Medicinal Chemistry & Drug Discovery

Design, Synthesis and Antidiabetic Activity of Biphenylcarbonitrile-Thiazolidinedione Conjugates as Potential α-Amylase Inhibitors

Chirag H. Rathod,[b] Pankajkumar B. Nariya,[a] Deepika Maliwal,[c] Raghuvir R. S. Pissurlenkar,[d] Naval P. Kapuriya,[e] and Anilkumar S. Patel*[a]

The α-amylase inhibition has been considered as an effective therapeutic approach against chronic Type 2 Diabetes mellitus (DM). In the present study, a series of biphenylcarbonitrile-thiazolidinedione conjugates have been synthesized and evaluated for their antidiabetic activity *via* α-amylase inhibition. It was found that most of the conjugates (**14a–j**) exhibited significant α-amylase inhibition activity compared to the standard drug Acarbose. Off these, compound **14b**, **14c** and **14d** were most potent with IC_{50} value 0.13 μM, 0.15 μM and 0.13 μM respectively. To ascertain ligand-receptor interactions, the *in silico* molecular docking studies of these conjugates (**14a–j**) have been carried out into the Acarbose active site of barley (malt) α-amylase enzyme. The results have shown fair corroboration between significant α-amylase inhibition activity of **14b**, **14c** and **14d** and their docking scores compared to the standard drug Acarbose. This study demonstrated that biphenylcarbonitrile-thiazolidinedione conjugate could be a plausible pharmacophore for targeting α-amylase for the treatment of Type 2 Diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease affecting millions of individuals worldwide.[1] Primarily, DM is characterized by sustained high levels of circulating glucose (hyperglycemia) caused by the lake of insulin (Type 1 DM) or insufficient insulin secretion (Type 2 DM) in the blood plasma by pancreatic β-cells.[2] Both conditions ultimately lead to uncontrolled blood glucose levels resulting in disruption of carbohydrate, protein, and fat metabolism.[3]

Type 1 DM can be treated by exogenous insulin replacement therapy to maintain the level of blood glucose.[4] On the other hand, treatment of Type 2 DM is complex and includes several therapeutic approaches such as (i) stimulation of the insulin secretion from pancreas (ii) increasing sensitivity of β-cell to insulin and (iii) retarding the glucose absorption from kidneys and intestine.[5–6] Accordingly, various enzymes that regulate gluconeogenic or glycogenolytic pathways have been considered as effective targets for Type 2 DM therapy.[7] For instance, PPAR-γ receptors which regulate the glucose metabolism served as an effective target for many antidiabetic drugs (Type 2 DM) based on Thiazolidinedione scaffolds (TZDs) such as Ciglitazone (**1**), Troglitazone (**2**), Rosiglitazone (**3**), and Pioglitazone (**4**) (Figure 1).[8] However, Ciglitazone (**1**) and Troglitazone (**2**) have been withdrawn from clinical use due to their hepatotoxicity.[9]

In the recent past, an alternative therapeutic approach *via* inhibition of α-amylase enzyme has been developed for the treatment of Type 2 DM.[10–12] Basically, α-amylase (α-1,4-glucan-4-glucanohydrolases) is secreted by the pancreas which has a catalytical role in the hydrolysis of α-(1,4)-glycosidic

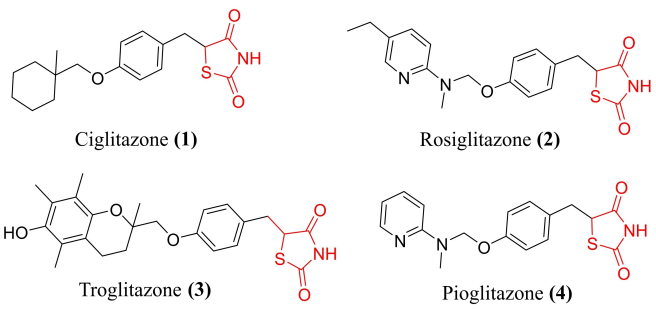

Figure 1. Structures of some antidiabetic drugs bearing thiazolidine-2,4-dione scaffold.

[a] *Dr. P. B. Nariya, Dr. A. S. Patel*
Department of Chemistry,
Atmiya University,
Kalawad Road, Rajkot, Gujarat, India-360005
E-mail: patelanil32@gmail.com
[b] *C. H. Rathod*
Research Scholar
Department of Chemistry,
School of Science,
RK University, Rajkot, Gujarat, India-360020
[c] *D. Maliwal*
Department of Pharmaceutical Sciences and Technology,
Institute of Chemical Technology, Matunga, Mumbai 400019, India
[d] *Dr. R. R. S. Pissurlenkar*
Department of Pharmaceutical and Medicinal Chemistry,
Goa College of Pharmacy,
18th June Road, Panaji Goa, India-403001
[e] *Dr. N. P. Kapuriya*
Department of Chemistry and Forensic Science,
Bhakta Kavi Narsinh Mehta University,
Bilkha Road, Khadia, Junagadh, Gujarat, India-362263

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linkages of the starch to oligosaccharides.[13–14] Therefore, inhibition of α-amylase thereby retarding the post-prandial hyperglycemia emerged as an effective strategy for insulin resistance condition.[15] Consequently, glycoside derivatives Voglibose (**5 a**) and Acarbose (**5 b**) have been developed as α-amylase inhibitors (Figure 2) for the clinical use.[16] Further, non-glycosidic inhibitors are also being explored which includes arylidine-pyrazolones (**6**),[17] chalcone-thiazolidinone conjugates (**7**),[18] pyrazole-thiazolidinone hybrids (**8**) etc.[19] as potential antidiabetic agents. These reports demonstrated the α-amylase enzyme as a druggable target.

As mentioned earlier, Thiazolidinedione (TZD) is a previleged scaffolds for the design of antidiabetic agents.[20–24] Besides antidiabetic properties, TZDs conjugates also exhibited broad spectrum of bioactivity including anti-microbial,[25] anti-tubercular activity,[26] anti-inflammatory,[27] anti-oxidant,[28] anti-viral etc.[29] Further, many studies have shown the beneficial effects of Thiazolidinediones (TZDs) based antidiabetic drugs in cancer treatments in vitro and in vivo when utilized alone or in combination with other medications.[30] Moreover, several Similarly, functionalized biphenyl derivatives bearing benzimidazole, imidazo[1,2-*b*]pyridazine, thiazolidinone moieties have exhibited potent antibacterial activity *via* inhibition of Bacterial Peptide Deformylase (PDF) enzyme.[31–32] More recently, thiazolidine-2,4-dione with biphenylcarbonitrile hybrid (**9**) reported to have a promising in vitro antidiabetic activity as PPAR-α/γ agonist and showed to have potent in vivo antidiabetic activity in non-insulin dependent diabetes mellitus rat model.[20] However, α-amylase inhibition potential of these conjugates is yet to be explored.

Therefore, in continuation of our research interest to develop potential bioactive heterocyclic compounds,[34–35] we employed scaffold combination strategy of drug design and sought to synthesize biphenylcarbonitrile-thiazolidinedione conjugates (Figure 3) to evaluate their α-amylase inhibition activities. We envisaged that biphenylcarbonitrile unit tethered on N-atom of thiazolidinone scaffolds will provide a spatial arrangement to bind with the active site of α-amylase. Herein, we describe, synthesis, in vitro evaluation and molecular docking studies of some biphenylcarbonitrile-thiazolidinedione conjugates as potential α-amylase inhibitors.

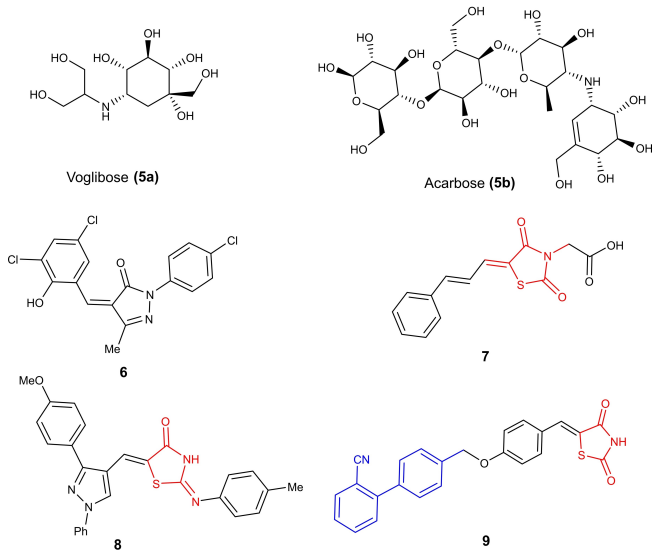


Figure 2. Representative examples of α-amylase inhibitors/PPAR-α/γ agonist.

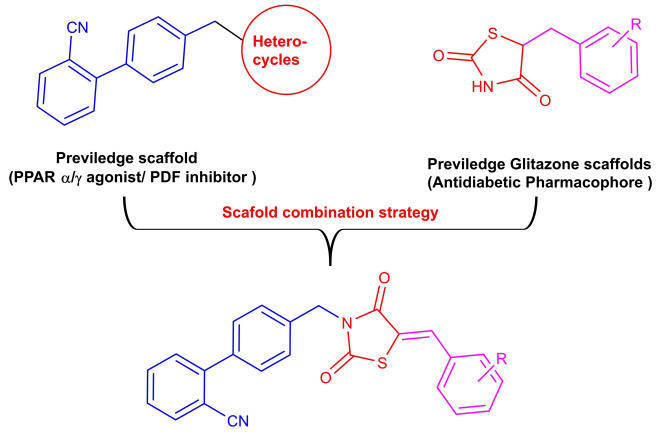
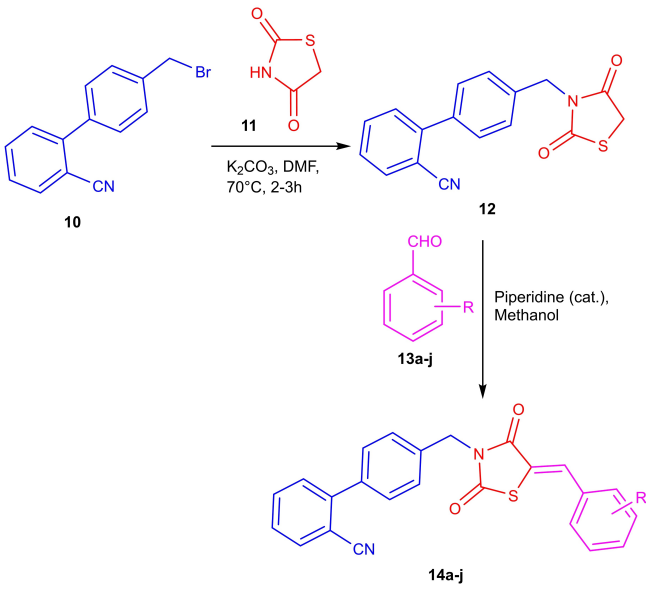


Figure 3. Design of biphenylcarbonitrile-thiazolidinedione conjugates.

Results and Discussion

Chemistry

The synthetic strategy for the targeted thiazolidinone-2,4-diones coupled with biphenylcarbonitile compounds is depicted in Scheme 1. The requisite intermediate 4′-(bromomethyl)-[1,1′-biphenyl]-2-carbonitrile (**10**) was synthesized from commercially available 4′-methylbiphenyl-2-carbonitrile by reacting with *N*-bromo succinimide (NBS) & H_2O_2 as per the reported procedure.[20,36]



Scheme 1. Synthesis of thiazolidine-2,4-dione/biphenylcarbonitrile conjugates (**14 a**–**j**).

Thiazolidine-2,4-dione (**11**) was synthesized by reacting commercially available ethyl chloroacetate with thiourea to generate 2-iminothiazolidin-4-one intermediate which was further treated with Con. HCl in refluxing ethanol to afford **11**in good yield.[37] The 4′-(bromomethyl)-[1,1′-biphenyl]-2-carbonitrile (**10**) was coupled with thiazolidine-2,4-dione (**11**) in the presence of K_2CO_3 in DMF at 70 °C to produce 4′-((2,4-dioxothiazolidin-3-yl)methyl)-[1,1′-biphenyl]-2-carbonitrile (**12**). Finally, Knoevenagel condensation of intermediate **12** with various aromatic aldehydes (**13a–j**) has furnished the targeted thiazolidine-2,4-dione/biphenylcarbonitrile conjugates (**14a–j**). The compounds **14a–j** were characterized by spectroscopic analysis using FT-IR, ^{1}H & ^{13}CNMR, ESI-Ms and elemental analyser.The spectral analysis of **14a–j** confirmed the proposed structures. For instance, ^{1}HNMR spectrum of **14a** display two signals at 3.76 and 3.85 δ (ppm) for two methoxy groups. The upfield singlet resonance at 4.93 was also the characteristic peak of benzylic CH_2 group, multiple signals between 6.95 to 7.95 represents 17 aromtic protons and a singlet in the downfield region at δ 8.08 ppm characteristic peak for benzylidine proton conjugated with thiazolidine ring. The mass spectrum of compound **14a** having m/z 456.13 (M^+) corresponding to molecular formula $C_{26}H_{20}N_2O_4S$ further confirmed its successful synthesis. (The detailed spectral data of **12** and **14a–j**provided with Supporting Information).

In vitroα-amylase inhibition

All the newly synthesized compounds **14a–j** were evaluated for their in vitro α-amylase activity studies using Acarbose as a positive control with different concentration (50-150 μg/mL) and the results are shown in Table 1. As evident, all the compounds **14a–j** exhibited significant α-amylase inhibition activity at the dose of 150 (μg/mL). The comparative analysis of % inhibition showed that antidiabetic activity linearly raised with respect to concentration (Figure 4). Off these, compound **14b**, **14c** and **14d** were most potent compared to the standard drug Acarbose with IC_{50} 0.13 μM, 0.15 μM and 0.13 μM respectively. The SAR study revealed that compound bearing methoxy (–OCH_3) or phenoxy (–OPh) function group exhibited higher % of inhibition (**14b**, **14d**) while compound **14e** having electron-withdrawing –NO_2 was the least active (IC_{50} 0.18 μM) of the series. These results demonstrated the stringent structure required for the α-amylase inhibition.

Table 1. In vitro α-amylase inhibition activity of biphenylcarbonitrile-thiazolidinedione conjugates (**14a–j**).

Compound	(R)[a]	Conc. (μg/mL)	OD at 540 nm	% Inhibition[b]	IC_{50} (μM)
14a	2,5-di-OMe	50	0.114	37.93 ± 0.68	0.15
		100	0.054	70.80 ± 3.07	
		150	0.026	85.67 ± 0.64	
14b	2-O-Ph	50	0.117	36.47 ± 1.40	0.13
		100	0.061	66.96 ± 1.53	
		150	0.018	90.01 ± 0.97	
14c	4-F	50	0.122	33.76 ± 0.46	0.15
		100	0.058	68.59 ± 1.25	
		150	0.014	92.55 ± 0.89	
14d	3,4,5-tri-OMe	50	0.112	39.02 ± 0.89	0.13
		100	0.052	71.86 ± 1.77	
		150	0.011	94.01 ± 0.51	
14e	4-NO_2	50	0.115	37.20 ± 1.31	0.18
		100	0.076	58.77 ± 3.86	
		150	0.034	81.50 ± 0.84	
14f	3-OMe, 4-OH	50	0.124	32.68 ± 3.06	0.17
		100	0.063	65.86 ± 4.10	
		150	0.019	89.46 ± 2.49	
14g	H	50	0.110	40.11 ± 3.43	0.17
		100	0.056	69.33 ± 0.69	
		150	0.015	92.03 ± 2.40	
14h	4-OH	50	0.114	37.95 ± 1.66	0.17
		100	0.065	64.63 ± 2.95	
		150	0.020	89.30 ± 2.68	
14i	4-N(Me)$_2$	50	0.117	36.13 ± 1.33	0.16
		100	0.062	66.06 ± 0.75	
		150	0.027	85.30 ± 0.99	
14j	4-Br	50	0.115	37.59 ± 2.69	0.15
		100	0.062	66.43 ± 0.38	
		150	0.029	84.40 ± 1.46	
Acarbose	–	50	0.113	38.46 ± 2.23	0.12
		100	0.071	61.14 ± 1.91	
		150	0.029	84.04 ± 2.90	

[a] Compound **14a**,**14c**,**14d** and **14g** are reported as PDF inhibitor elsewhere.[32][b] Each value is the mean ± S. D, standard deviation.

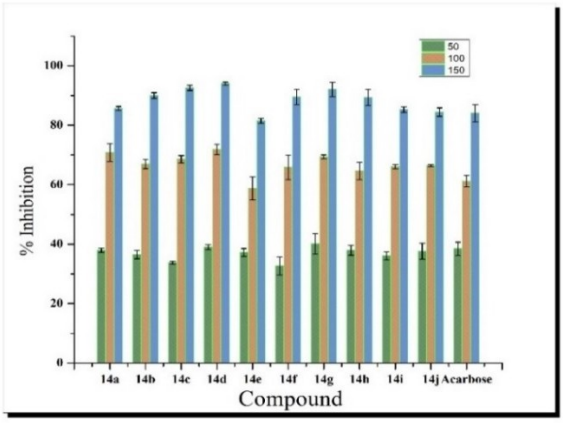


Figure 4. Comparative analysis of % Inhibition of compounds **14a–j**.

Molecular docking studies

The molecular docking is a useful tool to ascertain the possible drug-receptor interactions which might be responsible for the activity.[38] Acarbose ligand is known to bind with the active sites of barley (malt) α-amylase (PDB ID: 1RPK). Therefore to corroborate our in vitro inhibition result obtained from barley α-amylase activity, all the synthesized inhibitors (**14a–j**) along with Acarbose were docked into the active site of barley α-amylase. Subsequently, the inhibitor complexes with α-amylase were subjected to 10 ns molecular dynamics simulations to compute the binding energies using AMBER20/MMGPSA.py. The binding energies for the inhibitors with barley α-amylase is tabulated in Table 2. The docking protocol was validated for the bound structure of Acarbose. The RMSD calculated in-between the bound and the docked conformations of Acarbose were 0.899 Å. The figure depicting the overlay of the docked conformation of Acarbose (white carbons) on the bound conformation of Acarbose (green carbons) in the binding site of α-amylase is depicted in Figure 5. The computational studies revealed that all the inhibitors (**14a–j**) have a strong affinity towards Acarbose binding site with almost similar docking score and MMGBSA binding energies (Table 2). The binding interactions between the most potent inhibitor **14b**, **14c** and **14d** at the amino acid residues of barley α-amylase is depicted in Figure 6, while the same interactions is being tabulated in Table 3. The binding interaction and conformation study demonstrated that within the active site of barley α-amylase **14b** exhibited, π-π stacking interaction between biphenyl carbonitrile and Trp^{207} residue, **14c** showed H-bonding interaction with Arg^{183} and Asn^{209} through carbonyl and cyano group respectively and **14d** interacted with Arg^{178} & Arg^{183} residues *via* thiazolidinone motiey.

Thus, molecular docking study demonstrated that thiazolidinedione core and bipheylcarbonitrile unit of compound **14b**, **14c** and **14d** have strong interactions within the active site residues of α-amylase receptors which might be the cause of significant α-amylase inhibitory activities of these conjugates.

Table 2. Docking scores and MM-GBSA binding energies for the α-amylase inhibitors and Acarbose.

Sr. No.	Ligand	AutoDock/Vina (kcal/mol)	MM-GBSA binding energies (kcal/mol)
1	**14a**	−8.3	−47.12
2	**14b**	−9.1	−42.96
3	**14c**	−8.5	−33.10
4	**14d**	−8.2	−48.26
5	**14e**	−9.1	−46.37
6	**14f**	−8.3	−51.77
7	**14g**	−8.3	−43.38
8	**14h**	−8.3	−43.53
9	**14i**	−8.2	−30.07
10	**14j**	−8.4	−50.10
11	**Acarbose**	−7.5	−77.40

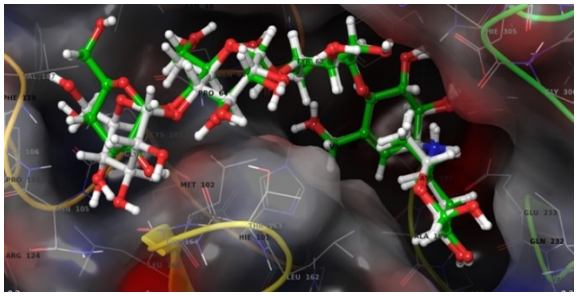


Figure 5. Overlay of the docked conformation of Acarbose (white carbons) on the bound conformation of Acarbose (green carbons).

Conclusion

A series of biphenylcarbonitrile-thiazolidinediones conjugates have been synthesized and evaluated for their antidiabetic activities. It was found that most of the synthesized conjugates (**14a–j**) demonstrated significant inhibitory potential against the enzyme α-amylase. Compound **14b**, **14c** and **14d** showed potent α-amylase inhibition compared to standard drug Acarbose. The molecular docking study of these conjugates into the active site of barley (malt) α-amylase enzyme revealed that inhibitors **14b**, **14c** and **14d** possessed strong binding affinity by interacting with Acarbose active site residues through thiazolidinediones and biphenylcarbonitrile moiety. This study has provided important contemplation about scaffold combination for targeting α-amylase. The potential

Table 3. Protein Ligand Non Covalent Interactions of the inhibitors **14b** and **14c** with the amino acid residues of the Acarbose binding site of barley alpha-amylase (PDB ID: 1RPK).

Compound	Hydro-phobic interaction	H-Bond donor interaction	π-stacking interaction
14b	Phe^{181}, Trp^{299}	–	Phe^{144}, Phe^{181}, Trp^{207}
14c	Phe^{181}, Trp^{299}	$Arg^{183(sc)}$, $Asn^{209(sc)}$	Phe^{144}, Trp^{207}, Trp^{299}
14d	Trp^{10}, Tyr^{52}, Phe^{181}, Trp^{207}	$Arg^{178(sc)}$, $Arg^{183(sc)}$, $Glu^{205(sc)}$, $Trp^{207(sc)}$, Met^{210}, $His^{290(sc)}$	Trp^{207}

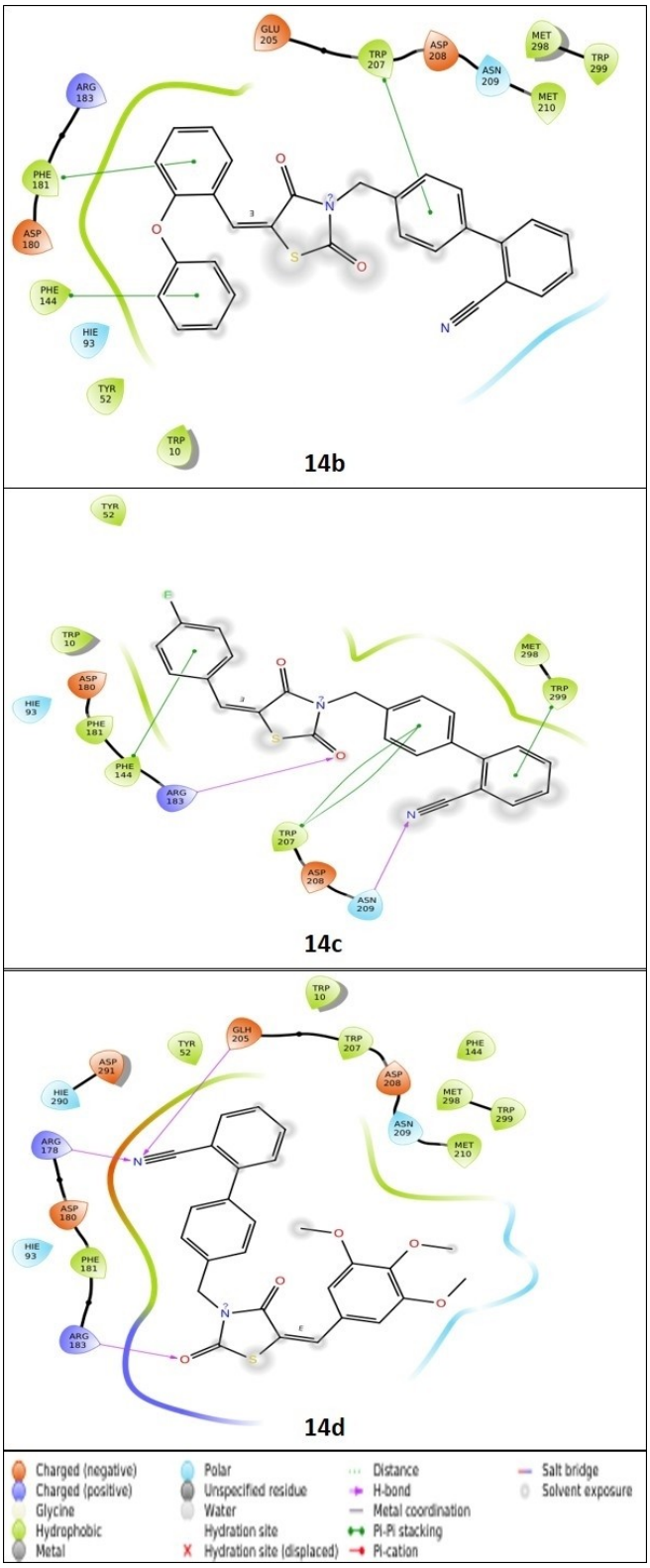


Figure 6. Two-dimensional (2D) binding site interactions of **14b**, **14c** and **14d** with the amino acids in the active site of barley α-amylase (PDB ID: 1RPK) predicted conformation of compound in the active site of α amylase.

candidates of the series, **14b**, **14c** and **14d** warrant further investigation for their utility in the management of type 2 DM.

Supporting Information Summary

For experimental procedures, three dimensional (3D) molecular docking interaction (Figure S1), representative NMR spectra and characterization of newly synthesized compounds see Supporting Information file.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: α-amylase inhibitor · antidiabetic activity · molecular docking · 2,4-thiazolidinedione · Type 2 Diabetes mellitus

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