Design, synthesis, molecular modelling, ADME prediction and anti-hyperglycemic evaluation of new pyrazole-triazolopyrimidine hybrids as potent α-glucosidase inhibitors

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\section{Introduction}

Diabetes mellitus is related to metabolic disorder, currently it became a major health problem around the world \cite{1,2}. International Diabetes Federation (IDF), estimated that 415 million people were affected by this disease in 2015 and this number may increase to 642 million by 2040 \cite{3–5}. The major form of diabetes is type-2 which is characterized by insulin resistance leads to the abnormal glucose levels in the blood called hyperglycemia \cite{6}. Hyperglycemia condition causes damage to various physiological processes in the body. D-glucose releases from the nonreducing end of the substrate by the hydrolase of the glucosidic O-linkage with the help of α-glucosidase enzyme \cite{7}. α-Glucosidase inhibitors prevent the hydrolysis of oligo or polysaccharides to glucose and thus reduce the postprandial rise of blood glucose \cite{8}. Inhibition of α-glucosidase enzyme in the digestive system is one of the best options to maintain postprandial glucose level by delaying carbohydrate absorption \cite{9}. The clinically used anti-diabetic drugs are effectively decreasing the glucose levels in type-2 diabetic patients. However, these drugs associated to side effects like flatulence, diarrhea and abdominal discomfort \cite{10,11}. Hence, there is an urgency to the design and development of new α-glucosidase inhibitors with higher efficacy and non-toxic nature.

In this context, pyrazole scaffolds have been reported as potent anti-diabetic agents in the literature \cite{12}. Pyrazole containing natural amino acid L-α-amino-β-(pyrazolyl-N)-propanoic acid isolated from \textit{Citrullus vulgaris} has potential anti-diabetic activity \cite{13}. Later, several entities of the pyrazole have been reported to possess potent anti-diabetic activity. For instance, pyrazole containing compound A (shown in Fig. 1) exhibited potent α-glucosidase inhibition activity \cite{14}. Kenneth et al. reported the pyrazole and pyrazolone derivatives as potent anti-hyperglycemic agents for the treatment of diabetes \cite{15} and Shuangjie et al. described the pyrazole containing derivatives as a potent glucagon receptor antagonist \cite{16,17}. The pyrazole heterocycles are also known to possess many other biological activities like anti-inflammatory, antimicrobial, anticancer and cyclooxygenase-2 inhibitor activities \cite{18}. Similarly, triazole and triazolopyrimidine derivatives are important...
K2CO3 for 4h. In order to optimize the reaction condition for the H₁-1,2,4-triazole under reflux condition in DMF and anhydrous with 1H-pyrazole-4-carbaldehyde substitution of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde.

2.1. Chemistry

The triazole linked compounds (Fig. 1, compound C) have shown good α-glucosidase activity. Satya and Shazia et al. have reported triazole based derivatives as potent α-glucosidase inhibitors. Triazolopyrimidines (Fig. 1, compound B) have been used for the treatment of diabetes as phosphodiesterase inhibitors through selective inhibition of dipeptidyl peptidase-4 (DPP4)

Further, in order to optimize the reaction condition, piperidine with different equivalents were tried. Notably, the reaction with 1.5 equivalents of piperidine gave the desired product 4a with a higher yield of 88% in 8 h and it was considered as the best-optimized reaction condition for the synthesis of target compounds derivatives 4a–n. Later, this reaction condition was successfully executed to synthesize the compounds 4a–n using various substituted acetophenones. Further, the final products were purified by the column chromatography. The compounds 4a–n were obtained in 6–10 h and yields ranging from 70 to 88% were depicted in Table 2.

The possible mechanism for the synthesis of the new pyrazole-triazolopyrimidine hybrid derivatives 4a–n was shown in Scheme 1. Initially, 3-methyl-1-phenyl-5-(1H-1,2,4-triazol-1-yl)-1H-pyrazole-4-carbaldehyde 1 was prepared by the nucleophilic substitution of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde with 1H-1,2,4-triazole under reflux condition in DMF and anhydrous KO2CO3 for 4 h. In order to optimize the reaction condition for the synthesis of the title compounds 4a–n, a pilot reaction was carried out by taking the trial reactants 3-methyl-1-phenyl-5-(1H-1,2,4-triazol-1-yl)-1H-pyrazole-4-carbaldehyde 1, acetophenone 2a and 4H-1,2,4-triazol-3-amine 3. The optimization results of the compound 4a were summarized in Table 1.

Initially, the reaction was carried out in different solvents such as methanol, ethanol, acetonitrile and dimethylformamide (DMF) under reflux condition resulting the product 4a with poor yields (Table 1, entries 1–4). Then, the reaction was tried in piperidine under reflux condition and observed that the compound 4a was formed with 78% yields in DMF solvent which is high compared to the other solvents (Entry 5–8). Later, the reaction was carried out in DMF with different bases such as triethylamine (TEA), DABCO and pyridine under reflux condition resulted in the product 4a with yields of 42%, 49% and 54% respectively (Entry 9–11). However, piperidine is high in terms of the yield and reaction time compared to the other bases.

The structures of all the synthesized compounds were well characterized by 1H NMR and 13C NMR, IR, mass spectral data and single crystal X-ray diffraction method (4j). For instance, the IR spectrum of 4j showed a band at 3435 cm⁻¹ corresponds to the N–H group of the pyrimidine ring. In the 1H NMR, the peak showed at δ 10.14 corresponds to N–H proton of the pyrimidine ring. The characteristic peaks appeared at δ 6.09 and 5.02 corresponds to the two protons attached to the C10, C11 carbons (Fig. 3). The 13C NMR spectrum showed the peaks at δ 94.52 and 51.25 corresponds C10, C11 carbons of pyrimidine ring (Fig. 3). Further, MS/MS spectra of the compounds (4h, 4j, 4k and 4m) were reported and consequently, the fragmentation pathway were reported (see supporting information). Here present MS/MS spectrum and fragmentation pattern of the compound 4j (Fig. 2 and Scheme 2).

The above all the spectral data confirms the structures of the compounds 4a–n and further confirmed by the single crystal X-ray
V. Pogaku, et al.

Bioorganic Chemistry 93 (2019) 103307

Table 1
Optimization conditions of the reaction parameters for the synthesis of 4a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>Methanol</td>
<td>–</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>–</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>ACN</td>
<td>–</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>Piperidine, 1 eq</td>
<td>8</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>Piperidine, 1 eq</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>Methanol</td>
<td>Piperidine, 1 eq</td>
<td>20</td>
<td>49</td>
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<td>7</td>
<td>Ethanol</td>
<td>Piperidine, 1 eq</td>
<td>18</td>
<td>54</td>
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<td>8</td>
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<td>Piperidine, 1 eq</td>
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<td>58</td>
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<tr>
<td>9</td>
<td>DMF</td>
<td>TEA, 1 eq</td>
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<td>10</td>
<td>DMF</td>
<td>Pyridine, 1 eq</td>
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<td>62</td>
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<td>11</td>
<td>DMF</td>
<td>DABCO, 1 eq</td>
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<td>88</td>
</tr>
<tr>
<td>12</td>
<td>DMF</td>
<td>Pyridine, 1.5 eq</td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td>13</td>
<td>DMF</td>
<td>Piperidine, 2.0 eq</td>
<td>8</td>
<td>84</td>
</tr>
</tbody>
</table>

* Reaction conditions: compound 1 (1 mmol), acetophenone 2a (1 mmol), 4H-1,2,4-triazol-3-amine 3 (1 mmol) and solvent under reflux condition.
* Isolated yields. Eq = equivalent.

2.2. Anti-diabetic activity

2.2.1. α-Glucosidase inhibitory activity

The new class of synthesized non-glycosidic pyrazole-triazolopyrimidine hybrids 4a-n was screened for their potency of α-glucosidase inhibitory activity against α-glucosidase enzyme [34,35] and acarbose was taken as a standard drug. The results were presented in Table 3 as IC50 values and the IC50 values were expressed in terms of µM. The IC50 values of the tested compounds ranged from 12.45 ± 0.59 to 52.58 ± 0.65 µM (Table 4) were calculated by statistical regression analysis. Among all the compounds, the compound 4h exhibited the excellent α-glucosidase inhibition activity with the IC50 value 12.45 µM, which is equal to the α-glucosidase inhibition activity of the standard drug acarbose (IC50: 12.68 µM). Similarly, the compounds 4f and 4i exhibited potent α-glucosidase inhibitory activity with IC50 values 14.47 and 17.27 µM. Further, the compounds 4g, 4n and 4j showed the significant activity with IC50 values 20.30 µM, 23.70 µM and 25.67 µM respectively. The compounds 4a, 4d, 4i and 4m exhibited moderate potency (IC50 values ≤ 40 µM), while rest of the compounds exhibited weak inhibitory potency (IC50 values > 40 µM) against the enzyme α-glucosidase.

2.2.2. Molecular docking studies

In silico docking studies were carried out to explore the binding mode of ligands and were docked into the active site of α-glucosidase enzyme (PDB ID: 3WY1) by employing the GOLD 5.6 tool [36]. The crystal structure of the α-glucosidase enzyme (3WY1) contains two chains A and B and for the docking studies chain A has selected with co-crystal ligand Polyacrylic acid. The binding profile for pyrazole-triazolopyrimidine hybrids 4a-n with α-glucosidase enzyme 3WY1 was determined and for each ligand ten conformations were generated. The conformation which is having the highest ranking was used for further analysis and gold fitness calculated using gold docking function. The gold score and interactions of the title compounds with receptors of the α-glucosidase protein 3WY1 have shown in Table 5.

All the compounds from this series 4a-n have exhibited prominent gold fitness docking scores ranging from 45.78 to 89.75. The analysis of the compound 4h (R = Chloro group) showed the highest gold score 89.45 and forms hydrogen bond, hydrophobic and van der waals interactions between compound 4h and α-glucosidase protein. Hydrogen bonds are formed with residues and with distances Asp62 (2.57 Å), Asp333 (2.58 Å) and Asp202 (2.56 Å). It also forms short contacts with residues His105 (2.55), Phe166 (2.63) and Phe203 (2.76). These interactions are similar to the crystal ligand octane-1,3,5,7-tetra-carboxylic acid with the following residues Arg400, Asp62, Arg200 Asp333 and Phe166. The nitrogen atom of the triazole ring was making a hydrogen bond with the oxygen atom of Asp 202 (2.56 Å). Moreover, the nitrogen atom of pyrazole ring was making a hydrogen bond with the oxygen atom of Asp62 (2.57 Å) and similarly Asp 333 forms two hydrogen bonds with the nitrogen atom of triazole and pyrimidine rings (Figs. 4 and 5).

The analysis of compound 4d (R = OC2H5 group) showed next highest gold score 63.67 and forms hydrogen bond, hydrophobic and van der waals interactions between compound 4d and α-glucosidase enzyme. Hydrogen bonds are formed with residues and with distances Arg200 (2.37), Glu271 (3.05), Gly228 (2.41) and Asp333 (2.62). It also forms short contacts with residues His105 (2.64), Phe166 (2.59), Arg333 (2.32) and Glu271 (2.39) (Fig. 4). The nitrogen atom of the...
Table 2
Synthesis of pyrazole-triazolopyrimidine derivatives 4a-n.

![Diagram of compounds 4a-n with reaction conditions: HCl (1 mmol), acetophenone 2a-n (1 mmol), 4H-1,2,4-triazol-3-amine 3 (1 mmol) in DMF (3 mL), piperidine (1.5 eq) under reflux condition.]

of absorption as shown in Table 6.

The violation of more than one of the Lipinski parameters (Table 6) may indicate problems in the bioavailability of the potential drugs. The results showed that most of the compounds complied with Lipinski's rule (Table 6), with exception slightly high molecular size more than 500 of compounds 4i, 4j and 4k and also some of the compounds like 4l and 4m were found to be 12 hydrogen bond acceptors upon their predicted value (> 10). All the analogues have shown logP values less than 5 which demonstrating good membrane permeability. TPSA which ranges from 91.29 to 137.11 Å and found to be less than 140 Å which is a very useful parameter for the transport of drug molecule. Finally summarizing the physicochemical properties of these analogs (4a-n), we could conclude that almost they obey the rule-of-five of Lipinski rule and meet all criteria for good orally active diabetic drug.

2.2.4. ADME predictions

The major parameters for pharmacokinetics are absorption, distribution, metabolism and excretion [38]. The in silico ADME properties of all the compounds 4a-n have shown satisfactory results. All the compounds have shown good intestinal absorption which are nearer to 100. The compounds have shown moderate permeability for in vitro Caco-2 cells ranges from 45.23 to 17.84 and low to moderate permeability for in vitro MDCK cells. Predicted In vivo blood-brain barrier penetration demonstrated that all the compounds have low absorption into the CNS and this indicates these compounds have less capability to cross the CNS. All the compounds have strong plasma protein binding value of more than 90% indicates strongly bound and also showed maximum skin permeability. Thus, from these results we observed that the synthesized pyrazole-triazolopyrimidine derivatives are having good drug likeliness and ADME property. The in silico predicted ADME properties and their values are shown in Table 7.

3. Conclusion

New pyrazole-triazolopyrimidine hybrids 4a-n were designed and synthesized with good yields by the multicomponent reaction. All the synthesized compounds were well characterized by IR, 1H NMR, 13C NMR, mass spectrometry and single crystal X-ray diffraction method (4j). The in vitro α-glucosidase inhibition activity of all the synthesized compounds was evaluated and six compounds were exhibited good α-glucosidase inhibition activity. Among these compounds, the compounds 4f and 4l have exhibited the potent activity with IC50 values 14.47 μM and 17.27 μM and particularly, the compound 4h (IC50 = 12.45 μM) exhibited excellent α-glucosidase inhibition activity to the standard drug acarbose (IC50 = 12.68 μM). The compounds 4g, 4n and 4j have exhibited the significant activity with IC50 values 20.30 μM, 23.70 μM and 25.67 μM. SAR studies indicate that, the chloro, fluoro and nitro substitution on phenyl ring would favour for the α-glucosidase inhibitory activity. Further, the in silico studies of the title compounds with α-glucosidase protein (PDB ID: 3WY1) were studied, the compounds 4h, 4l and 4f have shown the highest gold score (89.75, 63.18 and 57.30) which are highly correlated with in vitro α-glucosidase inhibition activity. The potent compounds 4h, 4l and 4f were exhibited good Drug-likeliness properties (ADME, Lipinski Parameters). Hence, these compounds could be promising hits for further development of new anti-diabetic drugs.

4. Experimental section

4.1. Chemistry

4.1.1. General procedure for the synthesis of title compounds 4a-n

A mixture of 3-methyl-1-phenyl-S-(1H-1,2,4-triazol-1-yl)-1H-pyrazole-4-carbaldehyde 1 (1 mmol), substituted acetophenones 2a-n (1 mmol) and 4H-1,2,4-triazol-3-amine 3 (1 mmol) were taken in 5 mL of dimethylformamide and added 1.5 equivalent of piperidine then
reflux the mixture for appropriate times (Tables 1 and 2). The progress of the reaction was monitored by TLC (eluent = n-hexane/ethyl acetate: 6/4). After completion of the reaction, the mixture was cooled to room temperature and added 20 mL of ice-cold water. The resulting solid was collected by filtration, washed with methanol and dried under vacuum. Further, the derivatives were purified by the column chromatography (n-hexane/ethyl acetate: 6/4).

4.1.2. General information

All the chemicals and solvents were purchased from Aldrich/Spectrochem. All melting points were checked by using Stuart SMP30 melting point apparatus (Bibby Scientific Ltd. United Kingdom) and were uncorrected. The reaction progress was checked with TLC plates (E. Merck, Mumbai, India) using UV light at 245 nm. Infrared spectra (IR) were recorded on KBr disc by using Perkin-Elmer 100S spectrophotometer (Perkin-Elmer Ltd., United Kingdom) from 400 to 4000 cm⁻¹. ¹H and ¹³C NMR spectra were recorded on Avance-III Bruker-400 MHz spectrometer (400 MHz, Bruker Corporation Ltd., Germany) using CDCl₃, DMSO-d₆ as solvent and TMS as an internal standard, chemical shifts are expressed as ppm and coupling constants (J values) were given in hertz (Hz). The CHN analysis was recorded on Carlo Erba EA 1108 automatic analyzer (Triad, NJ, USA) and the values are ± 0.4% of theoretical values. Mass spectra were determined on a Jeol JMSD-300 spectrometer (Jeol Ltd., Tokyo, Japan) and m/z values were represented on x-axis, the intensity values were reported on y-axis.

4.1.3. Crystallographic data of compound 4j

CCDC 1936467 contains the supplementary crystallographic data (.cif) of the compounds 4j. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

4.1.4. ESI-QTof-MS/MS condition

ToF-ESI-MS Experiments were carried on a Waters Xevo G2-MS time of flight (ToF) mass spectrometer (Waters, Milford, USA) connected to Waters H-Class inlet system. Spectra were acquired in ESI positive mode from m/z 50 to 1000. The capillary voltage set at 3 kV, sampling cone at
40 and source temperature was set at 120 °C. ToF-MS/MS Experiments were performed at different collision energies varying from 10 V to 55 V where argon gas was used for CID-MS/MS experiments. For ToF-MS and MS/MS analysis cone gas and desolvation gas (N₂) were set at 40 l/hr and 650 l/hr respectively with desolvation temperature adjusted at 300 °C. The inlet flow rate was adjusted at 0.1 mL/min with a mobile phase composition of water and acetonitrile mixed with 0.1% formic acid at a ratio of 15:85. Data processing and evaluation for MS experiments was performed with MassLynx v4.1 software SCN949 platform.

4.2. Biology

4.2.1. In vitro α-Glucosidase inhibitory activity

α-Glucosidase inhibitory activity was assayed by using 0.1 M phosphate buffer (pH 6.8) at room temperature [34,35]. The enzyme

![Scheme 2. Fragmentation pathway of the compound 4j.](attachment:image.png)
Inhibition 

\[ \frac{[A\text{A}]}{[\text{control}] \times 100} \]

×

Table 3
Salient crystallographic data and structure refinement parameters of the compound 4j.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>IC\text{50} (\mu M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>H</td>
<td>37.58 ± 0.98</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4-CH\text{3}</td>
<td>48.60 ± 0.37</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4-OCH\text{3}</td>
<td>52.58 ± 0.65</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-OC\text{H} \text{2}</td>
<td>27.56 ± 1.20</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>4-C\text{H} \text{5}</td>
<td>43.25 ± 0.54</td>
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<td>6</td>
<td>4f</td>
<td>4-F</td>
<td>14.47 ± 0.76</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>3-Cl</td>
<td>20.30 ± 0.19</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>4-Cl</td>
<td>12.45 ± 0.59</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>3-Br</td>
<td>30.79 ± 0.25</td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>4-Br</td>
<td>25.67 ± 0.43</td>
</tr>
<tr>
<td>11</td>
<td>4k</td>
<td>4-I</td>
<td>34.47 ± 0.83</td>
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<tr>
<td>12</td>
<td>4l</td>
<td>3-NO\text{2}</td>
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<tr>
<td>13</td>
<td>4m</td>
<td>4-NO\text{2}</td>
<td>35.33 ± 0.51</td>
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<tr>
<td>14</td>
<td>4n</td>
<td>4-CN</td>
<td>23.70 ± 1.50</td>
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<tr>
<td>15</td>
<td>Acarbose</td>
<td>—</td>
<td>12.68 ± 0.32</td>
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(0.1 U/mL) in phosphate buffer saline was incubated with various concentrations of pyrazole-triazolopyrimidine derivatives at room temperature for 20 min. Then 1.25 mM p-nitrophenyl-\( \alpha \)-D-glucopyranoside was added to the mixture as a substrate. The absorbance was measured spectrophotometrically at 405 nm after incubation at room temperature for 30 min. The sample solution was replaced by DMSO as a control. Acarbose was used as a positive control. IC\text{50} values were obtained as mean ± SD in triplicates as shown in Table 4.

%Inhibition = \[ \frac{[A\text{control} - A\text{sample}]}{A\text{control}} \times 100 \]

where \( A\text{control} \) = Absorbance of control; \( A\text{sample} \) = Absorbance of test compounds

4.2.2. Molecular docking calculations

All the molecules of pyrazole-triazolopyrimidine hybrids (4a-n) were built, then converted into 3D structures using Chimera and the structures were energy minimized by using AM1 method. The docking experiment were carried out on \( \alpha \)-glucosidase binding site (PDB ID: 3WY1, Resolution: 2.15 \AA) [https://www.rcsb.org/structure/3WY1],

which is a glycoside hydrolase family 13 (GH13), and hydrolysis \( \alpha-\) (1 → 4) linked disaccharides. The crude structure of the enzyme was cleaned by removing water molecules, other ligands are refined by competing the incomplete residues, then add hydrogen’s and optimized up to the RMS gradient 0.01. The optimized protein was saved as pdb file, which is further used for molecular docking studies. The docking simulation and calculations were carried out by using GOLD 5.6 and HERMES 1.9 interface software [https://www.ccdc.cam.ac.uk/products/gold_suite/] [36]. The active site selection was done by choosing the cavity having the maximum hydrophobic surface area and all the parameters are default settings for docking like rotation angle 30°, number of placements 30. So that the molecules would be rotated inside the receptor cavity to generate different ligand poses inside the cavity. At the end of the docking process, the minimum energy of interaction between the ligand and 3WY1 protein was obtained as gold

Table 5
Gold score and interactions of the title compounds with receptors of the protein 3WY1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Code</th>
<th>Gold score</th>
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<th>Short contacts (Å)</th>
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<tr>
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<td>4b</td>
<td>57.99</td>
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<tr>
<td>3</td>
<td>4c</td>
<td>35.58</td>
<td>Gly 228(2.17), Asp 333(2.54), Phe 297(2.70), Gly 271(2.31, 2.42, 2.58), Phe 147(2.57)</td>
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<tr>
<td>4</td>
<td>4d</td>
<td>63.67</td>
<td>Arg 200(2.37), His 105(2.64), Gly 271(3.05), Arg 333(2.32), Asp 333(2.62), Gly 228(2.12), Phe 147(2.58), Asp 333(2.44)</td>
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<tr>
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<td>4e</td>
<td>42.98</td>
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</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>57.30</td>
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<tr>
<td>7</td>
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<td>8</td>
<td>4h</td>
<td>89.75</td>
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<tr>
<td>12</td>
<td>4l</td>
<td>63.18</td>
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<td>13</td>
<td>4m</td>
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<tr>
<td>14</td>
<td>4n</td>
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<td>Gly 228(2.48), Gly 228(2.48), Gly 228(2.48), Gly 228(2.48), Gly 228(2.48), Gly 228(2.48), Gly 228(2.48), Gly 228(2.48)</td>
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<tr>
<td>15</td>
<td>Acarbose</td>
<td>—</td>
<td>12.68 ± 0.32</td>
<td></td>
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</table>

fitness as a scoring function. The results of the docking scores for each ligand are shown in Table 5. Interactions of 3D and 2D poses between protein and ligands were obtained by Pymol and Ligplot.

4.2.3. ADME predictions

The in silico ADME properties of these synthesized compounds were calculated by using the online server preADMET (http://preadmet.bmdrc.org/) [37,38]. The ADMET properties, human intestinal absorption (HIA), Caco-2 cell permeability, Maden Darby Canine Kidney (MDCK) cell permeability, plasma protein binding and blood brain barrier penetration (BBB) were predicted using this program.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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