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Trithiacrown ethers incorporating tetrahydropyridine subunit: synthesis, *in vitro* and *in silico* studies of inhibitory activity against α-glucosidase

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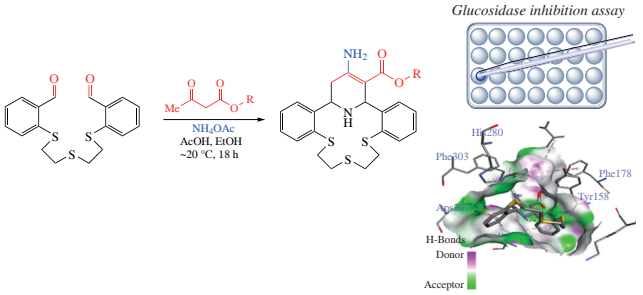
Several novel thiacrown ether derivatives incorpotating tetrahydropyridine subunits have been prepared by the three-component domino reaction of dialdehyde podand, alkyl acetoacetates and ammonium acetate as the nitrogen source. The inhibitory activity of the compounds obtained against α-glucosidase was tested, which revealed two excellent antidiabetic compounds with low IC_{50} values in comparison with control drug. Docking studies proposed the plausible interaction between the synthesized compounds and α-glucosidase receptor.



Keywords: trithiacrown ether, tetrahydropyridine, domino reaction, molecular docking study, α-glucosidase.

Heterocyclic compounds, particularly crown ethers, have garnered considerable scientific interest over time. The addition of heteroatoms such as S and N to novel structures thus giving aza- and thiacrown ethers is getting increasingly popular because such compounds have been proven to possess cytotoxic actions against cancer cells.[1–3] On the other hand, tetrahydropyridine is a heterocycle of multiple applications, *e.g.*, its derivatives are used as precursors for medication, enzyme inhibitors and stimulants.[4,5] These substances play a significant role in research into pharmacological interactions and biological activities such as anticancer, anti-inflammatory, and antibacterial properties.[6–9] They can also be used in materials and environmental research, especially in the production of functional compounds and polymers.[10,11]

Previously, we reported on the synthesis of dithiacrown ether derivatives using multicomponent condensations. The process involved various ketone derivatives to afford crown ether products incorporating 4-piperidone nuclei with different substituents at positions 3 and 5. However, when benzyl acetoacetate was used as the precursor, a product containing 4-aminotetrahydropyridine fragment was formed [Figure 1(*a*)].[12] In addition, several trithiacrown ether derivatives have demonstrated excellent α-glucose enzymatic activity [Figure 1(*b*)].[13]

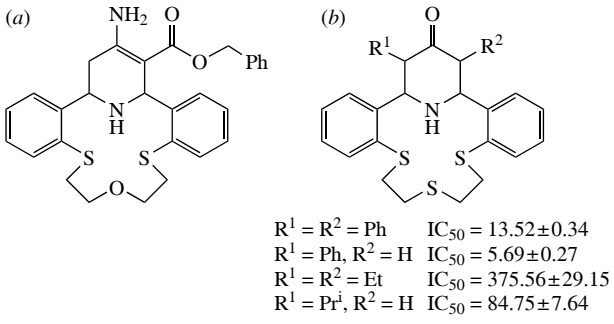
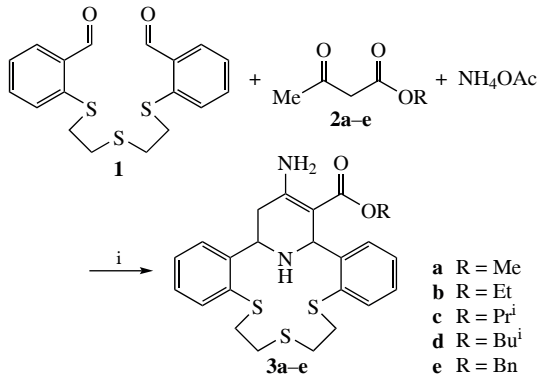


Figure 1 (*a*) Dithiacrown ether incorporating a 4-aminotetrahydropyridine unit; (*b*) structures of some previously documented trithiacrown ether compounds exhibiting α-glucose enzymatic (antidiabetic) activities.

In this study, the condensation between trithia podand, alkyl acetoacetates and ammonium acetate was revealed to result in unexpected 4-aminotetrahydropyridine trithia crown ethers. Biological activities of these compounds toward α-glucosidase enzyme were evaluated. By docking simulation and ADMET studies, the interaction of potential inhibitors with the target protein was investigated.

The synthesis of this series of trithiacrown ether derivatives was carried out in two steps. Step 1 was the previously reported[14] synthesis of dialdehyde podand **1** through the condensation of bis(2-mercaptoethyl) sulfide and 2-fluorobenzaldehyde in DMSO. Step 2 involved the three component reaction of podand **1**, alkyl acetoacetates **2a–d** and ammonium acetate in absolute ethanol in the presence of AcOH as the catalyst at room temperature for 18 h (Scheme 1).[†] In comparison with analogous oxa crown ethers, the yield of trithia derivatives **3a–e** was lower and ranged from 35 to 37%.[10,14,15] It may have risen from the

[†] *General procedure for the synthesis of trithiacrown ethers* **3a–e**. Equimolar amounts of podands **1** (0.10 mmol) and ketones **2a–e** (0.10 mmol) were stirred in ethanol/acetic acid at room temperature in the presence of ammonium acetate (0.30 mmol). The reaction was monitored by TLC and completed after 18 h. The reaction mixture was neutralized with K_2CO_3 solution followed by extracting with dichloromethane (3×30 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure affording the residue which was purified by column chromatography and recrystallized from ethanol to obtain pure products.



Scheme 1 *Reagents and conditions*: i, AcOH, EtOH, room temperature, 18 h.

lower electronegativity of sulfur atom over oxygen atom, which reduced the reactivity of podand **1**. The structures of the synthesized compounds were proven by IR, NMR, and HRMS spectra. The formation of 4-aminotetrahydropyridine core could be recognized by the signal for NH_2 group. In the IR spectrum, this group showed two vibrations around 3300 and 3250 cm^{-1}. The appearance of only one strong vibration around 1650 cm^{-1} belongs to CO bond of the ester group. Other information on ^1H NMR and HRMS supported the formation of target compounds **3a–e** (see Online Supplementary Materials).

One of the efficient ways to reduce postprandial hyperglycemia (PPHG) in diabetes mellitus is to lower the amount of absorbed glucose by inhibiting carbohydrate hydrolyzing enzymes in the digestive system, such as α-glucosidase and α-amylase. α-Glucosidase is a key enzyme that catalyzes the final stage of carbohydrate digestion. Therefore, the main task of α-glucosidase inhibitors is to reduce D-glucose content released from complex carbohydrates and delayed glucose absorption, resulting in lower postprandial plasma glucose levels and control of PPHG. To investigate the activity of synthesized compounds **3a–e** toward α-glucosidase enzyme, the assay was performed.‡ According to the results, among the five compounds, two compounds **3b**,**e** expressed their activities against α-glucosidase better than the acarbose whereas three compounds showed their negative inhibition (**3a**,**c**,**d**). The comparison of the IC_{50} values indicated that acarbose is less active 47 times than compound **3a** and 4.7 times than compound **3d** (see Online Supplementary Materials, Figure S1). The presence of ethyl ester group gave the best activities (compound **3b**) followed by the benzyl group (compound **3e**). Methyl, isopropyl and isobutyl esters showed negative results. In comparison with the piperidone subunit,[13] 4-aminotetrahydropyridine one shows the better activities on α-glucosidase enzyme. This means that changing of the heterocycle, piperidone or 4-aminotetrahydropyridine moieties and the substitutents attached at position 6 of these heterocycles has a great effect on the inhibition activities of the compounds toward α-glucosidase enzyme.

To investigate the interaction between the synthetic compounds and α-glucosidase receptor, a molecular docking was performed using AutoDockTool.[19,20] The three-dimensional structure of isomaltase (PDB ID code 3A4A) was retrieved from RCSB Protein Data Bank1 which shares 85% similar and 72% identical sequence with α-glucosidase.[21,22] After download, water molecules, co-ligand and heteroatoms were removed, polar hydrogens and Kollman charges were then added, and this was finally redocked with α-glucose into the binding sites of 3A4A to perform the verification process. The binding affinity of α-glucose was found to be –5.9 kcal mol^{-1}. The redocked interactions in the active site like the co-ligand in protein, including conventional hydrogen bonding with Asp69, Gln182, Arg442, Asp352, His351, Glu277. The docking process of the samples was performed using default parameters and in the same binding site with the co-crystallized ligand. After that, binding interactions between the ligands and the target protein were analyzed and visualized by Discovery Studio 2021. The calculation was carried out using an Intel (R) Core (TM) i3-10400 CPU @ 2.90 GHz workstation. The obtained results are presented in Table 1 and Figure S3.

The calculated result showed that compound **3e** had the lowest binding enery (–8.3 kcal mol^{-1}), followed by compound **3b** (–6.7 kcal mol^{-1}) and acarbose (–5.9 kcal mol^{-1}). However, the *in vitro* result indicated the best activity of compound **3b** followed by compound **3e**, and acarbose. Benzene rings of both compounds **3b** and **3e** interact with the key residues of the target protein by one π–anion bond (Asp207) and two π–akyl bonds (Arg315). Ethyl group of compound **3b** formed two π–alkyl bonds with Tyr158 and Phe178 residues whereas benzyl substituent of compound **3e** formed one π–anion bond with Asp352, one π–π T-shaped bond with Phe178 and one π–alkyl bond with Val216. Through this examination, with the same crown part, it is clear that R substituent plays a significant role in binding with residues of protein leading to a great impact on their antidiabetic results. Furthermore, physicochemical properties of compounds **3b** and **3e** were predicted using the ADMET tool.[23–25] The computed results indicated that thirteen parameters of compound **3b** fall within the optimal range, except its number of atoms in the largest ring (MaxRing) (Figure S4).

According to Lipinski's 'rule of five', the parameters of drug likeness will likely be orally active, if (i) the molecular weight (MW) < 500, (ii) the calculated octanol/water partition coefficient ($\log P$) < 5, (iii) there are less than five hydrogen bond donors (HBD) (OH and NH groups), and (iv) there are less than ten hydrogen bond acceptors (HBA) (notably N and O) and (v) topological polar surface area (TPSA) is less than 140 Å.[26–28] The calculated results demonstrated that compound **3e** violated

Table 1 The binding affinity and RMSD values of the potential compounds **3b**,**e** and α-glucose.

Sample	Binding energy /kcal mol^{-1}	2D interaction with amino acids
3b	–6.7	Arg315, Asp307, Tyr158, Phe178
3e	–8.3	Asp307, Arg315, Asp352, Phe178, Val216
α-Glucose	–5.9	Asp69, Tyr712, Arg442, His351, Asp352, Arg213, Glu277, Gln182

‡ The activity of synthesized compounds **3a–e** toward α-glucosidase enzyme was studied in a 96-well microtiter plate and monitored by the transformation of *p*-nitrophenyl-α-D-glucopyranoside (pNPG) mediated by α-glucosidase into α-D-glucose and *p*-nitrophenol.[16,17] Acarbose was used as the positive control. The sample solution was prepared by dissolving in DMSO and diluting in a series of concentrations: 256, 64, 16, 4, and 1 μg ml^{-1} or smaller with a very active compound.[18] A mixture of 40 μl of phosphate buffer (pH 6.8), 25 μl of α-glucosidase (0.4 U ml^{-1}) and 10 μl of each sample concentration was incubated for 15 min at 37 °C and for another 30 min at 37 °C with 50 μl of pNPG solution (5 mM). The reaction was stopped by quenching with 100 μl of 0.2 M Na_2CO_3. The amount of *p*-nitrophenol released by pNPG was measured at 410 nm which responded to the α-glucosidase activity. The percentage of inhibition was calculated according to the following equation:

$$I_G\,(\%) = 100 \times (A_C - A_S)/A_C,$$

where I_G is α-glucosidase inhibition in percent, A_C is the absorbance of control, A_S is the absorbance of sample. The IC_{50} value (half-maximal inhibitory concentration) was calculated for each compound based on the program TableCurve 2Dv4 software. The results are represented as a mean value of three independent tests (see Online Supplementary Materials, Figures S1, S2 and Table S1).

Lipinski's rule (in MW and log *P*) whereas compound **3b** could be considered as a potential orally active drug candidate. This prediction indicated a relative accordance with the *in vitro* bioassay of **3b** and **3e**.

In conclusion, five thiacrown ether derivatives incorporating 4-aminotetrahydropyridine subunit have been prepared. The *in vitro* assay showed that compound **3b** expressed its inhibitory activity against α-glucosidase with IC_{50} of 5.13 μM, lower than control drug by a factor of 47. The docking study indicated that the modification of alkyl substituents of acetoacetate has a great effect on both the outcome of the reaction and the bioactivities of final products. ADMET calculation shows that compound **3b** could be a potential orally active drug candidate.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7679.

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