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Synthesis, *α*-Glucosidase inhibitory activity and docking studies of Novel Ethyl 1,2,3-triazol-4-ylmethylthio-5,6-diphenylpyridazine-4-carboxylate derivatives

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Abstract

In this work, a novel series of pyridazine-triazole hybrid molecules were prepared and evaluated as inhibitors of rat intestinal *α*-glucosidase enzyme. Amongst all newly synthesized compounds, **10k** showed good inhibition in the series with IC_{50} value of 1.7 μM which is 100 folds stronger than positive control, acarbose. The cytotoxicity revealed that this compound is not toxic against normal cell line, HDF. The docking studies showed that triazole ring plays an important role in the binding interactions with the active site. The insertion of compound **10k** into the active pocket of *α*-glucosidase and formation of hydrogen bonds with Leu677 was observed from docking studies. The kinetic studies revealed that this compound has uncompetitive mode of inhibition against *α*-glucosidase enzyme.

Keywords Pyridizine, *α*-Glucosidase, Click reaction, Triazole, Copper iodide, Diabetes

Introduction

Diabetes Mellitus (DM) is considered as a progressive hormonic and metabolic disorder of endocrine system which is characterized by the body's loss of control over blood sugar (glucose) [1]. According to the WHO report, 422 million people worldwide [2] are suffering from diabetes which is associated with increased risks of quite a few micro- and macro-vascular complications such as stroke, retinopathy, neuropathy, nephropathy, coronary artery disease, hypertension and peripheral vascular disease [3–6]. This disease is divided into type 1 diabetes mellitus [T1DM] (resulted from insulin deficiency) and type 2 diabetes mellitus [T2DM] (resulted from resistance towards insulin). Type 2 is the most common type and accounts for 90% of all diabetic patients. Most of the medical approaches are focused on the

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reduction of the postprandial glucose (PG) level in blood. Current treatment approaches include oral antidiabetic drugs such as sulfonylureas, thiazolidinediones, metformin, α-glucosidase inhibitors and glycosurics. α-Glucosidase (EC3.2.1.20) belongs to a glycoside hydrolase enzyme releasing monosaccharides through the lysis of α-glucopyranoside bond in saccharide polymer, oligosaccharides, and disaccharides from the non-reducing portion of the oligomeric substrate [7]. Inhibiting the digestion and absorption of carbohydrates by using α-glucosidase inhibitors slows down carbohydrate digestion, stabilizes blood glucose level and consequently prevents hyperglycemia in diabetic patients. Three glucosidase inhibitors have been introduced to the market and all are carbohydrate mimics. Acarbose, voglibose, and miglitol have been used in the treatment of Type 2 diabetes (T2M) by inhibiting the activity of α-glucosidase and consequently the formation of glucose in the small intestine [8–12].

Heterocyclic rings along with sugar-mimic compounds have been emerged as privileged cores in inhibiting glucosidase [13]. Amongst diverse array of heterocyclic cores, nitrogen-containing rings have found a unique place as α-glucosidase inhibitors [14–17] and medicinal chemists are still exploring for new molecules containing these valuable pharmacophores. Since decades, pyridazines and its related compounds have attracted great attention because of their therapeutic importance. The literature survey revealed that this heterocyclic core is present in quite a few number of compounds with different pharmacological properties [18–26].

Click reaction, articulated by Sharpless [27, 28], has been considered as a reliable and practical strategy to improve inefficiencies and slownesses of conventional drug discovery. This method provides a facile and revolutionary approach to the invention of drug-like molecules and completion of combinatorial libraries without the need to professional skill and equipment. In addition, this reaction has provided a powerful way to assemble molecules with well-defined biological functions and proteomic applications through making carbon-heteroatom-carbon bond.

The copper-mediated azide–alkyne cycloaddition is a standard and ideal method to achieve triazole ring as a linker and functional moiety. This useful pharmacophore is one of the most important five-membered heterocyclic rings which could be easily synthesized with no sensitivity to water and oxygen and the need for purification techniques. This valuable scaffold also found in various drugs namely antifungal drugs and bioactive compounds with antibacterial, antiviral, and anti-HIV properties [29–31].

In recent years, we identified various heterocyclic cores as potential α-glucosidase inhibitors [32–35]. Keeping in mind that still there is an urgent need to develop lead candidates, we decided to synthesize novel pyridazine-containing compounds considering the bioisosteric relationship between pyridazine and triazine and the number of triazine-containing compounds with α-glucosidase inhibitory activity (Fig. 1) [36–41]. Triazoles were also reported in the literature as inhibitors of α-glucosidase enzyme [42]. In this regard, we combined both these cores in one molecule and evaluated their inhibitory activities against α-glucosidase enzyme along with kinetic, docking and cytotoxic studies.

Experimental section

Chemistry

Synthesis of hydrazono-1,2-diphenylethanone (2)

A solution of benzil and hydrazine hydrate in methanol was heated at reflux temperature for 15 min. Then, the reaction mixture was cooled to room temperature and the white solid was collected by filtration, washed with cold methanol and dried [43].

Synthesis of ethyl 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carboxylate (3)

A suspension of sodium (0.05 mol) in 200 mL ethanol was chilled to 0 °C and after 15 min, diethyl malonate (0.075 mol) and compound **2** (0.05 mol) were added to the mixture. The mixture was refluxed for 3 h. Upon solvent removal, the residue was acidified with HCl (1 N). The resultant solid was collected and washed with water.

Synthesis of ethyl 3-mercapto-5,6-diphenylpyridazine-4-carboxylate (4)

Lawesson's reagent (10 mmol) was added to the mixture of compound **3** (20 mmol) in toluene (150 mL). The mixture was stirred at reflux temperature for 18 h. After cooling, the solid was separated and washed with toluene, dried and recrystallized from petroleum ether/ethyl acetate.

Synthesis of ethyl 5,6-diphenyl-3-(prop-2-yn-1-ylthio) pyridazine-4-carboxylate (5)

Propargyl bromide (12 mmol) was added to the mixture of compound **4** (10 mmol) and K_2CO_3 (10 mmol) in DMF (10 mL), and the mixture was stirred at 50 °C. Upon completion, the reaction was stopped with ice/water mixture and the solid was filtered and washed with water.

Synthesis of 2-chloro-N-arylacetamide (8)

Chloroacetyl chloride (10 mmol) was added to the ice-cooled solution of aromatic amines (10 mmol) and triethylamine (12 mmol) in 1,2-dichloroethane (20 mL). After 6 h stirring at room temperature, petroleum ether was added to the mixture and the solid was filtered and recrystallized from ethanol.

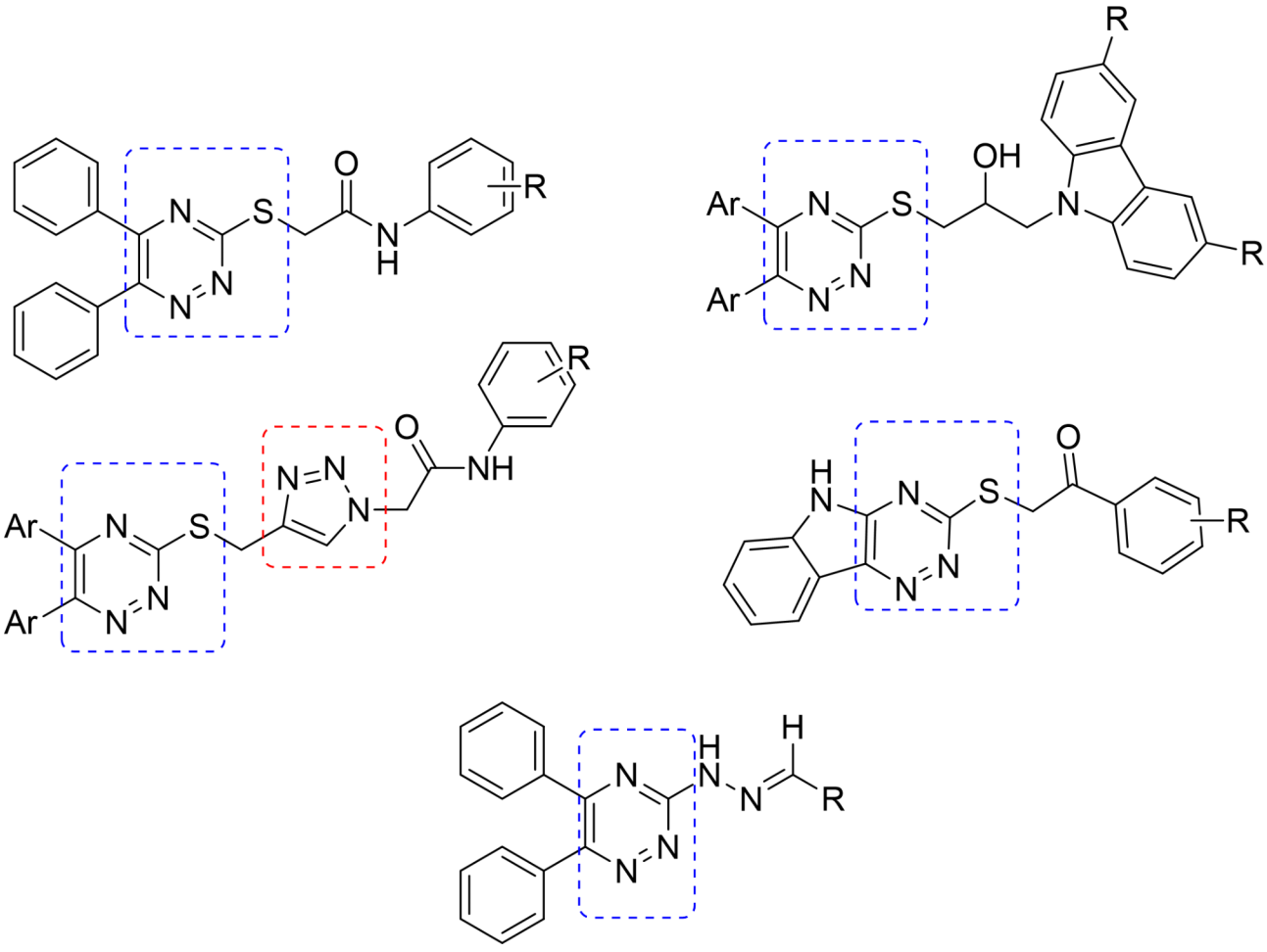


Fig. 1 Chemical structures of triazine-containing molecules with *α*-glucosidase inhibitory activity

Synthesis of 2-azido-N-phenylacetamide (9)

A solution of compound 8 (10 mmol) and sodium azide (15 mmol) in dimethyl sulfoxide (20 mL) was stirred at room temperature. Upon completion, indicated by TLC, The reaction mixture was poured into ice/water and the solid was filtered and recrystallized from petroleum ether/ethyl acetate.

Synthesis of target compounds (10a-r)

To the suspension of compound **9** (1 mmol) and compound 5 (1 mmol) in DMF (10 mL), CuI (10 mol %) and triethylamine (1 mmol) was added. The mixture was stirred at room temperature until TLC indicated the disappearance of starting materials. The reaction mixture was poured into ice/water and the solid was collected and washed with water. The solid was recrystallized from ethanol.

Ethyl 3-(((1-(2-oxo-2-(phenylamino)ethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10a)

Yield (65%, 0.36 g); Dark Yellow solid; M.p. = 147–149 °C; IR (KBr, cm^{-1}): 3611, 1730 (C=O), 1652, 1435, 1341, 1160; ^{1} H NMR (DMSO-d_6, 500 MHz): δ 0.86 (t, *J*=7.1 Hz, 3 H), 4.03 (q, *J*=7.2 Hz, 2 H), 4.79 (s, 2 H), 5.32 (s, 2 H), 7.07 (t, *J*=8.0 Hz, 1 H), 7.13 (d, *J*=8.1 Hz, 2 H), 7.25–7.32 (m, 10 H), 7.56 (d, *J*=8.3 Hz, 2 H), 8.13 (s, 1 H), 10.45 (s, 1 H); ^{13} C NMR (DMSO-d_6, 100 MHz): δ 13.4, 24.5, 52.9, 62.0, 116.5, 119.2, 124.7, 127.3, 128.3, 128.6 128.8, 129.2, 129.5, 131.2, 134.0, 135.0, 136.2, 138.3, 138.5, 142.0, 155.1, 157.5, 164.1, 166.3; Anal. Calcd. for $C_{30}H_{26}N_6O_3S$: C, 65.44; H, 4.76; N, 15.26. Found: C, 65.20; H, 4.57; N, 14.98; ESI-MS *m/z*: 550.2 $[M]^+$.

Ethyl 3-(((1-(2-oxo-2-(m-tolylamino)ethyl)- H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10b)

Yield (71%, 0.40 g); Dark Yellow solid; m.p. = 171–173 °C; IR (KBr, cm^{-1}): 3623, 1717 (C=O), 1638, 1422, 1319, 1195; ^{1} H NMR (DMSO-d_6, 300 MHz): δ 0.87 (t,

J=6.9 Hz, 3 H), 2.25 (s, 3 H), 4.03 (q, *J*=7.2 Hz, 2 H), 4.79 (s, 2 H), 5.30 (s, 2 H), 7.19–7.30 (m, 14 H), 8.12 (s, 1 H), 10.37 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 21.1, 24.7, 52.2, 62.1, 116.4, 119.7, 124.4, 127.8, 128.26, 128.33, 128.6, 128.8, 128.9, 129.0, 129.6, 130.4, 133.6, 135.2, 136.0, 138.1, 138.3, 142.4, 155.4, 157.3, 164.0, 166.4; Anal. Calcd. for $C_{31}H_{28}N_6O_3S$: C, 65.94; H, 5.00; N, 14.88. Found: C, 65.60; H, 4.72; N, 14.59; ESI-MS *m/z*: 564.2 $[M]^+$.

Ethyl 3-(((1-(2-oxo-2-(p-tolylamino)ethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10c)

Yield (70%, 0.39 g); Dark Yellow solid; m.p. = 207–209 °C; IR (KBr, cm^{-1}): 3617, 1720 (C=O), 1642, 1442, 1330, 1177; ^{1} H NMR (DMSO-d_6, 500 MHz): δ 0.89 (t, *J*=7.1 Hz, 3 H), 2.26 (s, 3 H), 4.05 (q, *J*=7.0 Hz, 2 H), 4.81 (s, 2 H), 5.31 (s, 2 H), 7.12–7.16 (m, 4 H), 7.27–7.36 (m, 8 H), 7.45–7.48 (m, 2 H), 8.14 (s, 1 H), 10.37 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): 13.2, 21.0, 24.6, 52.3, 62.0, 116.5, 119.8, 125.0, 126.9, 127.3, 127.7, 128.5, 128.9, 129.1, 129.7, 130.2, 132.9, 135.0, 136.1, 138.4, 142.2, 155.0, 157.1, 164.1, 166.2; Anal. Calcd. for $C_{31}H_{28}N_6O_3S$: C, 65.94; H, 5.00; N, 14.88. Found: C, 66.20; H, 4.73; N, 15.11; ESI-MS *m/z*: 565.1 $[M+H]^+$.

Ethyl 3-(((1-(2-((4-isopropylphenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10d)

Yield (68%, 0.40 g); Dark Yellow solid; m.p. = 183–185 °C; IR (KBr, cm^{-1}): 3611, 1719 (C=O), 1652, 1441, 1325, 1178; ^{1} H NMR (DMSO-d_6, 500 MHz): δ 0.83–0.90 (m, 9 H), 2.56–2.58 (m, 1 H), 4.03 (q, *J*=7.0 Hz, 2 H), 4.81 (s, 2 H), 5.33 (s, 2 H), 7.13–7.18 (m, 2 H), 7.29–7.37 (m, 12 H), 8.16 (s, 1 H), 10.53 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): δ 13.8, 24.3, 25.2, 33.6, 52.6, 62.6, 115.9, 116.0, 121.5, 126.0, 127.1, 128.3, 128.8, 129.1, 129.3, 129.5, 130.0, 130.1, 130.9, 134.1, 135.2, 136.5, 156.0, 157.9, 164.5, 164.6; Anal. Calcd. for $C_{33}H_{32}N_6O_3S$: C, 66.87; H, 5.44; N, 14.18. Found: C, 66.57; H, 5.12; N, 13.85; ESI-MS *m/z*: 592.2 $[M]^+$.

Ethyl 3-(((1-(2-((3-methoxyphenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10e)

Yield (72%, 0.41 g); Dark Yellow solid; m.p. = 155–157 °C; IR (KBr, cm^{-1}): 3622, 1718 (C=O), 1639, 1451, 1333, 1175; ^{1} H NMR (DMSO-d_6, 300 MHz): δ 0.87 (t, *J*=7.1 Hz, 3 H), 3.70 (s, 3 H), 4.06 (q, *J*=7.0 Hz, 2 H), 4.79 (s, 2 H), 5.31 (s, 2 H), 6.64 (d, *J*=6.8 Hz, 1 H), 7.07–7.32 (m, 13 H), 8.13 (s, 1 H), 10.44 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 24.7, 52.2, 55.0, 62.1, 104.9, 109.2, 111.4, 127.8, 128.3, 128.34, 128.58, 128.80, 128.86, 128.97, 129.6, 130.4, 133.6, 135.2, 136.0, 139.5, 142.4, 155.4, 157.3, 159.5, 164.0, 164.6; Anal. Calcd. for $C_{31}H_{28}N_6O_4S$: C, 64.12; H, 4.86; N, 14.47. Found: C, 63.88; H, 4.57; N, 14.72; ESI-MS *m/z*: 581.2 $[M+H]^+$.

Ethyl 3-(((1-(2-((4-methoxyphenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10f)

Yield (66%, 0.38 g); Dark Yellow solid; m.p. = 230–232 °C; IR (KBr, cm^{-1}): 3601, 1724 (C=O), 1644, 1439, 1327, 1180; ^{1} H NMR (DMSO-d_6, 300 MHz): δ 0.87 (t, *J*=7.1 Hz, 3 H), 3.70 (s, 3 H), 4.03 (q, *J*=7.0 Hz, 2 H), 4.79 (s, 2 H), 5.29 (s, 2 H), 6.88 (d, *J*=8.1 Hz, 2 H), 7.07–7.32 (m, 10 H), 7.49 (d, *J*=6.8 Hz, 2 H), 8.13 (s, 1 H), 10.33 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 24.7, 52.1, 55.1, 62.0, 113.9, 120.7, 125.4, 127.8, 128.3, 128.34, 128.8, 128.85, 129.6, 130.4, 131.4, 133.56, 133.62, 135.2, 136.0, 142.3, 155.5, 157.3, 163.6, 164.0; Anal. Calcd. for $C_{31}H_{28}N_6O_4S$: C, 64.12; H, 4.86; N, 14.47. Found: C, 63.90; H, 4.52; N, 14.74; ESI-MS *m/z*: 580.1 $[M]^+$.

Ethyl 3-(((1-(2-((4-fluorophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10 g)

Yield (79%, 0.45 g); Dark Yellow solid; m.p. = 211–213 °C; IR (KBr, cm^{-1}): 3616, 1731 (C=O), 1639, 1442, 1332, 1191; ^{1} H NMR (DMSO-d_6, 500 MHz): δ 0.89 (t, *J*=7.1 Hz, 3 H), 4.06 (q, *J*=7.0 Hz, 2 H), 4.81 (s, 2 H), 5.33 (s, 2 H), 7.15–7.17 (m, 2 H), 7.27–7.32 (m, 10 H), 7.64–7.66 (m, 2 H), 8.16 (s, 1 H), 10.82 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): δ, 13.8, 25.2, 52.6, 62.6, 115.9 (d, *J*=21 Hz), 121.5 (d, *J*=8 Hz), 128.2, 128.3, 128.8, 129.1, 129.3, 129.5, 129.6, 129.7, 130.1, 130.9, 134.1, 135.2, 136.5, 156.0, 157.9, 162.3 (d, *J*=248 Hz), 164.5, 165.6; Anal. Calcd. for $C_{30}H_{25}FN_6O_3S$: C, 63.37; H, 4.43; N, 14.78. Found: C, 63.02; H, 4.69; N, 15.01; ESI-MS *m/z*: 568.2 $[M]^+$.

Ethyl 3-(((1-(2-((2-chlorophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10 h)

Yield (62%, 0.36 g); Dark Yellow solid; m.p. = 161–163 °C; IR (KBr, cm^{-1}): 3607, 1730 (C=O), 1639, 1445, 1358, 1166; ^{1} H NMR (DMSO-d_6, 300 MHz): δ=0.87 (t, *J*=6.8 Hz, 3 H), 4.03 (q, *J*=6.7 Hz, 2 H), 4.79 (s, 2 H), 5.44 (s, 2 H), 7.13–7.15 (m, 2 H), 7.28–7.44 (m, 10 H), 7.49 (d, *J*=7.8 Hz, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 8.16 (s, 1 H), 10.04 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.2, 24.7, 51.9, 62.0, 125.7, 126.1, 126.6, 127.4, 127.8, 128.2, 128.3, 128.5, 128.76, 128.82, 128.94, 129.5, 129.6, 130.4, 133.6, 134.1, 135.1, 135.9, 155.4, 157.3, 164.0, 164.8; Anal. Calcd. for $C_{30}H_{25}ClN_6O_3S$: C, 61.59; H, 4.31; N, 14.36. Found: C, 61.80; H, 4.14; N, 14.69; ESI-MS *m/z*: 586.1 $[M+2]^+$.

Ethyl 3-(((1-(2-((3-chlorophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10i)

Yield (60%, 0.35 g); Dark Yellow solid; m.p. = 200–202 °C; IR (KBr, cm^{-1}): 3621, 1730 (C=O), 1639, 1429, 1341, 1175; ^{1} H NMR (DMSO-d_6, 300 MHz): δ=0.87 (t, *J*=7.0 Hz, 3 H), 4.03 (q, *J*=6.7 Hz, 2 H), 4.79 (s, 2 H), 5.33 (s, 2 H), 7.12–7.14 (m, 3 H), 7.26–7.44 (m, 10 H), 7.44 (d, *J*=8.1 Hz, 1 H), 8.13 (s, 1 H), 10.64 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 24.7, 52.2, 62.0, 117.6, 118.7, 123.4, 125.5, 127.8, 128.2, 128.3, 128.8, 128.9, 129.6, 130.4, 130.5, 133.1, 133.5, 133.6, 135.1, 135.9, 139.8, 155.4, 157.3, 164.0, 164.6; Anal. Calcd. for $C_{30}H_{25}ClN_6O_3S$: C, 61.59; H, 4.31; N, 14.36. Found: C, 61.31; H, 4.53; N, 14.02; ESI-MS *m/z*: 586.2 $[M+2]^+$.

Ethyl 3-(((1-(2-((4-chlorophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10j)

Yield (74%, 0.43 g); Dark Yellow solid; m.p. = 195–197 °C; IR (KBr, cm^{-1}): 3622, 1710 (C=O), 1646, 1442, 1331, 1192; ^{1} H NMR (DMSO-d_6, 500 MHz): δ=0.89 (t, *J*=7.0 Hz, 3 H), 4.06 (q, *J*=6.9 Hz, 2 H), 4.81 (s, 2 H), 5.43 (s, 2 H), 7.13–7.15 (m, 2 H), 7.20–7.30 (m, 10 H), 7.83 (d, *J*=8.5 Hz, 2 H), 8.18 (s, 1 H), 11.06 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): δ 13.8, 25.2, 52.8, 62.6, 119.5, 125.6, 128.3, 128.79, 128.86, 129.1, 129.3, 129.5, 130.0, 130.1, 130.9, 134.1, 135.7, 136.5, 143.1, 145.0, 155.9, 157.9, 164.5, 165.8; Anal. Calcd. for $C_{30}H_{25}ClN_6O_3S$: C, 61.59; H, 4.31; N, 14.36. Found: C, 61.25; H, 4.60; N, 14.02.

Ethyl 3-(((1-(2-((4-bromophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10k)

Yield (61%, 0.38 g); Dark Yellow solid; m.p. = 224–226 °C; IR (KBr, cm^{-1}): 3632, 1730 (C=O), 1651, 1440, 1352, 1191; ^{1} H NMR (DMSO-d_6, 300 MHz): δ=0.86 (t, *J*=6.9 Hz, 3 H), 4.02 (q, *J*=6.8 Hz, 2 H), 4.80 (s, 2 H), 5.33 (s, 2 H), 7.15–7.16 (m, 2 H), 7.27–7.37 (m, 10 H), 7.54 (d, *J*=8.9 Hz, 2 H), 8.14 (s, 1 H), 10.60 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 24.7, 52.2, 62.0, 115.4, 121.1, 127.8, 128.2, 128.3, 128.6, 128.8, 128.9, 129.0, 129.6, 130.4, 131.6, 133.6, 135.2, 135.9, 137.7. 155.4, 157.3, 164.0, 164.3; Anal. Calcd. for $C_{30}H_{25}BrN_6O_3S$: C, 57.24; H, 4.00; N, 13.35. Found: C, 57.00; H, 4.25; N, 13.60; ESI-MS *m/z*: 630.1 $[M+2]^+$.

Ethyl 3-(((1-(2-((3,5-dichlorophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10 l)

Yield (64%, 0.39 g); Dark Yellow solid; m.p. = 185–187 °C; IR (KBr, cm^{-1}): 3616, 1733 (C=O), 1631, 1444, 1330, 1166; ^{1} H NMR (DMSO-d_6, 500 MHz): δ=0.86 (t, *J*=7.1 Hz, 3 H), 4.02 (q, *J*=7.0 Hz, 2 H), 4.81 (s, 2 H), 5.40 (s, 2 H), 7.29–7.37 (m, 10 H), 7.77–7.78 (m, 3 H), 8.17 (s, 1 H), 10.90 (s, 1 H).; ^{13} C NMR (DMSO-d_6, 125 MHz): δ 13.8, 25.2, 52.8, 62.6, 106.1, 119.4, 119.8, 126.0, 128.8, 129.1, 129.3, 129.5, 130.1, 130.9, 133.8, 133.9, 134.1, 135.7, 136.5, 143.0, 155.9, 157.9, 164.5, 165.6.; Anal. Calcd. for $C_{30}H_{24}Cl_2N_6O_3S$: C, 58.16; H, 3.90; N, 13.57. Found: C, 57.95; H, 4.22; N, 13.80; ESI-MS *m/z*: 622.1 $[M+4]^+$.

Ethyl 3-(((1-(2-((3,4-dichlorophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10 m)

Yield (78%, 0.48 g); Dark Yellow solid; m.p. = 166–168 °C; IR (KBr, cm^{-1}): 3606, 1725 (C=O), 1639, 1441, 1330, 1175; ^{1} H NMR (DMSO-d_6, 500 MHz): δ=0.86 (t, *J*=6.4 Hz, 3 H), 4.02 (m, 2 H), 4.80 (s, 2 H), 5.35 (s, 2 H), 7.30–7.42 (m, 12 H), 7.54 (s, 1 H), 8.15 (s, 1 H), 10.77 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): δ 13.3, 24.7, 52.2, 62.1, 119.2, 120.4, 125.3, 125.5, 127.8, 128.3, 128.6, 128.8, 129.0, 129.6, 130.4, 130.8, 131.1, 133.5, 133.6, 135.1, 135.9, 138.4, 155.4, 157.3, 164.0, 164.8; Anal. Calcd. for $C_{30}H_{24}Cl_2N_6O_3S$: C, 58.16; H, 3.90; N, 13.57. Found: C, 58.42; H, 3.61; N, 13.39; ESI-MS *m/z*: 622.3 $[M+4]^+$.

Ethyl 3-(((1-(2-((3-cyanophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10n)

Yield (70%, 0.40 g); Dark Yellow solid; m.p. = 196–198 °C; IR (KBr, cm^{-1}): 3601, 2221, 1724 (C=O), 1644, 1439, 1327, 1180; ^{1} H NMR (DMSO-d_6, 500 MHz): δ=0.89 (t, *J*=6.4 Hz, 3 H), 4.06 (m, 2 H), 4.81 (s, 2 H), 5.32 (s, 2 H), 7.16–7.21 (m, 5 H), 7.29–7.33 (m, 6 H), 7.48–7.51 (m, 3 H), 8.15 (s, 1 H), 10.40 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): δ 13.8, 24.4, 52.7, 62.6, 119.8, 119.9, 126.0, 127.0, 127.1, 128.3, 128.8, 129.1, 129.3, 129.5, 130.2, 130.9, 134.1 (2 C), 135.7, 136.5, 136.6, 142.9, 144.3, 156.0, 158.0, 164.5, 166.4; Anal. Calcd. for $C_{31}H_{25}N_7O_3S$: C, 64.68; H, 4.38; N, 17.03. Found: C, 64.99; H, 4.55; N, 16.88; ESI-MS *m/z*: 575.2 $[M]^+$.

Ethyl 3-(((1-(2-((3-nitrophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10p)

Yield (81%, 0.48 g); Dark Yellow solid; m.p. = 201–203 °C; IR (KBr, cm^{-1}): 3592, 1730 (C=O), 1637, 1549, 1432, 1356, 1189; ^{1} H NMR (DMSO-d_6, 300 MHz): δ=0.87 (t, *J*=7.0 Hz, 3 H), 4.06 (d, *J*=6.8 Hz, 2 H), 4.80 (s, 2 H), 5.39 (s, 2 H), 7.13 (t, *J*=6.8 Hz, 2 H), 7.32–7.45 (m, 9 H), 7.61 (t, *J*=7.8 Hz, 1 H), 7.91 (t, *J*=8.0 Hz, 1 H), 8.17 (s, 1 H), 8.58 (s, 1 H), 10.97 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 24.7, 52.2, 62.1, 113.4, 118.3, 125.1, 127.8, 128.3, 128.4, 128.6, 128.8, 128.9, 129.0, 129.6, 130.4, 133.5, 133.6, 135.2, 136.0, 139.4, 147.9, 155.4, 157.3, 164.0, 165.1; Anal. Calcd. for $C_{30}H_{25}N_7O_5S$: C,

60.49; H, 4.23; N, 16.46. Found: C, 60.69; H, 3.99; N, 16.19; ESI-MS *m/z*: 595.2 $[M]^+$.

Ethyl 3-(((1-(2-((4-nitrophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10q)

Yield (73%, 0.43 g); Dark Yellow solid; m.p. = 221–223 °C; IR (KBr, cm^{-1}): 3610, 1712 (C=O), 1636, 1560, 1432, 1352, 1179; ^{1} H NMR (DMSO-d_6, 500 MHz): δ=0.89 (t, *J*=6.4 Hz, 3 H), 4.07 (m, 2 H), 4.81 (s, 2 H), 5.35 (s, 2 H), 7.16 (d, *J*=8.1 Hz, 2 H), 7.29–7.40 (m, 10 H), 7.16 (d, *J*=8.2 Hz, 2 H), 8.16 (s, 1 H), 10.61 (s, 1 H); ^{13} C NMR (DMSO-d_6, 125 MHz): δ 13.8, 25.2, 52.7, 62.6, 121.2, 121.3, 126.0, 127.8, 128.3, 128.8, 129.1, 129.2, 129.3, 129.5, 130.1, 130.9, 134.1, 135.7, 136.4, 137.8, 155.9, 157.8, 164.5, 164.9; Anal. Calcd. for $C_{30}H_{25}N_7O_5S$: C, 60.49; H, 4.23; N, 16.46. Found: C, 60.18; H, 4.09; N, 16.66; ESI-MS *m/z*: 596.1 $[M+H]^+$.

Ethyl 3-(((1-(2-((3-methyl-4-nitrophenyl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5,6-diphenylpyridazine-4-carboxylate (10r)

Yield (65%, 0.39 g); Dark Yellow solid; m.p. = 212–214 °C; IR (KBr, cm^{-1}): 3602, 1722 (C=O), 1641, 1551, 1448, 1352, 1182; ^{1} H NMR (DMSO-d_6, 300 MHz): δ=0.86 (t, *J*=6.4 Hz, 3 H), 1.10 (s, 3 H), 4.04 (m, 2 H), 4.80 (s, 2 H), 5.37 (s, 2 H), 7.13 (d, *J*=6.8 Hz, 2 H), 7.28–7.32 (m, 9 H), 7.40–7.43 (m, 1 H), 8.17 (m, 1 H), 8.33 (s, 1 H), 10.85 (s, 1 H); ^{13} C NMR (DMSO-d_6, 75 MHz): δ 13.3, 19.2, 24.7, 52.2, 62.1, 114.5, 123.7, 127.7, 127.8, 128.27, 128.34, 128.6, 128.8, 128.86, 128.97, 129.6, 130.4, 133.2, 133.6, 135.2, 136.0, 137.2, 148.5, 155.5, 157.3, 164.0, 164.8; Anal. Calcd. for $C_{31}H_{27}N_7O_5S$: C, 61.07; H, 4.46; N, 16.08. Found: C, 60.75; H, 4.19; N, 16.40; ESI-MS *m/z*: 609.2 $[M]^+$.

Biological studies

Rat α-glucosidase assay

Based on the reported method of Lossow et al., rat small intestine α-glucosidase (EC 3.2.1.20) was prepared. The *in-vitro* activity was determined by the measurement of 4-nitrophenol which was released from *para*-nitrophenyl *α*-D glucopyranoside [44, 45]. The preparation of 200 µL was performed as follows: the enzyme solution (190 µL, 0.15 units/ml), different concentrations of target compounds (1, 10, 20, 50, 100, 500 and 1000 µM (5 µL), potassium phosphate buffer. Final compounds were dissolved in DMSO (not exceed than 5% of final volume) and pre-incubated at 37 °C, *p*-nitrophenyl glucopyranoside and then substrate (5 µL, 3 mM), was added to the enzyme solution and incubated for further one hour at 37 °C. Finally, by using Cytation 3 hybrid microplate reader (BioTek, USA) any change in the absorbance was measured at 405 nm. By using GraphPadprism 6.0 (SanDiego, California, USA) (https://www.graphpad.com/scientific-software/prism/) was used to obtain IC_{50} values of tested compounds.

Kinetic analysis

Modes of enzyme inhibition were determined by recording the effect of various concentrations of the substrates 1, 2.5, 5 or 10 mM pNPG for *α*-glucosidase on Lineweaver–Burk plots using calculated V_{max} and K_m. For inhibition test of *α*-glucosidase: the concentrations applied for compounds **10k** was 0.1, 1, 5 and 10 nM. Inhibition constants (K_i) were determined by depicting the secondary plot of K_m against various concentrations of inhibitors.

Docking studies

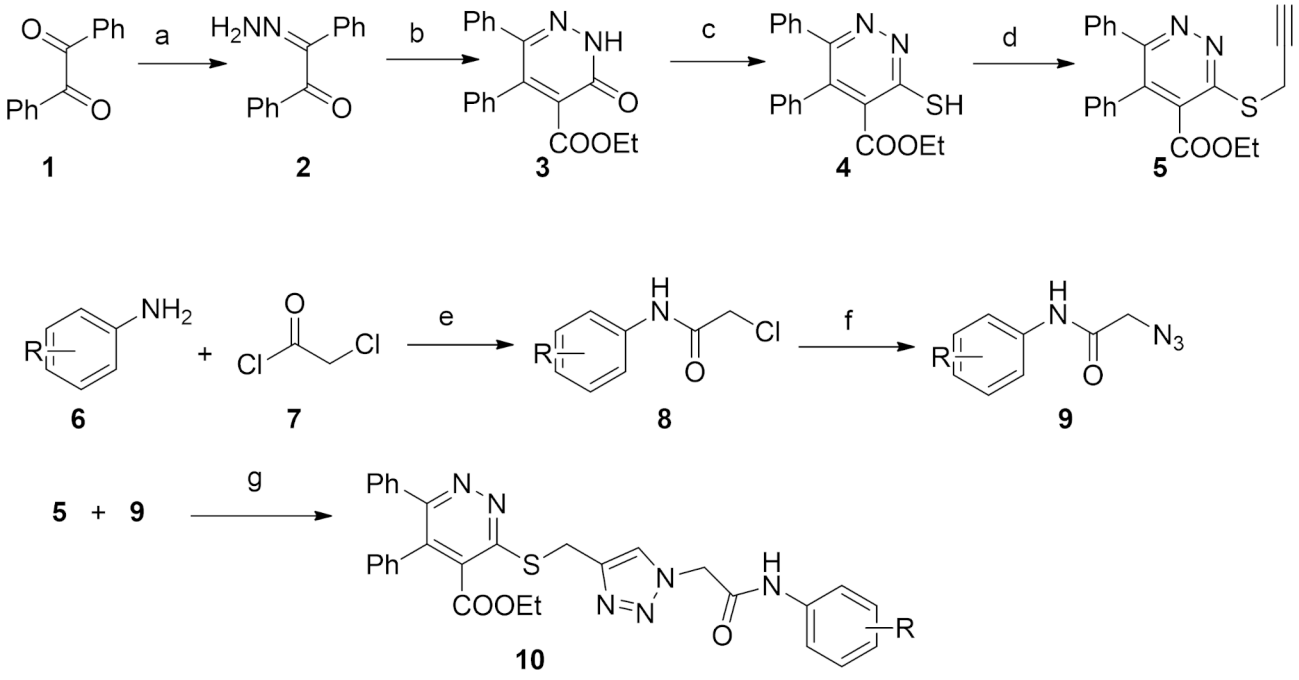
Docking study of compound 10k was done using Autodock 4.2.1 software. The structure of the targeted protein *α*-glucosidase (PDB: 5NN88) was taken from RCSB data bank [26]. The analysis of docking results were performed by Discovery Studio visualizer 4.5.

Results and discussions

Chemistry

The preparation of target compounds is described in scheme 1. Compound **2** was prepared from the previously reported procedure [43, 46]. Subsequently, the cyclization occurred with diethyl malonate and sodium in ethanol at reflux temperature to yield ethyl 3-oxo-5,6-diphenyl-2,3-dihydropyridazine-4-carboxylate. Then, the conversion of carbonyl group into SH was achieved by Lawesson's reagent in toluene after 18 h heating at reflux condition. The propargylated product **5**, ethyl 5,6-diphenyl-3-(prop-2-yn-1-ylthio)pyridazine-4-carboxylate, was obtained from the reaction of compound **4** and propargyl bromide in dimethyl formamide in the presence of K_2CO_3. On the other hand, the reaction of aromatic amines and chloroacetyl chloride was conducted in 1,2-dichloroethane and in the presence of triethylamine as a proton acceptor to obtain 2-chloro-*N*-arylacetamide. After work-up and crystallization, the substitution reaction of compound **8** with sodium azide in DMSO yielded compound **9**. The click reaction between compound **5** and **9** in DMF and in the presence of triethylamine and catalytic amounts of CuI resulted in target compounds **10a-r** in good yields.

The ^{1}H NMR of the most potent compound, **10k**, in DMSO-d_6 was recorded and clearly showed the characteristic triazole and NH protons as singlets at 8.14, 10.60 ppm, respectively. SCH_2 and NCH_2 were resonated as singlets at 4.80 and 5.33 ppm, respectively. The ethoxy group was appeared at 0.86 as triplet (*J*=6.9 Hz) and at 4.02 as quartet (*J*=6.8 Hz). The aromatic protons near bromine were appeared at 7.54 ppm as doublet showing



Scheme 1 Synthesis of target compounds. Synthesis of target compounds. Reagents and conditions: (a) hydrazine hydrate, methanol, reflux, 15 min.; (b) Na, EtOH, diethyl malonate, reflux; (c) Lawesson's reagent, toluene, reflux, 18 h; (d) propargyl bromide, DMF, K_2CO_3, 50 °C; (e) Et_3N, DCE, r.t.; (f) NaN_3, DMSO, r.t.; (g) Et_3N, DMF, CuI, r.t

Table 1 *In vitro α*-glucosidase inhibitory activities and yields of target compounds.[a,b]

Entry	Compound	R	IC_{50} (μM)	Yield (%)[c]
1	**10a**	H	35.6 ± 8.9	65
2	**10b**	3-Me	58.9 ± 7.5	71
3	**10c**	4-Me	> 250	70
4	**10d**	4-*i*Pr	86.5 ± 7.3	68
5	**10e**	3-OMe	35.7 ± 3.9	72
6	**10f**	4-OMe	25.2 ± 2.5	66
7	**10 g**	4-F	37.5 ± 7.2	79
8	**10 h**	2-Cl	14.9 ± 1.9	62
9	**10i**	3-Cl	> 250	60
10	**10j**	4-Cl	21.0 ± 5.3	74
11	**10k**	4-Br	1.7 ± 0.12	61
12	**10 L**	3,5-*di*Cl	14.1 ± 3.3	64
13	**10 m**	3,4-*di*Cl	27.7 ± 3.0	78
14	**10n**	3-CN	> 250	70
15	**10o**	4-CN	28.9 ± 3.3	77
16	**10p**	3-NO_2	84.0 ± 13.2	81
17	**10q**	4-NO_2	47.1 ± 5.6	73
18	**10r**	3-Me-4-NO_2	> 250	65
19	Acarbose		170.5 ± 23.1	

[a] Values are the means of three replicates ± standard deviation

[b] The activity against rat small intestine *α*-glucosidase

[c] Isolated yields

the *ortho* coupling constant of 8.9 Hz. Besides, other aromatic protons as multiplets at appropriate chemical shifts confirmed the proposed structure. The ^{13}C NMR spectrum in the same solvent at 75 MHz showed four aliphatic carbons at 13.3, 24.7, 52.2, 62.0 ppm related to CH_3, SCH_2, NCH_2 OCH_2. The number of aromatic carbons in the normal range is in accordance to the proposed structure.

In vitro α-glucosidase inhibitory activities

The SAR studies divulged that different substituents either electron-donating or withdrawing on aromatic moiety along with their positions affected the inhibition. The results are shown as IC_{50}s in Table 1. Compounds with unsubstituted phenyl ring and different substituents including methyl, methoxy, isopropyl, fluorine, chlorine, bromine, nitro and cyano at different positions of aryl ring were found to have varying degree of inhibitory potential. Except few ones, all compounds were active against *α*-glucosidase enzyme (IC_{50s} = 1.7 to 86.5 μM). Compound **10k** bearing 4-bromo substituent was found to be 100 folds more active with IC_{50} value of 1.7 μM compared to standard drug (IC_{50} = 173 μM). Compound 10l having 3,5-*di*chloro group was the second most active compound. Further studies indicated that compound **10 h** bearing chlorine (–Cl) group at *ortho* position of phenyl ring displayed stronger *α*-glucosidase inhibitory activity (IC_{50} = 14.9 μM) than *meta*- and *para*-chloro substituted analogues (**10i** and **10j**). Interestingly,

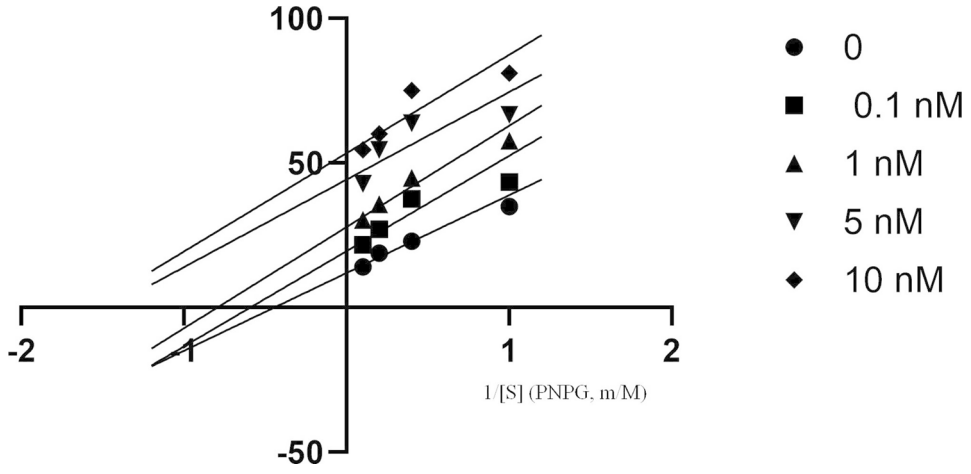


Fig. 2 The relative activity against the concentrations of *α*-glucosidase in the presence of compound **10k** (0, 0.1, 1, 5 and 10 nM)

p-bromo substituted analogue (**10k**) showed strong inhibitory activity compared to *p*-fluoro and *p*-chloro analogues. Interesting to observe that compound **10i** exhibited no inhibitory activity, while the combination of second chlorine atom (–Cl) generated active compounds (10 l, **10 m**). Electron-releasing substituted analogues is more active than electron-withdrawing substituted compounds which are exemplified by *meta*-methoxy, methyl (*m*–OMe, *m*-Me) substituted 1,2,3-triazoles being more active than *meta*-nitro (*m*–NO_2) and *meta*-cyano (*m*–CN) substituted analogues. While, 4-nitro substituted compound **10q** (IC_{50}=47.1 μM) was active, the introduction of methyl at *meta* position resulted in no activity at the resultant compound, **10r**. The movement of electron-withdrawing groups meaning nitro and cyano from *meta* to *para* generated active compounds (**10o** and **10q**). This trend was also observed in the case of chlorine-substituted compounds (**10i***vs.* **10j**). The cytotoxicity of compound **10k**, the most active compound, was investigated against the normal cell line. No toxicity was observed against HDF [28].

Kinetic studies

The activity of 4-nitrophenyl-*β*-*D*-galactopyranoside (PNPG) was investigated in the presence and absence of compound **10k**. The results were analyzed by Lineweaver-Burk and confirmed that this compound induced uncompetitive inhibition on *α*-glucosidase (Fig. 2). The slope was not altered by the presence of this compound and increasing concentrations of the substrate resulted in parallel lines. By using secondary plot, the inhibitor constant K_i was determined to be 125 nM.

Docking studies

To gain insights into possible binding modes with *α*-glucosidase, molecular docking was performed and the results are shown in Fig. 3. It is observed that the hydrogen bond, pi-sigma and the pi-sulfur and pi-alkyl interactions are the main interactions of compound **10k** contributing to the binding affinity of this compound with the enzyme. The most potent compound exhibited favorable interactions with amino acid residues. The triazole ring formed hydrogen bond with Leu677 to enhance the binding affinity. The van der Waals interactions are formed with Phe649, Trp 376, Asp616, Leu283, Asp282. The ethoxy group could form pi-sigma interaction with residue of the enzyme.

Conclusion

In summary, a newly synthesized series of pyridazine-triazole derivatives were synthesized from benzil and their inhibitory activity toward *α*-glucosidase were also evaluated. All synthesized compounds were new and evaluated by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The obtained results showed that most of the target compounds showed significant inhibitory potency. The kinetic studies revealed that the inhibition was uncompetitive. Besides, the suitable interactions and no toxicity of the most potent compound confirmed that these derivatives could be regarded as a good candidate for further investigation and optimization.

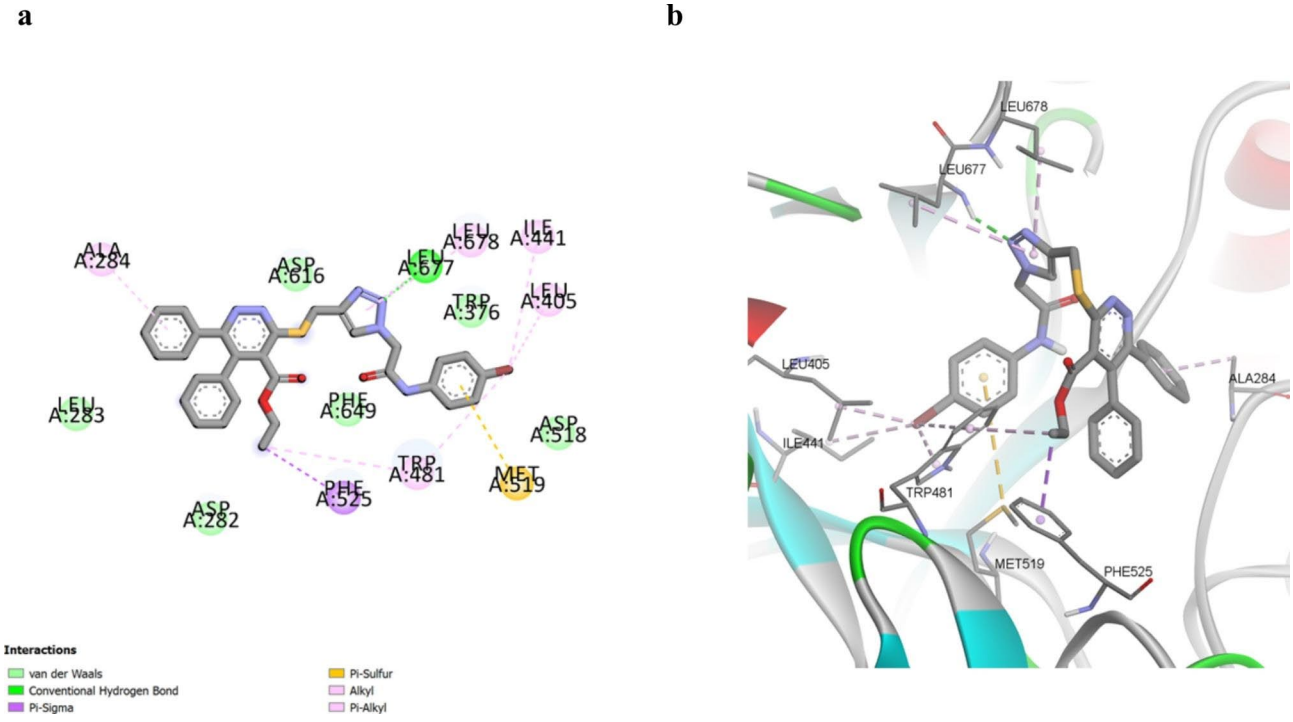


Fig. 3 2D (a) and 3D (b) binding modes the most active **10k** skeleton

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-023-00973-8.

Supplementary Material 1

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Authors' contributions
A.F. designed the target compounds. S.K. and S. E. S. E. interpreted the biological and chemical analysis. S. M. and S. S. wrote the manuscript. M. T. and L. F. performed docking studies. M. R. conducted the organic synthesis in the lab. R. P. and F. S. and S. M. S. performed biological tests. All authors read and approved the final manuscript.

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Data Availability
All data generated or analyzed during this study are included in this published article and its additional information files.

Declarations

Ethics approval and consent to participate
All methods were carried out in accordance with relevant guidelines and regulations of The Ministry of Health and Medical Education IR.TUMS.MEDICINE.REC.1400.1316. Protocols were conducted and approved by Shahid Beheshti University of Medical Sciences (SBMU).

Consent for publication
Not applicable.

Conflict of Interest
The authors declare that there are no conflicts of interest.

Competing interests
The authors declare that they have no competing interests.

Supporting information
Copies of ^{1}H-NMR ^{13}C-NMR spectra are available as supplementary data.

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