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Synthesis of novel mono and bis-indole conduritol derivatives and their α/β-glycosidase inhibitory effects

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ABSTRACT

Here we synthesized four novel indole conduritol derivatives **1–4** for the first time in the literature and probed their biological activities with the α and β-glucosidases. The compounds showed quite effective glucosidase inhibitory action. IC_{50} values of the compounds were compared with the known glucosidase inhibitor acarbose and it was determined that newly synthesized indole conduritols had more powerful effect against β-glucosidase in addition to exhibiting moderate influence against α-glucosidase. Our molecules thus constitute an important starting point for the design and exploitation of novel glucosidase inhibitors since glucosidase inhibitors have widespread applications in the treatment of diabetes, viral infections, lysosomal storage diseases and cancers.

The conduritol family compounds are cyclitol derivatives possessing four contiguous hydroxyl groups on cyclohexene ring. There are several possible stereoisomers; four couple of (+) and (−) enantiomers (conduritols B, C, E and F) and two *meso*-forms (conduritols A and D) (Fig. 1). Interest in conduritols and their analogues has been heightened due to the synthetic challenge that they represent and and presence of a variety of biological activities such as antifeedant, antibiotics, antileukemics and growth-regulation.[1]

Conduramines are an important member of the cyclitols compounds. Conduramines are analog of conduritols in which one of the hydroxyl group is replaced with amino group. Conduramines have gained much attention due to their biologic activities towards glycosidase and their usage in the synthesis of azosugars, amino sugars, sphinoganies, lactams, narcisus alkaloids as a intermediates. There are several stereoisomers of monoamine containg conduritols (A–F) but only nine enantiomers have been synthesized to date in literature (Fig. 2).[2]

Diamino contaning conduritols are derived from conduritols, in which two of the hydroxyl groups are replaced with two amino groups. There are four stereogenic centers of dimainoconduritols in which different substituent groups allow it to exist in four different structural isomers respectively 1,2-, 1,3-, 1,4- and 2,3-diaminoconduritols (Fig. 3).[3]

Currently, as a vital motif in potent anticancer narciclasine[4] and antidiabetic conduritol A,[5] facile and efficient synthetic approaches have been developed to produce optically pure conduritols in large quantity.[6] α-Glucosidase inhibitors are a class of compounds that inhibit the breakdown of oligo and disaccharides from dietary complex carbohydrates and slowdown the absorption of absorbable monosaccharides available[7a,b] and reduce the postprandial insulin and glucose peak. Delay in glucose absorption reduces postprandial hyperglycemia, which is associated with cardiovascular mortality. Acarbose was the first member of the α-glucosidase inhibitor family of therapeutic agents to be approved for the treatment of type 2 diabetes.[7]

Indole moieties occur in many synthetic and natural products, some of which are physiologically relevant or therapeutically used. 8a,b Melatonin, an important hormone containing the indole moiety, is known to regulate biological rhythms, and to act as a receptor-independent free-radical scavenger, being also a broad-spectrum antioxidant.[8] In recent investigations, antioxidant activity of synthetic indole derivatives and their possible mechanisms of action have been widely studied. Many of these compounds have been demonstrated to possess potent carbonic anhydrase inhibitor, anticarcinogenic, and antibacterial activities.[8]

Glycosidase inhibition is important not only for the insightful understanding of enzyme mechanism, but also for questing promising therapeutics in treatment of disorders such as diabetes[9] and metastatic cancer.[10a] The knowledge of the crystal structure of glycosidase and its complexes with known inhibitors provides a rich framework to design more potent inhibitors.[10]

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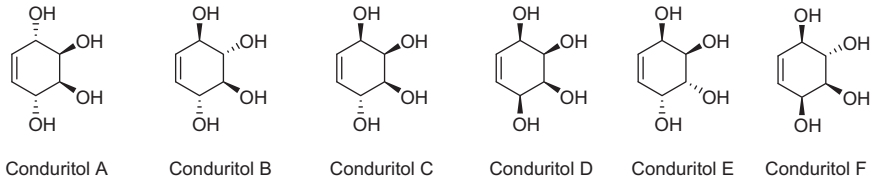


Figure 1. Structures of conduritols (A–F).

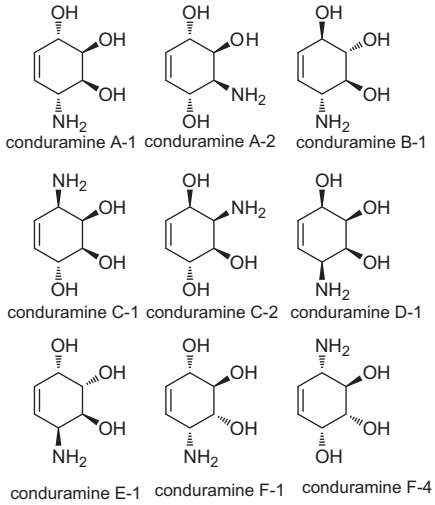


Figure 2. Structures of conduramines have been synthesized to date.

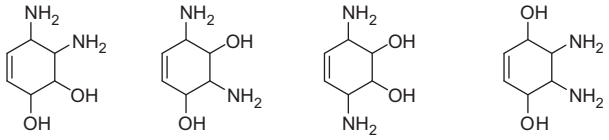


Figure 3. Structures of diaminoconduritols.

Considering above stated information, synthesis and discovery of novel glycosidase inhibitors are of particular interest due to their possible anti-diabetic capacities. Therefore, in this study, we analyzed the glycosidase inhibitory capacities of several molecules, mostly indole conduritol derivatives, four of which have been newly synthesized by our group (i.e. compounds **1**–**4**, see Scheme 2 and 3).

Our groups recently investigated the interaction of α and β-glucosidase with acarbose and some secondary metabolites, such as astragaloside IV, trojanoside H, astrasieversianin X and astragaloside VIII[11] (Fig. 4). We tested acarbose as a positive control for the α-glucosidase inhibition. Compound **4** behaved as the strongest α and β-glucosidase inhibitor with IC_{50} values of 11.6 and 23.1 μM, respectively (Table 1).

Indoline, one of the most common aromatic heterocyclic organic compounds, has a bicyclic structure, consisting of a six-membered benzene ring fused to 2C and 3C position of pyrrolidine ring (Fig. 5). The compound is based on the indole structure, but the 2–3 bond is saturated. By oxidation/dehydrogenation it can be converted to indoles easily. Indoline constitutes an important class of natural products and drug materials and also it is a key molecule in the sytnthesis of indole derivatives.[12a,b] A lot of biologically active compounds have indoline moiety in their chemical structures. For example, vincamine, a peripheral vasodilator that increases blood flow to the brain, is a natural product and has indoline skeleton.[12c,d]

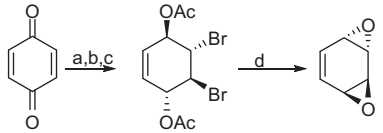
Indoline plays an important role in the synthesis of N substituted indole derivatives. The NH group in its structure attacks electrophilic compounds easily. Thus, N substituted indoline compounds can be obtained easily. Through oxidizing N substituted indoline compounds by several oxidants such as MnO_2, DDQ, chloroaniline and naphthoquinone, many N substituted indole derivatives have been synthesized.[12a,b]

Indole and conduritol molecules are present in an enormous number of natural products and pharmaceuticals. Thus, we aimed in this study to synthesize indole and conduritol containing compounds. For this aim, we first synthesized anti-bisepoxide using the reported procedure in the literature[1,13] (Scheme 1).

Indoline (2 equiv) was reacted with anti-bisepoxide (1 equiv) in the presence of CH_2Cl_2 and the aminoconduritol derivative (**1**) was obtained.[17] We were unable to oxidize this compound by MnO_2 or DDQ. Thus, we acetylated the hydroxyl group and then oxidized by MnO_2 and obtained (**2**) (Scheme 2).

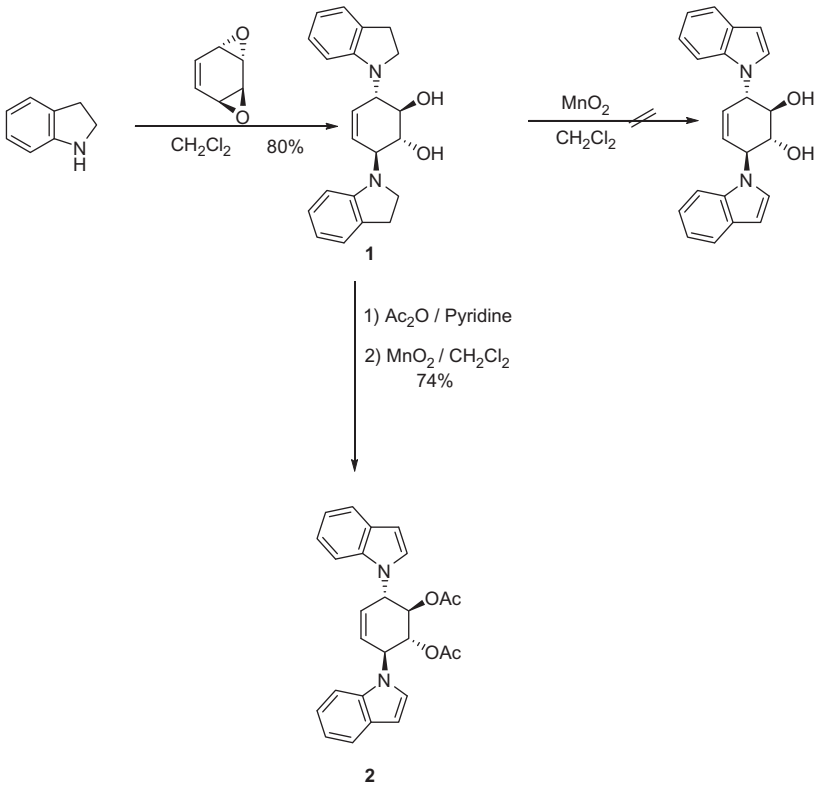
After that, indoline (1 equiv) was reacted with anti-bisepoxide (1 equiv) in order to synthesize mono indole conduritol derivative. The product was treated with AcO_2/pyridine to protect the hydroxyl groups, and subsequently (**3**) was obtained. Finally, *(1S,2S,3R,6R)-2-hydroxy-6-(indolin-1-yl)cyclohex-4-ene-1,3-diyl diacetate was oxidized by* MnO_2 at room temperature and (**4**) was synthesized (Scheme 3). By means of this procedure, we combined two very important groups indole and conduritol and synthesizes indole conduritol derivatives for the first time in the literature.

We report here the first study on the inhibitory effects of these compounds on α and β-glucosidase. Acarbose has been used as a positive control for α glucosidase in our experiments, and for comparison reasons.[18] Data of Table 1 show the following regarding inhibition of α and β-glucosidase with these compounds with 4-

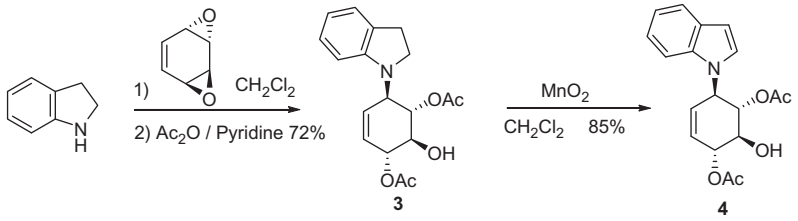


(a) 0°C Br_2, CH_2Cl_2, 70% (b) $NaBH_4$, H_2O/Et_2O, 84% (c) Ac_2O, Pyridine 75% (d) KOH, THF, 77%

Scheme 1. Reagents and conditions: (a) 0 °C Br_2, CH_2Cl_2, 70%; (b) $NaBH_4$, H_2O/Et_2O, 84%; (c) Ac_2O, Pyridine 75%; (d) KOH, THF, 77%.



Scheme 2.



Scheme 3.

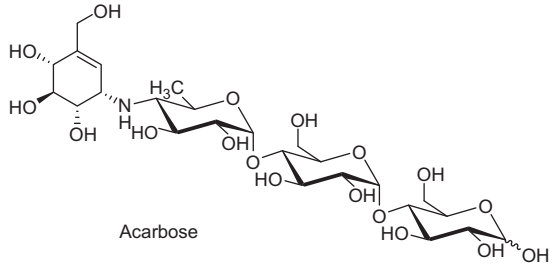


Figure 4. Structure of acarbose.

Table 1
$IC_{50\ I}$ values (μM) of α and β glucosidases by compounds **1**–**4**

Inhibitor	IC_{50} α glucosidase	IC_{50} β glucosidase
Acarbose[a]	9.24	103.12
1	18.1	67.7
2	19.3	52.8
3	12.4	24.3
4	11.6	23.1

[a] From Ref. 11.

nitrophenyl α-D-glucopyranoside and 4-nitrophenyl β-D-glucopyranoside as substrate:

(i) Against α glucosidase, compounds **1** and **2** behave as rather weak inhibitors, with IC_{50} values of 18.1 and 19.3 μM. A second group of compounds **3** and **4** showed better inhibitory activity as compared to the previously mentioned compounds, with IC_{50} values of 11.6 and 12.4 μM (Table 1). Therefore, the nature of the groups in *ortho*-, *para*- and *metha*- to the OAc and OH moiety strongly influences α glucosidase inhibitory activity. Acarbose is also a medium α glucosidase inhibitor with this assay and substrate against α glucosidase (IC_{50} of 9.24 μM).

(ii) A better inhibitory activity has been observed with the compounds for the inhibition of β-glucosidase (Table 1). Compounds **1** and **2** were quite effective β-glucosidase inhibitors, with IC_{50} values of 67.7 and 52.8 μM (Table 1). Compounds **3** and **4** exhibited more effective inhibitory activity with IC_{50} values of 24.3 and 23.1 μM.

Especially, indoline containing cyclohexene derivatives influence the activity of glycosidases due to the presence of the different functional groups (OH and OAc) present in their scaffold. Our findings indicate thus another class of possible glycosidase inhibitors of interest, in addition to the well-known conduritols in their

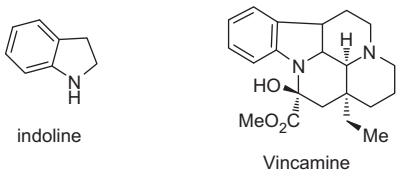


Figure 5. Structure of indoleine and vincamine.

molecules. Compounds **3** and **4** investigated here showed effective α and β glycosidase inhibitory activity, in the low micro molar range. These findings point out that substituted –OAc and –OH compounds may be used as leads for generating potent glycosidase inhibitors.

It is apparent that conduritol derivatives have many important roles. In addition, glycosidase inhibitors have gained great attention due to their impacts on cancer and diabetes. Thus, we synthesized novel conduritol derivatives and measured their potencies at glycosidase inhibition. In addition, we compared and discussed the novel conduritols α glycosidase inhibitory propensities with the simple precursor and commercially available compound acarbose. Our groups have reported several interactions of different functional groups with different enzymes.[14,15] However, this research is starting point for us to design and discover novel glycosidase inhibitors.

Consequently, conduritol derivatives used in this study affect the activity of α and β glucosidases due to the presence of the different functional groups present in their aromatic scaffold. Our findings here indicate thus another class of possible α and β glucosidases of interest, in addition to the well-known acarbose and conduritol F derivatives bearing bulky in their structures. Indeed, new conduritol derivatives investigated here showed very effective β glucosidases inhibitory activity compared to well known agents. These findings point out that novel substituted conduritol derivatives may be used as leads for generating potent glucosidases inhibitors. Thus, this approach may also be useful in the design and exploitation of novel drug candidates for diabetes, viral infections including HIV and influenza and cancer. However, these features of the compounds are beyond the scope of this study and merits further investigations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.038.

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17. *Detailed synthetic procedures for the preparation of all derivatives* ***1–4*** *can be found in*: *(1R,2R,3S,6S)-3,6-di(indolin-1-yl)cyclohex-4-ene-1,2-diol* (**1**) : To solution of indoline (119 mg, 1.0 mmol) and anti-bisepoxide (56 mg, 0.5 mmol) in 20 mL CH_2Cl_2 was stirred at room temperature for 16 h . After complete conversion as indicated by TLC, the solvent was removed by evaporation and the residue was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was submitted to column chromatography on silica gel (25 g) eluting with ethyl acetate/hexane (7%). Elution gave *(1R,2R,3S,6S)-3,6-di(indolin-1-yl)cyclohex-4-ene-1,2-diol* (**1**) as a sole product. Pale brown crystals from CH_2Cl_2/*n*-hexane (2:1), (140 mg, 80%, mp 82–83 °C).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.05 (m, 4H), 6.71–6.67 (m,2H), 6.56 (d, *J* = 8.1 Hz, 2H), 5.65 (br s, 2H), 4.26 (m, 2H), 4.06 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 2H), 3.56–3.51 (m, 2H), 3.30 (dd, *J* = 18.5 Hz, *J* = 9.7 Hz, 2H), 2.04–3.03 (m, 4H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.10, 130.80, 129.41, 127.51, 125.01, 118.65, 108.14, 72.20, 59.95, 48.30, 28.53. IR (KBr, cm^{-1}): 3367, 3042, 3019, 2925, 2845, 1605, 1486, 1457, 1254, 1085, 1023. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04 Found: C, 75.82; H, 6.95; N, 8.06;
*(1R,2R,3S,6S)-3,6-di(1H-indole-1-yl)cyclohex-4-ene-1,2-diyl diacetate (**2**)* : The pure product (**1**) (200 mg, 0.57 mmol) was acetylated in pyridine (1.00 g) and Ac_2O (0.50 g) at 1 day. Then, the mixture was cooled to 0 °C and poured into a cold solution (1%, 100 mL) of HCl. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Then, the crude product in CH_2Cl_2 (10 mL) was added activated MnO_2 (496 mg, 10 mmol).The mixture was stirred at rt for24 h. After filtration, the mixture was evaporated under vacuo. The residue was submitted to column chromatography on silica gel (20 g) eluting with ethyl acetate/hexane (10%). Elution gave *(1R,2R,3S,6S)-3,6-di(1H-indole-1-yl)cyclohex-4-ene-1,2-diyl diacetate* (**2**) as a sole product. White crystals from CH_2Cl_2/*n*-hexane (2:1), (181 mg, 74%, mp 103–104 °C).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.26–7.22 (m, 2H), 7.16–7.10 (m, 4H), 6.61 (d, *J* = 3.3 Hz, 2H), 6.13 (br s, 2H), 5.66 (dd, *J* = 6.4 Hz, *J* = 2.4 Hz, 2H), 5.47–5.46 (m, 2H), 1.62 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.31, 136.82, 129.64, 129.07, 125.16, 122.15, 121.60, 120.21, 109.67, 103.72, 73.07, 57.36, 20.40.
IR (KBr, cm^{-1}): 2924, 2854, 1744, 1611, 1514, 1460, 1372, 1311, 1222, 1052, 1014, 964, 904. . Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54 Found: C, 72.87; H, 5.66; N, 6.52;
*(1S,2S,3R,6R)-2-hydroxy-6-(indolin-1-yl)cyclohex-4-ene-1,3-diyl diacetate (**3**)*: To

a stirred solution of indoline (179 mg, 1.5 mmol) in 10 mL CH_2Cl_2 was added anti-bisepoxide (165 mg, 1.5 mmol) at room temperature. After the mixture was stirred for 18 h. The solvent was concentrated under reduced pressure. Then, the crude product was acetylated in pyridine (1.50 g) and Ac_2O (0.60 g) at 1 day. Then, the mixture was cooled to 0 °C and poured into a cold solution (1%, 100 mL) of HCl. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL), and then dried over Na_2SO_4. and concentrated in vacuo. The residue was submitted to column chromatography on silica gel (25 g) eluting with ethyl acetate/hexane (15%). Elution gave *(1S,2S,3R,6R)-2-hydroxy-6-(indolin-1-yl)cyclohex-4-ene-1,3-diyl diacetate* (**3**) as a sole product. White crystals from CH_2Cl_2/*n*-hexane (2:1), (358 mg, 72%, mp 112–113 °C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09–7.04 (m, 2H), 6.68–6.17 (m,2H), 5.91 (br s, 2H), 5.58 (t, J = 3.11 Hz 1H), 5.39 (dd, J = 8.3 Hz, J = 3.2 Hz, 1H), 4.51 (d, J = 8.3 Hz 1H), 4.40 (t, J = 3.2 Hz, 1H), 3.51 (dd, J = 17.00 Hz, J = 8.8 Hz, 1H), 3.36 (dd, J = 17.00 Hz, J = 8.8 Hz, 1H), 2.98 (t, J = 8.8 Hz, 2H), 2.14 (s, 3H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.44, 170.02, 150.74, 132.63, 129.96, 127.50, 125.20, 124.90, 118.08, 107.41, 71.67, 67.72, 54.85, 50.34, 48.76, 28.51, 21.17, 21.07.

IR (KBr, cm^{-1}): 2918, 2845, 1743, 1605, 1488, 1371, 1223, 1055, 1009, 959, 900.

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23 Found: C, 65.26; H, 6.37; N, 4.24.

(1S,2S,3R,6R)-2-hydroxy-6-(1H-indole-1-yl)cyclohex-4-ene-1,3-diyl diacetate (**4**): To a stirred solution of *(1S,2S,3R,6R)-2-hydroxy-6-(indolin-1-yl)cyclohex-4-ene-1,3-diyl diacetate* (**3**) (300 mg, 0.91 mmol) in 20 mL CH_2Cl_2 was added activated MnO_2(792 mg, 10 mmol).The mixture was stirred at rt for24 h. After filtration, the mixture was evaporated under vacuo. The residue was submitted to column chromatography on silica gel (30 g) eluting with ethyl acetate/hexane (18%). Elution gave *(1S,2S,3R,6R)-2-hydroxy-6-(1H-indole-1-yl)cyclohex-4-ene-1,3-diyl diacetate* (**4**) as a sole product. Cream crystals from CH_2Cl_2/*n*-hexane (2:1), (253 mg, 85%, mp 190–191 °C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.2 Hz 1H), 7.57 (d, J = 8.2 Hz 1H), 7.27–7.23 (m, 1H), 7.16–7.12 (m,2H), 6.56 (d, J = 4.3 Hz 1H), 6.08 (br s, 2H), 5.73–5.71 (m, 1H), 5.38 (dd, J = 7.5 Hz, J = 3.1 Hz, 1H), 5.27 (d, J = 7.5 Hz 1H), 4.41 (dd, J = 4.6 Hz, J = 3.1 Hz, 1H), 2.18 (s, 3H), 1.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.11, 169.87, 136.60, 129.86, 129.17, 126.89, 125.84, 122.29, 121.36, 120.32, 110.12, 103.16, 71.60, 71.50, 54.63, 48.33, 21.16, 20.83.

IR (KBr, cm^{-1}): 2924, 2862, 2330, 1755, 1608, 1510, 1457, 1367, 1309, 1232, 1051, 923.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25 Found: C, 65.66; H, 5.80; N, 4.26.

18. *In vitro inhibition studies*: α-Glucosidase from *Bacillus stearothermophilus* (E.C. 3.2.1.20) was purchased from Sigma–Aldrich (CAS Number: 9001-42-7) and β-glucosidase from almonds (E.C. 3.2.1.21) was purchased from Sigma–Aldrich (CAS Number: 9001-22-3) for using in inhibition studies. Enzyme assay was performed for four compounds **1–4** and acarbose. The reaction mixture containing 1 mM PNPG (4-nitrophenyl α-D-glucopyranoside or 4-nitrophenyl β-D-glucopyranoside), phosphate buffer (pH 6.8), and 10 μM of the corresponding isomers was incubated at 37 °C for 5 min then 0.075 unit of enzyme was added and the resulting mixture was incubated at 37 °C for 30 min, then and reaction was stopped with 2 mL of 100 mM Na_2CO_3 and the absorbance at 400 nm of the liberated *p*-nitrophenol was measured. All compounds were tested in triplicate at each concentration used. Different inhibitor concentrations were used. For α-glucosidase, the inhibitor concentrations used were: 1, 3, 10, 15 and 25 μM and for β-glucosidase, the inhibitor concentrations used were: 10, 20, 30, 50, 70, 80, 90 and 100 μM. Control cuvette activity in the absence of inhibitor was taken as 100%.[16] For each inhibitor an activity%–Log10[inhibitor] graph was drawn.