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SYNTHESIS, CHARACTERIZATION, DOCKING STUDIES AND ANTIMICROBIAL ACTIVITY OF 3-CHLORO-4-(2-OXIDO-2-(4-SUBSTITUTED PHENYL) BENZO [D] [1,3,2] DIOXAPHOSPHOL-5-YL)-1-(QUINOLIN-6-YL)AZETIDINE-2-ONE

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ABSTRACT

3-chloro-4-(2-oxido-2-phenoxy benzo[d][1,3,2]dioxaphosphol-5-yl)-1-(quinoline-6-yl)azetidin-2-one (7a-g) were synthesized by condensing 3-chloro-4-(3,4-dihydroxy phenyl)-1-(quinoline-6-yl)azetidin-2-one(5) with 4-substituted phenyl phosphorodichloridates(6a-g). The synthon (5) was synthesized by hydrolysis of 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline-6-yl)azetidin-2-one (4). The intermediate (4) was synthesized by condensing 1-(3,4-dimethoxy phenyl)-N-(quinoline-6-yl)methanimine (3) with monochloro acetyl chloride. Starting intermediate (3) was synthesized by condensation reaction between quinoline-6-amine (1) and 3,4-dimethoxy benzaldehyde (2). The target molecule (7a-g) were characterized by IR,^{1}H-NMR,^{13}C-NMR,Mass and elemental analysis. The target molecules were subjected to biological evaluation and docking studies. Some of the derivatives found to have promising activity.

KEYWORDS: Quinolin-6-amine, 3,4-dimethoxy benzaldehyde, 4-substituted phenyl phosphodi chloridates, Monochloro acetyl chloride, Condensation reaction, hydrolysis.

INTRODUCTION

Phosphorus chemistry has pioneered the application of nano,[1] techniques and several organophosphorus compounds have been synthesized to be used as insecticides, herbicides, fungicides, plant growth regulators, biological activity against broad spectrum of the bacteria and different kinds of pests and virus,[2] When compared to other chemical class of pesticides, organophosphorus pesticides were relatively safe and eco-friendly as they were easily degradable in environment after discharging their functions as pesticides. Further, the residues in water and soil act as fertilizers and nutrients.

Heterocycles possessing azetidin-2-one ring were found to show various types of biological activities.[3] Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial,[4] pesticidal, antitumor,[5] antitubercular,[6] anticancer,[7] cytotoxic,[8] enzyme inhibitors,[9] elastase inhibitors,[10] and cholesterol absorption inhibitors. Many β-lactam drugs had been reported in the literature.

Thus different 3-chloro-4-(2-oxido-2-(4-substituted phenyl) benzo [d][1,3,2] dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidine-2-one (7a-g) were synthesized The structures of these compounds have been established by Mass, ^{1}H NMR, IR studies, and synthesis. All the new compounds were screened for their anti-fungal activity. Some of the derivatives found to have better activity.

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 points were determined in open capillary tubes on Mel-Temp apparatus and are uncorrected column chromatography was performed of silica gel with different solvent systems as eluents to afford the pure compound. The IR spectra were recorded as KBr pellets on PERKIN-ELMER 1000units, instruments, All ^{1}H and ^{13}C-NMR spectra were recorded on a varian XL-300 spectrometer operating at 400MHZ for ^{1}H-NMR and 75MHZ for ^{13}C-NMR respectively.[31] P-NMR spectra were recorded on a varian XL-spectrometer operating at 161.89 MHZ. The compounds were dissolved in DMSO-d_6 and chemical shifts were referenced to TMS (^{1}H and ^{13}C-NMR) and 85%H_3PO_4(^{31}P-NMR). Elemental analysis was recorded on a Carlo Erba 1108 elemental

analyzer, Central Drug Research Institute, Lucknow, India.

Synthesis of1-(3,4-dimethoxy phenyl)-N-(quinolin -6-yl)methanimine (3)[11]: The mixture of quinoline-6-amine (**1**, 0.02mol) and 3,4-dimethoxy benzaldehyde (2, 0.025mol) were dissolved in absolute alcohol, to this one drop of acetic acid was added then heated on a steam bath for 5-6hrs at 100^0c. The progress of the reaction was monitored by TLC using Ethyl acetate: Acetone (9:1). After standing for 24hrs at room temperature, the product was dried and recrystalized from warm absolute alcohol was dried under suction. The m.p. of **(3)** was found to be 138-140°C with a yield of 82%, 0.012moles. The separated solid was identified as 1-(3,4-dimethoxy phenyl)-N-(quinolin -6-yl)methanimine **(3). IR (KBr pellet)** γ, cm^{-1}: Characteristic bands around 3040 str. Of Aromatic proton of benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1615 str.of $\gamma_{-C=NH-}$ of azomethine group, 1450 str. of γ_{-C-N} of quinoline ring and 1050 str.of $\delta_{-c-o-c-}$ of aromatic ether.**^{1}H-NMR (δ,ppm):** 3.80 s,6H,two –OCH_3 groups, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring, and 8.30 s, H, -C-H of azo methine group.

Synthesis of 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline -6-yl)azetidine-2-one(4)[12-13]: Monochloro acetyl chloride(0.025moles) was added drop wise to the1-(3,4-dimethoxy phenyl)-N-(quinolin -6-yl)methanimine **(3,** 0.02moles**)** and triethyl amine in dioxane (25ml, 0.02mol) at room temperature. The mixture was stirred for 8 hours and left at room temperature for 3-days. Pour the contents on crushed ice to afford 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline -6-yl)azetidine-2-one (4). The product thus formed was filtered and washed with sodium bicarbonate solution. The dried product was recrystallized with absolute alcohol. The progress of the reaction was monitored by TLC analysis. The m.p. of **(4)** was found to be 156-158°C with a yield of 70%, 0.014moles. The separated solid was identified as 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline -6-yl)azetidine-2-one **(4).**

IR (KBr pellet) γ, cm^{-1}: Characteristic bands around 3040 str. of Aromatic proton of benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1670 str. of $>c=o$ group of azetidinone, 1450 str. of γ_{-C-N} of quinoline ring, 1415 str. of C-N of azetidin-2-one ring, and 1050 str. of $\delta_{-c-o-c-}$ of aromatic ether.**^{1}H-NMR (δ,ppm):** 3.80 s,6H,two –OCH_3 groups, 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring.

Synthesis of 3-chloro-4-(3,4-dihydroxy phenyl)-1-(quinolin -6-yl)azetidine-2-one (5)[14]: A solution of 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline -6-yl)azetidine-2-one**(4,** 0.02moles**)** was dissolved in 30ml CH_2Cl_2 under liquid N_2 atmosphere and boron tri bromide (2.4ml, 0.025moles) was added at -78°C. The mixture was brought slowly to room temperature and stirred for 16 hours. Cold methanol and ice water was added to quench reaction and saturated aqueous $NaHCO_3$ solution was used to adjust P^H to 7~8. After extracting the reaction mixture three times by ethyl acetate, each time 25ml, the organic layer was merged and dried by anhydrous Na_2SO_4. It was then purified by column chromatography using Petrolium ether**:** Ethyl acetate 8:2 solvent mixture as an elutent to give the 3-chloro-4-(3,4-dihydroxy phenyl)-1-(quinolin -6-yl)azetidine-2-one **(5).** The m.p. of **(5)** was found to be 127-129°C, with a yield of 75%, 0.015moles. **IR (KBr pellet)** γ, cm^{-1} : 3350cm^{-1} intramolecular hydrogen bonding str.of –OH, 3040 str. of Aromatic proton of benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1670 str.of $>c=o$ group of azetidinone, 1450 str. of γ_{-C-N} of quinoline ring, 1415 str.of C-N of azetidin-2-one ring, and 672 str. of C-Cl. **^{1}H-NMR (δ,ppm):** 3.80 s,2H,two –OH groups, 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring.

Synthesis of 4-substituted phenyl phosphodichloridates (6a-g)[15]: 4-substituted phenyl phosphodichloridated **(6a-g)** were synthesized as reported in the literature.

General procedure for the synthesis of (4-substituted phenoxy) benzo[d][1,3,2] dioxaphosphol-5-yl)-1-(quinoline-6-yl)azetidine-2-one (7a-g)[16] A solution of phenyl phosphorodichloridate (**6a**, 0.025moles) in 25ml of dry toluene was added drop wise over a period of 20min to a stirred solution of 3-chloro-4-(3,4-dihydroxy phenyl) 1-(quinolin-6-yl) azetidine-2-one (**5**,0.02moles**)** and triethylamine (0.04moles)in 30ml of dry toluene and 10ml of Tetra Hydro Furan at 5°C. After completion of addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 2hours. Later the reaction mixture was heated to $50\text{-}60^0$C and maintained for 4hrs with stirring. The completion of the reaction was monitored by TLC analysis. Triethylamine hydrochloric acid was filtered from mixture and solvent was removed under reduced pressure. The residue was washed with water and then recrystallized from aqueous 2-propanol to get pure compound. The m.p. of **(7a)** was found to be 142-144°C with a yield of 60%, 0.012moles. The separated solid was identified as 3-chloro-4-(2-oxido-2-phenoxy benzo[d][1,3,2]dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidin-2-one **(7a).**

The similar procedure was adopted to synthesize (7a-g) by the reaction between 3-chloro-4-(3,4-dihydroxy phenyl) 1-(quinolin-6-yl) azetidine-2-one **(5)** with 4-methyl phenyl phosphorodichloridate **(6b),** 4-methoxyphenyl phosphodichloridate **(6c)**, 4-chloro phenyl phosphorodichloridate **(6d),** 4-fluoro phenyl phosphorodichloridate (6e), 4-nitro phenyl phosphorodichloridate **(6f),** 4-(trifluoromethyl) phenyl phosphorodichloridate **(6g)**.

Spectral, Physical and Analytical data for the compounds (7a-g)

7a: Yield:60%. m.p:142-144^{0}C. Anal. Found for $C_{24}H_{16}ClN_2O_5P$ (%): C 59.18, H 3.20, Cl 7.20, N 5.60 and P 6.10. IR, KBr pellet (γ, cm^{-1}): 3040 str. of Aromatic proton of benzene ring, 1670 str.of >c=o group of azetidinone, 1415 str.of C-N of azetidin-2-one ring, 1250 str.of P=O, 950 str.of P-O-$C_{(-Ar)}$ and 660 str.of C-Cl. ^{1}H-NMR (δ,ppm): 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3. ^{13}C-NMR(δ,ppm): 145.1, 120.6, 132.9, 121.0, 143.0, 126.7, 121.9, 141.5, 129.7, 68.1, 62.0, 162.2, 137.5, 119.6, 117.1, 143.2, 145.0, 114.0, 150.2, 120.3, 130.1 and 121.3 corresponding C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18}, C_{19}, C_{20} ,C_{21}, C_{22}& C_{26}, C_{23}&C_{25} and C_{24} respectively. ^{31}P-NMR (δ,ppm): -7.23. Mass (m/z %): 478 $[M]^+$.

7b: Yield:55%. m.p:175-176^{0}C. Anal. Found for $C_{25}H_{18}ClN_2O_5P$ (%): C 59.80, H 3.25, Cl 6.80, N 5.25 and P 6.10. IR, KBr pellet (γ, cm^{-1}) : 3025 str. of Aromatic proton of benzene ring, 1665 str.of >c=o group of azetidinone, , 1410 str.of C-N of azetidin-2-one ring, 1245 str.of P=O, 945 str.of P-O-$C_{(-Ar)}$ and 650 str.of C-Cl. ^{1}H-NMR (δ,ppm): 2.30 s,3H,-CH_3 of phenyl ring, 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring. ^{31}P-NMR (δ,ppm): -7.48.

7c: Yield :65%. m.p:143-144^{0}C. Anal. Found for $C_{25}H_{18}ClN_2O_6P$ (%): C 58.05, H 3.53, Cl 6.50, N 5.30 and P 18.60. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1680 str.of >c=o group of azetidinone, , 1420 str.of C-N of azetidin-2-one ring, 1255 str.of P=O, 960 str.of P-O-$C_{(-Ar)}$ and 670 str.of C-Cl. ^{1}H-NMR (δ,ppm): 3.80 s,3H,-OCH_3 of phenyl ring, 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring. ^{31}P-NMR (δ,ppm): -8.1.

7d: Yield :70%. m.p:170-172^{0}C. Anal. Found for $C_{24}H_{15}Cl_2N_2O_5P$ (%): C 55.09, H 2.80, Cl 13.40, N 5.10 and P 5.80. IR, KBr pellet (γ, cm^{-1}): 3035 str. of Aromatic proton of benzene ring, 1675 str.of >c=o group of azetidinone, 1417 str.of C-N of azetidin-2-one ring, 1253 str.of P=O, 955 str.of P-O-$C_{(-Ar)}$ and 665 str.of C-Cl. ^{1}H-NMR (δ,ppm): 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring. ^{31}P-NMR (δ,ppm): -6.8.

7e: Yield:60%. m.p:169-170^{0}C. Anal. Found for $C_{24}H_{15}ClFN_2O_5P$ (%): C 57.05, H 3.02, Cl 6.90, N 5.46 and P 6.13. IR, KBr pellet (γ, cm^{-1}) : 3035 str. of Aromatic proton of benzene ring, 1675 str.of >c=o group of azetidinone, , 1417 str.of C-N of azetidin-2-one ring, 1253 str.of P=O, 955 str.of P-O-$C_{(-Ar)}$ and 665 str.of C-Cl. ^{1}H-NMR (δ,ppm): 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring. ^{31}P-NMR (δ,ppm): -6.4.

7f: Yield:65%. m.p:185-186^{0}C. Anal. Found for $C_{24}H_{15}ClN_3O_7P$ (%): C 54.09, H 2.84, Cl 6.63, N 7.90 and P 5.72. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1680 str.of >c=o group of azetidinone, , 1420 str.of C-N of azetidin-2-one ring, 1260 e azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring. ^{31}P-NMR (δ,ppm): -6.1.

7g: Yield:66%. m.p:142-143^{0}C. Anal. Found for $C_{25}H_{15}ClF_3N_2O_5P$ (%): C 53.91, H 2.72, Cl 6.15, N 4.90 and P 5.45. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1690 str.of >c=o group of azetidinone, , 1425 str.of C-N of azetidin-2-one ring, 1270 str.of P=O, 970 str.of P-O-$C_{(-Ar)}$ and 675 str.of C-Cl. ^{1}H-NMR (δ,ppm): 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring. ^{31}P-NMR (δ,ppm): -6.6.

RESULTS AND DISCUSSION

The synthetic route followed for the synthesis of 3-chloro-4-(2-oxido-2-(4-substituted phenyl) benzo [d] [1,3,2] dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidine-2-one is presented in scheme-1.

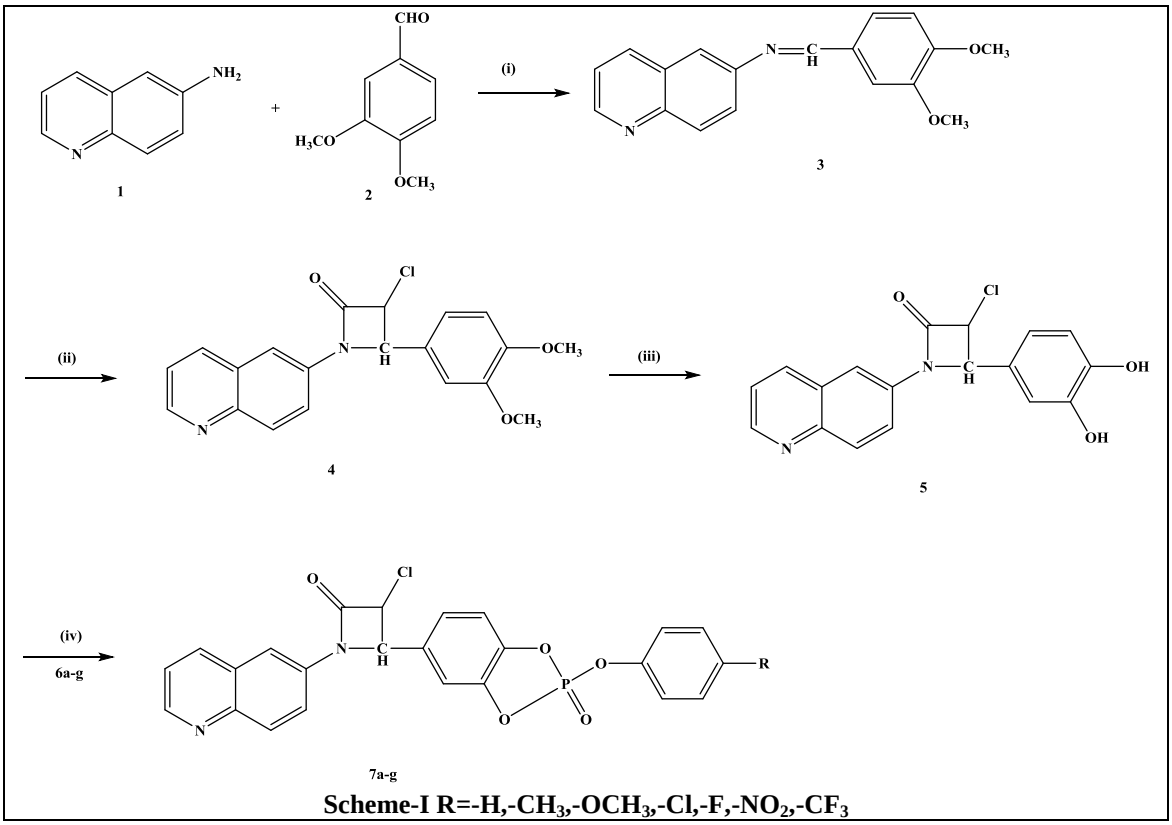
1-(3,4-dimethoxy phenyl)-N-(quinoline-6-yl)methanimine (3) was synthesized by condensation reaction between quinoline-6-amine (1) and 3,4-dimethoxy benzaldehyde (2). The IR spectra of 1-(3,4-dimethoxy phenyl)-N-(quinoline-6-yl)methanimine (3) exhibited bands around 3040 str. Of Aromatic proton of benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1615 str.of $\gamma_{-C=NH-}$ of azomethine group, 1450 str. of γ_{-C-N} of quinoline ring and 1050 str.of $\delta_{-c-o-c-}$ of aromatic ether. ^{1}H NMR of (3) showed one singlet at δ 3.80(s,6H,two –OCH_3 groups), and 6.9-7.3(m,5H, 3H of C_6H_3 ring and two thiophene protons) confirming the structure of compound (3).

3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline-6-yl) azetidin-2-one (4) was synthesized by condensing 1-(3,4-dimethoxy phenyl)-N-(quinoline-6-yl)methanimine (3) with monochloro acetyl chloride. The IR spectra of 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline-6-yl)azetidin-2-one (4) exhibited bands around 3040 str. of Aromatic proton of benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1670 str.of >c=o group of azetidinone, 1450 str. of γ_{-C-N} of quinoline ring, 1415 str.of C-N of

azetidin-2-one ring, and 1050 str.of $\delta_{-c-o-c-}$ of aromatic ether. ^{1}H NMR of (4) showed one singlet at δ 3.80 s,6H,two –OCH_3 groups, 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring confirming the structure of compound (4).

3-chloro-4-(3,4-dihydroxy phenyl)-1-(quinoline-6-yl)azetidin-2-one(5) was synthesized by hydrolysis of 3-chloro-4-(3,4-dimethoxy phenyl)-1-(quinoline-6-yl)azetidin-2-one (4). The IR spectra of 3-chloro-4-(3,4-dihydroxy phenyl)-1-(quinoline-6-yl)azetidin-2-one(5) exhibited bands around 3350cm^{-1} intramolecular hydrogen bonding str.of –OH, 3040 str. of Aromatic proton of benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1670 str.of >C=O group of azetidinone, 1450 str. of γ_{C-N} of quinoline ring, 1415 str.of C-N of azetidin-2-one ring, and 672 str.of C-Cl. ^{1}H NMR of (5) showed one singlet at δ 5.7 s,2H,two –OH groups, confirming the structure of compound (5).

3-chloro-4-(2-oxido-2-phenoxy benzo[d][1,3,2]dioxaphosphol-5-yl)-1-(quinoline-6-yl)azetidin-2-one (7a-g) were synthesized by condensing 3-chloro-4-(3,4-dihydroxy phenyl)-1-(quinoline-6-yl)azetidin-2-one(5) with 4-substituted phenyl phosphorodichloridates(6a-g). The IR spectra of 3-chloro-4-(2-oxido-2-phenoxy benzo[d][1,3,2]dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidin-2-one (7a) exhibited bands around 3040 str. of Aromatic proton of benzene ring, 1670 str.of >C=O group of azetidinone, , 1415 str.of C-N of azetidin-2-one ring, 1250 str.of P=O, 950 str.of P-O-$C_{(-Ar)}$ and 660 str.of C-Cl. ^{1}H NMR of (7a) showed one singlet at δ 5.10 d,1H,-CH- of azetidinone ring attached to phenyl ring, 5.40 d,1H,CH of azetidin attached to –Cl, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3, confirming the structure of compound (7a). Similarly remaining analogues (7b-g) were prepared.



Scheme-I R=-H,-CH_3,-OCH_3,-Cl,-F,-NO_2,-CF_3

Compound 7	A	B	C	D	E	F	G
R	-H	-CH_3	-OCH_3	-Cl	-F	-NO_2	-CF_3

Reagents and conditions: (i) Quinoline-6-amine,/ 3,4-dimethoxy benzaldehyde/ absolute alcohol / 5-6hrs at 100^{0}c (ii) Monochloro acetyl chloride/ TEA/ Dioxane/ RT /8hrs (iii) Boron tri bromide/ MDC (iv) Phenyl phosphorodichloridate/ TEA/ Toluene/THF

Biological activity: The antimicrobial activity,[17-19] of 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 (250 µg/ml). DMF as a solvent.

Antibacterial activity: The antibacterial activity,[20] of 3-chloro-4-(2-oxido-(4-substituted phenoxy) benzo[d] [1,3,2] dioxaphosphol-5-yl)-1-(quinoline-6-yl)azetidine-

2-one **(7a-g)** were screened against the Staphylococcus aureus (gram positive), Bacillus cereus, Escherichia coil (gram negative) and Pseudomonas aeruginosa organisms. The substituents nitro(7f), trifluoro methyl(7g) and fluoro (7e) showed more activity than other substituted compounds. The antibacterial activity of (7a-g) was shown in the Table-1 and Fig-1. Here Amoxicillin is used as the reference compound to compare the activity. Most of the compounds showed moderate to good antibacterial activity against both bacteria under present investigation.

Table-l: Antibacterial activity (Diameter zone of inhibition in mm) of Compounds of 7(a-g) (250 µg/ml).

S. NO	Comp	Zone of inhibition(mm)			
		Staphylococcus Aureus NCCS 2079	Bacillus cereus NCCS 2106	Escherichia coli NCCS2065	Pseudomonas aeruginosa NCCS 2200
1	7a	12	07	11	13
2	7b	11	06	10	12
3	7c	10	05	09	11
4	7d	14	08	12	14
5	7e	15	09	13	15
6	7f	18	12	16	19
7	7g	16	10	14	16
Amoxicillin		21	27	24	22

Antifungal activity: Antifungal activity of final compounds 3-chloro-4-(2-oxido-(4-substituted phenoxy) benzo[d] [1,3,2] dioxaphosphol-5-yl)-1-(quinoline-6-yl)azetidine-2-one **(7a-g)** were screened against Aspergillus niger, Candida albicans. The substituents nitro(7f), trifluoro methy(7g) and fluoro(7e) showed more activity than other substituted compounds. The antifungal activity of (7a-g) was shown in the Table-2 and Fig-2.Here Ketoconaazole is used as reference compound to compare the activity. Most of the compounds showed moderate to good antifungal activity against both fungi.

Table-2: Antifungal activity (Diameter zone of inhibition in mm) of Compounds 7(a-g) (250 µg/ml).

S.NO	COMP	Zone of inhibition (mm)	
		Aspergillus niger NCCS 1196	Candida albicans NCCS 3471
1	7a	13	09
2	7b	12	08
3	7c	11	07
4	7d	14	10
5	7e	15	11
6	7f	18	15
7	7g	16	12
Ketoconazole		22	25

The order of anti-bacterial and anti-fungal activity was found to be (7f > 7g > 7e > 7d > 7a > 7b > 7c).

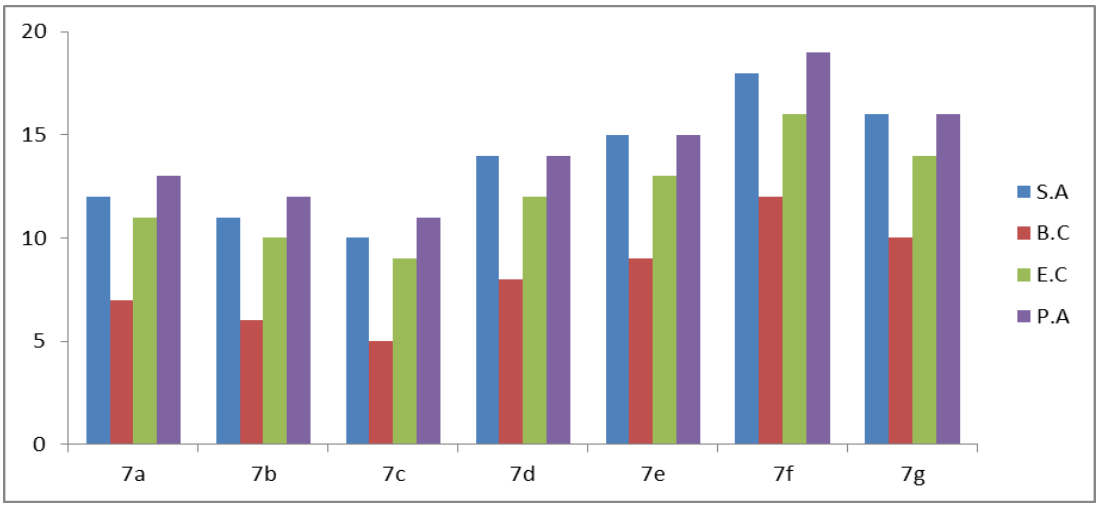


Fig. 1: Antibacterial activity of compound 7(a-g).

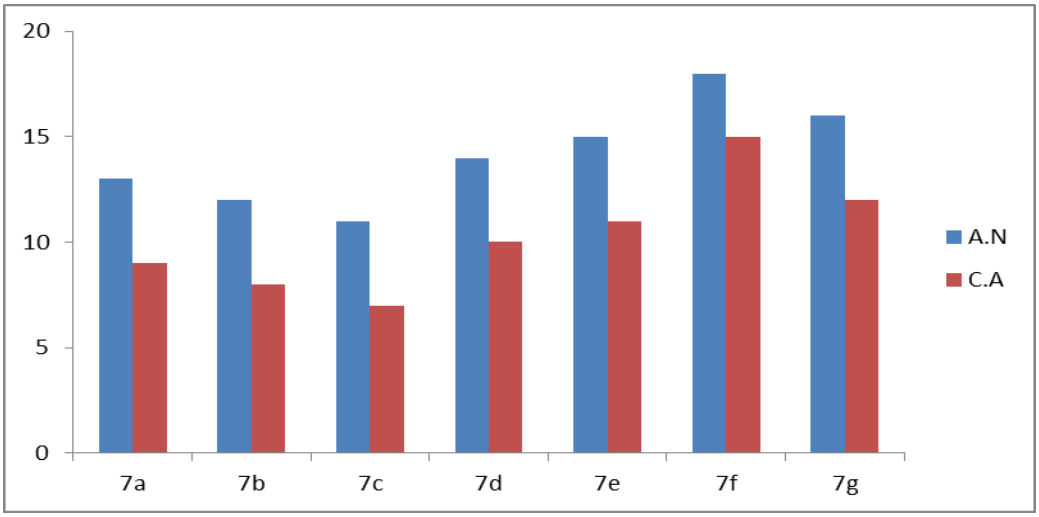
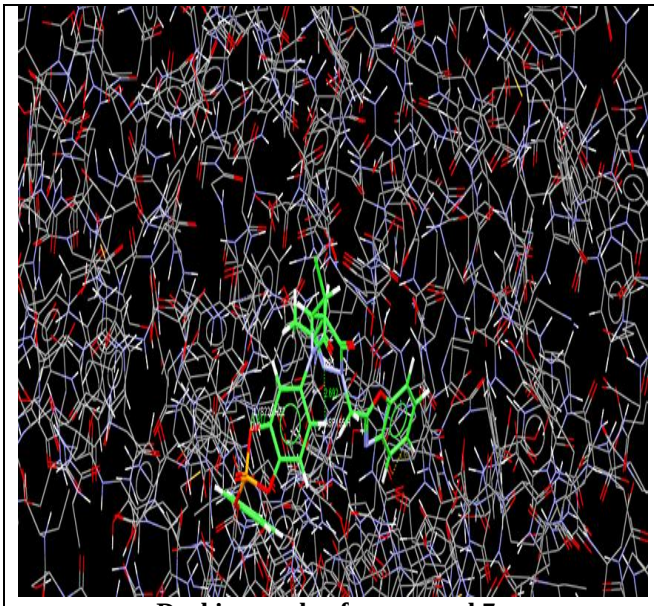


Fig. 2: Antifungal activity of compounds (7a-g).

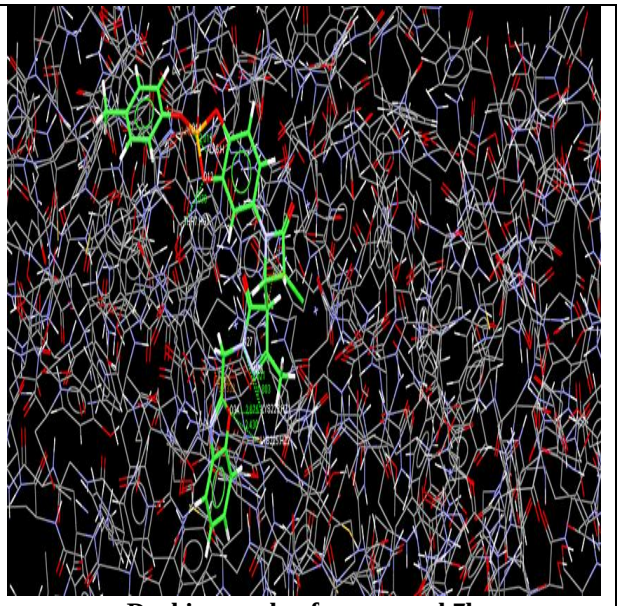
Docking study

Docking of the inhibitors (synthesized compounds from **(7a-g)** with B- cell lymphoma(Bcl-2). Docking[21] was performed using GOLD 3.0.1, which is based on Genetic algorithm(GA). The docking studies of **(7a-g)** were carried out on B-cell lymphoma(Bcl-2) protein. The docking ligands were found to have some interactions between an oxygen atom of the ligands and B-cell lymphoma(Bcl-2) protein. The results pertaining to Docking studies were shown in the Table-3-Table-4 and in Fig-3. Moreover, these docked conformations formed hydrogen bond interactions with the active site of the protein. The common hydrogen bonding interactions were formed between all the docked ligands and amino acid part of the protein. The hydrogen bonding was formed between the amino acid part of the protein and active oxygen atom of the (7a-g). The hydrogen bondings were noticed between ARG26PDB, LYS22, HIS184, TYR127PDB**.** The order of protein-ligand hydrogen bond score is **7f>7g>7e>7d>7a>7b>7c.** Besides hydrogen bonding interaction between ligand-protein, the vanderwaals forces of interactions between ligand-protein were also noticed. The order of protein-ligand vander waals score of interaction is found to be **7f >7g >7e>7d>7a>7b>7c** with the protein. However the ligands fail to exhibit minimum intramolecular strain. Finally, all the ligands exhibits moderate to good anticancer activity with B-cell lymphoma(Bcl-2) protein. The order of gold score fitness value of the ligands is found to be **7f >7g >7e>7d>7a>7b>7c.** According to gold score fitness value ligand **7f** exhibits high binding activity with the protein and ligand **7c** shows least binding activity with the protein.

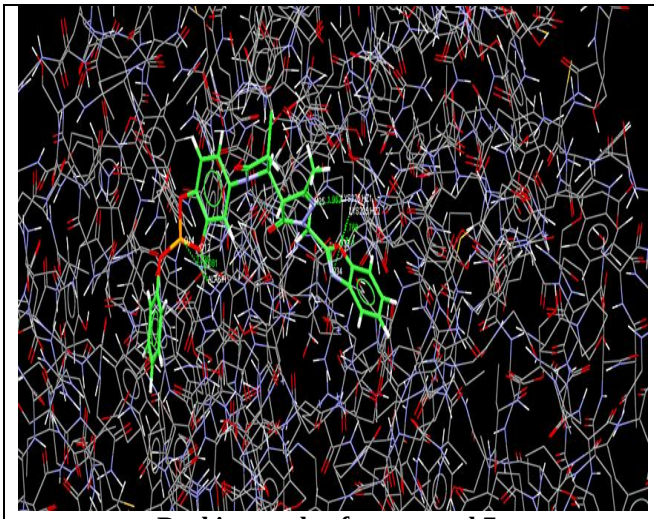
In Gold score evaluation of docking studies, electronic interactions, bonding interactions, steric interaction and conformations of proteins and docked ligand play significant role. However, in the evaluation of antimicrobial studies, electronic factors of the substituents play a significant role.



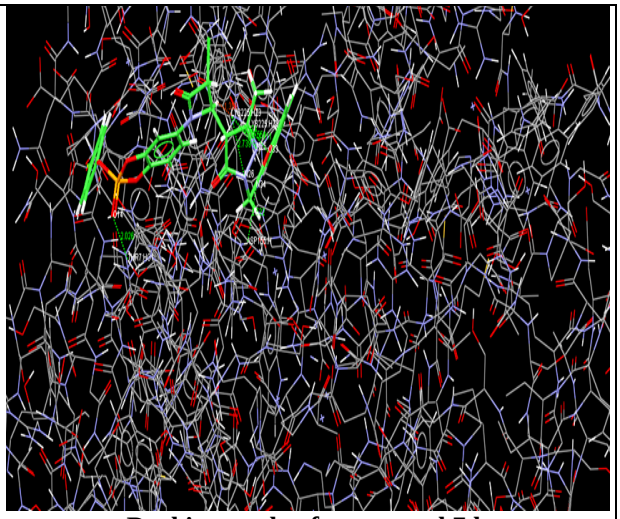
Docking study of compound 7a



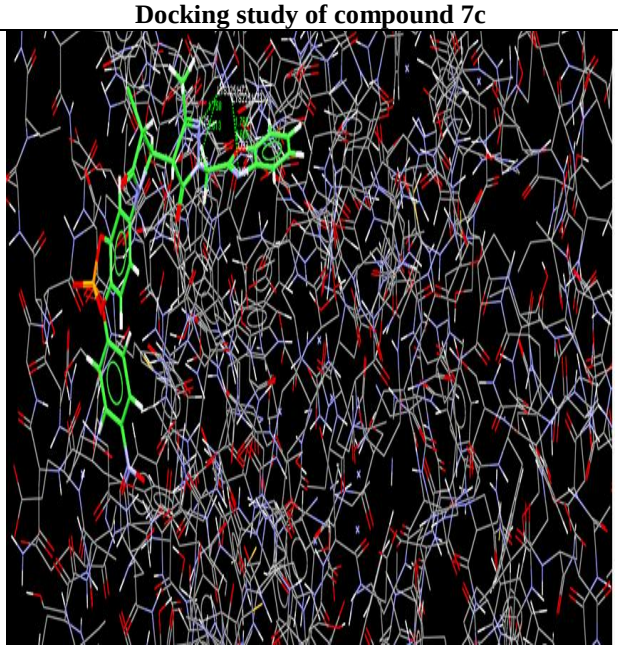
Docking study of compound 7b



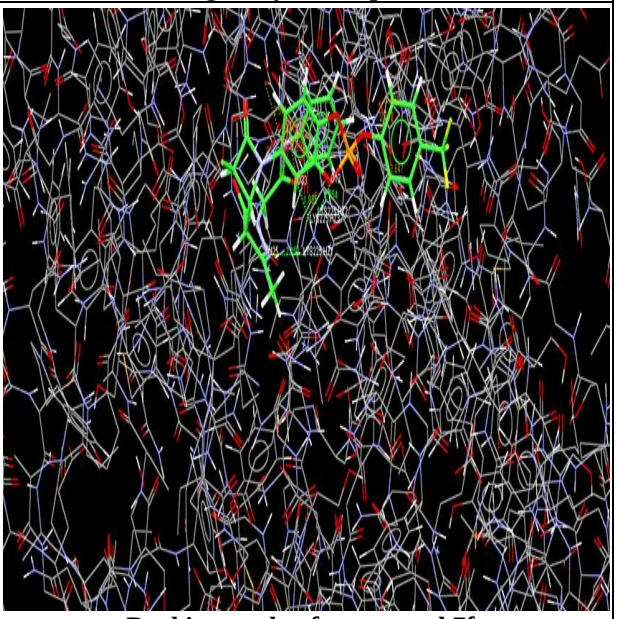
Docking study of compound 7c



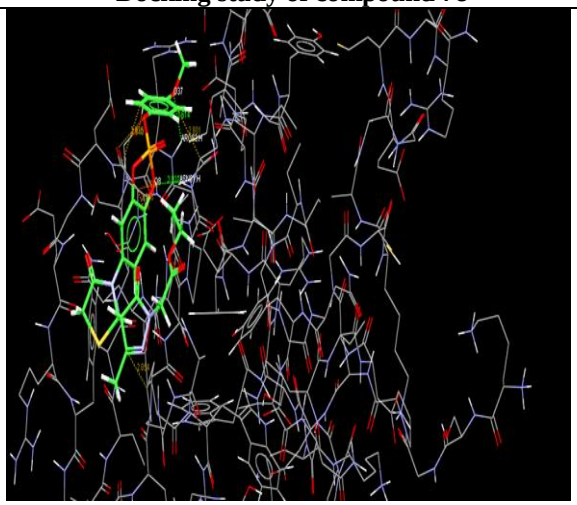
Docking study of compound 7d



Docking study of compound 7e



Docking study of compound 7f



Docking study of compound 7g

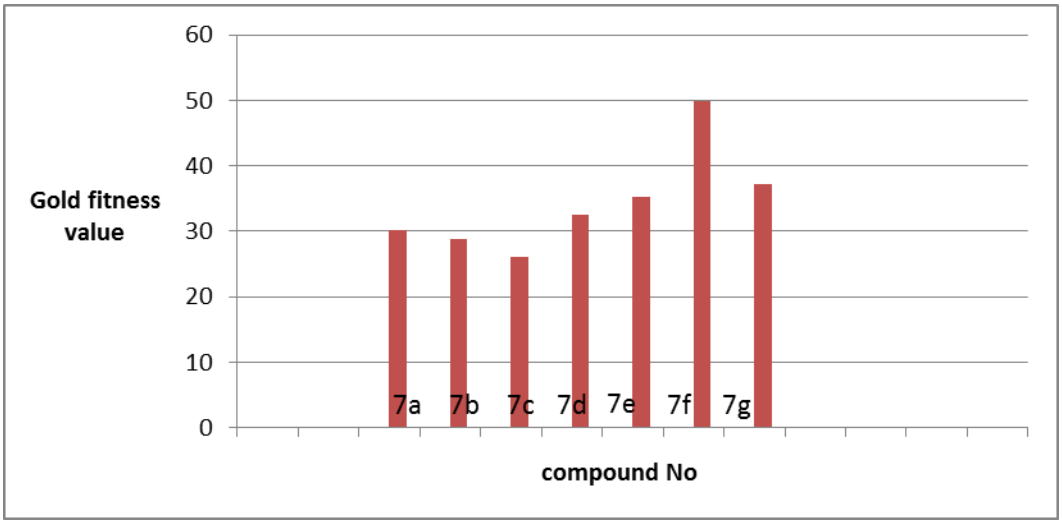


Fig. 3: Comparative Gold Score Fitness values for compound(7a-g).

Table-3: Docking results of (7a-g) on B-cell lymphoma (Bcl-2) protein.

Comp	R	Fitness	S(Hb_ext)	S(vdw_ext)	0.00	S(vdw_int)
7a	H	30.10	4.45	19.8	0.00	-3.10
7b	CH_3	28.75	4.05	18.6	0.00	-2.70
7c	OCH_3	26.10	3.80	17.10	0.00	-1.60
7d	Cl	32.50	5.00	22.65	0.00	-3.50
7e	F	35.23	6.00	24.91	0.00	-3.95
7f	NO_2	49.88	9.42	29.52	0.00	-4.73
7g	CF_3	37.23	12.10	27.70	0.00	-5.01

Table-4: Hydrogen bonding interactions of Compounds(7a-g) with B-cell lymphoma (Bcl-2).

Comp No	R	No of 'H' Bonds	Compounds		Bond Length (A^o)	Fitness
			Protein	Atoms		
7a	H	2	ARG26:PDB1H ASN34H	O:P=O(13) O:Azitidinone (2)	2.017 2.332	30.10
7b	CH_3	2	ARG26:PDB1H ASN34H	O:P=O(13) O:Azitidinone (2)	2.0 2.2	28.75
7c	OCH_3	2	ARG26:PDB1H ASN34H	O:P=O(13) O:Azitidinone (2)	1.9 2.0	26.10
7d	Cl	2	THR32:OG1 LEU33H	O:P=O(13) O:Azitidinone (2)	2.2 2.0	32.50
7e	F	2	THR32:OG1 LEU33H	O:P=O(13) O:Azitidinone (2)	2.5 2.3	35.23
7f	NO_2	3	ARG26:PDB1H ASN34H THR32:PDB3H	O:P=O(13) O:Azitidinone (2)	2.231 2.601 2.663	49.88
7g	CF_3	2	THR32:OG1 LEU33H	O:P=O(13) O:Azitidinone (2)	2.560 2.592	37.23

The results of docking study of newly synthesized derivatives of 3-chloro-4-(2-oxido-2-(4-substituted phenyl) benzo [d] [1,3,2] dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidine-2-one reveals that all the compounds are having good interaction in favourable pose with B-cell lymphoma(Bcl-2) protein. Among seven derivatives of 3-chloro-4-(2-oxido-2-(4-substituted phenyl) benzo [d] [1,3,2] dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidine-2-one, one derivatives (7f) showed better activity.

CONCLUSION

In current research work, few analogues of 3-chloro-4-(2-oxido-2-(4-substituted phenyl) benzo [d] [1,3,2] dioxaphosphol-5-yl)-1-(quinolin-6-yl)azetidine-2-one were successfully prepared and characterized. Biological activity and docking studies of these compounds were also conducted.

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