterization, Biological Evaluation and Docking studies of (8a-f) add new dimensions to the Organophosphorous Chemistry.

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