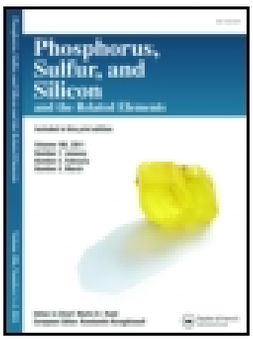

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PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
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# Synthesis, α-amylase inhibitory activity evaluation and *in silico* molecular docking study of some new phosphoramidates containing heterocyclic ring

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**ABSTRACT**

We have synthesized a series of phosphoramidates containing a heterocyclic moiety with good yields (88–95%) by the reaction of (E)-5-benzylidene-3-((2-hydroxyethoxy)methyl)thiazolidine-2,4-dione with ethyl phosphorodichloridate followed by the reaction with various heterocyclic amines. The designed compounds were primarily screened for their ability to inhibit pancreatic α-amylase enzyme using *in silico* molecular docking approach. The compounds with good binding energies (−8.0 to −6.9 kcal/mol) when compared with standard drug, acarbose (−8.0 kcal/mol) were prompted for the synthesis. The structures of the newly prepared compounds were confirmed by their spectroscopic analyses. They were further screened *in vitro* for their inhibition toward α-amylase enzyme using acarbose as standard drug. All compounds exhibited moderate to good inhibition potential with $IC_{50}$ values in the range of 54.14 ± 0.35 to 185.04 ± 0.53 μg/mL when compared with the standard drug ($IC_{50}$, 50.47 ± 0.28 μg/mL). Especially, the compound (E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylphosphoramidate (**6f**) ($IC_{50}$, 54.14 ± 0.35 μg/mL) and (E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl benzo[d]thiazol-2-ylphosphoramidate (**6c**) ($IC_{50}$, 57.02 ± 0.32 μg/mL) exhibited the best inhibition among the synthesized compounds.

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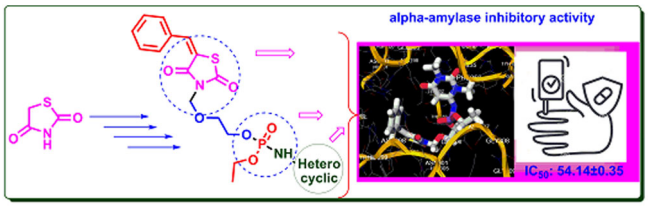
**KEYWORDS**
Phosphoramidates; thiazolidine-2,4-dione; α-amylase; acarbose; molecular docking approach

**GRAPHICAL ABSTRACT**




## Introduction

Organophosphorus (OP) chemistry has been growing rapidly since organophosphorus compounds occupy a variety of biological processes. In medicine and agriculture these molecules play a vital role.[1] Especially, phosphoramidates (PRs), which are a leading group of OP compounds, exhibit abroad range of biological activities and are useful as prodrug moieties to enhance the therapeutic potential of the parent drug.[2,3] In recent years, drugs possessing phosphoramidate moiety have played a vital role to treat diabetes,[4] cancer,[5] Alzheimer's disease,[6] and are used in antitumor therapy.[7] PRs are also useful as cardioprotective, antibacterial,[8] antioxidants,[9] antiviral,[10] anti-HIV[11] and antigene agents[12] (Figure 1). On the other hand, OP compounds containing heterocyclic systems have received considerable attention due to their variety of attractive pharmacological properties.[13–15] Due to the immense efficacy and possible applications of PRs in diverse fields of chemistry, mostly in pharmacy, tremendous interest has been paid to synthesize this class of compounds.

The compounds containing heterocyclic ring systems are of great importance due to their established efficacy in medicinal chemistry. Compounds bearing heterocyclic systems such as thiazole, benzothiazole,[16] thiazolidine-2,4-dione,[17] pyrazole,[18] pyrrole, indole,[19] benzoxazolone, oxazolone,[20] 1,3,4-oxadiazoles, 1,2,3-triazole,[21] furan[22] have been proven to be good anti-diabetic agents in the treatment of T2DM. Thiazolidinediones (TZDs) are oral anti-diabetic drugs that control type 2 diabetes *via* enhancement of insulin sensitivity. Pioglitazone, Rosiglitazone and Lobeglitazone (Figure 2) are examples of drugs belonging to the TZD category. They act as PPARγ agonists and showing their effectiveness in controlling T2DM. They are effective

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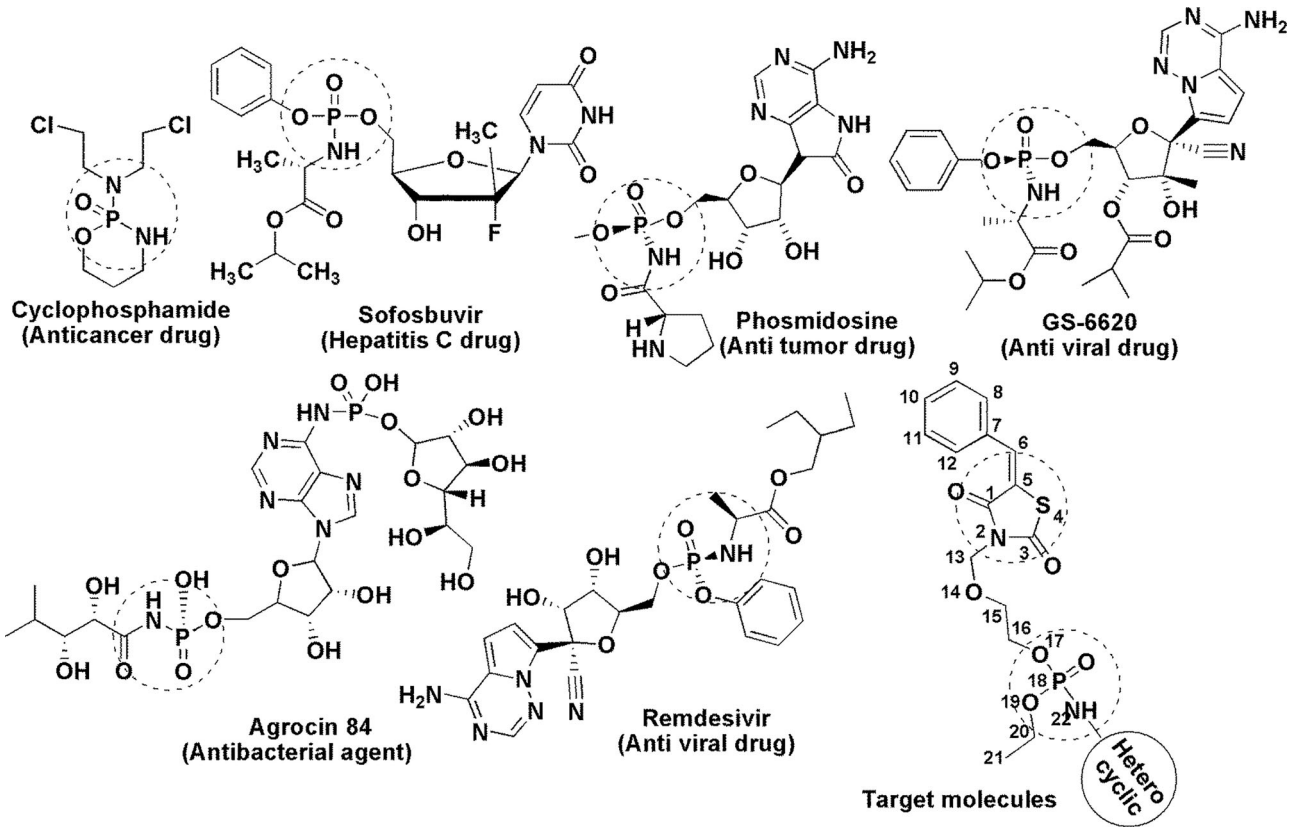



**Figure 1.** Some biologically active phosphoramidares.

in controlling T2DM however hepatotoxicity is certainly one of their severe side effects.[23]

On the other hand, decreasing the post-prandial glucose levels by delaying the absorption of glucose *via* inhibition of the carbohydrate-hydrolysing enzyme, α-amylase is one of the best approach to fight against T2DM.[24] In animals, inhibitors of α-amylase reduce the glucose levels (that can arise after a meal) by slowing down the speed with which α-amylase can convert starch to simple sugars until the body can deal with it.[25] Several α-amylase inhibitors, like acarbose, miglitol, and voglibose (Figure 2) are currently in use as medicine for T2DM.[26–28] Nevertheless, these drugs have several side effects like hepatotoxicity, diarrhea, flatulence, and abdominal distension.[29–32] Hence, researchers are looking forward for novel drug candidate to treat T2DM with a better safety profile.

Our recent studies demonstrated that, OP compounds containing TZD moiety exhibit significant inhibition toward the α-amylase enzyme.[33] With this motivation, in the present study we have designed some novel PRs and incorporated some heterocyclic amines at the phosphorus atom. These designed structures were applied to molecular docking studies. Based on the results obtained from these studies, structures which exhibited good binding affinity for the target protein were selected for the synthesis and screened for their *in vitro* α-amylase inhibition assay. The majority of the synthesized compounds exhibited good activity when compared with the standard drug.

## Results and discussion

### *Chemistry*

We undertook an efficient protocol for the preparation of new PRs containing heterocyclic moiety (**6a–j**) with good yields (88–95%) using 2,4-thiazolidinedione as a starting material. The schematic representation for the preparation of these target molecules **6a–j** is shown in Scheme 1.

The structures of all the prepared compounds were confirmed by NMR ($^{31}$P, $^{1}$H, $^{13}$C), IR spectroscopy, mass, and elemental analyses. The $^{31}$P NMR signals of the synthesized compounds (**6a–j**) are observed as singlet in the range 22.1.5–15.5 ppm.[34] The $^{1}$H NMR spectra gave a multiplet due to aromatic protons in the range of $\delta$ 7.53–7.25 ppm. The proton signals in the range of 8.16–8.15 as a singlet were assigned to methine protons, 5.75–3.64 as a multiplet for methylene protons and at 1.23 ppm as a triplet for methyl protons of compounds **6a–j**. $^{13}$C NMR chemical shifts for methine, methylene and methyl carbon were observed at $\delta$ 142.7, 71.2–65.3 and 16.4 ppm, respectively. The chemical shifts for the carbonyl carbon were observed at $\delta$ 171.2 for all the title compounds. In order to confirm the functional groups present in the title compounds, an infrared spectral study has been made. The IR spectra of the title compounds displayed strong absorption bands at 3329–3275 and 1724–1682 cm$^{-1}$ for secondary amine and carbonyl groups, respectively. The stretching vibrations for P = O and P–O–$C_{alip}$ were observed at 1237–1221 and 1019–1011 cm$^{-1}$, respectively, for compounds **6a–j**. All the title compounds gave $M^{+\cdot}$ ions as base peaks and isotopic cluster peaks with expected ratio. The calculated values of elemental analyses

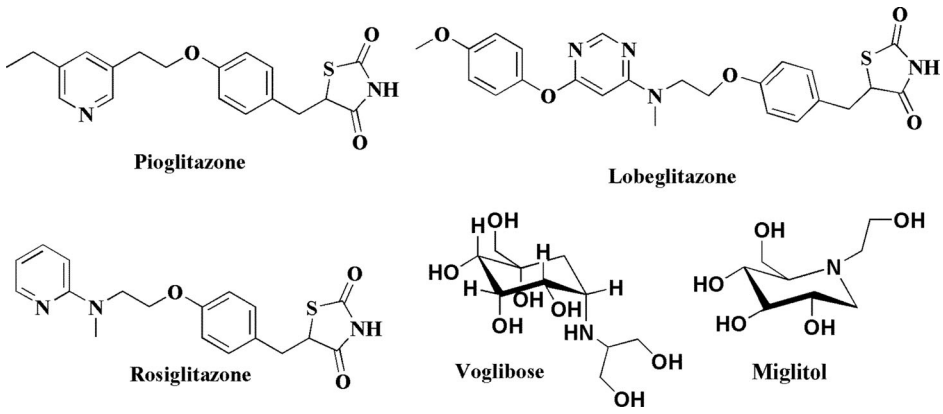
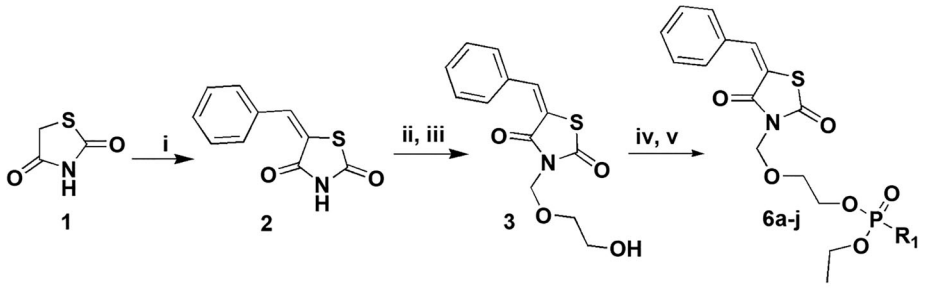
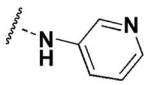
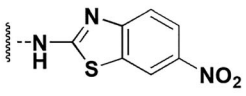
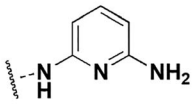
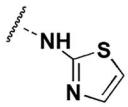
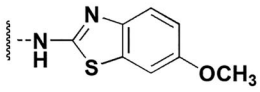
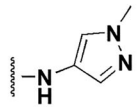
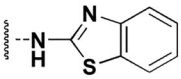
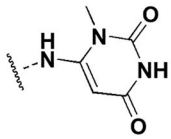
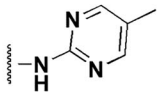
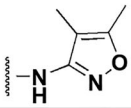



Figure 2. Some known anti-diabetic drugs.




i).Benzaldehyde, AcOH, AcOONa; ii). NaH, Diiodomethane, THF, 5-25 °C; iii). Ethane-1,2-diol,THF, $Et_3N$; iv).TMG,THF, $Cl_2(PO)OC_2H_5$,5-10 °C, 3h; v).TMG, THF, $R_1$-H (5a-j), r.t., 4h

| Compd | $R_1$ | Compd | $R_1$ | Compd | $R_1$ |
|---|---|---|---|---|---|
| 6a |  | 6d |  | 6g |  |
| 6b |  | 6e |  | 6h |  |
| 6c |  | 6f |  | 6i |  |
| | | | | 6j |  |

Scheme 1. Synthesis of phosphoramidates **6a–j**.

for the synthesized compounds were in good agreement with the observed values. The representative spectra of compounds **6a–j** are available in the Supplemental Materials (Figures S1–S30).

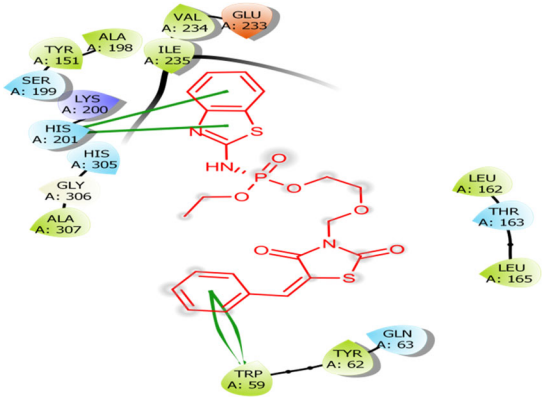
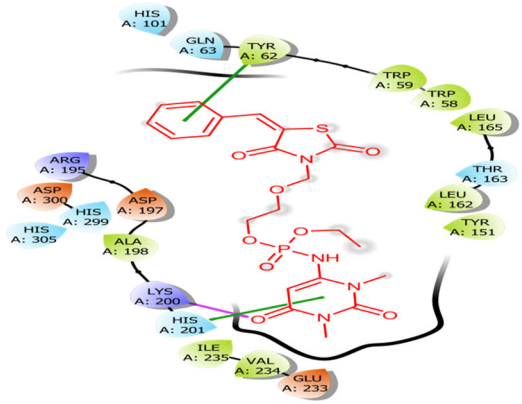
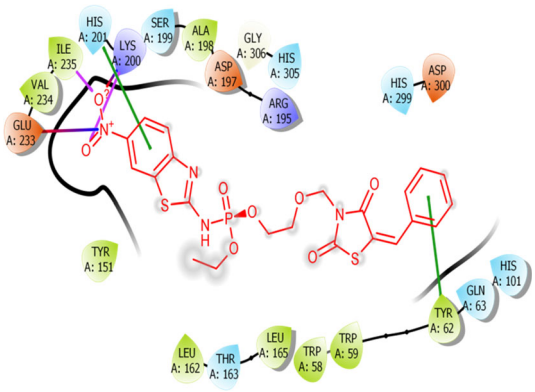
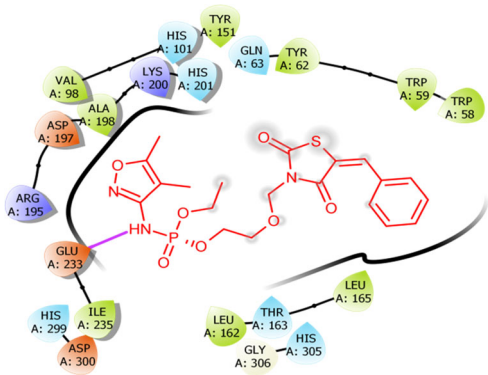
## Pharmacology

### In silico *molecular docking studies*

The docking studies were performed for the newly designed molecules **6a–j** to understand the binding interactions of the PR derivatives with the active site of the pancreatic α-amylase enzyme (PDB ID: 3IJ8) using 1-click docking online server tool. 1-Click docking is a web-based server (http://mcule.com/apps/1-click-docking/) powered by AutoDock Vina docking algorithm.[35] Ten compounds in this series were found to be active. From the docking results, it was observed that compounds **6f**, **6c, 6g, 6a** and **6j** exhibited good binding energies (−8.0, −7.9, −7.9, −7.8 and −7.5 kcal/mol) with the target enzyme, α-amylase when compared with the reference drug (−8.0 kcal/mol) and were fitted in the active site of the target gene properly. Binding energies and bonding pose of ligands with target enzyme are presented in detail in Table S1 (see Supplemental Materials). To understand the interactions between ligands and the target protein, 2D diagrams are widely used in the scientific literature. 2D ligand interactions of most active compounds (**6c**, **6d, 6f** and **6j**) with the target enzyme are shown in Table 1.

Compound **6f** is the most active compound in this series and the binding mode shows that the carbonyl oxygen of 1,3-

**Table 1.** 2D lig plot images of compounds **6c, 6d, 6j** and **6f**.

| Compd. | 2D structure | Compd. | 2D structure |
|---|---|---|---|
| **6c** |  | **6f** |  |
| **6d** |  | **6j** |  |

dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl moiety forms a hydrogen bond with the Lys200. Additionally, the pyrimidine and the phenyl ring forms π–π stacking with Lys200 and Tyr62, respectively. Additionally, the compound was also found to have hydrophobic interactions with Tyr 62, Trp59, Trp58, Leu165, Leu162, Tyr151, Ala198, Ile235 and Val234. In compound **6c**, the benzothiazole and phenyl ring forms π–π stacking with His201 and Trp99, respectively. Additionally, Val234, Ile235, Ala198, Tyr151, Ala307, Trp99, Tyr62, Leu165 and Leu162 form hydrophobic contacts with compound **6c**. In compound **6d**, hydrogen bonds are observed between the oxygen atoms of nitro group and Ile235 as well as Lys200. The benzothiazole and phenyl groups of this compound formed π–π stacking with His201 and Tyr62, respectively. A salt bridge was also observed between nitrogen atom of nitro group and Glu233 as well as oxygen atom of nitro group and Lys200. In addition to this, compound **6d** formed hydrophobic interaction with Val234, Ile235, Ala198, Tyr151, Leu162, Leu165, Trp58, Trp59 and Tyr62. The binding mode orientation of compound **6j** shows the formation of π–π stacking between the dimethylisoxazole group and phenyl ring with His201 and Tyr62, respectively. Besides, compound **6j** forms hydrophobic interaction with Leu165, Leu162, Tyr151, Tyr62, Trp59, Trp58, Ala198, Ala307, Ile235 and Val234.

### α-Amylase inhibitory activity

All the newly synthesized compounds were scrutinized for their α-amylase inhibitory activity at 25, 50, 100, 150 and 200 µg/mL concentrations using the method according to Nickavar and Amin,[36] which was at first proposed by Patil et al with slight modifications.[37] The analysis results (Figure 3) of **6a–j** showed that all the derivatives exhibit good α-amylase inhibition activity with $IC_{50}$ values in the range of 54.61 ± 0.08 to 185.59 ± 0.74 when compared with the standard drug, acarbose whose $IC_{50}$ was found to be 50.78 ± 0.54 (Figure 4). Especially compound **6f**, bearing 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl moiety ($IC_{50}$, 54.14 ± 0.35 µg/mL); **6c** bearing with benzo[d]thiazol-2-yl motif ($IC_{50}$, 57.02 ± 0.32 µg/mL); **6d** incorporated with 6-nitrobenzo[d]thiazol-2-yl motif ($IC_{50}$, 63.91 ± 0.33 µg/mL) and **6j** bearing with 4,5-dimethylisoxazol-3-yl moiety ($IC_{50}$, 65.65 ± 0.22 µg/mL) exhibited good inhibition when compared with the standard drug, acarbose ($IC_{50}$, 50.47 ± 0.28 µg/mL). The left over compounds **6h, 6a, 6e, 6g, 6b** and **6i** showed moderate inhibition on the enzyme with $IC_{50}$ values in the range 98.30 ± 0.62 to 185.04 ± 0.53 µg/mL.

## Experimental

### Materials and characterization techniques

The chemicals were purchased from Sd. Fine Chem. Ltd., India and a few of them were purified using standard procedures. The purity of the compounds was checked by TLC on Al sheet of silica gel. The reaction to synthesize the title compounds was carried out on magnetic agitator cum hot plate. *J* (coupling constants) and *δ* (chemical shift) values were

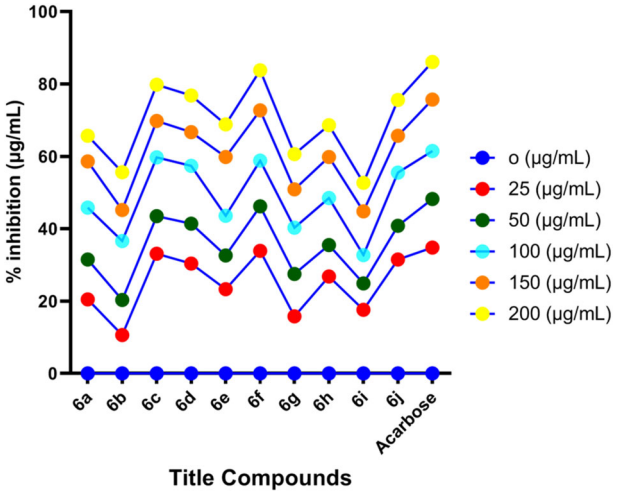



**Figure 3.** α-Amylase inhibition activity results of phosphoramidate derivatives (**6a–j**).

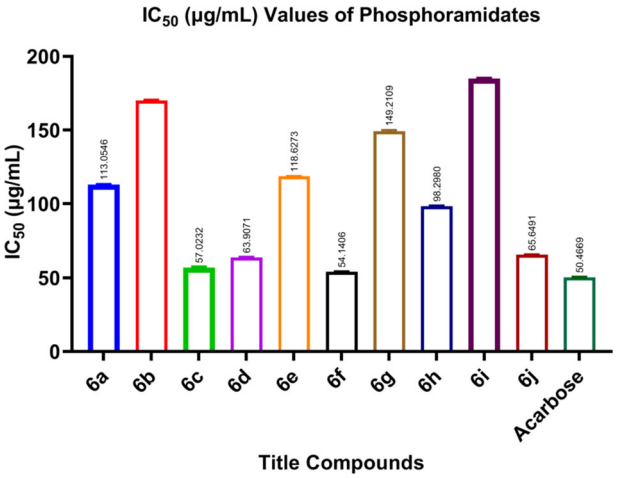



**Figure 4.** $IC_{50}$ values of phosphoramidates **6a–j**.

reported in Hz and ppm, respectively. Bruker AMX spectrometer was used to record $^{31}P$ (161.9 MHz), $^{1}H$ (400 MHz) and $^{13}C$ (100 MHz) NMR spectra. The symbol 's' for singlet, 'd' for doublet, 't' for triplet and 'm' for multiplet were used to represent peaks in NMR spectra. LC–MS were recorded on SHIMADZU 2010A. T. F. Flash 1112 apparatus was used for CHN analysis. Bruker IFS 55 (Equinox) FTIR spectrometer in KBr was used to record IR spectra. Marvin view software was utilized to draw the structures, to optimize and convert them into required format. 1-Click docking software powered by Auto Dock Vina docking algorithm was used for docking studies. Graph Pad Prism 8.4.3 (686) software was used to calculate $IC_{50}$ values and to draw the corresponding graphs.

## Procedures

### Synthesis of 5-benzylidene-2,4-thiazolidinediones (2)[38]

A mixture of 2,4-thiazolidinedione, (**1**) (2.4 g, 20 mmol), benzaldehyde, (2.12 g, 20 mmol), piperidine (1.4 g, 16 mmol) and ethanol (150 mL) in a round bottomed flask was refluxed for 20 h. The reaction mixture was poured into water (250 mL) and acidified with acetic acid to give compound **3** as solid, which was recrystalized from methanol to form pure (E)-5-benzylidenethiazolidine-2,4-dione (**2**). Completion of the reaction was confirmed using TLC using benzene:ethyl acetate as eluent (3:7). Bright yellow solid; m.p. 218–220 °C; Yield: 94%; $^{1}H$ NMR (400 MHz, δ, ppm, DMSO-$d_6$): 12.10 (s, 1H, NH), 7.72 (s, 1H, –CH=), 7.65–7.42 (m, 5H, Ar–H). $^{13}C$ NMR (400 MHz, δ, ppm, DMSO-$d_6$): 168.4 (C-3), 166.2 (C-1), 142.4 (C-6), 134.8 (C-7), 127.6 (C-9, C-11), 127.3 (C-8, C-12), 127.2 (C-10), 117.0 (C-5).

### Synthesis of (E)-5-benzylidene-3-((2-hydroxyethoxy)methyl) thiazolidine-2,4-dione (4)

(E)-5-benzylidenethiazolidine-2,4-dione (**2**) (2.5 g, 10 mmol) in THF was treated with sodium hydride (0.24 g, 10 mmol) at 0–5 °C for 1 h to give sodium salt of compound **2**. To this salt, diiodomethane (0.81 mL, 10 mmol) in tetrahydrofuran (THF) (30 mL) was added slowly at 5 °C and stirring was continued for about 3 h at room temperature. Then the reaction mixture was filtered to remove sodium iodide. The filtrate contained (E)-5-benzylidene-3-(iodomethyl)thiazolidine-2,4-dione. This compound was then treated with ethane-1,2-diol (0.6 mL, 10 mmol) in the presence of triethylamine (0.73 mL, 10 mmol) as base for 4 h to give crude product. The progress of the reaction was monitored by TLC using ethyl acetate-hexane (6:4) as an eluent. The pure compound (E)-5-benzylidene-3-((2-hydroxyethoxy)methyl)thiazolidine-2,4-dione (**3**) was obtained by recrystallization from methanol. Solid, m.p. 231–233 °C, Yield: 95%, $^{1}H$ NMR (400 MHz, δ, ppm, DMSO-$d_6$): 7.74 (s, 1H, =CH), 7.63–7.35 (m, 5H, Ar–H), 5.43 (s, 1H, –N–$CH_2$), 4.74 (s, 1H, –OH), 3.39 (t, $J = 7.6$ Hz, 2H, –$CH_2$), 3.27 (t, $J = 6.4$ Hz, 2H, –$CH_2$). $^{13}C$ NMR (400 MHz, δ, ppm, DMSO-$d_6$): 171.8 (C-3), 164.0 (C-1), 142.5 (C-6), 134.9 (C-7), 127.4 (C-9, C-11), 127.1 (C-8, C-12), 127.0 (C-10), 117.3 (C-5), 71.6 (C-13), 63.4 (C-15), 64.7 (C-16).

### Synthesis of PRs 6a–j[39]

To compound **3** (2.79 g, 10 mmol) in THF (25 mL) was added a solution of ethyl phosphorodichloridate (1.2 mL, 10 mmol) in THF (25 mL) drop wise in the presence of tetra methyl guanidine (TMG) (10 mmol) with stirring for about 15 min. After the addition was completed, stirring was continued for about 3 h at 5–10 °C. Once the reaction was completed, as checked by TLC using hexane:ethyl acetate (3:7) as eluent, the reaction mixture was filtered to remove tetra methyl guanine hydrochloride to yield (E)-5-benzylidene-3-((2-hydroxyethoxy)methyl)thiazolidine-2,4-dione (**4**). To this compound, pyridin-3-amine (**5a**) (0.094 g, 10 mmol) in THF (30 mL) was added in the presence of TMG (10 mmol) at 0 °C with stirring and the stirring was continued for 4 h at reflux temperature. Once the reaction was completed as checked by TLC using hexane:ethyl acetate (4:6) as eluent; the reaction mixture was filtered to remove tetra methyl guanine hydrochloride. The solvent from the filtrate was removed using rota evaporator to acquire crude product. It was washed twice with chloroform and recrystallized from ethanol to obtain (E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl pyridin-3-ylphosphoramidate (**6a**).

The similar experimental protocol was applied to synthesize the remaining compounds **6b–j**.

### *Characterization of title compounds 6a–j*

***(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl pyridin-3-ylphosphoramidate (6a).*** Yield: 92%; solid, m.p. 243–244 °C; $^{1}$H NMR (DMSO-$d_6$): 8.25 (d, $J$ = 8.4 Hz, 1H, Pyridine–H), 8.16 (s, 1H, =C–H), 8.09 (s, 1H, Pyridine–H), 7.53 (d, $J$ = 7.2 Hz, 2H, Ar–H), 7.36 (t, $J$ = 7.2 Hz, 2H, Ar–H), 7.30 (t, $J$ = 7.2 Hz, 1H, Pyridine–H), 7.25 (t, $J$ = 6.4 Hz, 1H, Ar–H), 7.20 (d, $J$ = 6.8 Hz, 1H, Pyridine–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 144.4 (C-23), 142.7 (C-6), 136.7 (C-26), 135.5 (C-24), 134.6 (C-7), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 124.4 (C-27), 122.3 (C-28), 117.5 (C-5), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 15.5 ppm; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3118 (NH), 1730, 1681 (C = O), 1212 (P = O), 1012 (P–O–$C_{alip}$); LC–MS ($m/z$, %): 464 (M + H$^+$, 100); For $C_{20}H_{22}N_3O_6PS$; calcd: C, 51.83; H, 4.78; N, 9.07%; found: C, 51.91; H, 4.70; N, 9.14%.

***(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl thiazol-2-ylphosphoramidate (6b).*** Yield: 90%; solid, m.p. 255–257 °C; $^{1}$H NMR (DMSO-$d_6$): 8.16 (s, 1H, =C–H), 7.53 (d, $J$ = 7.2 Hz, 2H, Ar–H), 7.36 (t, $J$ = 7.2 Hz, 2H, Ar–H), 7.30 (d, $J$ = 8.4 Hz, 1H, Thiazole–H), 7.25 (t, $J$ = 6.4 Hz, 1H, Ar–H), 6.84 (d, $J$ = 8.0 Hz, 1H, Thiazole–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 142.7 (C-6), 137.4 (C-25), 134.6 (C-7), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.5 (C-5), 115.2 (C-26), 73.4 (C-23), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 18.2 ppm; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3287 (NH), 1714, 1682 (C = O), 1237 (P = O), 1013 (P–O–$C_{alip}$); LC–MS ($m/z$, %): 470 (M + H$^+$, 100); For $C_{18}H_{20}N_3O_6PS_2$; calcd: 46.05; H, 4.29; N, 8.95%; found: C, 46.12; H, 4.21; N, 9.04%.

***(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl benzo[d]thiazol-2-ylphosphoramidate (6c).*** Yield: 88%; solid, m.p. 248–250 °C; $^{1}$H NMR (DMSO-$d_6$): 8.15 (s, 1H, =C–H), 8.13 (d, $J$ = 8.0 Hz, 1H, Ar–H), 8.07 (d, $J$ = 7.6 Hz, 1H, Ar–H), 7.53 (d, $J$ = 7.2 Hz, 2H, Ar–H), 7.49 (d, $J$ = 7.6 Hz, 2H, Ar–H), 7.36 (t, $J$ = 7.2 Hz, 2H, Ar–H), 7.25 (t, $J$ = 6.4 Hz, 1H, Ar–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 151.4 (C-25), 142.7 (C-6), 134.6 (C-7), 131.3 (C-30), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 124.9 (C-27), 124.6 (C-28), 120.9 (C-29), 117.8 (C-26), 117.5 (C-5), 73.7 (C-33), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 17.6 ppm; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3296 (NH), 1716, 1691 (C = O), 1228 (P = O), 1015 (P–O–$C_{alip}$); LC–MS ($m/z$, %): 520 (M + H$^+$, 100); For $C_{22}H_{22}N_3O_6PS_2$; calcd: C, 50.86; H, 4.27; N, 8.09%; found: C, 50.93; H, 4.19; N, 8.16%.

***(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 6-nitrobenzo[d]thiazol-2-ylphosphoramidate (6d).*** Yield: 94%; solid, m.p. 266–268 °C; $^{1}$H NMR (DMSO-$d_6$): 8.55–7.25 (m, 8H, Ar–H), 8.16 (s, 1H, =C–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 157.9 (C-25), 145.1 (C-28), 142.7 (C-6), 134.6 (C-7), 130.3 (C-30), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 122.5 (C-27), 118.7 (C-29), 117.5 (C-5), 116.8 (C-26), 73.6 (C-23), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 18.5 ppm; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3312 (NH), 1719, 1695 (C = O), 1233 (P = O), 1018 (P–O–$C_{alip}$); LC–MS ($m/z$, %): 565 (M + H$^+$, 100); For $C_{22}H_{21}N_4O_8PS_2$; calcd: C, 46.81; H, 3.75; N, 9.92%; found: C, 46.88; H, 3.68; N, 9.98%.

***(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 6-methoxybenzo[d]thiazol-2-ylphosphoramidate (6e).*** Yield: 89%; solid, m.p. 281–282 °C; $^{1}$H NMR (DMSO-$d_6$): 8.15 (s, 1H, =C–H), 7.53–7.25 (m, 8H, Ar–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.81 (s, 3H, $OCH_3$), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 154.7 (C-28), 143.9 (C-25), 142.7 (C-6), 134.6 (C-7), 131.4 (C-30), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.8 (C-26), 117.5 (C-5), 116.7 (C-27), 104.9 (C-29), 73.5 (C-23), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 54.9 (C-33), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 17.9 ppm; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3286 (NH), 1712, 1688 (C = O), 1226 (P = O), 1014 (P–O–$C_{alip}$); LC–MS ($m/z$, %): 550 (M + H$^+$, 100); For $C_{23}H_{24}N_3O_7PS_2$; Calcd: C, 50.27; H, 4.40; N, 7.65%; found: C, 50.34; H, 4.31; N, 7.74%.

***(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylphosphoramidate (6f).*** Yield: 92%; solid, m.p. 238–240 °C; $^{1}$H NMR (DMSO-$d_6$): 8.15 (s, 1H, =C–H), 7.53–7.25 (m, 5H, Ar–H), 5.75 (s, 2H, –$CH_2$–), 4.50 (s, 1H, Pyrimidine–CH), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 3.11 (s, 3H, N–$CH_3$), 3.05 (s, 3H, N–$CH_3$), 2.35 (s, 1H, N–H), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 161.4 (C-23), 160.4 (C-25), 150.2 (C-27), 142.7 (C-6), 134.6 (C-7), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.5 (C-5), 74.7 (C-24), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 28.4 (C-29), 27.8 (C-30), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 20.2 ppm; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 3315 (NH), 1724, 1687 (C = O), 1223 (P = O), 1014 (P–O–$C_{alip}$); LC–MS ($m/z$, %): 525 (M + H$^+$, 100); For $C_{21}H_{25}N_4O_8PS$; calcd: C, 48.09; H, 4.80; N, 10.68%; found: C, 48.16; H, 4.72; N, 10.77%.

*(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 6-amino pyridin -2-ylphosphoramidate (6g).* Yield: 90%; solid, m.p. 291–293 °C; $^{1}$H NMR (DMSO-$d_6$): 8.16 (s, 1H, =C–H), 7.53–7.25 (m, 5H, Ar–H), 7.09 (t, 1H, Py–H), 6.58 (br–s, 2H, $NH_2$), 5.84 (d, 2H, Py–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 2.39 (s, 1H, NH), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 159.4 (C-23), 154.6 (C-25), 142.7 (C-6), 138.6 (C-27), 134.6 (C-7), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.5 (C-5), 100.5 (C-28), 96.1 (C-25), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 19.3 ppm; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3294 (NH), 1716, 1686 (C = O), 1232 (P = O), 1016 (P–O–$C_{alip}$); LC–MS (*m/z*, %): 479 ($M + H^+$, 100); For $C_{20}H_{23}N_4O_6PS$; calcd: C, 50.21; H, 4.85; N, 11.71%; found: C, 50.07; H, 4.93; N, 11.79%.

*(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 1-methyl-1H-pyrazol-4-ylphosphoramidate (6h).* Yield: 95%; solid, m.p. 256–259 °C; $^{1}$H NMR (DMSO-$d_6$): 8.16 (s, 1H, =C–H), 7.76 (s, 1H, Pyrazole–H), 7.53–7.25 (m, 5H, Ar–H), 7.21 (s, 1H, Pyrazole–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.86 (s, 3H, N–$CH_3$), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 142.7 (C-6), 134.6 (C-7), 131.2 (C-23), 129.2 (C-24), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.5 (C-5), 116.8 (C-27), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 37.8 (C-28), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 22.1 ppm; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3329 (NH), 1715, 1683 (C = O), 1230 (P = O), 1019 (P–O–$C_{alip}$); LC–MS (*m/z*, %): 467 ($M + H^+$, 100); For $C_{19}H_{23}N_4O_6PS$; calcd: C, 48.92; H, 4.97; N, 12.01%; found: C, 48.99; H, 4.89; N, 12.09%.

*(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 5-methylpyrimidin-2-ylphosphoramidate (6i).* Yield: 91%; solid, m.p. 277–279 °C; $^{1}$H NMR (DMSO-$d_6$): 8.48 (s, 2H, pyrimidine–H), 8.15 (s, 1H, =C–H), 7.53–7.25 (m, 5H, Ar–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 2.29 (s, 3H, –$CH_3$), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 165.5 (C-23), 163.2 (C-1), 156.8 (C-25, C-27), 142.7 (C-6), 134.6 (C-7), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.5 (C-5), 116.4 (C-26), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.5 (C-29), 16.4 (C-21); $^{31}$P NMR (DMSO-$d_6$): 20.7 ppm; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3315 (NH), 1718, 1687 (C = O), 1228 (P = O), 1015 (P–O–$C_{alip}$); LC–MS (*m/z*, %): 479 ($M + H^+$, 100); For $C_{20}H_{23}N_4O_6PS$; calcd: C, 50.21; H, 4.85; N, 11.71%; found: C, 50.29; H, 4.78; N, 11.79%.

*(E)-2-((5-benzylidene-2,4-dioxothiazolidin-3-yl)methoxy)ethyl ethyl 4,5-dimethylisoxazol-3-ylphosphoramidate (6j).* Yield: 94%; solid, m.p. 247–248 °C; $^{1}$H NMR (DMSO-$d_6$): 8.16 (s, 1H, =C–H), 7.53–7.25 (m, 5H, Ar–H), 6.35 (s, 1H, N–H), 5.75 (s, 2H, –$CH_2$–), 4.36 (m, 2H, O–$\underline{CH_2}CH_3$), 4.18 (q, 2H, P–O–$CH_2$–), 3.64 (t, $J$ = 6.0 Hz, 2H, O–$CH_2$–), 2.39 (s, 3H, –$CH_3$), 2.34 (s, 3H, –$CH_3$), 1.23 (t, $J$ = 6.8 Hz, 3H, O–$CH_2\underline{CH_3}$); $^{13}$C NMR (DMSO-$d_6$): 171.2 (C-3), 163.2 (C-1), 156.9 (C-26), 152.4 (C-23), 142.7 (C-6), 134.6 (C-7), 127.7 (C-9, C-11), 127.3 (C-8, C-12), 126.8 (C-10), 117.5 (C-5), 102.3 (C-27), 71.2 (C-13), 65.6 (C-15), 65.3 (C-16), 61.7 (C-20), 16.4 (C-21); 10.6 (C-29), 6.9 (C-28); $^{31}$P NMR (DMSO-$d_6$): 18.9 ppm; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3283 (NH), 1714, 1682 (C = O), 1232 (P = O), 1013 (P–O–$C_{alip}$); LC–MS (*m/z*, %): 482 ($M + H^+$, 100); For $C_{20}H_{24}N_3O_7PS$; calcd: C, 49.89; H, 5.02; N, 8.73%; found: C, 49.96; H, 5.10; N, 8.64%.

### In silico *molecular docking studies with α-amylase*

Molecular docking studies of the newly prepared compounds were performed against α-amylase enzyme, in order to understand the possible binding mechanism prior to their synthesis. Marvin view software was utilized to optimize the structures of the title compounds and the standard drug acarbose. In order to reveal the binding modes of the title compounds, docking simulation was performed targeting the crystal structure of pancreatic alpha amylase which was retrieved from RCSB, Protein Data Bank (PDB ID: 3IJ8) and the structure was optimized by removing the water molecules, hetero atoms and co-factors. Hydrogen bonds, missing atoms and charges were computed. The PDB structures of target protein (A) and standard drug, acarbose (B) are shown in Figure S7 (see Supplemental materials). The molecular docking method was performed using 1-click docking online server tool (https://mcule.com), 1-click docking uses a Vina filter and dock multiple ligands into a single target. Default binding site center specification of in 1-click docking default binding site center *X*: 7.2178, *Y*: 16.2957, *Z*: 42.1167. The docked process and interactions of compounds and protein were analyzed by using discovery studio visualizer V16.1.0.15350.[40]

### *α-Amylase inhibitory activity*

The α-amylase inhibitory activity had been executed employing standard procedure according to Nickavar and Amin[36] which was at first proposed by Patil et al.[37] with minor changes (see Supplemental Materials for detailed procedure).

The $IC_{50}$ values, concentration required to inhibit the α-amylase activity by 50% were calculated by a Fit Spline/LOWESS analysis using a Graph Pad Prism 8.4.3 (686) software for concentrations (*X* axis) versus percentage inhibition (*Y* axis), and then row means with SD was calculated using grouped analysis.

## Conclusion

A series of PRs containing a heterocyclic moiety were synthesized from 2,4-thiazolidinedione with high yields using simple chemistry. Prior to their synthesis, molecular docking studies were performed to know their binding affinity against pancreatic α-amylase enzyme. The compounds with good binding energy were provoked for synthesis. This is a

resource saving method which allowed us to synthesize active compounds without waste of time and chemicals. Further, all the synthesized compounds were screened *in vitro* for their ability to inhibit α-amylase using spectrophotometric method. The compounds exhibited good to moderated inhibition toward the target enzyme when compared with the standard drug, acarbose. Especially compound **6f**, **6c**, **6d** and **6j** exhibited good inhibition with $IC_{50}$ values in the range $54.14 \pm 0.35$ to $65.65 \pm 0.22$ µg/mL in comparison with standard ($50.47 \pm 0.28$ µg/mL). The present investigation demonstrate that the synthesized compounds will be the promising next generation anti-diabetic drugs, which can be effectively used in the treatment of symptom of diabetic complications.

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## Disclosure statement

The authors declare no conflict of interest.

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