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Article

Design, Synthesis and *In Vitro* Evaluation on Glucosamine-6P Synthase of Aromatic Analogs of 2-Aminohexitols-6P

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A glicosamina-6-fosfato sintase (GlmS) catalisa a formação de glicosamina-6-fosfato a partir de frutose-6-fosfato. Esta é a primeira etapa da via biossintética de aminoaçúcares, componentes estruturais importantes da parede celular de fungos e bactérias. Este trabalho descreve o planejamento, a síntese e a avaliação da atividade inibitória da GlmS de dois novos compostos aromáticos enantioméricos, análogos de 2-amino-2-desoxi-D-glucitol-6-fosfato (ADGP) e de seu epímero 2-amino-2-desoxi-D-manitol-6-fosfato (ADMP), dois importantes inibidores da GlmS. Os análogos aromáticos apresentaram atividade inibitória modesta, na faixa de mmol L^{-1}.

The aminosugars are very important structural components of bacterial and fungi cell walls. Glucosamine-6-phosphate synthase (GlmS), which catalyses the first step of the aminosugar biosynthetic pathway i.e. the formation of D-glucosamine-6-phosphate from D-fructose-6-phosphate, is therefore an interesting target in the fight against microorganisms. In this work is described the synthesis of aromatic analogs of 2-amino-2-deoxy-D-glucitol-6-phosphate (ADGP) and its epimer 2-amino-2-deoxy-D-manitol-6-phosphate (ADMP), two important inhibitors of GlmS. The aromatic analogs displayed modest inhibitory activity against GlmS, with IC_{50} in the mmol L^{-1} range.

Keywords: glucosamine synthase, inhibitors, aminohexitols derivatives

Introduction

Systemic fungi infections remain a problem in modern chemotherapy. Current therapeutic arsenal does not fulfill all medical needs. The increasing number of immunocompromised patients, due to anticancer chemotherapy, organ transplantation and AIDS, along with drug resistance, makes things more complicated.[1,2] Thus the search for new antifungal agents is mandatory. Glucosamine-6-phosphate synthase (GlmS) catalyses the transformation of D-fructose-6-phosphate (Fru-6P) into D-glucosamine-6-phosphate (GlcN-6P). This is, in turn, converted into UDP-GlcNAc, the nucleotide form of *N*-acetylglucosamine that is the building block for the biosynthesis of chitin.[3,4] The enzyme has been validated as a new target for the development of new antifungal agents.[4,5] GlmS has two catalytic domains, namely, a glutaminase and an isomerase domains. The glutaminase domain is responsible for the hydrolysis of glutamine and generation of ammonia and glutamate. The ammonia released travels across a hydrophobic tunnel to reach the isomerase domain, where it is transferred to enzyme-bound Fru-6P.[6,7]

Several inhibitors of both domains have been reported.[8-11] Inhibitors of the glutaminase domain are L-glutamine mimics whereas inhibitors of the isomerase domain have been trying to mimic the putative transition state intermediates.[4] Therefore 2-amino-2-deoxy-D-glucitol-6-phosphate (ADGP) and 2-amino-2-deoxy-D-manitol-6-phosphate (ADMP) are, along with D-arabinose-oxime-6-phosphate, the most potent inhibitors described thus far.[9,10] Nevertheless, these compounds possess weak *in vitro* antifungal activity which was attributed to low cell penetration due to the high hydrophilic character of these compounds.[12] Lipophilic derivatives of ADGP

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were prepared and some of them did display enhanced *in vitro* activity,[11] reinforcing the importance of hydrophilic/lipophilic balance for good activity.

The replacement of carbohydrate moieties of bioactive compounds by an aromatic ring has been a useful strategy for the obtention of active analogs.[13] Besides increasing the lipophilic character, the ring introduces conformational restriction, which might eventually enhances activity by selecting the bioactive conformation. The 6-phosphate and 2-amino groups of ADGP have been suggested as crucial for its enzyme inhibitory potency.[11] Substitution of the C3-C6 backbone chain by a meta phenyloxy ring linking the two groups was envisaged as one possibility for aromatic introduction. This was supported by molecular modeling (docking) which points out a similar distance between C2 and O6 atoms in the two molecules (5.3 Å for ADGP *vs* 5.7 Å for **2**), and the good fitting for some of the aromatic molecule conformers with the crystallographic structure of ADGP in the active site of GlmS (*E. coli*) (Figure 1).

With this in mind we planned the synthesis of compounds **1** and **2**, according to the retrosynthetic analysis shown in Figure 2.

The synthesis of **1** and **2** were then carried out according to the synthetic route shown in Figure 3.

Results and Discussion

Initially, the commercially available protected serine **3** was reacted with $LiBH_4$ in THF/CH_3OH at –10 °C to give the alcohol **4.**[14] Reaction of **4** with 3-benzoyloxyphenol under Mitsunobu conditions[15] at 80 °C afforded the corresponding ether **5.** Removal of the benzoyl protecting group was achieved upon treatment with CH_3ONa in CH_3OH at 0 °C to afford **6** in high yield. Phosphorylation with dibenzylphosphite ($HPO(BnO)_2$), in the presence of NaOH and CBr_4,[16] gave the aromatic phosphate **7** in 90% yield**.** Hydrogenolysis of the benzyl phosphate (H_2, Pd-C, Parr hydrogenator, 40 psi) and subsequent removal of *N*-Boc and dimethyl acetal groups with TFA[17] followed by preparative HPLC purification gave the target compounds **1*S*** or **2*R***, in 19% and 30% overall yield, respectively. Inhibitory assay against GlmS from *E. coli* was performed according to published procedures.[18] Results are given in Table 1.

As shown in Table 1, compounds **1** and **2** were poor inhibitors of GlmS, displaying IC_{50} in the millimolar range. Although the replacement of the hydroxyl groups in ADGP and ADMP by an aromatic ring can provide higher lipophilicity to the resulting analogs, as predict by ACD

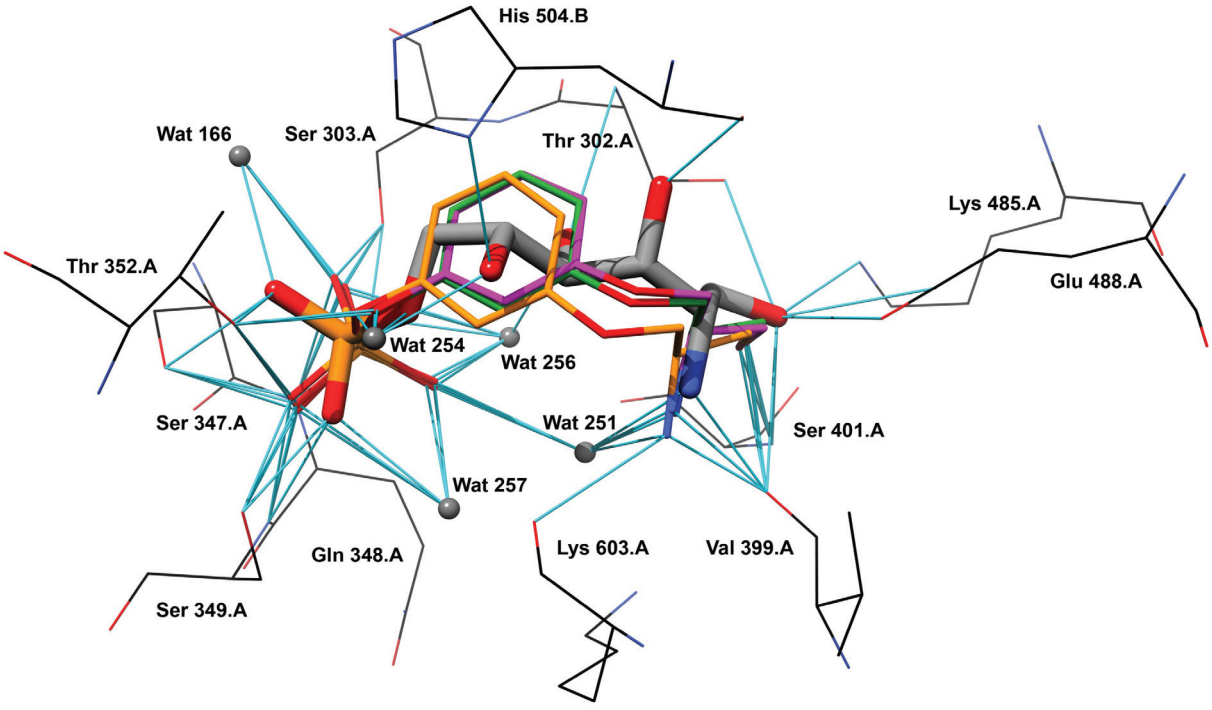

Figure 1. Comparison between crystal structure of ADGP (Stick model, colored by heteroatom) and docked conformers of **2** (orange, green and magenta) in the active site of Glms (*E.coli*). Potential hydrogen bonds are represented by Blue lines. Conserved crystallographic water molecules are shown as grey spheres.

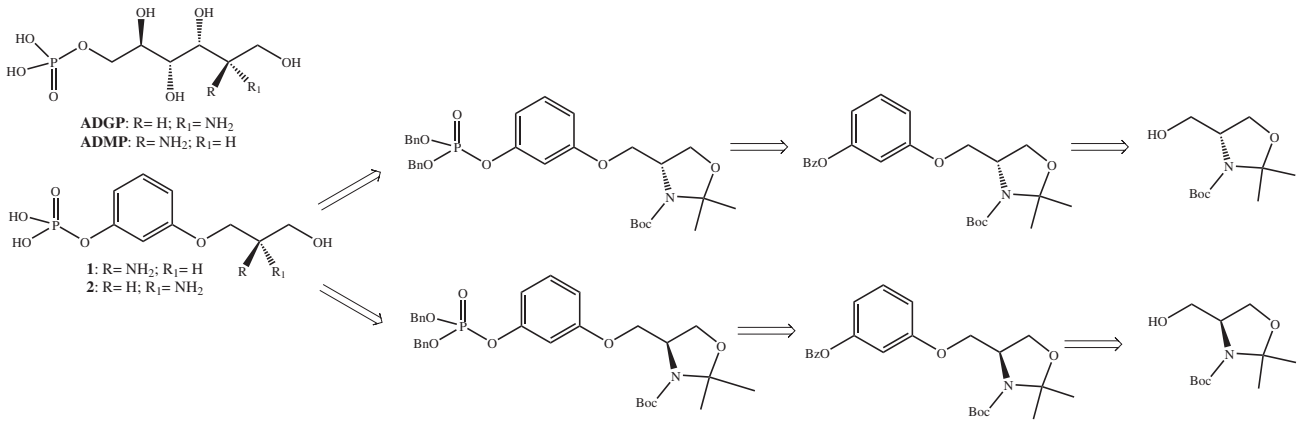

Figure 2. Retrosynthetic analysis leading to compounds **1** and **2**, aromatic analogs of ADGP and ADMP, respectively.

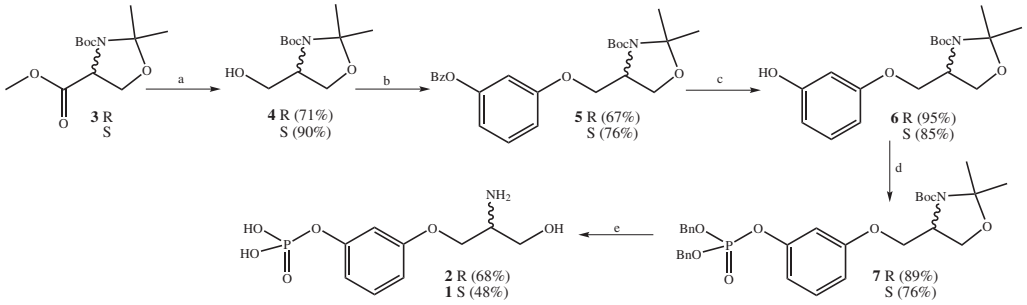

Figure 3. Synthetic route to compounds **1** and **2**. Reagents and conditions (a) $LiBH_4$, THF, CH_3OH, –10 °C; (b) 3-benzoyloxyphenol, DEAD, PPh_3, toluene, 80 °C; (c) CH_3ONa/ CH_3OH, 0 °C; (d) CBr_4, TEBA, 30% NaOH, CH_2Cl_2, $HPO(OBn)_2$; (e) 1- H_2, Pd-C, THF; 2- TFA, CH_3OH.

Table 1. Inhibition of GlmS by ADGP and compounds **1**-**2**

Compounds	IC_{50} / (mmol L^{-1})[a]
ADGP	0.294 (± 0.07)
1	3.156 (± 1.0)
2	3.220 (± 1.7)

[a]Values are means of three experiments, standard deviation is given in parentheses.

software calculations of Clog D pH 7 (–6.5 for ADGP and ADMP *vs* –4.6 for **1** and **2**), it is deleterious for their interaction with the enzyme active site.

Conclusions

In conclusion, we reported the design, synthesis and evaluation of two chiral aromatic analogs of the GlmS inhibitors ADGP and ADMP. Although the target compounds displayed weak inhibitory activity, they represent a new class of Glms inhibitors whose activity can be improved by further modification. This is in progress and will be reported in due time.

Experimental

General procedures

The reactions were monitored by thin-layer chromatography (TLC) performed on silica gel 60 F254 (Merck®). Melting points were determined with a Microquímica MQAPF 301 apparatus and are uncorrected. Flash chromatography was performed on silica gel 230-600 mesh (Merck®). NMR spectrum was recorded on a Bruker AC300 or AC500 spectrometer at ambient temperature or under heating at 363K. Chemical shifts (δ) were reported in ppm and standardized to the residual undeuterated solvents as the reference peaks and coupling constants (J) in Hz. The products **1*S*** and **2*R*** were purified on Atlantis® Prep dC_{18} OBD preparative column (19 mm × 150 mm, 5 µm) using an HPLC apparatus (Waters) equipped with a photodiode array detector. Gradient elution was employed using solvent A (10 mmol L^{-1} NH_4OAc), solvent B (CH_3CN); gradient: 0-7 min 100% A; 7-9 min linear change to A-B (40:60); 9-30 min, isocratic elution with 60% B (column rinsing); 30-50 min 100% A (column equilibration). The flow rate was kept at

17 mL min^{-1} and the sample injection volume was 0.5 mL. The alcohol 4 was synthesized following standard procedure.[14,19]

Synthesis of (R)-tert-butyl 4-((3-(benzoyloxy)phenoxy) methyl)-2,2-dimethyl-oxazolidine-3-carboxylate ***5R***

Diethyl azodicarboxylate (0.20 mL, 1.20 mmol) was added to a mixture of 3-benzoyloxyphenol (0.25 g, 1.20 mmol), alcohol **4*R*** (0.20 g, 1.00 mmol) and PPh_3 (0.31 g, 1.20 mmol) in toluene (8 mL) at room temperature under an argon atmosphere and the reaction mixture was stirred for 40 h at 80 °C. The solution was cooled to room temperature and was washed with 1 mol L^{-1} NaOH solution (20 mL) and then H_2O (2 × 20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc 9:1) to give the desired ether **5*R*** (0.23 g, 67%). $[\alpha]_D^{20}$ −49.0 (*c* 1.0, $CHCl_3$). HRMS (ESI+) calculated for $C_{24}H_{29}NO_6Na$ (M+Na), 450.1893. Found: 450.1898. ^{1}H NMR (500 MHz, DMSO-*d6*, 363 K) δ 1.44 (s, 9H, ^{t}Bu); 1.48 and 1.54 (2s, 6H, ^{i}Pr); 3.96-4.18 (m, 5H); 6.88-6.94 (m, 3H, C*H*-aromatics); 7.36 (t, 1H, ^2J 7.75 Hz, C*H*-aromatic); 7.60 (t, 2H, ^2J 7 Hz; *m*C*H*-benzoyl group); 7.73 (t, 1H, ^2J 7.5 Hz, *p*C*H*-benzoyl group); 8.13 (d, 2H, ^2J 7.5 Hz, *o*C*H*-benzoyl group). ^{13}C NMR (125 MHz, DMSO-*d*6, 363K) δ 23.32 (*C*H_3-^{i}Pr); 26.17 (*C*H_3-^{i}Pr); 27.56 (*C*H_3-^{t}Bu); 55.15 (*C*H); 64.47 (*C*H_2); 67.0 (*C*H_2); 79.09 (C-^{t}Bu); 92.81 (C-^{i}Pr); 108.15 (C-aromatic); 112.09 (*C*H-aromatic); 113.74 (*C*H-aromatic); 128.24 (*mC*H-benzoyl group); 128.80 (*C*-benzoyl group); 129.10 (*oC*H-benzoyl group); 129.37 (*mC*H-aromatic); 133.19 (*pC*H-benzoyl group); 150.86 (*C*=O *N*Boc); 151.32 (*C-ipso*); 158.89 (*C-ipso*); 163.83 (*C*=O benzoyl group).

Synthesis of (S)-tert-butyl 4-((3-(benzoyloxy)phenoxy) methyl)-2,2-dimethyl-oxazolidine-3-carboxylate ***5S***

The ***S*** enantiomer was prepared following the same procedure described above to prepare **5*R*** (0.21 g, 0.9 mmol) to give **5*S*** (0.29 g, 76%). $[\alpha]_D^{20}$ 49.2 (*c* 1.05, $CHCl_3$). HRMS (ESI+) calculated for $C_{24}H_{29}NO_6Na$ (M+Na), 450.1893. Found: 450.1892. ^{1}H NMR and ^{13}C NMR spectra, as for **5R**.

Synthesis of (R)-tert-butyl 4-((3-hydroxyphenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate ***6R***

To a solution of **5*R*** (0.19 g, 0.44 mmol) in dry CH_3OH (3 mL), was added CH_3ONa (24 mg, 0.44 mmol) at 0 °C. After 30 min. the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-hexane/ AcOEt 8:2) to give pure **6*R*** as a white solid, (0.14 g; 95%). mp 110.6-111.6 °C. $[\alpha]_D^{20}$ −34.5 (*c* 1.0, $CHCl_3$). HRMS (ESI+) calculated for $C_{17}H_{25}NO_5Na$ (M+Na), 346.1631. Found: 346.1634. ^{1}H NMR (500 MHz, DMSO-*d6*, 363K) δ 1.45 (s, 9H, CH_3-^{t}Bu); 1.47 (s, 3H, CH_3-^{i}Pr); 1.53 (s, 3H, CH_3-^{i}Pr); 3.87 (t, 1H, ^2J 9.4Hz, CH_2); 3.93 (d, 1H, ^2J 8.5Hz, CH_2); 4.00 – 4.02 (m, 1H, CH_2); 4.05 (t, 1H, ^2J 9.4Hz, CH_2); 4.13 (br, s, 1H, C*H*); 6.38 – 6.42 (m, 3H, C*H*-aromatics); 7.04 (t, 1H, ^2J 8 Hz, *m*C*H*-aromatic); 8.98 (br, s, 1H, O*H*). ^{13}C NMR (125 MHz, DMSO-*d*6, 363 K) δ 23.37 (*C*H_3-^{i}Pr); 26.17 (*C*H_3-^{i}Pr); 27.59 (*C*H_3-^{t}Bu); 55.30 (*C*H); 64.51 (*C*H_2); 66.52 (*C*H_2); 79.02 (C-^{t}Bu); 92.76 (C-^{i}Pr); 102.08 (*C*H-aromatic); 105.04 (*C*H-aromatic); 108.04 (*C*H-aromatic); 129.16 (*C*H-aromatic); 150.86 (*C*=O *N*Boc); 158.16 (*C-ipso* phenolic); 159.22 (*C-ipso*).

Synthesis of (S)-tert-butyl 4-((3-hydroxyphenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate ***6S***

The ***S*** enantiomer was prepared following the same procedure described above to prepare **6*R*** (0.18 g, 0.42 mmol) to give pure phenol **6*S*** (0.12 g, 85%). mp 110.7-111.6 °C. $[\alpha]_D^{20}$ 36.0 (*c* 1.02, $CHCl_3$). HRMS (ESI+) calculated for $C_{17}H_{25}NO_5Na$ (M+Na), 346.1631. Found: 346.1636. ^{1}H NMR and ^{13}C NMR spectra, as for **6*R***.

Synthesis of (R)-tert-butyl 4-((3-(bis(benzyloxy) phosphoryloxy)phenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate ***7R***

A solution of dibenzylphosphite (0.12 g, 0.46 mmol) and phenol **6*R*** (0.10 g, 0.31 mmol) in CH_2Cl_2 (2 mL) was added to an ice-cold two-phase system consisting of CBr_4 (0.053 g, 0.16 mmol), 30% (m/v) aqueous NaOH (100 µL), H_20 (1 mL) and CH_2Cl_2 (1 mL). The system was stirring for 30 min at room temperature. CH_2Cl_2 (10 mL) was added and the organic layer was separated, washed with H_2O (3 × 5 mL), dried over $MgSO_4$ and filtrated. Concentration followed by flash chromatography on silica gel of the crude material afforded the product **7*R*** (0.17 g, 89% yield) as colorless oil. $[\alpha]_D^{20}$ −37.0 (*c* 1.03, $CHCl_3$). HRMS (ESI+) calculated for $C_{31}H_{38}NO_8PNa$ (M+Na), 606.2233. Found: 606.2230. ^{1}H NMR (500 MHz, DMSO-*d6*, 363 K) δ 1.44 (br, s, 9H, CH_3-^{t}Bu); 1.47 (s, 3H, CH_3-^{i}Pr); 1.53 (s, 3H, CH_3-^{i}Pr); 3.90-4.14 (m, 5H); 5.15-5.17 (m, 4H, CH_2-benzyl group); 6.77-6.64 (m, 3H, C*H*-aromatics); 7.26 (t, 1H, ^2J 8.5 Hz; C*H*-aromatic); 7.36 (br, s, 10H, C*H*-benzyl group). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.30; 24.50; 27.00; 27.80 (*C*H_3-^{i}Pr); 28.60; 28.70 (*C*H_3-^{t}Bu); 56.00; 56.20 (*C*H); 65.40; 65.6 (*C*H_2); 66.50; 67.10 (*C*H_2); 70.10; 70.20 (*C*H_2-benzyl group); 80.50; 80.80 (*C*-^{t}Bu); 93.80; 94.30 (*C*-^{i}Pr); 107.20; 107.30 (*C*H-aromatic); 111.40; 111.7 (*C*H-aromatic); 112.7; 112.80 (*C*H-aromatic); 128.20; 128.80 (*C*H-aromatic benzyl group); 130.30 (*C*H-aromatic); 135.60; 135.70 (*C-ipso* benzyl group); 151.60; 151.90 (*C*-aromatic and *C*=O *N*Boc), 159.70 (C-*ipso*). ^{31}P NMR (121.5 MHz, $CDCl_3$, external 85% H_3PO_4) δ −6.38 and −6.43.

*Synthesis of (S)-tert-butyl 4-((3-(bis(benzyloxy) phosphoryloxy)phenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate **7S***

The ***S*** enantiomer was prepared following the same procedure described above to prepare **7*R*** (0.12 g, 0.37 mmol) to give **7*S*** (0.15g, 76% yield). $[\alpha]_D^{20}$ 37.4 (*c* 1.01, $CHCl_3$). HRMS (ESI+) calculated for $C_{31}H_{38}NO_8PNa$ (M+Na), 606.2233. Found: 606.2228. ^1H NMR and ^{13}C NMR spectra, as for **7*R***.

*Synthesis of 3-(2-(S)-amino-3-hydroxypropoxy)phenyl dihydrogenphosphate **1***

A solution of dibenzylphosphate **7*R*** (0.16 g, 0.27 mmol) in THF (2 mL) was hydrogenolyzed under hydrogen pressure (40 psi) in presence of 10% activated Pd-C (40 mg) at room temperature for 1h. The reaction mixture was filtered and the THF evaporated under vacuum. TFA (1 mL) was then added to a solution of the residue in CH_3OH (2 mL). The reaction mixture was stirred at room temperature for 3h. TFA was eliminated by co-distillation with CH_2Cl_2 and CH_3OH. The product **1*S*** was purified by preparative RP-HPLC and obtained as an amorphous white solid (35 mg, 48% yield). mp 168.0-168.7 °C. $[\alpha]_D^{20}$ 7.2 (*c* 0.5, H_2O). HRMS (ESI+) calculated for $C_9H_{14}NO_6PNa$ (M+Na), 286.0456. Found: 286.0455. ^1H NMR (500 MHz, D_2O) δ 3.79-3.84 (m, 1H, C*H*); 3.92 (dd, 1H, J_{gem} 12.3 Hz, ^2J 6.6 Hz, CH_2); 3.99 (dd, 1H, J_{gem} 12.2 Hz, ^2J 4.7 Hz, CH_2); 4.26 (dd, 1H, J_{gem} 10.5 HZ, ^2J 6.6 Hz, CH_2); 4.36 (dd, 1H, J_{gem} 10.5 Hz, ^2J 3.8 Hz, CH_2); 6.77 (dd, 1H, ^2J 8.2 Hz, ^3J 2.2 Hz, C*H*-aromatic); 6.89 (d, 1H, ^2J 8.3 Hz, C*H*-aromatic); 6.95 (s, 1H, C*H*-aromatic); 7.32 (t, 1H, ^2J 8.1 Hz, C*H*-aromatic). ^{13}C NMR (125 MHz, D_2O) δ 52.18 (*C*H); 58.74 (*C*H_2); 65.01 (*C*H_2); 107.15 (d, ^3J 4.6 Hz, *C*H-aromatic); 108.81 (*C*H-aromatic); 113.96 (d, ^3J 4.6 Hz, *C*H-aromatic); 129.96 (*C*H-aromatic); 154.87 (d, ^2J 6.4 Hz, *C-ipso*); 158.31 (*C-ipso*). ^{31}P NMR (202.5 MHz, D_2O, external 85% H_3PO_4) δ –0.273.

*Synthesis of 3-(2-(R)-amino-3-hydroxypropoxy)phenyl dihydrogenphosphate **2***

The ***R*** enantiomer was prepared following the same procedure using **7*S*** (0.13g, 0.22 mmol) to give the desired phosphate **2*R*** (39 mg; 68% yield). mp 163.9-165.0 °C. $[\alpha]_D^{20}$ –7.5 (*c* 0.5, H_2O). HRMS (ESI+) calculated for $C_9H_{14}NO_6PNa$ (M+Na), 286.0456. Found: 286.0451. ^1H NMR and ^{13}C NMR spectra, as for **1**.

Determination of enzyme activity

GlmS was purified to homogeneity using a protocol adapted from the procedure first reported by Badet and co-workers.[20] GlmS activity was spectrophotometrically assayed using the modified microplate Morgan-Elson method.[18] The assay mixture contained, in a final volume of 100 µL for each well of the microplate, 100 mmol L^{-1} phosphate buffer, pH 7.2, 50 mmol L^{-1} KCl, 1 mmol L^{-1} EDTA, 0.4 mmol L^{-1} D-Fru-6P (a concentration close to the K_m value was chosen), and 4 mmol L^{-1} Gln (saturating concentration). Inhibitors were used at the following concentrations: ADGP at 0-0.5 mmol L^{-1}, **1** or **2** at 0-7 mmol L^{-1}. Following preincubation at 37 °C for 10 min, the enzymatic reaction was initiated by the addition of 0.06 unit of GlmS. Precisely 30 min later (initial rate conditions), the reaction was stopped by the addition of 10 µL of a 1.5% (v/v) acetic anhydride solution in acetone (prepared daily) followed by 50 µL of a 0.2 mol L^{-1} borate solution. After being heated to 80 °C for 30 min, the microplate (containing the various reaction mixtures) was centrifuged before addition of 130 µL of Ehrlich reagent (10% (m/v) solution of *p*-dimethyl-aminobenzaldehyde in acetic acid/ concentrated HCl mixture (87/13; v/v) to each well. Then, the amount of GlcN-6P formed was measured from the absorbance of the Ehrlich adduct at 585 nm (ε value was determined daily from a GlcN-6P standard solution). The initial rate of formation of Glc-N6P as a function of the inhibitor concentration allowed the determination of the IC_{50} value (inhibition that gives an initial rate equal to 50% of the rate in the absence of inhibitor).

Molecular modeling

The tridimensional structures of compounds **1** and **2** were constructed using Corina v3.44. Docking studies were performed on the dimer structure of GlmS (PDB code 2J6H)[21] with Gold 4.0,[22] using the default parameters and the GoldScore scoring function. A number of five water molecules (W166, W251, W254, W256, W257), which are conserved in all GlmS structures, were considered in the docking procedure. Ligand 2-deoxy-2-amino-D-glucitol-6-phosphate (ADGP) from the structure 1MOS [23] was used as reference in the docking analysis. Raytraced image was produced with UCSF Chimera[24] and POV-Ray.[25]

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