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A NEW SERIES OF C_3-AZA CARBOCYCLIC INFLUENZA NEURAMINIDASE INHIBITORS: SYNTHESIS AND INHIBITORY ACTIVITY[1]

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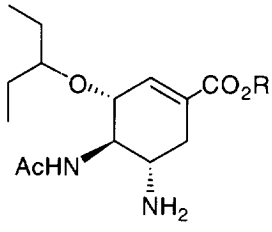
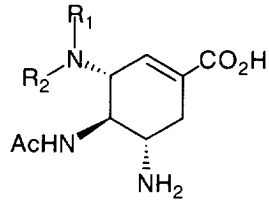
Abstract: The synthesis and influenza neuraminidase inhibitory activity of a new series of C_3-aza carbocyclic neuraminidase inhibitors are described. Analogues **3c** and **3j**, bearing a 3-pentyl group, exhibit influenza A inhibitory activities comparable to that of **1**.

Recently, we have described a new class of carbocyclic influenza neuraminidase (NA) inhibitors as transition state analogues for the NA catalyzed cleavage of terminal sialic acid residues.[2] A key feature in this series is the incorporation of lipophilic side chains at the C_3-position of the cyclohexene ring system that bind in a conformationally induced hydrophobic pocket in the NA active site. Extensive structure–activity relationship studies[2,3] have identified compound **1** (GS 4071) to be one of the most potent influenza NA inhibitors in this series. Currently, the ethyl ester prodrug **2** (GS 4104, also known as Ro 64-0796) is being evaluated for the oral treatment and prophylaxis of influenza infection in phase II/III clinical studies.

Early structure–activity relationship studies have demonstrated that the corresponding C_3-thia and C_3-carba isosteres in this series exhibit comparable influenza neuraminidase inhibitory activity relative to the C_3-oxa analogue.[3b] As part of our continuing efforts in this area we were interested in the corresponding C_3-aza isostere **3**. To this end, a series of C_3-aza analogues were prepared and evaluated for influenza neuraminidase inhibitory activity.



1 R = H GS 4071
2 R = Et GS 4104 (Ro-64-0796)



3 R_1 and R_2 = H, alkyl, acyl

The corresponding C_3-aza analogues were prepared according to Scheme 1. Amino alcohol **5**, prepared from (-)-quinic acid (**4**),[2] was acetylated with acetic anhydride to furnish allylic acetate **6** in 81% yield. Treatment of **6** with excess dialkyl amine (R_1R_2NH; see Table 1) and 5 mol% tetrakis(triphenylphosphine)palladium(0)[4] provided the coupled products in yields ranging from 38–60%. Reduction of the azide group with triphenylphosphine followed by saponification with aqueous KOH furnished the desired amino acids **3a–h** in yields of 80–90%.

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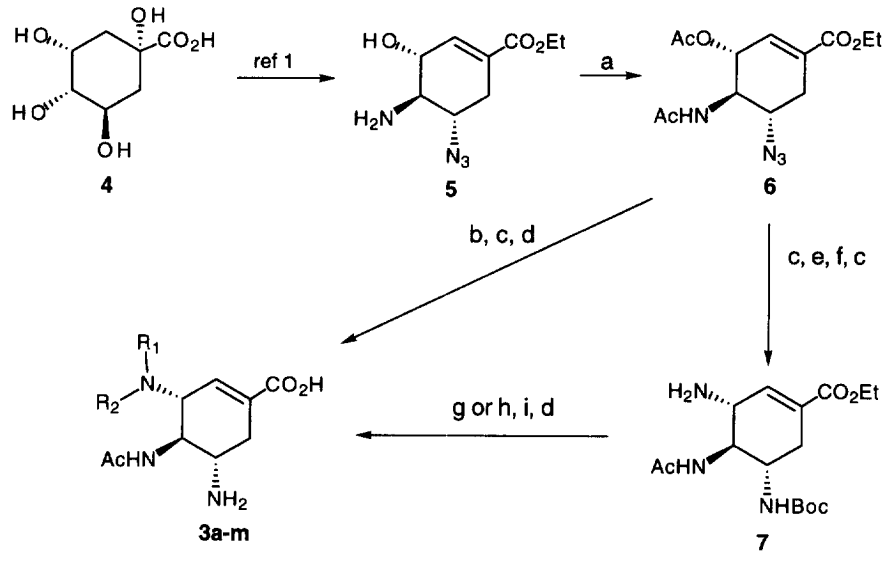
Scheme 1[a]



[a]Reagents: (a) Ac_2O, pyridine. (b) R_1R_2NH (2.5 eq), 5 mol% $Pd(PPh_3)_4$, THF. (c) PPh_3, H_2O, THF.(d) aq. KOH, THF. (e) $(Boc)_2O$, CH_3CN. (f) NaN_3, 5 mol% $Pd(PPh_3)_4$, H_2O,THF. (g)R_2CHO,$ZnCl_2$/$NaCNBH_3$. (h) R_2COCl, pyridine. (i) CF_3CO_2H, CH_2Cl_2.

The palladium coupling of **6** with less reactive primary amines was not successful due to aromatization of the allyl-palladium intermediate.[5] Therefore, an alternate route was required for the preparation of the corresponding mono N-alkyl and amide derivatives. Compound **6** was converted to the mono N-Boc protected amine **7** by a four-step sequence: (1) reduction of the azide group with triphenylphosphine (90%), (2) protection of the amine with di-*t*-butyl dicarbonate (95%), (3) palladium(0) catalyzed azidation with sodium azide (75%), and (4) reduction of the azide group with triphenylphosphine (89%). The amine **7** was then converted into either the mono N-alkyl derivative via reductive alkylation with the corresponding aldehyde (R_2CHO) and $ZnCl_2$/$NaCNBH_3$ (69–80%) or the amide by acylation with the corresponding acid chloride (R_2COCl) in pyridine (89–97%). Removal of the N-Boc protecting group with trifluoroacetic acid (50–90%) followed by ester hydrolysis with aqueous KOH provided amino acids **3i–m** in 77–95% yield.

The neuraminidase inhibitory activities of **3a–m** were evaluated in an enzymatic assay[6] with the results summarized in Table 1. Compounds **3c** and **3j**, which are direct side chain analogues of **1**, exhibit influenza A neuraminidase inhibitory activities comparable to **1**. In fact, the X-ray crystal structure of **3c** bound with influenza neuraminidase confirm that the 3-pentyl group of **3c** binds in the hydrophobic pocket formed by the hydrocarbon side chains of Glu 276, Ala 246, Arg 224 and Ile 222 in a manner similar to that of **1** (Figure 1).[2]

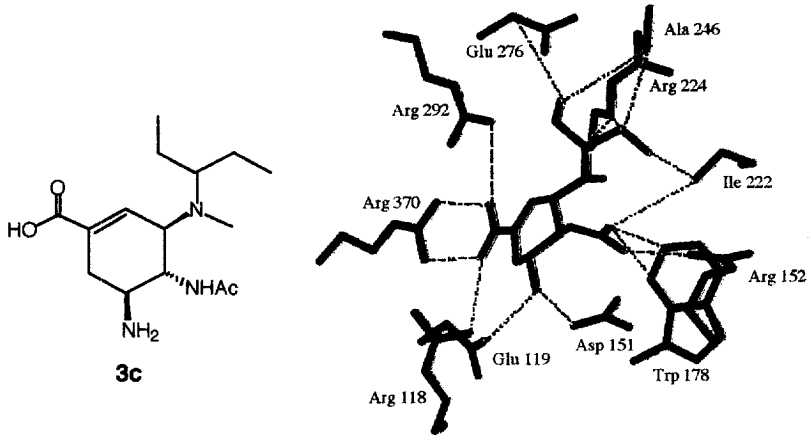


Figure 1. X-ray structure of **3c** bound with influenza neuraminidase

Table 1. Influenza Neuraminidase Inhibition

compound[a]	R_1	R_2	enzyme IC_{50}(nM) Flu A[b]	Flu B[c]
3a	CH_3	$CH_2CH_2CH_3$	65	65
3b	CH_3	$CH_2CH_2CH_2CH_3$	180	ND[d]
3c	CH_3	$CH(CH_2CH_3)_2$	6	60
3d	CH_3	CH_2CH_2Ph	100	565
3e	CH_3	c-C_6H_{11}	200	>1000
3f	CH_2CH_3	$CH_2CH_2CH_3$	90	ND[d]
3g	CH_2CH_3	$CH_2CH_2CH_2CH_3$	85	175
3h	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	12	60
3i	H	$CH_2CH_2CH_3$	200	240
3j	H	$CH(CH_2CH_3)_2$	11	100
3k	H	$COCH_2CH_3$	2700	500
3l	H	$COCH(CH_3)_2$	6400	1700
3m	H	$COCH(CH_2CH_3)_2$	4000	3200
1		GS 4071	1	4

[a]All compounds gave satisfactory spectral and analytical data;
[b]A/PR/8/34 (H1N1); [c]B/Lee/40; [d]not determined.

Compound **3h** also exhibits comparable influenza A inhibition to that of **3c** and **3j**, which may be due to the two propyl groups binding in a conformation in the NA active site approximating that of the 3-pentyl group. The amide analogues **3k–m** exhibit a substantial decrease in potency compared to the corresponding mono and dialkyl analogues which may be a result of inductive and conformational effects of the amide group. Presently, the effects of the C_3 nitrogen atom on binding affinity and the differences in potencies observed against influenza B neuraminidase have not been established. Further investigation into the structure–activity relationship as well as X-ray crystallographic analysis and optimization of this series of compounds is in progress and will be reported in due course.

References and Notes

1. Presented in part in: Lew, W.; Wu, H.; Mendel, D.B.; Escarpe, P.A.; Laver, W.G.; Graves, B.J.; Kim, C.U. "Synthesis and Activity of a New Series of C_3-Aza Carbocyclic Influenza Neuraminidase Inhibitors" 11th International Conference on Antiviral Research, San Diego, CA, USA, April 5-10, 1998.
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5. Reaction of **6** with 3-aminopentane as well as with other primary amines in the Pd(0) catalyzed amination reaction leads exclusively to formation of ethyl N-acetyl-4-aminobenzoate resulting from elimination of the C_5 azido group of **6**.
6. A full protocol for the enzymatic assay is found in: Li, W.; Escarpe, P.A.; Eisenberg, E.J.; Cundy, K.C.; Sweet, C.; Jakeman, K.J.; Merson, J.; Lew, W.; Williams, M.A.; Zhang, L.; Kim, C.U.; Bischofberger, N.; Chen, M.S.; Mendel, D.B. *Antimicrob. Agents Chemother.* **1998**, *42*, 647.