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A NOVEL INHIBITOR OF HUMAN α-L-FUCOSIDASE: ENANTIOSELECTIVE SYNTHESIS OF L-FUCOAMIDRAZONE

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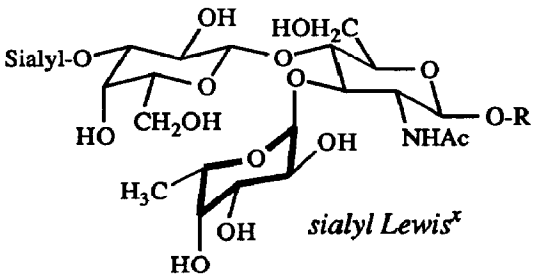
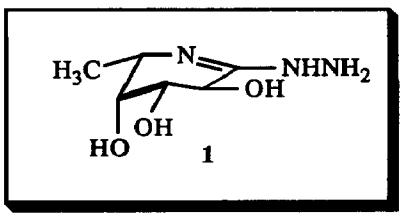
Abstract: A short, chiral synthesis of the title inhibitor **1** is reported from D-galactosamine by chain end interchange. The L-fucoamidrazone is a good competitive inhibitor of human α-L-fucosidase (K_i = 820 nM).

The phenomenon of cell-cell adhesion is one of several key recognition events between leukocytes and endothelial cells responsible for orchestrating the appropriate immune response to inflammation.[1] Cytokines trigger endothelial cells to produce cell-surface endothelial-leukocyte adhesion molecules (ELAMs) which bind to a tetrasaccharide, sialyl Lewis^x, expressed on the leukocyte surface. Sialyl Lewis^x (shown below) is the minimal carbohydrate ligand for many ELAMs, and adhesion has been shown to depend critically on the presence of a 1,3-linked L-fucose residue (bold ring in figure).[2-4] For these reasons, inhibitors of the corresponding fucose-processing enzymes which mediate trimming (L-fucosidase) and attachment (L-fucosyltransferase) are currently of considerable interest, not only for mechanistic study, but also as prospective anti-inflammatory and antitumor drugs. Here we report the synthesis and bioevaluation of L-fucoamidrazone **1** which, as expected from studies of related monosaccharide analogs,[5] is a potent inhibitor of human α-L-fucosidase.



sialyl Lewis^x



Many glycosidases are inhibited by polyhydroxylated piperidines and pyrrolidines resembling the enzyme's cognate saccharide substrate, prompting several groups to target fucose-related polyhydroxylated heterocycles as prospective fucosidase inhibitors. Thus Fleet's group[6] and others[7] have prepared 1,5-dideoxy-1,5-imino-L-fucitol, which is a potent competitive inhibitor of human α-L-fucosidase ($K_i = 10^{-8}$ M). Several closely-related iminoalditols and glycals also inhibit fucosidase, some with K_i values in the low micromolar range.[8] A complementary approach involved the synthesis of iminoalditol-containing Lewis^x and sialyl Lewis^x oligosaccharides,[9] as well as sulfur-linked disaccharides of fucose.[10] No bioassays on the former were reported, and the latter substances required millimolar concentrations for fucosidase inhibition.

Amidrazone analogs of D-monosaccharides have been shown to be potent and effective inhibitors of a wide range of glycosidases.[5] Based on that earlier methodology, a synthesis of L-fucoamidrazone **1** required access to the known[11] L-fuconic-δ-lactam **5**, for which a more expedient synthesis has now been developed from D-galactosamine **2** using a chain end interchange strategy (Scheme). Thus, the known[12] galacturonic acid **3** was prepared by platinum and oxygen dehydrogenation of protected **2** in good yield on a multigram scale.[13] After hydrolysis of the glycosidic bond in **3**, thioacetalization of the latent aldehyde using ethanethiol afforded **4** in 60% overall yield. Upon exposure under acidic conditions to Raney nickel, desulfurization was accompanied with N-deprotection and concomitant cyclization to generate the known lactam **5** (76%), whose physical and spectroscopic properties were identical with published values.[11] Exhaustive silylation of **5**, followed by treatment with Lawesson's reagent furnished thionolactam **6** after desilylation in the acidic workup. Reaction of **6** with hydrazine in CH_3OH gave the target amidrazone **1** in 90% yield after flash column chromatography.

The activity of **1** as a fucosidase inhibitor was evaluated using recombinant human α-L-fucosidase. Under steady-state assay conditions[14] using p-nitrophenyl-α-L-fucopyranoside (Fuc-OpNP) as substrate (K_M = 230 μM, citrate buffer, pH 5.0) the enzyme was well-behaved, and Dixon plots of 1/V versus [I] revealed clean competitive inhibition in the presence of L-fucose (K_i = 400 μM). Competitive inhibition was also observed in the presence of **1** (see Figure; facing page), with K_i = 820 nM. Thus with its appropriately flattened (i.e. half-chair) conformation, ease of protonation, and good stability, L-fucoamidrazone **1** represents a promising new lead in the search for potent fucosidase inhibitors, including sialyl Lewis^x oligosaccharides incorporating **1** and its congeners.

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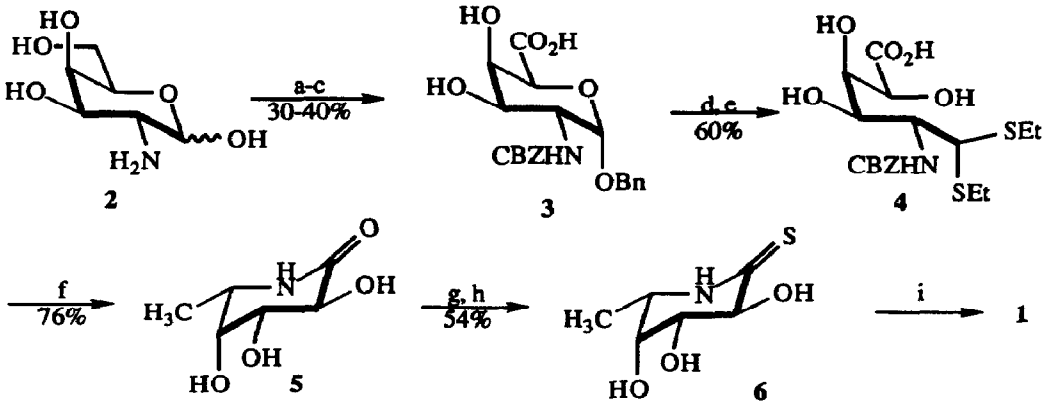
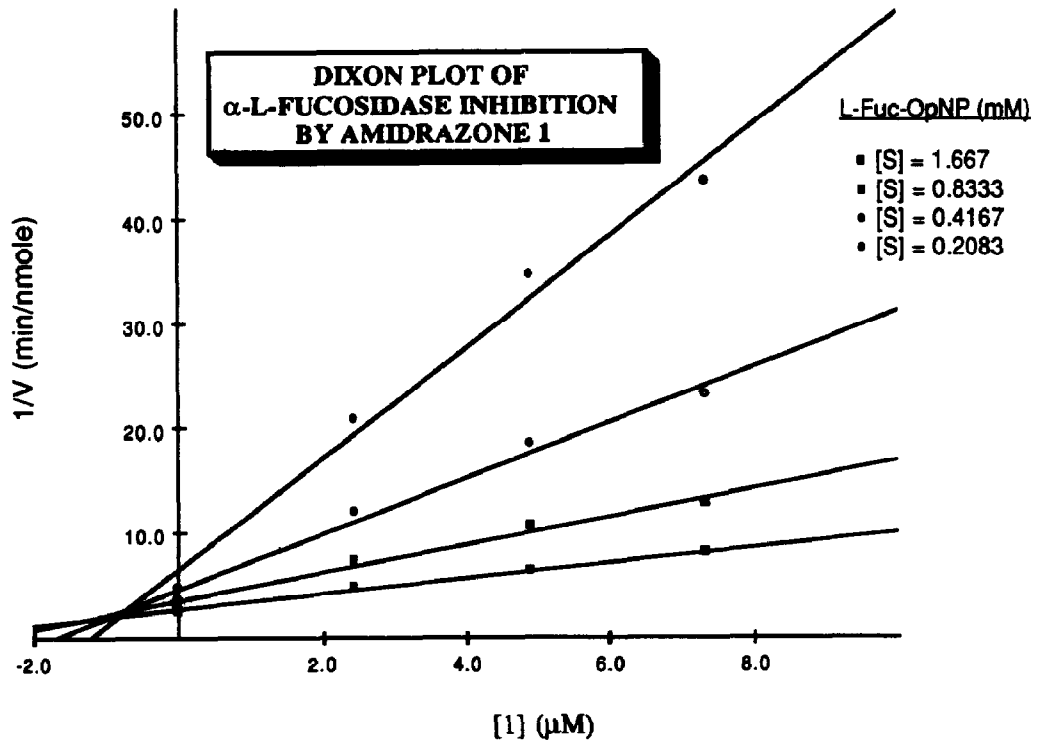
SCHEME



(a) CBZCl, H_2O; (b) BnOH, CH_3COCl; (c) Pt, O_2, H_2O-EtOH; (d) 1:4 TFA:H_2O, 90°C; (e) EtSH, HCl; (f) RaNi-EtOH; (g) TMSCl, $(TMS)_2NH$, pyr; (h) Lawesson's reagent, C_6H_6, reflux, 2 h; then CH_3OH-HCl; (i) NH_2NH_2-CH_3OH, 0°C, 3 h.



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