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Amplification of the inhibitory activity of miglitol by monofluorination

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ABSTRACT

Selective monofluorination of the α-glycosidase inhibitor and antidiabetic agent Miglitol at position C(2) creates an competitive inhibitor of five times higher activity than the parent compound. Its screening against a panel of human cell lines showed a low cytotoxicity therefore making this compound an interesting candidate for further clinical investigations.

Miglitol (Glyset™) (**1**) is used, alone or with other drugs, to treat type-2 diabetes in people whose diabetes cannot be controlled by diet alone. Miglitol (Fig. 1) slows down the breakdown and adsorption of table sugar and other oligosaccharides in the small intestine, therefore resulting in lowered blood sugar levels following meals. It acts[1] as a competitive inhibitor of α-glucosidases, and —in addition—**1** suppresses the postprandial increase in interleukin-6 and increases active glucagon-like peptide 1 secretion.

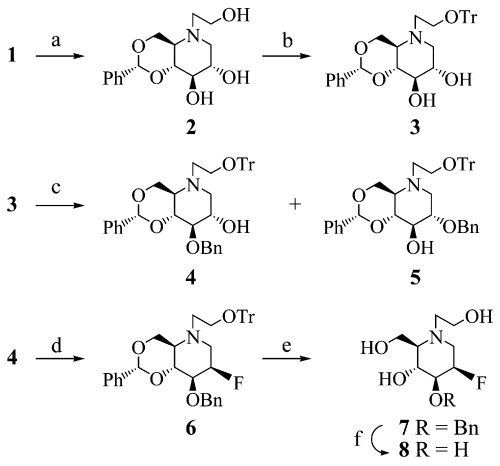
Total sales for **1** in the USA were approx. 22 Mill $ for 2007 with a total annual growth of 267% compared to 2006. The daily doses, however, are high (50–300 mg/d). In addition, miglitol as well as various N-alkylated derivatives have become pharmacological agents to treat metabolic disorders, for example, Gaucher's disease.[2] Therefore, it seemed of interest to look out for compounds being stronger competitive inhibitors of α-glucosidases than miglitol.

Inspection of models and interpreting in-silico docking experiments[3] suggested that a miglitol derivative bearing an epimeric fluorine substituent at position C(2) should bind more strongly to the active site of the α-glucosidase (from baker's yeast).

To corroborate this theory we set out for a synthesis (Scheme 1) of this target compound. Since **1** is commercially available we decided to start our synthetic approach from miglitol (**1**).

Thus, starting material **1** was treated with benzaldehyde in the presence[4] of anhydrous $ZnCl_2$ to yield 90% of the corresponding benzylidene acetal **2**. Tritylation[5] of **2** gave **3** whose benzylation with benzylbromide in the presence of bis(tri-*n*-butyltin)oxide[6] afforded a mixture of the monobenzylated compounds **4** and **5** in a 5:1 ratio. Reaction of monobenzylated **4** with DAST[7] in dry dichloromethane for 3 h at room temperature gave 70% of fluorinated **6**.

Compound **6** was successively deprotected: First, the benzylidene acetal and the trityl group were cleaved off by treatment[8] of compound **6** with acetyl chloride in methanol; this resulted in an almost quantitative yield of **7** that was hydrogenated[9] for 24 h in the presence of palladium on charcoal at 40 °C to yield compound **8** (ca. 100 mg) in 68% yield after chromatographic work-up.



Scheme 1. Reactions and conditions: (a) benzaldehyde, $ZnCl_2$, 50 °C, 48 h, 90%; (b) TrCl, pyridine, DMAP, 50 °C, 48 h, 83%; (c) bis(tri-*n*-butyltin)oxide, toluene, BnBr, 90 °C, 5d, **4**:**5** = 5:1, together 65%; (d) DAST, dichloromethane, 25 °C, 3 h, 70%; (e) MeOH, AcCl, 25 °C, 5d, quant.; (f) MeOH, Pd/C (10%), H_2, 40 °C, 24 h, 68%.

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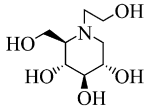

Figure 1. Structure of antidiabetic miglitol (**1**).

Biological screening of compounds **1** and **8** was performed using a 4-nitrophenolate-based assay[10] starting from the corresponding glucoside and the α-glucosidase from baker's yeast. Whereas miglitol shows an IC_{50} of 9.9 mM in this test for compound **8**[11] an IC_{50} of 2.1 mM was observed—therefore showing an approx. fivefold stronger inhibition of the enzyme. Evaluation of the enzyme kinetics revealed **8** as a competitive inhibitor of the enzyme. Biological screening revealed **8** as a strong competitive inhibitor against a α-glucosidase. Screening of **8** against a panel of human cell lines showed a low cytotoxicity of **8** therefore making this compound an interesting candidate for further clinical investigations.

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11. *Selected analytical data for* **4**: oil, $[\alpha]_D = -5.69$ (*c* 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50–7.20$ (m, 25H, H-aromat.), 5.54 (s, 1H, C*H*-benzylidene), 5.00 (d, 1H, $J_{H'',H'} = 11.5$, CH''_2OBn), 4.65 (d, 1H, $J_{H',H''} = 11.5$, CH'_2OBn), 4.50 (dd, 1H, $J_{6'',5} = 4.3$, $J_{6'',6'} = 10.5$, H-6′′), 3.74–3.56 (m, 3H, H-2, H-6′, H-4), 3.36 (dd, 1H, $J_{3,2} = 9.0$, $J_{3,4} = 9.0$, H-3), 3.19–3.16 (m, 2H, H-2$''_e$, H-2$'_e$), 2.98 (dd, 1H, $J_{1'',2} = 5.1$, $J_{1'',1'} = 11.0$, H-1$''_e$), 2.76 (ddd, 1H, $J_{H\text{-}1'',\ H\text{-}2'} = 5.9$, $J_{H\text{-}1'',\ H\text{-}2''} = 5.9$, $J_{H\text{-}1'',\ H\text{-}1'} = 13.9$, H-1′′), 2.62–2.51 (m, 2H, H-1$'_e$, H-5), 2.21 (dd, 1H, $J_{1',2} = 10.7$, $^2J_{1',1''} = 11.0$, H-1′) ppm; MS (ESI–MeOH): *m*/*z* (%) = 628.1 ([M+H]$^+$, 100), 650.3 ([M+Na]$^+$, 11), 1254.7 ([M_2+H]$^+$, 5), 1277.0 ([M_2+Na]$^+$, 14); selected analytical data for **8**: $[\alpha]_D = -65.77$ (*c* 0.06, MeOH); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 4.40$ (dddd, 1H, $J_{2,1''} = 4.2$, $J_{2,3} = 7.1$, $J_{2,1'} = 9.1$, $J_{2,F} = 49.5$, H-2), 3.94 (dd, 1H, $J_{6'',5} = 2.7$, $J_{6'',6'} = 12.1$, H-6′′), 3.90 (dd, 1H, $J_{6',5} = 2.5$, $J_{6',6''} = 12.1$, H-6′), 3.74 (ddd, 1H, $J_{H\text{-}2'',\ H\text{-}1'} = 4.5$, $J_{H\text{-}2'',\ H\text{-}1''} = 7.5$, $J_{H\text{-}2'',\ H\text{-}2'} = 11.3$, H-2$''_e$), 3.71 (ddd, 1H, $J_{H\text{-}2',\ H\text{-}1'} = 3.7$, $J_{H\text{-}2',\ H\text{-}1''} = 7.6$, $J_{H\text{-}2',\ H\text{-}2''} = 11.3$, H-2$'_e$), 3.49–3.44 (m, 2H, H-3, H-4), 3.40 (ddd, 1H, $J_{1'',2} = 4.2$, $J_{1'',1'} = 10.9$, $J_{1'',F} = 13.6$, H-1′′), 3.14 (ddd, 1H, $J_{H\text{-}1'',\ H\text{-}2'} = 7.6$, $J_{H\text{-}1'',\ \text{-}H\text{-}2''} = 7.5$, $J_{H\text{-}1'',\ H\text{-}1'} = 12.6$, H-1$''_e$), 2.78 (ddd, 1H, $J_{H\text{-}1',\ H\text{-}2'} = 3.7$, $J_{H\text{-}1',\ H\text{-}2''} = 4.5$, $J_{H\text{-}1',\ H\text{-}1''} = 12.6$, H-1$''_e$), 2.65 (ddd, 1H, $J_{1',2} = 9.1$, $J_{1',1''} = 10.9$, $J_{1',F} = 14.2$, H-1′), 2.50 (m, 1H, H-5) ppm; ^{13}C NMR (100 MHz, CD_3OD): $\delta = 90.4$ (d, $^1J_{2,F} = 175.7$, C2), 77.3 (d, $^2J_{3,F} = 18.0$, C3), 70.6 (d, $^3J_{4,F} = 10.4$, C4), 67.5 (C5), 59.3 (ethylene-C2), 58.4 (C6), 54.8 (ethylene-C1), 54.0 (d, $^2J_{1,F} = 26.6$, C1) ppm; ^{19}F NMR (188 MHz, CD_3OD): $\delta = -195.21$ (m, 1F, F) ppm; MS (ESI–MeOH): *m*/*z* (%) = 200.5 ([cluster]$^{2+}$, 6), 210.3 ([M+H]$^+$, 100), 232.3 ([M+Na]$^+$, 16), 250.3 ([M+Na,H_2O]$^+$, 28).