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A POTENT INHIBITOR OF β-N-ACETYLGLUCOSAMINIDASES· 6-ACETAMIDO-6-DEOXYCASTANOSPERMINE

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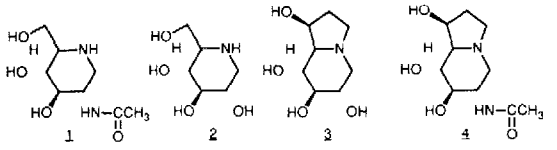
Abstract: A facile synthesis of 6-acetamido-6-deoxycastanospermine (4) is described The target compound inhibits mammalian β-N-acetylglucosaminidases at or below 1 μM

Inhibitions of β-N-acetylglucosaminidases, enzymes which catalyze the hydrolysis of β-N-acetylglucosamine residues of lipid- or protein-linked oligosaccharides, are potentially useful targets for cancer chemotherapy [1] β-N-acetylglucosaminidases may be associated with the invasiveness of certain tumors High activity levels of these enzymes have been found in serum and urine of patients with various malignancies [2]

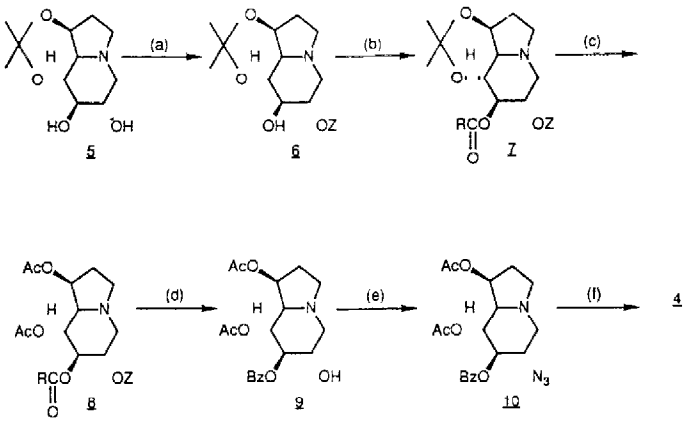
The recently synthesized azapyranose, 2-acetamido-1,5-imino-1,2,5-trideoxy-D-glucitol (1), is a potent and selective inhibitor of β-N-acetylglucosaminidases [3] Deoxynojirimycin (2), related to 1 and D-glucopyranose, inhibits a wide variety of α-glucosidases [4] The indolizidine alkaloid, castanospermine (3), which may be regarded as a conformationally restrained analog of 2, is a significantly more potent inhibitor of α-glucosidases than 2 [4] This report describes the synthesis and enzyme inhibitory activities of 4, the N-acetylglucosamine analog of castanospermine



The readily available castanospermine derivative 5[5] was treated with benzylchloroformate/Et_3N in THF to provide 6-O-carbobenzyloxy-1,8-O-isopropylidenecastanospermine (6) in 90% yield (Scheme I). Subsequent acylation of 6 with p-bromobenzoyl chloride gave the crystalline ester 7 in 84% yield Removal of the ketal protecting group (HCl/MeOH) from 7 followed by peracetylation (Ac_2O/pyridine) provided compound 8 in 77% overall yield Selective deprotection of the 6-hydroxyl function was accomplished by transfer hydrogenolysis (10% Pd/C, cyclohexene) and the resultant alcohol 9 was mesylated (mesyl chloride/Et_3N) and converted into azide 10 upon successive invertive displacements with sodium iodide and sodium azide Methanolysis of 10 (NaOMe, MeOH) followed by catalytic hydrogenation (10% Pd/C, H_2) and N-acetylation (Ac_2O, acetone, water) afforded the target compound, 4, in 83% yield The well-resolved 300 MHz ^1H nmr spectrum of 4 showed signals centered at δ 3.86, 3 38 and 3 65 ppm for H_6, H_7 and H_8, respectively ($J_{6,7}$=10.2 Hz; $J_{7,8}$=9 0 Hz), indicative of the trans-diaxial disposition of these vicinal protons

Compound 4 was tested against a panel of glycosidases and was found to be a very potent inhibitor of β-N-acetylglucosaminidases from human placenta (IC_{50}=0 5 μM), bovine kidney

Scheme I



Conditions (a) Cbz-Cl, Et_3N, THF (90%); (b) pBr-BzCl, Et_3N (84%), (c) HCl, MeOH, Ac_2O, pyridine (77%), (d) Pd/C, MeOH, cyclohexene (91%), (e) mesyl chloride, Et_3N, NaI, $CH_3COC_2H_5$; NaN_3, DMF (65%); (f) NaOMe, MeOH; Pd/C, H_2, Ac_2O, acetone, H_2O (83%)

(IC_{50}=1 5 µM), jack bean (IC_{50}=1 6 µM), porcine placenta (IC_{50}=0 4 µM) and bovine epididymis (IC_{50}=0 7 µM) [6] The potential utility of 4 in tumor growth inhibition is currently under investigation

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6 Inhibition of β-N-hexosaminidase activity was determined by employing p-nitrophenyl-N-acetyl-β-D-glucosaminide (2.5 mM) as substrate at pH 4 5
7 **Compound 6:** oil, ^1H NMR ($CDCl_3$) δ 1 4 (2s, 2 x 3H), 1 9 (m, 1H), 2 2 (m, 1H), 2 8-2 9 (m, 2H), 3.0 (m, 2H), 3 4 (dd, 1H), 3 7 (m, 2H), 4 5 (m, 1H), 4.8 (m, 1H), 5.2 (s, 2H), 7.3-7 4 (m, 5H); MS (CI-CH_4) 364 (MH^+), 346 (MH^+-H_2O).
Compound 7: mp 139-141°C, ^1H NMR ($CDCl_3$) δ 1 25 (s, 3H), 1 35 (s, 3H), 1.8-2 3 (m, 2H), 2 8-3 4 (m, 5H), 3 9 (t, 1H), 4 6 (m, 1H), 5 05 (s, 2H), 5 1 (m, 1H), 5 3 (t, 1H), 7 1-7 4 (m, 5H), 7 55 (d, 2H), 7.9 (d, 2H), MS (CI-CH_4) 546 (MH^+), 488 (MH^+-CH_3COCH_3)
Compound 8: oil, ^1H NMR ($CDCl_3$) δ 1 85 (s, 3H), 1 90 (m, 1H), 2 05 (s, 3H), 2 2-2 5 (m, 4H), 3 25 (dd, 1H), 3 5 (dd, 1H), 5 05 (s, 2H), 5 1 (m, 1H), 5 25-5 50 (m, 3H), 7 1-7 3 (m, 5H), 7.5-7 6 (d, 2H), 7 8 (d, 2H); MS (CI-CH_4) 590 (MH^+), 530 (MH^+-CH_3CO_2H)
Compound 9: oil, ^1H NMR ($CDCl_3$) δ 1 8 (s, 3H), 2 0 (s, 3H), 1 7-2 5 (m, 5H), 3 0-3 4 (m, 2H), 3 9 (m, 1H), 4.8-5.4 (m, 3H), 7 3-7 6 (m, 3H), 7 9-8 1 (m, 2H); MS (CI-CH_4) 378 (MH^+), 360 (MH^+-H_2O)
Compound 10: oil; ^1H NMR ($CDCl_3$) δ 1 8 (s, 3H), 2 0 (s, 3H), 1 9-2 4 (m, 5H), 3 0-3 9 (m, 3H), 5 1-5.7 (m, 3H), 7 2-7 6 (m, 3H), 7 8-8 1 (m, 2H), MS (CI-CH_4) 403 (MH^+), 360 (MH^+-HN_3).
Compound 4: mp 199-203°C, ^1H NMR (D_2O) δ 1 6-1 8 (m, 1H), 1 9-2 1 (m, 5H), 2 15-2 4 (m, 2H), 3 0-3 15 (m, 2H), 3.38 (dd, $J_{6,7}$=10 2 Hz, $J_{7,8}$=9 0 Hz, 1H, H_7), 3.65 (dd, $J_{7,8}$=9 0 Hz, $J_{8,8a}$=9 8 Hz, 1H, H_8), 3.86 (dt, $J_{5,6}$=$J_{6,7}$=10 2 Hz, $J_{5,6}$=4 8 Hz, 1H, H_6), 4 41 (ddd, J=7 1, 4 4, 1 8 Hz, 1H, H_1), MS (CI-CH_4) 231 (MH^+), 213 (MH^+-H_2O) Anal Calcd for $C_{10}H_{18}N_2O_4 \cdot H_2O$ C, 48 38, H, 8 12; N, 11.28. Found· C, 48 53; H, 7 96; N, 10.91.

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