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Synthesis, Characterization and Antimicrobial Evaluation and molecular docking studies of 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-4-substituted phenoxy)-benzo[d] [1,3,2] dioxaphosphol-2-oxide

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Abstract

5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-4- substituted phenoxy)benzo[d] [1,3,2] dioxaphosphol-2-oxide (7a-g) were synthesized by condensing 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols(5) with 4-substituted phenyl phosphorodichloridates(6a-g). The synthon (5) was synthesized by hydrolysis of 2-(3,4-dimethoxy phenyl)-5-(quinolin-4-yl)-1,3,4-oxadiazole (4). The intermediate (4) was synthesized by condensing quinoline-4-carbohydrazide(2) with 3,4-dimethoxy benzoic acid(3). Starting intermediate (2) was synthesized by condensation reaction between ethyl quinoline-4-carboxylate (1) and hydrazine hydrate, ethanol. The reagent and conditions were shown in a,b,c and d. The synthetic route was shown in **scheme-I**. 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. The results observed in the present investigation were reported in the present research article.

KEYWORDS : Quinoline-4-carbohydrazide, 3,4-dimethoxy benzoic acid, 4-substituted phenyl phosphodichloridates, target molecule, Biological evaluation, molecular docking..

INTRODUCTION

Phosphorus chemistry has pioneered the application of nano[1] and combinatorial techniques in the development of new pharmaceutical material with novel properties. Due to the numerous commercial applications of organo phosphoruscompounds, there is an impressive progress in the study of phosphorus chemistry in recent years. Several organo phosphorus compounds compounds have been synthesized to be used as insecticides[2], herbicides, fungicides, plant growth regulators, biological activity against broad spectrum of the bacteria and different kinds of pests and virus. organophosphorus pesticides when compared to other chemical class of pesticides are relatively safe and eco-friendly as they are easily degradable in environment after discharging their functions as pesticides. Further, the residues in water and soil act as fertilizers and nutrients.

1,3,4-oxadiazoles and its derivatives are associated with a variety biological activities[2]. 1,3,4-oxadiazoles are very important class of compounds possessing wide range of biological activities such as antimicrobial [3], antifungal [4], anti-inflammatory [5],anticonvulsant [6], antioxidant, analgesic [7] and mutagenic activities [8]. 1,3,4-oxadiazoles are used as catalyst in the synthesis of phosphonates. Thus different 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-4- substituted phenoxy)benzo[d] [1,3,2] dioxaphosphol-2-oxide (7a-g) were synthesized. The structures of these compounds have been established IR,^{1}H-NMR,^{13}C-NMR,^{31}P and Mass spectral studies. All the new compounds were screened for antimicrobial activity and docking studies.

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-3000 spectrometer operating at 400MH_Z for ^{1}H-NMR and 75MH_Z for ^{13}C-NMR respectively. ^{31}P-NMR spectra were recorded on a varian XL-spectrometer operating at 161.89 MH_Z. 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 of quinoline-4-carbohydrazide (2)[9] : A solution of ethyl quinoline-4-carboxylate **(1)(**2.41gr, 1.2m.mol) and hydrazine hydrate(0.07gr, 1.4m.mol), in ethanol(0.074gr, 1.6m.mol) refluxed for 5hours. The progress of the reaction was monitored by TLC using ethylacetate : acetone (9:1) as eluent. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystalised from ethanol **(2).** The m.p of (2) was found to be 222-224^{0}C with a yield of 75%, 0.015 moles. **IR (KBr pellet)** γ, cm^{-1} :Characteristic bands around 3420 & 3400 str.of γ_{-NH2} of hydrazide, 3248 str.of γ_{-NH} of hydrazide, 1660 str.of $>C=O$ group of hydrazide, 1590, 995 str. of δ_{c-c} of quinoline ring, 1450 str. of γ_{-C-N} of quinoline ring. **^{1}H-NMR (δ,ppm):** 2.10 s,2H, $-NH_2$ **,** 6.9-7.30 m,6H,C_9H_6 of quinoline ring and 9.1 s,1H,-NH- of hydrazide.

Synthesis of 2-(3,4-dimethoxy phenyl)-5-(quinolin-4-yl)-1,3,4-oxadiazole (4)[10,11] :

A mixture of 3,4-dimethoxy benzoic acid (2.19gr, 0.012m.mol) with compound **(2**)(1.87gr, 10m.mol) in phosphoryl chloride(15ml) was refluxed over a steam bath for 5-6hrs. The progress of the reaction was monitored by TLC using ethylacetate : acetone(9:1) as eluent. The reaction mixture was cooled and poured on to crushed ice (~200g) with continuous stirring . The solid mass seperated with continuous stirring. The solid mass neutralised with sodium bicarbonate solution (10% w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried in vaccum and recrystalized from absolute ethanol.. The m.p of (4) was found to be 153-155^{0}c with a yield of 70%, 0.012 moles. The separated solid was identified as 2-(3,4-dimethoxy phenyl)-5-(quinolin-4-yl)-1,3,4-oxadiazole (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, 1450 str. of γ_{-C-N} of quinoline ring, 1614, 1148, 1132

str.of 1,3,4-oxadiazole, 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.

Synthesis of 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols (5)[12]: A solution of 2-(3,4-dimethoxy phenyl)-5-(quinolin-4-yl)-1,3,4-oxadiazole **(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 chromate graphy (elutent Petrolium ether**:** Ethyl acetate 8:2 solvent mixture as an elutent to give the 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols **(5)**. The m.p. of **(5)** was found to be 163-165°C, with a yield of 75%, 0.015moles. **IR (KBr pellet)** γ, cm^{-1} : Characteristic 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, 1450 str. of γ_{-C-N} of quinoline ring, 1614, 1148, 1132 str.of 1,3,4-oxadiazole. **^{1}H-NMR (δ,ppm):** 5.6 s,2H, two –OH groups, 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 (7a-g)[13] : 4-substituted phenyl phosphodichloridated **(7a-g)** were synthesized as reported in the literature.

General procedure for the synthesis of 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-2- 4-substituted phenoxy)-benzo[d] [1,3,2] dioxaphosphol-2-oxide [14] 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 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols (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 50-60^{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(7a). The m.p. of **(7a)** was found to be 130-132°C with a yield of 60%,

0.012moles. The separated solid was identified as 2-phenoxy -5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzo[d][1,3,2] dioxaphosphol 2-oxide **(7a).**

The similar procedure was adopted to synthesize (7a-g) by the reaction between of 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols (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:130-132^{0}C. Anal. Found for $C_{23}H_{14}N_3O_5P$ (%): C 61.01, H 3.12, N 9.41 and P 6.87. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1614, 1148, 1132 str.of 1,3,4-oxadiazole, 1250 str.of P=O, 950 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 6.9-7.3 m,14H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_5 of benzene ring. ^{13}C-NMR(δ,ppm): 152.2, 111.9, 143.7, 124.0, 127.0, 129.9, 128.9, 152.5, 123.1, 120.1, 114.3, 125.7, 146.2, 117.8, 108.9, 124.5, 120.3, 130.1, 121.3 and 123.6 corresponding C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}&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): -7.3. Mass (m/z %) : 443.07 $\overline{M}^{+\cdot}$.

7b: Yield :65%. m.p:159-161^{0}C. Anal. Found for $C_{24}H_{16}N_3O_5P$ (%): C 61.82, H 3.47, N 9.12 and P 6.68. IR, KBr pellet (γ, cm^{-1}) : 3025 str. of Aromatic proton of benzene ring, 1615, 1149, 1133 str.of 1,3,4-oxadiazole, 1245 str.of P=O, 945 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 2.30 s, 3H, Ar-CH_3, 6.9-7.3 m,13H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_4 of benzene ring.^{31}P-NMR (δ,ppm): -7.6.

7c: m.p: Yield :70%. 136-138^{0}C. Anal. Found for $C_{24}H_{16}N_3O_6P$ (%): C 59.69, H 3.35, N 8.81 and P 6.42. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1615, 1149, 1134 str.of 1,3,4-oxadiazole, 1255 str.of P=O, 960 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 3.80 s, 3H, Ar-OCH_3, 6.9-7.3 m,13H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_4 of benzene ring.^{31}P-NMR (δ,ppm): -7.9.

7d: Yield :60%. m.p:151-153^{0}C. Anal. Found for $C_{23}H_{13}ClN_3O_5P$ (%): C 58.62, H 2.68,

N 8.42 Cl 7.41 and P 6.39. IR, KBr pellet (γ, cm^{-1}) : 3035 str. of Aromatic proton of benzene ring, 1620, 1155, 1137 str.of 1,3,4-oxadiazole, 1253 str.of P=O, 955 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 7.0-7.3 m,14H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_4 of benzene ring. ^{31}P-NMR (δ,ppm): -6.7.

7e: Yield :65%. m.p:126-128^{0}C. Anal. Found for $C_{23}H_{13}FN_3O_5P$ (%): C 58.68, H 2.78,

N 9.94 F 3.98, P 6.61. IR, KBr pellet (γ, cm^{-1}) : 3035 str. of Aromatic proton of benzene ring, 1617, 1150, 1135 str.of 1,3,4-oxadiazole, 1253 str.of P=O, 955 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 7.1-7.4 m,14H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_4 of benzene ring. ^{31}P-NMR (δ,ppm): -6.3.

7f: Yield : Yield :66%. m.p:165-167^{0}C. Anal. Found for $C_{23}H_{13}N_4O_7P$ (%): C 55.27, H 2.62, N 11.39 P 6.24. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1620, 1156, 1135 str.of 1,3,4-oxadiazole, 1260 str.of P=O, 965 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 7.1-7.4 m,14H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_4 of benzene ring. ^{31}P-NMR (δ,ppm): -5.9.

7g: Yield :72%. m.p:145-147^{0}C. Anal. Found for $C_{24}H_{13}F_3N_3O_5P$ (%): C 55.17, H 2.49, N 8.15 P 5.98 and F 11.02. IR, KBr pellet (γ, cm^{-1}) : 3040 str. of Aromatic proton of benzene ring, 1617, 1158, 1137 str.of 1,3,4-oxadiazole, 1270 str.of P=O, 970 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 7.0-7.4 m,13H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_4 of benzene ring. ^{31}P-NMR (δ,ppm): -6.5.

RESULT AND DISCUSSION

The synthetic route followed for the synthesis of 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-2-4-substituted phenoxy)-benzo[d] [1,3,2] dioxaphosphol-2-oxide is presented in scheme-1.

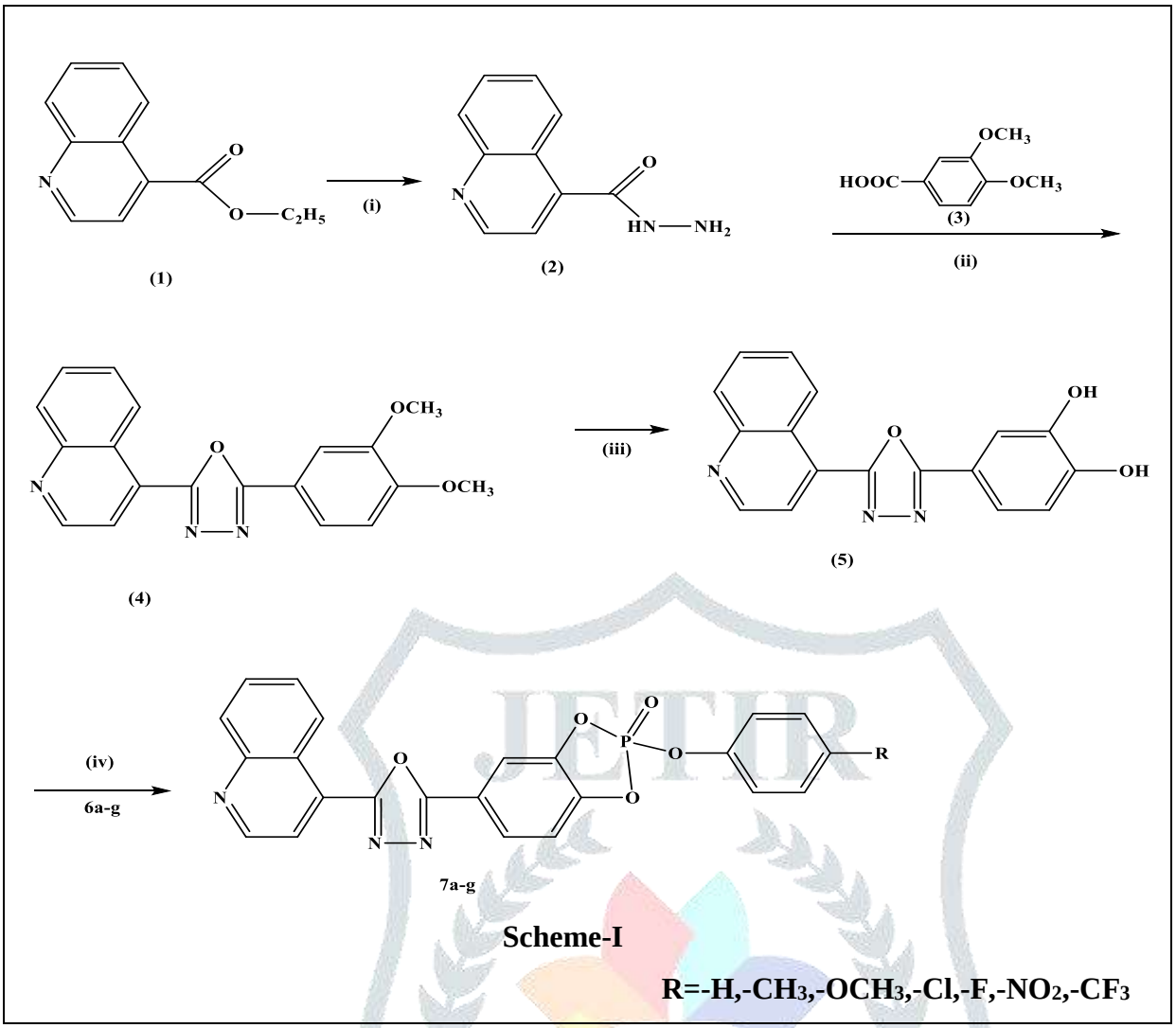
Quinoline-4-carbohydrazide (2) was synthesized by condensation reaction between ethyl quinoline-4-carboxylate(1) and hydrazine hydrate, ethanol. The IR spectra of quinoline-4-carbohydrazide (2) exhibited bands around 3420 & 3400 str.of γ_{-NH2} of hydrazide, 3248 str.of γ_{-NH} of hydrazide, 1660 str.of $>^{c=o}$ group of hydrazide, 1590, 995 str. of δ_{c-c} of quinoline ring, 1450 str. of γ_{C-N} of quinoline ring. **^{1}H-NMR (δ,ppm):** 2.10 s,2H, $-NH_2$ **,** 6.9-7.30 m,6H,C_9H_6 of quinoline ring and 9.1 s,1H,-NH- of hydrazide, Confirming the structure of compound (2).

2-(3,4-dimethoxy phenyl)-5-(quinoline-4-yl)-1,3,4-oxadiazole (4) was synthesized by condensing quinoline-4-carbohydrazide (2) and 3,4-dimethoxy benzoic acid (3). The IR spectra of 2-(3,4-dimethoxy phenyl)-5-(quinoline-4-yl)-1,3,4-oxadiazole (4) exhibited bands around 3040 str. of Aromatic proton of

benzene ring, 1590, 995 str. of δ_{c-c} of quinoline ring, 1450 str. of γ_{-C-N} of quinoline ring, 1614, 1148, 1132 str.of 1,3,4-oxadiazole, 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, confirming the structure of compound (4).

4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols **(5)** was synthesized by hydrolysis of 2-(3,4-dimethoxy phenyl)-5-(quinoline-4-yl)-1,3,4-oxadiazole (4). The IR spectra of 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols **(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, 1450 str. of γ_{-C-N} of quinoline ring, 1614, 1148, 1132 str.of 1,3,4-oxadiazole. **^{1}H-NMR (δ,ppm):** 5.6 s,2H, two –OH groups, 6.9-7.3 m,9H,C_9H_6 of quinoline ring and C_6H_3 of benzene ring.

2-phenoxy -5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzo[d][1,3,2] dioxaphosphol 2-oxide **(7a-g)** were synthesized by condensing 4-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzene-1,2,-diols with 4-substituted phenyl phosphorodichloridates(6a-g). The IR spectra of 2-phenoxy -5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)benzo[d][1,3,2] dioxaphosphol 2-oxide (7a) exhibited bands around 3040 str. of Aromatic proton of benzene ring, 1614, 1148, 1132 str.of 1,3,4-oxadiazole, 1250 str.of P=O, 950 str.of P-O-$C_{(-Ar)}$. ^{1}H-NMR (δ,ppm): 6.9-7.3 m,14H,C_9H_6 of quinoline ring and C_6H_3 and C_6H_5 of benzene ring, 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

Reagent & Conditions :

i) Hydrazine hydrate,C_2H_5OH,5hrs ii) 3,4-dimethoxy benzoic acid/phosphoryl chloride/ 5-6 hrs iii)Boron tri bromide/MDC iv) Phenyl phosphodichloridate/TEA/Toluene/THF.

Biological activity : The antimicrobial activity[15-17] 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[18]) of 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-2- 4-substituted phenoxy)-benzo[d] [1,3,2] dioxaphosphol-2-oxide(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	13	09	09	08
2	7b	12	08	08	07
3	7c	11	07	07	06
4	7d	14	12	10	09
5	7e	15	13	11	10
6	7f	18	16	14	13
7	7g	16	14	12	11
Amoxicillin		21	27	24	22

Antifungal activity: Antifungal activity of final compounds 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-2-4-substituted phenoxy)-benzo[d] [1,3,2] dioxaphosphol-2-oxide **(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	11	09
2	7b	10	08
3	7c	09	07
4	7d	12	10
5	7e	13	11
6	7f	16	14
7	7g	14	12
Ketoconazole		22	25

The order of anti-bacterial and anti-fungal activity was found to be

(7f > 7g > 7e > 7d > 7a > 7b > 7c).

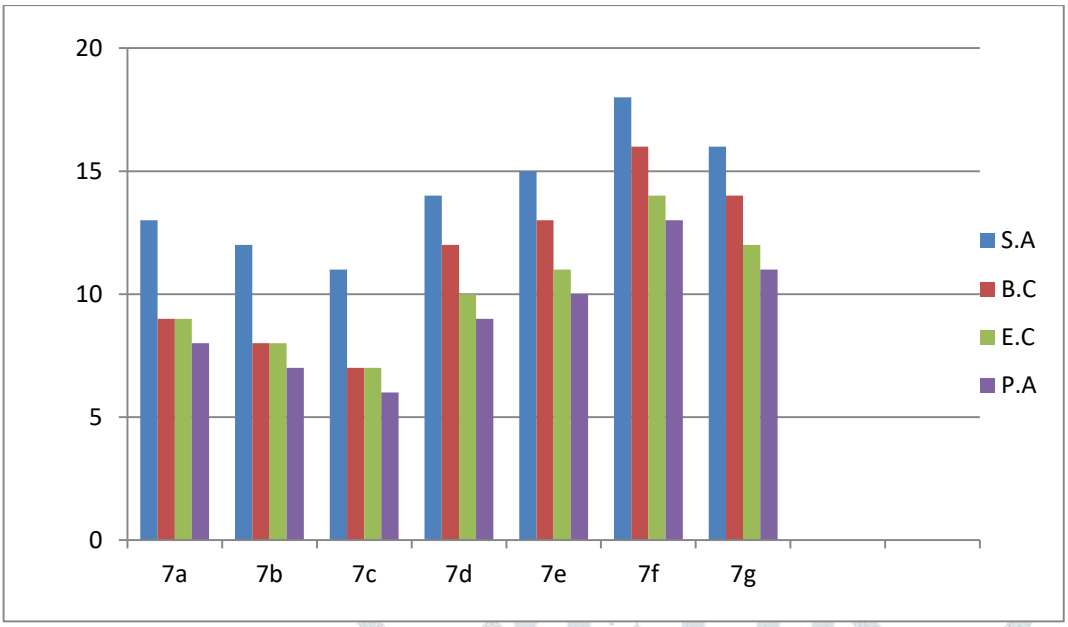


Fig.1.Antibacterial activity of compound 7(a-g)

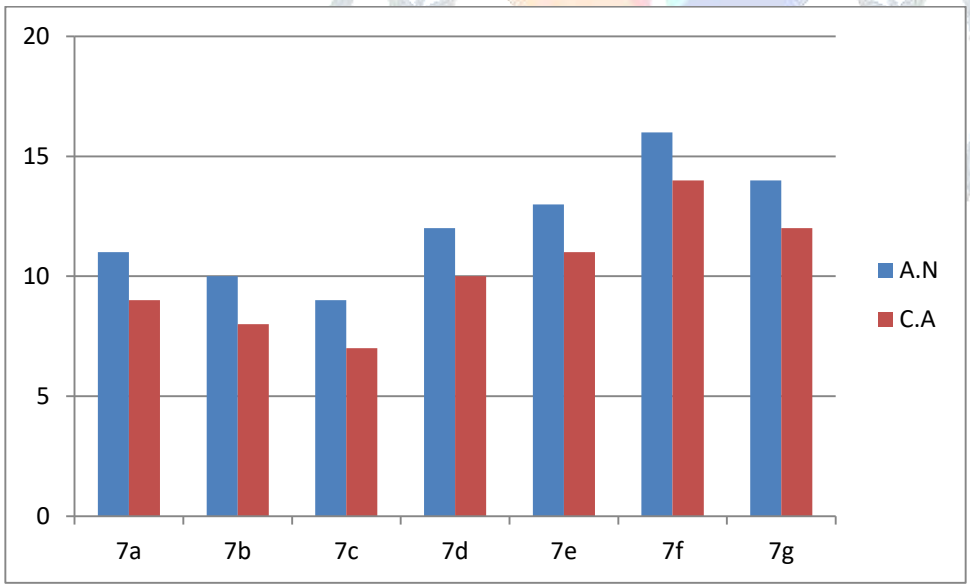


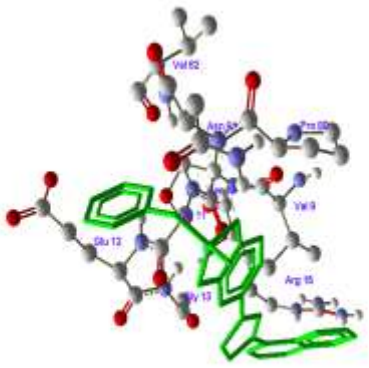
Fig.2. Antifungal activity of compounds (7a-g)

Docking study

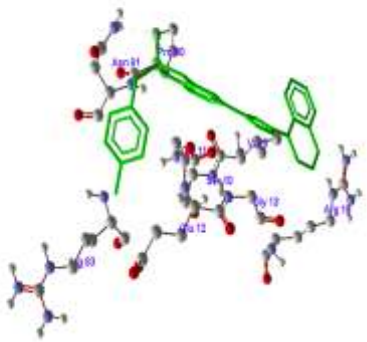
Docking[19] of the inhibitors (synthesized compounds from **(7a-g)** with Phytase[20] domain was performed using GOLD 3.0.1, which is based on Genetic algorithm(GA). The docking studies of **(7a-g)** were carried out on Phytase protein. The docking ligands were found to have some interactions between an oxygen

atom of the ligands and Phytase 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 ARG26,PDB3H,, LYS22,HIS184,TYR127 order of protein-ligand hydrogen bond score is mentioned in the table**.** 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 **7g >7c>7f>7b>7d>7a>7e** with the protein. However the ligands fail to exhibit minimum intramolecular strain. Finally, all the ligands exhibits moderate to good antifungal activity with Phytase protein. The order of gold score fitness value of the ligands is found to be **7d >7b>7a>7f>7e>7g>7c.** According to gold score fitness value ligand **7d** 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



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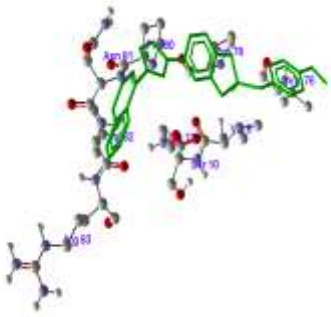

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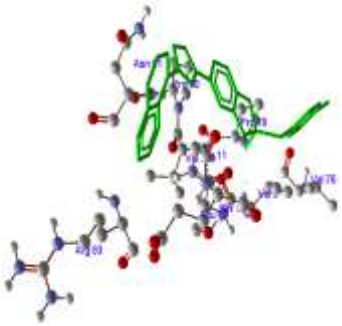

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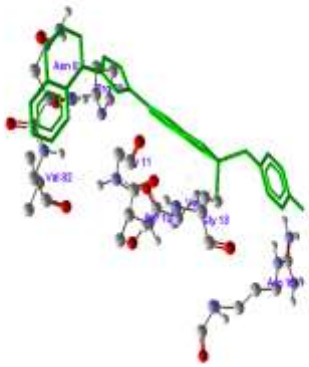

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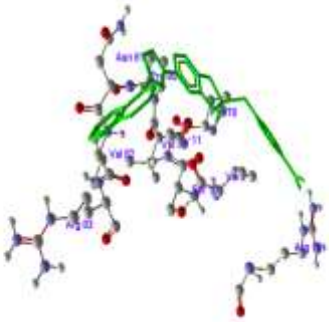
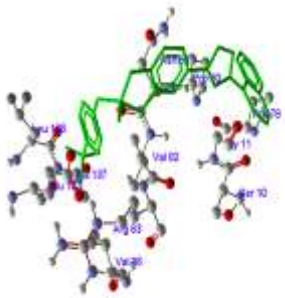


Docking study of compound 7f



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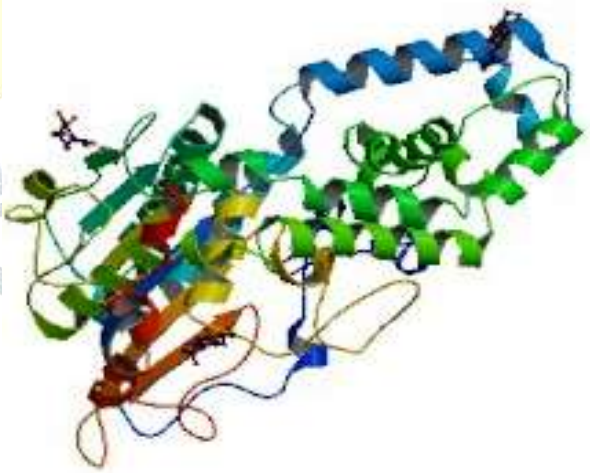

Structure of Protein phytase

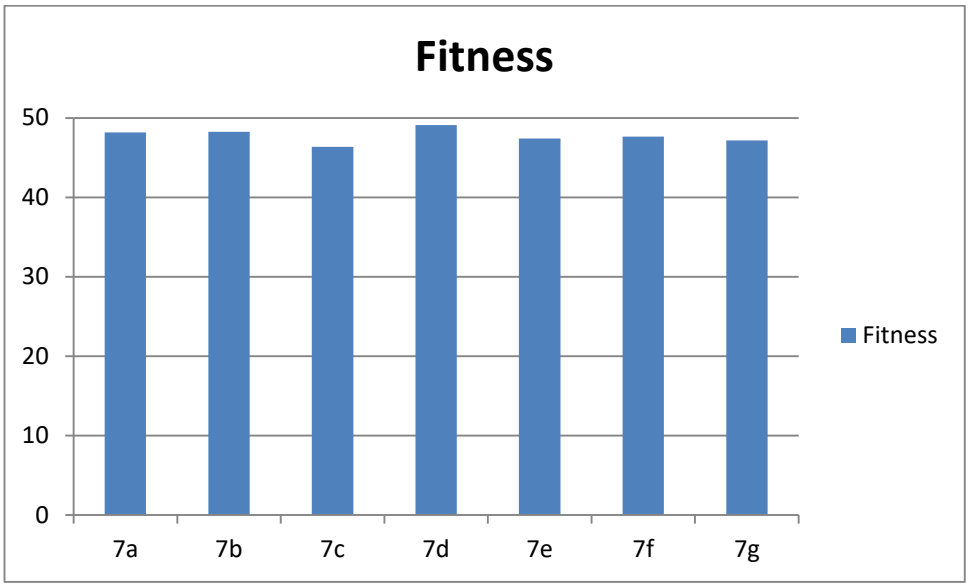

Fig:.3. Comparative Gold Score Fitness values for compound(7a-g)

Table-3: Docking results of (7a-g) on 1,3,4-oxadiazole on-Phytase protein

Comp	R	Fitness	S(Hb_ext)	S(vdw_ext)	0.00	S(vdw_int)
7a	H	48.17	5.01	33.28	0.00	-2.60
7b	CH_3	48.24	4.94	34.11	0.00	-3.61
7c	OCH_3	46.34	0.00	37.86	0.00	-5.72
7d	Cl	49.08	4.94	34.03	0.00	-2.66
7e	F	47.41	5.31	32.43	0.00	-2.49
7f	CF_3	47.66	2.78	35.89	0.00	-4.47
7g	NO_2	47.14	0.00	37.78	0.00	-4.81

Table-4: Hydrogen bonding interactions of Compounds(7a-g) with Catalase-peroxodase

Comp No	R	No of 'H' Bonds	Compounds		Bond Length (A°)	Fitness
			Protein	Atoms		
7a	H	2	ARG26:PDB3H LYS22	O:P=O(20) O: of oxadiazoles	1.90 1.98	48.17
7b	CH_3	2	ARG26:PDB3H LYS22	O:P=O(20) O: of oxadiazoles	1.80 1.90	48.24
7c	OCH_3	2	ARG26:PDB3H LYS22	O:P=O(20) O: of oxadiazoles	1.75 1.86	46.34
7d	Cl	2	HIS 184 TYR 127	O:P=O(20) O: of oxadiazoles	1.98 2.10	49.08

7e	F	2	HIS 184 TYR 127	O:P=O(20) O: of oxadiazoles	2.05 2.17	47.41
7f	CF_3	2	ARG26:PDB3H TYR 127	O:P=O(20) O: of oxadiazoles	2.42 2.234	47.66
7g	CF_3	2	ARG26:PDB3H TYR 127	O:P=O(20) O: of oxadiazoles	2.38 2.230	47.14

CONCLUSION

In current research work, few anologues of 5-(5-(quinolin-4-yl)-1,3,4-oxadiazol-2-yl)-2- 4-substituted phenoxy)-benzo[d] [1,3,2] dioxaphosphol-2-oxide **(7a-g)** were successfully prepared and characterized. Biological activity and docking studies of these compounds were also conducted.

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