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C_3-THIA AND C_3-CARBA ISOSTERES OF A CARBOCYCLIC INFLUENZA NEURAMINIDASE INHIBITOR, (3*R*,4*R*,5*S*)-4-ACETAMIDO-5-AMINO-3-PROPOXY-1-CYCLOHEXENE-1-CARBOXYLIC ACID

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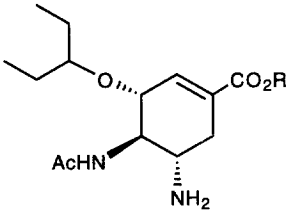
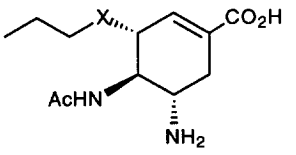
Abstract. The importance of the oxygen atom in the C_3 ether side chain of a carbocyclic influenza neuraminidase inhibitor **3** was investigated by replacement of the C_3 ether oxygen atom of **3** with either a sulfur atom (compound **4**) or a carbon atom (compound **5**). The regio- and stereospecific syntheses of both isoteres are described starting from (-)-quinic acid. © 1997 Elsevier Science Ltd.

Recently, we have described a new class of potent carbocyclic influenza neuraminidase (NA) inhibitors, which are transition-state analogues of the sialic acid cleavage reaction by NA.[1] In this series, a new hydrophobic pocket in the region corresponding to the glycerol subsite of sialic acid was identified. In order to understand the structure-activity relationships of this class of compounds systematic modifications of substituents attached to the cyclohexene ring were investigated.[2] Of these, the C_3-lipophilic side chains proved to play a significant role for NA inhibitory activity. From extensive structure-activity relationship studies of the C_3 lipophilic side chain and X-ray crystallographic analysis, the 3-pentyloxy side chain as shown in compound **1** appeared to be optimal for NA inhibition.[1] On the basis of in vitro and in vivo activity, compound **2** (designated as GS4104) was selected as a clinical candidate for the oral treatment and prophylaxis of influenza infection.[3]



1: R = H GS4071
2: R = Et GS4104



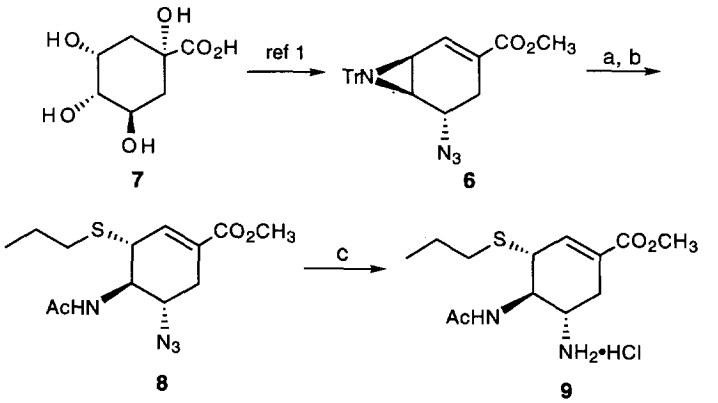
3: X = O
4: X = S
5: X = CH_2

The present investigation addresses the importance of the ether oxygen at the C_3 position for NA inhibition. It has been proposed that the catalytic mechanism for the cleavage of sialic acid from glycoconjugates involves the formation of a C_2 carbonium cation, which in turn is stabilized by the neighboring oxygen atom.[4] We expected that inhibitory activity might be affected by replacement of the oxygen atom of the ether side chain at the C_3 position with either a sulfur or a carbon atom since they would have different electronic and binding properties.

The preparation of the sulfide analogue **4** was accomplished starting from the trityl protected aziridine **6**, which is synthesized from (-)-quinic acid **7** (Scheme 1). Ring opening of **6** with 1-propanethiol under BF_3•Et_2O catalysis followed by acetylation with acetyl chloride gave acetamide **8**. Catalytic hydrogenation of the azide group in **8** over Lindlars catalyst at atmospheric pressure gave the amine that was directly converted into the

corresponding hydrochloride salt **9**. Surprisingly, attempted saponification of **9** with aqueous KOH gave mostly decomposed material. At the present time it is not clear as to why **9** is unstable to basic hydrolysis. Consequently, **9**, which is in essence the methyl ester prodrug of the amino acid **4**, was used for the enzymatic assay.[5]

Scheme 1[a]

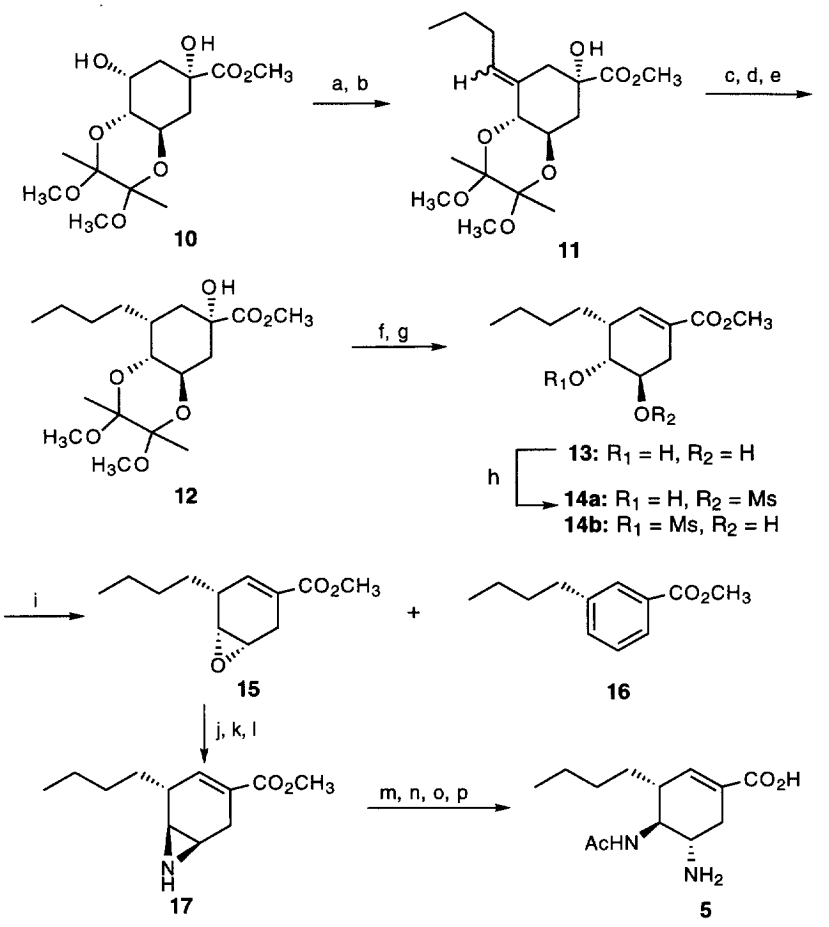


[a]Reagents: (a) 1-propanethiol, BF_3•Et_2O; 73% (b) AcCl, Et_3N, CH_2Cl_2; 98% (c) H_2, Lindlars catalyst, EtOAc then 1 N HCl; 67%.

The *n*-butyl side-chain analogue **5** was synthesized starting from the readily accessible protected quinic acid **10**[6] (Scheme 2). Oxidation of **10** with PCC followed by Wittig olefination gave olefin **11** as a 2:1 mixture of double-bond isomers. Protection of the tertiary hydroxyl group followed by catalytic hydrogenation at atmospheric pressure gave exclusively the *n*-butyl derivative with the desired α stereochemistry.[7] The hydrogenated product was then deprotected with TBAF to afford hydroxy ester **12** and then directly eliminated in a regiospecific manner with sulfuryl chloride to the α,β-unsaturated ester. Subsequent deprotection with 40% TFA affords diol **13**. Treatment of **13** with 1.1 equivalents of methanesulfonyl chloride gave a 6:1 mixture of C_5 and C_4 mesylates **14a** and **14b**, which was treated with DBU at ambient temperature to give the desired epoxide **15** and the aromatic *n*-butyl derivative **16**. The epoxide **15** was converted to aziridine **17** by sequential treatment of **15** with NaN_3/NH_4Cl, mesylation of the resultant alcohol and followed by aziridine formation with PPh_3. The aziridine **17** was then opened in a regio- and stereospecific manner with NaN_3/NH_4Cl and acetylated with acetyl chloride. Finally, reduction of the azide group with PPh_3 followed by saponification with aqueous KOH provides the amino acid **5**.

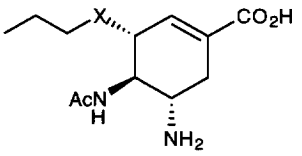
The enzymatic neuraminidase inhibitory activities for the three analogues are shown in Table 1.[8] It can be seen that when the ether oxygen atom of **3** is replaced with a methylene group (compound **5**) there is a small decrease in activity. This suggests that the electronic difference at the C_3 position has a minimal effect on NA inhibitory activity. Further confirming this, the neuraminidase inhibitory activity of the sulfide analogue **4** was also very comparable to that of **3**. However, it cannot be ruled out that the thioalkyl chain of **4** is considerably longer than the ether side chain of **3**, which may result in different hydrophobic interactions in the active site.

Scheme 2[a]



[a]Reagents: (a) PCC, pyridine; 74% (b) *n*-BuPPh$_3$Br, *n*-BuLi, THF; 81% (c) Et$_3$SiOTf, 2,6-lutidine; 93% (d) H$_2$,10% Pd/C; 97% (e) TBAF, THF; 77% (f) i. SO_2Cl_2 ii. MeOH; 90% (g) 40% TFA, CH_2Cl_2; 75% (h) MsCl, Et$_3$N; 87% (i) DBU, THF; 71% (j) NaN_3, NH_4Cl, MeOH, H_2O; 95% (k) MsCl, Et$_3$N; 97% (l) i. PPh_3, THF ii. Et$_3$N/H_2O;71% (m) NaN_3, NH_4Cl, DMF; 86% (n) AcCl, pyridine; 68% (o) PPh_3, THF, H_2O; 95% (p) aq. KOH; 85%.

Table 1. Influenza Neuraminidase Inhibition



compound[a]	X	enzyme[b] IC_{50} (nM)
3	O	130
4	S	212[c]
5	CH_2	220

[a]All compounds gave satisfactory spectral and analytical data.
[b]NA (H1N1)
[c]Compound **9** was incubated in rat plasma at 37 °C prior to assay.

References and Notes:

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3. Kim, C. U.; Lew, W.; Williams, M. A.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Li, W.; Tai, L.; Escarpe, P.; Cundy, K. C.; Eisenberg, E. J.; Lacy, S.; Sidwell, R. W.; Stevens, R. C.; Laver, W. G. **1996**. New Potent, Orally Active Neuraminidase Inhibitors as Anti-Influenza Agents: In Vitro and In Vivo Activity of GS4071 and Analogs, abstr. H44, P171. *In* Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Washington, D.C.
4. (a) Taylor, N. R.; von Itzstein, M. *J. Med. Chem.* **1994**, *37*, 616. (b) Chong, A. K. J.; Pegg, M.S.; von Itzstein, M. *Biochem. Int.* **1991**, *24*, 165. (c) Janakiraman, M. N.; White, C. L.; Laver, W. G.; Air, G. M.; Luo, M. *Biochemistry*, **1994**, *33*, 8172.
5. Compound **9** was incubated in rat plasma for 30 min at 37 °C to convert the methyl ester to the parent amino acid **4**. This was then used directly in the enzymatic assay.
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7. The steric bulk of the triethylsilyl group is essential for the stereochemical outcome of the hydrogenation since direct hydrogenation of **11** under the same conditions yields a 2:1 mixture of α:β *n*-butyl derivatives.
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