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Synthesis, characterization, antimicrobial evaluation and docking studies of 3-(5-(2-oxido)-(4-substituted phenoxy)-benzo[d]dioxaphosphole-tetrazol-thiophene-2-carboxamides

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Abstract
3-(5-(2-oxido)-(4-substitutedphenoxy)-benzo[*d*][1,3,2]dioxaphosphol-5-yl)-1*H*-tetrazol-1-yl)thiophene-2-carboxamides(9a-g) were synthesized by condensing 3-(5-(3,4-dihydroxyphenyl)-1*H*-tetrazol-1-yl)thiophene-2-carboxamide (7) with 4-substituted phenyl phosphoro dichloridates (8a-g). The synthon (7) was synthesized by hydrolysis of 3-(5-(3,4-dimethoxyphenyl)-1*H*-tetrazol-1-yl)thiophene-2-carboxamide (6). The intermediate (6) was synthesized by condensing 3-((3,4-dimethoxy benzylidine)amino)thiophene-2-carboxamide (5) with sodium azide in Tetrahydrofuron. The synthon (5) was synthesized by reaction between 3-aminothiophene-2-caroxamide (3) and 3,4-dimethoxybenzaldehyde (4). Starting intermediate (3) was synthesized by condensation reaction between 2-cyano acetamide (1) and 1,4-dithiane-2,5-diol (2). The reagents and conditions were shown in a, b, c, d and e. The synthetic route was shown in Scheme-I.
The target molecules (9a-g) were characterized by IR, ^{1}HNMR, ^{13}C-NMR, Mass and elemental analysis. The target molecules were subjected to biological evaluation and molecular docking studies. The results observed in the present investigation were reported in this present research article.

Keywords: sodium azide, 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 phosphorus compounds, there is an impressive progress in the study of phosphorus chemistry in recent years. Several organo phosphorus compounds have been synthesized to be used as insecticides [2], herbicides [2, 3], fungicides [2, 4], plant growth regulators [3], biological activity against broad spectrum of the bacteria and different kinds of pests and virus [5, 6]. Organo phosphorus 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 residue in water and soil act as fertilizers and nutrients.
Tetrazoles and its derivatives are associated with a variety biological activities such as antifungal [7], antinociceptive [8-9], anti convulsant [10], antidiabetic [11], cyclo-oxygenase inhibitors [12], hypoglycaemic [13], antibacterial [14] and anti-inflammatory [15] activities. Tetrazoles are used as catalysts in the synthesis of phosphonates. Thus different (4-substituted phenoxy)-benzo[d]dioxaphosphol-1*H*-tetrazol-thiophene-2-carboxamides (9a-g) were synthesized. The structures of these compounds have been established by IR, ^{1}HNMR, ^{13}C-NMR, P^{31} 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 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 ^{1}H and ^{13}C-NMR spectra were recorded on a Varian XL-3000 spectrometer operating at 400MHz for ^{1}H-NMR and 75MHz for ^{13}C-NMR. ^{31}P-NMR spectra were recorded on a Varian XL-spectrometer operating at 161.89MHz. 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.

Results and Discussion

Proposed synthetic scheme for the preparation of (9a-g) was reported in 5 steps and presented in the Scheme-I.

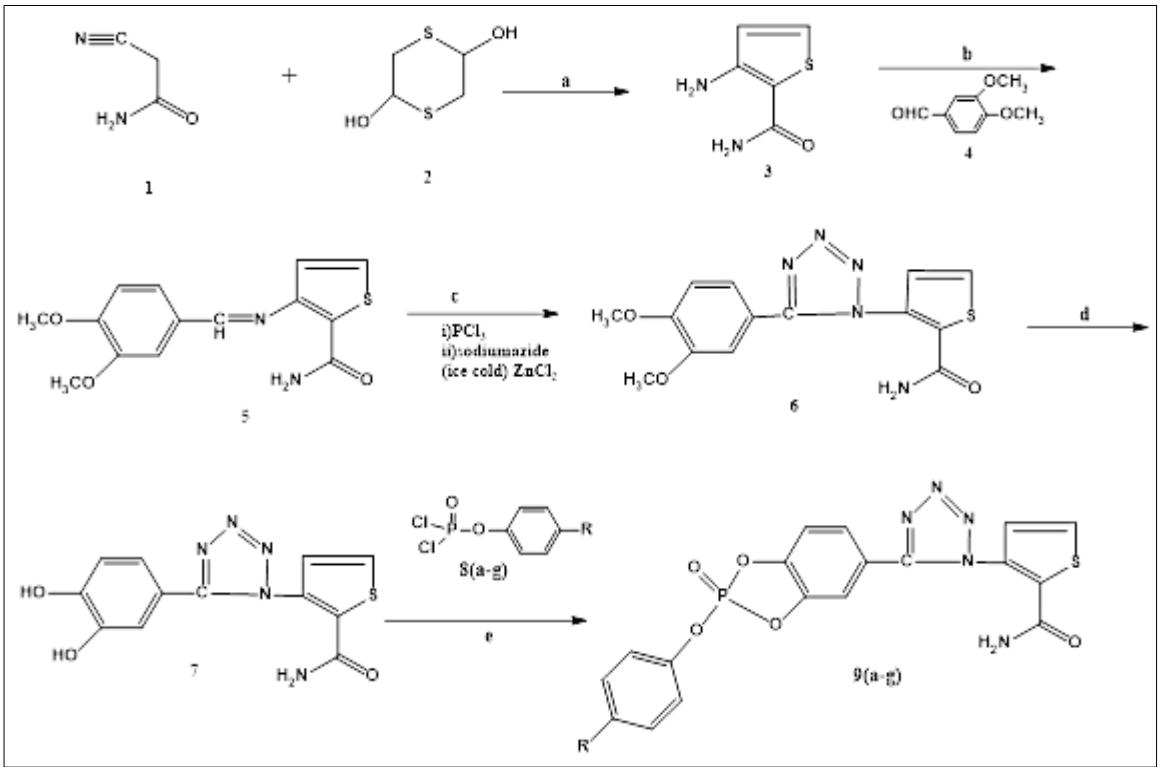

Fig 1: Scheme 1

Compound 9	a	b	c	d	e	f	g
R	-H	-CH3	-F	-Cl	-Br	-CF3	-NO2

Synthesis of 3-aminothiophene-2-carboxamide (3) [16, 17]

A solution of 2-cyano acetamide (1, 0.02 moles), 2,5-dihydroxy-1,4-dithiane (2, 0.025 moles) in ethanol (50 ml) was refluxed in the presence of catalytic amount of triethyl amine for 8 hours. The reaction was monitored by TLC using alumina as an adsorbent and 7:3 solvent mixture of n-hexane-ethyl acetate as an elutent. After the completion of reaction, the solvent was evaporated under reduced pressure and the reaction mass kept at room temperature. The isopropyl alcohol was added and maintained the reaction mass at room temperature for 1 hour. The solid was filtered and washed the wet material with isopropyl alcohol and dried under suction. The residue was recrystallized from 2-propanol. The m.p. of (3) was found to be 122-124 ◦C with a yield of 75%, 0.015 moles. The separated solid was identified as 3-aminothiophene-2-carboxamide (3). IR (KBr pellet), γ, cm^{-1}: Characteristic bands around 3400 and 3420 (str. of amide group), 3330, 3345 str. of amine group, 3020 str. of Aromatic proton of thiophene ring, 1670 str. of $-\overset{O}{\overset{\|}{C}}-$ of amide –I band and 1450, 675 characteristic bands of thiophene ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 5.20 bs 2H $-NH_2$ group of amine, 7.80 s 2H $-NH_2$ of amide group, $-\overset{O}{\overset{\|}{C}}-NH_2$ and 7.1-7.4 m 2H Aromatic protons of thiophene ring.

Synthesis of 3-((3,4-dimethoxybenzylidene)amino) thiophene-2-carboxamide(5) [18]

Equimolar quantities of 3,4-dimethoxy benzaldehyde (4, 0.02 moles) and 3-aminothiophene-2-carboxamide (3, 0.02 moles) were dissolved in absolute alcohol (50 ml). To this, three drops of acetic acid was added. The reaction mixture was heated on a steam bath for 5 hours at 100 ◦C. The reaction was monitored by TLC using Alumina as an adsorbent and 7:3 solvent mixture of n-hexane-ethyl acetate as an elutent. The reaction mixture was kept for 24hours at room temperature. The product was dried and recrystallized from warm absolute alcohol. The separated solid was identified as 3-((3,4-dimethoxybenzylidene)amino)thiophene-2-carboxamide (5). The m.p. of (5) was found to be 160-162 ◦C with a yield of

75%, 0.015 moles. IR (KBr pellet), γ, cm^{-1}: Characteristic bands around 3400 and 3420 str. of $–NH_2$ of amide, 3040 str. of Ar-H of Benzene ring and thiophene ring, 1670 str. of $—\overset{O}{\overset{\|}{C}}—$ of amide –I band, 1620 str. of -CH=N- of azomethine, 1450, 675 characteristic bands of thiophene ring and 1050 $\delta_{\text{-c-o-c-}}$ of aromatic ether. ^{1}H-NMR (DMSO-d_6) δ, ppm: 3.80 s 6H two $–OCH_3$ groups, 7.80 s 2H $-NH_2$ of amide group, $—\overset{O}{\overset{\|}{C}}—NH_2$ and 7.1-7.3 m 5H C_6H_3 and two thiophene protons and 8.30 s H C-H of azomethine group.

Synthesis of 3-(5-(3,4-dimethoxyphenyl)-*1H*–tetrazol-1-yl)thiophene-2-carboxamide(6) [19, 20]

The compound 3-((3,4-dimethoxybenzylidene)amino)thiophene-2-carboxamide (5) was converted to 3-(5-(3,4-dimethoxyphenyl)-*1H* –tetrazol-1-yl)thiophene-2-carboxamide (6) on treatment with PCl_5, sodium azide in Tetrahydrofuran. The reaction mixture was heated for one hour at 100 °C. The progress of the reaction was monitored by TLC with n-hexane**:** ethylacetate (7:3) as an elutent. The m.p. of (6) was found to be 123-125°C with a yield of 75%, 0.015moles. IR (KBr pellet), γ, cm^{-1}: Characteristic bands around 3400 and 3420 str. of $–NH_2$ of amide group, 3040 str. of Ar-H of Benzene ring and thiophene ring, 1670 str. of $—\overset{O}{\overset{\|}{C}}—$ of amide –I band, 1450 and 675 characteristic bands of thiophene ring, 1415 stretching of C-N of tetrazole ring, 1050 $\delta_{\text{-c-o-c-}}$ of aromatic ether and 1157, 2120 cm^{-1} due to stretching vibrations of tetrazole and azide respectively. ^{1}H-NMR (DMSO-d_6) δ, ppm: 3.80 s 6H two $–OCH_3$ groups, 7.80 s 2H $-NH_2$ of amide group, $—\overset{O}{\overset{\|}{C}}—NH_2$ and 6.90-7.3 m 5H C_6H_3 and two thiophene protons.

Synthesis of 3-(5-(3,4-dihydroxyphenyl)-1*H*–tetrazol-1-yl) thiophene-2-carboxamide (7) [21]

A solution of 3-(5-(3,4-dimethoxyphenyl)-1*H*-tetrazp;-1-yl)thiophene-2-carboxamide (6, 0.02 moles) was dissolved in 30ml CH_2Cl_2 under N_2 and boron tri bromide (2.4ml, 0.025 moles) was added at -78 °C. The mixture was warmed 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 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 (elutent Petrolium ether**:** Ethyl acetate 8:2) to give the product 3-(5-(3,4-dihydroxyphenyl)-*1H*–tetrazol-1-yl)thiophene-2-carboxamide(7)**.** The m.p. of (7) was found to be 163-165 °C, with a yield of 75%, 0.015 moles.

IR (KBr pellet), γ, cm^{-1}**:** Characteristic bands around 3350 cm^{-1}intramolecular hydrogen bonding str. of -OH, 3400 and 3420 str. of $–NH_2$ of amide group, 3040 str. of Ar-H of Benzene ring and thiophene ring, 1670 str. of $—\overset{O}{\overset{\|}{C}}—$ of amide –I band, 1450 & 675 characteristic bands of thiophene ring, 1415 str. of C-N of tetrazole ring and 1157 cm^{-1} and 2120 cm^{-1} (stretching vibrations of tetrazole and azide respectively). ^{1}H-NMR (DMSO-d_6) δ, ppm: 5.6 s 2H two -OH groups, 7.80 s 2H $-NH_2$ of amide group, $—\overset{O}{\overset{\|}{C}}—NH_2$ and 6.90-7.3 m 5H C_6H_3 and 2H of thiophene ring.

Synthesis of 4-substituted phenyl phosphorodichloridates(8a-g) [2, 22]

4-substituted phenyl phosphorodichloridates (8a-g) were synthesized as reported in the literature.

General procedure for the synthesis of 3-5-(2-oxido)-(4-substituted phenoxy)-benzodioxaphosphol-tetrazole-thiophene-2-carboxamides(9a-g) [23]

A solution of phenyl phosphorodichloridate (8a, 0.025 moles) in 25ml of dry toluene was added drop wise over a period of 20 minutes to a stirred solution of 3-(5-(3,4-dihydroxyphenyl)-1*H*–tetrazol-1-yl)thiophene-2-carboxamide (7, 0.02 moles) and triethylamine (0.04 moles) 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 °C and maintained for 4hours with stirring. The completion of the reaction was monitored by TLC analysis. Triethylamine hydrochloric acid was filtered from the 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 3-(5-(2-oxido-2-phenoxybenzo[*d*][1,3,2]dioxaphosphol-5-yl)-1*H*-tetrazol-1-yl)thiophene-2-carboxamide (9a). The m.p. of (9a) was found to be 85-87 ◦C with a yield of 60%, 0.012 moles. The separated solid was identified as 3-(5-(2-oxido-2-phenoxybenzo[*d*][1,3,2]dioxaphosphol-5-yl)-1*H*-tetrazol-1-yl)thiophene-2- carboxamide (9a).

The similar procedure was adopted to synthesize (9b-g) by the condensation reaction between 3-(5-(3,4-dihydroxyphenyl)-1*H*–tetrazol-1-yl)thiophene-2-carboxamide (7) with 4-methyl phenyl phosphorodichloridate (8b), 4-fluorophenyl phosphorodichloridate (8c), 4-chlorophenyl phosphorodichloridate (8d), 4-bromophenyl phosphorodichloridate (8e), 4-trifluoromethyl phenyl phosphorodichloridate (8f) and 4-nitrophenyl phosphorodichloridate (8g).

Spectral, physical and analytical data for the compounds (9a-g)

9a: Yield: 60%. m.p:85-87 °C. Anal. Found for $C_{18}H_{12}N_5O_5PS$ (%): C 48.22, H 2.20, N 15.21, P 6.34 and S 6.70. IR (KBr pellet), γ, cm^{-1}: 3400 & 3420 $-NH_2$ of amide group, 3040 Ar-H of Benzene ring and thiophene ring, 1670 str. of $—\overset{O}{\overset{\|}{C}}—$ of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1250 stretching frequency of P=O, 950 str. of P-O-C $_{(-Ar)}$, 1415 1138 1285 1105 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.80 s 2H -NH_2 group of amide group $—\overset{O}{\overset{\|}{C}}—NH_2$ and 7.1-7.3 m 10H C_6H_3, C_6H_5 and 2H of thiophene ring. ^{13}C-NMR (DMSO-d_6) δ, ppm: 144.3, 135.8, 129.0, 156.5, 163.5, 124.6, 114.3, 145.7, 145.2, 117.8, 123.3, 150.2, 120.3, 130.1, 121.3, 130.1, 120.3 and 162.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} respectively. The molecule has 16 non-equivalent carbon atoms. P^{31}-NMR (δ, ppm): -7.80. Mass (m/z %): 441 $\overline{M}^{\cdot+}$.

9b: Yield: 60%. m.p:96-98 °C. Anal. Found for $C_{19}H_{14}N_5O_5PS$ (%): C 49.46, H 2.43, N 14.72, P 6.25 and S 6.28. IR (KBr pellet), γ, cm^{-1}: 3390 & 3410 $-NH_2$ of amide

group, 3025 Ar-H of Benzene ring and thiophene ring, 1665 str. of —C(=O)— of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1245 stretching frequency of P=O, 945 str. of P-O-$C_{(-Ar)}$, 1410 1133 1280 1100 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 2.40 s 3H of –CH_3 group, 7.80 s 2H -NH_2 group of amide group —C(=O)—NH$_2$ and 6.9-7.3 m 9H C_6H_3, C_6H_4 and 2H of thiophene ring. P^{31}-NMR (δ, ppm): -8.20.

9c: Yield: 60%. m.p: 77-79 °C. Anal. Found for $C_{18}H_{11}FN_5O_5PS$ (%): C 46.43, H 1.86, F 3.56, N 14.58, P 6.20 and S 6.42. IR (KBr pellet), γ, cm^{-1}: 3410 & 3430 -NH_2 of amide group, 3040 Ar-H of Benzene ring and thiophene ring, 1680 str. of —C(=O)— of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1255 stretching frequency of P=O, 960 str. of P-O-$C_{(-Ar)}$, 1420 1147 1295 1115 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.80 s 2H -NH_2 group of amide group —C(=O)—NH$_2$ and 7.1-7.3 m 9H C_6H_3, C_6H_4 and 2H of thiophene ring. P^{31}-NMR (δ, ppm): -7.3.

9d: Yield: 65%. m.p: 104-106°C. Anal. Found for $C_{18}H_{11}ClN_5O_5PS$ (%): C 44.82, H 1.80, N 14.18, P 5.93, S 6.15 and Cl 6.84. IR (KBr pellet), γ, cm^{-1}: 3405 & 3420 -NH_2 of amide group, 3035 Ar-H of Benzene ring and thiophene ring, 1675 str. of —C(=O)— of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1253 stretching frequency of P=O, 955 str. of P-O-$C_{(-Ar)}$, 1417 1142 1290 1110 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.80 s 2H -NH_2 group of amide group —C(=O)—NH$_2$ and 7.10-7.3 m 9H C_6H_3, C_6H_4 and 2H of thiophene ring. P^{31}-NMR (δ, ppm): -7.5.

9e: Yield: 60%. m.p: 112-114°C. Anal. Found for $C_{18}H_{11}BrN_5O_5PS$ (%): C 40.96, H 1.58, N 12.88, P 5.40, S 5.54 and Br 12.88. IR (KBr pellet), γ, cm^{-1}: 3400 & 3425 -NH_2 of amide group, 3035 Ar-H of Benzene ring and thiophene ring, 1675 str. of —C(=O)— of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1253 stretching frequency of P=O, 955 str. of P-O-$C_{(-Ar)}$, 1417 1141 1288 1108 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.80 s 2H -NH_2 group of amide group —C(=O)—NH$_2$ and 7.10-7.3 m 9H C_6H_3, C_6H_4 and 2H of thiophene ring. P^{31}-NMR (δ, ppm): -7.5.

9f: Yield: 70%. m.p: 105-107°C. Anal. Found for $C_{19}H_{11}F_3N_5O_5$ PS (%): C 44.23, H 1.64, N 13.25, P 5.52, S 5.68 and F 10.75. IR (KBr pellet), γ, cm^{-1}: 3420 & 3447 -NH_2 of amide group, 3030 Ar-H of Benzene ring and thiophene ring, 1680 str. of —C(=O)— of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1260 stretching frequency of P=O, 965 str. of P-O-$C_{(-Ar)}$, 1420 1146 1293 1113 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.80 s 2H -NH_2 group of amide group —C(=O)—NH$_2$ and 7.10-7.3 m 9H C_6H_3, C_6H_4 and 2H of thiophene ring. P^{31}-NMR (δ, ppm): -8.4.

9g: Yield: 70%. m.p: 121-123°C. Anal. Found for $C_{18}H_{11}N_6O_7PS$ (%): C 43.86, H 1.68, N 16.72, P 5.78, S 6.02. IR (KBr pellet), γ, cm^{-1}: 3430 & 3450 -NH_2 of amide group, 3040 Ar-H of Benzene ring and thiophene ring, 1680 str. of —C(=O)— of amide –I Band, 1450 and 675 characteristic bands of thiophene ring, 1270 stretching frequency of P=O, 970 str. of P-O-$C_{(-Ar)}$, 1425 1153 1300 1120 characteristic bands of tetrazole ring. ^{1}H-NMR (DMSO-d_6) δ, ppm: 7.80 s 2H -NH_2 group of amide group —C(=O)—NH$_2$ and 7.10-7.30 m 9H C_6H_3, C_6H_4 and 2H of thiophene ring. P^{31}-NMR (δ, ppm): -9.2.

Biological activity: The antimicrobial activity [24] of newly synthesized compounds was performed according to disc diffusion method, as recommended by the National Committee for Clinical Laboratory [25]. The synthesized compounds were used at the concentration of 250µg/ml. DMF as a solvent.

Antibacterial activity: The antibacterial activity [26] of 3-5-(2-oxido)-(4-substituted phenoxy)-benzodioxaphosphol-tetrazole-thiophene-2-carboxamides (9a-g) were screened against the *Staphylococcus aureus* (gram positive), *Bacillus cereus*, *Escherichia coli* (gram negative) *and Pseudomonas aeruginosa* organisms. The compounds with substituents nitro (9g), trifluoro methyl (9f) and fluoro (9c) showed more activity than other substituted compounds. The antibacterial activity of (9a-g) was shown in the Table-1 and Fig-1. Here Amoxicillin is used as the reference compound to compare the activity.

Table 1: Antibacterial activity (Diameter zone of inhibition in mm) of compounds (9a-g) (250 µg/ml)

S. No.	Comp	Zone of inhibition (mm)			
		Staphylococcus aureus **NCCS 2079**	***Bacillus cereus*** **NCCS 2106**	***Escherichia coli*** **NCCS 2065**	***Pseudomonas aeruginosa*** **NCCS 2200**
1	9a	11	6	7	9
2	9b	9	6	7	8
3	9c	15	9	11	12
4	9d	13	8	10	11
5	9e	12	7	8	10
6	9f	16	10	12	14
7	9g	18	13	14	16
Amoxicillin		21	27	24	22

Antifungal activity: Antifungal activity of final compounds 3-5-(2-oxido)-(4-substituted phenoxy)-benzodioxaphosphol-tetrazole-thiophene-2-carboxamides (9a-g) were screened against *Aspergillus niger*, *Candida albicans* [27]. The

compounds with substituents nitro (9g), trifluoro methyl (9f) and fluoro (9c) showed more activity than other substituted compounds. The antifungal activity of (9a-g) was shown in the Table-2 and Fig-2. Here Ketoconazole is used as reference compound to compare the activity.

Table 2: Antifungal activity ((Diameter zone of inhibition in mm) of compounds (9a-g) (250µg/ml)

S. No.	Comp	Zone of inhibition (mm)	
		Aspergillius niger **NCCS 1196**	**`*Candida albicans*** **NCCS 3471**
1	9a	10	8
2	9b	8	7
3	9c	15	13
4	9d	13	11
5	9e	12	10
6	9f	17	14
7	9g	19	16
Ketoconazole		22	25

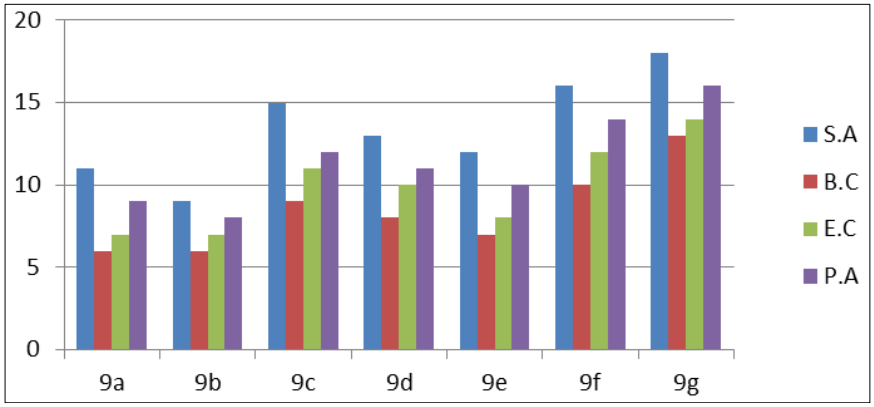

Fig 2: Antibacterial activity of compounds 9 (a-g)

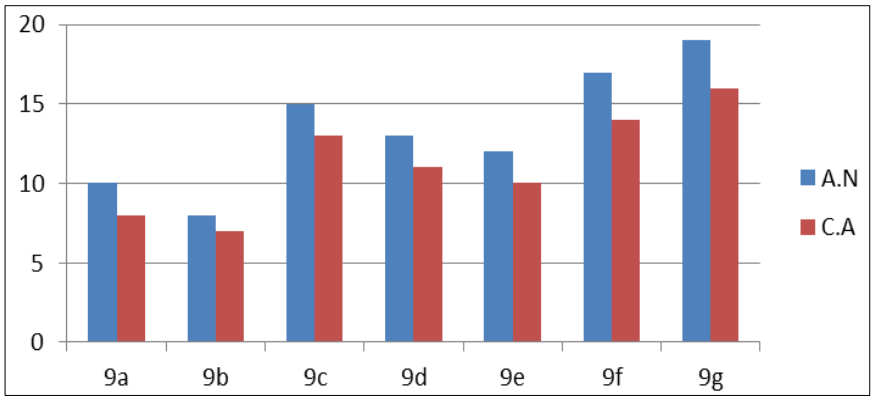

Fig 3: Antifungal activity of compounds 9 (a-g)

The order of anti-bacterial and anti-fungal activity was found to be (9g>9f >9c>9d>9e>9a>9b).

Docking studies of the compounds (9a-g)

Docking [28] of the inhibitors (synthesized compounds) from (9a-g) was carried out with Reverse Transcriptase domain using GOLD (Genetic Optimization of Ligand Docking) software 3.0.1, which is based on genetic algorithm (GA). The docking studies of (9a-g) were carried out as model compounds on HIV reverse transcriptase [29]. The docking ligands were found to have some interactions between an oxygen atom of the ligands and HIV reverse transcriptase protein. The results pertaining to Docking studies were shown in the Table-3-Table-4 and in Fig-4. Moreover, these docked conformations form 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 (9a-g). The hydrogen bondings were noticed between Arginine [15]. The order of protein-ligand vanderwaals score of interaction was found to be 9e>9b>9f>9d>9c>9a>9g with the protein. However the ligands fail to exhibit intramolecular hydrogen bonding with the ligand. The ligands exhibit minimum intramolecular strain. Finally, all the ligands exhibit moderate to good antimicrobial activity with protein. The order of gold score fitness value of the ligands is 9e>9b>9f>9d>9c>9a>9g. According to gold score fitness value ligand 9e exhibits high binding activity with the protein and ligand 9g showed least binding activity with the protein. Comparative Gold Score fitness values for (9a-g) were shown in Fig. 4.

In Gold score evaluation of docking studies, electronic interactions, bonding interactions and 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.

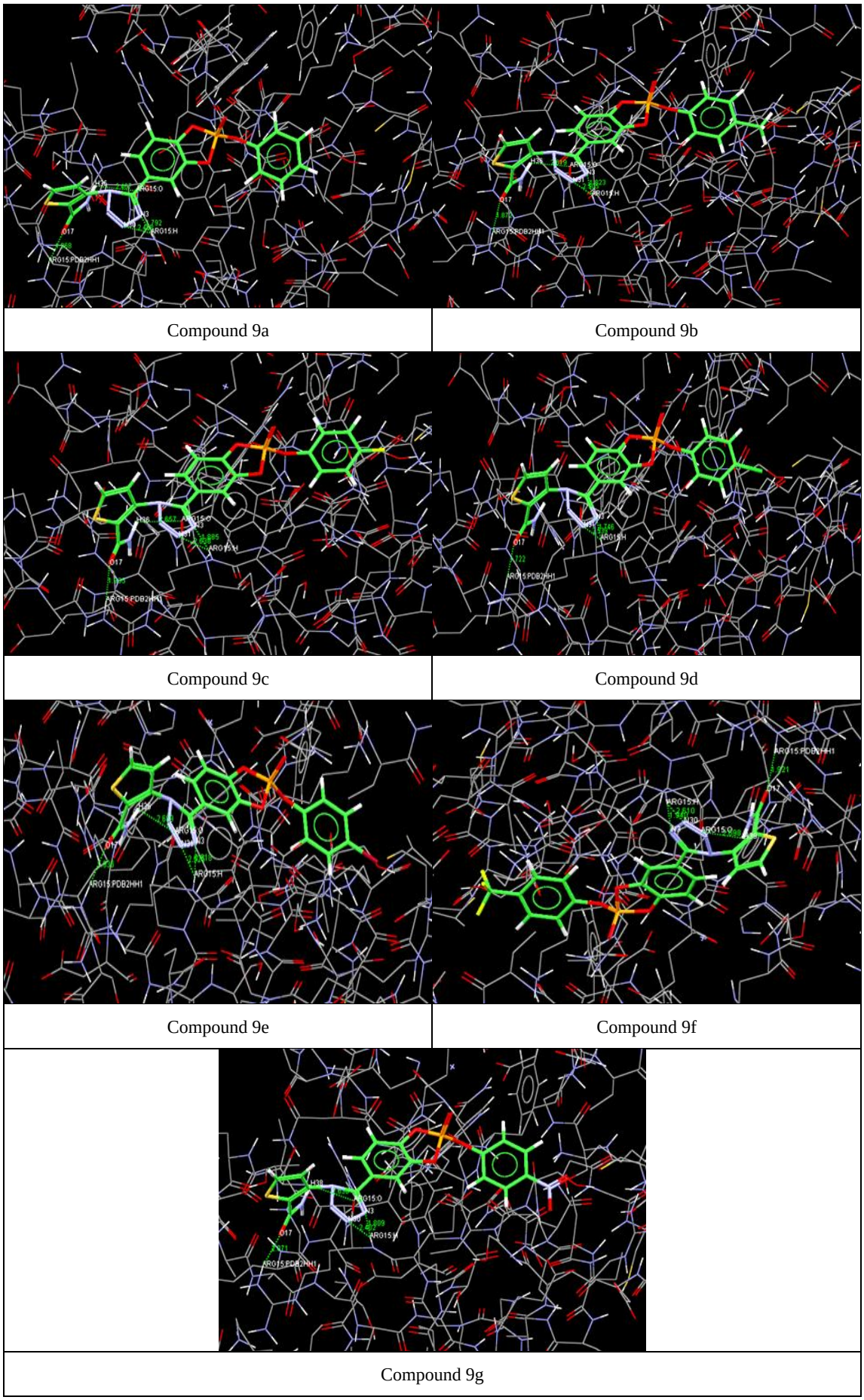

Fig 4: Docking studies of compounds (9a-g)

Table 3: Docking results of (9a-g) on HIV reverse transcriptase protein

Comp	R	Fitness	S (Hb_ext)	S(vdw_ext)	S (Hb_int)	S (vdw_int)
9a	H	46.84	0.55	36.12	0.00	-3.38
9b	CH_3	49.64	6.74	34.59	0.00	-4.66
9c	F	46.90	6.40	32.89	0.00	-4.71
9d	Cl	48.71	6.84	33.13	0.00	-3.69
9e	Br	50.47	6.64	34.64	0.00	-3.81
9f	CF_3	49.30	6.74	34.00	0.00	-4.18
9g	NO_2	45.85	1.26	36.05	0.00	-4.99

Table 4: Hydrogen bonding interactions of compounds (9a-g) with HIV reverse transcriptase

Comp No.	R	No of 'H' bonds	Compounds		Bond length (Ao)	Fitness
			Protein	Atoms		
9a	H	4	ARG15:H ARG15:H ARG15: O ARG15:PDB2HH1	N3 N30 H36 O17	1.792 2.088 2.467 1.968	46.84
9b	CH_3	4	ARG15:H ARG15:H ARG15: O ARG15:PDB2HH1	N3 N31 H36 O17	1.823 2.505 2.619 1.872	49.64
9c	F	4	ARG15:H ARG15:N31 ARG15: O ARG15:PDB2HH1	N3 N31 H36 O17	1.885 2.638 2.657 1.935	46.91
9d	Cl	3	ARG15:H ARG15:H ARG15:PDB2HH1	N3 N31 O17	1.746 2.539 3.722	48.70
9e	Br	4	ARG15:H ARG15:H ARG15: O ARG15:PDB2HH1	N3 N31 H36 O17	1.818 2.920 2.689 3.936	50.46
9f	CF_3	4	ARG15:H ARG15:H ARG15:O ARG15:PDB2HH1	N3 N30 H38 O17	1.941 2.610 2.698 4.921	49.31
9g	NO_2	4	ARG15:H ARG15:H ARG15:O ARG15:PDB2HH1	N3 N30 H38 O17	1.809 2.402 2.835 2.971	45.84

Conclusion

In current research work, few analogues of 3-5-(2-oxido)-(4-substitutedphenoxy)-benzodioxaphosphol-tetrazol-thiophene-2-carboxamides were successfully prepared and characterized. Biological activity and docking studies of these compounds were also conducted.

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