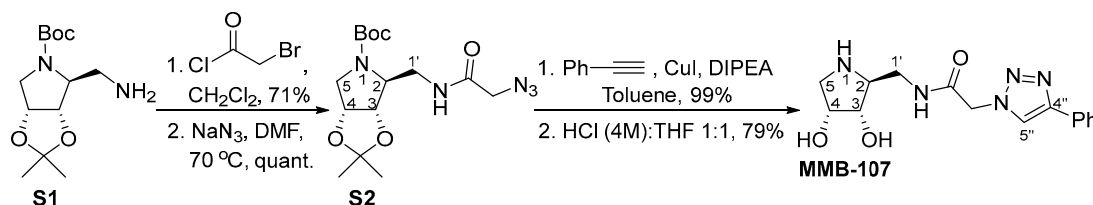


Supplementary information

COMPOUND SYNTHESIS

(2*S*,3*S*,4*R*)-2-[2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)acetylaminoethyl]-pyrrolidine-3,4-diol (MMB-107)



To a solution of **S1** [Ref.A] (245 mg, 0.899 mmol) in anhydrous CH₂Cl₂ (9 mL) at 0 °C, bromoacetyl chloride (283 mg, 1.80 mmol) and Et₃N (256 μL, 1.80 mmol) were added and the mixture was stirred at r.t. for 2 h. The solution was washed with sat. aq. soln. of NaHCO₃, water and brine and the organic layer was dried over Na₂SO₄, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:1) to give the corresponding protected pyrrolidine-(bromo)amide (252 mg, 0.641 mmol, 71%) as an oil. To a solution of this compound (234 mg, 0.595 mmol) in DMF (5 mL), NaN₃ (97 mg, 1.5 mmol) was added. After stirring at 70 °C for 2 h, the solvent was removed under reduced pressure and the crude product was dissolved in CH₂Cl₂, washed with water and brine, dried over Na₂SO₄, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:1) to give **S2** (213 mg, 0.595 mmol, quantitative) as a colourless oil.

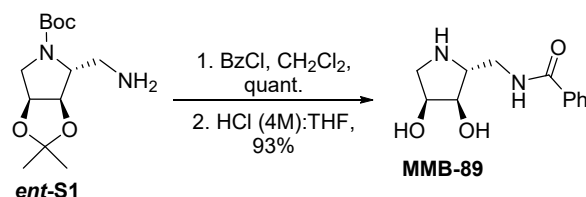
Characterization data for S2. [α]_D²⁶ + 31.1 (*c* 0.79, CH₂Cl₂). IR (ν cm⁻¹) 3304 (NH), 2980, 2105 (N₃), 1668 (C=O), 1537, 1407, 1366, 1158, 1052, 853. ¹H-NMR (300 MHz, CDCl₃, δ ppm, *J* Hz, mixture of rotamers) δ 7.25, 6.58 (br. s, 1H, NH), 4.70 (ap. t, 1H, H-4), 4.45-4.43 (m, 1H, H-3), 4.27-4.10 (m, 1H, H-2), 4.02-3.82 (m, 3H, -CH₂N₃, H-5a), 3.47-3.22 (m, 3H, H-1'a, H-5b, H-1'b), 1.47 (s, 9H, -C(CH₃)₃), 1.43 (s, 3H, -C(CH₃)₂), 1.29 (s, 3H, -C(CH₃)₂). ¹³C-NMR (75.4 MHz, CDCl₃, δ ppm, mixture of rotamers) δ 167.5 (C=O, amide), 155.7 (C=O, Boc), 112.2 (-C(CH₃)₂), 83.2, 82.6 (C-3), 80.8 (-C(CH₃)₃), 79.4, 78.9 (C-4), 63.5, 62.6 (C-2), 52.8 (-CH₂N₃), 51.5, 51.1 (C-5), 41.3, 40.0 (C-1'), 28.4 (-C(CH₃)₃), 27.0 (-C(CH₃)₂), 25.1 (-C(CH₃)₂). HRESIMS *m/z* found 378.1745, calc. for C₁₅H₂₅N₅O₅Na [M+Na]⁺: 378.1748.

To a solution of **S2** (143 mg, 0.402 mmol) in toluene (4 mL), phenylacetylene (91 μL, 0.81 mmol), DIPEA (268 μL, 1.53 mmol) and CuI (47 mg, 0.24 mmol) were added and the solution was stirred at r.t. for 2 h. The solvent was evaporated and the resulting residue was dissolved in EtOAc and sat. aq. soln. of NaHCO₃ was added. The aqueous phase was extracted with EtOAc (x2) and the organic layers were dried over Na₂SO₄, filtered and evaporated. The resulting residue was

purified by chromatography column on silica gel (EtOAc:cyclohexane 2:1→4:1) to give the corresponding protected pyrrolidine-triazole (182 mg, 0.398 mmol, 99%) as a colourless solid. A solution of this compound (87 mg, 0.19 mmol) in HCl (4M):THF (1:1, 4.6 mL), was stirred at r.t. for 3 h. Evaporation of the solvent and chromatographic purification on Dowex 50WX8 eluting with MeOH, H₂O and NH₄OH 25%, yielded **MMB-107** (49 mg, 0.15 mmol, 79%) as a white solid.

Characterization data for MMB-107. $[\alpha]_D^{26} - 26.0$ (*c* 0.56, DMSO). IR (ν cm⁻¹) 3305, 3239 (OH, NH), 2902, 1662 (C=O), 1566, 1464, 1277, 1083, 835, 760. ¹H-NMR (300 MHz, DMSO-*d*₆, δ ppm, *J* Hz) δ 8.51 (s, 1H, H-5''), 8.30 (t, 1H, $J_{\text{NH},1'} = 5.3$, -NHCO), 7.87-7.85 (m, 2H, H-aromat.), 7.48-7.43 (m, 2H, H-aromat.), 7.36-7.30 (m, 1H, H-aromat.), 5.15 (s, 2H, -CH₂CO), 4.53 (br. s, 2H, OH-3, OH-4), 3.86 (ap. q, 1H, H-4), 3.49 (ap. t, 1H, H-3), 3.39-3.24 (m, 2H, H-1'a, NH), 3.11-3.04 (m, 1H, H-1'b), 3.03-2.97 (m, 1H, H-5a), 2.95-2.89 (m, 1H, H-2), 2.64 (dd, 1H, $^2J_{5b,5a} = 11.1$, $J_{5b,4} = 4.1$, H-5b). ¹³C-NMR (75.4 MHz, DMSO-*d*₆, δ ppm) δ 165.5 (C=O), 146.1 (C-4''), 130.8 (Cq aromat.), 128.9 (C aromat.), 127.8 (C aromat.), 125.1 (C aromat.), 122.9 (C-5''), 74.3 (C-3), 70.8 (C-4), 61.7 (C-2), 51.8 (-CH₂CO), 51.6 (C-5), 42.2 (C-1'). HRESIMS *m/z* found 318.1559, calc. for C₁₅H₂₀N₅O₃ [M+H]⁺: 318.1561.

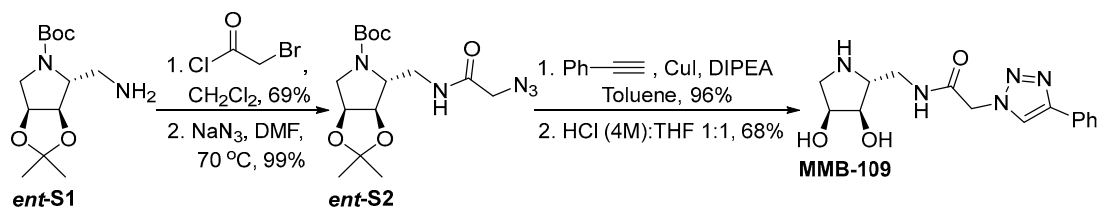
(2*R*,3*R*,4*S*)-2-Benzoylaminomethyl-pyrrolidine-3,4-diol (MMB-89)



To a solution of **ent-S1** [Ref.D] (67 mg, 0.25 mmol) in anhydrous CH₂Cl₂ (3 mL) at 0 °C, benzoyl chloride (58 mL, 0.50 mmol) and Et₃N (70 mL, 0.49 mmol) were added and the mixture was stirred at r.t. for 2 h. The solution was washed with sat. aq. soln. of NaHCO₃, water and brine and the organic layer was dried over Na₂SO₄, filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:2→1:1) to give the corresponding protected pyrrolidine-amide (95 mg, 0.25 mmol, quantitative) as a colourless oil. A solution of this compound (56 mg, 0.15 mmol) in HCl (4M):THF (1:1, 3.6 mL), was stirred at r.t. for 3 h. Evaporation of the solvent and chromatographic purification on Dowex 50WX8 eluting with MeOH, H₂O and NH₄OH 25%, yielded **MMB-89** (33 mg, 0.14 mmol, 93%) as a white solid.

Characterization data for MMB-89. $[\alpha]_D^{26} + 36.2$ (*c* 0.74, MeOH). HRESIMS *m/z* found 237.1230, calc. for C₁₂H₁₇N₂O₃ [M+H]⁺: 237.1234. IR and NMR data match with those of its enantiomer [Ref.A].

(2R,3R,4S)-2-[2-(4-Phenyl-1H-1,2,3-triazol-1-yl)acetylaminoethyl]-pyrrolidine-3,4-diol
(MMB-109)



To a solution of *ent*-**S1** [Ref. D] (198 mg, 0.727 mmol) in anhydrous CH_2Cl_2 (7 mL) at 0 °C, bromoacetyl chloride (229 mg, 1.46 mmol) and Et_3N (208 μL , 1.46 mmol) were added and the mixture was stirred at r.t. for 2 h. The solution was washed with sat. aq. soln. of NaHCO_3 , water and brine and the organic layer was dried over Na_2SO_4 , filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:1) to give the corresponding protected pyrrolidine-(bromo)amide (198 mg, 0.503 mmol, 69%) as an oil. To a solution of this compound (187 mg, 0.476 mmol) in DMF (4.5 mL), NaN_3 (78 mg, 1.2 mmol) was added. After stirring at 70 °C for 2 h the solvent was removed under reduced pressure and the obtained residue was dissolved in CH_2Cl_2 , washed with water and brine, dried over Na_2SO_4 , filtered and evaporated. The crude product was purified by chromatography column on silica gel (EtOAc:cyclohexane 1:1) to give *ent*-**S2** (167 mg, 0.470 mmol, 99%) as a colourless oil.

Characterization data for *ent*-S2**.** $[\alpha]_D^{26} - 32.3$ (c 0.81, CH_2Cl_2). HRESIMS m/z found 378.1746, calc. for $\text{C}_{15}\text{H}_{25}\text{N}_5\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 378.1748. IR and NMR data match with those of compound **S2**.

To a solution of *ent*-**S2** (140 mg, 0.394 mmol) in toluene (3.5 mL), phenylacetylene (89 μL , 0.79 mmol), DIPEA (262 μL , 1.50 mmol) and CuI (46 mg, 0.24 mmol) were added and the solution was stirred at r.t. for 1.5 h. The solvent was evaporated and the resulting residue was dissolved in EtOAc and sat. aq. soln. of NaHCO_3 was added. The aqueous phase was extracted with EtOAc (x2) and the organic layers were dried over Na_2SO_4 , filtered and evaporated. The resulting residue was purified by chromatography column on silica gel (EtOAc:cyclohexane 2:1→4:1) to give the corresponding protected pyrrolidine-triazole (173 mg, 0.378 mmol, 96%) as a colourless solid. A solution of this compound (86 mg, 0.19 mmol) in HCl (4M):THF (1:1, 4.6 mL), was stirred at r.t. for 3 h. Evaporation of the solvent and chromatographic purification on Dowex 50WX8 eluting with MeOH, H_2O and NH_4OH 25%, yielded **MMB-109** (42 mg, 0.13 mmol, 68%) as a white solid.

Characterization data for **MMB-109.** $[\alpha]_D^{26} + 29.3$ (c 0.61, DMSO). HRESIMS m/z found 318.1560, calc. for $\text{C}_{15}\text{H}_{20}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 318.1561. IR and NMR data match with those of compound **MMB-107**.

REFERENCES

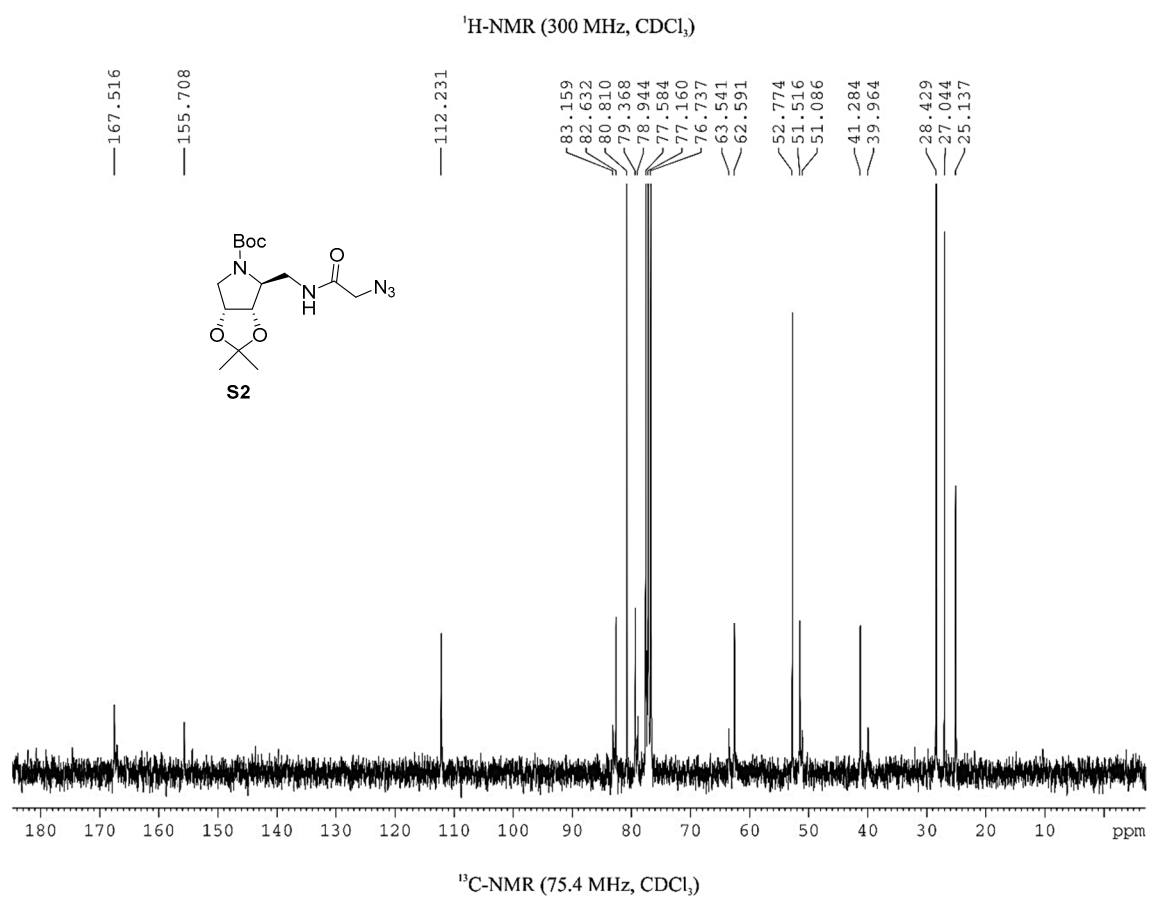
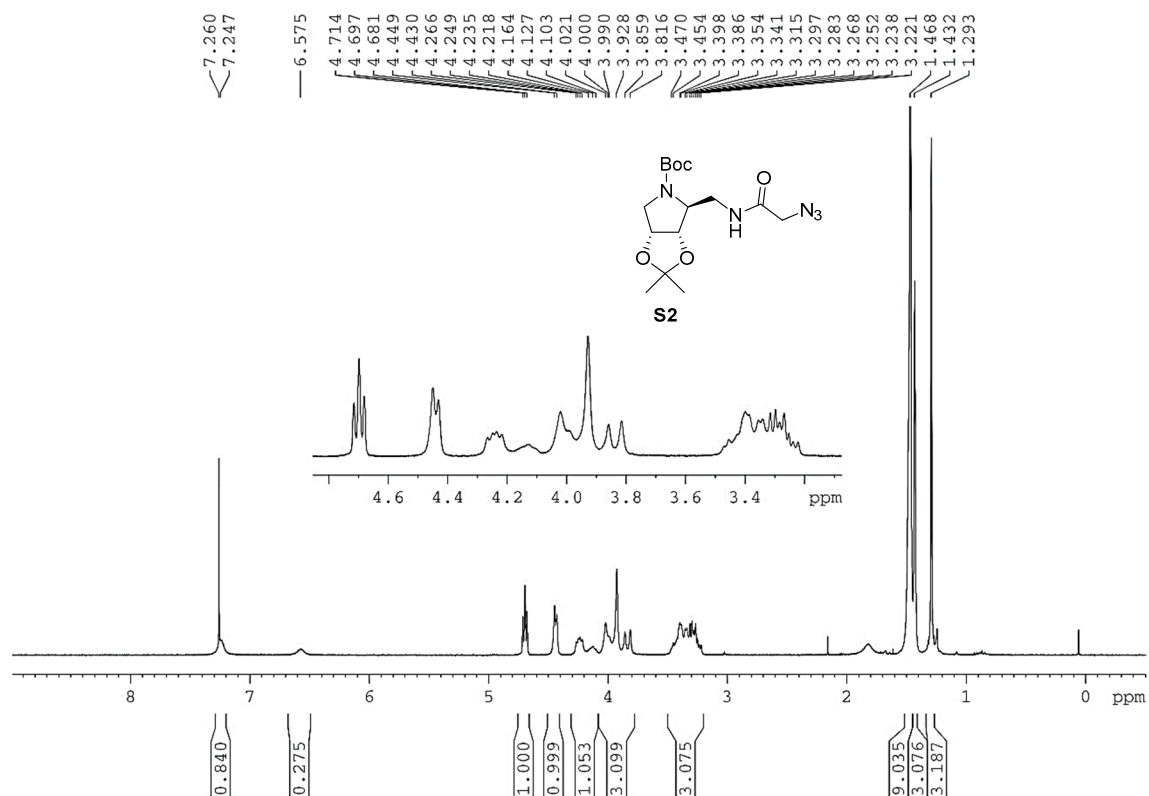
Ref. A: Martínez-Bailén, M.; Carmona, A.T.; Moreno-Clavijo, E.; Robina, I.; Ide, D.; Kato, A.; Moreno-Vargas, A.-J. Tuning of β -glucosidase and α -galactosidase inhibition by generation and *in situ* screening of a library of pyrrolidine-triazole hybrid molecules. *European Journal of Medicinal Chemistry* **2017**, *138*, 532–542, doi:10.1016/j.ejmech.2017.06.055.

Ref. B: Martínez-Bailén, M.; Carmona, A.T.; Patterson-Orazem, A.C.; Lieberman, R.L.; Ide, D.; Kubo, M.; Kato, A.; Robina, I.; Moreno-Vargas, A.-J. Exploring substituent diversity on pyrrolidine-aryltriazole iminosugars: Structural basis of β -glucocerebrosidase inhibition. *Bioorganic Chemistry* **2019**, *86*, 652–664, doi:10.1016/j.bioorg.2019.02.025.

Ref. C: Martínez-Bailén, M.; Galbis, E.; Carmona, A.T.; de-Paz, M.-V.; Robina, I. Preparation of water-soluble glycopolymers derived from five-membered iminosugars. *European Polymer Journal* **2019**, *119*, 213–221, doi:10.1016/j.eurpolymj.2019.07.027.

Ref. D: Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodríguez-García, E.; Carmona-Asenjo, A. T.; Robina, I.; Vogel, P. Derivatives of (2*R*,3*R*,4*S*)-2-aminomethylpyrrolidine-3,4-diol are selective α -mannosidase inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2001**, *11*, 2489–2493, doi:10.1016/S0960-894X(01)00477-2.

NMR SPECTRA



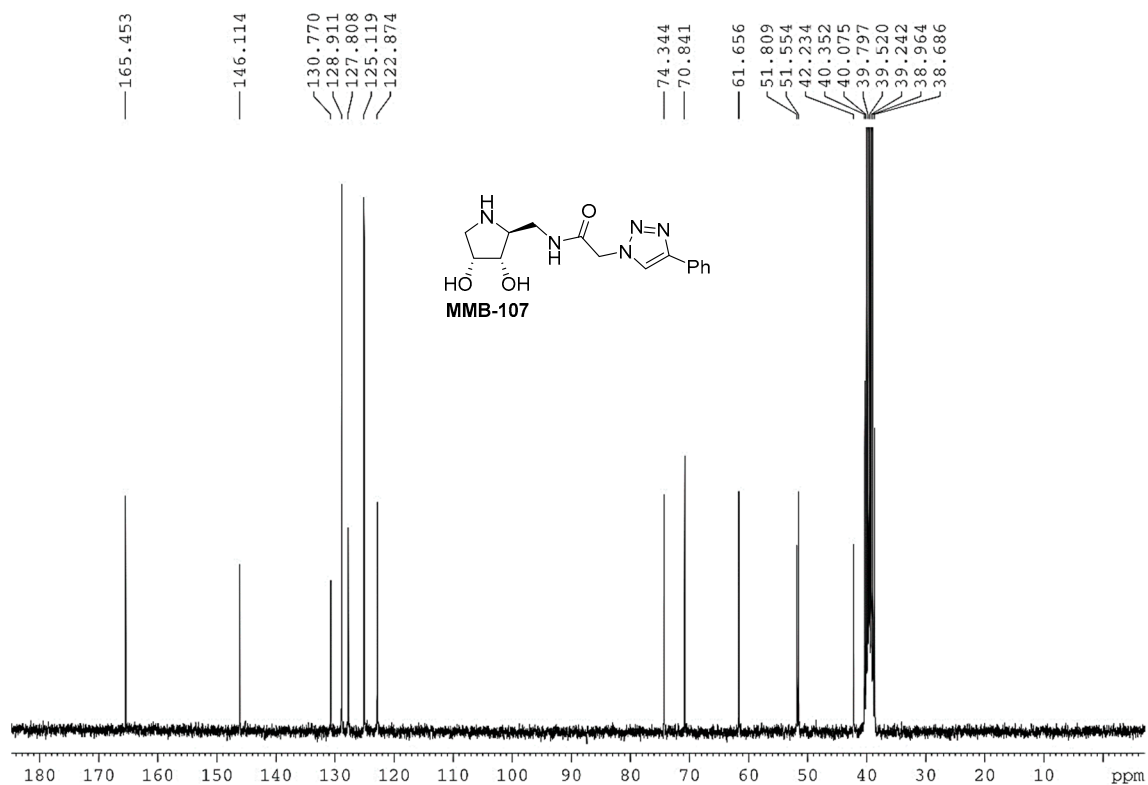
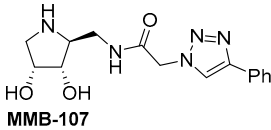
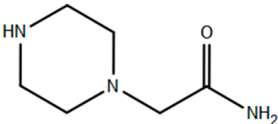
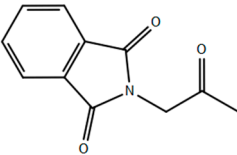
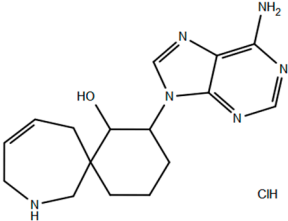
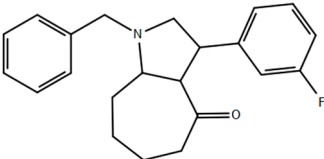
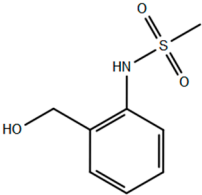
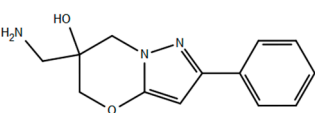
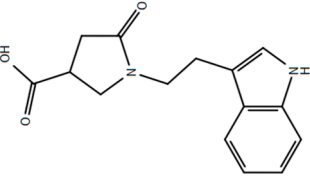
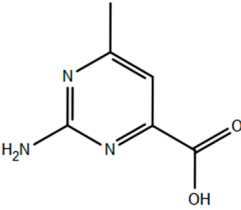
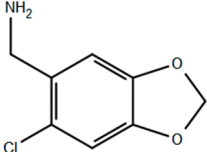
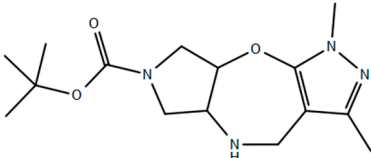
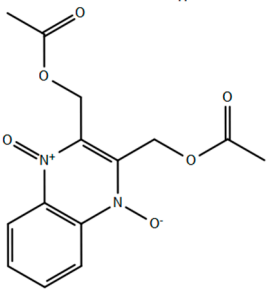
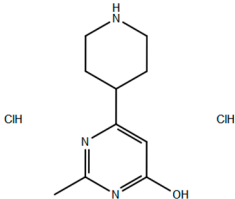
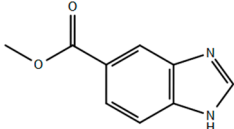
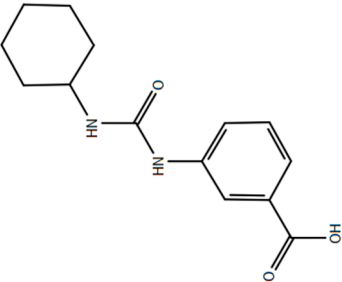
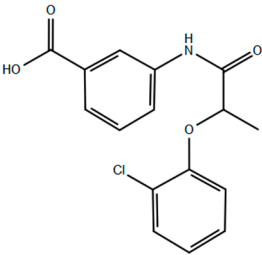
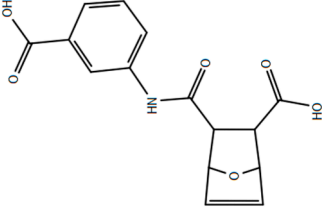
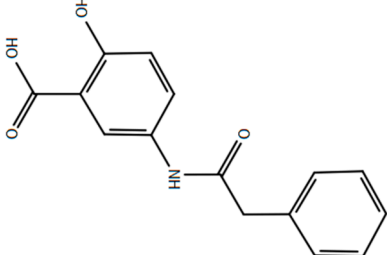
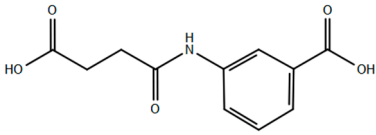
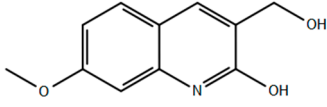
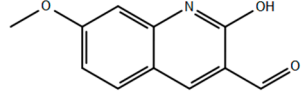
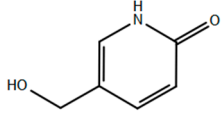
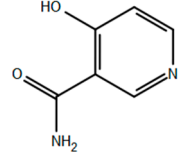
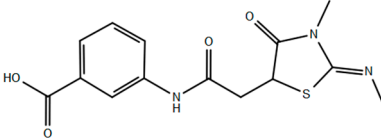
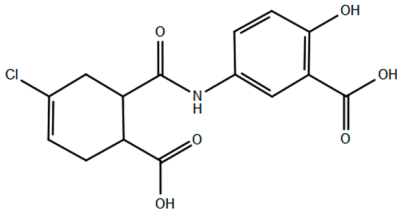
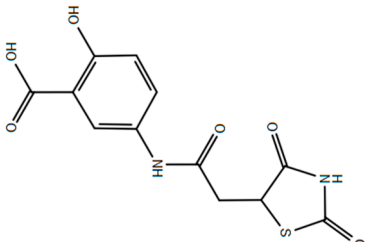
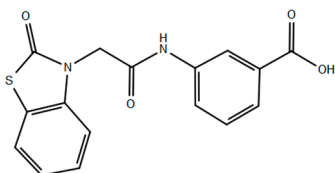
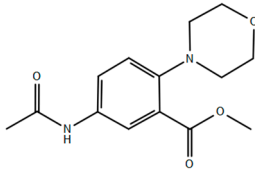
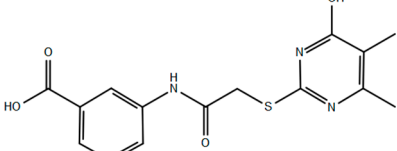
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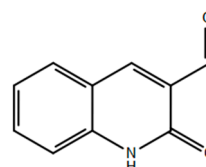
Table S1. Details of chemical structures of tested compounds as putative hNAPRT inhibitors.

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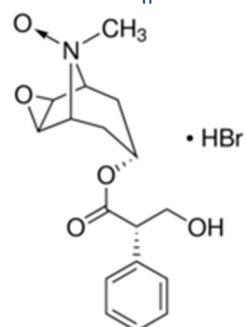
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17	MCULE	IM 40	

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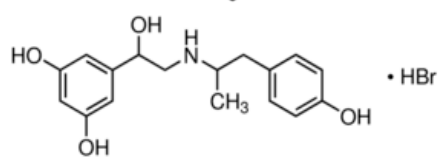
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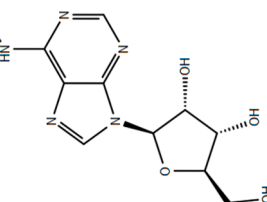
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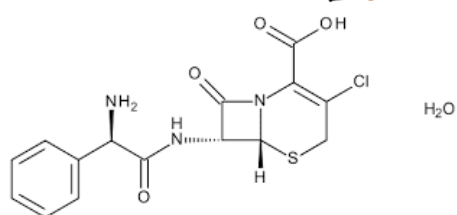
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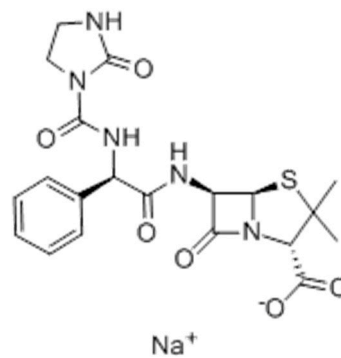
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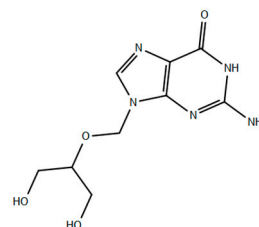
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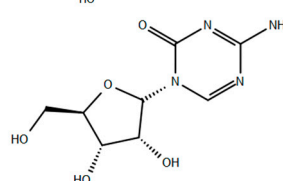
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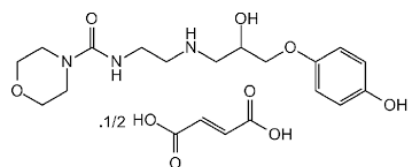
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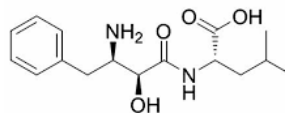
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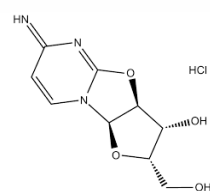
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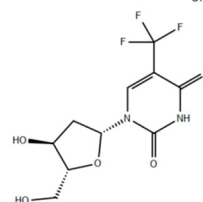
38 PRESTWICK IM 61



39 PRESTWICK IM 62



40 PRESTWICK IM 63



41 U. SEVILLE MMB-69
[Ref. A]

42 U. SEVILLE MMB-105-B
[Ref. A]

43 U. SEVILLE MMB-107

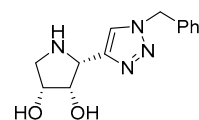
44 U. SEVILLE MMB-23-2
[Ref. A]

45 U. SEVILLE MMB-24
[Ref. A]

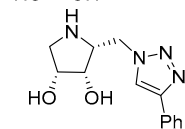
46 U. SEVILLE MMB-89

47 U. SEVILLE MMB-109

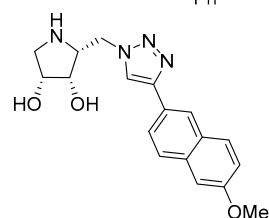
48 U. SEVILLE MMB-150
[Ref. A]



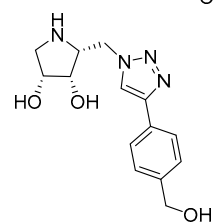
49 U. SEVILLE MMB-238
[Ref. A]



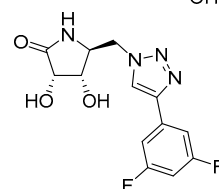
50 U. SEVILLE MMB-239
[Ref. A]



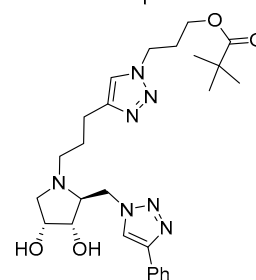
51 U. SEVILLE MMB-241
[Ref. A]



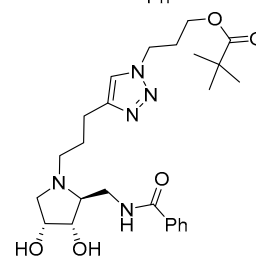
52 U. SEVILLE CVL-16
[Ref. B]



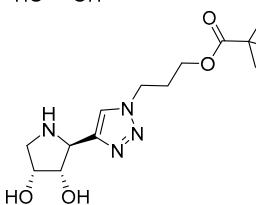
53 U. SEVILLE MMB-131
[Ref. C]



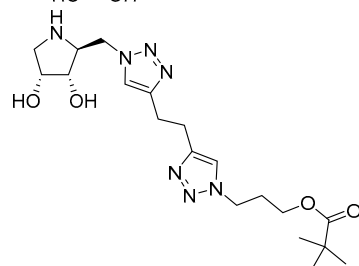
54 U. SEVILLE MMB-128
[Ref. C]

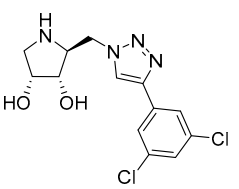
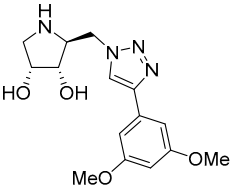
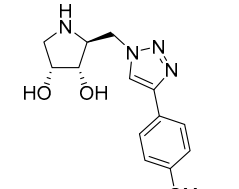
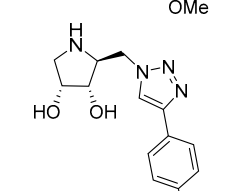
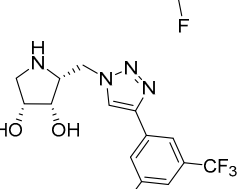
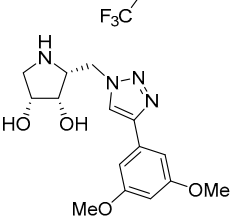


55 U. SEVILLE MMB-294
[Ref. C]



56 U. SEVILLE MMB-136
[Ref. C]



57	U. SEVILLE	MMB-266 [Ref. B]	
58	U. SEVILLE	MMB-310 [Ref. B]	
59	U. SEVILLE	MMB-260 [Ref. B]	
60	U. SEVILLE	MMB-311 [Ref. B]	
61	U. SEVILLE	MMB-268 [Ref. B]	
62	U. SEVILLE	MMB-312 [Ref. B]	

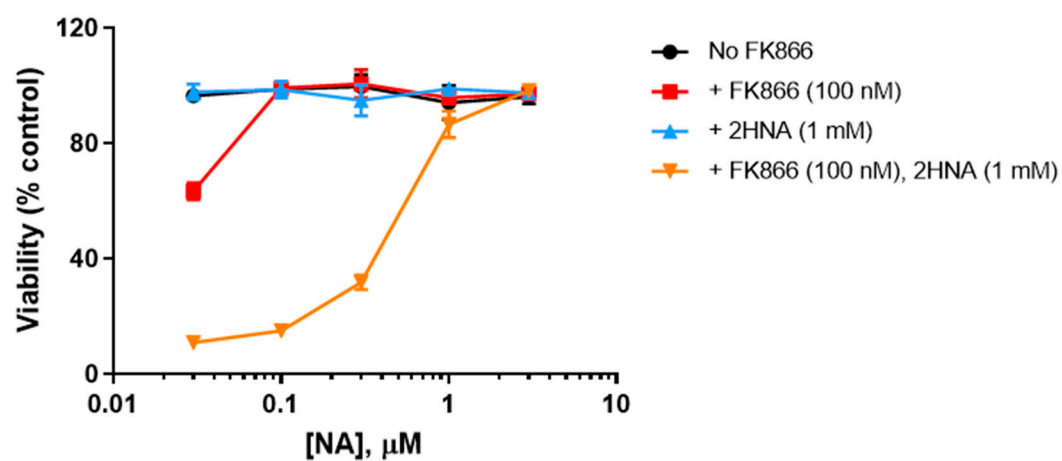


Figure S1. The concentration of nicotinic acid in culture medium determines the susceptibility of the OVCAR-5 cell line to treatments with FK866 and 2-hydroxynicotinic acid. Cells were cultured in RPMI 1640 medium supplemented with different concentrations of NA and combinations of FK866 and 2-hydroxynicotinic acid. Cell viability was determined following 72 h treatments and expressed as percentage of control cells.