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Synthesis and pharmacological profiling of *cis*-1-amino-2-indanol derivatives as α -glucosidase inhibitors

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By treating *cis*-1-amino-2-indanol with different functionalized isocyanates and isothiocyanates, a group of 15 indanol derivatives were synthesized. The synthesis was effectively performed employing a previously proven method and the resulting products were characterized through multiple spectroscopic techniques including NMR spectroscopy and the α -glucosidase inhibitory assay was used to evaluate their α -glucosidase inhibitory capacity. The results indicated a varied level of inhibitory activity against α -glucosidase and 2h showed the highest potency with IC_{50} value of $9.64 \pm 0.24 \mu\text{M}$, while compounds 2g, 2c, and 3i also exhibited significant inhibition. The kinetic analysis of the most active inhibitor 2h showed its competitive mode of inhibition, with a K_i value of $7.39 \pm 0.088 \mu\text{M}$. The binding modes of compounds were predicted by molecular docking analysis within the active site of α -glucosidase enzyme, where our molecules showed significant binding and docking scores. Docking analysis revealed that the thiourea and urea moieties play a critical role in facilitating the interaction of the molecules with one of the catalytic triad residues. The current study provides a basis for the development of a possible lead compound that can inhibit α -glucosidase.

Keywords Aminoindanol, Iso(thio)cyanates, α -glucosidase, Kinetics, Docking

Aminoindanol is an essential scaffold in organic chemistry and medicine. A major focus of organic chemistry encompasses the synthesis of these molecules and the development of innovative methodologies for their acquisition^{1–4}. These scaffolds have gained the attention of academic and industrial researchers to generate their derivatives with novel applications through multiple synthetic routes. A sequence of enantioselective enzymatic processes has been reported where lipases and transaminases were employed to produce *trans*-(1R, 2R) and *cis*-(1S, 2R)-1-amino-2-indanols, while the (R)-2-hydroxy indanone, 2-acetoxyindanone was hydrolyzed enantioselectively by Lipase. In water-saturated ethyl acetate, (R)-2-hydroxy indanone was used as an amino donor for the synthesis of *trans*-1-amino-2-indanol (de >98%), and reductive amination was used to obtain the *cis*-isomer from the same starting material. The kinetic resolution was carried out using enantioselective ω -transaminase (ω -TA), whose enantioselectivity rose to 22.1 when 5% γ -cyclodextrin was present^{5,6}. These include rigidity, the orientation of the two stereogenic centers, along with the ability of amino and hydroxy groups to coordinate with certain metals or act as hydrogen bond donors or acceptors, and diverse activities exhibited by these entities and their potential for further derivatization⁷. According to reports, the *cis*-1-amino-2-indanol's rigid cyclic structure makes it an essential ligand or chiral auxiliary in chemical synthesis. Furthermore, *cis*-1-amino-2-indanol is also employed as a chiral auxiliary in several asymmetric transformations, including diastereoselective reduction and diastereoselective enolate alkylation (Fig. 1)⁸. The substructure of indanol is very interesting for the design of

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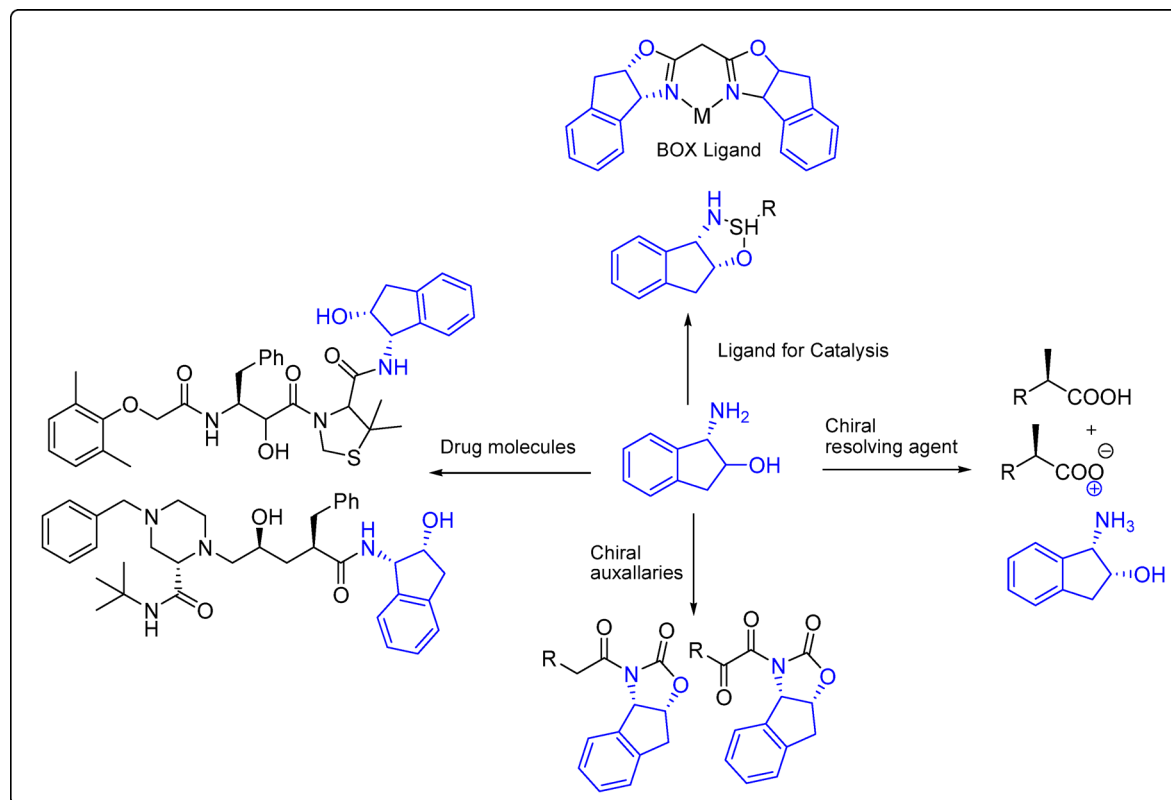


Fig. 1. Derivatives of Cis indanol.

drugs. It is also in KNI-10,006, which is used to treat malaria, or in Indinavir sulfate (Crixivan[®]), an HIV protease inhibitor created by Merck (Rahway, NJ, USA) to treat AIDS, etc^{9–12}.

The World Health Organization (WHO) estimates that around 90% of people with diabetes globally have type 2 diabetes mellitus (T2DM), a situation projected to impact 439 million people by the year 2030. Between 2012 and 2014, almost 1.5 million people lost their lives due to complications associated with diabetes^{13,14}. T2DM is an extremely complicated metabolic disease, and despite the availability of FDA-approved anti-diabetic medications, the patients still have hyperglycemia and severe consequences.

α -Glucosidase (EC 3.2.1.20), a crucial metabolic enzyme that catalyzes the digestion of massive, non-absorbable carbohydrates into smaller glucose molecules to be absorbed by the small intestine. Consequently, the enzyme has become an excellent drug target for the treatment of T2DM¹⁵. The rise of blood sugar after consumption of a carbohydrate-rich diet is suppressed when the α -glucosidase enzyme activity is prevented¹⁶. Clinically prescribed α -glucosidase inhibitors (AGIs), including acarbose, voglibose, and miglitol, effectively lower postprandial glucose levels in individuals with T2DM¹⁷. Nevertheless, these AGIs have inhibitory activity against the α -glucosidase enzyme; however, they are linked to several issues such as diarrhea, flatulence, and gastrointestinal pain¹⁸. The adverse effects of these medications demand new small-molecule inhibitors of this enzyme with a high efficacy and safety profile for the management of T2DM.

The biological activity of indanes, indanols, and iso(thio)cyanates, as well as the demand for other new bioactive compounds and structural diversity, prompted us to combine the above moieties into a single pharmacophoric substance. Indanol serves as an important structural precursor for the synthesis of numerous pharmacologically active compounds. Owing to its unique bicyclic framework and versatile functionalization potential, indanol derivatives have demonstrated significant α -glucosidase inhibitory activity, making them valuable scaffolds in the design and development of novel antidiabetic agents^{4,10,19–22}. The designed target molecules are similar in structure, differing by the presence of oxygen (in isocyanate) and sulfur (in isothiocyanate) and the alkyl groups present at the side chains (Fig. 1). These tiny variations allow us to figure out how this change would affect interactions with biological targets using α -glucosidase and cytotoxic analyses. Furthermore, the in-silico studies including molecular docking were also performed for better interpretation of results.

Experimental section

General methods

For all reactions, the commercially available chemicals were purchased from Sigma-Aldrich. Chemical reactions were carried out in commercially available solvents, which were dried prior to the chemical reactions. The precoated silica gel plates (Merck, G60 F-254, UV-254) were used for Thin-Layer Chromatography (TLC) experiments. The visualization of the TLC plates was done by using a 254 nm and 366 nm UV light. The IR spectra was recorded on Bruker ATR-Tensor 37 spectrophotometer (ν_{\max} in cm^{-1}). Optical rotations were measured on

KRUS P3000 polarimeter (A. Kruss Optronic, Germany). ^1H NMR spectra were recorded on Bruker Avance 600 (150 MHz for ^{13}C) spectrometer; chemical shift values (δ) were recorded in ppm, with residual peak of CDCl_3 , δ (H) 7.26, δ (C) 77.0) used for referencing.

Chemical synthesis

All the compounds (**2a** to **4o**) were synthesized at room temperature. The equimolar amounts of (1R,2S)-*cis*-1-Amino-2-indanol were used to react with the substituted iso(thio)cyanates in toluene for 1–2 h. The precipitates were then filtered and dried. The products obtained were in good yields.

1-(4-chlorophenyl)-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl) thiourea (2a)

A mixture of (1R,2S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 4-chlorophenylisothiocyanate (85 mg, 0.5 mmol) in dry toluene (5 mL) stirred at room temperature for 4 h. After the reaction was complete, the precipitates were filtered and dried. The resulting off-white solid weighed 151 mg, yielding 95%, m.p: 168 °C; IR: 3392.8, 2929.8, 2316.5, 1693.5, 1519.9 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.93 (d, 1H, J = 14.6, CH_2) and 3.25 (dd, 1H, J = 5.1, CH_2), 4.80 (m, 1H, J = 5.1, CH), 5.98 (s, 1H, OH), 6.8 (t, 1H, J = 6.6 Hz, CH), 7.2 (m, 1H, NH), 7.23–7.29 (m, 6 H, ArH), 7.35–7.38 (m, 2 H, ArH), 8.21 (d, 1H, NH, J = 25.9), ^{13}C NMR ppm; 39.8, 72.7, 73.6, 124.7, 125.5, 126.1, 127.4, 128.2, 128.6, 129.1, 130.2, 132.7, 134.7, 139.8, and 180.9; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{OS}$ [$\text{M} + \text{H}$] $^+$ 319.8190, found 319.8193.

1-(4-fluorophenyl)-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)thiourea (2b)

A mixture of (1R,2S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 4-Fluorophenylisothiocyanate (76.6 mg, 0.5 mmol) in dry toluene (5 mL) was stirred at room temperature for 4 h. After the reaction was complete, the precipitates were filtered and dried, yielding 138 mg of an off-white solid with a 92% yield, m.p: 144 °C; IR: 3394.8, 2926, 2312.6, 1697.3, 1523.7 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.93 (d, 1H, J = 16.6, CH_2) and 3.25 (dd, 1H, J = 5.7, CH_2), 4.79 (s, 1H, CH), 5.97 (s, 1H, OH), 6.66 (s, 1H, CH), 7.18 (t, 2 H, J = 8.4 Hz, ArH), 7.2–7.29 (m, 5 H, ArH, NH), 7.26 (d, 2 H, J = 7.02 Hz, ArH), 8.19 (m, 1H, NH), ^{13}C NMR ppm; 39.7, 63.1, 73.5, 117.0, 117.2, 124.7, 125.5, 127.4, 127.4, 128.6, 132.0, 139.8, 162.2, 181.2; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{15}\text{FN}_2\text{OS}$ [$\text{M} + \text{H}$] $^+$ 303.3674, found 303.3677.

*1-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(*m*-tolyl) thiourea (2c)*

A mixture of (1R,2S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 3-Methylphenylisothiocyanate (63 μl , 0.5 mmol) was dissolved in dry toluene (5 mL) and stirred at room temperature for 4 h. Upon completion of the reaction, the resulting precipitate was filtered and dried. This process yielded 130 mg of an off-white solid with a 90% yield. m.p: 137 °C; IR: 3307.9, 2912.5, 2024.3, 1591.3, 1519 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.34 (s, 3 H, CH_3), 2.94 (d, 1H, J = 16.62, CH_2) and 3.25 (d, 1H, J = 12.84, CH_2), 4.79 (s, 1H, CH), 5.99 (s, 1H, OH), 6.79 (d, 1H, J = 7.92 Hz, CH), 7.04–7.11 (m, 4 H, ArH), 7.25–7.28 (m, 4 H, ArH), 7.38 (d, 1H, NH, J = 6.72 Hz) 8.11 (d, 1H, NH, J = 13.8 Hz). ^{13}C NMR ppm; 21.3, 39.7, 63.3, 73.6, 121.8, 122.7, 124.7, 125.5, 126.3, 127.3, 128.2, 128.5, 129.3, 130.0, 135.9, 139.9, 140.4, 180.8; (ESI) m/z : calculated for protonated $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OS}$ [$\text{M} + \text{H}$] $^+$ 299.4040, found 299.4043.

1-ethyl-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl) thiourea (2d)

A mixture of (1R,2S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and ethyl isothiocyanate (43.7 μl , 0.5 mmol) in 5 mL of dry toluene was stirred at room temperature for 4 h. After the reaction was complete, the precipitates were filtered and dried, resulting in 108 mg of an off-white solid with a 92% yield, m.p: 118 °C; IR: 3306, 3034, 2318.4, 1670.3, 1523.7 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 1.24 (t, 3 H, CH_3 , J = 7.2 Hz), 2.91 (d, 1H, CH_2 , J = 10.6 Hz), 3.25 (dd, 1H, CH_2 , J = 4.7 Hz), 3.40 (s, 2 H, CH), 4.59 (s, 1H, CH), 5.78 (s, 1H, OH), 6.48 (s, 2 H, ArH), 7.22–7.28 (m, 4 H, 3 ArH & 1NH), 7.34 (d, 1H, NH, J = 7.1 Hz), ^{13}C NMR ppm; 14.1, 39.3, 62.6, 73.6, 124.7, 125.2, 127.2, 128.5, 140.1, 180.9; (ESI) m/z : calculated for protonated $\text{C}_{12}\text{H}_{16}\text{N}_2\text{OS}$ [$\text{M} + \text{H}$] $^+$ 237.3330, found 237.3334.

1-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(naphthalen-1-yl) thiourea (2e)

A mixture of (1R,2S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 1-Naphthylisothiocyanate (92.62 mg, 0.5 mmol) in dry toluene (5 mL) was stirred at room temperature for 4 h. Then after completion of the reaction, the precipitates were filtered with the help of a filter paper and dried. The white solid obtained (148 mg, yield 90%), m.p: 169 °C; IR: 3255.8, 2976.1, 1975.1, 1537.2 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.82 (d, 1H, CH_2 , J = 16.6 Hz), 3.15 (dd, 1H, J = 3.54 Hz, CH_2), 4.73 (s, 1H, CH), 5.98 (m, 1H, OH), 6.48 (d, 1H, J = 6.4 Hz, CH), 7.13 (t, 1H, J = 7.1 Hz, ArH), 7.16–7.19 (s, 3 H, 2 ArH & 1NH), 7.23 (m, 1H, ArH), 7.48 (t, 1H, J = 7.7 Hz, ArH), 7.52 (d, 1H, J = 7.1 Hz, ArH), 7.48 (t, 1H, J = 7.4 Hz, ArH), 7.64 (t, 1H, J = 7.5 Hz, ArH), 7.85 (d, 1H, J = 8.1 Hz, ArH), 7.91 (d, 1H, J = 8.1 Hz, ArH), 8.13 (d, 1H, J = 8.34 Hz, NH), 8.38 (d, 1H, J = 24.5 Hz); ^{13}C NMR ppm; 39.5, 63.2, 73.4, 122.4, 124.5, 125.1, 125.8, 127.1, 127.2, 127.5, 128.3, 128.6, 129.1, 129.7, 131.5, 134.6, 139.7, 139.8, 181.9; (ESI) m/z : calculated for protonated $\text{C}_{20}\text{H}_{18}\text{N}_2\text{OS}$ [$\text{M} + \text{H}$] $^+$ 335.4370, found 335.4373.

1-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(2-morpholinoethyl) thiourea (2f)

A mixture of (1R,2S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 2-Morpholinoethylisothiocyanate (121.12 μl , 0.5 mmol) in dry toluene (5 mL) was converted into compound 7, obtained (140 mg, yield 88%), m.p: 206 °C; IR: 3265.4, 2983.8, 1978.9, 1539.2, 1506.4 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.42 (s, 2 H, CH_2), 2.59 (s, 2 H, CH_2), 2.69 (t, 1H, J = 6.7 Hz, CH_2), 2.60 (d, 1H, J = 6.6 Hz, NH), 2.98 (dd, 2 H, J = 2.5 Hz, CH_2), 3.27 (s, 1H, J = 5.5 Hz, CH_2), 3.62 (t, 1H, J = 6.1 Hz, CH_2), 3.74 (s, 2 H, CH_2), 4.81 (d, 1H, CH), 5.81 (s, 1H, OH), 6.74 (s, 1H,

CH), 7.25 (d, 1H, CH), 7.26 (d, 1H, NH), 7.30 (m, 2 H, CH), 7.37 (d, 1H, NH, $J=7.3$ Hz), 8.86 (1H, NH); ^{13}C NMR ppm; 39.4, 41.4, 42.90, 53.32, 53.6, 57.6, 66.2, 66.9, 73.5, 125.1, 125.5, (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2\text{S} [\text{M} + \text{H}]^+$ 321.4550, found 321.4553.

1-(3-chlorophenyl)-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl) thiourea (2g)

Compound **2g** was synthesized by the reaction of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 3-Chlorophenylisothiocyanate (89.4 mg, 0.5 mmol) in dry toluene (5 mL), at room temperature. After completion of the reaction, the precipitates were filtered and dried. White solid (140 mg, yield 87%), m.p: 128 °C; IR: 3251.9, 2983.8, 1541.1, 1508.3 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.94 (d, 1H, $J=16.6$ Hz, CH_2), 3.23 (dd, 1H, $J=5.1$ Hz, CH_2), 4.78 (t, 1H, $J=4.2$ Hz, CH), 5.97 (s, 1H, OH), 6.95 (d, 1H, $J=7.7$ Hz, CH), 7.17–7.22 (m, 3 H, ArH), 7.25 (m, 1H, CH), 7.27–7.33 (m, 3 H, ArH, 1H, NH), 7.39 (d, 1H, $J=7.1$ Hz, ArH), 8.38 (s, 1H, NH); ^{13}C NMR ppm; 39.8, 63.1, 73.5, 122.5, 124.6, 125.3, 125.4, 126.9, 127.3, 128.2, 128.6, 129.0, 130.9, 135.5, 137.6, 139.7, 139.8, 180.6; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{OS} [\text{M} + \text{H}]^+$ 319.8190, found 319.8193.

1-(2-hydroxy-2,3-dihydro-1 H-inden-1-yl)-3-(4-methoxyphenyl) thiourea (2h)

(1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 2-Morpholinoethylisothiocyanate (69 μl , 0.5 mmol) were reacted in dry toluene (5 mL), at 25 °C for 4 h with stirring. Filtered the reaction mixture and dried. The white solid obtained (135 mg, yield 86%), m.p: 124 °C; IR: 3255.8, 2985, 1535.3, 1510.2 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.83 (dd, 1H, $J=1.9$ Hz, CH_2), 3.14 (dd, 1H, $J=5.3$ Hz, CH_2), 4.72 (ddd, 1H, $J=2.2$ Hz, CH), 5.8 (dd, 1H, $J=5.2$ Hz, CH), 6.41 (d, 1H, $J=8.1$ Hz, OH), 6.82 (d, 1H, $J=2.1$ Hz, ArH), 7.13 (d, 2 H, $J=8.9$ Hz, ArH), 7.14–7.17 (m, 3 H, ArH), 7.25 (d, 1H, NH), 7.75 (s, 1H, NH); ^{13}C NMR ppm; 39.6, 55.5, 63.2, 73.5, 115.4, 124.6, 125.4, 127.3, 127.4, 128.2, 128.5, 139.9, 140.1, 181.5; (ESI) m/z : calculated for protonated $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S} [\text{M} + \text{H}]^+$ 315.4030, found 315.4033.

1-(4-chlorophenyl)-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl) urea (3i)

A mixture of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 4-Chlorophenylisocyanate (63.9 μl , 0.5 mmol) reacted in dry toluene (5 mL) with stirring for 4 h at room temperature. Filtered the precipitates and dried. The white solid obtained (139 mg, 93% yield), m.p: 244 °C; IR: 3261.6, 2982, 1539.1, 1508.3 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.86 (dd, 1H, $J=16.3$ Hz, CH_2), 3.05 (dd, 1H, $J=4.6$ Hz, CH_2), 4.49 (d, 1H, $J=4.4$ Hz, CH), 4.78 (d, 1H, $J=4.5$ Hz, OH), 5.16 (dd, 1H, $J=5.1$ Hz, OH), 6.46 (d, 1H, $J=8.6$ Hz, NH), 6.82 (d, 1H, $J=7.9$ Hz, ArH), 7.08–7.17 (m, 2 H, ArH), 7.25 (d, 1H, ArH), 7.65 (d, 2 H, NH), 8.68 (s, 1H, NH); ^{13}C NMR ppm; 39.9, 57.8, 73.8, 116.1, 117.8, 121.1, 125.1, 126.5, 127.5, 129.8, 134.0, 140.4, 141.9, 142.6, 155.8; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2 [\text{M} + \text{H}]^+$ 303.7580, found 303.7582.

1-(4-fluorophenyl)-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl) urea (3j)

Compound **3j** was obtained by the mixing of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 4-Fluorophenylisocyanate (56.8 μl , 0.5 mmol) in dry toluene (5 mL) and the precipitates were obtained after 4 h stirring of the reaction mixture at 25 °C. The white solid was 120 mg, 87% yield; m.p: 248 °C; IR: 3261.8, 2985.8, 1537.2, 1508.3 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.81 (d, 1H, $J=16.3$ Hz, CH_2), 3.15 (dd, 1H, $J=4.6$ Hz, CH_2), 4.48 (t, 1H, $J=4.4$ Hz, CH), 4.77 (t, 1H, $J=4.3$ Hz, OH), 5.16 (dd, 1H, $J=5.0$ Hz, CH), 6.46 (d, 1H, $J=8.6$ Hz, ArH), 6.82 (d, 2 H, $J=7.9$ Hz, ArH), 7.69 (d, 1H, $J=6.5$ Hz, ArH), 7.34–7.38 (m, 2 H, ArH), 7.66 (d, 1H, $J=5.22$ Hz, NH), 8.53 (d, 1H, NH); ^{13}C NMR ppm; 40.1, 57.9, 72.8, 115.1, 115.1, 119.5, 119.5, 124.4, 125.1, 126.5, 127.4, 136.7, 140.5, 142.8, 156.2; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{15}\text{FN}_2\text{O}_2 [\text{M} + \text{H}]^+$ 287.3064, found 287.3067.

1-(2-hydroxy-2,3-dihydro-1 H-inden-1-yl)-3-phenylthiourea (2k)

From the reaction of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) with Phenyl Isothiocyanate (60 μl , 0.5 mmol), compound **2k** was obtained in the form of white solid (123 mg, 90% yield), in dry toluene (5 mL) after 4 h stirring at 25 °C. The m.p: 127 °C; IR: 3296.3, 2983.8, 2324.2, 1975.1, 1595.1, 1545 cm^{-1} ; ^1H NMR ($\text{DMSO}-d^6$) δ ppm; 2.83 (d, 1H, $J=16.2$ Hz, CH_2), 3.12 (dd, 1H, $J=4.6$ Hz, CH_2), 4.54 (q, 1H, CH), 5.42 (d, 1H, CH), 5.87 (t, 1H, OH), 7.13 (t, 1H, ArH), 7.22 (p, 2 H, $J=7.5$ Hz, ArH), 7.26 (d, 1H, $J=7.0$ Hz, ArH), 7.31–7.35 (m, 3 H, 3CH, ArH), 7.57 (d, 2 H, $J=7.7$ Hz, ArH), 7.81 (d, 1H, NH), 9.99 (s, 1H, NH); ^{13}C NMR ppm; 39.8, 61.8, 72.4, 123.3, 124.6, 124.7, 125.5, 126.8, 127.8, 129.1, 139.8, 140.9, 142.5, 180.9; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{16}\text{N}_2\text{OS} [\text{M} + \text{H}]^+$ 285.3770, found 285.3773.

1-benzyl-3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl) thiourea (2L)

According to the above procedure compound **2L** was obtained (142 mg, 86% yield), by the reaction of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and Benzyl Isothiocyanate (89.5 mg, 0.5 mmol). m.p: 121 °C; IR: 3342.6, 2991.6, 2320.3, 2029.1, 1977, 1579.7 cm^{-1} ; ^1H NMR (CDCl_3 -*d*) δ ppm; 2.81 (dd, 1H, $J=16.6$ Hz, CH_2), 3.09 (dd, 1H, $J=4.4$ Hz, CH_2), 4.49 (q, 1H, $J=4.4$ Hz, CH), 4.77 (s, 1H, OH), 5.3 (s, 1H, CH), 5.82 (s, 1H, ArH), 7.15–7.20 (p, 2 H, $J=7.4$ Hz, ArH), 7.24 (d, 2 H, $J=6.9$ Hz, ArH), 7.29 (t, 1H, $J=6.5$ Hz, ArH), 7.38 (q, 4 H, $J=7.3$ Hz, ArH), 7.69 (d, 1H, $J=1.86$ Hz, NH), 8.3 (s, 1H, NH); ^{13}C NMR ppm; 39.8, 72.5, 124.5, 125.4, 126.6, 127.4, 127.9, 128.8, 140.5, 173.3; (ESI) m/z : calculated for protonated $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OS} [\text{M} + \text{H}]^+$ 299.4040, found 299.4043.

1-(2-hydroxy-2,3-dihydro-1 H-inden-1-yl)-3-(m-tolyl) Urea (3m)

Compound **3m** was synthesized by the reaction of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and *m*-Tolyl Isothiocyanate (64.44 μl , 0.5 mmol) into product in dry toluene (5 mL) at room temperature for 4 h. Precipitates were obtained and filtered/dried (115 mg, 90% yield), m.p: 236 °C; IR: 3346.5, 2983.8, 2318.4,

1977.1, 1589.3 cm^{-1} ; ^1H NMR (DMSO- d^6) δ ppm; 2.26 (s, 3 H, CH_3), 2.81 (d, 1H, $J=16.1$ Hz, CH_2), 3.08 (dd, 1H, $J=4.7$ Hz, CH_2), 4.45 (q, 1H, $J=8.3$ Hz, CH), 5.1 (q, 1H, $J=4.9$ Hz, CH), 5.10 (dd, 1H, $J=4.3$ Hz, OH), 5.27 (d, 1H, $J=4.3$ Hz, CH), 6.44 (d, 1H, $J=8.6$ Hz, ArH), 6.74 (d, 1H, $J=7.4$ Hz, ArH), 7.13 (t, 1H, $J=7.8$ Hz, ArH), 7.18–7.24 (m, 4 H, ArH), 7.23 (m, 1H, NH), 7.28 (s, 1H, ArH), 8.7 (s, 1H, NH); ^{13}C NMR ppm; 39.8, 57.7, 72.5, 115.4, 118.4, 122.2, 124.4, 125.3, 126.7, 127.3, 140.9, 143.6, 155.7; (ESI) m/z : calculated for protonated $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 283.3430, found 283.3432.

1-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)-3-(4-nitrophenyl) Urea (3n)

(1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 4-Nitrophenylisocyanate (82 mg, 0.5 mmol) were reacted to give compound **3n** in dry toluene (5 mL) at room temperature by 4 h stirring. The yellowish solid was obtained (144 mg, yield 94%), m.p: 243 °C; IR: 3311.7, 2991.6, 2322.3, 1979, 1558.5 cm^{-1} ; ^1H NMR (DMSO- d^6) δ ppm; 2.83 (d, 1H, $J=16.2$ Hz, CH_2), 3.11 (dd, 1H, $J=16.2$ Hz, CH_2), 4.47 (s, 1H, CH), 5.12 (s, 1H, OH), 5.35 (s, 1H, CH), 6.72 (s, 1H, $J=7.45$, NH), 7.20–7.24 (t, 4 H, $J=7.8$ Hz, ArH), 7.68 (d, 2 H, ArH), 8.19 (t, 2 H, CH), 9.64 (s, 1H, NH); ^{13}C NMR ppm; 40.1, 57.6, 72.4, 117.2, 124.4, 125.4, 125.7, 126.8, 127.7, 128.6, 140.9, 143.1, 147.6, 155.7; (ESI) m/z : calculated for protonated $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 314.3130, found 314.3132.

1,1'-(1,4-phenylene)bis(3-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)urea) (4o)

A mixture of (1R,2 S)-*cis*-1-amino-2-indanol (74.5 mg, 0.5 mmol) and 1,4-Phenylenediisocyanate (80.1 mg, 0.5 mmol), in dry toluene (5 mL), at room temperature, was reacted to afford compound **4o** (white solid precipitates; 144 mg, yield 95%), m.p: 267 °C; IR: 3338.7, 3280.9, 2941.4, 1637.5, 1564.2 cm^{-1} ; ^1H NMR (DMSO- d^6) δ ppm; 2.81 (dd, 2 H, $J=16.1$ Hz, CH_2), 3.08 (dd, 2 H, $J=3.9$ Hz, CH_2), 4.43 (d, 2 H, $J=3.4$ Hz, CH_2), 5.09 (q, 2 H, $J=12.8$ Hz, OH), 5.24 (d, 2 H, $J=3.1$ Hz, CH), 6.35 (d, 2 H, $J=8.6$ Hz, NH), 7.19–7.23 (m, 8 H, $J=11.7$ Hz, ArH), 7.32 (s, 4 H, ArH), 8.69 (s, 2 H, NH); ^{13}C NMR ppm; 40.2, 57.7, 72.6, 118.8, 124.4, 125.3, 126.7, 127.5, 134.9, 140.9, 143.7, 155.9; (ESI) m/z : calculated for protonated $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 459.5180, found 459.5183.

α -Glucosidase inhibition of synthetic derivatives

The α -glucosidase inhibitory activity of the synthesized compounds was measured in 50 mM phosphate buffer, pH 6.8. The enzyme (from *Saccharomyces cerevisiae*) was diluted to 1 U/2 mL in the phosphate buffer, and 20 L of enzyme was added per well. Each sample was incubated in a reaction buffer of 135 L of phosphate buffer per well with 20 L of each sample dissolved in 0.5 mM DMSO and transferred to 96-well plate. The plates were then incubated at normal temperature of 37 °C for 15 min. After incubation, 0.7 mM of the substrate “*p*-nitrophenyl-D-glucopyranoside” was added to the plates and the absorbance was measured at 400 nm wavelength. Acarbose and 7% DMSO were used as positive controls²³.

Molecular docking

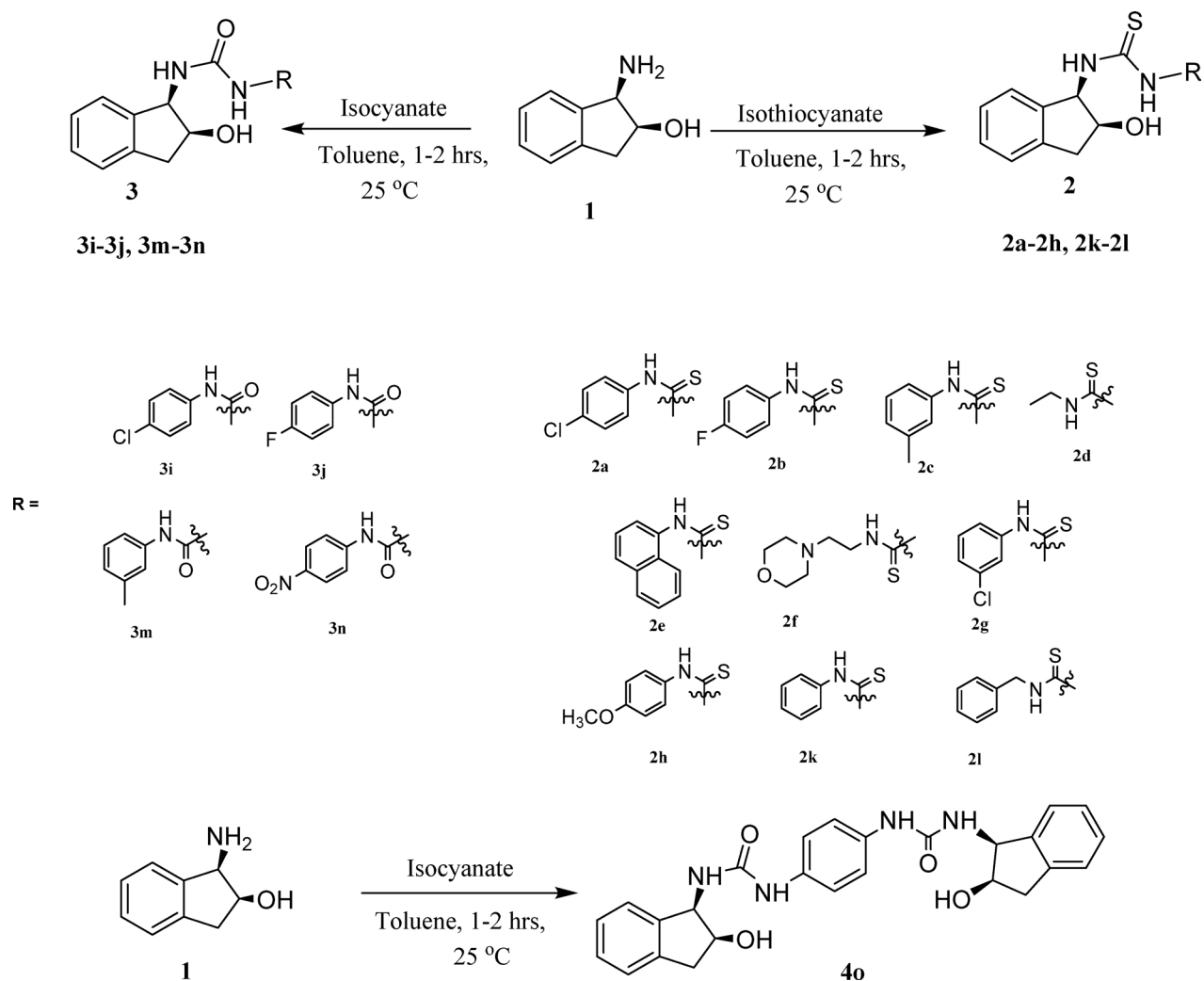
The 3D coordinate (PDB ID: 3A4A) of α -glucosidase (*Saccharomyces cerevisiae*) complexed with the inhibitor (maltose) was retrieved from the Protein Data Bank (RCSB) at a resolution of 1.60 Å¹¹. The Loop modeler tool within the Molecular Operating Environment (MOE) version 2024.06 was utilized to reconstruct the absent residues in the protein structure to complete overall structure^{12,24}. Amber14:EHT forcefield was applied which integrates the ff14SB Amber forcefield with Extended Huckel Theory (EHT) for molecular modeling, enabling precise predictions and optimizations of the geometry, energy, and interactions of biomolecules, especially proteins and nucleic acids. The C- and N- terminals of α -glucosidase were charged electrically to indicate the appropriate beginning and ending positions²⁵.

Ligands were prepared in ChemDraw and imported into MOE for 3D-minimization of structures. AM1-BCC charges were added to each structure, and their structures were minimized with the MMFF-94x forcefield with an RMS gradient of 0.1 Kcal/mol/Å². Afterwards, docking was carried out using the Triangle Matcher algorithm with the London dG scoring function with a total of 30 conformations for each ligand²⁶. The appropriate binding mode of each molecule was further selected by conformational sampling. Protein-ligand interactions between our docked derivative and α -glucosidase were quantitatively evaluated using Protein-Ligand Interaction Fingerprints (PLIF) in MOE²⁷ which measures several types of interactions like hydrogen bonds, water-ligand-residue bridges, surface contact, metal coordination and arene interactions²⁸.

Results and discussion

Aminoindanol scaffolds are recognized as versatile building blocks in various chemical and biological applications due to their unique structural, chemical, and biological properties. These properties include their inherent rigidity, the spatial arrangement of two stereogenic centers, and the ability of hydroxy and amino groups to coordinate with metals as well as hydrogen-bond donors/acceptors. Additionally, their distinct catalytic activities and potential for derivatization further enhance their utility. Aminoindanol derivatives have been widely utilized in asymmetric catalysis and as ligands in organometallic catalytic complexes. Notable examples include their application in transfer-hydrogenation reactions catalyzed by bifunctional chiral ruthenium complexes, which are employed in synthesizing peptide mimics containing the intriguing trifluoroethylamine moiety^{29–33}. The aminoindanol core is also a recurrent motif in several organocatalytic species, gaining prominence in asymmetric organo-catalysis^{34,35}.

Key examples of *cis*-aminoindanol applications include the enantioselective reduction of ketones *via* the in situ formation of catalytically active oxazaborolidines^{36,37} and the synthesis of cooperative thiourea-urea-based organo-catalysts³⁸. Similarly, the use of *trans*-aminoindanol as an efficient organo-catalyst has been reported in the enantioselective synthesis of natural products, such as the TMC-954 core^{39,40}. These and other examples⁴¹ show the high catalytic potential of this versatile motif and prompted us towards the synthesis of its derivatives in the present study (Scheme 1).



Scheme 1. Synthesis of compounds 2a-4o.

Chemistry

The urea and thiourea derivatives were prepared based on the versatile applications of the aminoindanols and the iso(thio)cyanate in organic and medicinal chemistry. The chemical reactions were carried out at room temperature employing dry toluene as the solvent. The equimolar amounts of the aminoindanols and variously substituted iso(thio)cyanate were reacted for approximately 4 h to afford the desired products in good to excellent yields. The molecular structure of compounds 2c, 2f, and 3n were confirmed by single crystal X-ray diffraction studies. Single crystals of compound 2c, 2f, and 3n were grown *via* slow evaporation from ethyl hexane-acetate mixture (1:9) solvent (Fig. 2 and Table S1).

In vitro α -glucosidase Inhibition of synthetic derivatives

The α -glucosidase inhibitory potential of compounds was assessed, with acarbose being used as a standard inhibitor. Except for 2d, all the compounds showed inhibitory potential for α -glucosidase better than that of the reference inhibitor. Compound 2h exhibited the highest inhibitory potency with IC_{50} of $9.64 \pm 0.24 \mu\text{M}$, followed by 2g, 2c, 3i and 2a that exhibited IC_{50} in range of 11.60 ± 0.47 to $13.20 \pm 0.28 \mu\text{M}$. Later compounds 3n, 3j, 3m and 2k also displayed IC_{50} values from 15 to $17.73 \mu\text{M}$, indicating their significant inhibitory capability. While five compounds (2l, 2b, 2f, 2e and 4o) exhibited the IC_{50} values from 23 to $> 35 \mu\text{M}$. The % inhibition and IC_{50} values of compounds are given in Table 1.

Kinetic analysis

To elucidate the inhibition mechanism, the most potent compound 2h was subjected to detailed in vitro kinetic analysis. The compound exhibited a concentration-dependent inhibitory effect, consistent with a competitive mode of inhibition, with a K_i value of $7.39 \pm 0.088 \mu\text{M}$. In this inhibition type, the inhibitor competes with the substrate for binding at the enzyme's active site, leading to an increase in K_m while the V_{max} remains unchanged (Fig. 3). These findings confirm that compound 2h directly interacts with the catalytic site residues, thereby preventing substrate access without altering the enzyme's maximal catalytic efficiency.

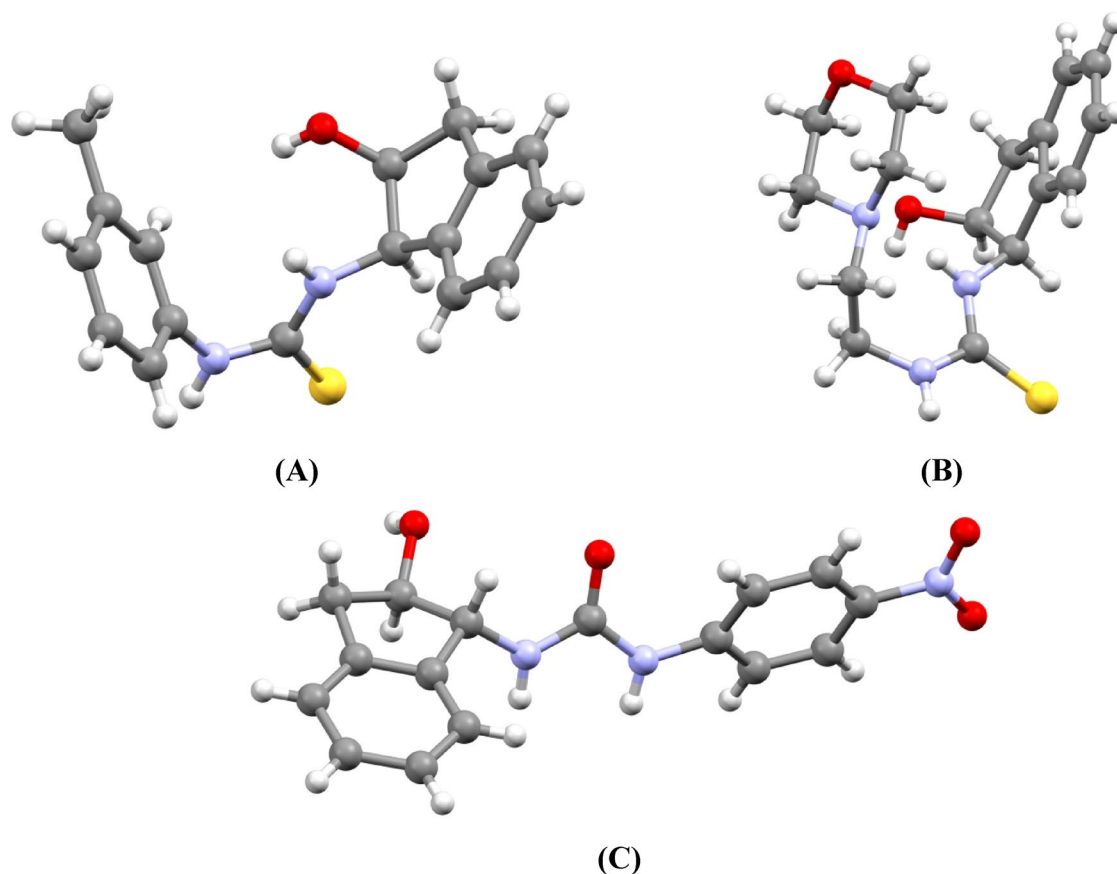


Fig. 2. X-ray crystal structures of **2c** (A), **2f** (B), and **3n** (C).

S. No.	Compounds	%Inhibition (0.5 mM)	IC ₅₀ ± μM (SEM)
1	2a	90.58	13.20 ± 0.28
2	2b	89.73	24.69 ± 0.41
3	2c	90.86	12.33 ± 0.36
4	2d	43.27	N/A
5	2e	87.59	32.70 ± 0.61
6	2f	88.62	28.21 ± 0.56
7	2g	91.44	11.60 ± 0.47
8	2h	91.70	9.64 ± 0.24
9	3i	90.38	12.89 ± 0.25
10	3j	90.13	16.56 ± 0.37
11	2k	90.33	18.73 ± 0.36
12	2L	89.40	23.11 ± 0.48
13	3m	90.75	17.59 ± 0.24
14	3n	91.16	15.36 ± 0.36
15	4o	84.7	35.72 ± 0.80
Standard	Acarbose	58.49	873.34 ± 1.67

Table 1. α -glucosidase inhibitory activities of **2a-4o**.

Molecular docking results and predictive structure-activity relationship

All the compounds (except **2d**) displayed good inhibitory potential for α -glucosidase; hence, their mode of binding was predicted by molecular docking within the active site of α -glucosidase. The residues ASP352, ASP69, ARG213, HIS351, ARG442, TYR72, PHE178, and HIS112 of α -glucosidase interact with the inhibitor (maltose). To ensure the effectiveness of our docking method, we conducted a thorough evaluation by re-docking the co-crystallized ligands in the active pocket. The RMSD value between the co-crystallized and re-docked ligands

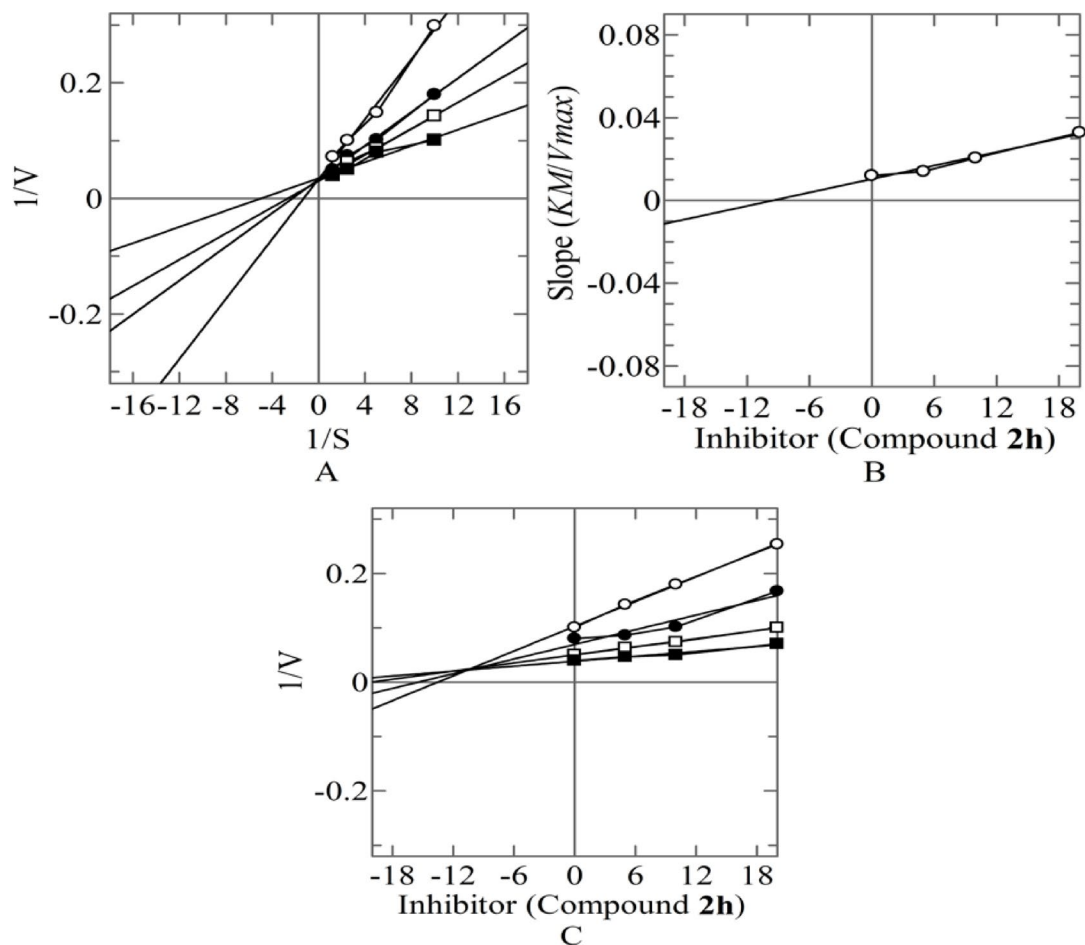


Fig. 3. The inhibition of α -glucosidase by compounds **2h** (A) Lineweaver-Burk plot presented $1/V$ (velocities) on their Y-axis, while that of reciprocal of substrate (4-Nitrophenyl α -D glucopyranoside) on their X-axis. Order of the concentrations of inhibitor include in the absence of compound (\bullet), and in the presence of 20.00 μM (\circ), 10.00 μM (\bullet), and 5.00 μM (\square) of compounds **2h**. (B) Secondary replot of Lineweaver-Burk was plotted between the slopes (Km/V_{max}) on Y-axis and $1/\text{Inhibitor}$ on X-axis, and (C) Dixon plot presented $1/V$ on Y-axis, while $1/\text{Inhibitor}$ on X-axis.

calculated is 0.28 Å (Fig. 4), indicating accuracy of applied docking method as the docking method accurately predicts the experimentally determined orientations of co-crystallized ligand.

Our new compounds exhibited good binding interaction with the active pocket of α -glucosidase with good docking scores. Compound **2h** shows the highest activity with the IC_{50} value of $9.64 \pm 0.24 \mu\text{M}$. When tested in the kinetic analysis, this molecule showed competitive mode of inhibition. Interestingly when docked with α -glucosidase, this molecule fitted well in the active site and mediated excellent interaction with GLU277 which is a part of catalytic triad (ASP215, ASP352 and GLU277). The thiourea moiety of **2h** which links the indanol group with R group, participates in the binding of molecule with the surrounding residues. In compound **2h**, one of the amino groups donate hydrogen bond to the side chain of GLU277 while thiol group accepted a hydrogen bond from the side chain of GLN353. Moreover, the indanol -OH group also mediates a hydrogen bond with the side chain of GLU279. The methoxy phenyl (R group) is nicely fitted between several hydrophobic residues including TYR72, HIS112, TYR158, PHY159 and PHY178. Due to these excellent interactions and well fitted orientation of compound, the ligand **2h** produces highly negative docking score of -6.52 Kcal/mol, which is the highest docking score among all the docked molecules, further confirming the robustness of the docking protocol. Compound **2g** shows the second highest activity in in-vitro findings. We observed similar binding pattern of **2g** and **2h** with minor conformational variation. Both the amino moieties of **2g** mediated hydrogen bonding with two residues of catalytic triad (GLU277 and ASP352). While thiol and the indanol groups did not show any polar interactions with the surrounding residues. The chlorophenyl ring of **2g** is fitted well among the hydrophobic residues. This molecule produced the docking score of -6.41 Kcal/mol. The docking score and binding interaction clearly reflect differences in the inhibitory potency of ligands **2h** and **2g**.

Later, compound **2c**, **2a**, **2k**, **2b**, **2f**, **2e** and **2L** showed IC_{50} values in range of (12 to >23 μM). We observed the conformational changes to predict the structure activity relationship (SAR) among these compounds. In compound **2c** (docking score = -6.37 kcal/mol), we observed the slight variation in its orientation as compared to **2g**. The indanol linked amino group formed a hydrogen bond with ASP352, while the hydroxyl group formed

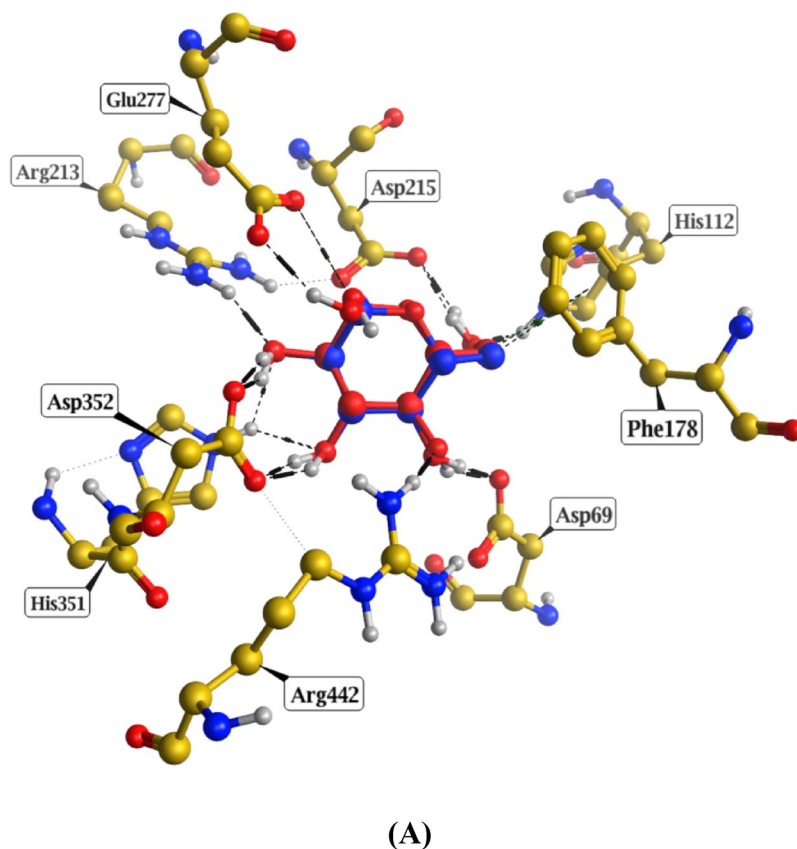


Fig. 4. (A) Re-docked conformation of co-crystallized ligand (blue) with RMSD of 0.28 Å is shown at its X-ray conformation (red) (B) The binding mode of compound 2h is shown in the active site of α -glucosidase enzyme.

a hydrogen bond with the side chain of GLU411. The thiol group lost interaction with GLU277 or GLU279, which may be the reason for slightly lesser activity of this inhibitor than the **2g** and **2h**. In compound **2a** (docking score = -6.25 Kcal/mol), **2k** (-6.12 kcal/mol) **2L** (-6.09 kcal/mol) and **2b** (-6.06 kcal/mol), the indanol moiety slipped towards the entrance of active site. Due to this movement, the indanol $-OH$, the amino and the thiol moieties did not interact with the surrounding residues, however the other amino group formed a hydrogen bond with the side chain of ASP352 in **2a**, Glu277 in (**2k** and **2b**) and ASP352 in **2L**. In these compounds, we observed that the R moiety has moved out of the hydrophobic groove. In compound **2f**, the propyl morpholine is added as a R group. The addition of morpholine group has made the molecule adopt a more bent orientation, thus, the thiourea and morpholine moieties did not interact with residues while indanol $-OH$ group retained hydrogen bond with the side chain of GLU114 with a docking score of -6.06 kcal/mol. The addition of naphthalene moiety in **2e** made the molecule tilted conformation to be fitted inside the active site. The R group (i.e. naphthalene) instead of fitting in the core of active site, faces the entrance of active site while indanol group is oriented towards the core of active site. Due to this drastic conformational change, this molecule has lost all the polar interactions, while only HIS351 and PHE303 provided hydrophobic interactions to this molecule. The docking score of **2e** (-5.81 kcal/mol) reflects its lesser activity as observed in in-vitro.

The docking results of compounds **3i**, **3n**, **3j** and **3m** were compared, these molecules exhibited IC_{50} in range of 12 to >17 μ M. Structurally, compound **3i** is similar to **2a** with the replacement of thiourea moiety in **2a** with urea moiety in **3i**. Interestingly, both **2a** and **3i** showed exactly similar conformation and docking score (**3i** = -6.35 kcal/mol) where one of the amino group mediates hydrogen bonding with ASP352 in **3i**. Interestingly, the benzoic moiety (R-group) of **3n** formed a hydrogen bond with the side chain of HIS112 while its amino group interacted with GLU277. Compound **3n** exhibited a docking score of -6.52 kcal/mol which is slightly higher than that of **2a**. Compound **3j** is similar to **3b** with the exception of thiourea moiety replaced with urea. In **2b**, the thiourea moiety interacts with GLU277 while in **3j**, the urea moiety formed bi-dentate interaction with the side chain of ASP352 which is making **3j** more active than **3b**, this is also reflected by the docking score of **3j** (-6.23 kcal/mol). In compound **3m**, the amino group interact with the side chain of GLU411 with the docking score of -6.21 kcal/mol. At last, compound **4o** showed lesser activity than the rest of the compounds and compound **2d** was found inactive in this study. As the molecular size increased in **4o**, the molecule moved more towards the entrance of active site. One of the indanol moieties remained surface exposed, while the other indanol moiety and a thiol group mediated hydrogen bonds with the side chain of GLU411 and GLN279, respectively. Furthermore, the benzamide group was stabilized by a hydrophobic interaction provided by HIS280. It is noted that the urea and thiourea moieties play vital role in binding with the one of residue of catalytic triad

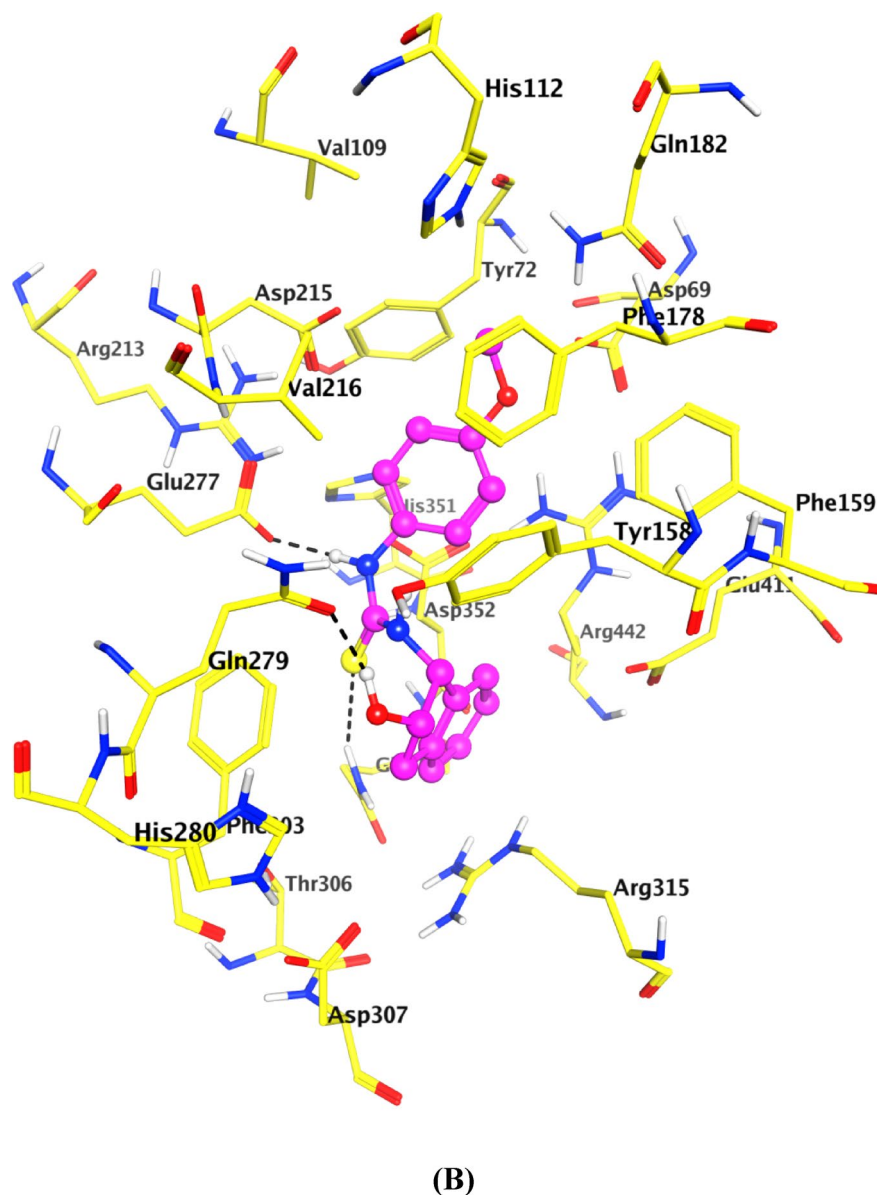


Fig. 4. (continued)

while indanol moiety (-OH group) further stabilize the molecule at active site entrance loop. We obtained a clear correlation between the experimental IC_{50} value and the docking score of compounds. The docking results are tabulated in Table 2 and the binding mode of the most active compound (**2h**) is depicted in Fig. 4.

Conclusion

The convenient synthesis of iso(thio)cyanates derivatives of aminoindanols have been reported in the present study. The NMR spectroscopy and other spectral techniques were used for the structure elucidation of the synthesized products. The α -glucosidase inhibition studies suggest **2h**, **2g**, **2c** and **3i** as promising anti-diabetic molecules. While the rest of the compounds (except **2d**) also showed good to moderate to low inhibition of the α -glucosidase enzyme. The kinetic analysis of the most potent inhibitor (**2h**) reflects its competitive mode of inhibition, suggesting that these molecules directly bind at the active site of enzyme which is also confirmed by molecular docking analysis. Docking results highlight the crucial role of the thiourea and urea moieties in mediating interactions with key residues, identifying them as the primary pharmacophoric features of these scaffolds. The current study, thus, provided an insight into the biological potential of the synthesized molecules, and provided a basis for designing new and improved α -glucosidase inhibitors.

Compounds	Ligand's Atom	Residue's Atom	Types of Interactions	Bond Distance (Å)
2a	N1	OD2-ASP352	HBD	2.89
	6-ring	CE1-HIS280	π -H	3.91
2b	N1	OE2-GLU277	HBD	3.23
2c	N1	OD2-ASP352	HBD	3.22
	O36	OE2-GLU411	HBD	2.81
2e	6-ring	NE2-HIS351	π -H	3.97
	6-ring	6-ring-PHE303	π - π	3.75
2f	O42	OE2-GLU411	HBD	2.57
2g	N1	OE1-GLU277	HBD	2.85
	N5	OD2-ASP352	HBD	2.95
2h	N5	OE2-GLU277	HBD	2.79
	O37	OE1-GLN279	HBD	2.78
	S4	NE2-GLN353	HBA	3.40
2k	N5	OE2-GLU277	HBD	3.25
2L	N1	OD2-ASP352	HBD	2.93
3i	N1	OD2-ASP352	HBD	2.84
3j	N1	OD2-ASP352	HBD	2.74
	N5	OD2-ASP352	HBD	3.25
3m	N1	OE2-GLU411	HBD	2.88
3n	N5	OE2-GLU277	HBD	3.21
	O36	NE2-HIS112	HBA	3.03
4o	N34	OE1-GLN279	HBD	2.59
	O55	OE2-GLU411	HBD	2.76
	6-ring	CE1-HIS280	π -H	3.90

Table 2. Docking interaction of compounds in the active pocket of α -glucosidase. HBA, Hydrogen bond acceptor, HBD, hydrogen bond donor.

Data availability

No datasets were generated or analyzed during the current study.

Received: 31 July 2025; Accepted: 18 November 2025

Published online: 01 December 2025

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Acknowledgements

The authors are thankful to The Oman Research Council (TRC) through the Research Grant Program (BFP/RGP/CBS/18/096). The authors also extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through large Research project grant number RGP2/191/46.

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S.K.: Methodology, Writing—original draft, F.S.: Conceptualization, Supervision, Project administration, Writing—review & editing. L.A.: Methodology, Formal analysis, A.K.: Software, Validation, Writing—original draft. M.U.A.: Methodology, Formal analysis, Data curation. A.U.: Methodology, Validation, Software. S.A.H.: Software, Formal analysis and Writing—review & editing. F.K.: Methodology, Data curation. S.U.: Methodology, Data curation. J.U.: Funding acquisition, Resources, Formal analysis, A.A.-H.: writing—review & editing, Supervision & Project administration. J.H.: writing—review & editing, Supervision & Project administration.

Funding

The authors are thankful to The Oman Research Council (TRC) through the Research Grant Program (BFP/RGP/CBS/18/096). The authors also extend their appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through large Research project grant number RGP2/191/46.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-29712-w>.

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